Thromboembolic Risks of the Procedural Process in Second-Generation Cryoballoon Ablation Procedures

Analysis From Real-Time Transcranial Doppler Monitoring

See Editorial by Schmidt and Chun

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BACKGROUND: Atrial fibrillation ablation is associated with substantial risks of silent cerebral events (SCEs) or silent cerebral lesions. We investigated which procedural processes during cryoballoon procedures carried a risk.

METHODS AND RESULTS: Forty paroxysmal atrial fibrillation patients underwent pulmonary vein isolation using second-generation cryoballoons with single 28-mm balloon 3-minute freeze techniques. Microembolic signals (MESs) were monitored by transcranial Doppler throughout all procedures. Brain magnetic resonance imaging was obtained pre- and post-procedure in 34 patients (85.0%). Of 158 pulmonary veins, 152 (96.2%) were isolated using cryoablation, and 6 required touch-up radiofrequency ablation. A mean of 5.0±1.2 cryoballoon applications was applied, and the left atrial dwell time was 76.7±22.4 minutes. The total MES counts/procedures were 522 (426–626). Left atrial access and Flexcath sheath insertion generated 25 (11–44) and 34 (24–53) MESs. Using radiofrequency ablation for transseptal access increased the MES count during transseptal punctures. During cryoapplications, MES counts were greatest during first applications (117 [81–157]), especially after balloon stretch/deflations (43 [21–81]). Pre– and post–pulmonary vein potential mapping with Lasso catheters generated 57 (21–88) and 61 (36–88) MESs. Reinsertion of once withdrawn cryoballoons and subsequent applications produced 205 (156–310) MESs. Touch-up ablation generated 32 (19–62) MESs, whereas electric cardioversion generated no MESs. SCEs and silent cerebral lesions were detected in 11 (32.3%) and 4 (11.7%) patients, respectively. The patients with SCEs were older than those without; however, there were no significant factors associated with SCEs.

CONCLUSIONS: A significant number of MESs and SCE/silent cerebral lesion occurrences were observed during second-generation cryoballoon ablation procedures. MESs were recorded during a variety of steps throughout the procedure; however, the majority occurred during phases with a high probability of gaseous emboli.

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Key Words: atrial fibrillation ■ catheter ablation ■ pulmonary vein ■ risks ■ stroke

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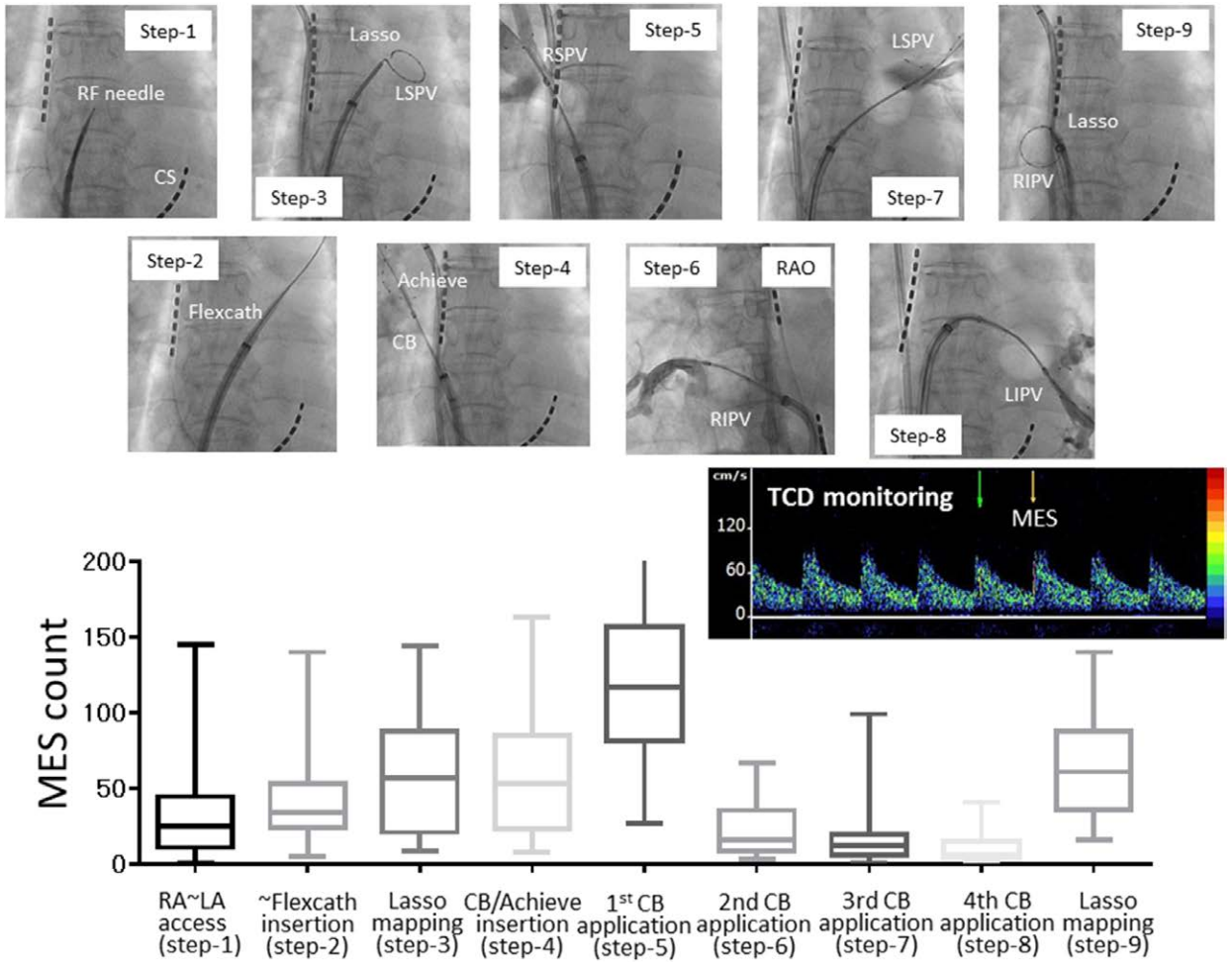

WHAT IS KNOWN?

- Catheter ablation is associated with a substantial risk of silent cerebral events/lesions detected on magnetic resonance imaging.
- The pathogenesis and mechanisms of silent cerebral events/lesions are still under debate because of the lack of a real-time monitoring method.

WHAT THE STUDY ADDS?

- A large number of microembolic signals were detected by transcranial Doppler during the standard second-generation cryoballoon procedure despite a simple procedure and short procedure time.
- Microembolic signals were detected during a variety of procedural steps throughout the procedure; however, the majority were recorded during phases with a high probability of gaseous emboli.
- The incidence of silent cerebral events and silent cerebral lesions was 32.3% and 11.7%, respectively.

Catheter ablation has become an essential therapeutic option for the treatment of atrial fibrillation (AF).[1] Recently, emerging cryoballoon technology shows a comparable efficacy and safety as radiofrequency ablation,[2] and second-generation cryoballoons are widely accepted because of the significantly higher performance than first-generation cryoballoons.[2–4]

Several studies have clarified that radiofrequency ablation is associated with a substantial risk of silent cerebral events/lesions (SCEs/SCL) detected on magnetic resonance imaging (MRI) that are presumed to be embolic in origin,[5] but little data are available about SCEs/SCLs during second-generation cryoballoon ablation procedures. Moreover, the pathogenesis and mechanisms of SCEs/SCLs are still under debate because of the lack of a real-time monitoring method.[5] The detection of microembolic signals (MESs) in the cerebral arteries by transcranial Doppler has been reported in many clinical settings, and there are reports supporting an association between MESs and the risk of strokes.[6–10] This study aimed to investigate the timing of the detec-

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tion of intraprocedural MESs and the incidence of SCEs/SCLs during the pulmonary vein isolation (PVI) using second-generation cryoballoons to better understand the mechanisms of SCEs/SCLs.

METHODS

Study Population

This study consisted of 40 patients with paroxysmal AF who underwent their first PVI using a second-generation cryoballoon. All patients underwent transcranial Doppler monitoring throughout the procedure to monitor for MESs. A brain MRI was obtained before and after the procedure to detect any SCEs/SCLs in 34 patients (85.0%). PVI was performed with a single balloon 3-minute freeze technique using exclusively a 28-mm second-generation cryoballoon (Arctic Front Advance, Medtronic, Minneapolis, MN).[11] AF was classified according to the latest guidelines.[1] All patients gave their written informed consent. The study protocol was approved by the hospital's institutional review board. The study complied with the Declaration of Helsinki.

Mapping and Ablation Protocol

The detailed procedure has been described elsewhere.[11,12] Briefly, the procedure was performed under moderate sedation obtained with dexmedetomidine. Anticoagulants (warfarin or direct oral anticoagulants) were skipped on the morning of the procedure and restarted from the evening post-procedure. A 100 IU/kg body weight of heparin was administered immediately after the venous access, and heparinized saline was additionally infused to maintain the activated clotting time at 300 to 350 seconds. A single transseptal puncture was performed using a radiofrequency needle (Baylis Medical, Montreal, QC) and 8F long sheath (SL-0, SJM, Minneapolis, MN) in all cases. The transseptal sheath was exchanged over a guidewire for a 15F steerable sheath (Flexcath Advance, Medtronic). The Flexcath sheath was continuously irrigated with heparinized saline with a rate of 100 mL/h throughout the procedure. A 20-mm circular mapping catheter (Lasso, Biosense-Webster, Diamond Bar, CA) was used for mapping all the pulmonary veins (PVs) before and after the cryoablation to confirm the isolation because the accuracy of ostial PVIs with only Achieve catheters is inferior to that of circular mapping catheters.[13,14] A 20-mm spiral catheter (Achieve, Medtronic) was used as a guidewire and mapping catheter. A 23-mm cryoballoon was not used in any cases. Complete sealing of the PV was verified with a contrast medium injection. This was followed by a freeze cycle of 180 seconds. No additional applications were performed after the isolation. To avoid any phrenic nerve injury, all cryoballoon applications were applied under electromyography monitoring.[12] As the standard deflation technique, the intraballoon shaft was manually straightened (balloon stretch) when the balloon temperature reached 15°C before the deflation to rewrap the balloon.[11] This technique is recommended by the manufacturer and widely used in other centers.[15] The procedural end point was defined as an electric PVI verified by the 20-mm Lasso catheter in sinus rhythm.[13] Internal cardioversion was undertaken for sustained AF. If necessary, additional point-by-point touch-up ablation was performed with an irrigated-tip catheter (FlexAbility, SJM).

Real-Time Microemboli Monitoring With Transcranial Doppler

The detailed technique has been described elsewhere.[6] The transducer was held in place by a proprietary headpiece supplied with the system. The middle cerebral arteries were unilaterally insonated from transtemporal windows by using a 2 MHz frequency Doppler (SONARA, CareFusion, San Diego, CA). A sample volume of 10 mm was used, and the insonation depth was 35 to 65 mm. The minimum power was used according to the principle of as low as reasonably achievable. The spectra from all saved embolic signals were recorded onto the hard drive of the computer (Figure 1). All signals were reviewed by an observer experienced in MES detection blinded to the procedural time segment period. Using standard consensus criteria, true MESs were identified.

The MES counts were collected and evaluated separately during the different steps of the procedure as follows (Figure 2): (1) catheter manipulation and a sheath flush in the right atrium; (2) placing an SL-0 wire in the ascending aorta as a landmark until a successful transseptal puncture (n=10); (3) a transseptal puncture with (n=36) or without an radiofrequency delivery (radiofrequency needle passed into left atrium (LA) before radiofrequency delivery; n=4; step 1); (4) introducing an SL-0 wire into the LA, dilation of the transseptal hole with an SL-0 sheath, and an exchange to a Flexcath sheath via the SL-0 wire (step-2); (5) pre-4-PV mapping with a Lasso (step 3); (6) introducing the cryoballoon/Achieve into the LA (step 4); (7) selection of the PV branch with the Achieve catheter, then the cryoballoon inflation and PV occlusion; (8) contrast injection to optimize the cryoballoon position; (9) 3-minute freezing phase; (10) thawing phase until the balloon temperature reached 15°C (ie, balloon stretch); (11) from a cryoballoon temperature of 15°C (balloon stretch) to the cryoballoon deflation, (7)–(11) were repeated until achieving an isolation of all 4 PVs (steps 5, 6, 7, and 8); and (12) post-4-PV isolation mapping with the Lasso catheter (step 9). In addition to the above steps, MESs were also counted during the below steps: (13) internal electric cardioversions (n=18); (14) introducing the cryoballoon, once withdrawn outside the body, into the LA and a subsequent cryoballoon application when an incomplete PVI was confirmed by the Lasso catheter (n=17); (15) introducing a new cryoballoon into the LA and a subsequent application when catheter trouble/malfunction occurred (n=4); (16) touch-up radiofrequency ablation (n=5); and (17) coronary angiography (n=2). Because of the delay between the emboli generation in the PVs/LA and arrival of those emboli into the cerebral vessels, a 15-second period after the end of each step was included.[16] In all steps, microbubbles were carefully removed from the system according to the manufacture's recommendation by experienced electrophysiologists.

Cerebral MRI

A brain MRI was performed the day before and 1 day after the procedure either with a 1.5-T or 3.0-T scanner (Ingenia,

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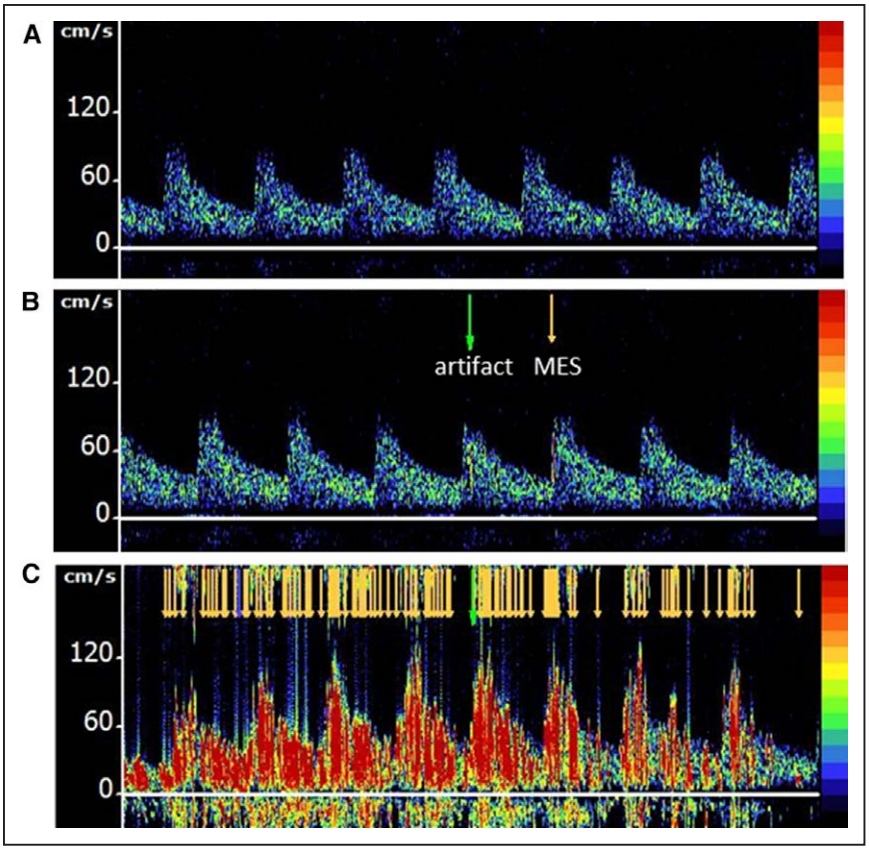

Figure 1. Representative pictures of transcranial Doppler microembolic signal (MES) images showing a baseline curve (A), solitary MES (B), and a burst of MESs (C). The yellow arrows indicate MESs and green arrows artifact.

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Philips, the Netherlands) to identify new procedure-related SCEs/SCLs. The imaging protocol for all images consisted of a T2-weighted axial fluid-attenuated inversion recovery (FLAIR) sequence and a diffusion-weighted MRI (DWI) sequence. The parameters of the FLAIR sequence were as follows: repetition time, 12 000 ms; echo time, 120 ms; slice thickness, 5 mm; field of view, 230 mm; and resolution, 214×288. The parameters of the DWI sequence were as follows: repetition time, 3500 ms; echo time, 94 ms; slice thickness, 5 mm; field of view, 230 mm; and resolution, 128×166. For each DWI sequence, the apparent diffusion coefficient (ADC) map was obtained to rule out any shine through artifact. The slices and orientation of the DWI and FLAIR sequences were matched to evaluate the correlation between the DWI and FLAIR images. According to the latest recommendations,[5] SCEs/SCLs were defined as below.

1. SCE=diffusion positive (DWI hyperintense)+ADC reduced
2. SCL=diffusion positive (DWI hyperintense)+ADC reduced+FLAIR positive

The size and localization of the SCE/SCL were analyzed. All MRI images were analyzed independently by 2 certified radiologists blinded to the clinical status of the patients. A systematic neurological examination was performed at the time of the pre- and postprocedural MRI by a physician trained in neurological examinations.

Statistical Analysis

Continuous data are expressed as the mean±SD for normally distributed variables or as the median (25th–75th percentiles) for non-normally distributed variables and were compared using a Student *t* test or Mann–Whitney *U* test, respectively. In the boxplots, the central box represents the values from the lower to upper quartile (25th–75th percentiles) with a line extending from the minimum to the maximum value. Categorical variables were compared using the χ^2 test. A *P* value of <0.05 was considered statistically significant.

RESULTS

Procedure Results

The patient characteristics are summarized in Table 1. In 40 patients, a total of 158 PVs including 2 left common PVs were identified. Overall, 152 of 158 (96.2%) PVs were isolated successfully using exclusively a 28-mm cryoballoon. The mean number and duration of the cryoballoon applications per patient were 5.0±1.2 and 866±214 seconds. Touch-up lesions were created in the remaining 6 PVs (3.8%) among 5 patients (12.5%). The LA dwell time and total fluoroscopic time were 76.7±22.4 and 20.9±12.5 minutes, respectively. No complications were observed.

Transcranial Doppler Findings

The median MES count per patient was 522 (426–626). The distribution of the MES counts during the different stages of the procedure is depicted in Figure 2. A total

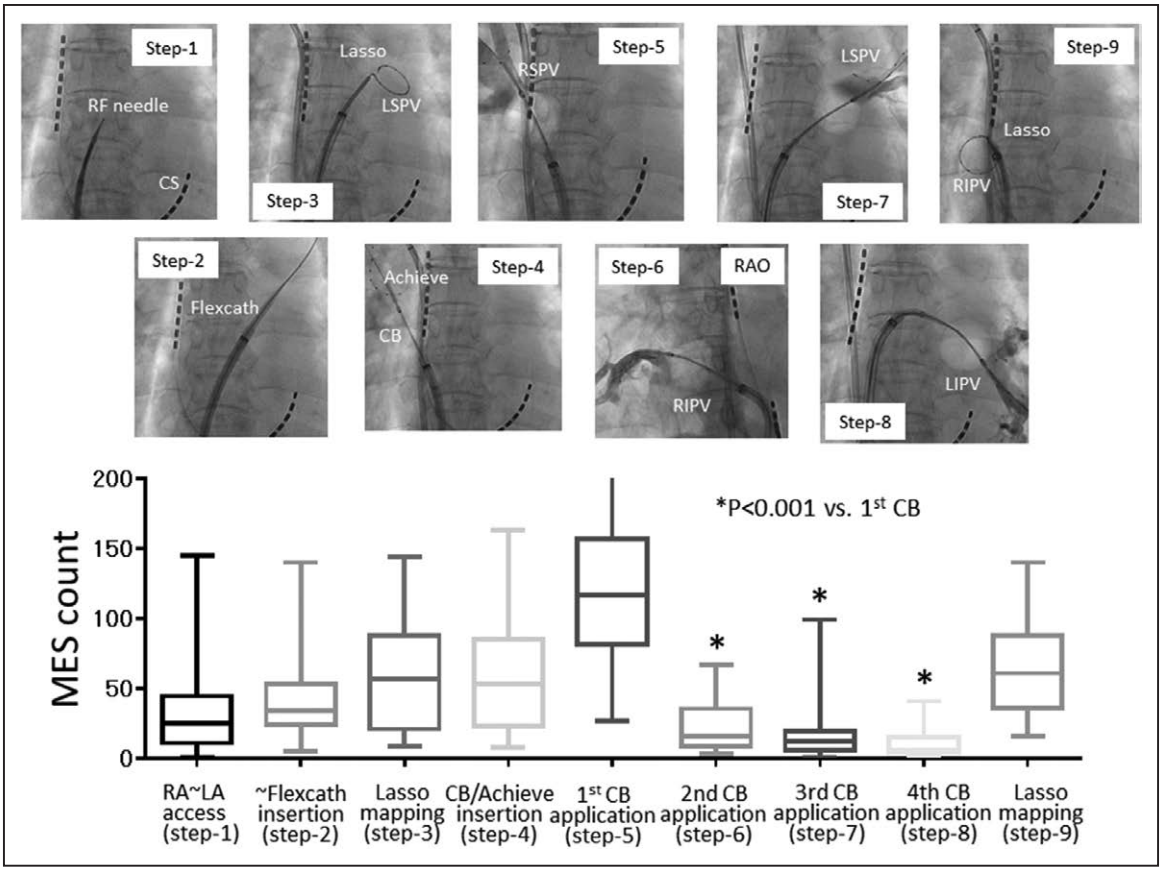

Figure 2. The number of microembolic signals (MESs) during each procedural step (step 1–9) are shown. Fluoroscopic images show each procedural step. CS indicates coronary sinus; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein; RIPV, right inferior pulmonary vein; and RSPV, right superior pulmonary vein.

of 25 (11–44) MESs were observed by a successful LA access (step 1). In detail, no MESs were counted during the catheter manipulation in the right atrium and failed radiofrequency delivery for the transseptal puncture. Placement of an SL-0 wire in the ascending aorta produced 3 (1–13) MESs. The number of MESs during successful transseptal punctures was significantly greater when using radiofrequency energy than without (P=0.038; Figure 3A).

A total of 34 (24–53) MESs were detected from a successful LA access to the insertion of the Flexcath (step 2). In detail, introducing the SL-0 wire into the LA produced 21 (8–29) MESs, and dilation of the transseptal hole by the SL-0 sheath generated 8 (2–15) MESs (step 2; Figure 4A). Pre-PV potential mapping by the Lasso catheter generated 57 (21–88) MESs (step 3), and the subsequent cryoballoon/Achieve insertion into the LA produced 53 (23–85) MESs (step 4).

The total number of MESs during each cryoapplication (from manipulation to deflation) was significantly greater during the first (step 5) than second, third, and fourth applications (steps 6, 7, and 8; 117 [81–157] versus 16 [9–35], 12 [6–19], and 6 [3–15]; P<0.001; Figure 2). In detail, during the first cryoballoon application, the MES count was greatest after the balloon stretch/deflation (43 [21–81]; Figure 4B). This observation always started after the balloon stretch and was enhanced after the balloon deflation. All MES counts during the Achieve/cryoballoon manipulation, contrast injection, 3-minute freeze, and

Table 1. Characteristics of the Study Population

N	40
Paroxysmal AF, n (%)	40 (100)
Age, y	56.3±13.2
Female, n (%)	5 (12.5)
Structural heart disease, n (%)	1 (2.5)
Hypertension, n (%)	10 (25.0)
Body mass index, kg/m2	24.3±3.8
LA diameter, mm	36.3±5.6
LV ejection fraction, %	67.0±5.0
Pro-BNP, pg/mL	169±383
eGFR, mL/min	74.4±12.2
$CHADS_2$	0.53±0.75
CHA_2DS_2-VAS_c	0.95±0.90

AF indicates atrial fibrillation; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration ratio; LA, left atrial; and LV, left ventricular.

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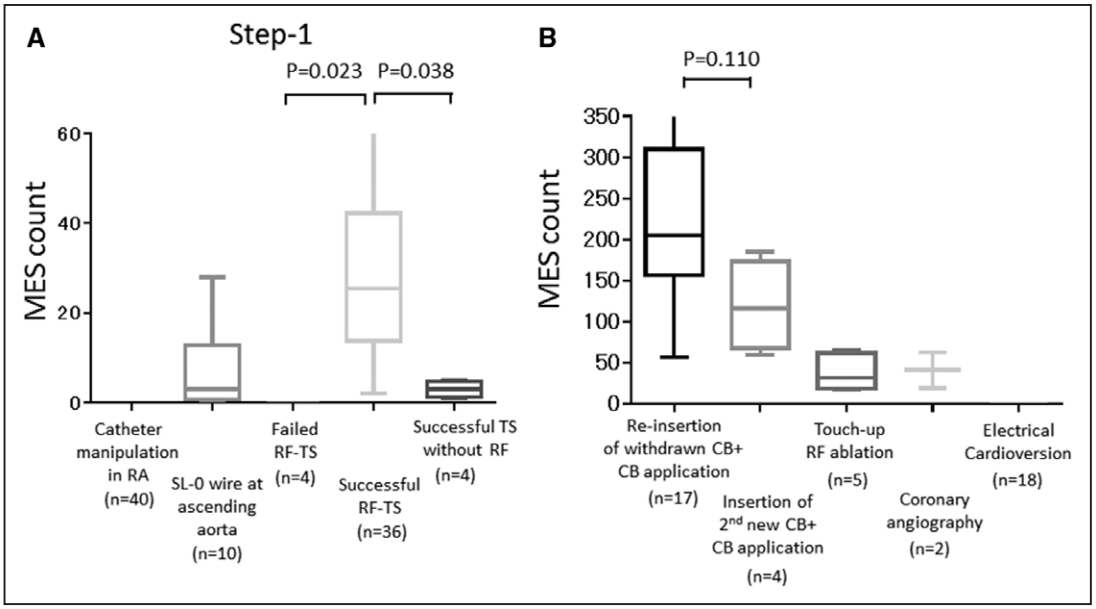

Figure 3. The details of the microembolic signal (MES) count during step 1 (A) and additional procedural processes (B).
CB indicates cryoballoon; RA, right atrium; RF, radiofrequency; and TS, transseptal.

after the balloon stretch/deflation significantly decreased during subsequent applications when compared with the first cryoballoon application (*P*<0.001; Figure IA through ID in the Data Supplement). In addition, in 3 patients in whom the initial cryoballoon application resulted in a failed isolation, the MES count after the balloon stretch/deflation was smaller during the failed initial application than successful subsequent application (4 [0–97] versus 40 [39–50]; *P*=0.784). Before the first cryoballoon application, the balloon inflation/deflation had already been performed in 7 patients because a complete occlusion was not obtained, and the target branch was changed. In those 7 patients, the MES count was significantly smaller after the balloon stretch/deflation phase (Figure 5A), whereas it was significantly greater during the Achieve/cryoballoon manipulation phase than in the remaining 33 patients (Figure 5B).

Post-PV potential mapping by the Lasso catheter generated 61 (36–88) MESs (step 9). Reinsertion of the cryoballoon after once withdrawn outside the body and a subsequent cryoballoon application when an incomplete PVI was confirmed with the Lasso catheter produced 205 (156–310) MESs (n=17). Reinsertion of a new cryoballoon and a subsequent cryoballoon application because of the malfunction of the cryoballoon produced 116 (68–174) MESs (n=4). Touch-up ablation with an irrigated radiofrequency catheter generated 32 (19–62) MESs (n=5), and coronary angiography produced 41 (20–63) MESs (n=2). However, electric cardioversion did not generate any MESs among 12 patients (n=18; Figure 3B). The MES count was greater in patients with AF during the procedure than in those without (752±489 versus 535±192; *P*=0.073) but did not reach statistical significance.

MRI Findings

Among 34 patients (85.0%) who underwent a brain MRI, SCEs and SCLs were detected in 11 patients

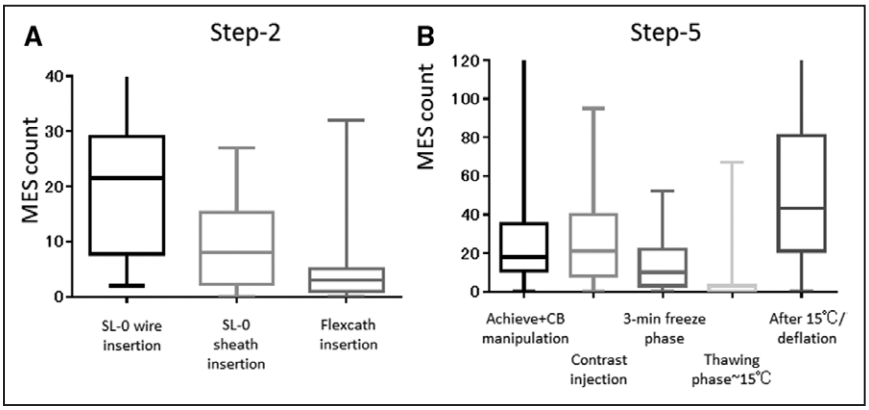

Figure 4. The details of the microembolic signal (MES) count during step 2 (A) and step 5 (B).
CB indicates cryoballoon.

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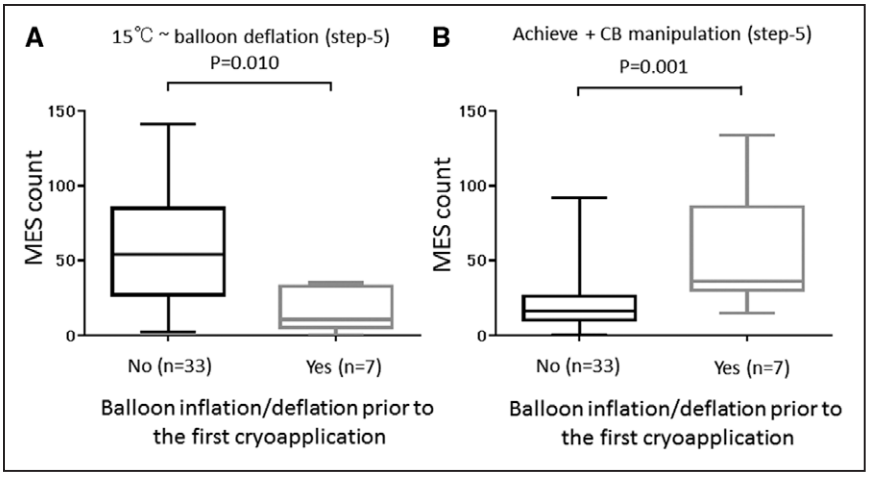

Figure 5. The number of microembolic signals (MESs) after the cryoballoon (CB) stretch/deflation phase (A) and during the Achieve/CB manipulation phase (B) in step 5 in patients with and without a preballoon inflation/deflation before the first CB application.

(32.3%) and 4 patients (11.7%), respectively. Eight patients had a single lesion, and the remaining 3 patients had multiple (range, 2–4) lesions. None of the patients reported neurological symptoms. We assessed the potential factors (patient-specific factors, procedure-related factors, and MESs) (Table 2) related to periprocedural brain lesions. The patients with SCEs were older than those without (*P*=0.050); however, there were no significant factors associated with the SCEs.

Table 2. Patient-Specific and Procedure-Related Factors Associated With SCEs

	SCE (+)	SCE (–)	*P* Value
N	11 (32.3%)	23 (67.7%)	
Paroxysmal/persistent AF	11/0	23/0	1.000
Age, y	63.3±8.5	52.7±15.1	0.050
Female, n (%)	2 (18.2)	1 (4.4)	0.183
Structural heart disease, n (%)	0 (0)	1 (4.4)	0.483
Hypertension, n (%)	1 (9.1)	7 (30.4)	0.170
Body mass index, kg/m^2	24.3±4.5	24.7±3.8	0.770
LA diameter, mm	37.4±5.6	35.8±5.7	0.454
LV ejection fraction, %	67.6±5.3	66.1±5.5	0.458
Pro-BNP, pg/mL	94±70	244±519	0.376
eGFR, mL/min	73.5±10.5	75.2±11.6	0.682
$CHADS_2$	0.64±1.03	0.52±0.67	0.697
CHA_2DS_2-VAS_c	1.36±0.81	0.83±0.94	0.113
Total no. of CB application, n	5.0±1.5	4.9±1.1	0.775
Total CB application duration, s	896±278	850±205	0.593
LA dwell time, min	80.2±16.6	75.0±24.9	0.539
ACT, s	321±35.8	316±42.7	0.757
Touch-up ablation, n (%)	1 (9.1)	2 (8.7)	0.970
Electric cardioversion, n (%)	1 (9.1)	9 (39.1)	0.072
MES, n	656±466	591±267	0.607

ACT indicates activated clotting time; AF, atrial fibrillation; BNP, brain natriuretic peptide; CB, cryoballoon; eGFR, estimated glomerular filtration ratio; LA, left atrial; and LV, left ventricular; MES, microembolic signal; and silent cerebral event.

DISCUSSION

The present study initially showed that several processes in the second-generation cryoballoon procedure carried the risk of silent strokes. We found that (1) a large number of MESs were detected during the standard second-generation cryoballoon procedure despite a simple procedure and short procedure time; (2) MESs were detected during a variety of procedural steps throughout the procedure; however, the majority was recorded during phases with a high probability of gaseous emboli; and (3) the incidence of SCEs and SCLs was 32.3% and 11.7%, respectively.

MESs During Cryoballoon Ablation

The real-time monitoring of the embolic traffic in the brain is a useful approach to determine which part of the procedure is strongly associated with MESs. The method of detecting cerebral emboli cannot provide information on the composition of the observed emboli, but the moment of the occurrence can provide an indication about the nature of the observed emboli. Cryoablation is generally regarded as tissue-friendly and is associated with a significantly lower incidence of thrombus formation compared with radiofrequency ablation.[1,12] A few groups examined the total MESs during the first-generation cryoballoon procedure and reported consistent results in which the total MES count/procedure was 1057 (n=13),[17] 834 (n=10),[18] and 935 (n=10),[16] respectively, which were significantly lower than other technologies, yet the number of MESs during each procedural step was not examined. The significantly smaller number for the total MES count in our study could be explained by the smaller number of cryoballoon applications and shorter LA dwell time because of the single 3-minute freeze technique enabled by the second-generation cryoballoon. Importantly, in contrast to radiofrequency ablation, the majority of the MESs were detected

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during steps other than during the applications in the cryoballoon ablation.[16]

Major Factors Generating MESs

A considerable number of MESs were detected during the cryoballoon/Achieve insertion, Lasso catheter insertion, and Flexcath sheath flushes. Animal studies demonstrated that a significantly larger air volume was measured during the introduction of the ring catheter.[19,20] This is likely because of the complex catheter geometry in its extended configuration causing it to capture small amounts of air during its introduction across the hemostatic valve compared with the smooth bullet shape of a typical ablation catheter. To minimize air entrapment, it might be recommended that the catheters be submerged and inserted into an introduction device in a saline bath before insertion into the Flexcath sheath. Also, all sheath flushes and injections should be performed at a slow speed to prevent any cavitation as suggested by Takami et al.[20] Deneke et al[21] elegantly showed that exchanging catheters over a single transseptal access to perform an LA ablation was associated with a significantly higher incidence of SCEs. Introducing and withdrawing a catheter over the transseptal sheath may lead to the introduction of gas or thrombotic debris from within the transseptal sheath or catheter. In addition, exchanges of catheters over a single transseptal sheath may influence the patency of the sheath's valve and may then lead to the introduction of small air bubbles. Given these data, it is recommended that the procedure be completed with a single cryoballoon and an adjunctive Achieve catheter without any catheter exchanges. Because the Lasso has been the gold-standard catheter for PV potential mapping and the mapping precision is more superior with the use of an additional Lasso catheter than with the Achieve catheter alone,[13,14] we used an additional Lasso catheter for mapping in the present study. However, because our study clarified that reinsertion of the cryoballoon generated a huge number of MESs, it is recommended that the PV potentials be evaluated with the Achieve catheter alone and that the reinsertion of the cryoballoon and use of an additional Lasso catheter be minimized.

A large number of MESs was also detected after the balloon stretch/deflation after the initial successful cryoballoon application. This observation started from the balloon stretch and was enhanced by the balloon deflation. Moreover, the MES count after the balloon stretch/deflation phase was significantly smaller in the patients in whom the balloon inflation/deflation was already performed before the initial cryoapplication. Furthermore, the MESs count was highest during the initial application than the following applications and higher after the successful application than failed application (not achieving a PVI). All these findings suggest that the MESs were generated by the release of microbubbles trapped inside ice chips formed at the balloon–PV interface and the release of microbubbles in the trapped blood and injected contrast behind the occluding balloon. It is likely that the attached microbubbles on the balloon surface cannot be completely removed by a simple repeated inflation/deflation but can be removed by complete ice cap formation enabled by a complete occlusion. In addition, this observation was reproduced when the cryoballoon that was once withdrawn outside the body was reintroduced or a new cryoballoon was introduced into the LA. During the other steps of the cryoballoon application (manipulation of Achieve/cryoballoon, contrast injection, and freezing phase), the MES count was greatest during the first successful application than the following applications. All these support that, despite careful removal of microbubbles, the microbubbles remaining in the cryoballoon system are the major cause of MESs.

Other Factors Generating MESs

The MES count was significantly greater during a successful transseptal puncture with radiofrequency energy than during those without, and a failed puncture did not produce any MESs. The potential source of the MES generation was tissue overheating. Indeed, MESs were recorded at the time of the energy delivery during nonirrigated radiofrequency ablation.[16] Our data suggest that the transseptal access without radiofrequency energy might reduce the MES count.

Inserting an SL-0 guidewire into the ascending aorta and LA generated a median of 3 and 21 MESs, respectively. An SL-0 wire is a coil wire, and this likely entraps many microbubbles on the wire. The small count in the descending aorta relative to the LA could be explained by lesser wire manipulation. It might be recommended that the wire be submerged in a saline bath before insertion. MESs were also detected during the dilation of the transseptal hole with the SL-0 sheath; however, this might have been because of the released microbubbles from the wire by brushing the wire against the SL-0 sheath.

No MESs were detected during a total of 18 successful internal electric cardioversions. The relation between the cardioversion and SCEs/SCLs is still controversial.[5] However, our results suggested that cardioversion itself did not result in SCEs/SCLs.

Touch-up ablation generated a median of 32 MESs. However, this number was much less when compared with the total MES count during the cryoballoon procedure.

The anticoagulation therapy was skipped on the morning of the procedure; however, heparin was immediately administered after the femoral puncture and an optimal activated clotting time was obtained. Indeed, Kiss et al[17] reported >1000 MESs during the

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first-generation cryoballoon procedure even under uninterrupted anticoagulation therapy. Moreover, the different activated clotting times did not result in a statistically significant impact on the MES count, similar to another study.[18] The potential benefit of a more aggressive anticoagulation protocol needs to be assessed in larger-scale studies, although its impact on mostly gaseous microemboli is questionable.

Mechanisms of SCEs/SCLs and MESs

It has been established that thrombi, gas bubbles, and particulate debris (coagulum) can be introduced or produced with an LA ablation,[19] and SCLs can be produced experimentally with cerebral embolisms of solid small-size particles or gaseous microbubbles.[22] During AF ablation, both particle debris and bubbles can be produced with aggressive radiofrequency tissue ablation, and air bubbles can be introduced into the LA by a variety of mechanisms associated with catheter insertion into the transseptal sheath.

Our study clarified that several procedural steps were predominantly responsible for the generation of MESs. Although solid and gaseous emboli are not distinguished accurately, most MESs were recorded during phases with a high probability of gaseous emboli. Takami et al[20] elegantly showed that sheath/catheter procedural steps are a source of microbubbles but not microparticles (clot/thrombi) in an animal model. Therefore, it seems a reasonable hypothesis that the observed MESs during these phases are mainly caused by iatrogenic gas injections. It should be noted that despite our best efforts to remove microbubbles from the system according to the manufacture's standard recommendations, we still had >500 MESs per patient. Importantly, when SCLs were observed regardless of the thromboembolic materials, there was invariably histopathologic evidence of cerebral injury.[22] Therefore, reducing the incidence of brain lesions is extremely important given that a considerable number of patients will undergo multiple cardiac catheterizations in their lifetime.

Multiple publications support an association between the number of MESs and neurological impairment and strokes during different cardiovascular procedures.[6–10] However, although the MES count was greater in patients with SCEs than in those without, the difference did not reach a statistical significance in our study. This might be because of the small study population that underwent MRI and also the methodological limitation that MESs were monitored in the middle cerebral artery and not in other cerebral arteries as in the previous studies.[6–10,16–18] We also speculated that the cause of SCEs was multifactorial and differed among the patients. Nevertheless, we think that modifying each procedural step to reduce the MES count is important because all MESs are potential embolic sources during the procedure. Modifications of different procedural steps by physicians and improvements of the cryoballoon system by the manufacturer may lead to a reduction in the SCE incidence, and efforts to minimize the production of microbubbles and microembolic particle debris during each procedural step is necessary. We believe that our data would be helpful for modifying each procedure step to reduce any potential embolic sources.

Study Limitations

First, the study was a single-center observational study, and the size was small. Because of the relatively small population that underwent a brain MRI, it was likely underpowered for identifying any specific predictors of SCEs/SCLs. Second, the characterization of individual emboli by their size and composition is uncertain; however, before studies clarified that 80% to 90% of MESs were gaseous regardless of the technologies.[18] Third, although we cannot evaluate the impact of balloon stretch on the MES count during the thawing phase, this is the common technique[15] recommended by the manufacturer. Fourth, follow-up MRI was not performed. However, previous studies demonstrated that the vast majority of asymptomatic cerebral lesions observed acutely after AF ablation procedures healed without scarring during a follow-up >2 weeks after ablation.[23] Fifth, we monitored MESs from the middle cerebral arteries according to the guidelines,[6] and not all cerebral arteries were monitored as in the other studies.[7–10,16–18]

Conclusions

A significant number of MESs and the incidence of SCEs/SCLs were observed during the standard second-generation cryoballoon ablation procedure. MESs were recorded at a variety of steps throughout the procedure; however, the majority were recorded during phases with a high probability of gaseous emboli. Our study data suggested that modifications of the different procedural steps may lead to a further reduction in the potential embolic sources. Further study is necessary to clarify the mechanisms of SCEs during cryoballoon ablation.

AFFILIATIONS

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DISCLOSURES

None.

FOOTNOTES

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Thromboembolic Risks of the Procedural Process in Second-Generation Cryoballoon Ablation Procedures: Analysis From Real-Time Transcranial Doppler Monitoring

Shinsuke Miyazaki, Tomonori Watanabe, Takatsugu Kajiyama, Jin Iwasawa, Sadamitsu Ichijo, Hiroaki Nakamura, Hiroshi Taniguchi, Kenzo Hirao and Yoshito Iesaka

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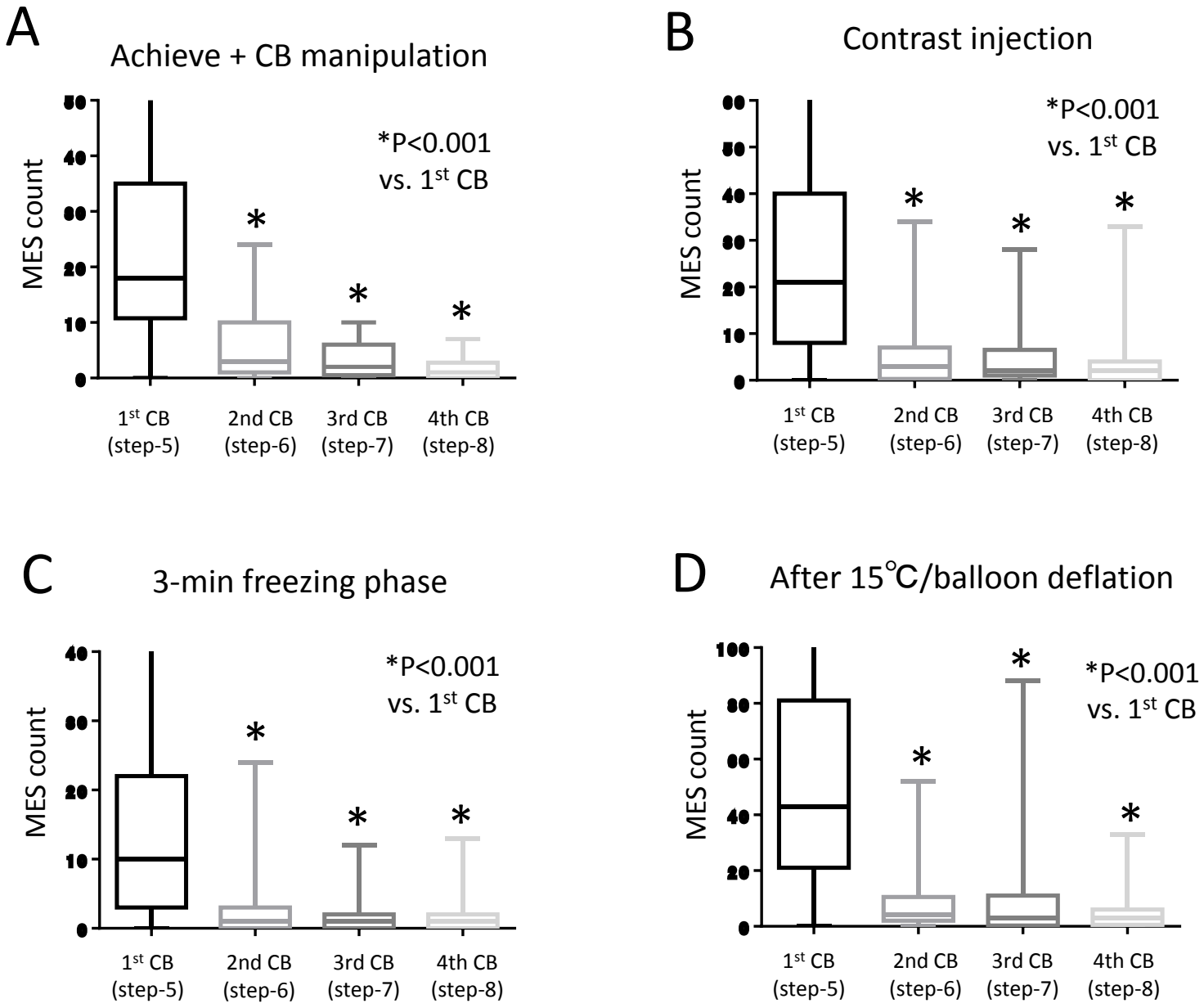
SUPPLEMENTAL MATERIAL

Supplementary Figure 1. The MES counts during the Achieve/CB manipulation (A), contrast injection (B), and freezing phase (C), and after the balloon stretch/deflation (D) during the 1st (step-5), 2nd (step-6), 3rd (step-7), and 4th (step-8) CB applications.


A
Achieve + CB manipulation
MES count
*P<0.001
vs. 1st CB
1st CB (step-5)
2nd CB (step-6)
3rd CB (step-7)
4th CB (step-8)
B
Contrast injection
MES count
*P<0.001
vs. 1st CB
1st CB (step-5)
2nd CB (step-6)
3rd CB (step-7)
4th CB (step-8)
C
3-min freezing phase
MES count
*P<0.001
vs. 1st CB
1st CB (step-5)
2nd CB (step-6)
3rd CB (step-7)
4th CB (step-8)
D
After 15℃/balloon deflation
MES count
*P<0.001
vs. 1st CB
1st CB (step-5)
2nd CB (step-6)
3rd CB (step-7)
4th CB (step-8)