Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Assessment of Device Neoendothelialization With Cardiac Computed Tomography Angiography After Transcatheter Closure of Atrial Septal Defect

Ah Young Kim, MD; Wongi Woo, MD; Beom Jin Lim, MD, PhD; Jo Won Jung, MD, PhD; Jae Young Choi, MD, PhD; Young Jin Kim, MD, PhD

BACKGROUND: Although the transcatheter closure of atrial septal defect was established as the treatment of choice several decades ago, the process of device neoendothelialization (NE) in humans is not well understood. We aimed to measure the extent of device NE using cardiac computed tomography angiography and analyze its risk factors.

METHODS: Between January 2005 and February 2021, we retrospectively reviewed 164 devices of 112 patients on cardiac computed tomography angiography. We investigated device shape, contrast opacification within the device that differentiated device NE, and device-related thrombosis or vegetation. Risk factor analysis for major adverse cardiovascular events and incomplete NE according to the postprocedural period was performed.

RESULTS: Seventy patients (62.5%) were women, with a median (range) age at the time of device closure of 44.5 (0.6–79.2) years. The mean (±SD) defect size was 16.6 (±7.8) mm, and patients were followed for 35.9±33.9 months. After 6 months of device implantation, 35% of the devices (42/120) had incomplete NE. The intensity of intradevice opacification shifted from complete to partial or nonopacification over time ($P<0.001$), and a similar pattern was observed in the shunt flow ($P<0.001$). The bulkiness of devices also decreased in proportion to the postprocedural period ($P<0.001$). Risk analysis revealed device diameter (hazard ratio, 1.18 [95% CI, 1.04–1.27]; $P<0.001$) as the only significant factor of incomplete NE and major adverse events.

CONCLUSIONS: Incomplete NE of atrial septal defect devices was identified on cardiac computed tomography angiography in significant numbers after 6 months of the procedure. The device diameter was related to incomplete NE and major adverse events. Further prospective and multicenter studies are warranted to validate this new assessment of device NE.

Key Words: computed tomography angiography ■ heart septal defects, atrial ■ prostheses and implants ■ risk factors ■ thrombosis

Transcatheter device closure of Secundum atrial septal defect (ASD) has become the current gold standard treatment strategy in patients with suitable anatomy.[1,2] The Amplatzer septal occluder (ASO; St. Jude Medical, Inc, Plymouth, MN) has been widely used to close ASDs in the last 2 decades due to its proven long-term efficacy.[3,4] Other recent-generation devices have also been broadly approved as feasible, safe, and comparable options for device closure of ASDs with favorable long-term outcomes.[5,6] However, although rare,

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CLINICAL PERSPECTIVE

Monitoring of the implanted devices for atrial septal defect is important for the assessment of long-term clinical outcomes. However, the process of device neoendothelialization (NE) in humans is not well understood. We investigated device NE with cardiac computed tomography angiography and revealed that incomplete NE existed in a large proportion (35%, 42/120) even 6 months post-procedure. Most devices tend to be flattened, and intradevice contrast enhancement, which implied incomplete NE, decreased over time ($P<0.001$). The device diameter was the only related factor associated with incomplete NE. Antiplatelet therapy and antibiotic prophylaxis beyond 6 months may be selectively considered in patients implanted with larger implanted devices for atrial septal defect. However, due to this study's selection bias and the retrospective nature of this study, caution is required when applying our results to routine clinical practice. Further prospective and multicenter studies are warranted to validate this new assessment of device NE.

Nonstandard Abbreviations and Acronyms

ASD	atrial septal defect
ASO	Amplatzer septal occluder
CCTA	cardiac computed tomography angiography
CT	computed tomography
IE	infective endocarditis
NE	neoendothelialization
TTE	transthoracic echocardiography

there have been severe complications, including device thrombosis, stroke, or device-related infective endocarditis (IE).[7–15] These complications may be associated with an incomplete neoendothelialization (NE) of the ASD closure device.[9,16–20]

Although few reports regarding the process of device NE in humans exist, most are case reports, and the level of evidence is insufficient. The American Heart Association/American College of Cardiology guidelines recommend antibiotic prophylaxis for 6 months following prosthetic material implantation based on the results of animal experiments[21]; however, the time required for the complete NE of the device in humans is still unknown, and rising concerns regarding the adequate duration of antiplatelet and IE prophylaxis after the procedure remain controversial. To date, there is no specific method for confirming complete endothelialization on the surface of the device in individual patients. In the case of incomplete NE, there is still a delayed risk of device infection or thrombosis, suggesting prolonged antibiotic prophylaxis antiplatelet therapy in these patients.[16,17] Therefore, a reliable and safe imaging method is needed to assess the ASD device and confirm complete NE. We hypothesized that a significant proportion of ASD closure devices are found to have incomplete NE even 6 months after the procedure. The present study aimed to evaluate the imaging characteristics of the ASD device to demonstrate the process of device NE and present a new definition of incomplete or complete NE based on cardiac computed tomography angiography (CCTA) findings and discuss prognostic factors that may aid future therapeutic interventions.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Selection Process

The patients who underwent ASD device closure and CCTA at least once during the postprocedural follow-up period in a single tertiary center were included and reviewed retrospectively. We excluded patients with non-ECG gated images or patients who had an intervention for congenital heart diseases other than ASD, such as Fontan fenestration closure and patent foramen ovale closure.

ASD Device Closure and Follow-Up Management Protocol

The implantation procedure was mainly performed by 2 interventionalists. Hemodynamic study and assessment of morphological characteristics of the defect were undertaken by cardiac catheterization. Patients received intravenous heparin (60–100 IU/kg for children and 5000 IU for adults) at the beginning of the procedure. The activated clotting time was maintained between 200 and 300 s to prevent thrombosis during the procedure. The device was selected primarily based on the stretched diameter of the defect, which was determined using a compliant balloon catheter (sizing balloon catheter; St. Jude Medical or Nu MED, Inc, Nicholville, NY). The balloon catheter was placed across the defect and controlled by a color Doppler intracardiac echocardiography with a stop-flow technique. The stop-flow diameter, which was measured from the perspectives of fluoroscopy and intracardiac echocardiography, was recommended as the standard measurement to avoid oversizing. In self-centering devices such as the ASO, the recommended device size was the same or slightly larger (<2 mm) than stop-flow diameter. The selection for device size was individualized considering the deficiency of rims, spatial relationship with adjacent cardiac structures, and the size of the heart. In cases of aortic rim deficiency, the usual recommendation was to avoid an oversized device because of the potential risk of erosion. The device-positioning techniques were similar in devices, and intracardiac echocardiography and fluoroscopy were used to verify correct positioning. When the placement was judged satisfactory, the device was released completely.

After the procedure, we checked the migration of devices via serial chest radiographs at 6 and 24 hours after the procedure.

Further, patients have prescribed aspirin (5 mg/kg; maximum, 100 mg) daily for 6 months and recommended prophylactic antibiotics therapy before the selected procedures for up to 6 months, and transthoracic echocardiography (TTE) was performed at 1 month, 3 to 6 months, 12 months, and annually after implantation during follow-up.

Imaging Guideline

CCTA was not routinely performed; however, we conducted CCTA to check the spatial relationship of the implanted multiple devices in the following cases: (1) if patients had nonspecific chest discomfort after the procedure, we performed CCTA to rule out coronary artery occlusive disease (n=45). (2) When the device looks bulky, multiple devices are implanted, or devices encroach with other intracardiac structures such as a mitral valve or aortic valve in TTE, CCTA was done to verify the device position (n=31). (3) When patients had fever without any specific causes, CCTA was done to detect possible IE (n=15). (4) When significant pericardial effusion, vegetation, or thrombi were suspected in the echocardiography, CCTA was performed to visualize the characteristics of the device (n=11). (5) If patients exhibited neurological symptoms suggestive of stroke or transient ischemic attack, CCTA was also performed to identify possible thrombus formation around the devices (n=10).

Computed Tomography Protocol

Computed tomography (CT) images were obtained using various equipment (Sensation 64, Somatom Definition Flash, and Somatom Definition Force [Siemens Healthcare, Forchheim, Germany]; Revolution CT [GE Healthcare, Milwaukee, WI]), but all images were obtained by ECG synchronization, and radiation reduction techniques that were available at the time of imaging such as tube current modulation, automatic tube potential selection, and iterative reconstruction were used. The total amount of iodinated contrast agent was 1.5 to 2.0 mL/kg of body weight in children and 50 to 70 mL in adults. The contrast injection rate was 1.5 to 3.0 mL/s depending on the body weight in pediatric patients and 5 mL/s in adults. CT images were evaluated using multiplanar reformatted images on dedicated 3-dimensional software (Aquaris iNtuition, version 4.4.13; TeraRecon, Inc, San Mateo, CA). At least 2 planes (parallel to and perpendicular to the device) were used for CT analysis.

Newly Suggested Radiological Criteria to Differentiate Device Morphology

The images were assessed for thrombosis or vegetation attached to the devices, device shape (bulky or flattened), and contrast opacification within the device (complete opacification, partial opacification, or nonopacification). We differentiated device shapes (bulky, partially flattened, and flat) based on the thickness (central, aortic side, and posterior side) and asymmetry along the septum. As the devices' central thickness was generally 3 to 4 mm when they were typically deployed, we applied 6 mm (1.5 or 2× the original diameter) as a cutoff value to determine device shape. Therefore, if the central thickness was ≤6 mm, it was considered flat, and devices with a central thickness >6 mm were categorized as bulky or partially flattened. Subsequently, the asymmetricity along the septum was used to differentiate bulky and partially flattened shapes: the symmetrical one was considered bulky, and the asymmetrical one was partially flattened.

Incomplete NE was defined according to the extent of intradevice contrast opacification, which is expressed as a full or partial enhancement. Contrast enhancement in the entire device was considered full opacification, while any visible diffusions of contrast through the atrial surface of the device in part of the discs were classified as partial opacification. We also analyzed them according to the sidedness of intradevice opacification (Figure S1) and described LA and RA disc interface. If there was no contrast opacification within the device and the shape of the device was flattened, NE was considered completed. Device thrombosis was defined as the presence of focal low-attenuation thickening on the atrial surfaces of the device or a mass attached to the surface of the device. It was judged as device-related vegetation only if the patients were suspected of having IE based on modified Duke criteria, including clinical, biological, and echocardiographic findings.

Statistical Analysis

Basic demographic and clinical information were presented as median and interquartile range or mean±SD for continuous variables after testing the normality via the Shapiro-Wilk test and as numbers or percentages for categorical variables. Continuous variables were compared using 2-sample *t* tests or Mann-Whitney *U* tests, and categorical variables were compared using the Fisher exact test. After comparing implanted device characteristics in the 3 groups, the Fisher exact test was conducted, and pairwise comparisons were performed using the Bonferroni method. Cox proportional-hazards regression analyses were used to identify independent risk factors of incomplete NE. A receiver operating characteristic curve was constructed to estimate the cutoff diameter of the device to determine incomplete NE. C statistics were calculated with their 95% CIs. A 2-tailed *P* of <0.05 was considered significant in all statistical analyses. Statistical analyses were performed using R, version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics Statement

This study was approved by the Yonsei University College of Medicine Institutional Review Board and the Research Ethics Committee of Severance Hospital (study approval number: 4-2021-1267). The requirement for individual consent was waived because of the retrospective medical record review nature of this study.

RESULTS

Demographic Data and Procedural Characteristics

Between January 2007 and February 2021, 2011 patients had ASD device closure in our institution, and there were 193 CCTAs performed after the procedure. Of those CCTA scans, we excluded 29 scans of patients with Fontan fenestration closure (n=4), patent foramen ovale closure (n=3), nongated CT (n=5), ASD surgery (n=4), and duplicate examinations during

a similar period (n=13). Finally, we enrolled 164 CCTA scans of 112 patients.

Approximately two-thirds of patients (n=70, 62.5%) were women, and the median (range) age at device closure was 44.5 (0.6–79.2) years. About one-third of patients (n=33, 29.5%) had pulmonary hypertension, and 27.7% had atrial fibrillation. There were 25 (22.3%) patients with multiple ASDs, and 16 (14.3%) patients had received at least 2 devices during the procedure (Table 1).

The mean (±SD) ASD defect size, which was measured through TTE before the procedure, was 16.6±7.8 (range, 10.0–21.0) mm. We deployed 4 different types of devices: ASO (n=106, 64.6%), Occlutech Figulla Flex II (FSO; Occlutech GmbH, Jena, Germany; n=47, 28.7%), Cocoon Septal Occluder (Vascular Innovations Co, Nonthaburi, Thailand; n=7, 4.3%), and Gore Septal Occluder (W.L. Gore & Associates, Inc, Flagstaff, AZ; n=7, 4.3%). The mean (±SD) device size was 21.1±9.0 mm, and one-third of patients (n=54, 32.9%) received the large sized device, which was >25 mm (Table 1).

Table 1. Patients' Characteristics and Device-Related Parameters

Factors	Total patients (N=112)
Demographic variables	
Women	70/112 (62.5)
Age at device closure, y	44.5 (18.8–52.6)
Weight at device closure, kg	41.6 (7.5–95.0)
Atrial arrhythmias	31/112 (27.7)
Cardioversion	3/31 (9.7)
RFCA	5/31 (16.1)
Arrhythmia surgery	2/31 (6.5)
Follow-up duration, mo	35.9±33.9
Echocardiographic and procedural parameters	
Pulmonary hypertension	33/112 (29.5)
Tricuspid regurgitation (>grade 2/4)	30/112 (26.8)
Mitral regurgitation (>grade 2/4)	5/112 (4.5)
Multiple defects	25/112 (22.3)
Single device implanted	96/112 (85.7)
Multiple devices implanted	16/112 (14.3)
2 devices	12/16 (75.0)
>2 devices	4/16 (25.0)
	Total devices (N=164)
Size of defects, mm	16.6±7.8
Types of devices	
Amplatzer septal occluder	106/164 (64.6)
Occlutech Figula Flex II	47/164 (28.7)
Cocoon septal occluder	7/164 (4.3)
Gore septal occluder	7/164 (4.3)
Stop-flow diameter, mm	22 (13–32)
Size of devices, mm	21.1±9.0
Amplatzer septal occluder	21.9±5.3
Occlutech Figula Flex II	18.7±8.7
Cocoon septal occluder	13.5±7.2
Gore septal occluder	30±5.5
Very large size device (size >35 mm)	15/164 (9.1)
Large size device (25 mm<size≤35 mm)	39/164 (23.8)
Device diameter/TSL in patient weight under 20 kg*	0.4±0.1
Procedural time, min	18.7±9.9

Data are median (IQR), mean±SD, or n (%). IQR indicates interquartile range; RFCA, radiofrequency catheter ablation; and TSL, total septal length.
*Data from 14 devices in 11 patients.

Analysis of ASD Devices With CCTA

The mean interval between device implantation and the CCTA scan was 35.9±33.9 months. Patients were categorized into 3 groups based on the interval (Table 2): within 6 months (n=43; group 1), 6 months to 1 year (n=21; group 2), and after 1 year (n=100; group 3). We found significantly more flattened devices over time (6%, 12%, and 83% in groups 1, 2, and 3, respectively; $P<0.001$). The number of bulky shaped devices was 13 (30.2%) in group 1 and none in group 3. We also assessed the device opacification via intradevice contrast enhancement, which implies the portion of incomplete NE of the device. The device opacification was prominently observed in images within 6 months (45.2%, 4.8%, and 0% in groups 1, 2, and 3, respectively; $P<0.001$). The complete or partial enhancement was considered incomplete NE, and it was observed in 16 (38.1%), 9 (42.9%), and 32 (32.3%) images in groups 1, 2, and 3, respectively. Nonenhancement, which implied complete NE, was found in 7 (16.7%), 11 (52.4%), and 67 (67.7%) cases in groups 1, 2, and 3, respectively, and the difference was significant ($P<0.001$; Figure 1). The shape and partial opacification of the devices are shown in Table S1 according to the device's sidedness. Further, one-third of devices (35%, 42/120) remained incompletely neoendothelialized even after 6 months of the procedure (Figure 2; Table 3). Additionally, the proportion of residual peri- or through-device shunt flow on TTE was the highest in group 1, with 26 (78.8%), 8 (53.3%), and 12 (13.5%) cases in groups 1, 2, and 3, respectively ($P<0.001$). We compared patient characteristics, clinical outcomes, and CCTA assessment of the 2 main devices, ASO and FSO. ASO showed a higher proportion of incomplete NE than FSO during the follow-up period ($P<0.001$). However, there were significant differences in the numbers of devices under evaluation (ASO: n=87 versus FSO: n=26) and the length of the follow-up periods (ASO: median, 54.0 months versus FSO: median, 12.0 months; $P<0.001$).

The quality in terms of reproducibility of CCTA evaluation was assessed. The κ-coefficient was 0.47 (95% CI,

Table 2. Cardiac Computed Tomography Angiography Findings of Implanted Devices According to the Postprocedural Periods

	Group 1	Group 2	Group 3	
	Within 6 mo (n=43)	6 mo to 1 y (n=21)	After 1 y (n=100)	*P* value
Multiple devices	19/43 (44.2)	11/21 (52.4)	18/100 (18.0)	<0.001
Device shape				<0.001
Bulky	13/42* (31.0)	2/21 (9.5)	21/99* (21.2)	
Partially flattened (RA or LA side)	20/42* (47.6)	7/21 (33.3)	12/99* (12.1)	
Flattened	9/42* (21.4)	12/21 (57.1)	66/99* (66.7)	
Device asymmetry	23/42* (54.8)	8/21 (38.1)	15/99* (15.2)	<0.001
Device thickness, mm				
Central	8.15 (6.48–11.12)	5.50 (4.00–8.00)	5.10 (3.80–6.75)	<0.001
Aortic side	11.80 (9.33–14.57)	9.80 (5.80–12.80)	9.90 (7.45–12.45)	0.03
Posterior side	10.15 (8.53–12.40)	9.20 (6.30–11.40)	8.70 (7.00–10.50)	0.015
Device opacification				<0.001
Full opacification	19/42* (45.2)	1/21 (4.8)	0/99* (0)	
Partial opacification	16/42* (38.1)	9/21 (42.9)	32/99* (32.3)	
Nonopacification	7/42* (16.7)	11/21 (52.4)	67/99* (67.7)	
Visible shunt flow†				<0.001
No	7/33 (21.2)	7/15 (46.7)	77/89 (86.5)	
Yes	26/33 (78.8)	8/15 (53.3)	12/89 (13.5)	
Suspicious thrombus or vegetation	0/43 (0.0)	3/21 (14.3)	5/100 (5.0)	0.161
Suspicious protrusion	9/43 (20.9)	8/21 (38.1)	31/100 (31.0)	0.259

Data are median (IQR), mean±SD, or n (%). Continuous variables were compared using 2-sample *t* tests or Mann-Whitney *U* tests, and categorical variables were compared using the Fisher exact test. IQR indicates interquartile range; LA, left atrium; and RA, right atrium.

*One case was not suitable for analysis due to poor image quality.

†It was measured by transthoracic echocardiography. Due to poor visibility, 27 devices (group 1, 10 [23.3%]; group 2, 6 [28.6%]; and group 3, 11 [11.0%]) were not properly examined and removed in the analysis.

0.34–0.61) between observers A and B for interobserver agreement and a mean value of 0.93 (0.88–0.99) for intraobserver agreement.

Major and Minor Complications

There were 5 major adverse cardiovascular events (Table S2; Figures 3 and 4): cerebral embolic infarction due to large thrombus in the left atrial sided disc surface (n=1), transient ischemic attack related to device thrombus (n=2), IE requiring surgery (n=1), and pericardial effusion leading to the removal of the device (n=1). The patient who presented with IE was indicated for surgery due to extensive vegetation on the right atrial disc of the device and persistent fever 10 years after device closure with an ASO of 36 mm. The gross morphology of the removed device revealed a large thrombus on the right atrium disc side. The histopathologic finding showed smooth muscle cell infiltration and endothelial cell lining on the surface, corresponding with CCTA findings (Figure 3). A 42-year-old woman who presented for a checkup was found to have newly developed pericardial effusion, and echocardiography and CT revealed device protrusion and focal intradevice contrast opacification, which was suspected as incomplete NE of the ASO device (36 mm) after 9 years of follow-up. The device was deeply embedded into the left and right atrial wall in the surgical field. Still, it did not penetrate the wall, and an incomplete NE of the device's left atrial side was identified (Figure 4). There were 10 minor complications: suspicious thrombus related to the device on CT image (n=6), pericardial effusion (n=3), and transient ischemic attack without evidence of device thrombus (n=1).

Risk Factors for Clinical Outcomes and Incomplete NE

In the comparative analysis of the devices with complete and incomplete NE 6 months after the procedure (Table 3), residual peri- or through-device shunt flow (P=0.038) and moderate-to-severe tricuspid regurgitation (P=0.050) were found more frequently in incomplete NE devices. However, the incomplete NE group had a significantly larger defect size (P<0.001), balloon size (P<0.001), and device diameter (P<0.001). Therefore, Cox proportional-hazards analysis was undertaken to determine the risk factors related to incomplete NE 6 months post-procedure (Table 3; Table S3). The mean defect size by preprocedural TTE, stop-flow diameter during the procedure, and device

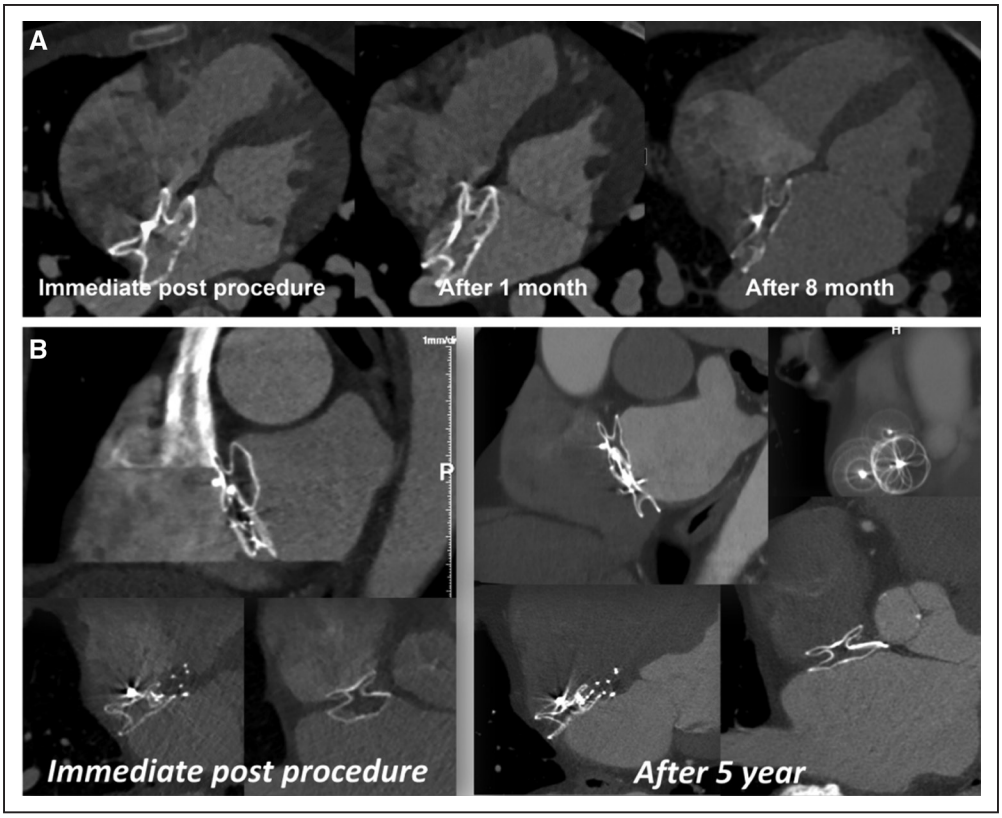

Figure 1. Serial morphological change and neoendothelialization process of devices.
A, Figulla Flex II device, 21 mm. **B**, Multiple devices: Amplatzer septal occluder 19 mm, Gore septal occluder 30 mm, and Figulla Flex II 12 mm.

diameter were significant in univariate analysis. On multivariate analysis, device diameter (hazard ratio, 1.11 [95% CI, 1.04–1.18]; *P*=0.001) was the only significant risk factor. The predictive ability of the device diameter for incomplete NE was evaluated using the receiver operating characteristic curve; the area under curve (with 95% CI) was 0.832 (0.761–0.904), and the cutoff diameter was 21 mm with a sensitivity of 67.9% and specificity of 83.3%. When we compared incomplete NE with a 21-mm diameter as a cutoff, the proportion of complete NE was significantly lower in devices >21 mm (*P*=0.002) in diameter (Figure 5). The device's thickness in the central, aortic, and posterior side was larger in the incomplete NE group, while the proportion of the flattened device was lower.

Additionally, we analyzed risk factors related to major adverse cardiovascular events, and the device diameter was the only significant factor in the Cox proportional-hazards analysis (hazard ratio, 1.25 [95% CI, 1.05–1.48]; *P*<0.0001; Table S4).

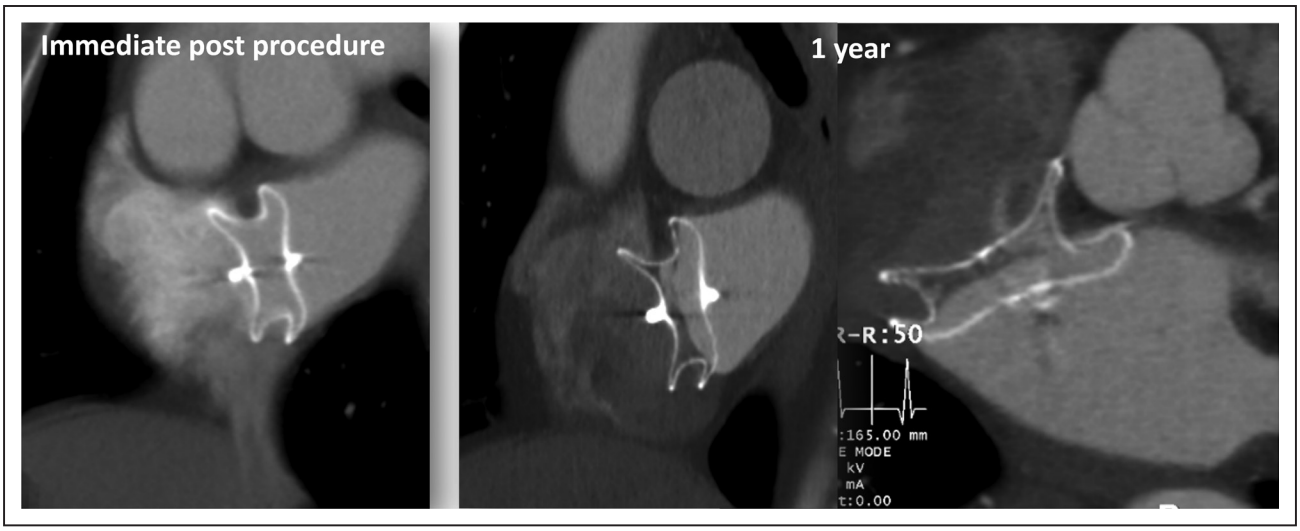

Figure 2. Incomplete neoendothelialization of Amplatzer septal occluder 32 mm after 1 year of implantation.

Table 3. Comparison of Patient and Device Characteristics According to the Status of Neoendothelialization After 6 mo of Procedure

	Complete neoendothelialization (n=78)	Incomplete neoendothelialization (n=42)	*P* value
Patients' characteristics			
Age, y	44.6 (18.0–52.8)	44.5 (30.6–54.2)	0.345
Pulmonary hypertension	16/74 (21.6)	15/39 (38.5)	0.076
Arrhythmia	19/74 (25.7)	18/40 (45.0)	0.058
Echocardiographic parameters			
Visible shunt flow	8/64 (12.5)	12/39 (30.8)	0.038
MR			0.459
Grade 0	62/76 (81.6)	29 (74.4)	
Grade 1	9/76 (11.8)	8/39 (20.5)	
Grade 2	5/76 (6.6)	2/39 (5.1)	
TR			0.050
Grade 0	22/76 (28.9)	9/39 (23.1)	
Grade 1	37/76 (48.7)	16/39 (41.0)	
Grade 2	15/76 (19.7)	7/39 (17.9)	
Grade 3	2/76 (2.6)	7/39 (17.9)	
Device characteristics			
Defect diameter	13.0 (9.0–18.0)	22.0 (18.0–28.0)	<0.001
Balloon size	15.0 (10.5–22.0)	32.5 (26.5–37.0)	<0.001
Defect diameter/TSL	0.26 (0.22–0.32)	0.43 (0.41–0.47)	0.015
Device diameter	16.0 (11.3–22)	29.0 (22.5–34.0)	<0.001
Multiple defects	28/78 (35.9)	10/42 (23.8)	0.219
No. of devices			0.076
Single	55/78 (70.5)	36/42 (85.7)	
Multiple	23/78 (29.5)	6/42 (14.3)	
Device shape			
Thickness: central	4.00 (3.60–5.67)	6.85 (5.43–9.40)	<0.001
Thickness: aortic side	8.00 (6.40–9.90)	13.1 (11.6–15.9)	<0.001
Thickness: posterior side	7.45 (6.30–8.95)	11.2 (9.45–14.0)	<0.001
Device asymmetry	1/78 (1.3)	22/42 (52.4)	<0.001
Device bulkiness			<0.001
Bulky	15/78 (19.2)	8/42 (19.0)	
Partially flattened	1/78 (1.3)	18/42 (42.9)	
Flattened	62/78 (79.5)	16/42 (38.1)	
Suspicious device thrombus*	9/78 (11.5)	5/42 (11.9)	1.00

Data are median (IQR), mean±SD, or n (%). Continuous variables were compared using 2-sample *t* tests or Mann-Whitney *U* tests, and categorical variables were compared using the Fisher exact test. CT indicates computed tomography; IQR, interquartile range; MR, mitral regurgitation; TR, tricuspid regurgitation; and TSL, total septal length.

*Based on contrast CT findings.

DISCUSSION

This study first evaluated the NE of ASD devices by analyzing CT images and assessing risk factors. We differentiated the degree of NE according to intradevice residual contrast opacification on CCTA. Notably, over a third of all devices had incomplete NE after >6 months of device closure.

Knowing the fate of the implanted ASD device is essential for assessing clinical outcomes such as device-related thrombus or IE, which is attributable to delayed NE of exposed fabric and metal with seeding of microorganisms after the procedure and development of thrombus and bacteremia. Several experimental studies found that complete NE occurred within a few weeks after device implantation, and nearly complete NE occurred in 3 months in vivo.[22–24] Thus, in the real-world clinical setting, administration of antiplatelet therapy and prophylactic use of antibiotics has generally been recommended for 6 months after ASD implantation.[25] However,

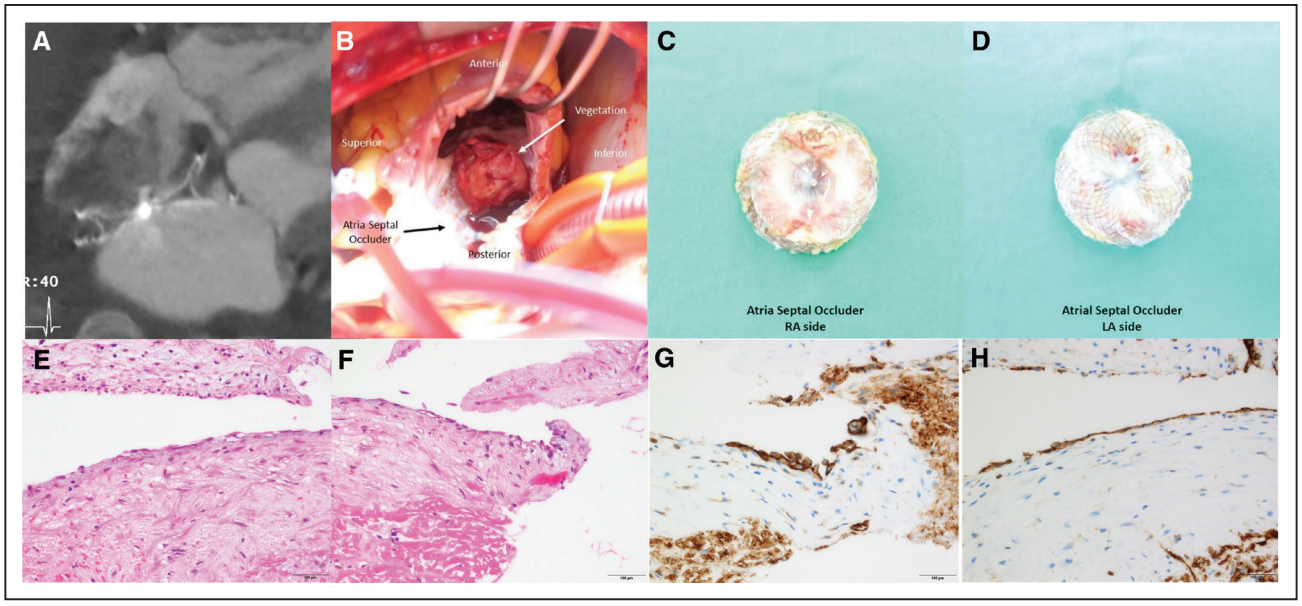

Figure 3. Device-related vegetation and incomplete neoendothelialization.
A, Cardiac computed tomography angiography, (**B**) intraoperative findings, and (**C** and **D**) devices removed by surgery. Hematoxylin-eosin (**E** and **F**) and immunohistochemistry-CD31 examinations (**G** and **H**) revealed endothelial cell lining above the fibrous tissue. CD31 indicates cluster of differentiation 31; LA, left atrium; and RA, right atrium.

limited numbers of human autopsy cases and device extraction revealed almost no endothelialization on the metallic mesh surface beyond 6 months, even though the devices seemed uneventful on previous echocardiography.[26] Herein, we observed varying degrees of NE and suggested that the complete NE of the device takes longer than expected. Rising concerns regarding the adequate duration of antiplatelet/antibiotics prophylaxis after the procedure need to be readdressed.[17,18,22,23,27–30] Therefore, as we suggested, a reliable imaging method to measure complete NE is essential to assess the long-term safety of ASD devices.

Notably, our study showed several novelties in assessing the degree of NE in ASD devices, and suggesting a new way to define complete NE based on CCTA images. Assessment of intracardiac device characteristics and especially the degree of NE by echocardiography is complex due to poor visibility and reproducibility. Considering these limitations, studies related to left atrium appendage devices recently reported the benefit of CT in describing the incomplete NE of devices[31–33] and suggested that CT could overcome those limitations and evaluate the device characteristics in detail; however, this has not been established in ASD devices yet. Immediately after device implantation, the fabric of the device is porous and allows blood and radiographic contrast agents to pass through; it could be used as a way to assess the status of surfaces. Although this study showed that CCTA can be utilized to identify the incomplete NE by measuring intradevice contrast opacification, the use of this modality has not yet been validated. Since it is unclear whether the contrast enhancement results from the gap at the device margins or incompletely covered surface of the implanted devices, a standardized definition of NE, as evaluated by CCTA, is required. We addressed this issue with strategies that previously described the NE of left

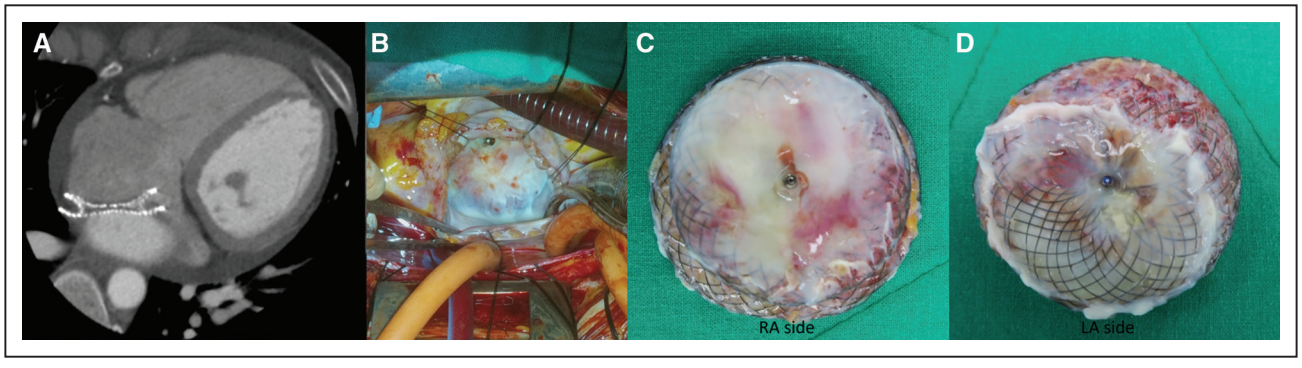

Figure 4. Suspicious device protrusion and incomplete neoendothelialization.
A, Cardiac computed tomography angiography, (**B**) intraoperative findings, and (**C** and **D**) devices removed by surgery. LA indicates left atrium; and RA, right atrium.

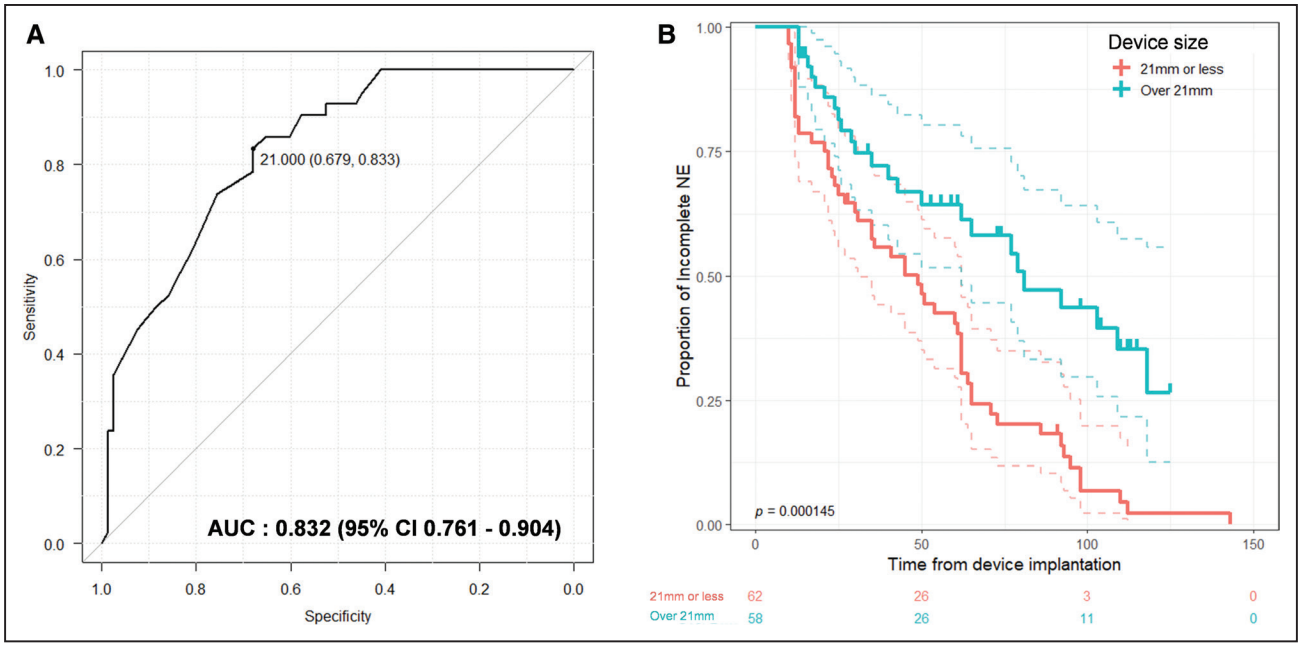

Figure 5. Analysis of device neoendothelialization (NE) according to device diameter.
A, Area under curve (AUC) for incomplete NE after 6 mo of the procedure, categorized by device size and (**B**) Kaplan-Meier curve for incomplete NE, categorized by device size of 21 mm.

atrium appendage devices: the fabric leak reported by Qamar et al[34] (visible diffusion of contrast through the nonendothelialized atrial surface of the device) or the enhancement defect on the atrial surface of the device.[35] Nevertheless, this study not only represents an important progress in the development of an accurate NE assessment method but also reemphasizes the usefulness of the CCTA imaging method for patient follow-up after ASD device closure. A standard definition of NE with a broad scientific consensus would be necessary in the future.

The natural course of ASD devices after the procedure remains controversial due to the limited accessibility of intracardiac devices. Progressive fibrin condensation and accumulation of thrombotic material within the mesh-covered cavity is one of the device healing process.[30,36] To lower any adverse thrombotic events that could cause clinical consequences, prophylactic use of antiplatelet has been suggested. However, when the devices were extracted after the implantation from 1 week to 3 months in animals, most devices were completely or almost completely covered by a white, nonthrombotic glistening pseudointima of variable thickness, which is NE of implanted devices.[37,38] The healing process began with controlled inflammation, consisting of smooth muscle cell infiltration and fibrous tissue generation, leading to endothelial coverage, which resembles the endocardium that develops as a final, biocompatible blood-contacting interface.[39,40] On the contrary, several case reports of extracted devices in humans revealed incomplete NE from 18 months to 7 years after device implantation.[15–17] These were also observed in our histopathologic review of cases with extracted devices. A recently published study based on angioscopy evaluation of ASD devices also supported the possibilities of delayed incomplete NE.[41] Although it is challenging to describe the more reliable mechanism, our assessment via CCTA could aid in understanding the natural course of devices with noninvasive and objective modalities.

In the risk factor analysis for incomplete NE, we found that a larger device size could be attributable to it, consistent with previous findings in the left atrium appendage occluder devices and earlier case repo rts.[31,33,35,42,43] Additionally, our study showed that bulky shape (greater device thickness) was highly correlated with incomplete NE. Structural components of the device might interfere with the NE process; for instance, the fixed stainless steel pin buttons at the center of the device discs might interfere with NE.[44,45] Several reports showed a significant association between bulky shape with greater device thickness and incomplete device NE.[39,41] Although we suggested the cutoff of 21 mm as a predictor for incomplete NE, it is too early to use this value itself to make clinical decisions. Due to the selection bias and other contributing factors, this cutoff value would not necessarily present relevant clinical implications, and this was rather represented to demonstrate the increased risk of incomplete NE in larger devices. To find device-related risk factors, further prospective studies would be necessary.

Regarding the different device types, previous studies observed similar trends of NE regardless of the types (Amplatzer, FFII, Ceraflex, and Helex septal occlude) in animal studies.[36,46–48] Here we compared the CCTA

image findings and clinical outcomes between 2 main devices (ASO versus FSO; Table S5). Although there was no difference in patients' characteristics, defect size assessed through TTE was greater in ASO. The Kaplan-Meyer curve with the log-rank test for the incomplete NE exhibited a higher proportion of incomplete NE in ASO (Figure S2). However, this should be interpreted with caution because of significant differences in case numbers and follow-up periods; the median follow-up time was greatly tweaked (ASO, 54 months; FSO, 12 months; $P<0.001$). Our current data are limited to draw any conclusion about long-term durability issues according to device types. However, finding morphology-related factors would assist in improving the development of durable instruments.

Our work has several limitations because of its retrospective nature, which inherently makes it susceptible to certain biases. Selection bias is a significant limitation as only patients who underwent CCTA due to several clinical causes were included in this study. Therefore, the percentage of NE may also be overestimated as we did not evaluate CCTA on patients without any specific concerns. In addition, the incomplete NE defined by the degree of intradevice opacification could have problems estimating its actual proportion. There may also be incomplete NE in those without opacification within devices; for instance, the extensive thrombosis attached to device surface could affect how contrast agents pass through the device; this study could not differentiate possible mechanisms underlying it. Moreover, due to the limited major adverse cardiovascular events observed in this cohort, it is hard to suggest the predictive factors for worse clinical outcomes. We could not follow-up on the same patients consecutively, and patients were divided into 3 groups according to the time interval between the procedure and CCTA. Therefore, any confounding factor may not have been assessed appropriately. Considering this caveat and the aforementioned limitations, the findings here need to be validated with real-world data from device healing process in the general population.

In conclusion, our study was the first attempt to identify the extent of NE through CCTA and suggested several radiological findings with respect to it. Incomplete NE was observed in a significant number of patients after 6 months of ASD device closure; the device diameter was related to incomplete NE. However, cautious interpretation of these findings in the context of routine clinical practice, such as the duration of antiplatelet or antibiotics therapy, is required. Further investigation on the clinical consequences of incomplete NE is needed to guide the postprocedural therapy strategy.

ARTICLE INFORMATION

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None.

Supplemental Material

Figures S1 and S2
Tables S1–S5

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