Transcranial Measurement of Cerebral Microembolic Signals During Endocardial Pulmonary Vein Isolation: Comparison of 3 Different Ablation Techniques

LOES D. SAUREN, M.Sc.,* YVES VAN BELLE, M.D.,¶ LUC DE ROY, M.D., Ph.D.,§
LAURENT PISON, M.D.,† MARK LA MEIR, M.D.,* FREDERICK H. VAN DER VEEN, Ph.D.,*
HARRY J. CRIJNS, M.D., Ph.D.,† LUC JORDAENS, M.D., Ph.D.,¶
WERNER H. MESS, M.D., Ph.D.,‡ and JOS G. MAESSEN, M.D., Ph.D.*

From the *Department of Cardiothoracic Surgery, †Department of Cardiology, and ‡Department of Clinical Neurophysiology, Academic Hospital Maastricht, Maastricht, The Netherlands; §Department de Rythmologie de Mont-Godine, Namur, Belgium; and ¶Department of Clinical Electrophysiology, Thoraxcentre, Erasmus Medical Centre, Rotterdam, The Netherlands

Cerebral MES During PVI. ***Introduction:*** **Isolation of the pulmonary veins (PVI) using high ablation energy is an effective treatment for atrial fibrillation (AF) with a success rate of 50–95%; however, postoperative neurological complications still occur in 0.5–10%. In this study the incidence of cerebral microembolic signals (MES) as a risk factor for neurological complications is examined during 3 percutaneous endocardial ablation procedure strategies: segmental PVI using a conventional radiofrequency (RF) ablation catheter, segmental PVI using an irrigated RF tip catheter, and circumferential PVI with a cryoballoon catheter (CB).**

Methods and Results: **Thirty patients underwent percutaneous endocardial PVI. Ostial isolation was performed in 10 patients with a conventional 4-mm RF catheter (CRF) and in 10 patients with a 4-mm irrigated RF catheter (IRF). A circumferential PVI was performed in 10 patients with a CB. Transcranial Doppler (TCD) monitoring was used to detect MES in the middle cerebral arteries.**

The total number of cerebral MES differs significantly among the 3 PVI groups; 3,908 cerebral MES were measured with use of the CRF catheter, 1,404 cerebral MES with use of the IRF catheter, and 935 cerebral MES with use of the CB catheter.

Conclusion: **This study demonstrates a significant difference in cerebral MES during PVI with 3 different ablation procedures. The use of an irrigated RF and a cryoballoon produces significantly fewer cerebral MES than the use of conventional RF for a PVI procedure, suggesting a higher risk for neurologic complications using conventional RF energy during a percutaneous PVI procedure.** *(J Cardiovasc Electrophysiol, Vol. 20, pp. 1102-1107, October 2009)*

atrial fibrillation, ablation, cryoablation, pulmonary vein isolation, stroke, transcranial Doppler

Introduction

Atrial fibrillation (AF) is a highly prevalent cardiac arrhythmia, with an age-dependent increase in incidence. It is an independent risk factor for death and stroke.[1] Antiarrhythmic drug treatment and pulmonary vein isolation (PVI) are standard treatment options. PVI has become a mainstream treatment for AF whereby ablation energy is applied to electrically isolate the pulmonary veins.[2,3] Catheter PVI procedures are efficacious, with success rates approximating 80%. However, one of the complications of PVI procedure is the occurrence of cerebroembolic complications in 0.5–10% of the patients.[2,4,5] Several publications support an association between the number of cerebral MES and neurological impairment and stroke.[4,6–9] Therefore, in this study the number of cerebral MES was considered as a risk factor of neurological complications and examined during 3 different catheter-based PVI approaches: (1) segmental isolation with a conventional radiofrequency (RF) ablation catheter (CRF), (2) segmental isolation with an irrigated RF tip ablation catheter (IRF), and (3) circumferential isolation with a cryoballoon catheter (CB).

Methods

Patients

A total of 30 consecutive patients suffering from drug-refractory and symptomatic AF undergoing a PVI were included in this study. We compared three separate cohorts in three different centers: Academic Hospital Maastricht (the Netherlands), Cliniques Universitaires de Mont-Godinne, Yvoir (Belgium), and Erasmus Medical Centre, Rotterdam (the Netherlands). Three groups were defined according to the ablation catheter used in each center: (1) conventional RF catheter (CRF), (2) irrigated RF tip catheter (IRF), and (3) cryoballoon catheter (CB).

Procedures

The investigation was approved by the Human Research and Ethics Committee of the Academic Hospital

Address for correspondence: Loes D. Sauren, M.Sc., Department of Cardiothoracic Surgery, Academic Hospital Maastricht, P. Debyelaan 25, 6229HX, Maastricht, The Netherlands. Fax: +31-43-3875993; E-mail: l.sauren@ctc.unimaas.nl

Manuscript received 6 February 2009; Revised manuscript received 13 March 2009; Accepted for publication 9 April 2009.

doi: 10.1111/j.1540-8167.2009.01509.x

Maastricht (the Netherlands), Cliniques Universitaires de Mont-Godinne, Yvoir (Belgium), and Erasmus Medical Centre, Rotterdam (the Netherlands).

Segmental PVI

These procedures were performed under local anesthesia and with femoral vein punctures. Two echo-guided transseptal punctures were performed and a steerable circular electrophysiologic catheter (Lasso®, Biosense Webster, Diamond bar, CA, USA) was positioned at the orifice of the targeted veins. Ablation was performed at the atriovenous junction at sites showing the earliest PV potentials. The introducers were continuously flushed to prevent the formation of thrombi on the catheter. Details about the segmental ablation have been published earlier.[3]

The ablation catheter used for the conventional RF ablation was a 4-mm bidirectional RF ablation catheter (Saphire®, St. Jude Medical, Minnetonka, MN, USA). The maximum power limit for the RF ablation was set on 25 W to 30 W, with a maximum temperature limit of 55°C to 60°C.

The ablation catheter used for the irrigated tip RF ablation was a 4-mm externally irrigated tip catheter (Celius Thermocool®, Biosense Webster, Diamond Bar, CA, USA). The maximum power limit for the RF ablation was set on 25 W, with a maximum temperature limit of 48°C.

Circumferential Cryoballoon Procedure

The procedure was performed with femoral access and through a single transseptal puncture, guided by intracardiac echocardiography. The ablation was performed with a 28-mm double-lumen balloon catheter (Arctic front®, Cryocath, Montreal, Quebec, Canada), through a 14 F transseptal sheath and positioned over an exchange wire to occlude the ostium of each PV. The introducers were continuously flushed to prevent the formation of thrombi on the catheter. Cryoenergy was given for 5 minutes per application of −80°C, with a minimum of 2 applications per vein. After ablation, a circular 20-polar catheter was positioned at the ostium of every vein to check for PV potentials. The procedural endpoint was the absence of PV potentials in all of the targeted veins. If isolation could not be achieved with the cryoballoon, an additional segmental isolation was performed with a 8-mm-tip cryocatheter (Freezor Max®, Cryocath, Montreal, Quebec, Canada). Details on this approach have been published previously.[10,11]

Periprocedural Anticoagulation Management

All patients of all the three groups were on oral anticoagulation for a minimum of 1 month before the procedure. This was stopped 2 to 3 days before the ablation. Transesophageal echocardiography was performed 24–48 hours before the procedure to rule out presence of intracardiac thrombi. The activated clotting time (ACT) was kept above 350 seconds during the entire procedure in the CRF procedures, between 200 and 250 seconds in the IRF procedures, and an ACT of 350 seconds was maintained in the cryoballoon procedures. After the procedure, oral anticoagulation was resumed with a target international normalized ratio between 2 and 3.

Transcranial Doppler (TCD) Monitoring

TCD, (PMD 100, Spencer Technologies, Seattle, WA, USA) was used to monitor both middle cerebral arteries through the temporal windows for microemboli using two 2.0 MHz probes, fixed with a headband (Marc 600, Spencer Technologies). The probes were by an experienced physician installed after the patient was positioned for both PVI procedures. Patients were monitored continuously starting from 30 minutes before the procedure until termination of the procedure. TCD recordings were stored for later offline analysis. In our study the detection of cerebral MES was performed by a blinded trained physician according the guidelines of the consensus committee.[12] The TCD analyses were divided into different periods. The period from transseptal puncture until the first ablation was considered the placement period (placement period). The period during which ablation energy was delivered was classified as the ablation period. Due to the delay between emboli generation in the pulmonary veins and arrival of these emboli in the cerebral vessels, a 10-second period after the end of ablation was included in the ablation period in all of the different methods (ablation period). The period from the first ablation until the end of the procedure, minus the ablation periods, was considered the manipulation period (manipulation period).

Data Analysis

The different patterns of cerebral MES were categorized according to previously defined criteria.[4,13,14] Type I embolic showers were defined as 1 to 10 cerebral MES in 1 minute of ablation. Type II embolic showers were defined as 11 to 60 cerebral MES in 1 minute of ablation. Type III embolic showers were defined as more than 61 cerebral MES in 1 minute of ablation. Figure 1 demonstrates the three mentioned types of embolic showers.

Statistical Method

All data were analyzed using the statistical software package SPSS® version 12.0 (SPSS Inc., Chicago, IL, USA). A Mann-Whitney U test was used to compare the three different types of embolic showers in the different ablation groups. A P-value of <0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 30 patients were enrolled in this study. Table 1 presents patients' characteristics of the three PVI groups. There were no significant differences in the baseline characteristics.

PVI Procedures

A total of 741 energy applications were delivered in 30 patients: in the CRF group 318 applications, in the IRF group 314 applications, and in the CB group 109 applications. The CRF and IRF procedures had a significantly shorter total ablation time than the CB procedures ($P = 0.01$) (Table 2). The total procedural time was significantly longer in the CRF group (274 minutes) versus IRF and CB group (185 minutes $P = 0.032$ and 178 minutes $P < 0.0001$). The ACT levels in the IRF group were significantly lower ($ACT = 210$) than in

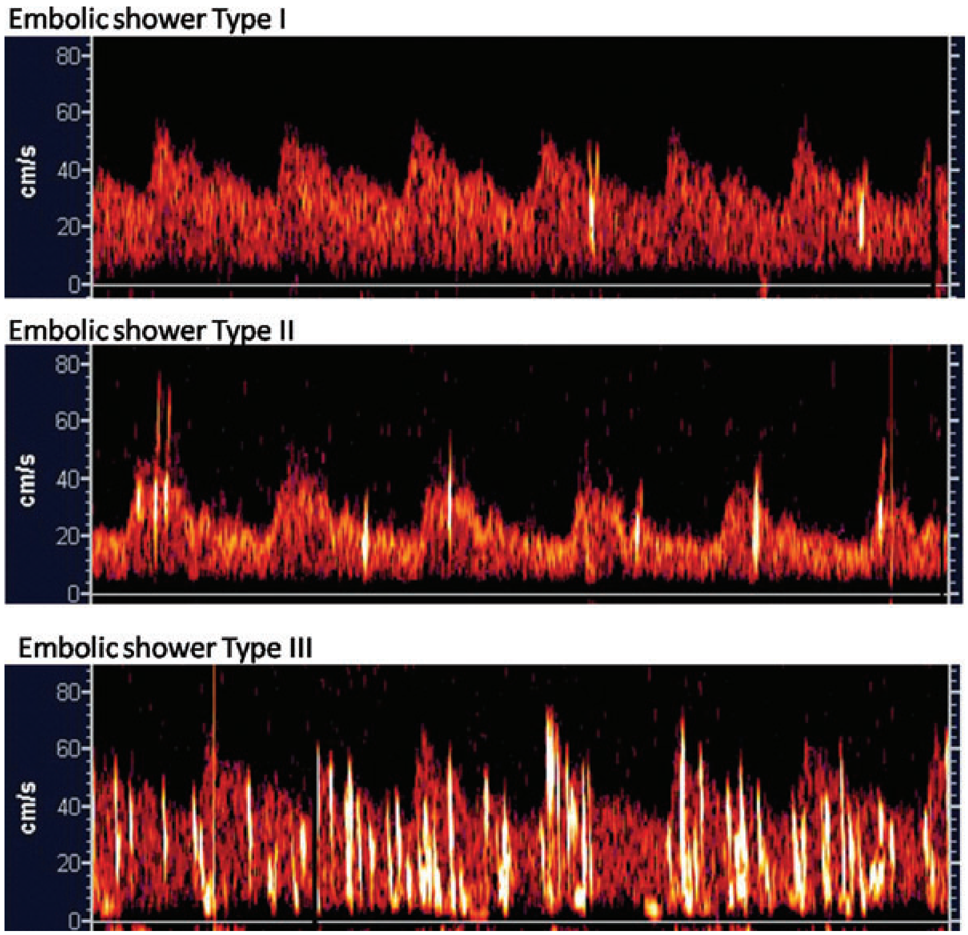

Figure 1. *Examples of the 3 types of showers in the velocity spectrum of the transcranial Doppler (TCD) screen.*

the CRF (ACT = 371, P = 0.017) and the CB groups (ACT = 364, P = 0.05).

Total Number of Cerebral MES

The number of cerebral MES in the three procedures are represented in Table 3. The total number of cerebral MES differs significantly among the 3 groups. The number of cerebral MES detected during the entire PVI procedure was significantly lower in the IRF group (1,404 MES) and in the CB group (935 MES), compared to the CRF group (3,908 MES, respectively, P = 0.0019, P = 0.001). The number of cerebral MES during the placement period was significantly higher in the IRF group (745 cerebral MES) compared to the other 2 groups (CB = 377 cerebral MES, P = 0.03; and CRF = 332 cerebral MES, P = 0.015). During the ablation period, less cerebral MES were generated in the IRF group (105 MES) and in the CB group (163 MES) compared to the CRF group (2,566 MES, respectively, P = 0.01, P = 0.0001). When considering the number of MES per minute of ablation, the CB group demonstrated the lowest number of three cerebral MES per minute of ablation compared to both the other procedures (CRF = 92 MES, P < 0.0001; IRF = 7 MES, P = 0.03).

TABLE 1

Patients' Characteristics in the Irrigated RF (IRF) Group, the Conventional RF (CRF) Group, and the Cryoballoon (CB) Group

	Conventional RF	Irrigated RF	Cryoballoon
N	10	10	10
Male	9	10	7
Age (year)	50 (11)	53 (14)	58 (11)
PAF/CAF	9/1	9/1	10/0
PFO	2	1	1
Previous TIA	0	0	1
Previous percutaneous ablation	3	1	2

CAF = consistent atrial fibrillation; PAF = paroxysmal atrial fibrillation; PFO = patent foramen ovale; RF = radiofrequency; TIA = transient ischemic stroke.

MES in the CB Procedures

The number of MES during contrast injections and single-point ablation in the CB group were analyzed separately. On average, 13 ± 2 cerebral MES were observed during each contrast injections in the CB procedure, resulting in an average of 132 ± 37 MES per procedure caused by contrast injections. Single segmental ablations with the freezer max did not contribute significantly to the total number of cerebral MES, as only 2 ± 1 cerebral MES were observed in the complete segmental ablation period, consisting of 8 applications.

TABLE 2

Procedure Characteristics in the Conventional RF (CRF) Group, the Irrigated RF (IRF) Group, and in the Cryoballoon (CB) Group

	CRF		IRF		CRF Versus IRF	CB		CB Versus CRF	CB Versus IRF
	Mean	SD	Mean	SD		Mean	SD		
Ablation time (minutes)	24	10	16	9	P = 0.347	79	42	P < 0.0001	P = 0.01
Time per ablation (seconds)	45	15	34	17	P = 0.008	300	0	P < 0.0001	P < 0.0001
Procedural time (minutes)	274	92	185	49	P = 0.032	178	57	P < 0.0001	P = 0.711
ACT (seconds)	371	106	210	33	P = 0.017	364	90	P = 0.909	P = 0.05
Impedance (Ω)	200	10	115	14	P = 0.04				
Power (W)	24	6	24	2	P = 0.906				
Temperature (°C)	49	5	36	2	P = 0.01				

ACT = activated clotting time; RF = radiofrequency.

Ablation Characteristics and Type of Embolic Showers in CRF Procedures

Type I showers occurred during the CRF procedure at an average ablation application time of 41 seconds (±16 seconds), with an average temperature per ablation of 47°C (±4°C). Type II showers occurred at an average similar ablation application duration (44 seconds ±16 seconds) but with a significant higher temperature of 49°C (±5°C) (P = 0.025). Type III showers occurred at significant higher ablation application time of 52 seconds (±11 seconds) than both type I and type II embolic showers (P < 0.0001) and at significant higher temperatures of 52°C (±5°C) than both other types of showers (P < 0.0001).

Discussion

This study demonstrates that cerebral MES are generated in patients undergoing catheter-based PV ablation procedures. However, the number of cerebral MES generated during PVI procedures is dependent on the type of the ablation catheter. The CB generates a lower number of cerebral MES during the ablation application than methods involving RF-based ablation catheters. When comparing the irrigated tip RF catheter and the conventional RF catheter, the former generates the lowest number of cerebral MES. The duration and temperature of each ablation application could play a role in the difference in generation of emboli when RF energy is used.

It has been proven that cerebral MES are an indicator of systemic and cerebral embolization, and are associated with a significant risk of neurologic damage.[4,6–9,15,16] Lickfett *et al.*[5] demonstrated with diffusion-weighted magnetic resonance imaging that 10% of patients undergoing PVI with a RF catheter had cerebral embolic lesions postprocedurally. Kilicislan *et al*. and Marrouche *et al.*[4] have shown that patients with cerebroembolic events had significantly higher numbers of cerebral MES, suggesting that without the knowledge of the constitution of those emboli, the cerebral emboli during catheter RF ablation are responsible for neurological complications. The method of detecting cerebral emboli cannot provide information of the composition of the observed emboli, but the moment of occurrence can provide an indication about the nature of the observed emboli. In cryoballoon ablation, a majority of MES are observed during the placement and manipulation phase and at end of each ablation. Since placement of a 14 Fr transseptal sheath and contrast injections during placement of the cryoballoon are involved in the placement and manipulation phases, it seems a reasonable hypothesis that the observed MES during these phases are mainly caused by iatrogenic gas injection. At the end of the ablation phase, however, the balloon that occluded the PV ostium (trapping injected contrast inside the PV) is deflated. The cerebral MES detected at that moment could be the release of ice chips formed at the balloon-PV interface or the release of thrombi formed in the trapped blood column behind the occluding balloon. But it could also be the release of trapped contrast including some injected air that could be responsible for MES formation. Although the nature of the detected emboli in the CB procedures cannot be determined with certainty, it is clear from this study that a lower number of MES are detected during the CB procedure compared to the methods involving RF. The observed low number of MES during cryoenergy delivery with the cryoballoon and the absence of MES during with cryothermal segmental ablations confirms the previously proven low thrombogenity of cryoablation.[17–20]

Both RF groups show a higher number of observed MES compared to the CB procedure during the ablation phase. It has been shown that RF energy is not only highly thrombogenic,[17–19,21,22] but also causes the gaseous emboli to emerge

TABLE 3

Number of Microembolic Signals (MES) in the Conventional RF (CRF) Group, the Irrigated Tip RF (IRF), and the Cryoballoon (CB) Group

	CRF		IRF		IRF Versus CRF	CB		CB Versus CRF	CB Versus IRF
	Mean	SD	Mean	SD		Mean	SD		
MES total	3,908	2,816	1,404	981	P = 0.019	935	463	P = 0.001	P = 0.186
MES placement period	332	193	745	467	P = 0.015	377	297	P = 0.624	P = 0.03
MES ablation period	2,566	2,296	105	71	P = 0.01	163	91	P = 0.001	P = 0.266
MES manipulation period	1,010	733	554	601	P = 0.143	395	186	P = 0.027	P = 0.874
MES per 1 minute of ablation	92	144	7	20	P < 0.0001	3	5	P < 0.0001	P = 0.03

due to tissue disruption and temperature rises.[13,14,23] Since this study confirms the significant correlation between increasing number of cerebral MES with higher power, duration, and temperatures of the RF ablation, it confirms that the emboli are correlated with the energy delivery. In the CRF ablations the type III cerebral embolic showers may be prevented by reducing the duration of each ablation. It also shows that reducing the catheter tip temperatures by irrigated cooling is an effective means for reduction of cerebral MES, probably through prevention of thrombus formation as was suggested earlier.[22,24] This shows that when using RF energy for PVI, with a high number of ablation lesions in the left atrium, an irrigated tip catheter is preferable to a conventional RF catheter since systemic embolization can have devastating consequences and is a frequently occurring complication.[5,6,20,25]

Study Limitations

The activated clotting times during the ablation was not entirely uniform in all groups. The CRF and IRF maintained lower anticoagulation levels than the CB group that may pose a serious bias in this study. However, in the IRF group, although being the least anticoagulated, a significant lower MES were observed than in the CRF group, indicating the major determinant of MES was the method of power delivery and not the anticoagulation level during the procedure.

The standard MES evaluation is the off-line evaluation of a recorded TCD signal by a human expert;[12] and although the agreement rates of MES detection by TCD are higher than the agreement rates for interpretation of computed tomography or magnetic resonance imaging,[26,27] a human dependency factor remains present by MES evaluation.

This study did not include a neurological examination of the patients. No observations were made of postprocedural neurological complications. However, due to reports that have demonstrated a correlation between cerebral emboli and brain damage,[4-6,8,9,15,16,28] a lower incidence of neurological complications in the cryoablation and the irrigated RF-treated patients can be expected.

Conclusion

This study demonstrates that the generated cerebral MES during a PVI procedure are significant lower with the use of a CB catheter and an IRF catheter compared to the use of a CRF catheter. The risk of postprocedural neurological complications can therefore be expected to be higher with the use of a CRF catheter during a PVI procedure.

References

1. Wolf PA, Abbott RD, Kannel WB: Atrial fibrillation as an independent risk factor for stroke: The Framingham study. Stroke 1991;22:983-988.
2. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Packer D, Skanes A: Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation 2005; 111:1100-1105.
3. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J: Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-666.
4. Kilicaslan F, Verma A, Saad E, Rossillo A, Davis DA, Prasad SK, Wazni O, Marrouche NF, Raber LN, Cummings JE, Beheiry S, Hao S, Burkhardt JD, Saliba W, Schweikert RA, Martin DO, Natale A: Transcranial Doppler detection of microembolic signals during pulmonary vein antrum isolation: Implications for titration of radiofrequency energy. J Cardiovasc Electrophysiol 2006;17:495-501.
5. Lickfett L, Hackenbroch M, Lewalter T, Selbach S, Schwab JO, Yang A, Balta O, Schrickel J, Bitzen A, Luderitz B, Sommer T: Cerebral diffusion-weighted magnetic resonance imaging: A tool to monitor the thrombogenicity of left atrial catheter ablation. J Cardiovasc Electrophysiol 2006;17:1-7.
6. Marrouche NF, Martin DO, Wazni O, Gillinov AM, Klein A, Bhargava M, Saad E, Bash D, Yamada H, Jaber W, Schweikert R, Tchou P, Abdul-Karim A, Saliba W, Natale A: Phased-array intracardiac echocardiography monitoring during pulmonary vein isolation in patients with atrial fibrillation: Impact on outcome and complications. Circulation 2003; 107:2710-2716.
7. Muth CM, Shank ES: Gas embolism. N Engl J Med 2000;342:476-482.
8. Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M, Newman S: The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. Stroke 1994;25:1393-1399.
9. Clark RE, Brillman J, Davis DA, Lovell MR, Price TR, Magovern GJ: Microemboli during coronary artery bypass grafting. Genesis and effect on outcome. J Thorac Cardiovasc Surg 1995;109:249-257; discussion 57-58.
10. Van Belle Y, Janse P, Rivero-Ayerza MJ, Thornton AS, Jessurun ER, Theuns D, Jordaens L: Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: Feasibility, complications, and short-term outcome. Eur Heart J 2007;28:2231-2237.
11. Van Belle Y, Janse P, Theuns D, Szili-Torok T, Jordaens L: One year follow-up after cryoballoon isolation of the pulmonary veins in patients with paroxysmal atrial fibrillation. Europace 2008;10:1271-1276.
12. Ringelstein EB, Droste DW, Babikian VL, Evans DH, Grosset DG, Kaps M, Markus HS, Russell D, Siebler M: Consensus on microembolus detection by TCD. International Consensus Group on Microembolus Detection. Stroke 1998;29:725-729.
13. Bruce GK, Bunch TJ, Milton MA, Sarabanda A, Johnson SB, Packer DL: Discrepancies between catheter tip and tissue temperature in cooled-tip ablation: Relevance to guiding left atrial ablation. Circulation 2005 16;112:954-960.
14. Wood MA, Shaffer KM, Ellenbogen AL, Ownby ED: Microbubbles during radiofrequency catheter ablation: Composition and formation. Heart Rhythm 2005;2:397-403.
15. Gottesman RF, Wityk RJ: Brain injury from cardiac bypass procedures. Semin Neurol 2006;26:432-439.
16. Sylivris S, Levi C, Matalanis G, Rosalion A, Buxton BF, Mitchell A, Fitt G, Harberts DB, Saling MM, Tonkin AM: Pattern and significance of cerebral microemboli during coronary artery bypass grafting. Ann Thorac Surg 1998;66:1674-1678.
17. Khairy P, Chauvet P, Lehmann J, Lambert J, Macle L, Tanguay JF, Sirois MG, Santoianni D, Dubuc M: Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation. Circulation 2003;107:2045-2050.
18. Lustgarten DL, Keane D, Ruskin J: Cryothermal ablation: Mechanism of tissue injury and current experience in the treatment of tachyarrhythmias. Prog Cardiovasc Dis 1999;41:481-498.
19. van Oeveren W, Crijns HJ, Korteling BJ, Wegereef EW, Haan J, Tigchelaar I, Hoekstra A: Blood damage, platelet and clotting activation during application of radiofrequency or cryoablation catheters: A comparative in vitro study. J Med Eng Technol 1999;23:20-25.
20. 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;10:611-620.
21. Lee DS, Dorian P, Downar E, Burns M, Yeo EL, Gold WL, Paquette M, Lau W, Newman DM: Thrombogenicity of radiofrequency ablation procedures: What factors influence thrombin generation? Europace 2001;3:195-200.
22. Yokoyama K, Nakagawa H, Wittkampf FH, Pitha JV, Lazzara R, Jackman WM: Comparison of electrode cooling between internal and open irrigation in radiofrequency ablation lesion depth and incidence of thrombus and steam pop. Circulation 2006;113:11-19.
23. Pinchuk LS, Kravtsov AG, Zotov SV: Thermally stimulated depolarization of human blood. Technical Physics 2001;46:620-622.
24. Padanilam BJ: Cerebral microembolism during AF ablation: An innocent bystander or an accessory to brain injury? J Cardiovasc Electrophysiol 2006;17:502-503.
25. Wazni OM, Rossillo A, Marrouche NF, Saad EB, Martin DO, Bhargava M, Bash D, Beheiry S, Wexman M, Potenza D, Pisano E, Fanelli

R, Bonso A, Themistoclakis S, Erciyes D, Saliba WI, Schweikert RA, Brachmann J, Raviele A, Natale A: Embolic events and char formation during pulmonary vein isolation in patients with atrial fibrillation: Impact of different anticoagulation regimens and importance of intracardiac echo imaging. J Cardiovasc Electrophysiol 2005;16:576-581.

26. Dittrich R, Ritter MA, Kaps M, Siebler M, Lees K, Larrue V, Nabavi DG, Ringelstein EB, Markus HS, Droste DW: The use of embolic signal detection in multicenter trials to evaluate antiplatelet efficacy: Signal analysis and quality control mechanisms in the CARESS (Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis) trial. Stroke 2006;37:1065-1069.
27. Markus HS, Ackerstaff R, Babikian V, Bladin C, Droste D, Grosset D, Levi C, Russell D, Siebler M, Tegeler C: Intercenter agreement in reading Doppler embolic signals. A multicenter international study. Stroke 1997;28:1307-1310.
28. Lund C, Sundet K, Tennoe B, Hol PK, Rein KA, Fosse E, Russell D: Cerebral ischemic injury and cognitive impairment after off-pump and on-pump coronary artery bypass grafting surgery. Ann Thorac Surg 2005;80:2126-2131.