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Increased number of cerebral emboli during percutaneous endocardial pulmonary vein isolation versus a thoracoscopic epicardial approach

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Abstract

Objective: Pulmonary vein isolation (PVI) using ablation energy appears an effective treatment for atrial fibrillation (AF) with a success rate of approximately 80%. However, post-procedural neurological complications still occur in 0.5—10% of all patients undergoing PVI, presumably due to embolism. Therefore, we investigated the occurrence of cerebral micro-embolic signals (MES) as a surrogate marker for the risk of neurological impairment of two different PVI methods: (1) percutaneous endocardial radio-frequency (RF) ablation and (2) thoracoscopic epicardial ablation using RF energy. **Methods:** Ten patients (eight persistent AF and two paroxysmal AF) underwent a minimally invasive thoracoscopic epicardial (EPI) RF ablation and 10 patients (one persistent AF and nine paroxysmal AF) underwent a percutaneous endocardial (ENDO) isolation. Transcranial Doppler (TCD) was used to detect an MES in the middle cerebral arteries. **Results:** An average of 5 (±6) MES were detected during epicardial PVI procedure versus 3908 (±2816) MES during percutaneous endocardial PVI procedure. During the ablation application period, respectively, 1 (±1) and 2566 (±2296) cerebral MES were detected. **Conclusions:** Cerebral micro-emboli during epicardial ablation are almost absent when compared to the thousands of emboli measured during percutaneous endocardial ablation.

Keywords: Transcranial Doppler; Cerebral emboli; Pulmonary vein isolation; Ablation

1. Introduction

Atrial fibrillation (AF) is a common, potentially disabling, disease, with an increasing incidence as the population ages and an incremental risk factor for death and stroke [1]. Standard treatment options for AF are anti-arrhythmic drugs and pulmonary vein isolation (PVI). The PVI procedure has become a routine treatment for AF whereby an ablation energy source can be applied endocardially or epicardially around the pulmonary veins by a percutaneous or surgical approach [2,3]. Catheter endocardial PVI procedures are efficacious providing a ±80% success rate in terms of AF treatment with multiple procedures. One of the complications of PVI, however, is the occurrence of cerebro-embolic events, which occurs in 0.5—10% of the catheter endocardial PVI patients [2,4—9]. The occurrence of emboli in the cerebral vessels is the main cause of these complications. Although a single intravascular measured micro-embolic signal (MES) in itself is not accompanied by clinically relevant symptoms, several publications suggest a correlation between the number of cerebral MES and neurological impairment or even stroke [4,10—12]. We examined the number of cerebral MES as a surrogate marker for the risk of neurological complications during commonly used (1) catheter-based percutaneous endocardial (ENDO) PVI procedure and (2) a recently developed minimally invasive video-assisted thoracoscopic epicardial (EPI) PVI approach on a beating heart. The latter procedure uses a bipolar radio-frequency (RF) ablation device, which can reliably create bilateral lesions around the atrial cuff of the right and left pulmonary veins. The purpose of this study is to compare both PVI methods concerning cerebral MES. A different frequency of cerebral MES in the PVI procedure might indicate a different risk of neurological complications.

2. Material and methods

2.1. Patients

Between August 2007 and February 2008, 21 patients suffering from paroxysmal or persistent AF undergoing PVI

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were included. All patients were assigned for PVI by their attending physician after unsuccessful treatment with anti-arrhythmic drugs. If a focal isolation seemed sufficient a percutaneous endocardial PVI (ENDO group) was performed. If more ablation lines were likely to be required, a minimally invasive thoracoscopic epicardial PVI (EPI group) was chosen. Exclusion criteria consisted of the presence of a thrombus in the left atrial appendage (LAA) and a left ventricular ejection fraction <30%. The present study did not influence the decision regarding which ablation technique was used in a given patient.

2.2. Procedure

The investigation was approved by the Human Research and Ethics Committee of the University Hospital Maastricht, The Netherlands.

2.3. ENDO PVI approach

All patients started taking oral anticoagulants for a minimum of 4 weeks until 2 days before the start of the procedure, followed by subcutaneous fractionated heparin until the day of the procedure. Trans-oesophageal echocardiography (TEE) was performed 24—48 h before the procedure to rule out the presence of an intra-cardiac thrombus and to identify the possible presence of a patent foramen ovale (PFO). All ENDO PVIs were performed under local anaesthesia. Two diagnostic catheters were positioned through the femoral veins into the coronary sinus and at the His-bundle region, respectively, as a reference for the ENSITE system (St. Jude Medical, Minnetonka, MN, USA). One steerable multiplex electrophysiologic LASSO (12 mm—15 mm—20 mm) catheter (Biosense Webster, Diamond Bar, CA, USA) and an RF ablation catheter (Safire 4 mm bi-directional (St. Jude Medical, Minnetonka, MN, USA) were positioned at the orifice of the different veins. Placement in the left atrium was performed by means of a trans-septal puncture. If a PFO was present, no trans-septal puncture was required. The introducers were continuously flushed to prevent the formation of thrombi on the tip of the catheter. At this stage, heparin was injected and the activated clotting time (ACT) was kept above 350 s during the remaining procedure. Ablation was performed at the atrio-venous junction at sites showing the earliest PV potentials. The maximum power and temperature limit for RF ablation was set on 30 W and 55—60 °C. RF energy applications were repeated to achieve total elimination of PV potentials. All patients underwent 24-h Holter monitoring at their 3- and 6-month follow-up.

2.4. EPI PVI approach

Oral anticoagulation was halted in all patients 3 days before ablation followed by subcutaneous fractionated heparin until the procedure. All epicardial ablation procedures were performed by means of a minimally invasive thoracoscopic approach on a beating heart by the same cardiac surgeon (MLM) [13]. The EPI intervention was performed under complete anaesthesia using three right-sided thoracoscopic ports. This procedure has been described extensively elsewhere [8,9]. In short, the procedure is conducted after achievement of general anaesthesia administered with a double-lumen endotracheal tube. TEE is performed in the operating room to verify the absence of a left atrial thrombus before the start of the procedure and adequacy of LAA excision at the end of the procedure. The right pulmonary veins are accessed first by an articulated lighted dissector (AtriCure Inc., Cincinnati, OH, USA). Next, the bipolar clamp is introduced through the port incision. This bipolar RF clamp (Isolator, AtriCure Inc., Cincinnati, OH, USA) is used to achieve linear, transmural ablation lesions. Bipolar RF energy is applied to electrically isolate the pulmonary veins; three overlapping lesions are created to ensure isolation. When the conductance of the tissue decreases to less than 0.0025 S, typically after 8 s, an audible signal is automatically generated to indicate transmurality of the lesion. The technique is repeated on the left side with the addition of division of the Marshall ligament. As on the right side, the bipolar clamp is positioned into place to ablate the left atrial cuff adjacent to the left pulmonary veins. After completion of the energy applications, electrical isolation was checked by pacing on the left atrium near the right superior pulmonary vein. All patients underwent 24-h Holter monitoring at their 3- and 6-month follow-up.

2.5. Transcranial Doppler (TCD) monitoring

TCD is the standard non-invasive monitoring technique for the detection of MES in the cerebral circulation. TCD (PMD 100, Spencer Technologies, Seattle, USA) was used to monitor both the middle cerebral arteries (MCAs) through the temporal bone windows for MES using two 2-MHz probes, fixed with a headband (Marc 600, Spencer technologies, Seattle, USA). The probes were installed after the patient was positioned for the PVI procedure. They were monitored continuously from 30 min 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 to the guidelines of the consensus committee [14].

2.6. Statistics

Mann—Whitney *U* tests (SPSS, version 12.0, SPSS Inc., Chicago, IL, USA) were used to compare the EPI group ($n = 10$) with the ENDO group ($n = 10$). A p-value <0.05 was considered statistically significant. Data are expressed as mean ± SD (standard deviation) unless stated otherwise.

3. Results

Table 1 represents pre- and postoperative patient's characteristics of both the groups. In Table 2 the amount of detected cerebral MES of both the PVI groups are shown. No cerebral vascular attacks (CVAs) were observed peri- and post-procedurally. One patient was excluded from this study, because no TCD monitoring was possible.

Table 1
Patient's characteristics in the EPI group and in the ENDO group.

	EPI	ENDO
N	10	10
Male (*n*)	7	9
Age (±SD)	53 (±11)	54 (±13)
PAF/persistent AF	2/8	9/1
PFO	1	3
Previous TIA	1	–
Previous percutaneous ablation	4	2
Post operatively (months)	6 (±2)	7 (±2)
Post in sinus rhythm	10	9
Post in PAF	0	1
Post in persistent AF	0	0

PAF: paroxysmal atrial fibrillation, PFO: patent foramen ovale, and TIA: transient ischaemic attack.

3.1. ENDO PVI approach

In the 10 patients, an average of 34 (±14) applications with a mean of 33 (±5) s per application resulted in 22 (±10) min of actual ablation time in this patient group. The total procedural time was 257 (±72) min.

3.2. EPI PVI approach

In all 10 patients, an average of 6 (±2) RF energy deliveries, with an average of 15 s, was performed. The total procedural time was 135 (±42) min.

3.3. Number of emboli

A total number of 5 (±6) cerebral MESs were detected during the EPI procedure. The average number of cerebral MES during manipulation was 4 (±5) and during the total duration of ablation applications 1 (±1).

A total number of 3908 (±2816) cerebral MES were detected during the ENDO procedure, of which the most of them occurred during the RF ablation applications 2566 (±2296) as shown in Table 2.

4. Discussion

Both epicardial and percutaneous endocardial PVI procedures generate emboli. However, the number of cerebral MES detected during both the PVI procedures differs significantly (Table 2). The EPI procedure induces scarcely cerebral MES compared to the abundant MES during the ENDO procedure.

4.1. Causes of emboli

Several interventions or manipulations can be identified, which may explain the cause and the differences in occurrence of cerebral MES during the EPI and ENDO PVI method.

(i) ENDO PVI method

During the ENDO PVI approach, air can enter the systemic circulation during insertion, manipulation and flushing of introducers or catheters. In this study, 332 (±193) cerebral MES were detected prior to the first energy application, which represents 8% of all the MES detected during the whole ENDO procedure, as shown in Table 2. When applying ablation energy on the endocardial wall of the ostia of the PV, the cardiac endothelium is damaged; this may lead to platelet adhesion and activation, thus resulting in clot formation [15]. Another cause of emboli during the applications could be linked to high temperatures. To accomplish PV isolation interface temperatures can rise up to 100 °C [16,17]. This high temperature may cause denaturation of proteins and formation of thrombi in the blood and can also cause electrolytic phenomena creating gaseous emboli into the systemic circulation [16,17]. The generation of thrombi and gas bubbles during the ablation applications are known to be associated with endocardial ablation procedures. Thrombus formation on the surface of the catheters (i.e., char formation) is another possible source of emboli [18]. These emboli can be released from the catheter surface during manipulation.

(ii) EPI PVI method

In the EPI PVI approach there is no invasion of major blood vessels, and the ablation catheter is positioned epicardially around the pulmonary veins. No intravascular emboli can be injected into the systemic circulation. Nevertheless, the positioning procedure of the RF clamp could theoretically release small parts of atheroma due to palpation of the heart [19]. The few cerebral MES detected during this period could be induced by the positioning procedure; however, AF by

Table 2
Number of micro-embolic signals in the EPI group and in the ENDO group.

	EPI (*n* = 10)				ENDO (*n* = 10)			
	PAF (*n* = 2, mean)	Persistent AF (*n* = 8, mean)	Total EPI		PAF (*n* = 9)	Persistent AF (*n* = 1)	Total ENDO	
			Mean	SD (range)			Mean	SD (range)
Total number of cerebral MES	10	7	8	±6	4128	1925	3908	±2816 (872–9971)*
Number of cerebral MES prior to energy application	9	5	6	±5	336	296	332	±193 (41–773)*
Number of cerebral MES during energy applications	1	2	2	±1	2804	426	2566	±2296 (184–7931)*

Mean ± SD, Mann–Whitney comparisons EPI (*n* = 10) versus ENDO (*n* = 10).
* $p < 0.0001$.

itself could be responsible for the generation and migration of thrombi [1,20].

During the energy applications, the blood temperature during the EPI PVI ablation is not likely to increase significantly, as no direct contact between the ablation catheter and the blood occurs. Although accomplishment of transmurality by epicardial ablation could activate a cascade of clotting mechanisms, the damage instigated to the endothelium will be less than that created by the ENDO PVI approach [21] and will most likely not be sufficient to generate micro-emboli. No thrombus has been observed on the endocardial surface of the ablation line in animals [8].

4.2. Clinical relevance

The number of peri-procedural cerebral emboli is correlated with neurological complications such as stroke, cerebral vascular attack, transient ischaemic attack (TIA) and cognitive decline [4,10—12]. Although solid emboli are assumed to cause more (or more permanent) brain injury compared to gaseous emboli, both solid and gaseous emboli are associated with postoperative neurological impairment [4,11,12]. Therefore, the composition of the cerebral emboli should be considered when assigning neurological risk, as suggested by Padanilam [22]. The possible causes and thereby the possible nature of the emboli found in both the ablation techniques are mentioned earlier. Because there is no invasion in the blood vessels during the EPI PVI approach, no air can enter the systemic circulation and all emboli detected in this procedure will most likely be solid, due to manipulation or possible intravascular overheating. The composition of the emboli detected during ENDO PVI could be different depending on the various phases of the procedure. During the period of flushing the catheters will most likely be responsible for introduction of gaseous emboli. The nature of emboli recorded during energy application (66% of the total number of cerebral MESs), and manipulation between the applications in the ENDO PVI (26% of the total cerebral MESs), are not completely understood. Both thrombi [15,18] as gaseous formation [16,17] could occur in both phases. Lickfett et al. [6] demonstrated with diffusion-weighted (DW)-MRI that 10% of the patients treated by a percutaneous endocardial ablation method had cerebral embolic lesions post-procedurally. Kilicaslan et al. [4] showed that by reducing cerebral emboli during percutaneous ablation a reduction of neurological complications could be achieved, suggesting that even without the knowledge of their constitution, the detected emboli during percutaneous ablation are responsible for neurological complications.

The correlation between the number of cerebral emboli during a cardiac procedure and neurological complications is well documented [4,10—12]. A reduction of the peri-procedural number of cerebral emboli results in a reduction of post-procedural neurological complications [4,10,12]. Marrouche et al. [10] and Kilicaslan et al. [4] demonstrated a similar correlation between cerebral micro-emboli and post-procedural neurological complications during ENDO PVI procedures. Our study showed that during the EPI PVI procedure the number of cerebral MES originated can be abolished compared to the abundant number of cerebral MES detected during the ENDO PVI procedure, indicating that the patients undergoing an EPI PVI are potentially less likely to develop neurological complications.

Furthermore, the two PVI approaches in this study are relatively different in procedural aspects. The applied anaesthesia and the use of radiographs are examples, which could be of importance for the choice of treatment. The efficiency of isolation of the pulmonary veins is evidently the main goal of the PVI procedures. The success rate of both ENDO and EPI PVI procedures was not the main focus of this study. The success rates found in this study seem to resemble the success rates found in literature. For the RF bilateral epicardial approach, the previous studies have shown a success rate of 91% [7,8], all the 10 patients treated with the EPI PVI approach in this study had a sinus rhythm after a 5-month follow-up. The success rate of the ENDO PVI method in paroxysmal AF patients in this study is 90%, which is consistent with the previous studies in paroxysmal endocardial catheter approach PVI (75—95%) [2].

4.3. Study limitations

The EPI group mainly exists of patients with persistent AF and the ENDO group of patients with paroxysmal AF. The success rate of both groups is not comparable due to the difference in AF patients, but emboli generation is not influenced by the type of AF and will therefore not influence the result of this study.

The results of this study should be interpreted with caution since the sample size is small. Nevertheless, the difference in the number of cerebral MES between both groups is very large.

Only one percutaneous endocardial ablation catheter was examined in this study. The percutaneous endocardial RF ablation catheter used in this study was the standard catheter used in the Academic Hospital Maastricht. Others catheters could generate a different number of cerebral micro-emboli.

With the current available TCD systems, the nature (gaseous or solid) and size of cerebral emboli cannot be reliably determined. In theory, the relative intensity of the reflected signal of gaseous as compared to solid emboli differs when insonated by different emitting ultrasound frequencies [23]. Yet, the existing dual-frequency transducer cannot accurately discriminate between solid and gaseous emboli [24]. Therefore, no discrimination of emboli was possible in this study. Similarly, no indication of size of emboli can be given due to the fact that a small gaseous embolus could reflect the same level of ultrasound as big solid emboli.

This study examined cerebral MES as a surrogate marker of the risk of neurological complications. Clinical outcome was not investigated in this study. Although a correlation between the number of cerebral MES and neurological complications has been reported in the previous studies, future studies should focus on the clinical impact of the demonstrated difference in cerebral MES in the two examined PVI procedures. In this respect, pre- and post-procedural cognitive examination and/or cerebral MRI scans in a multicentre study is recommended to define the clinical impact of the findings of this study.

4.4. Conclusions

The number of cerebral MES detected during thoracoscopic epicardial PVI can be neglected compared to the abundant number of cerebral MES occurring during percutaneous endocardial PVI. Taking into account the other procedural aspects, and the reported success rate in AF, the minimally invasive thoracoscopic epicardial PVI approach might become a feasible alternative to endocardial catheter PVI procedures.

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