

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

**Cerebral microembolization during pulmonary vein isolation
performed with the circular multipolar radiofrequency
catheter**

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UNIVERSITY OF DEBRECEN

KÁLMÁN LAKI DOCTORAL SCHOOL

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Members of the Examination Committee: Prof. Dr. Kálmán Tóth MD, DSc

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The Examination takes place at the Department of Pediatrics, Faculty of Medicine, University of Debrecen

April 24, 2014. 11:00

Head of the **Defense Committee:** Prof. Dr. György Balla MD, MHAS

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The PhD Defense takes place at the Lecture Hall of the building A of the Department of Internal Medicine, Faculty of Medicine, University of Debrecen

April 24, 2014. 13:00

1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias affecting a large patient population. The prevalence of AF is increasing in developed countries due to the aging population. Different treatment strategies are available for rhythm control. Drug therapy is used in a wide range of patients. However, their success rate to maintain sinus rhythm is very low and the incidence of side effects is high. Catheter ablation is another treatment option to cure AF. The most common technique is pulmonary vein isolation (PVI) with point-by-point ablation. However, this technique requires an experienced operator. Recently, new ablation technologies were developed to overcome the difficulties of PVI. The Cryoballoon and the Pulmonary Vein Ablation Catheters (PVAC) were developed as single-shot techniques. Similar success rates were achieved with these methods compared to the point-by-point ablation. In our Institution we perform Cryoballoon ablations since 2008 and PVAC procedures since 2009.

1.1 Risk for stroke/TIA during catheter ablation of atrial fibrillation

The transcatheter treatment of AF is a complex intervention which requires the introduction of often bulky hardware into the left atrium (LA), energy applications over a large area of the LA endocardium and prolonged indwelling in the systemic circulation. Further, these procedures are performed in patients, who are at inherently increased risk of a thromboembolic complication, including stroke. It is not surprising therefore, that cerebrovascular accidents have been among the most feared complications, evoking significant concern, since the inception of AF ablation.

The first worldwide survey on catheter ablation for AF, reflecting the early up to the year 2005 concluded that clinical stroke occurred in 0.28% and transient ischaemic attack (TIA) in 0.66% of the patients. The update of that survey, relating to AF ablations performed between 2003 and 2006, indicated similar rates of cerebrovascular complications (0.23% for stroke, 0.71% for TIA) despite an apparently more difficult patient population with a more enlarged LA and more persistent AF.

A meta-analysis based on the data of 6936 patients who underwent AF ablation by the end of 2006 found that stroke and TIA occurred in 0.3% and 0.2% respectively. Stroke incidences as high as 5% and as low as 0% have also been reported as single-center findings. Although the complication rates associated with any procedure, including AF ablation, generally decrease as the experience gained, this was not demonstrated in a high-volume

center: while the overall complication rate fell in a 10-year period from 11.1% to 1.6%, the incidence of stroke and TIA remained unchanged. Thromboembolic events typically occur within 24 hours of the ablation procedure, with the high-risk period extending for 2 weeks thereafter. Importantly, stroke is a significant cause of periprocedural death during AF ablation: an international survey on AF ablation in 162 centers reported details of 32 deaths in 32,569 patients. The fatal outcome was attributed to stroke in 5 (16%) of these 32 cases. On the other hand, patients who survive a stroke associated with AF ablation often have a favorable long-term prognosis. During a mean 38-month follow-up of 26 patients who suffered AF ablation-related stroke in a high-volume center (2 patients died), complete long-term functional and neurocognitive recovery was documented in most patients, irrespective of the severity of the periprocedural stroke.

1.2. Background of our research:

Manifest stroke and TIA are among the most fearful adverse events during transcatheter ablation for AF, with an occurrence rate of around 1%. Recent data suggest, that clinically apparent cerebral ischemia is only the “tip of the iceberg” as silent ischemic lesions can be demonstrated by diffusion-weighted cerebral MRI in a much higher proportion of the patients undergoing LA ablation.

Importantly, a significant correlation has been demonstrated between the incidence of these cerebral lesions and the ablation technology used: circular multipolar phased radiofrequency (RF) ablation has consistently been associated with the highest incidence of new lesion formation, in up to 37% of the procedures, while cryoenergy seems to be the safest technique.

Real-time assessment of the thromboembolic risk during LA ablation with the potential to guide energy delivery, thereby improving procedure safety, is intriguing. Two methods have been used so far for this purpose: the monitoring of microbubbles on intracardiac echocardiography (ICE) and the detection of microembolic signals (MESs) in the cerebral arteries by transcranial Doppler (TCD).

The titration of RF energy based on the intensity of microbubble formation during LA ablation was first proposed by Kilicaslan et al. and has become routine practice in many centers. Limited data are available on the number of MESs during LA ablation for AF. In a recent report, significantly more MESs were detected with the use of irrigated RF energy as compared with cryoablations, confirming previous MRI findings, which suggested an ablation technology-dependent risk of non-clinical cerebral ischemia.

However, as of present, there no data are available regarding the composition of these MESs although multifrequency TCD has the ability to discriminate between the solid and the gaseous types. Furthermore, the distribution of MESs during the different stages of AF ablation procedures involving different types of energy and the potential influence of different anticoagulation regimes on the number of MES have not been studied yet. Limited data are available regarding the possible mechanism of the increased thrombogenicity of the PVAC.

2. Aims

1. Comparison of Cryoballon and PVAC with respect to the number of MESs detected by TCD.
2. Assesment of the number of cerebral microemboli during different stages of the procedure.
3. Determination of the percentage of solid and gaseous emboli.
4. Invastiagtion of the impact of different anticaogaulation strategies on MES count.
5. Assesment of correlation between the semiquantitative scale of bubble formation seen on ICE and the number of MESs detected by TCD.
6. Identification of biophysical ablation parameters possibly responsible for the increased thrombogenicity of the PVAC.

3. Methods

The study was approved by the local ethics committee. All patients provided their signed written informed consent prior to inclusion.

3.1 Patients, preparation and ablation procedure:

3.1.1. Transcranial measurement of cerebral microembolic signals during pulmonary vein isolation performed with two single-shot techniques:

Patients undergoing PVI for symptomatic paroxysmal or persistent AF not adequately controlled by at least one antiarrhythmic drug were eligible for inclusion in the study. The exclusion criteria included long-standing persistent AF, hyper- and hypothyroidism, valvular heart disease, heart failure of NYHA class III or IV, a left ventricular ejection fraction $\leq 40\%$, a LA diameter exceeding 50 mm, a LA thrombus, documented carotid stenosis, previous ischemic stroke or TIA, prior cardiac surgery or ablation in the LA, unstable angina or myocardial infarction within the last 3 months, severe chronic obstructive pulmonary disease, known bleeding disorders, contraindication to oral anticoagulation and pregnancy.

After inclusion, patients were randomized into 3 different treatment groups: PVI with a CB catheter and the intraoperative administration of heparin to reach a minimum activated clotting time (ACT) level of 250 s according to the Venice Chart Consensus Protocol on Atrial Fibrillation Ablation (CRYO group); PVI with the PVAC and also the conventional intraoperative anticoagulation protocol (ACT $>$ 250 s) (PVAC group); and PVI performed with the PVAC using an anticoagulation protocol with an ACT target of $>$ 320 s (PVAC high ACT group).

In patients taking oral anticoagulation, the drug was continued and the procedure was performed with an international normalized ratio in the therapeutic range. In all other patients, low molecular weight heparin was started twice daily in a weight-adjusted dose and administered until 12 h prior to the procedure. Transesophageal echocardiography was carried out within 24 h prior to the procedure to rule out the presence of a cardiac thrombus.

All procedures were performed with the femoral vein access. The transseptal sheath was used in the LA and flushed continuously with heparinized saline at a steady rate of 30 ml/h throughout the procedure in order to minimize microbubble generation on ICE. This sheath was used as a guide with either the PVAC or the Cryoballoon catheter. Immediately after transseptal puncture, a 150 IU/kg body weight intravenous heparin bolus was given, followed by a continuous infusion to maintain the predefined minimum target ACT level (250 or 320 s). ACT was always checked prior to the first ablation and every 20 min thereafter. Additional 2000-5000 IU iv boluses of heparin were administered if needed to reach the minimum target ACT level.

A 28-mm balloon was used exclusively in all Cryoballoon procedures. Occlusion of the vein was assessed by means of a hand-held injection of contrast medium through the transseptal sheath. A minimum of two 5-min freezing cycles were applied per PV. PVI was assessed on the basis of signals recorded by the Achieve wire.

During PVAC ablations the position of the electrodes relative to the PV ostium were always confirmed before the first RF delivery by means of selective contrast injection through the transseptal sheath. The PVAC was connected to the GENius™ 14.3 RF generator, which is capable of delivering RF current in different bipolar/unipolar mode ratios to any or all of the five bipolar channels in a duty cycled mode. The target temperature was 60 °C, measured separately for all bipoles. Bipolar/unipolar RF delivery was started at a ratio of 4:1 for each PV and changed to a bipolar/unipolar proportion of 2:1 or 1:1 for a deeper lesion when a sufficient reduction in local electrogram amplitude could not be achieved after multiple RF deliveries. RF energy was applied for 60 s, at least 3-4 times per PV. RF was delivered to all poles during initial applications at each PV. Later, usually after multiple energy deliveries, electrode pairs were selected on the bases of local electrograms. Importantly, any electrode pair that failed to reach at least 50 °C during RF delivery was switched off so as to avoid ineffective energy delivery and thrombus formation due to improper contact at the electrode-tissue interface. Furthermore, when any electrode reached the target temperature while delivering very low power (1-2 W), it was considered a sign of an undesirably strong electrode-tissue contact or a wedge position of the electrode, and energy delivery to that particular electrode was switched off. The endpoint was electrical isolation of all PVs, as confirmed by demonstrating an entrance block.

During the procedure the unipolar:bipolar mode of each energy delivery as well as the number of concomitantly active poles were manually recorded to compare with MES counts.

3.1.2. Effect of different biophysical ablation parameters on MES count during PVAC procedures

Patients undergoing PVI for symptomatic paroxysmal or persistent AF not adequately controlled by at least one antiarrhythmic drug were eligible for inclusion in the study. The exclusion criteria included long-standing persistent AF, hyper- and hypothyroidism, valvular heart disease, heart failure of NYHA class III or IV, a left ventricular ejection fraction \leq 40%, a LA diameter exceeding 50 mm, a LA thrombus, documented carotid stenosis, previous ischemic stroke or TIA, prior cardiac surgery or ablation in the LA, unstable angina or

myocardial infarction within the last 3 months, severe chronic obstructive pulmonary disease, known bleeding disorders, contraindication to oral anticoagulation and pregnancy.

All patients received oral anticoagulation before the PVI, with a target international normalized ratio of 2.0 to 3.0, which was maintained for the procedure.

The technique of PVAC procedures has been detailed in the previous section. during this study the GENius™ 14.4 RF generator was used. The target ACT level in this study was >350sec.

Before the initiation of this study it has been published that there is a possibility of a significant interaction of the current densities in electrode 1 (E1) and electrode 10 (E10) when these are in close proximity evidenced by an impedance drop below 110 Ohms. Simultaneous ED on these poles was therefore attempted only after fluoroscopic assessment of the interelectrode distance, which was considered adequate if the space between E1 and E10 was at least double the usual 3-mm interelectrode distance as assessed from multiple views.

3.2 TCD monitoring:

The middle cerebral arteries (MCA) were bilaterally insonated from transtemporal windows by using a multifrequency Doppler, which insonates simultaneously with 2- and 2.5- MHz frequencies. The system is capable of the automatic online identification of true MESs with a sensitivity of 100% and a specificity of 99.3%, and also of discrimination between gaseous and solid emboli with a specificity of 96.5%.

TCD parameter settings as recommended by the consensus criteria were kept constant during the procedures. The insonation depth was 45-55 mm, the sample volume was 8 mm, and the power was 60-100 mW.

MES counts were collected and evaluated separately during different stages of the procedure as follows:

1. Transseptal puncture: the 30-s period after crossing the interatrial septum with the transseptal needle.
2. PV angiography: contrast injection through the injection port of the CryoCath catheter or the transseptal sheath during PVAC ablation.
3. Energy delivery: from the start to 15 s after the termination of energy delivery
4. The remainder of the procedure: that part of the LA access period during which none of the aforementioned maneuvers were performed.

3.3 ICE monitoring:

ICE monitoring was used in the study that compares the MES counts during the two single-shot ablation techniques.

During each ablation phase, ICE was used for a semiquantitative characterization of the bubble formation by grouping them into three categories based on the bubble density. Isolated bubbles were categorized as “FEW”, those with a continuous but not dense appearance as “MODERATE”, and those with a continuous and dense appearance as “SHOWER”.

3.4 Data collection from the GENius 14.4 generator:

Generator files for each ablation during the procedure were collected. The files included information on the ablation (mode, electrodes enabled), the power for each electrode sampled at 1 Hz, and the temperature for each electrode sampled at 8 Hz. Parameters analyzed off-line for potential correlation with the MES data included the bipolar/unipolar ratio, the average power delivered, the total energy delivered, the number of electrodes on during the ED, the simultaneous use of E1 and E10, the average temperature, and the presence of a temperature overshoot. A temperature overshoot was defined as ≥ 62 °C during the ED, and the integral over 62 °C was calculated as the area under the temperature curve above 62 °C.

For the evaluation of the electrode-tissue contact, two additional metrics were calculated. The respiratory contact failure score was based on the analysis of temperature variability at respiration frequency in order to quantify improper contact attributed to respiratory movements. This score was calculated for each electrode, by filtering the temperature signal and then calculating the power spectrum at the respiration frequency between 10 and 20 breaths per minute. The other parameter was the template deviation score, which compared the actual temperature curve during ablation with an ideal template. The ideal template was created from in vitro results featuring a quick temperature rise with the target temperature of 60 °C reached within 20 seconds, followed by a steady state for the remainder of the ablation. Template deviation was considered negative in the case of a slow rise or if the temperature remained < 60 °C, and positive for a quick temperature rise, and a temperature > 60 °C. Template deviation scores were calculated as the sum of the squared

errors between the real electrode temperature and the ideal template at each time point for each electrode during ED. The score for each RF delivery representing the mean of the electrodes was related to the MES count.

3.5 Statistics

3.5.1. Transcranial measurement of cerebral microembolic signals during pulmonary vein isolation performed with two single-shot techniques:

Data were derived by summing signal counts over the entire intervention, and also for the categories of each investigated factor defined by the ablation stage, whether or not electrodes 1 and 10 were simultaneously operating, and the bipolar-to-unipolar energy ratio. Gaseous and solid signal counts were summed (total signal count). Variables for signal count data were natural log-transformed to improve normality. Multilevel mixed-effects linear regression was used to evaluate the effects of the ablation type and the investigated factors (procedure stage, electrode 1+10 simultaneous operation, bipolar/unipolar ratio) on the total signal count. The number of models and the number of investigated factors fitted were the same, with interaction terms between the ablation type and the factor in each. The models were also adjusted for further variables found to be useful additions due to the consequential improvement of the model fit and/or the elimination of confounding. Fixed effects were expressed as estimated differences in the log-transformed outcome, 95% confidence intervals, and p values. Model checking was based on inspection of the normality of residuals. P values less than 0.05 were interpreted as indicating statistical significance.

For unadjusted descriptive tables of patient clinical characteristics and procedural data, Fisher's exact test was used to compare the three groups in terms of categorical variables: for continuous variables, appearing in these tables, and in the descriptive figure for total signal count, the assumptions regarding normality (D'Agostino's test) and homoscedasticity (Levene's robust test) were checked and analysis of variance was used if both were satisfied; otherwise, the Kruskal-Wallis test was applied.

The statistical package Stata (Stata Corp. 2009, Statistical Software: Release 11. College Station, Tx, USA: Stata Corp LP) was used for statistical analysis.

3.5.2. Effect of different biophysical ablation parameters on MES count during PVAC procedures

Gaseous and solid signal counts were summed (total MES). As bilateral recording of MCA was not possible in all cases, mean MES counts per MCA were calculated, using either the mean of the bilateral counts when both sides were measured, or the unilateral data when only one side was available. To improve normality, signal count data were natural log-transformed, and ablation parameters were transformed by using whichever formula (square, square root or natural log) provided the closest fit to a normal distribution.

Relationships between ablation parameters and total MES count were descriptively quantified using unadjusted Pearson's correlation coefficients (r) as a first approach. For in-depth analysis multilevel mixed-effects linear regression was used to evaluate the effect of ablation parameters on the total MES count. Models were adjusted for total energy delivered and average temperature. Interaction terms were used to assess effect heterogeneity across levels of potential effect-modifying factors. Fixed effects were expressed as estimated differences in the log-transformed outcome, 95% confidence intervals, and p values. Model checking was based on inspection of the normality of residuals.

Applications were excluded from the analysis if temporary signal problems on the TCD occurred. Additionally, energy delivery sessions interrupted earlier than 40 seconds were excluded from the respiratory contact failure, the template deviation and the number of active electrodes analyses.

p values less than 0.05 were interpreted as indicating statistical significance.

4. Results

4.1. Transcranial measurement of cerebral microembolic signals during pulmonary vein isolation performed with two single-shot techniques:

4.1.1. Patient characteristics:

A total of 34 patients who participated in 35 procedures were enrolled in this study. There were no significant differences in the baseline characteristics (age, gender, type of AF, CHADS2 score, left ventricular ejection fraction, left atrial diameter, periprocedural INR).

4.1.2. Procedural data:

The total procedure time, the total fluoro time and the total energy delivery time were significantly longer in the CRYO group than in the PVAC groups. The mean ACT values also differed significantly in the three treatment groups according to the predefined protocol. No procedure-related complication was encountered in any patient.

4.1.3. MES count:

As bilateral insonation of the MCA could not be achieved in all patients for technical reasons, MES counts were based on TCD recording of 16,22 and 23 arteries in the CRYO, PVAC and PVAC high ACT treatment groups, respectively. Mean MES counts per patient were calculated using either the mean of the bilateral counts when both sides were measured, or the unilateral data when only one side was available. Cerebral MES count was significantly lower in the CRYO group as compared with the two PVAC groups ($p=0.0005$). No statistical difference was found between the two PVAC groups at this sample size ($p=0.1419$).

As regards the MES count during the different stages of the procedure, a relatively even distribution of embolus formation was found across the whole LA access time with CB, whereas the embolus formation was concentrated in the energy delivery period with PVAC. The statistically significant difference seen in the total MES count could therefore be attributed to the difference during energy delivery.

Fewer than 20% of all microemboli were categorized as solid in all three groups. This ratio was constant across the different stages of the procedure.

Two ablation parameters potentially influencing the MES counts during the PVAC procedures were also analyzed: RF delivery with different bipolar/unipolar ratios, and the use versus the avoidance of simultaneous energy delivery on PVAC electrodes 1 and 10. The latter was a significant predictor for a higher MES count in the normal-ACT PVAC group ($p=0.036$), but the bipolar/unipolar ratio did not influence MES formation.

4.1.4. Correlation between ICE and MES count:

A significant correlation was found between bubble formation on ICE and the generation of MESs in all three groups during the procedure ($p<0.001$). Bubble formation on ICE required a critical amount of MESs, and was not sensitive to detect infrequent microembolization.

4.1.5. Miscellaneous observations:

A shower of bubbles on ICE mostly appeared 5-10 s after RF delivery had been started. The onset of the shower of bubbles was followed by bursts of MESs, usually 5-10 s later. The gradual decrease and disappearance of the MESs and bubbles was usually observed within 10-15 s after the termination of energy delivery. Catheter manipulation, and especially rotation, during this period often resulted in a new burst of microemboli detected by both techniques. Switching off poles that did not reach the target temperature during RF delivery did not result in an apparent change in the degree of microembolus generation. However, in those rare instances when PVAC electrodes were dislodged from the ostium deeper into the PV, a rapid rise in temperature with low delivered power (1-2 W) was usually observed, indicating an excellent contact or a poor cooling effect from the blood. An abrupt and very marked microembolization was also observed in the majority of these cases, prompting an immediate termination of RF delivery.

During Cryoballoon procedures, a burst of MESs was usually observed after the balloon had deflated following the application.

4.2. Effect of different biophysical ablation parameters on MES count during PVAC procedures:

A total of 834 RF application sessions were performed during phased RF ablation with the PVAC in 48 patients. All patients had an INR value above 2.0 confirmed on the day of the procedure. 6 patients had values slightly above 3.0 but below 4.

The number of concomitantly active electrodes during ED was found to increase the MES count significantly (Pearson Correlation Coefficient $r=0.252$, adjusted $p<0.0001$). Accordingly, increase of the total energy delivered to all active poles correlated with an increase in MES count (Pearson Correlation Coefficient $r=0.340$, adjusted $p<0.0001$).

RF energy was delivered simultaneously on E1 and E10 in 285 instances with an impedance drop below 110 Ohm observed in 3 cases. Concomitant use of E1 and E10 resulted in significantly higher MES counts than in ablations where these two poles were not coactive (mean MES per patient 36.3 SD:51.4 vs. mean MES 23.8 SD:38.3 Pearson Correlation Coefficient $r=0.160$, adjusted $p<0.0001$).

Both lower average temperatures (in the range 45-55 °C) and a higher temperature integral over 62 °C resulted in an increased MES count (Pearson Correlation Coefficient $r=0.257$, 0.145, respectively, adjusted $p<0.0001$). Moreover, higher temperature

integrals over 62 °C were found in those ablations where the average temperature was in the range 45-55 °C.

Positive template deviation scores did not affect the MES count (Pearson Correlation Coefficient $r=0.110$, adjusted $p=0.342$). Negative template deviation scores were associated with an increase in MES count (Pearson Correlation Coefficient $r=0.323$, adjusted $p<0.0001$). Higher respiratory contact failure was associated with higher MES count. (Pearson Correlation Coefficient $r=0.165$, adjusted $p=0.0002$), while an inverse relationship was found between the respiratory contact failure score and the average temperature (Pearson Correlation Coefficient $r=0.389$, adjusted $p<0.0001$).

No significant relationship was found between the MES count and the bipolar/unipolar ablation mode: mean MES per patient: 26.7 SD:43.6, 28.2 SD:44.3 and 25.2 SD:28.37 were found during EDs with 4:1, 2:1 and 1:1 bipolar:unipolar modes, respectively (Pearson Correlation Coefficient $r=0.051$, adjusted $p=0.35$).

5. Discussion

The clinical significance of silent cerebral lesions demonstrated by diffusion-weighted MRI studies is currently unknown. Recent data indicate that the majority of them are only transient phenomena with a clear tendency to disappear within a few weeks, especially those with small diameters.

Although cerebral MRI studies were of utmost importance in drawing attention to the entity of subclinical cerebral ischemia, its recognition after ablation is too late for the individual patient. The real-time monitoring of embolic traffic in the brain might be a useful approach if backed up by more clinical data. Kilicaslan et al. first reported on the MES count detected by TCD during point-by-point pulmonary antrum isolation with the use of non-irrigated RF catheters. They demonstrated that cerebral microembolization occurs during all PVI procedures. Moreover, an unexpectedly high number of cerebral microemboli was found as compared with those seen during cardiac surgery. Additionally, a significant correlation was demonstrated between the occurrence of manifest stroke and the number of MESs detected during the ablation procedure. Importantly, that study also proved the correlation between the MES count and the degree of microbubble formation on ICE. Similar data regarding the potential clinical significance of MES generation during CB ablation have not been published. Two other studies reported on cerebral microembolization detected by TCD

during different AF ablation approaches recently. In concordance with the MRI data, the number of MESs in these studies was dependent on the ablation technology.

For the first time to our knowledge, our study has also provided data regarding the composition of these microemboli by demonstrating that the majority of them are gaseous, solid particles occurring in less than 20% of them regardless of the technology and the anticoagulation scheme used. Although not supported by scientific evidence, it is a general belief that gaseous emboli are less harmful than solid particles. However, with similar proportions of solid MESs in the three treatment groups the absolute number is significantly higher during PVAC ablation. Importantly, none of our patients sustained a clinical stroke or TIA.

We found significant differences between Cryoballoon and PVAC ablation in the temporal distribution of microembolus formation throughout the whole LA access time. The even distribution with Cryoballoon technology suggests that catheter manipulation, inflation and deflation of the balloon, and contrast injections into PVs are mainly responsible for MES generation. In contrast, the majority of MESs during PVAC ablation were recorded at the time of energy delivery: microemboli usually appeared in large quantities 10-15 s after RF delivery had been started. While RF delivery with different bipolar/unipolar ratios did not influence MES formation, simultaneous RF delivery on PVAC electrodes 1 and 10 was a significant predictor for a higher MES count in the normal ACT PVAC group. The likely explanation for this finding is a reduced interelectrode distance or electrode overlap due to anatomical constraint of the PVAC loop arguing for a careful assessment on fluoroscopy or even routine avoidance of simultaneous RF delivery on poles 1 and 10.

Similarly to our findings, a significant correlation was reported between the quantity of MESs and the degree of bubble formation detected by ICE, the latter being used as a guide for power titration. An important difference between point-by-point RF and PVAC ablation, however, is that the power can not be adjusted with the GENius ablator; indeed, the power management is entirely automatic, with no opportunity for the operator to exert control. Similar data regarding the potential clinical significance of MES generation during Cryoballoon ablation have not been published.

The use of different ACT targets for intraprocedural heparinization did not result in a statistically significant impact on the MES count in this relatively small group of patients.

The potential benefit of a more aggressive anticoagulation protocol needs to be assessed in larger-scale studies although its impact on the mostly gaseous microemboli is questionable.

Although several clinical and procedural predictors of both manifest and silent cerebral embolization have been identified, the direct correlation between thrombus formation and the biophysical parameters during RF ED in the LA is poorly understood. Our data, collected at a high sampling rate from the GENius 14.4 generator with simultaneous recording of MESs during PVI, provide information on multiple aspects of cerebral microembolization.

The E1-E10 interaction is the only known predictor of new lesions on DW MRI after a phased-RF ablation. Furthermore we recently demonstrated that the number of microemboli detected by TCD during PVI was higher on the concomitant use of E1-E10. This is probably due to a reduced interelectrode distance or electrode overlap when the PVAC loop is compressed which may result in an increased local current density and thereby increased MES production. Significantly higher MES counts with coactive E1 and E10 were also demonstrated in this study, despite a careful fluoroscopic assessment of the electrode positions. We propose two possible explanations: (a) the E1-E10 interaction was due to catheter displacement resulting in a shortened E1-E10 distance during the ablation; (b) the E1-E10 combination was used almost exclusively when most of the electrodes were also enabled, resulting in a higher total energy delivery which was an independent predictor of MES production in this study. Importantly, an impedance drop below 110 Ohms, considered an indication for E1-E10 interaction by Wieczorek et al occurred in a negligible number of energy deliveries in our study.

A specific feature of duty-cycled ablation with the PVAC is RF delivery with different bipolar/unipolar mode ratios. A study by Haines et al. revealed significantly lower MES count and microembolic volume with the unipolar mode than with any of the ED modes with a bipolar component. The unipolar mode was not used in this study and, in accord with our previous results, no significant difference in the MES count was found during ED in 4:1 vs. 2:1 mode.

Intermittent contact has also been proposed as a potential mechanism of embolus formation during ED. This appears to be the first investigation of the role of improper tissue-catheter contact in microembolus production during RF ablation. It is known that lower average temperatures achieved with a non-irrigated catheter usually indicate an improper electrode-

tissue contact, and higher power is necessary to achieve the target temperature in these instances. Moreover, in the event of intermittent contact, the power increase during the off-contact period can lead to a temperature overshoot once better tissue contact is established. We therefore evaluated the average power, average temperature and temperature integral over 62 °C as indicators of the electrode-tissue contact. To further characterize the contact during ED, a template deviation score was used to quantify the difference between an ideal and the real temperature. As contact problems may relate to respiration, a respiratory contact failure score was also calculated to analyze the temperature variability at the respiration frequency. All of these metrics demonstrated a significant correlation with embolus formation: a lower average temperature (45-55 °C), a higher average power, a higher temperature integral over 62 °C, a higher template deviation score and a higher respiratory contact failure score were independent predictors of an increased MES count. Of note, all ablation procedures were performed under conscious sedation in this study. Ventillation under general anesthesia might result in different respiratory variability and MES count.

Contact becomes especially critical when multipolar ablation catheters are used. It is important, that the simultaneous attainment of sufficient electrode-tissue contact on multiple poles, with either a circular or a linear arrangement, may not be feasible in the majority of cases due to the complex anatomy. Modifications in the power handling of the RF generator to ensure a gradual and limited increase during temporary no contact scenarios, which has been implemented in the most recent software version of the GENius generator may prove to be useful to avoid high-temperature peaks when better contact is reestablished. Another, although technically ponderous strategy which could be beneficial is the incorporation of contact force sensors in these electrodes thereby enabling the assessment of contact before an electrode is selected for RF delivery. Moreover, the overall delivered energy is necessarily higher with simultaneous ablation on multiple electrodes, and our data reveal that the higher the total energy delivered, the greater the number of emboli. It could be argued, however, that, with the longer lesion created by applying RF to multiple poles, fewer ED sessions are required. However, it is unknown whether the total MES count itself is related to the thrombogenic potential of the ablation procedure, or whether the intensity of MES formation (the MES count in a given time) is also of importance.

To evaluate the clinical relevance of our results longitudinal assessment of the cognitive function seems justified in these patients.

6. Summary

The summary of our research investigating Cerebral microembolization during pulmonary vein isolation performed with the circular multipolar radiofrequency catheter was given in this thesis. Our new observations:

1. Procedures performed with the previous version of the GENius generator, GENius 14.3 were associated with a significantly increased MES count as compared to Cryoballoon procedures. The different level of intraprocedural heparinization did not affect the MES count during PVAC procedures
2. While during Cryoballoon ablations an even distribution of microemboli generation was seen between different stages of the procedure, the MES formation in case of PVAC procedures was concentrated to the energy delivery period.
3. 80% of detected microemboli were gaseous in nature with both ablation techniques.
4. An excellent correlation was found between the semiquantitative scale of bubble density seen on ICE and the number of MESs detected by TCD.
5. The analysis of ablation parameters from the GENius 14.4 generator proved that both the total energy delivered and the number of concomitantly active electrodes correlated with the MES count.
6. Simultaneous use of E1 and E10 in case of PVAC procedures was associated with an increased MES generation despite a careful fluoroscopic assessment of a proper interelectrode distance between them.
7. All parameters related to an improper or intermittent tissue-catheter contact, including average temperature, temperature overshoot, negative template deviation score, respiratory contact failure score, were independent predictors of MES formation.

7. In extenso publication of the author



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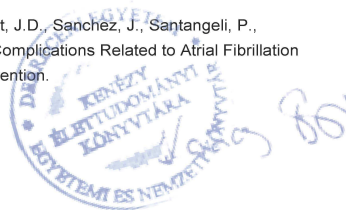
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List of publications related to the dissertation

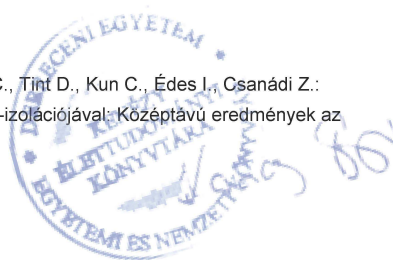
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Total IF of journals (all publications): 17.863

Total IF of journals (publications related to the dissertation): 10.992

The Candidate's publication data submitted to the Publication Database of the University of Debrecen have been validated by Kenezy Life Sciences Library on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

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