Microembolism and Catheter Ablation I
A Comparison of Irrigated Radiofrequency and Multielectrode-phased Radiofrequency Catheter Ablation of Pulmonary Vein Ostia

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Background—Cerebral diffusion-weighted MRI lesions have been observed after catheter ablation of atrial fibrillation. We hypothesized that conditions predisposing to microembolization could be identified using a porcine model of pulmonary vein ablation and an extracorporeal circulation loop.

Methods and Results—Ablations of the pulmonary veins were performed in 18 swine with echo monitoring. The femoral artery and vein were cannulated and an extracorporeal circulation loop with 2 ultrasonic bubble detectors and a 73-μm filter were placed in series. Microemboli and microbubbles were compared between ablation with an irrigated radiofrequency system ( Biosense-Webster) and a phased radiofrequency multielectrode system (pulmonary vein ablation catheter [PVAC], Medtronic, Inc, Carlsbad, CA) in unipolar and 3 blended unipolar/bipolar modes. Animal pathology was examined. The size and number of microbubbles observed during ablation ranged from 30 to 180 μm and 0 to 3253 bubbles per ablation. Microbubble volumes with PVAC (29.1 nL) were greater than with irrigated radiofrequency (0.4 nL; P=0.045), and greatest with type II or III microbubbles on transesophageal echocardiography. Ablation with the PVAC showed fewest microbubbles in the unipolar mode (P=0.012 versus bipolar). The most occurred during bipolar energy delivery with overlap of proximal and distal electrodes (median microbubble volume, 1744 nL; interquartile range, 737–4082 nL; maximum, 19 516 nL). No cerebral MRI lesions were seen, but 2 animals had renal embolization.

Conclusions—Left atrial ablation with irrigated radiofrequency and PVAC catheters in swine is associated with microbubble and microembolus production. Avoiding overlap of electrodes 1 and 10 on PVAC should reduce the microembolic burden associated with this procedure. (Circ Arrhythm Electrophysiol. 2013;6:16-22.)

Key Words: atrial fibrillation ■ ablation ■ complications ■ diffusion-weighted MRI ■ embolism

Systemic embolic complications are uncommon but serious adverse events that are observed with left-sided catheter ablation procedures. The risk of stroke and transient ischemic attack after atrial fibrillation (AF) ablation typically ranges from 0.2% to 2.0%. The mechanisms of embolic stroke and transient ischemic attack are hypothesized to be owing to embolism of thrombus, char, coagulum, or gas bubbles that occur at the site of ablation or are related to catheter introduction or manipulation in the left atrium. Studies of AF ablation have documented showers of bubbles or debris on intracardiac echocardiography and transcranial Doppler associated with higher ablation power delivery. The other mechanisms could include atrial stunning with stasis of blood and thrombus formation, similar to that observed after electric cardioversion, or endocardial disruption creating a thrombogenic state. Recent reports have described a high prevalence of asymptomatic cerebral lesions after AF ablation procedures observed on diffusion-weighted MRI (DWI) that are presumed to be embolic in origin. However, the exact mechanism and composition of the embolic material have not been characterized. The present study created an experimental model of left atrial ablation in swine to fully characterize and quantify the production of microbubble and particulate emboli to determine its potential for creation of asymptomatic cerebral ischemic lesions.

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Methods
Porcine Ablation Model
The investigational protocol was reviewed and approved by the Medtronic Animal Use Committee, and animals were cared for in an Association for Assessment and Accreditation of Laboratory Animal Care-approved facility. Eighteen common farm swine weighing...
86±18 kg were sedated with telazol and acepromazine, then anesthetized with isoflurane and buprenorphine. The animals were mechanically ventilated using a combination of medical air and oxygen, targeting a $P_{0.1}$ level of 100 to 150 mm Hg. A left femoral cutdown incision was made and a 19-Fr cannula was placed into the left femoral artery, and a 20-Fr cannula into the left femoral vein. A 5-Fr catheter was placed in the right femoral artery for continuous arterial pressure monitoring, and a Swan-Ganz catheter was advanced from the right external jugular vein to the pulmonary artery for pulmonary capillary wedge pressure and cardiac output measurements. The right femoral vein was punctured percutaneously and a 10-Fr guiding sheath was advanced to the fossa ovalis. Heparin 15 000 IU and an infusion of 1500 IU/h were administered to maintain an activated clotting time of >350 seconds. Transesophageal echocardiography (GE Vivid system, GE Medical, Inc, Horten, Norway) or intracardiac echocardiography (AcuNav, Siemens Medical Solutions, Malvern, PA) was used continuously throughout the case to monitor cardiac function, intracardiac catheter manipulation, and microbubble generation at the ablation sites. Transseptal puncture was performed using hemodynamic, fluoroscopic, and echo guidance. A subset of 6 animals underwent cerebral MRI scanning. At the conclusion of all testing, animals were euthanized by inducing ventricular fibrillation with direct current applied to the right ventricle. Necropsy was performed and after careful gross inspection, sections of the heart, brain, rete mirabile, and kidney were dissected for histological examination.

**Extracorporeal Blood Circulation**

The 19-Fr left femoral arterial and 20-Fr femoral venous cannula were connected through a loop of PVC perfusion tubing (9.5 mm inner diameter) ≈60 cm in length (Figure 1). An in-line filter housing (Pall Inc #1119) was fitted with a replaceable 73 μm polyester filtration membrane (Sefar-Petex #07-73-40 membrane) placed in the extracorporeal circuit. Two microbubble detectors (BC100, GAMPT Ultrasonic Solutions, Merseburg, Germany) were positioned proximal and distal to the filter. A flowmeter (Bioconsole 560, Medtronic, Minneapolis, MN) was also placed in line to confirm a baseline extracorporeal flow rate of at least 1 L/min. Hemodynamics were evaluated with thermodilution cardiac outputs (4.0 L/min with shunt closed versus 5.2 L/min with shunt open) and pulmonary capillary wedge pressures from the pulmonary arterial catheter. The shunt flow rate (1.79±0.18 L/min) was continuously monitored for evidence of hemodynamic deterioration.

**Catheter Ablation**

Radiofrequency ablation catheters were inserted through the transseptal sheath into the left atrial chamber. Extracorporeal pulmonary vein catheter ablation with either the PVAC (Medtronic, Inc, Carlsbad, CA) or an irrigated radiofrequency (IRF) catheter (Thermocoool, BioSense-Webster, Inc, Diamond Bar, CA) was performed. The PVAC catheter is a 9-F, over-the-wire, catheter with a 25-mm diameter circular array of 10 electrodes each measuring 3 mm in length with 3 mm interelectrode spacing. Radiofrequency energy was delivered via a multichannel, duty-cycled phased RF generator (GENius, Medtronic, Inc) that delivered power in a unipolar mode (to a dispersive skin electrode), or blended mode in a 1:1, 2:1, or 4:1 bipolar:unipolar ratio as has been previously described. Power was delivered for 1 minute per ablation in a temperature-feedback power control mode (maximum of 10 W per electrode in 1:1 and 2:1 modes, or 8 W in 4:1 mode) to target an electrode temperature of 60°C. Ablation with the irrigated ablation catheter was performed for 1 minute at a fixed power output of 30 W with 30 cc/min saline cooling flow (CoolFlow, BioSense-Webster, Inc). During ablation, microbubble production was assessed qualitatively by transesophageal echocardiography. Large bursts of microbubbles observed in a small minority of ablations were defined as type II microbubbles as previously described. Microbubbles and microemboli were measured quantitatively with the 2 in-line bubble detectors in the extracorporeal loop, and embolic particulate debris was assessed by inspecting the in-line filter after each mode of ablation. After early observations suggested the importance of interaction of electrodes 1 and 10 on the PVAC catheter, prospective evaluation of these interactions was conducted in 24 ablations. Electrode 1-10 interactions were defined as proximity of these 2 electrodes by fluoroscopic imaging of <3 mm.

**Statistics**

All data were recorded prospectively in an Excel database and tested with Statistics Analysis System (SAS, Inc, Cary, NC). Normal data are expressed as means±SD. Ablation microbubble data are expressed as gas volume or number of gas bubbles per 1 minute ablation time, including the bubbles released when the catheter was moved, immediately after an ablation. In the case of catheter introductions, data are recorded per event. Comparisons among non-normally distributed data were made with the Mann–Whitney test. Comparisons among proportions were made with a 2-sided Fisher exact test. Volume and bubble counts were compared on the square root scale using the generalized estimating equation method and an exchangeable working correlation to account for within-pig correlation. Hypothesis tests were performed using the Rotnitzky–Jewell score test.

A P value of <0.05 was considered statistically significant.

**Results**

**Systemic Microbubble Embolism**

A total of 177 pulmonary vein lesions were created with the PVAC (24 unipolar, 32 1:1 bipolar to unipolar ratio, 48 2:1 ratio, and 73 4:1 ratio), and 105 lesions were created with IRF. During catheter ablation in all ablation conditions, microbubble production was observed. On echocardiography, the bubble production ranged from low density, isolated bubbles, to large quantity of bubbles with bursts (type II–III microbubbles). After a time delay of ≥3 seconds, bubbles were detected on the first extracorporeal bubble detector, then immediately thereafter on the second detector (Figure 2), with a similar contour of the quantitative bubble detection curve. The volumes of microbubbles during each mode of catheter ablation are displayed in Figure 3. Bubble size ranged from 30 to 180 μm and bubble count ranged from 0 to 3253 bubbles per ablation. Median microbubble volumes observed with PVAC were small but greater than those seen with IRF ablation (29.1 versus 0.4 nL; P=0.045). Greatest bubble volumes with IRF were observed during the 3 of 105 cases where type II–III microbubbles were detected on echo and quantified by the bubble detectors (1777, 2182, and 12436 nL). Ablation with the PVAC showed lowest bubble production in the unipolar mode (median count, 13; median volume, 12.7 nL) and increased significantly to median bubble counts of 63, 72,
and 55 and median bubble volumes of 33.0, 40.2, and 33.3 nL for 1:1, 2:1, and 4:1 bipolar:unipolar energy delivery ratios, respectively (P=0.012). In the 3 of 179 cases where type II–III microbubbles were seen with the PV AC, the gas volumes were 1779, 2090, and 19516 nL.

The greatest microbubble production with PVAC ablation occurred with overlap of electrodes 1 and 10 when the electrode loop diameter was constrained by the PV, and energy delivery was in the blended bipolar modes. Of the 24 cases that fulfilled criteria for electrode 1-10 interaction (Figure 4), 18 occurred during 4:1 bipolar:unipolar delivery and 6 during 2:1 delivery. The median bubble number was 1437 (interquartile range [IQR], 524–2410; maximum, 4191) and bubble volume was 1549 nL (IQR, 737–4082 nL; maximum, 19516 nL). In these electrode overlap cases, stopping energy delivery to electrode pair 1 (electrodes 1 and 2) or pair 5 (electrodes 9 and 10) or changing to unipolar energy delivery resulted in immediate cessation of microbubble (MB) generation (Figure 5). Other sources of bubble production were injection of contrast through the transseptal sheath and catheter introduction into the sheath. Despite meticulous attention to sheath management, microbubbles were typically observed after the catheter was passed through the hemostatic valve. During normal PVAC exchanges, median bubble count was 516 and median bubble volume was 410 nL (IQR, 136–825 nL), compared with the IRF catheter exchanges with a median of 8 bubbles and a volume of 4.7 nL (IQR, 1.3–61 nL; P=0.046). When the PVAC introductions were performed after capturing the electrode array under the surface in a bath of saline (underwater loading), the median volume of bubbles decreased to 192 nL.

**Particulate Debris Production**

Two different types of debris were collected on the in-line filter. Unrelated to ablations, the prevalent material found on every filter was white or pink in appearance, and varied from scattered thin strands to a collection of material measuring 1 cm in diameter and 1 mm thick. This material was determined to be white thrombus and was characterized pathologically as a mixture of thrombin and platelets. The other debris collected on a minority of filters was consistent with the product of thermal denaturation of blood proteins (coagulum) (Figure 6). After IRF ablation, 3 of 9 filters analyzed showed evidence of coagulum. One specimen demonstrated connective tissue on
Histopathology and probably represented avulsed embolized cardiac endothelial tissue after an ablation with excessive subendocardial heating during IRF energy delivery. The median diameter of the captured emboli was 225 μm (IQR, 200–400 μm; maximum, 1300 μm). After PVAC ablation, 8 of 28 filters showed evidence of coagulum (median diameter, 250 μm; IQR, 180–400 μm; maximum, 600 μm). Of these, 7 filters were collected after ablation where the catheter was manipulated to create electrode 1-10 interaction, and all 7 (100%) had evidence of coagulum. Each filter was compared with the ablation conditions and the magnitude of microbubble formation. In ablation series where thermal coagulum was subsequently identified in the extracorporeal filter, the median MB volume per ablation was 0.30 μL (IQR, 0.024–2.23 μL) compared with 0.047 μL (IQR, 0.010–0.164 μL) with ablations where no subsequent embolic debris was found (P=0.031). After PVAC ablations with electrode 1-10 overlap conditions, thermal coagulum was always found in the filter. Coagulum was found in 3 filters after IRF ablations, but there was no apparent association with type II–III microbubble formation or steam pops in these cases.

Pathology After Catheter Ablation

The hearts and vital organs of all swine that underwent PV ablation were examined grossly, and samples were selected for histopathologic study. All hearts showed evidence of repeated ablation in the right common and left inferior (caudal) pulmonary vein ostia, as well as some lesions in the left atrial appendage. The acute, RF-induced PVAC ablations presented as grayish-white, well-demarcated, focal or linear endocardial lesions that extended with a similar morphology into the myocardium when observed on cross sections, with a very narrow red rim surrounding each lesion (unless subendocardial, contact-induced hemorrhage superimposed this observation). Gross findings were consistent with a diagnosis of thermal necrosis. Lesion shape and size corresponded to the PVAC catheter electrode array. PVAC ablations consisted of closely apposed foci that for the most part merged on gross observation. When gaps of presumably nonablated myocardium were observed between the foci, histopathologic examination yielded contiguity of the thermal necrosis based on the presence of cardiomyocytes with contraction bands. None of the PVAC ablations caused endocardial avulsion, cardiac perforation, or steam-pocket formation. Very rarely, delicate, firmly adhered, red-brown, blunt and irregular thermal coagula were noted in the center of the foci in tissues.

Figure 3. Box and whisker plot of microbubble (MB) volume detected during a variety of experimental conditions. A, Scale from 0 to 1000 nL, (B) the same data on an expanded scale from 0 to 25 000 nL. MB production is shown for catheter introduction into the transseptal sheath with the pulmonary vein ablation catheter (PVAC) (PVAC intro) or the thermocool catheter (TC intro), and during ablation with the PVAC catheter in a variety of unipolar or blended unipolar/bipolar modes or the irrigated radiofrequency (RF) catheter. PVAC ablations with interaction of electrodes 1 and 10 are presented separately (see text for details).

Figure 4. Fluoroscopic image of pulmonary vein ablation catheter positioned in right (septal) pulmonary veins. Left, The catheter is normally positioned at the origin of the right pulmonary vein antrum. Electrodes 1 and 10 (arrows) show good separation. Left, The catheter loop is constrained by the vein resulting in overlap of electrodes 1 and 10 (arrow).
that received repeated ablations. Likewise, endocardial rupture was a rare exception and if present, restricted to single lesion foci. The IRF catheter ablations resulted also in focal thermal necrosis, but in 3 pigs, lesions were associated with a complete perforation of the atrial septum, a near-perforation of the atrial wall, and with evidence of a large steam-pocket formation accompanied by substantial mural hemorrhage. No evidence of emboli was observed in the brain or spleen. Two animals showed evidence of a renal embolism, one of which had clear evidence of thermal thrombus. Distal to the renal arterial occlusion, wedge-shaped sections of tubular necrosis were observed.

Cerebral Findings
None of the 6 pigs that underwent MRI showed any evidence of acute lesion hyperintensities on diffusion-weighted scans. The brains of all swine were dissected and sectioned into 1 cm slices. No gross lesions were found and no lesions were found on histopathologic examination.

Discussion
Catheter ablation of AF offers a promise of arrhythmia modification or elimination in most of the patients with this symptomatic arrhythmia. The benefits of ablation must, however, be balanced against the procedure-related risks. Thromboembolic complications continue to be of major concern.\textsuperscript{19,20} Recently, identification of asymptomatic lesions on DWI scans after ablation has led to the discussion that significant embolic events may be underestimated if clinical signs and symptoms alone are used to identify these patients.\textsuperscript{11–16} Therefore, it has been the goal to understand the source and composition of the microemboli that account for the
DWI lesions in patients, and to modify factors that may be contributing to their production.

The present study used an in vivo swine model with an extracorporeal perfusion circuit in which microbubbles and microembolic debris could be measured and correlated with various ablation conditions. Several important patterns were elucidated. First, microbubbles were seen with catheter introduction into the left atrium, and that the volume of those microbubbles was greater with PVAC than IRF. This is likely owing to the complex catheter geometry in its extended configuration to capture small amounts of air during introduction across the hemostatic valve compared with the smooth bullet shape of a typical ablation catheter. Second, microbubble production was greatest when bursts of microbubbles were observed on transesophageal echocardiography (type II–III microbubbles).7 This was observed with both catheter technologies. Finally, the phenomenon observed solely with the PVAC catheter was MB production that was orders of magnitude greater during the special condition of blended unipolar:bipolar energy delivery when there was visible overlap on fluoroscopy between electrodes 1 and 10 of the circular catheter. When either the #1 to 2 or the #9 to 10 electrode pair was inactivated, the microbubble production ceased immediately. During ablation with the PVAC catheter when electrodes 1 and 10 were overlapping, the appearance of particulate debris that had histological characteristics of thermal coagulum correlated with microbubble production; therefore, with some technologies, microbubble count and volume may be useful as surrogate markers for particulate embolus production.31 However, absence of this association between microbubble volume and appearance of particulate emboli during ablation with the PVAC during placements without an electrode overlap condition or with the IRF system shows that this cannot be universally applied.

Mechanism of Electrode 1-10 Interaction

The PVAC catheter delivers RF energy in a blended unipolar and bipolar fashion. During unipolar delivery, all RF energy is in phase and is delivered between the 10 electrodes and dispersive electrodes applied to the patient’s skin. During pure bipolar energy delivery, energy can be delivered from each electrode to the contiguous electrodes around the entire circular catheter including between electrode 1 and 10 at both extremities of the circular catheter. All odd-numbered electrodes are out of phase with the even-numbered electrodes. In the blended mode, the ratio between unipolar and bipolar delivery is achieved by adjusting the phase angle of the alternating RF current between contiguous electrodes. If the RF energy is completely in phase, then the energy is in a unipolar delivery mode. If contiguous electrodes are completely out of phase, then the energy will be transmitted in a combined unipolar and bipolar fashion. By alternating between in phase and out of phase on adjacent electrodes, different bipolar:unipolar ratios are obtained. Uniform bipolar energy delivery is dependent on a constant interelectrode distance between the bipole. If, owing to compression and constraint of the circular catheter by pulmonary vein anatomy, 2 electrodes (#1 and 10) come in closer proximity than the 3-mm interelectrode distance on the catheter, a disproportionationate amount of current density would be shunted to the 1-10 bipole, resulting in excessive heating and an increase in MB and thermal coagulum formation. It is hypothesized that this phenomenon is the dominant factor accounting for production of microembolic debris and creation of DWI lesions in the clinical setting. Of note, if electrodes 1 and 10 have actual physical contact, then the short circuit would prevent any tissue heating at that site. Thus, close proximity without contact seems to be the prerequisite for excess heating during bipolar delivery.

Limitations

Measuring microbubbles and microemboli in an extracorporeal circulation loop does not directly measure the embolic load that travels to the cerebral circulation, but the assumption was that the proportion of blood flow (about 1.8 L/min) was similar and, therefore, should be representative. Significant anatomic differences exist between swine and humans. In particular, the left atrial and pulmonary vein anatomies differ considerably. Thus, the results of ablation in pigs differ considerably from what are achieved in human patients. Absence of cerebral lesions on pathology may be owing to a low relative proportion of cardiac output devoted to cerebral perfusion in pigs, and the filtering effects of the rete mirabile, a plexus of vessels that protects the cerebral circulation in swine and other large nonprimate mammals.

Conclusions

Microembolic debris likely contributes to the development of cerebral lesions by DWI scan after catheter ablation of AF. Production of microemboli is inherent with all modes of hyperthermic ablation, but may be greater in the setting of high current densities associated with specific ablation conditions. Invoking technologies that prevent high subsurface tissue temperatures and steam pops will minimize risk of microembolization. Elimination of the potential for bipolar energy delivery between close proximity electrodes in multielectrode catheters will minimize risk of high current densities that produce microemboli. Failure to do so may result in an unsafe procedure. In addition, optimization of energy coupling from the catheter to the tissue, and improved temperature sensing with temperature-feedback power control should substantially mitigate the microembolic risk.

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Disclosures

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References

lesions on DWI. Phased RF catheters, should minimize the production of microemboli and reduce the prevalence of asymptomatic cerebral thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation. Circulation. 2006;114:759–766.


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Correction

In the article “Microembolism and Catheter Ablation I: A Comparison of Irrigated Radiofrequency and Multielectrode-phased Radiofrequency Catheter Ablation of Pulmonary Vein Ostia,” by Haines et al, which was published in the February 2013 issue (Circ Arrhythm Electrophysiol. 2013;6:16-22), an author’s name was spelled incorrectly.

The correct author’s name is Sarah Ahlberg, not Sarah Dahlberg. The full author listing is as follows: David E. Haines, MD; Mark T. Stewart, BS; Sarah Ahlberg, PhD; Noah D. Barka, DVM; Cathy Condie, MS; Gary R. Fiedler, BS; Nicole A. Kirchhof, DVM, AVCP; Franck Halimi, MD; Thomas Deneke, MD.

The online version of the article has been corrected. The publisher regrets the error.