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Silent Cerebral Events after Atrial Fibrillation Ablation – Overview and Current Data

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Abstract

Silent cerebral lesions (SCL) have been identified on brain magnetic resonance imaging (MRI) in apparently asymptomatic patients after cardiovascular procedures. After atrial fibrillation (AF) ablation incidences range from 1 to over 40% depending upon different factors.

MRI definition should include diffusion weighted imaging (DWI) to detect hyperintensities (bright spots) due to acute brain ischemia correlated with a hypointensity in the apparent diffusion coefficient mapping (ADC-map) to rule out artifacts. The genesis of SCL appears to be multifactorial and appears to be a result of embolic events either from gaseous or solid particles. The MRI pattern appears to be comparable not hinting towards a specific mechanism. One may distinguish two different MRI definition: one, more sensitive, for silent ischemic events (SCE) not proven to be related to cell death (DWI positive but FLAIR negative); and one for SCL that are due to edema caused by cell death which will lead to glial cell scar formation (DWI positive and FLAIR positive). For ease of data interpretation, future studies should ensure both definitions, and that DWI and FLAIR data is acquired using identical slice thickness and orientation.

Risk factors associated with increased SCL-incidences involve patient-specific, technology-associated and procedural determinants. When using a high-sensitive MRI definition, differences in SCE-rates among technologies seem to be less prominent. Further studies on the effects of different periprocedural anticoagulation regimen, different steps of the ablation procedure and new technologies are needed. For now, SCL incidence may determine the thrombogenic potential of an ablation technology and further studies to reduce or avoid SCL generation are desirable. It appears reasonable, that any SCE should be avoided.

Introduction

Patients with atrial fibrillation (AF) have been identified to have progressive cerebral disease manifested by magnetic resonance imaging (MRI)-detected lesions in formally asymptomatic patients.[7] Thromboembolic stroke remains the most devastating complication of AF. Catheter ablation has been documented to be an effective and safe treatment option in patients with symptomatic AF. Complications may involve thromboembolic stroke during the ablation procedure. Recently, MRI of the brain in asymptomatic patients after AF ablation revealed lesions consistent with acute ischemia.[1] These lesions were termed "silent cerebral lesions" (SCL) and have been identified not only in AF ablation but also in nearly any other cardiovascular intervention like coronary angiography (15%) and transfemoral aortic valve interventions in up to 68%.[2-4] Differences in SCL definition and used MRI technology may affect the reported rates between studies. In regard to SCL related to AF ablation a number of publications using different MRI definition, different ablation technologies and different patient groups are available indicating post-ablation SCL rates in between 6% up to 41%.[3,5-13]

The term SCL is preferred to asymptomatic cerebral lesions (ACL) or asymptomatic cerebral embolism (ACE) because asymptomatic may not be completely correct. Whereas so far no study has proven sequela related to the occurrence of SCL, subtle changes in neuropsychological performance may not be completely ruled out. For now, the best timing to perform these tests remains unclear and further studies on large patient groups comparing patients with SCL to those without and not compared to other control groups (not undergoing AF interventions) are needed.

The mechanism of SCL appears to be multifactorial and may involve gaseous or particulate embolic events during AF ablation. In recent publications different factors associated with higher incidences of SCL have been identified to involve 1. patient-specific characteristics, 2. ablation technology-associated characteristics and 3. procedural technique-associated characteristics.

An important point to consider is that over 60% of patients with AF appear to have asymptomatic cerebral lesions independent of

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cardiovascular procedures.[7,14] Whereas the mechanism of these lesions is unclear they represent an underlying substrate of cerebral damage directly related to AF. Predictors of progressive cerebral disease in these AF patients included hypertension, $CHADS_2$, and CHA_2DS_2-VASc scores, and larger left atrial diameter.[7] These pre-existing "white matter lesions" are occurring as result of the disease processes and their relative magnitude is much higher compared to the minimal number and size of SCL caused by cardiovascular procedures in AF patients.

Definition of SCL

Detection of SCL per definition is restricted to asymptomatic patients in gross neurological evaluation. The intensity of neurological work-up remains undefined and one needs to keep in mind that subtle changes in neurological appearance (especially if lesions in the cerebellum are concerned) or neuropsychological testing have not been consistently evaluated in published reports.

There is still debate about the exact criteria defining SCL in MRI of the brain. Diffusion weighted imaging (DWI) MRI has been shown to be highly sensitive and specific in detecting brain ischemia. DWI MRI assesses the net random movement of water in brain tissue and is a sensitive and objective reflection of ischemic-related cytotoxic edema injury. For each DWI sequence, the apparent coefficient map (ADC) must be calculated to increase specificity of classification of ischemic lesions and to rule out shine-through artifacts. The T2-weighted fluid-attenuated inversion recovery (FLAIR) – usually in the clinical set-up performed as a 5 to 6mm thick-sliced MRI sequence – is sensitive to fluid accumulations due to vasogenic edema. Hyperintensities seen on FLAIR are used to verify permanent injury in ischemic sites. FLAIR aids in determining acute from chronic lesions and has been included in some studies into the SCL definition criteria.[10,15] The FLAIR sequence may turn positive over the course of time of demarcation of a DWI-positive event (but may still be negative as early as the initial days). Although, the FLAIR sequence may be important because it detects edema formation in regions where cell-death has been induced. The FLAIR sequence also provides a more precise anatomical image than that seen in the more distorted DWI which allows more accurate lesion dimensional measurements. A recent study indicates that 2/3 of acute DWI detected findings are FLAIR negative.[3] Therefore, a more sensitive, newer definition based solely on DWI and ADC map may more easily document the overall load and incidence of silent cerebral ischemic events (SCE). This definition involves a hyperintensity on DW image and a corresponding hypointensity on ADC map (but does not include a corresponding hyperintensity in the FLAIR sequence). Whether FLAIR positive and negative SCL represent different entities or may have different effects remains so far unclear. In animal studies FLAIR positive SCL represent irreversible cerebral damage and lead to glial scarring.[16] With regard to reversibility of ischemic injury, it has been documented in a stroke case study that a reduction in area of DWI hyperintensity over time could be correlated with neurological symptom resolution, suggesting that at least a portion of the area affected by the ischemic insult did not form a permanent lesion.[17]

An important issue is the slice thickness and orientation of the FLAIR and DW MRI-sequences. Both DWI and FLAIR should be acquired using the same slice thickness and orientation. For SCL studies it is crucial to request a decisive MRI protocol enabling exact correlation of different sequences. Based on our experience, a good recommendation would be for such studies of SCL/SCE to use as a standard, 5mm slice thickness in the axial plane in the DWI and T2 FLAIR sequences. Post procedure MRI should be scheduled at a minimum to be the day after a procedure but a 24-48hr window may be appropriate to detect both DWI and T2 FLAIR hyperintensities.

As conclusion, DWI represents a more sensitive measure of brain ischemic events related to the embolic potential of an AF ablation procedure but may not positively detect lesion formation due to cell death. A positive finding in the FLAIR (which may become positive during the course of the first days after embolism) is related to definitive cell death and relates to brain scar formation.[16]

Most studies on SCL have been performed using 1.5Tesla MRIs but a recent report using a 3Tesla machine indicates a higher incidence of SCL when using bigger magnets. Further studies are needed but results using MRI machines with different magnets should not be compared.[8]

SCL Incidences in AF Ablation

There has been a wide range of reported SCL rates depending on the definition used and the methodology and specification of ablation. It remains important to identify potentially modifiable factors that may help to reduce SCL rates.

In reports incidence of SCL after AF ablation ranges from 1.7% up to 41%.[7,8] Overall, in 930 published patients 19% had documented cerebral lesions. Of interest, most SCL are not single events and the median number of SCL per patients depends upon ablation technology used (in between 2 to 4/pat).[1,3,5-9,12,13,15] In some patients multiple SCL can be identified (up to 25/pat reported).

In our own patient collective approximately 2/3 of SCL have a diameter of 3mm or less (usually FLAIR negative) and 1/3 of lesions ranges in between 4 to 10mm in diameter. Only in rare cases (1%) SCL-diameters are above 10mm (up to 25mm reported) and these are usually also still detectable on follow-up MRI. The smaller lesions appear to become undetectable on MRI within 4 days up to 2 weeks after AF ablation.[6,16] Whether different diameters of SCL represent different mechanisms remains unclear and needs further investigation.

The mechanism of SCL still remains poorly understood. Whereas it appears clear that SCL are a consequence of the ablation procedure and in direct timely relation gaseous or particulate embolization may cause the same MRI appearance of SCL. In an animal model with direct injection of either air-microbubble or blood-coagulum preparations into the carotid artery in a dog model produced MRI patterns and appearances comparable to what is seen in post-ablation human brain MRI. Of interest though, even high loads of emboli did

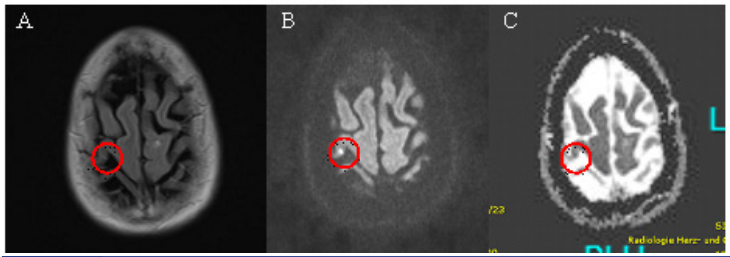

Figure 1: FLAIR (A), DWI (B) and ADC-map (C) of a patient with a single SCE (red circle) only documented on DWI (B) and ADC-map (C) but not identified on FLAIR (A) imaging indicating higher sensitivity of a novel MRI definition of SCE.

not produce SCL in all animals indicating that brain vasculature and blood supply via collateral routes may play an important role in the occurrence of SCL.[16]

In these animal models FLAIR-positive SCL represent sites of permanent injury verified by histopathology which revealed glial cell scaring in these regions.

Predictors of SCL

When considering potential confounding factors 1. patient-specific, 2. technology-associated and 3. procedure-related aspects needs to be evaluated. It may be speculated that only a minority of all confounding variables are yet studied.

Patient-Specific Factors

In our own experience only left atrial dilation and patient age is associated with an increased risk of SCL. Further studies are urgently needed to further elucidate patient characteristics associated with higher SCL rates.

Of interest, a recent unpublished report indicates that left atrial fibrosis detected on intraprocedural left atrial bipolar voltage mapping may influence the occurrence of SCL (Müller et al, 2013, unpublished data presented at European Society of Cardiology Scientific meeting 2013, Amsterdam).

Factors like left atrial dilation and left atrial fibrosis may point towards a common mechanism of atrial substrate associated thromboembolism although in all cases obvious left atrial thrombus was ruled out on transesophageal echocardiography.

Technology-Associated Factors

Initial reports on SCL indicated differences in SCL rates comparing different AF ablation technologies. Two comparative studies (using the older MRI SCL-definition) indicated a significantly higher incidence of SCL in patients undergoing ablation using phased radiofrequency technology (PVAC™-catheter: 37.5 and 38.9%) compared to single-tip RF (7.4 and 8.3%) or cryoballoon (4.3 and 5.6%) PVI.[10,15] Further studies have identified high incidences of SCL in patients treated with phased RF technology (see figure 2).[6] Subtle changes of procedural aspects of phased RF ablation including a higher target ACT, underwater-loading of the device and most of all excluding an interaction between electrodes 1 and 10 has led to relevant reductions of SCL down to less than 2% in the ERACE study (again using the old MRI definition).[3,7] In an analysis of patients treated with phased RF and applying the ERACE protocol, incidence rates using the new MRI definition documented SCE in approximately 30% of patients (unpublished data, Deneke et al., 2013).

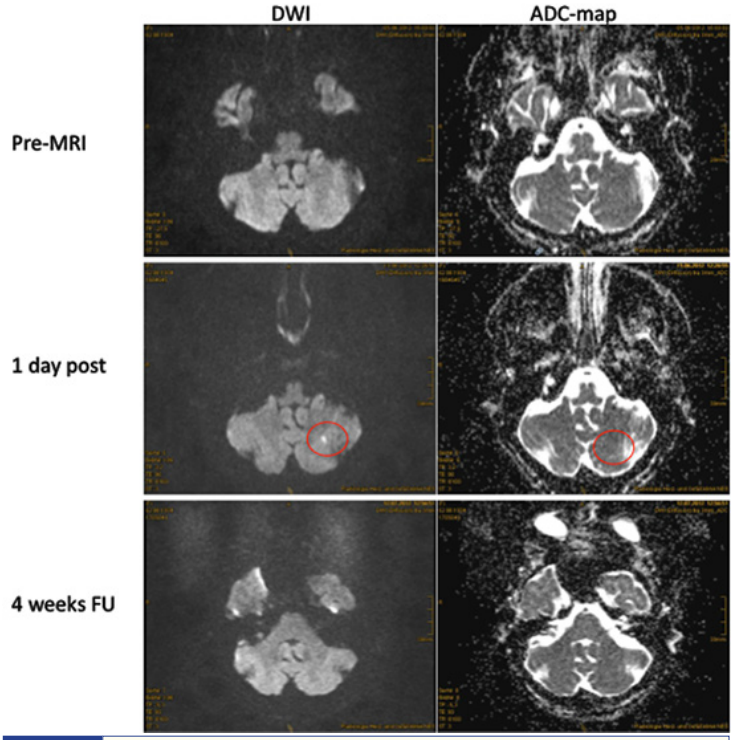

Figure 2: MRI pre (a), 1 day post (b) and at 4 weeks follow-up (c) of a patient undergoing irrigated RF PVI: DWI indicates a hyperinsense lesion (red circle) in the cerebellum corresponding to a hypoattenuation on ADC-map. During follow-up MRI lesion is not detected any more on DWI.

The mechanism behind the high incidence of SCL in PVAC patients was considered to be at least partly an interaction of out of phase ablation with electrodes 1 and 10 leading to higher current densities. In an animal model a close proximity of electrodes 1 and 10 of the circular ablation array catheter was shown to be associated with a dramatic increase in micro-bubble formation and embolic particles during ablation.[18]

Two studies have evaluated differences in SCL versus SCE rates in between different ablation technologies using the novel SCE definition (not requiring positive FLAIR findings). In a randomized study by Schmidt et al.[19] incidences of SCL were relevantly higher in the single tip irrigated RF group (24%) and the cryoballoon (18%) when compared to the older MRI definition. In our own experience (figure 3) incidences of SCE were 20% for the irrigated RF and 21% for the cryoballoon group. Schmidt et al. compared their data to patients treated with the laser-balloon (SCL rate 24%) and did not find significant differences in between technologies. In our own experience there were no differences in regard to SCL rates comparing irrigated RF, cryoballoon, laser-balloon (37%), phased RF using the ERACE[7] procedural modifications (PVAC) (33%) and nMARQ™ (32%; a novel irrigated multipolar ablation catheter). The overall incidence using different periprocedural anticoagulation regimen in patients undergoing only PVI are displayed in figure 3. Using the novel MRI definition appears to reduce inter-technology differences and no significant differences appear to become apparent in these studies. This may suggest that microemboli generation that lead to more sensitive SCE findings are generated by common factors incurred in any invasive EP catheter procedure in the left atrium.

The only exception appears to be in persistent AF patients when phased RF PVI (using the PVAC catheter) plus additional left atrial ablation of complex fractionated atrial electrograms (CFAE) using other phased RF ablation catheters (MASC™, MAAC™) with an incidence of 85% in our own "historic" experience. Experience in these patients, though, was still using older RF-generator software (with aggressive energy delivery), multiple catheter exchanges over a single transseptal sheath and no continued oral anticoagulation during the procedure. More studies are needed to determine what role the AF disease state may play in incidence of SCL/SCE.

As a conclusion, differences in between PVI ablation technologies become mitigated when using a more sensitive MRI definition of SCE and no significant inter-group differences were detected in two comparative studies[9] (data presented by Deneke et al, American Heart Association Annual Scientific meeting 2013, Dallas). One has

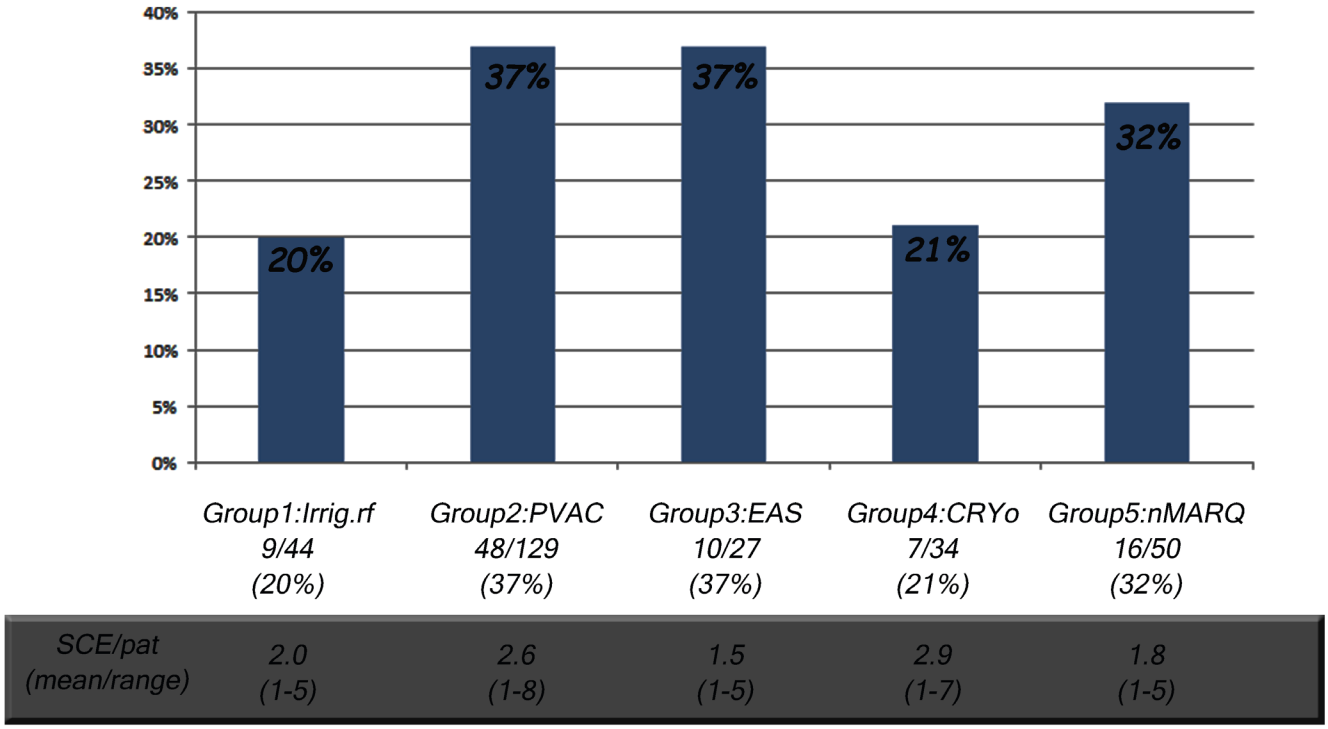

Figure 3: **SCE (silent cerebral ischemic event) rates related to ablation technology in a collection of patients including multiple variations of periprocedural anticoagulation and ablation technological aspects (no significant differences in between groups).**

to pay caution on the different time-spans and procedure-related factors involved with different ablation techniques and studies on SCL.

Procedure-Related Factors

Recent studies have identified intraprocedural ACT,[12,20,21] intraprocedural cardioversion,[12,21] echocontrast on pre-ablation transesophageal echo[20,21] and ablation of sites with complex fractionated electrograms[21,22] as independent predictors of SCL. Although, data on all of these variables is controversial .[10,12,15,20]Recent studies have not confirmed the effect of intraprocedural ACT levels and cardioversion as relevant predictors of SCL.

In our experience two factors have a major impact on the risk for SCL: 1. Intraprocedural multiple exchanges of catheters over a single transseptal sheath and 2. Intraprocedural anticoagulation regimen.

Whereas exchanging catheters over a single transseptal sheath may introduce air or detach thrombus associated to the sheath the valve itself may become worn out and therefore further gas introduction may occur with movements of the catheter. Compared to patients with two transseptal accesses (one for the diagnostic and one for the ablation catheter) the incidence of SCL was significantly higher (Deneke et al., manuscript under review 2013) in the group of patients with catheter exchanges. Exchanges of catheters should be prevented or minimized in regard to SCL rates.

Continued oral anticoagulation using warfarin or coumadin has been associated with a lower incidence of SCL compared to patients undergoing bridging during the course of the preparation for the procedure (DiBiase et al, American Heart Association 2013, Dallas). Whereas in patients under continued oral anticoagulation, the achieved minimum ACT during the procedure is higher and there appears to be additional benefits in regard to brain protection.

Further studies on both factors are needed to clearly define the number of catheter exchanges crucial and the optimum way of periprocedural anticoagulation management.

Future Aspects

SCL has become a topic potentially indicating the thrombogenic potential of different ablation technologies and approaches. So far long-term follow-up data on effects of SCL is missing and no clinical study has yet revealed clinically evident influence on brain function. On the other hand one has to consider the differences in between ablation technologies and procedural steps opening the potential for modifying the individual risk of a patient. Further studies are needed to deeper engage in the field of procedural steps involved in the process of SCL occurrence. So far either gaseous or thrombotic embolic events may be the initiators of SCL. Whether different sizes of SCL or locations are related to different mechanisms needs to be further elucidated.

In future studies MRI findings using both the older SCL and newer and more sensitive SCE method should both be reported. This will allow future studies access to allow comparisons as more is learned about the implications of DWI and FLAIR findings. Whether biomarkers may give more clues to which patient is at high risk needs to be determined. It may be at least speculated if detection of SCL may play a role in certifying new ablation technologies for human use.

A way to determine intraprocedural occurrence of thromboembolism is desirable. So far, transcranial Doppler technology has been used to detect solid and gaseous emboli passing by the intracranial arteries during ablation and other cardiovascular procedures. There appears to be only a poor correlation between high-intensity transient signals and SCL. Automated algorithms have helped to identify solid

and gaseous microemboli during transcranial Doppler but strict correlation even of solid microemboli and SCL appears unclear. Sensitive methods to identify the embolic load of different steps of the ablation procedure are needed.

For now, in clinical practice the safest technology and procedure should be used to avoid increasing the likelihood of SCL generation. It appears reasonable, that any cerebral ischemic event should be avoided in a "zero SCL"-approach.

Conclusions:

MRI of the brain is a potential technology to detect cerebral ischemic events related to AF ablation procedures. DWI is a sensitive method to identify cerebral ischemia and may help to distinguish the potential thromboembolic risk of different AF ablation procedures. SCL (when using the definition including a positive FLAIR finding) represent cerebral ischemia (small brain infarcts) leading to glial cell scars and factors leading to their formation should therefore be avoided. Comparison in between technologies has pondered intensive evaluation of mechanisms and potential confounders. The differences in SCE rates in between different ablation technologies appear to be less pronounced when using a sensitive DWI-only MRI definition depending. Patient-specific, technology-associated and procedure-determined factors exist, increasing the risk for SCL. The minimal number and size of SCL due to AF ablations should be weighed in the context of a high incidence of pre-existing "white matter lesions" in AF patients. It may even be speculated, that AF ablation may avoid having further brain lesions occurring during the process of AF.

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