JACC: CLINICAL ELECTROPHYSIOLOGY VOL. ■, NO. ■, 2018

Incidence and Clinical Significance of Cerebral Embolism During Atrial Fibrillation Ablation With Duty-Cycled Phased-Radiofrequency Versus Cooled-Radiofrequency

A Randomized Controlled Trial

Fehmi Keçe, MD,[a] Eline F. Bruggemans, MSc,[b] Marta de Riva, MD,[a] Reza Alizadeh Dehnavi, MD, PhD,[a] Adrianus P. Wijnmaalen, MD, PhD,[a] Tamara J. Meulman, MD,[c] Julia A. Brugman, MSc,[d] Anouk M. Rooijmans, MSc,[d] Mark A. van Buchem, MD, PhD,[c] Huub A. Middelkoop, PhD,[d] Jeroen Eikenboom, MD, PhD,[e] Martin J. Schalij, MD, PhD,[a] Katja Zeppenfeld, MD, PhD,[a] Serge A. Trines, MD, PhD[a]

ABSTRACT

OBJECTIVES The purpose of this study was to randomly compare the incidence of asymptomatic cerebral embolism (ACE) between the second-generation pulmonary vein ablation catheter (PVAC Gold) and the irrigated Thermocool catheter.

BACKGROUND Pulmonary vein isolation (PVI) with the pulmonary vein ablation catheter (PVAC) is associated with ACE. The PVAC Gold was designed to avoid this complication.

METHODS Patients with paroxysmal atrial fibrillation were randomized 1:1 to PVI with the PVAC Gold or Thermocool catheter. Cerebral magnetic resonance imaging was performed in the days before and after ablation and repeated after 3 months in case of a new lesion. Monitoring for microembolic signals (MES) was performed by using transcranial Doppler ultrasonography. Parameters of coagulation were determined before, during, and after ablation. Neuropsychological tests and questionnaires were applied 10 days before and 3 months after ablation.

RESULTS Seventy patients were included in the study (mean age 61 ± 9 years; 43 male subjects; CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category] score 1.6 ± 1.2; international normalized ratio 2.7 ± 0.5; activated clotting time 374 ± 24 s; $p > 0.05$ for all parameters). Procedural duration was shorter in the PVAC Gold group (140 ± 34 vs. 207 ± 44 min; $p < 0.001$). Eight (23%; 7 infarcts) patients in the PVAC Gold group exhibited a new ACE, compared with 2 (6%; no infarcts) patients in the Thermocool group ($p = 0.042$). Median number of MES was higher in the PVAC Gold group (1,111 [interquartile range, 715-2,234] vs. 787 [interquartile range, 532-1,053]; $p < 0.001$). There were no differences between groups regarding coagulation and neuropsychological outcomes.

CONCLUSION PVI with the new PVAC Gold was associated with a higher incidence of ACE/cerebral infarcts and number of MES. Both catheters induced a comparable procoagulant state. Because there were no measurable differences in neuropsychological status, the clinical significance of ACE remains unclear. (Cerebral Embolism (CE) in Catheter Ablation of Atrial Fibrillation (AF) (CE-AF); NCT01361295) (J Am Coll Cardiol EP 2018;■:■-■) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiology, Heart Lung Center, Leiden University Medical Center, Leiden, the Netherlands; [b]Department of Cardio-thoracic Surgery, Heart Lung Center, Leiden University Medical Center, Leiden, the Netherlands; [c]Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands; [d]Department of Neurology & Clinical Neuropsychology, Leiden University Medical Center, Leiden, the Netherlands; and the [e]Department of Internal Medicine, Division of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands. The Department of Cardiology Leiden receives

ISSN 2405-500X https://doi.org/10.1016/j.jacep.2018.11.008

ABBREVIATIONS AND ACRONYMS

ACE = asymptomatic cerebral embolism

ACT = activated clotting time

AF = atrial fibrillation

FLAIR = fluid-attenuated inversion recovery

INR = international normalized ratio

IQR = interquartile range

MES = microembolic signals

MRI = magnetic resonance imaging

PVAC = pulmonary vein ablation catheter

PVI = pulmonary vein isolation

RF = radiofrequency

The pulmonary vein ablation catheter (PVAC; Medtronic, Minneapolis, Minnesota) is a multipolar, non-cooled, duty-cycled radiofrequency (RF) device for pulmonary vein isolation (PVI). Although short procedure times with similar effectiveness compared with cooled point-by-point RF ablation have been described (1), the reported incidence of asymptomatic cerebral embolism (ACE) up to 42% on cerebral magnetic resonance imaging (MRI) raised significant concerns (2-4). Subsequent studies suggested temperature overshoot during intermittent tissue contact and electrical short-circuit between electrodes 1 and 10 as the main causes (5,6). Accordingly, the 9-electrode PVAC Gold was developed to prevent these issues, which led to a 2.1% incidence of ACE (7). This study lacked a control group, however, and the ACE definition did not comply with international consensus (3). Nonetheless, the clinical significance of ACE remains unclear (8,9).

The main purpose of the current study was to randomly compare the incidence of ACE between the PVAC Gold and an irrigated RF catheter. A second goal was to expand the understanding of ACE by analysis of transcranial Doppler and coagulation parameters. The third aim was to evaluate the clinical significance of ACE by using neuropsychological tests.

METHODS

STUDY POPULATION. Consecutive patients referred for a first ablation of paroxysmal, drug-refractory atrial fibrillation (AF) between March 2015 and December 2016 were included and randomized 1:1 to PVI using the PVAC Gold (n = 35) or the Thermocool catheter (Navistar Thermocool, Biosense Webster, Diamond Bar, California; n = 35). Twenty patients with AF (age and education matched) not undergoing ablation served as a reference group for neuropsychological testing (baseline and 3 months). Patients with previous AF ablation, persistent AF, contraindications for MRI, and/or the inability to perform neuropsychological testing were excluded. To avoid bias based on different anticoagulant drugs, we chose to start only vitamin K antagonists in all patients. Patients were maintained on vitamin K antagonists from at least 2 months before until 3 months after the procedure. For their anticoagulant control, all patients were monitored by the regional anticoagulation clinic. Because of the high expertise and structured protocols followed in these clinics, little deviation from the therapeutic international normalized ratio (INR) range is normally observed. All anticoagulation clinics in the Netherlands, in fact, follow the guidelines of the Dutch Federation of Anticoagulation Clinics, which are published in "Kunst van het doseren" (10) and are updated regularly. Data collection was performed by using our electronic patient information system (EPD-Vision). All patients provided written informed consent before study entry. The study was approved by the institutional ethical review board and registered at clinicaltrials.gov (NCT01361295).

ABLATION. Pre-ablation phase. Ablation was performed under continued vitamin K antagonist therapy with a targeted peri-procedural INR of 2.0 to 3.0. Patients were treated under deep sedation with propofol/remifentanil or conscious sedation with midazolam/fentanyl. After venous access, a dose of 5,000 IU of heparin was administered. Single (PVAC Gold) or double (Thermocool) transseptal access was obtained with the needle introduced by using the stylet and under intracardiac echocardiography guidance. Mapping of the left atrium (Thermocool) and pulmonary venography (both groups) was performed. Activated clotting time (ACT) was checked every 30 min after transseptal access and maintained >350 s. Energy delivery was not commenced before ACT was >350 s. **Ablation phase.** For ablation in the left atrium, only ablation lesions to achieve PVI were allowed. For the PVAC Gold, duty-cycled RF energy applications of 60 s (Genius Generator software version 15.1; Medtronic) were delivered in a bipolar:unipolar ratio of either 4:1 (10 W) or 2:1 (8 W) until PVI was achieved. PVI was mainly (99%) performed in the 2:1 energy mode. This method was common practice in our center already

unrestricted research and fellowship grants from Abbott, Boston Scientific, Medtronic, and Biotronik. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

Manuscript received September 10, 2018; revised manuscript received November 1, 2018, accepted November 8, 2018.

with the first-generation PVAC, as in general we often failed to isolate pulmonary veins with the 4:1 energy mode. No touch-ups with a single-tip catheter were performed. For the Thermocool catheter, a point-by-point ablation around both ipsilateral veins was performed until PVI was achieved. RF power was set at 30 to 35 W with a flow rate of 17 to 20 ml/min and a maximum temperature of 43°C for the post-ablation phase. Pulmonary vein isolation (PVI) was confirmed after a waiting period of 30 min, and 5,000 IU protamine was administered before sheath removal. In this study, no additional measures (e.g., adenosine testing) were taken to ensure lesion durability.

CEREBRAL MRI. A cerebral MRI (1.5-T; Philips Medical Systems, Best, the Netherlands) was performed on the days before and after ablation. Hyperintensities on the diffusion-weighted image were identified, and the corresponding apparent diffusion coefficient maps were calculated. In addition, turbo fluid-attenuated inversion recovery (FLAIR) and T2 weighted turbo spin echo sequences were performed. Technical details of the MRI sequences are described in Online Table A. White matter lesions were categorized with the modified Fazekas scale (11). ACE was defined as a new diffusion abnormality on the diffusion-weighted image sequence with an apparent diffusion coefficient reduced map. Cerebral infarcts were defined as positive ACE with a positive FLAIR. Patients with ACE or cerebral infarcts underwent follow-up MRI using the same protocol 3 months later. MRI results were confirmed by 2 independent radiologists.

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY. Transcranial Doppler ultrasonography (2 MHz; DWL Multidop-P, DWL, Sipplingen, Germany) of the right middle cerebral artery was continuously performed from venous access to catheter removal. Raw Doppler signals were recorded as MP3 (Eridol R-09, Roland Corporation, Nakagawa, Japan) for off-line analysis. Microembolic signals (MES) were automatically detected and discriminated from artifacts by using a locally developed MATLAB algorithm (MATLAB R2007b, The MathWorks, Inc., Natick, Massachusetts) (12). Number and concentration of MES (MES per unit of time) were calculated for the entire procedure and according to ablation phase: pre-ablation, ablation (10 s before first RF until 60 s after last RF), and post-ablation.

LABORATORY MEASUREMENTS. Citrated blood samples (2 × 5 ml) were collected the day before ablation (T1), during the procedure before the first RF application (T2), before sheath removal (T3), and the day after ablation (T4). Samples were centrifuged at 2,700 *g* for 10 min at 18°C. Markers of intrinsic and extrinsic coagulation (activated partial thromboplastin time, prothrombin time/INR), fibrin turnover (D-dimer), acute phase markers, and coagulant potential (fibrinogen) were measured directly. Other coagulation parameters were analyzed on frozen -70°C aliquots: von Willebrand factor antigen as a marker of endothelial damage, prothrombin fragment 1 + 2 as a marker of thrombin generation, tissue plasminogen activator as a marker of fibrinolysis, and soluble P-selectin as a marker of platelet activation. Measurements are described in the Online Methods.

NEUROPSYCHOLOGICAL ASSESSMENT. Two weeks before and 3 months after the ablation, patients underwent neuropsychological testing for global cognitive functioning and intelligence level, memory function, attention and concentration, executive functioning, psychomotor speed, and mood. The age and education matched (based on Verhage) (13) reference group underwent the same tests. The tests are described in the Online Methods.

STATISTICAL ANALYSIS. Power analysis was based on the outcome of 3 previous studies (2,4,14) and the results of our pilot study (15). Combining the outcomes of these studies, 56 (39.4%) of the 142 patients reported ACE after PVAC ablation, and 8 (9.8%) of 82 patients reported ACE after cooled-tip ablation. The rate difference was therefore 29.6%, with a required sample size of 64 to detect a difference in ACE with 80% power at a 0.05% probability level (SPSS Sample Power 2.0; IBM SPSS Statistics, IBM Corporation, Armonk, New York). Accordingly, the group size was set to 35. All continuous data were checked for normality with the Shapiro-Wilk or Kolmogorov-Smirnov test and are expressed as mean ± SD or median and interquartile range (IQR), when appropriate. Data were compared by using an unpaired *t*-test or Mann-Whitney *U* test. For categorical data, numbers and frequencies were provided and compared by using a chi-square test or Fisher exact test for low expected count. A mixed linear model with between-subject (group) and within-subject (time) factors was used for the laboratory values and neuropsychological measures. Kaplan-Meier survival curves were constructed (log-rank test) to compare the AF-free survival between the 2 groups. Values of $p < 0.05$ (2-sided) were considered statistically significant. Data were analyzed by using SPSS version 23.

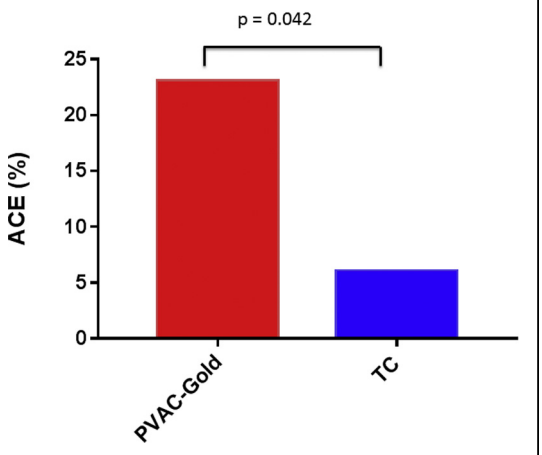
TABLE 1 Baseline Characteristics

	PVAC Gold (n = 35)	Thermocool (n = 35)	p Value
Age, yrs	59 ± 9	62 ± 9	0.157
Male	23 (66)	20 (57)	0.461
BMI, kg/m^2	26.2 ± 3.5	26.9 ± 3.6	0.392
Left atrial diameter, mm	39 ± 7	40 ± 4	0.282
CHA_2DS_2-VASc score	1.6 ± 1.2	1.6 ± 1.3	0.924
ECV last 12 months	8 (23)	12 (34)	0.290
Ejection fraction (>55)	35 (100)	35 (100)	-
Antiplatelet drugs	3 (9)	1 (3)	0.999
Comorbidity			
Hypertension	16 (46)	18 (51)	0.632
Dyslipidemia	14 (40)	11 (31)	0.454
Diabetes	2 (6)	1 (3)	0.999
Coronary artery disease	4 (11)	6 (17)	0.495
CVA/TIA history	6 (17)	5 (14)	0.743

Values are mean ± SD or n (%).

AF = atrial fibrillation; BMI = body mass index; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; CVA = cerebrovascular accident; ECV = electrical cardioversion; PVAC Gold = Pulmonary Vein Ablation Catheter Gold; TIA = transient ischemic attack.

FIGURE 1 Incidence of ACE



Asymptomatic cerebral embolism (ACE) in the Pulmonary Vein Ablation Catheter Gold (PVAC Gold) group (n = 8 of 35) and the Thermocool (TC) group (2 of 35).

RESULTS

BASELINE CHARACTERISTICS. Patients' mean age was 59 ± 9 years in the PVAC Gold group and 62 ± 9 years in the Thermocool group. The groups were predominantly male (66% and 57%, respectively). There were no significant differences in any of the baseline characteristics between the 2 groups (Table 1).

TABLE 2 Procedural Details

	PVAC Gold (n = 35)	Thermocool (n = 35)	p Value
TEE before ablation	1 (3)	6 (17)	0.053
Procedural time, min	149 ± 34	207 ± 44	<0.001
Ablation time, min	28 ± 9	48 ± 12	<0.001
INR day of ablation	2.8 ± 0.6	2.6 ± 0.4	0.066
SR before ablation	30 (86)	28 (80)	0.526
Mean ACT during procedure, s	369 ± 26	378 ± 24	0.118
ACT before energy delivery, s	377 ± 32	370 ± 32	0.280
Minimum measured ACT, s	337 ± 47	348 ± 41	0.286
Total administered heparin during procedure (IU)	8,357 ± 2,095	8,071 ± 2,579	0.613
ECV during procedure	5 (14)	12 (34)	0.051
Deep sedation	29 (83)	29 (83)	0.999
Postprocedural time to MRI, h	25 ± 17	28 ± 19	0.589

Values are n (%) or mean ± SD.

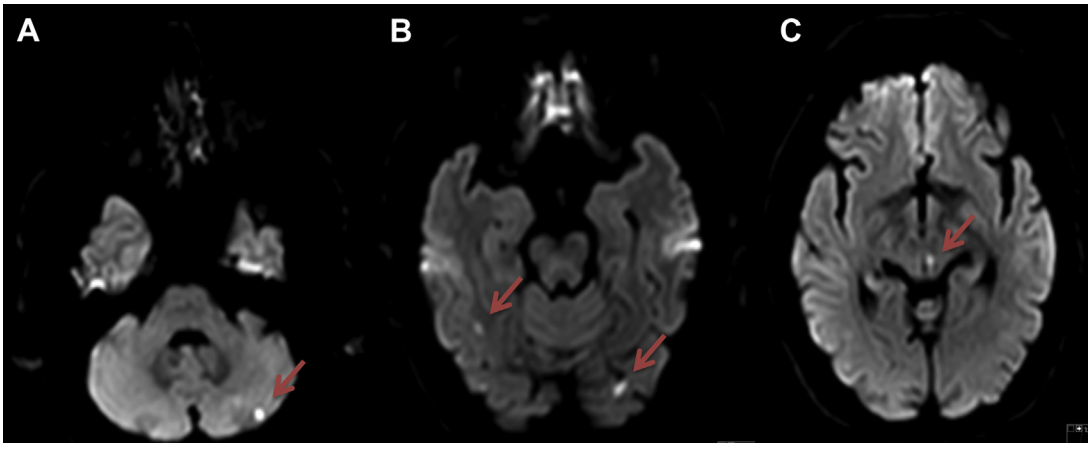
ACT = activated clotting time; INR = international normalized ratio; IU = international unit; MRI = magnetic resonance imaging; SR = sinus rhythm; TEE = transesophageal echocardiography; other abbreviations as in Table 1.

PROCEDURAL DETAILS. Procedure time and RF duration with PVAC Gold were shorter compared with the Thermocool group (Table 2). During the ablation, 99% of the applications were performed in 2:1 bipolar:unipolar mode. The ACT values before electrical cardioversion were always >350 s, except in 1 patient in the PVAC Gold group (327 s).

CEREBRAL EMBOLISM. All patients underwent pre- and post-procedural MRI, and no patients were excluded because of missing data. At pre-procedural MRI, 42 (60%) patients had white matter lesions (25 PVAC Gold-treated patients and 17 Thermocool-treated patients; p = 0.087) with modified Fazekas scores of 0.7 ± 0.6 and 0.7 ± 0.8 (p = 0.725), respectively. Ten patients (5 in each group) had a previous infarction. In 8 patients, the previous infarction was asymptomatic. MRI at a median of 21 h (IQR, 18 to 25 h) after ablation showed 16 new cerebral lesions in 8 (23%) patients (7 patients with cerebral infarction) of the PVAC Gold group compared with 2 ACE in 2 (6%) patients (no cerebral infarction) of the Thermocool group (p = 0.042) (Figure 1). One patient in the PVAC Gold group experienced symptomatic diplopia with corresponding embolism in the nucleus of the oculomotor nerve. The symptoms resolved a few hours after ablation. At follow-up MRI, 6 (38%) of 16 ACE in 4 (11%) patients in the PVAC Gold group but none in the Thermocool group persisted as cerebral infarcts.

Figure 2 shows an example of a patient with 4 cerebral lesions. Details about lesion size and location

FIGURE 2 Diffusion-Weighted Images of a Patient With Several Cerebral Lesions After PVAC Gold Ablation

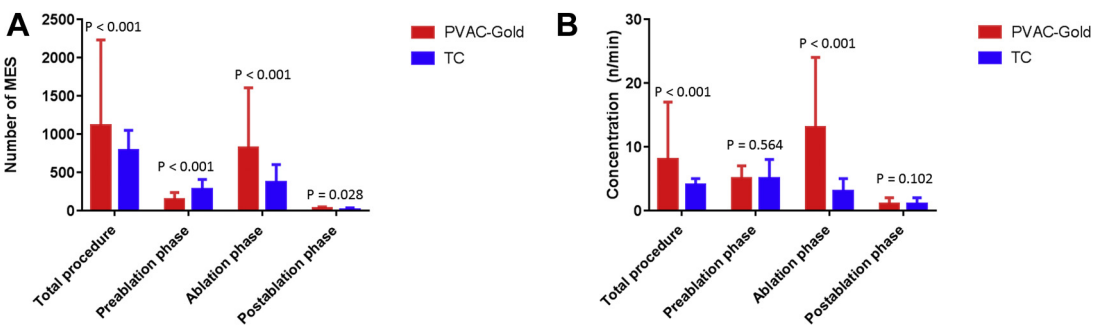


(A) Lesion located in the left cerebellum, **(B)** left occipital and right temporal and **(C)** left midbrain (region of the nucleus of the oculomotor nerve). PVAC Gold = Pulmonary Vein Ablation Catheter Gold.

are described in Online Table B. In the PVAC Gold group, there was no significant difference in the median number of MES between patients with and without cerebral lesions. There was no relation between peri-procedural electrical cardioversion and ACE. The patient who underwent electrical cardioversion with an ACT of 327 s had no cerebral lesion after ablation. There were 9 patients (4 patients in the PVAC Gold group vs. 5 patients in the Thermocool group) with an INR of 1.8 to 1.9 before ablation. However, none of these patients experienced cerebral embolism.

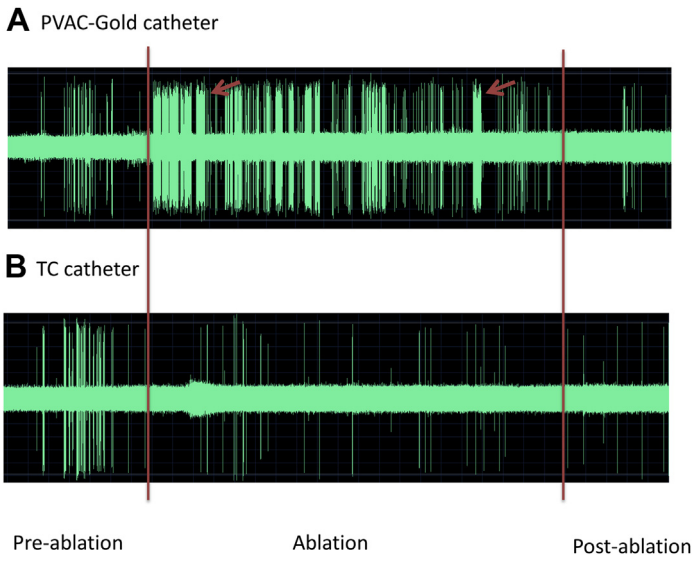
TRANSCRANIAL DOPPLER. The median number and concentration of MES during the total procedure were higher with the PVAC Gold compared with the Thermocool catheter (1,111 [IQR, 715 to 2,234] vs. 787 [IQR, 532 to 1,053], $p < 0.001$, respectively, and 8 [IQR, 5 to 17] MES/min vs. 4 [IQR, 3 to 5] MES/min, $p < 0.001$) (Figure 3). Figure 4 provides an example of procedural MES detection. In the pre-ablation phase, median number but not median concentration of MES was higher in the Thermocool group. In contrast, in the ablation phase, median MES number and concentration were significantly higher in the PVAC Gold group

FIGURE 3 Number and Concentration of MES



(A) Number and **(B)** concentration of microembolic signals (MES) for the PVAC Gold catheter and TC catheter for the entire procedure and per ablation phase. Median and interquartile range are displayed. Other abbreviations as in Figure 1.

FIGURE 4 Example of Transcranial Doppler Recordings



(A) PVAC-Gold. **(B)** Thermocool catheter. The procedure was divided in a pre-ablation, ablation, and post-ablation phase. In the pre-ablation phase, contrast venography and catheter manipulation were associated with MES detection. This was more present in the TC group due to the additional mapping procedure. During the ablation phase, showers of MES (see **red arrows**) were seen with the PVAC Gold during the radiofrequency applications. In the post-ablation phase, low MES numbers were seen for both catheters. Abbreviations as in Figure 1.

(819 [IQR, 509 to 1,608] vs. 354 [IQR, 181 to 593], $p < 0.001$ and 13 [IQR, 7 to 24] MES/min vs. 3 [IQR, 2 to 5] MES/min, $p < 0.001$).

PARAMETERS OF COAGULATION. Ablation with both catheters induced a procoagulant state. This outcome was observed by an increase in D-dimer with no significant difference between the groups (Online Table C). In addition, fibrinogen and prothrombin fragment 1 + 2 were slightly lower during the procedure, whereas von Willebrand factor was elevated post-ablation. No differences in activation of coagulation were observed between the 2 catheters.

NEUROPSYCHOLOGICAL ASSESSMENT. Study group. No significant differences in test performance were observed between the PVAC Gold and the Thermocool groups for all cognitive domains (Online Table D). For both groups, an increase in the Groninger Intelligence Test-2 results and an increase in memory functioning, executive functioning and psychomotor speed as measured with several subtests was observed 3 months after the ablation. Both groups reported significantly better results on the Hospital Anxiety and Depression Scale after 3 months. No significant differences in neuropsychological test results were observed 3 months after the procedure between patients with and without cerebral infarcts.

Reference group. The mean age (60 ± 8 years), sex (70% male), and education level (5.6 ± 1.5, equivalent to Higher Professional Education) in the reference group were not significantly different compared with the combined study groups. No significant differences in neuropsychological test results were found between the reference group and the combined study group (Online Table E).

OUTCOME AND COMPLICATIONS. One-year antiarrhythmic drug-free AF survival was 49% in the PVAC Gold group and 63% in the Thermocool group ($p = 0.229$). In the PVAC Gold group, 1 patient had asymptomatic severe (>70%) pulmonary vein stenosis, and 1 patient had a urinary tract infection. In the Thermocool group, there was 1 tamponade and 1 groin hematoma.

DISCUSSION

To the best of our knowledge, this analysis is the first randomized controlled trial comparing cerebral embolism with the new nonirrigated PVAC Gold catheter and with the irrigated Thermocool catheter. The main findings are that: 1) ablation with the PVAC Gold catheter is associated with a higher incidence of cerebral lesions (23% vs. 6%) and in addition, in the PVAC Gold group, the majority of these lesions were cerebral infarcts compared with none in the Thermocool group; 2) there was a significantly higher number of MES on transcranial Doppler in the PVAC Gold group; and 3) coagulation activity and cognitive functioning did not differ between the groups.

INCIDENCE OF ACE. In the first-generation PVAC, a high incidence of ACE (up to 42%) was reported in several studies (2,3). Investigations revealed a suboptimal ACT, air entrapment during catheter introduction, peri-procedural cardioversion, temperature overshoot during intermittent catheter-tissue contact (6), and electrical interaction between electrodes 1 and 10 as possible causes (16). After implementation of procedural modifications (ACT >350 s, catheter submersion before introduction, and deactivating of electrode 10), ACE incidence was reduced to 1.7% (17). Subsequently, the 9-polar PVAC Gold was developed to prevent temperature overshoot and electrode interaction, which yielded an ACE incidence of 2.1% (7). However, discussions were raised about MRI timing and ACE definition in these studies (3). A positive FLAIR sequence was required for ACE diagnosis although scans were performed 16 to 72 hours'

post-ablation (7,17). Because the FLAIR sequence usually becomes positive after 2 to 7 days, underestimation of the real ACE incidence may have occurred (3). In the current trial, ACE incidence with PVAC Gold was 23%, >10-fold compared with the previous studies. In the PVAC Gold group, in 7 of 8 patients, the lesions were cerebral infarctions, compared to none in the Thermocool group. Although we performed the MRI 21 h (IQR, 18 to 25 h) after ablation, FLAIR positivity was seen in 83% of all lesions. Therefore, MRI timing cannot fully explain the differences found in ACE.

In addition, the total duration of RF delivery was similar to other studies (7,17). However, in this study, 99% of the applications were performed in the 2:1 mode. In previous studies (7, 17), respectively 57% and 67% of the ablations were performed in 2:1 mode, 7% in 1:1 mode, and 36% and 26% in 4:1 mode. Accordingly, the mixture in energy mode may have influenced the results.

At 3 months' follow-up, a lower incidence of cerebral lesions was detected compared with directly post-ablation. In a study with 3-T MRI instead of 1.5-T MRI, the incidence of ACE was doubled to tripled due to the higher spatial resolution, a slice thickness of 2.5 mm instead of 5 mm, and an improved signal-to-noise ratio (18). Because the lesion size of ACE in the current trial was between 3 and 6 mm, and lesions tend to decrease in size during follow-up (14), lesions may have been missed on follow-up MRI.

TRANSCRANIAL DOPPLER. Across the entire procedure, the number and concentration of MES were much higher in the PVAC Gold group. In the preablation phase, however, the Thermocool catheter showed a higher number of MES. In addition to energy delivery, catheter manipulation contributes to the generation of MES (6). The additional mapping procedure before ablation may therefore explain this finding. During ablation, a higher number and concentration of MES were detected with PVAC Gold. In our pilot with the first-generation PVAC and ACT >300 s, we detected a mean MES number of 2,324 ± 1,406 (15), comparable to other reports with relatively high MES numbers with this catheter (8,19). In the current study with ACT >350 s, we still detected a higher number of MES with PVAC Gold compared with the Thermocool catheter. We therefore believe that several factors (energy mode, temperature overshoot, anticoagulation protocol, and aspect of nonirrigation) may contribute to the incidence of ACE in the PVAC Gold catheter.

PARAMETERS OF COAGULATION ACTIVITY. There are no other studies comparing coagulation activity between cooled RF ablation and PVAC. During and after the procedure, we observed a progressive increase in D-dimer levels that reflects fibrin formation and subsequent breakdown of fibrin, suggesting activation of coagulation during the procedure. In addition, a progressive increase of von Willebrand factor antigen was observed, reflecting endothelial damage and/or acute phase response. These observations may indicate that the ablation procedure in itself is prothrombotic. However, no significant differences were observed between the 2 groups. Accordingly, the difference in ACE cannot solely be attributed to the observed changes in the pro-coagulant state. One study comparing PVAC with the cryoballoon catheter also found no significant differences in coagulation activity (20), similar to our results.

CLINICAL SIGNIFICANCE OF ACE. In the current study, 42 (60%) patients had pre-existent white matter lesions and 14% exhibited a previous lacunar infarction. It is known that preexistent white matter lesions can cause cognitive decline (21). However, the additive cognitive effect of new ACE in AF-ablation patients is still a matter of debate. In previous studies, both the presence (9) and absence (8) of negative cognitive effects of ACE have been described. In our study, we detected no decline in cognitive function in patients with and without ACE. It is difficult to determine which numerical decline (whether statistically significant) is also clinically meaningful. There are limited data about cognitive functioning after AF ablation (22). In several studies on other procedures (e.g., after coronary artery bypass grafting), statistical techniques have been implemented to determine "true" (i.e., statistically significant) cognitive decline at the individual level (23). In addition, for major neurocognitive disorder as defined by using international diagnostic guidelines for mental disorders (24), a meaningful decrease in test performance is typically ≥2 SDs below appropriate norms or reference groups (third percentile or below). However, because we did not observe any significant difference but also not a trend toward impaired test results in patients with ACE, we believe that a clinically relevant decline in cognitive function is unlikely. Cerebral location of the lesions between studies may explain the differences in cognitive effects of ACE. Lesion symptom mapping studies have shown that the impact on cognition depends on lesion volume but also on location (25). Lesions in strategic brain regions cause more cognitive impairment. It is more difficult to detect lesions in cortical regions with mechanisms compensating for the

affected neuropsychological function. In our study, most of the lesions were located in the cortical regions of the brain.

ADVERSE EVENTS. In the PVAC Gold group, 1 patient experienced an asymptomatic pulmonary vein stenosis, which was detected during a second procedure. Because this patient underwent re-ablation of both left pulmonary veins, it is possible that the second ablation contributed to the progression of the stenosis. Importantly, it is well known that pulmonary vein stenosis might be underdiagnosed due to the lack of a specific clinical presentation (26) and the absence of systematic screening after ablation. In a cohort of 62 patients using the first-generation PVAC, we also observed mild (25% to 50%) narrowing in 37% of the PVs, a moderate (50% to 70%) narrowing in 9%, and severe narrowing (>70%) in 3% (27). Von Bary et al. (28) reported a detectable narrowing of the pulmonary vein diameter after first-generation PVAC ablation in 23% of the patients.

STUDY LIMITATIONS. This analysis was a single-center study with a relatively small number of patients in each arm. The size of the study sample was calculated based on the estimates of differences in ACE. Strong conclusions regarding the neuropsychological effects of ACE cannot be drawn, and larger trials are required to confirm the results. We have no detailed information available on the INR values and time in therapeutic range for individual patients in the weeks before and after the procedure. Impedance data could have revealed possible interaction between PVAC Gold electrodes; however, impedance data were not available. The final blood sample was taken 1 day after the ablation. Delayed coagulation effects 3 days after the ablation could not be detected. We did not correct ACE and MES for total RF duration or energy because total RF energy data were not available. Differentiation between solid and gaseous MES would widen the scope of transcranial Doppler MES detection. Dual-frequency insonation during transcranial Doppler could have aided in this differentiation. However, despite developments in both signal acquisition techniques and MES classification algorithms, it remains difficult to reliably determine MES composition, especially in clinical settings in which periods with numerous MES may occur. A complete neurological evaluation by a neurologist according to the National Institutes of Health Stroke Scale could have provided more information on the neuropsychological status of patients with ACE. Only 20 patients were included in the reference group for neuropsychological testing. Neuropsychological tests may not have been sensitive enough to detect changes in complex cognitive functions. Long-term effects on cognitive functioning of the new ACE were not studied.

CONCLUSIONS

PVI with the new PVAC Gold is associated with a higher incidence of ACE/cerebral infarctions and a higher number of MES on transcranial Doppler compared with ablation with an irrigated tip catheter. Both ablation technologies induced a similar increase in the procoagulant state. We detected no cognitive decline in patients according to the available test results. Because the purpose of the redesign of the PVAC catheter was to reduce the high incidence of ACE, it can be stated that the improvement of this device was unsuccessful. Therefore, the manufacturer of the PVAC Gold should continue to improve the device.

ADDRESS FOR CORRESPONDENCE: Dr. Serge A. Trines, Department of Cardiology, Heart Lung Center, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, the Netherlands. E-mail: s.a.i.p.trines@lumc.nl.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: ACE is an important complication of AF ablation. The embolic load of noncooled ablation catheters is higher than cooled-RF catheters. In this trial, 23% of the patients undergoing ablation with the PVAC Gold exhibited one or more lesion on MRI, compared with 6% in the Thermocool group. Cognitive functioning was unimpaired, however.

TRANSLATIONAL OUTLOOK: When counseling patients for AF ablation, the risk of cerebral emboli for different catheters should be discussed, and neurological examination should be considered after ablation. The long-term effects of asymptomatic cerebral embolism need to be further evaluated in well-designed studies.

REFERENCES

1. Gal P, Aarntzen AE, Smit JJ, et al. Conventional radiofrequency catheter ablation compared to multi-electrode ablation for atrial fibrillation. Int J Cardiol 2014;176:891–5.

2. Herrera Siklody C, Deneke T, Hocini M, et al. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation: comparison of different atrial fibrillation ablation technologies in a multicenter study. J Am Coll Cardiol 2011;58:681–8.

3. Deneke T, Jais P, Scaglione M, et al. Silent cerebral events/lesions related to atrial fibrillation ablation: a clinical review. J Cardiovasc Electrophysiol 2015;26:455–63.

4. Gaita F, Caponi D, Pianelli M, et al. Radiofrequency catheter ablation of atrial fibrillation: a cause of silent thromboembolism? Magnetic resonance imaging assessment of cerebral thromboembolism in patients undergoing ablation of atrial fibrillation. Circulation 2010;122:1667–73.

5. Haines DE, Stewart MT, Dahlberg S, et al. Microembolism and catheter ablation I: a comparison of irrigated radiofrequency and multielectrode-phased radiofrequency catheter ablation of pulmonary vein ostia. Circ Arrhythm Electrophysiol 2013;6:16–22.

6. Nagy-Balo E, Kiss A, Condie C, Stewart M, Edes I, Csanadi Z. Predictors of cerebral microembolization during phased radiofrequency ablation of atrial fibrillation: role of the ongoing rhythm and the site of energy delivery. Pacing Clin Electrophysiol 2014;37:1436–41.

7. De Greef Y, Dekker L, Boersma L, et al. Low rate of asymptomatic cerebral embolism and improved procedural efficiency with the novel pulmonary vein ablation catheter GOLD: results of the PRECISION GOLD trial. Europace 2016;18:687–95.

8. Kochhauser S, Lohmann HH, Ritter MA, et al. Neuropsychological impact of cerebral microemboli in ablation of atrial fibrillation. Clin Res Cardiol 2015;104:234–40.

9. Schwarz N, Kuniss M, Nedelmann M, et al. Neuropsychological decline after catheter ablation of atrial fibrillation. Heart Rhythm 2010;7:1761–7.

10. Federatie van Nederlandse Trombosediensten. De kunst van het Doseren 2018. Available at: https://www.fnt.nl/kwaliteit/de-kunst-van-het-doseren. Accessed November 22, 2018.

11. Kim KW, MacFall JR, Payne ME. Classification of white matter lesions on magnetic resonance imaging in elderly persons. Biological Psych 2008;64:273–80.

12. Van Dijk A, De Wilde RB, Bruggemans EF. Fundamental tone purity: a powerful parameter for classification of High Intensity Transient Signals in Transcranial Doppler. Biomedizinische Technik 2005;50 (Suppl 1, Part 2).

13. Verhage F. Intelligentie en leeftijd: Onderzoek bij Nederlanders van twaalf tot zevenenzeventig jaar. Assen: Van Gorcum, 1964.

14. Deneke T, Shin DI, Balta O, et al. Postablation asymptomatic cerebral lesions: long-term follow-up using magnetic resonance imaging. Heart Rhythm 2011;8:1705–11.

15. Compier MG, Bruggemans EF, Van Buchem MA, et al. Silent cerebral embolism after PVAC and irrigated-tip ablation for atrial fibrillation: incidence and clinical implications. Results from the CE-AF trial pilot (Abstract). Eur Heart J 2012;33:32.

16. Wieczorek M, Lukat M, Hoeltgen R, et al. Investigation into causes of abnormal cerebral MRI findings following PVAC duty-cycled, phased RF ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2013;24:121–8.

17. Verma A, Debruyne P, Nardi S, et al. Evaluation and reduction of asymptomatic cerebral embolism in ablation of atrial fibrillation, but high prevalence of chronic silent infarction: results of the evaluation of reduction of asymptomatic cerebral embolism trial. Circ Arrhythm Electrophysiol 2013;6:835–42.

18. Haeusler KG, Koch L, Herm J, et al. 3 Tesla MRI-detected brain lesions after pulmonary vein isolation for atrial fibrillation: results of the MACPAF study. J Cardiovasc Electrophysiol 2013;24:14–21.

19. Nagy-Balo E, Martirosyan M, Sandorfi G, et al. Cerebral micro-embolization during pulmonary vein isolation: relation to post-ablation silent cerebral ischemia. Cardiol J 2017;24:234–41.

20. Malmborg H, Christersson C, Lonnerholm S, Blomstrom-Lundqvist C. Comparison of effects on coagulation and inflammatory markers using a duty-cycled bipolar and unipolar radiofrequency pulmonary vein ablation catheter vs. a cryoballoon catheter for pulmonary vein isolation. Europace 2013;15:798–804.

21. Kloppenborg RP, Nederkoorn PJ, Geerlings MI, van den Berg E. Presence and progression of white matter hyperintensities and cognition: a meta-analysis. Neurology 2014;82:2127–38.

22. Fink HA, Hemmy LS, MacDonald R, et al. AHRQ Technology Assessments. Cognitive Outcomes After Cardiovascular Procedures in Older Adults: A Systematic Review. Rockville (MD): Agency for Healthcare Research and Quality (US), 2014.

23. Collie A, Darby DG, Falleti MG, Silbert BS, Maruff P. Determining the extent of cognitive change after coronary surgery: a review of statistical procedures. Ann Thorac Surg 2002;73:2005–11.

24. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. Arlington, VA: American Psychiatric Association, 2013.

25. Biesbroek JM, Weaver NA, Biessels GJ. Lesion location and cognitive impact of cerebral small vessel disease. Clin Sci (Lond) 2017;131:715–28.

26. Edriss H, Denega T, Test V, Nugent K. Pulmonary vein stenosis complicating radiofrequency catheter ablation for atrial fibrillation: a literature review. Respir Med 2016;117:215–22.

27. Compier MG, Leong DP, Marsan NA, et al. Duty-cycled bipolar/unipolar radiofrequency ablation for symptomatic atrial fibrillation induces significant pulmonary vein narrowing at long-term follow-up. Europace 2013;15:690–6.

28. von Bary C, Weber S, Dornia C, et al. Evaluation of pulmonary vein stenosis after pulmonary vein isolation using a novel circular mapping and ablation catheter (PVAC). Circ Arrhythm Electrophysiol 2011;4:630–6.

KEY WORDS asymptomatic cerebral embolism, atrial fibrillation, catheter ablation, cooled radiofrequency ablation, pulmonary vein isolation, PVAC Gold

APPENDIX For supplemental tables and an expanded Methods section, please see the online version of this paper.