Incidence and predictors of silent cerebral embolism during pulmonary vein catheter ablation for atrial fibrillation

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Aims	Left atrial catheter ablation of the pulmonary veins (PV) has evolved as an important therapeutic option for the treatment of atrial fibrillation (AF). We aimed to investigate the incidence and predictors of silent cerebral embolism associated with PV catheter ablation, detected by diffusion-weighted magnetic resonance imaging (DW-MRI).
Methods and results	We performed a prospective analysis of 53 consecutive patients with persistent or paroxysmal AF that underwent PV ablation and post-procedural cerebral MRI 1 day after lasso catheter-guided ostial PV ablation. Patients were analysed for possible demographical, medical, echocardiographical, and procedural predictors of embolic events. A mean of 3.5 ± 0.5 PVs were ablated per patient. In six patients, DW-MRI depicted new clinically silent microembolism after PV ablation (11%). The number of ineffective medical antiarrhythmic agents prior to ablation procedure was significantly higher in the embolism group (3.3 ± 0.5 vs. 2.2 ± 1.4, $P = 0.014$). Coronary heart disease (CAD) was more frequent in patients with cerebral embolisms (33 vs. 2%, $P = 0.031$); left ventricular volume (130 ± 12 vs. 103 ± 26 mL, $P = 0.002$), and septal wall thickness (13.0 ± 1.4 vs. 7.9 ± 4.8 mm, $P = 0.025$) were significantly increased.
Conclusion	This study shows a high incidence of silent micro-embolic events after PV ablation. CAD, left ventricular dilatation, and hypertrophy were potential predictors of this complication.
Keywords	Atrial fibrillation • Pulmonary vein ablation • Cerebral thromboembolism • MRI

Introduction

Pulmonary vein (PV) ablation has become an important therapeutic option for the treatment of patients with drug refractory paroxysmal and persistent atrial fibrillation (AF).[1–8] Despite the relatively high success rate, this approach is still limited by potentially serious complications.[4,9–13] Among these are transient cerebral ischaemia and strokes. Cerebral embolism can also occur as clinically silent events.[1,4,9–11,14–21] Cerebral magnetic resonance imaging (MRI) in combination with diffusion-weighted imaging (DWI) is the standard investigation for the detection of small acute cerebral ischaemic lesions. It also has been proven successful for verification of silent thromboembolism associated with cerebral angiography, neuro-interventional procedures, carotid endarterectomy, left heart catheterization, and also left atrial ablation procedures.[17,22–26]

To estimate the thromboembolic risk of PV ablation procedures and to identify predisposing factors, knowledge of not only apparent, but also clinically silent cerebral thromboembolism is essential. The target of the present study was to evaluate the incidence and potential predictors of apparent as well as silent cerebral thromboembolism associated with PV ablation, using post-procedural cerebral MRI.

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Methods

Patient characteristics

The study complies with the Declaration of Helsinki. It was approved by the institutional review board of the University of Bonn and all patients gave informed consent before inclusion in the study. Fifty-three consecutive patients (eight female), 53 ± 12 years of age, with paroxysmal (89%) or persistent (11%) AF undergoing lasso catheter-guided ostial PV ablation were prospectively included before ablation procedure. Patients with previous pacemaker implantation or other contraindications for MRI, severe valvular heart disease or documented thrombus of the left atrial appendage were excluded. The absence of atrial thrombi was confirmed by transesophageal echocardiography in all patients (Table 1).

Study protocol

In the patients receiving oral anticoagulation, phenprocoumon was stopped 5 days before ablation. Nadroparin or enoxaparin (1 mg/kg body weight; maximum 100 mg) was administered subcutaneously twice daily for at least 2 days preceding the ablation procedure.

On the day before the ablation, all patients underwent a thorough physical examination including assessment of the neurological status. Transthoracic and transesophageal echocardiography were performed in all patients 1 day prior to or on the same day of the ablation procedure. Physical examination with neurological assessment was repeated and cerebral diffusion-weighted magnetic resonance imaging (DW-MRI) was conducted the day after the procedure.

Pulmonary vein ablation

The ablation was performed using the technique described by Haissaguerre et al.[3] First, diagnostic catheters were positioned in the coronary sinus and at the His-bundle region via the right femoral vein. Then, the interatrial septum was punctured and a guide wire was inserted into the left superior PV. An irrigated tip ablation catheter (Thermocool, Biosense Webster or Sprinklr, Medtronic; constant flow rate for both 1000 mL/h) was advanced along the guide wire. After this, the long transseptal sheath was again advanced over the guide wire into the left atrium.

In all patients, heparin was injected as a bolus of 75 IU/kg body weight from a peripheral vein. The activated clotting time (ACT) was kept >250 s throughout the whole procedure and was monitored every $20{-}30$ min. Heparin was later given through the heparinized

Table 1 Patient characteristics, ablation procedure, and echocardiography

	Total population ($n = 53$)	No embolism (MRI; $n = 47$)	Embolism (MRI; $n = 6$)	P-value
Age (years)	53 ± 12	52 ± 12	59 ± 13	0.242
Gender (male/female)	45/8	39/8	6/0	—
Hypertension (%)	52	47	83	0.192
Coronary heart disease (%)	6	2	33	0.031
Previous cerebral ischaemia	6	4	17	0.310
Time since first AF occurrence (months)	117 ± 106	120 ± 111	89 ± 38	0.263
Persistent AF (%)	11	11	0	1.000
Paroxysmal AF (%)	89	89	100	1.000
Frequency of AF episodes per month	27 ± 100	29 ± 105	9 ± 7	0.306
Average duration of AF (h)	14 ± 23	13 ± 24	23 ± 6	0.088
Number of failed antiarrhythmic drugs	2.3 ± 1.4	2.2 ± 1.4	3.3 ± 0.5	0.014
Previous left atrial ablation (%)	4	2	17	0.220
Previous oral anticoagulation (%)	30	28	50	0.357
Previous platelet inhibitor (%)	30	28	33	—
Ablation procedure				
Duration (min)	199 ± 54	197 ± 53	210 ± 66	0.686
Fluoroscopy duration (min)	61.4 ± 24.1	60.6 ± 23.6	66.7 ± 29.7	0.678
Total RF energy (Ws)	$55\,780 \pm 7743$	$55\,660 \pm 7583$	$56\,621 \pm 6805$	0.890
Number of PVs ablated	3.5 ± 0.5	3.5 ± 0.5	3.2 ± 0.4	0.113
Transthoracic echocardiogram				
Left ventricular ejection fraction (%)	60 ± 9	60 ± 9	57 ± 5	0.422
Left ventricular volume (mL)	106 ± 26	103 ± 26	130 ± 12	0.002
Septal wall thickness (mm)	8.7 ± 4.9	7.9 ± 4.8	13.0 ± 1.4	0.025
Left atrial volume (mL)	73 ± 29	71 ± 14	87 ± 17	0.382
Left atrial diameter (mm)	38.3 ± 13.1	36.8 ± 14.2	44.5 ± 6.4	0.382
Transesophageal echocardiogram				
Spontaneous LAA echo contrast (%)	19	17	33	0.315
Reduced LAA flow velocity <0.5 m/s (%)	11	13	0	—
Relevant mitral regurgitation (%)	7	9	0	—

AF, atrial fibrillation; PVs, pulmonary veins; LAA, left atrial appendage.

cooling fluid of the cooled-tip ablation catheter (1000 mL/h) and additionally injected intravenously, as needed.

Venography of all four PVs was performed by administration of a contrast agent through the transseptal sheath or through a six French multi-purpose catheter. Next, a circumferential mapping catheter (Lasso, Biosense Webster or Encirclr, Medtronic) was introduced into the proximal PVs. Radiofrequency (RF) energy was applied in a power-controlled mode with a power limit of $25-30$ W and a temperature of maximum $47°$C. Lesions were delivered for 60 s each. Ablation was performed at the atriovenous junction proximal to the circumferential mapping catheter at sites showing the earliest PV potentials. The endpoint of ablation was defined as complete disconnection of the PV, resulting in electrical isolation of the vessel.

Sheaths were removed as soon as the ACT fell below 200 s. Nadroparin or enoxaparin, twice daily s.c. in weight-adapted dose (1 mg/kg), was started 4 h after sheath removal. Oral anticoagulation with phenprocoumon was restarted the same evening in all patients. Enoxaparin was continued until the international normalized ratio was above 2.

Cerebral magnetic resonance imaging

Cerebral MRI (1.5 T Intera, Philips Medical Systems, Best, The Netherlands) was performed the day after the ablation procedure in all patients, as described before.[17] In short, the imaging protocol included a diffusion-weighted single-shot spin echo echoplanar sequence [diffusion gradient *b*-values of 0, 500, and 1000 s/mm^2, repetition time (TR) 4000 ms, echo time (TE/TEd) 120/85 ms, slice thickness 5 mm, matrix 128×256], fluid attenuated inversion recovery (TR/TE 6000/110 ms), and T2-weighted turbo spin echo (TR/TE 4800/110 ms) sequences. The acquisition time for the diffusion-weighted sequences was 30 s. Diffusion gradients were applied in three orthogonal directions during DWI. In addition, apparent diffusion coefficient (ADC) maps were calculated in every patient with hyperintense lesions in the DW images to differentiate acute ischaemia from 'T2 shine through'.

Acute embolic cerebral ischaemia was defined as focal or wedge-shaped hyper-intense lesions in the DW images with corresponding hypo-intensity in the ADC map in a typical vascular pattern. The size and localization of focal diffusion abnormalities were analysed. All MRIs were analysed independently by two certified radiologists, blinded to the clinical status of the patients. In instances where the readings were different, a consensus was obtained.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation. The Student's *t*-test or, for discrete variables, the Fisher's exact test was used to compare patient groups. A value of $P \leq 0.05$ was considered statistically significant.

Results

Ablation procedure

The transseptal catheterization and PV angiography were performed before PV disconnection without complications in all patients. Extracted catheter material was thoroughly examined for signs of clotting. No evidence of clot formation or charring was seen at any ablation electrode or the mapping catheter. No significant differences regarding procedural characteristics were present in the patients with and without diagnosis of cerebral embolism. Total RF energy applied to the patients was equal among the groups. No RF was administered to PV electrically silent. Details of the ablation procedure are outlined in *Table 1*.

Incidence and localization of thromboembolic cerebral events

Six patients (11%) developed cerebral microembolism due to thromboembolic events during the PV ablation procedure (demographical and clinical data see *Table 1*), as detected by cerebral DW-MRI (*Figure 1*). In the six patients, one to three microembolic lesions were detected (*Table 2*). Only one of these patients showed slight reflex augmentation (biceps, triceps, supinator reflexes) on the site contralateral to the embolic lesion (left arm), which disappeared during follow-up.
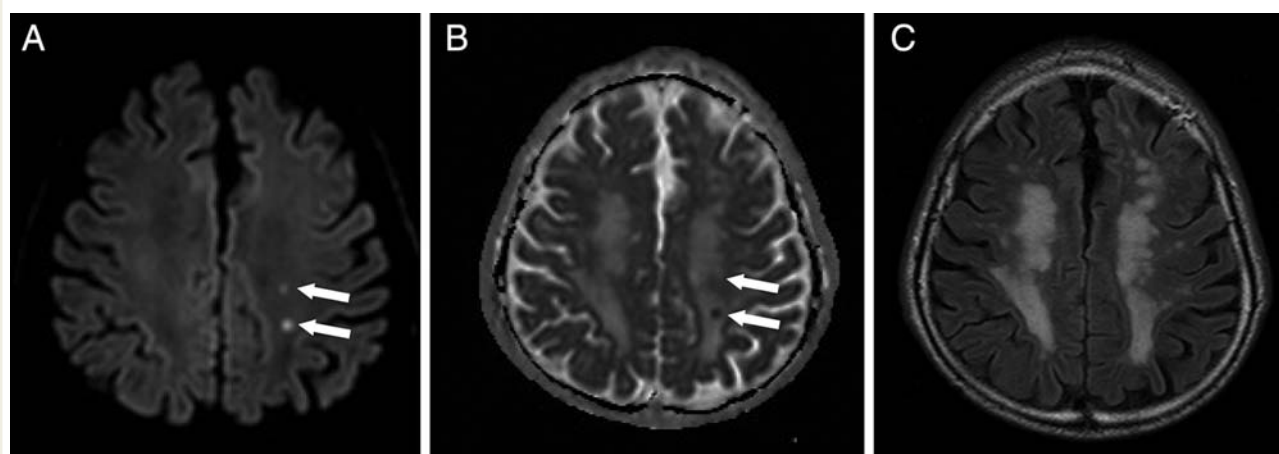

Figure 1 Periprocedural clinical silent cerebral micro-embolism after PV ablation. Diffusion-weighted image (DWI, *A*) and apparent diffusion coefficient (ADC) map (*B*) demonstrate two bright white matter lesions in the DWI (arrows in *A*) corresponding to a signal hypoattenuation in the ADC map (arrows in *B*), consistent with acute embolic cerebral infarctions in the left centrum semiovale. Fluid attenuated inversion recovery (FLAIR, *C*) image displays extensive white matter lesion due to microangiopathy.

Table 2 Localization and characteristics of periprocedural cerebral microembolisms

	Number of lesions	Lesions size	Localization
Patient 1, asymptomatic	2	2 mm, 3 mm	Left frontoparietal region
Patient 2, asymptomatic	1	2 mm	Left parietal lobe
Patient 3, asymptomatic	2	2 mm, 3 mm	Left parietal lobe
Patient 4, asymptomatic	3	2 mm, 2 mm, 2 mm	Right frontal lobe (1), right cerebellar hemisphere (2)
Patient 5, asymptomatic	2	3 mm, 2 mm	Left frontal lobe (1), right frontal lobe (1)
Patient 6, reflex abnormalities	2	1 mm, 1 mm	Right parietooccipital region

Predictors of cerebral embolism

Analysis of the patients groups with ($n = 6$) and without ($n = 47$) cerebral microembolism showed no significant differences in age, the presence of diabetes mellitus, or hypertension. All patients with embolism were male, yet this was not statistically significant. When compared with the unaffected group, history of coronary heart disease (CAD) was found significantly more often in the group of patients with cerebral microembolism (two of six patients vs. one of 47 patients, $P = 0.031$). This was independent from the presence of diabetes mellitus as factor possibly contributing to elevated incidence of CAD in the embolus group. In the control group, we found three patients with diabetes mellitus, all without history of coronary artery disease; and two patients in the smaller cohort with embolic events (33%), one of those with coronary artery disease. Despite the tendency towards a higher incidence in the embolus group, there is no significant difference regarding this parameter ($P = 0.094$). We did though not systematically screen for insulin-resistance in the groups. The number of antiarrhythmic agents previously used for the medical treatment of AF was significantly higher in the patients with cerebral embolism (3.3 ± 0.5 vs. 2.2 ± 1.4 antiarrhythmic drugs, $P = 0.014$). No further statistical significant differences were found (Table 1).

Echocardiographic examination

No differences were found regarding left atrial size and diameter, spontaneous echo contrast, mitral valve regurgitation, or further valvular diseases. When compared with patients without thromboembolism, the left ventricular volume was significantly larger in the group with embolic events. Even though there was no difference in the prevalence of hypertension, the septal wall was found to be thickened in patients that suffered from cerebral embolic events (Table 1).

Discussion

In this study, we evaluated the incidence and potential predicting factors of cerebral embolism associated with left atrial, ostial PV ablation. Previously, DW-MRI has been shown to be an adequate tool for the detection of cerebral microembolism associated with left atrial ablation[17] and other interventional and diagnostic procedures.[22–26] We now analysed the incidence of cerebral embolism in a consecutive cohort of patients that underwent catheter-guided PV ablation and correlated MRI-detected cerebral embolic events with demographical, clinical, and procedural

characteristics. Despite the fact that we investigated a low-risk patient population, characterized by a minor rate of structural heart disease, relatively young age, and predominant paroxysmal AF, we found a high incidence of subclinical periprocedural embolic events associated with AF ablation. In a prove of principle study performed by our group,[17] ten patients underwent MRI prior to PV ablation, which was preceded by the same anticoagulation protocol as conducted in the actual investigation. None of these patients showed signs of microembolism. These results suggest that the embolic events occurring in the present study were exclusively associated with the PV ablation procedure.

Procedural characteristics of pulmonary vein ablation

Radiofrequency catheter ablation is well known to be associated with a risk of thrombus formation at the catheter tip or on the surface of the injured, ablated area.[27] The thrombogenic potential of ablation procedures has been substantiated by the proof of increased laboratory values of parameters of coagulation, platelet, and fibrinolysis activation after cardiac ablations. Interestingly, it has been shown that the level of thrombin–antithrombin III as a direct marker of thrombin generation was already significantly enhanced by insertion and presence of the catheters in the heart; it was not further elevated by RF energy application.[27]

The association between RF ablation and thromboembolic events is well established. A meta-analysis of seven large scale studies showed an overall incidence of 0.6% of symptomatic arterial embolisms, increasing up to 2% when left atrial ablation was performed.[28] All important studies of PV ablation describe clinical relevant embolic complications associated with this innovative therapy in the treatment of AF,[1,4,9–11,14–16,18,19,21,29] ranging from 0.2 to 0.5%. The impact of irrigated RF catheters on the activation of platelets and plasma coagulation has not yet been examined systematically, but it is likely that these electrodes are able to reduce periprocedural thrombus formation. Yet, even with the newer cryo-technique, which is supposed to be less thrombogenic, a stroke occurred in one of 52 investigated patients.[30]

Risk factors for cerebral embolism associated with pulmonary vein ablation

Until now, proposed risk factors for cerebral embolism are age more than 60 years and history of stroke or transient ischaemic attack.[16] Furthermore, low flow flushing of the transseptal sheath during left atrial ablation procedure[14] has been described to

promote thrombosis and thromboembolism. In contrast to most reports of PV ablation and to minimize the likelihood of left atrial thrombus formation, we used only one transseptal sheath for insertion of the circumferential mapping catheter into the left atrium. The ablation catheter was advanced along a guidewire into the left atrium after successful initial transseptal puncture.

In our study, we found six of 53 patients with silent cerebral thromboembolism. Medical treatment was less effective in these patients, indicated by the greater number of antiarrhythmic drugs administered for AF in their history. Under the above described procedural setting, we identified a history of CAD as well as echocardiographic parameters of left ventricular dilatation and hypertrophy as risk factors of these cerebral ischaemic events. This was independent from the presence of hypertension and diabetes mellitus as factors independently contributing to hypertrophy and CAD in the embolus collective. Interestingly, left atrial volume or history of previous stroke or cerebral ischaemia was not associated with an elevated thromboembolic risk in the investigated population of relatively healthy and young patients. Apparently, patients with more severe left ventricular diseases are more prone to silent cerebral embolism after PV ablation. It must be mentioned that all patients underwent transesophageal echocardiography to exclude left atrial thrombi prior to the ablation procedure.

Prevention of cerebral microembolism

The presence of silent embolism proves the potential danger of cerebral embolic events, which indicates the still high thrombogeneity of catheter ablation. In the present investigation, the amount of RF energy applied was equal in the groups, so embolisms do not seem dependent on the RF energy administered. This substantiates the fact that further protective means (high flow flush, ACT screening) are essential, but still not able to fully prevent silent microembolism. Additional protective measures (i.e. higher ACT, minimizing procedure time, and manipulation in the left atrium) are possibly necessary to further decrease thromboembolic risk.

Intracardiac echocardiography (ICE) has been shown to be successful in detecting thrombus formation throughout PV ablations.[31] A high incidence of thrombus formation in 24 of 232 patients (10.3%) with thrombi attached to a transseptal sheath in 57% and to the circumferential mapping catheter in 43% was found. None of the patients showed clinical evidence of a clinical thromboembolic complication. The incidence of silent cerebral embolism, however, was not examined in this study. Risk factors for left atrial thrombus formation were previous spontaneous echo contrast, increased left atrial diameter, and persistent rather than paroxysmal AF. Yet, in another study, microbubble formation during RF application was shown by ICE and these microbubbles were detected in the carotid arteries by transcranial Doppler sonography. These findings prove the thromboembolic risk of left atrial RF ablation.[32]

Study limitations

Magnetic resonance imaging was only performed after but not before the ablation procedure. The hyperintense appearance of the lesion in DW-MRI however is a typical radiological feature of embolic events that occurred in the preceding 7 days and that is absent in older lesions. From an imaging standpoint, it is also possible that the lesions could have been caused by infection or acute demyelination, but no patient had a history of an infectious or demyelination disorder, or previous neurological symptoms. The findings on post-procedure DW images are thus very unlikely to be caused by mechanisms or embolic events prior the ablation procedure. Nevertheless, there remains a possibility that a part of embolic events found is associated to changes in the anticoagulation regime (withdrawal of phenprocoumon and bridging with enoxaparine) in the period prior to the ablation. Actually, there are no big randomized, prospective studies systematically evaluating the risk of silent microembolic events potentially associated with such changes in the anticoagulation prior to cardiac interventions. Yet, a previous pilot study showed no microembolisms in a small group of 10 consecutive patients prior to ablation undergoing analogous changes in the anticoagulation procedure[17] as in our study.

Heparin was given after transseptal puncture in the present study. Some centres nowadays administer heparin before the transseptal access to avoid thrombus formation before left atrial access. This might influence the present results; a possible protective effect of earlier heparin administration or higher ACT values ($>300–350$ s) as suggested by other investigators[33] should be evaluated in further studies based on the present results.

A relatively small total number of patients were investigated, but a great part of these patients was affected by embolic events, which made statistical analyses for risk factors in this cohort possible. We are possibly still limited in the detection of all relevant predictors for cerebral embolic complications secondary to PV ablation and could not perform analyses of hazard ratios for the predictors identified.

Conclusion

This study shows a high incidence of clinically not apparent cerebral microembolism associated with left atrial ablation of the PV orifice, as detected by post-procedural DW-MRI. Microembolism is associated with the presence of CAD, a greater number of ineffective medical antiarrhythmic agents administered previously, and parameters of left ventricular dilatation and hypertrophy. This study proves the still high thrombogenic potential of left atrial RF ablation even under maximum procedural safety measures.

Conflict of interest: none declared.

References

1. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC *et al.* Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. *Circulation* 1999;**100**:1879–86.
2. Gerstenfeld EP, Callans DJ, Dixit S, Russo AM, Nayak H, Lin D *et al.* Mechanisms of organized left atrial tachycardias occurring after pulmonary vein isolation. *Circulation* 2004;**110**:1351–7.
3. Haissaguerre M, Shah DC, Jais P, Hocini M, Yamane T, Deisenhofer I *et al.* Electrophysiological breakthroughs from the left atrium to the pulmonary veins. *Circulation* 2000;**102**:2463–5.
4. Lickfett LM, Calkins HG, Berger RD. Radiofrequency ablation for atrial fibrillation. *Curr Treat Options Cardiovasc Med* 2002;**4**:295–306.
5. Oral H, Scharf C, Chugh A, Hall B, Cheung P, Good E *et al.* Catheter ablation for paroxysmal atrial fibrillation: segmental pulmonary vein ostial ablation versus left atrial ablation. *Circulation* 2003;**108**:2355–60.

6. Pappone C, Rosanio S, Oreto G, Tocchi M, Gugliotta F, Vicedomini G et al. Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation. Circulation 2000;**102**:2619–28.

7. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ et al. HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2007;**4**:816–61.

8. Natale A, Raviele A, Arentz T, Calkins H, Chen SA, Haissaguerre M et al. Venice Chart international consensus document on atrial fibrillation ablation. J Cardiovasc Electrophysiol 2007;**18**:560–80.

9. Mansour M, Ruskin J, Keane D. Efficacy and safety of segmental ostial versus circumferential extra-ostial pulmonary vein isolation for atrial fibrillation. J Cardiovasc Electrophysiol 2004;**15**:532–7.

10. Pappone C, Santinelli V. The who, what, why, and how-to guide for circumferential pulmonary vein ablation. J Cardiovasc Electrophysiol 2004;**15**:1226–30.

11. Vasamreddy CR, Lickfett L, Jayam VK, Nasir K, Bradley DJ, Eldadah Z et al. Predictors of recurrence following catheter ablation of atrial fibrillation using an irrigated-tip ablation catheter. J Cardiovasc Electrophysiol 2004;**15**:692–7.

12. Bertaglia E, Zoppo F, Tondo C, Colella A, Mantovan R, Senatore G et al. Early complications of pulmonary vein catheter ablation for atrial fibrillation: a multicenter prospective registry on procedural safety. Heart Rhythm 2007;**4**:1265–71.

13. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation 2005;**111**:1100–5.

14. Cauchemez B, Extramiana F, Cauchemez S, Cosson S, Zouzou H, Meddane M et al. High-flow perfusion of sheaths for prevention of thromboembolic complications during complex catheter ablation in the left atrium. J Cardiovasc Electrophysiol 2004;**15**:276–83.

15. Hsu LF, Jais P, Sanders P, Garrigue S, Hocini M, Sacher F et al. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 2004;**351**:2373–83.

16. Kok LC, Mangrum JM, Haines DE, Mounsey JP. Cerebrovascular complication associated with pulmonary vein ablation. J Cardiovasc Electrophysiol 2002;**13**:764–7.

17. Lickfett L, Hackenbroch M, Lewalter T, Selbach S, Schwab JO, Yang A et al. Cerebral diffusion-weighted magnetic resonance imaging: a tool to monitor the thrombogenicity of left atrial catheter ablation. J Cardiovasc Electrophysiol 2006;**17**:1–7.

18. Marrouche NF, Dresing T, Cole C, Bash D, Saad E, Balaban K et al. Circular mapping and ablation of the pulmonary vein for treatment of atrial fibrillation: impact of different catheter technologies. J Am Coll Cardiol 2002;**40**:464–74.

19. Marrouche NF, Martin DO, Wazni O, Gillinov AM, Klein A, Bhargava M et al. Phased-array intracardiac echocardiography monitoring during pulmonary vein isolation in patients with atrial fibrillation: impact on outcome and complications. Circulation 2003;**107**:2710–6.

20. Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S et al. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation 2002;**105**:1077–81.

21. Vasamreddy CR, Dalal D, Eldadah Z, Dickfeld T, Jayam VK, Henrickson C et al. Safety and efficacy of circumferential pulmonary vein catheter ablation of atrial fibrillation. Heart Rhythm 2005;**2**:42–8.

22. Barth A, Remonda L, Lovblad KO, Schroth G, Seiler RW. Silent cerebral ischemia detected by diffusion-weighted MRI after carotid endarterectomy. Stroke 2000;**31**:1824–8.

23. Bendszus M, Koltzenburg M, Burger R, Warmuth-Metz M, Hofmann E, Solymosi L. Silent embolism in diagnostic cerebral angiography and neurointerventional procedures: a prospective study. Lancet 1999;**354**:1594–7.

24. Feiwell RJ, Besmertis L, Sarkar R, Saloner DA, Rapp JH. Detection of clinically silent infarcts after carotid endarterectomy by use of diffusion-weighted imaging. AJNR Am J Neuroradiol 2001;**22**:646–9.

25. Omran H, Schmidt H, Hackenbroch M, Illien S, Bernhardt P, von der Recke G et al. Silent and apparent cerebral embolism after retrograde catheterisation of the aortic valve in valvular stenosis: a prospective, randomised study. Lancet 2003;**361**:1241–6.

26. Rordorf G, Bellon RJ, Budzik RE Jr, Farkas J, Reinking GF, Pergolizzi RS et al. Silent thromboembolic events associated with the treatment of unruptured cerebral aneurysms by use of Guglielmi detachable coils: prospective study applying diffusion-weighted imaging. AJNR Am J Neuroradiol 2001;**22**:5–10.

27. Lee DS, Dorian P, Downar E, Burns M, Yeo EL, Gold WL et al. Thrombogenicity of radiofrequency ablation procedures: what factors influence thrombin generation? Europace 2001;**3**:195–200.

28. Zhou L, Keane D, Reed G, Ruskin J. Thromboembolic complications of cardiac radiofrequency catheter ablation: a review of the reported incidence, pathogenesis and current research directions. J Cardiovasc Electrophysiol 1999;**10**:611–20.

29. Pappone C, Oreto G, Lamberti F, Vicedomini G, Loricchio ML, Shpun S et al. Catheter ablation of paroxysmal atrial fibrillation using a 3D mapping system. Circulation 1999;**100**:1203–8.

30. Tse HF, Reek S, Timmermans C, Lee KL, Geller JC, Rodriguez LM et al. Pulmonary vein isolation using transvenous catheter cryoablation for treatment of atrial fibrillation without risk of pulmonary vein stenosis. J Am Coll Cardiol 2003;**42**:752–8.

31. Ren JF, Marchlinski FE, Callans DJ. Left atrial thrombus associated with ablation for atrial fibrillation: identification with intracardiac echocardiography. J Am Coll Cardiol 2004;**43**:1861–7.

32. Kilicaslan F, Verma A, Saad E, Rossillo A, Davis DA, Prasad SK et al. Transcranial Doppler detection of microembolic signals during pulmonary vein antrum isolation: implications for titration of radiofrequency energy. J Cardiovasc Electrophysiol 2006;**17**:495–501.

33. Ren JF, Marchlinski FE, Callans DJ, Gerstenfeld EP, Dixit S, Lin D et al. Increased intensity of anticoagulation may reduce risk of thrombus during atrial fibrillation ablation procedures in patients with spontaneous echo contrast. J Cardiovasc Electrophysiol 2005;**16**:474–7.