Microembolism and Catheter Ablation I: A Comparison of Irrigated Radiofrequency and Multielectrode Phased Radiofrequency Catheter Ablation of Pulmonary Vein Ostia

Running title: Haines et al.; Microembolism in Radiofrequency Catheter Ablation

David E. Haines, MD1; Mark T. Stewart, BS2; Sarah Ahlberg, PhD2; Noah D. Barka, DVM2; Cathy Condie, MS2; Gary R. Fiedler, BS2; Nicole A. Kirchhof, DVM, AVCP2; Franck Halimi, MD3; Thomas Deneke, MD4

1Department of Cardiovascular Medicine, Oakland University William Beaumont School of Medicine, Royal Oak, MI; 2Medtronic, Inc., Minneapolis, MN; 3Centre Médico-Chirurgical Parly II, Le Chesnay, France; 4Heart Center Bad Neustadt, Bad Neustadt, Germany

Corresponding Author:
David E. Haines, MD
Professor of Cardiovascular Medicine
OUWB School of Medicine
Director, Heart Rhythm Center
Beaumont Health System
3601 West 13 Mile Road
Royal Oak, MI 48073
Tel: 248-898-7350
Fax: 248-898-4238
E-mail: dhaines@beaumont.edu

Abstract:

**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 (IRF) system (Biosense-Webster) and a phased radiofrequency multi-electrode system (PVAC, Medtronic) in unipolar and 3 blended unipolar/bipolar modes. Animal pathology was examined. The size and number of microbubbles observed during ablation ranged from 30 - 180 μm and 0–3253 bubbles per ablation. Microbubble volumes with PVAC (29.1 nl) were greater than with IRF (0.4 nl, p = 0.045), and greatest with type II or III microbubbles on TEE. 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 MB volume 1744 nl, IQR 737 - 4082 nl, maximum 19,516 nl). No cerebral MRI lesions were seen, but two animals had renal embolization.

**Conclusions** - Left atrial ablation with IRF 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.

**Key words:** atrial fibrillation, ablation, embolism, diffusion-weighted MRI, complications
Introduction

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 ablation typically ranges from 0.2 to 2.0%. The mechanisms of embolic stroke and TIA are hypothesized to be due 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 electrical cardioversion, or endocardial disruption creating a thrombogenic state. Recent reports have described a high prevalence of asymptomatic cerebral lesions after atrial fibrillation (AF) ablation procedures observed on diffusion weighted magnetic resonance imaging (DWI) that are presumed to be embolic in origin. However, the exact mechanism and composition of the embolic material has not been characterized. The present study created an experimental model of left atrial ablation in swine in order to fully characterize and quantify the production of microbubble and particulate emboli in order to determine its potential for creation of asymptomatic cerebral ischemic lesions.

Methods

Porcine ablation model - The investigational protocol was reviewed and approved by the Medtronic Animal Use Committee, and animals were cared for in an AAALAC-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 pO$_2$ level of 100 – 150 mmHg. 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/hr 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 DC 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 cannulae were connected through a loop of PVC perfusion tubing (9.5 mm inner diameter) approximately 60 cm in length (figure 1). An in-line filter housing (Pall Inc #1119) was fitted with a replaceable 73 um 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
flow meter (Bioconsole 560, Medtronic, Inc., Minneapolis, MN) was also placed in line to confirm the baseline an extracorporeal flow rate of at least 1 l/min. Hemodynamics were evaluated with thermodilution cardiac outputs (4.0 l/min with shunt closed vs 5.2 l/min with shunt open) and pulmonary capillary wedge pressures from the pulmonary arterial catheter. The shunt flow rate (1.79 l/min ±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. Extraostial pulmonary vein catheter ablation with either the PVAC (Pulmonary Vein Ablation Catheter, Medtronic, Inc., Carlsbad, CA) or an irrigated RF catheter (Thermocool, BioSense Webster, Inc., Diamond Bar, CA) were 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., Carlsbad, California) 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.17 Power was delivered for one 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 one minute at a fixed power output of 30 W with 30cc/min saline cooling flow (CoolFlow, BioSense Webster, Inc., Diamond Bar, CA). During ablation, microbubble production was assessed qualitatively by TEE. Large bursts of microbubbles observed in a small minority of ablations were defined as type II microbubbles as previously described.7 Microbubbles and microemboli were measured quantitatively with the two 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 two electrodes by fluoroscopic imaging of less than 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 ± standard deviations. Ablation microbubble data are expressed as gas volume or number of gas bubbles per one 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 two-sided fisher’s exact test. Volume and bubble counts were compared on the square root scale using the generalized estimating equation (GEE) 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 < 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 approximately 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 - 180 μm and bubble
count ranged from 0 – 3253 bubbles per ablation. Median microbubble volumes observed with
PVAC were small but greater than those seen with irrigated RF ablation (29.1 vs 0.4 nl, p =
0.045). Greatest bubble volumes with irrigated RF 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 12,436 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 PVAC, the gas volumes were 1779, 2090 and
19,516 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 (IQR 524 – 2410, maximum 4191) and bubble
volume was 1549 nl (IQR 737 - 4082 nl, maximum 19,516 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 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 to 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)\(^{18} \) (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 \( \mu \text{m} \) (IQR 200 – 400 \( \mu \text{m} \), maximum1300 \( \mu \text{m} \)). After PVAC ablation, 8 of 28 filters showed evidence of coagulum (median diameter 250 \( \mu \text{m} \), IQR 180 – 400 \( \mu \text{m} \), maximum 600 \( \mu \text{m} \)). 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 to 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 to 0.047 μl (IQR
0.010 – 0.164 μl) with ablations where no subsequent embolic debris was found (p = 0.031).
Following PVAC ablations with electrode 1-10 overlap conditions, thermal coagulum was
always found in the filter. Coagulum was found in three 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 histopathological
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 non-ablated myocardium
were observed between the foci, histopathological 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 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 three 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 six pigs that underwent MR imaging 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 histopathological examination.

Discussion
Catheter ablation of atrial fibrillation offers a promise of arrhythmia modification or elimination in a majority of 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.19,20 Recently, identification of asymptomatic lesions on DWI scans post ablation have led to the discussion that significant embolic events may be underestimated if clinical signs and symptoms alone are used to identify these patients.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 employed 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 irrigated RF. This is likely due to the complex catheter geometry in its extended configuration to capture small amounts of air during introduction across the hemostatic valve compared to 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). 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 #1-2 or #9-10 electrode pairs 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. 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 irrigated RF 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 to unipolar ratios are obtained. Uniform bipolar energy delivery is dependent upon a constant interelectrode distance between the bipoles. If, due to compression and constraint of the circular catheter by pulmonary vein anatomy, two electrodes (#1 and 10) come in closer proximity than the 3 mm interelectrode distance on the catheter, a disproportionate 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 anatomical 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 due 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 non-primate mammals.

Conclusions – Microembolic debris likely contributes to the development of cerebral lesions by DWI scan post catheter ablation of atrial fibrillation. 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 multi-electrode 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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References:


Figure Legends:

Figure 1. Schematic representation of the experimental pig with the extracorporeal perfusion circuit.

Figure 2. Graphical output of ultrasonic microbubble detector during a representative pulmonary vein ablation. The top two histograms are data from two different time series and represent the number of MBs detected (y-axis) versus the bubble size (x-axis). The blue bars are data from the first detector in series and the red bar from the second detector distal to the filter. The bottom tracing is a graph of MB number over time for the two detectors during two sequential ablations.

Figure 3. Box and whisker plot of MB volume detected during a variety of experimental conditions. Graph 3a shows a scale from 0 – 1000 nl, and graph 3b shows the same data on an expanded scale from 0 – 25,000 nl. MB production is shown for catheter introduction into the transseptal sheath with the PVAC (PVAC intro) or the Thermocool catheter (TC intros), and during ablation with the PVAC catheter in a variety of unipolar or blended unipolar/bipolar modes or the irrigated RF catheter. PVAC ablations with interaction of electrodes 1 and 10 are presented separately (see text for details).

Figure 4. Fluoroscopic image of PVAC catheter positioned in right (septal) pulmonary veins. In the left panel, the catheter is normally positioned at the origin of the right pulmonary vein antrum. Electrodes 1 and 10 (arrows) show good separation. In the left panel, the catheter loop is constrained by the vein resulting in overlap of electrodes 1 and 10 (arrow).


**Figure 5.** Graphical representations from the microbubble detectors as described in figure 2 during a PVAC ablation where electrode 1 was closely positioned to electrode 10. In the time series graph (bottom), electrode pair 1 (electrodes 1 and 2) was turned off with immediate cessation of MB formation. Another energy delivery with only electrode pairs 1 and 5 activated (electrodes 1, 2, 9 and 10) shows significant MB production.

**Figure 6.** Image of the filter membrane after IRF ablation and its removal from the in-line filter canister. Several small (< 0.5 mm) particles of thermal coagulum (confirmed histologically) are found (arrows). The white-pink material was white thrombus which is a mixture of thrombin and platelets, and an artifact of the extracorporeal circulation.
All pairs on, then pair-1 turned off at arrow. All bubbles stop

Abl 113

Pairs 1 and 5 ON

Abl 114
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