Intraprocedural and Long-Term Incomplete Occlusion of the Left Atrial Appendage Following Placement of the WATCHMAN Device: A Single Center Experience

RONG BAI, M.D., F.H.R.S.,*,† RODNEY P. HORTON, M.D.,*,‡
LUIGI DI BIASE, M.D., PH.D., F.H.R.S.,*,‡,§ PRASANT MOHANTY, M.B.B.S., M.P.H.,*
AGNES PUMP, M.D.,* DEB CARDINAL, R.N.,* CHANTEL SCALLON, R.N.,*
SANGHAMITRA MOHANTY, M.D.,* PASQUALE SANTANGELI, M.D.,*
MAURICIO C. BRANTES, M.D.,*,¶ JAVIER SANCHEZ, M.D.,*
J. DAVID BURKHARDT, M.D., F.A.C.C.,* JASON D. ZAGRODZKY, M.D.,*
G. JOSEPH GALLINGHOUSE, M.D.,*
and ANDREA NATALE, M.D., F.H.R.S., F.A.C.C., F.E.S.C.*, ‡, #,**,††

From the *Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, Texas, USA; †Department of Internal Medicine, Tong-Ji Hospital, Tong-Ji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China; ‡Department of Biomedical Engineering, University of Texas, Austin, Texas, USA; §Department of Cardiology, University of Foggia, Foggia, Italy; ¶Universidad de Chile, Hospital Clínico, lndependencia, Santiago, Chile; #Division of Cardiology, Stanford University, Palo Alto, California, USA; **Interventional Electrophysiology, Scripps Clinic, San Diego, California, USA; and ††School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA

Incomplete LAA Occlusion by WATCHMAN Device. ***Introduction:*** **Transcatheter left atrial appendage (LAA) closure with the WATCHMAN device has become one of the therapeutic options in atrial fibrillation (AF) patients who are at high risk for ischemic stroke. However, the incidence and evolution of incomplete occlusion of the LAA during and after placement of the WATCHMAN device has not been reported.**

Methods and Results: **Fifty-eight consecutive patients who had undergone WATCHMAN device implant were included in the study. Intraprocedural, 45-day and 12-month transesophageal echocardiogram images were reviewed and analyzed. Peridevice gap was noted in 16 (27.6%), 17 (29.3%), and 20 (34.5%) patients across the 3 time points. Intraprocedural gaps are more likely to be persistent until 12 months and become larger in size over time. New gap also occurs during follow-up even if the LAA was completely sealed at implantation. One patient had an ischemic stroke 4.7 months after implant; another patient developed a left atrial thrombus over the device 21.6 months after implant. Both patients had intraprocedural gap and discontinued warfarin therapy after the 45-day evaluation.**

Conclusion: **Incomplete LAA occlusion with a gap between the WATCHMAN device surface and the LAA wall is relatively common. Intraprocedural gaps are more likely to become bigger over time and persist, while new gaps also occur during follow-up. Further studies are warranted to verify whether the presence and persistence of a peridevice gap is associated with increased risk of thromboembolic event in AF patients implanted with a WATCHMAN device.** *(J Cardiovasc Electrophysiol, Vol. 23, pp. 455-461, May 2012)*

atrial fibrillation, closure, left atrial appendage, stroke, thrombus, WATCHMAN device

Introduction

Atrial fibrillation (AF) is associated with increased risk of thromboembolic event, making stroke prevention one of the major goals of the therapeutic strategy in AF population. Oral anticoagulation agent, mainly referring to warfarin, is recommended by current guideline to all AF patients at high risk of ischemic stroke. However, chronic anticoagulation

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Address for correspondence: Andrea Natale, M.D., Texas Cardiac Arrhythmia Institute, St. David's Medical Center, 3000 N. I-35, Suite 720, Austin, TX 78705, USA. Fax: +512-544-8184; E-mail: dr.natale@gmail.com

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therapy is contraindicated, untolerated, or refused by 14–44% patients who are at risk for stroke.[1] Because 90% of thrombus formation occurs in the left atrial appendage (LAA) of patients with nonvavular AF, closure of LAA and occlusion of blood flow between LAA and left atrium (LA) may prevent the thrombus formation process and, hence, reduce the stroke events.[2] Several percutaneous devices have been used for LAA occlusion including Amplatzer/Amplatzer Plug, PLAATO, and WATCHMAN.[3] Although the published data demonstrated the feasibility and possible noninferiority in preventing stroke when compared to an anticoagulation drug,[4] only the WATCHMAN device is under consideration for FDA approval. The latest results on the safety and efficacy of WATCHMAN device implantation is encouraging,[5] but the incidence and evolution of incomplete occlusion of the LAA during and after placement of the WATCHMAN device has not been studied. We reported in this study our single-center experience on the incidence, size of the gap, and leak between WATCHMAN device and LAA wall at the implant procedure and during the follow-up.

Methods

Study Population

Consecutive patients undergoing WATCHMAN device (Atritech, Plymouth, MN, USA) implant at the Texas Cardiac Arrhythmia Institute at St. David's Medical Center (Austin, TX, USA) between November 2008 and June 2010 were included in this study. The inclusion and exclusion criteria for WATCHMAN device implantation are as follows.

Inclusion criteria:

- Patient has paroxysmal, persistent, or permanent nonvalvular AF.
- Eligible for chronic warfarin according to the Guideline on treatment of AF.
- CHADS2 score ≥ 1 (congestive heart failure, history of high blood pressure, 75 years of age or older, diabetes, prior stroke, or transient ischemic attack).

Exclusion criteria:

- Contraindicated for warfarin or antiplatelet agent.
- Cardiac function NYHA Class IV or left ventricular ejection fraction (LEVF)$<$ 30%.
- Implanted mechanical valve.
- With closure device for atrial sepal defect (ASD) or patent foramen ovale (PFO).
- Platelets $<$100,000 or hemoglobin $<$10.

WATCHMAN Device Implant Procedure

The procedure of WATCHMAN device implant was previously described.[6] In brief, LA access is obtained via a transseptal route. After that, a delivery catheter is advanced to approach the LAA. The self-expanding device is constrained within the delivery catheter until deployment into the LAA. To ensure enough compression for stable positioning of the device, the device size (21 mm, 24 mm, 27 mm, 30 mm, or 33 mm) was chosen to be 20% larger than the diameter of LAA measured by the intraprocedural transesophageal echocardiogram (TEE). The WATCHMAN device was deployed into the LAA by retracting the covering sheath. LAA angiogram and TEE were performed to verify an appropriate position of the device in the LAA. A final position was deemed satisfactory if the WATCHMAN device was stable in the LAA, the LAA was completely sealed or only one gap with jet size $\leq$5 mm was present between the WATCHMAN device and the LAA wall, determined by the operator and the echocardiographer based on real-time TEE measurement and fluoroscopy. Then the device was released from the delivery catheter. However, the device can be partially recaptured and redeployed if the position was not acceptable to the operator.

Intraprocedural and Follow-Up TEE

The entire implant procedure was guided by TEE, which helps in evaluating the LAA seal quality by the WATCHMAN device. If a gap was present on B mode image, the width of the gap was measured at the ostium of LAA at the best view of the gap. Immediately after the device was released, the final deployed device diameter was measured by TEE and compared with the diameter of original implant (device size), from which the device compression ratio was calculated and expressed in percentage.

A repeat TEE was scheduled 45 days and 12 months after the implantation to assess the gap and residual peridevice flow, as well as device position and stability. All the TEE images (intraprocedural, 45-day and 12-month) were stored on disk and reviewed by a single cardiologist who was blinded to the implant procedure. The results of this study were based on the off-line measurement.

Periprocedural Anticoagulant Therapy

Before WATCHMAN device implant, patients' warfarin therapy was adjusted and the last preprocedure (usually within 24 hours of the procedure) international normalized ratio (INR) was $<$2.0. Patients were fully heparinized throughout the procedure with a recommended minimum active clotting time of 200–300 seconds after the transseptal puncture. After device placement and before discharge, warfarin therapy was restarted to achieve an INR of 2.0–3.0 together with 81 mg daily aspirin, which were maintained through the 45-day follow-up visit. If the 45-day TEE evaluation indicated complete LAA occlusion or residual blood flow jet size $<$5 mm, the patient was allowed to discontinue warfarin therapy but begin daily one 325 mg aspirin and clopidogrel (dosage per physician order). If any TEE evaluation indicated residual blood flow with a jet size $>$5 mm around the margins of WATCHMAN device, the patient continued or reinitiated warfarin therapy and a daily 81 mg aspirin until the LAA occlusion occurred or a jet size $<$5 mm was noted.

Follow-Up

Patients were followed up by office visits at 45 days, 6 months, 12 months, and semiannually thereafter. In addition to required 45-day and 12-month TEE, patients were monitored for stroke, systemic embolic event, and death. When necessary, a neurological consult and evaluation were performed.

Statistics

Continuous data are described as mean $\pm$ standard deviation and as counts and percent if categorical. Kruskal–Wallis analysis of variance, chi-square test, and Fisher's exact test were used to compare groups. The change in gap size over

time was assessed using within-subject repeated measures design with general linear model procedure. Correlation between parameters was evaluated using Spearman's correlation coefficients. All tests were 2-sided and P value 0.05 was considered significant. Analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Fifty-eight consecutive patients (74 ± 9 years, male 37 [63.8%], LVEF 56 ± 7, LAA orifice diameter 19.7 ± 4.1 mm, LAA length 26.4 ± 5.2 mm) undergoing LAA occlusion using WATCHMAN device were included in the study. The average CHADS2 score in the study population was 2.2 ± 1.0, with 43 (74%) having a score ≥2. Successful implantation was achieved in all 58 patients. Nine (16%) patients received a 21 mm, 29 (50%) a 24 mm, 14 (24%) a 27 mm, and 6 (10%) a 30 mm device. Warfarin was discontinued in 55 patients after the 45-day visit, but it was not interrupted in the other 3 patients.

Twenty-two (37.9%) patients were classified as paroxysmal AF at enrollment and 20 (34.5%) patients had permanent ventricular pacing lead(s). All patients had history of AF. AF was present in 44 patients (75.9%) at the implant day, in 43 patients (74.1%) at the 45-day visit, and in 42 patients (72.4%) at the 12-month follow-up evaluation (P = 0.91). The LA diameter did not show any significant change over time (baseline 42.3 ± 9 mm vs 41.6 ± 8 mm at 12-month, P = 0.461). No changes in the AF type were seen at follow-up. When assessing the relation between the change in gap size and change in LA diameter at 12-month, no significant correlation was observed (correlation coefficient = 0.34, P = 0.76).

All gaps regardless of the size noted at the intraprocedural or follow-up TEEs were counted and included in the final analysis. Although the majority of patients (33 [56.9%]) showed optimal closure of the LAA with no peridevice flow (group 1) at any of the 3 TEE evaluations, 7 (12.1%) patients with no intraprocedural gap developed new gap at 45-day follow-up (group 2); 4 (6.9%) had intraprocedural gap that closed at subsequent assessments (group 3); in 2 patients new gap developed after the 45th day, while in other 2 patients intraprocedural gap closed at the 45th day but reopened at the 12-month follow-up (6.9%; group 4); in the remaining 10 (17.2%) cases the intraprocedural gaps persisted at 45-day and 12-month follow-up (group 5). At the 12-month TEE evaluation, there were still 20 patients (34.5%) with gap (Fig. 1). The patients' characteristics are presented in Table 1.

In all patients who presented with a gap, the average gap size was 2.53 ± 1.21 mm at the time of the procedure (16 patients, 27.6%), 3.02 ± 1.38 mm at 45th day (17 patients, 29.3%), and 3.36 ± 0.51 mm at 12-month follow-up (20 patients, 34.5%). As demonstrated in the results from the repeated measure analysis, the change over time was not significant (P = 0.765). The change in gap size over time was further assessed among patients with intraprocedural gaps that persisted until 12 months. The results showed that the size of gap increased over time: intraprocedural 2.55 ± 1.27 mm, 45-day 3.49 ± 1.52 mm, and 12-month 3.60 ± 0.85 mm (P = 0.037; Fig. 2).

The compression ratio was 16.29 ± 4.51% (8.3–25.7%, Table 1) after the WATCHMAN device was deployed at its final position. A subanalysis was performed with grouping the cohort into 3 levels of device compression: 8–12% (level 1), 13–17% (level 2), and 18–26% (level 3) compression, and distribution of intraprocedural gap. However, there was no significant difference among the 3 levels in terms of incidence of intraprocedural gap (33%, 36%, and 28% for level 1, 2, 3, respectively; P = 0.85) and size of intraprocedural gap (2.43 ± 0.69 mm, 2.43 ± 1.18 mm, 2.78 ± 1.66 for level 1, 2, 3, respectively; P = 0.42).

The WATCHMAN device was implanted successfully in all 58 patients. Only 1 patient (1.7%) developed postprocedural pericardial effusion with cardiac tamponade, which was resolved with pericardial drainage. No device dislodgement was seen in the study population. Warfarin was discontinued in 55 patients after an office visit and TEE evaluation 45 days after the procedure.

During 25.9 ± 13.4 months follow-up, 1 patient (1.7%) developed a stroke 4.7 months after the WATCMAN device implantation. This patient was noted to have a 3-mm intraprocedural gap and a 4-mm gap at 45-day evaluation when warfarin was withdrawn at the physician's discretion because the leak was smaller than 5 mm and considered "acceptable and safe" (Fig. 3). After the thromboembolic event, the patient was treated with surgical resection of WATCMAN device and complete removal of LAA. Interestingly, no gap was seen on the gross specimen of the LAA with the WATCHMAN device. In another patient, intraprocedural TEE detected a 3-mm gap, which was considered closed at the 45-day and 12-month TEE assessments. Warfarin was discontinued. However, a repeat TEE at 21.6 months after the procedure showed a large clot (10.98 × 14.87 mm) over the WATCMAN device (LA-facing surface; Fig. 4). Dense "smoke" was also detected in the LA. Warfarin therapy was reinitiated in this patient even though there was no evidence of stroke or systemic embolism.

Discussion

The main findings of this study are: (1) incomplete occlusion of the LAA with gap and blood leak is commonly seen in patients undergoing WATCHMAN device implant; (2) the size of the gap may increase; and (3) patients without intraprocedural gap may develop new gap after the device implant.

The frequency of thrombus formation in LAA in patients with AF has led to the hypothesis that exclusion of the LAA may reduce the risk of stroke. Concurrent prophylactic LAA exclusions have been performed as an adjunct to cardiac surgery in patients at high risk of LAA related thromboembolism, while occlusion of the LAA can also be formed by percutaneous catheter-based techniques as opposed to surgical ligation or amputation.[7] The WATCHMAN device, designed for LAA occlusion, is composed of a self-expanding nitinol frame structure with fixation barbs and a polyethylene membrane that covers LAA-facing surface of the device. The safety and feasibility of the WATCHMAN device was initially assessed by a pilot study followed by a prospective randomized clinical trial. The PROTECT-AF study is the first one that directly compared a LAA occlusion device (WATCHMAN) head-to-head with warfarin therapy in AF patients. The results showed that the primary efficacy event rate for occurrence of all-cause stroke, systemic embolism, or all-cause death was 3/100 patient-year in the

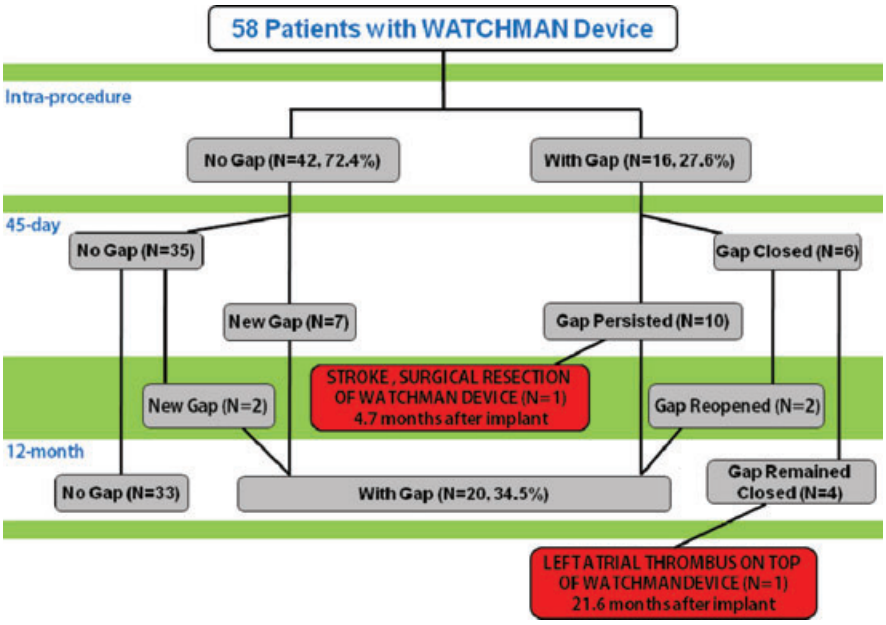

Figure 1. *Incidence of peridevice gap and thromboembolic event in the study population at the time of implant of the WATCHMAN device and during follow-up.*

Table 1

Baseline Demographics and Procedure Parameters of Patients in Different Group Categorized by the Characteristics of Peridevice Gap

Variable	Total Population (n = 58)	Group 1 (n = 33)	Group 2 (n = 7)	Group 3 (n = 4)	Group 4 (n = 4)	Group 5 (n = 10)	P Value
LVEF (%)	55.86 ± 7.41	55.92 ± 8.31	57.14 ± 3.93	53.75 ± 6.29	55 ± 9.13	56 ± 7.75	0.915
LAA Ostim dimension (mm)	19.72 ± 4.07	20.12 ± 4.68	16.71 ± 3.25	21.75 ± 4.86	19.5 ± 1.73	20.13 ± 2.47	0.163
LAA length (mm)	26.05 ± 5.4	24.69 ± 5.37	25.79 ± 5	26 ± 2.83	26.5 ± 4.43	29.46 ± 6.15	0.191
BMI	29.19 ± 6.56	29.63 ± 7.34	28.97 ± 5.28	30.5 ± 3.79	27.23 ± 2.12	28.5 ± 7.9	0.893
Age (years)	73.78 ± 8.55	73.28 ± 9.51	73.29 ± 2.14	74.25 ± 8.26	75.75 ± 6.95	74.4 ± 10.57	0.961
INR before procedure	1.48 ± 0.32	1.41 ± 0.29	1.52 ± 0.23	1.33 ± 0.23	1.3 ± 0.14	1.78 ± 0.39	0.252
Selected device size (mm)	25.04 ± 2.84	25.13 ± 3.4	24 ± 2.45	27 ± 2.45	25.5 ± 1.73	24.6 ± 1.9	0.415
Device dimension on intraprocedural TEE (mm)	20.95 ± 2.51	21.03 ± 2.94	19.93 ± 2.35	23 ± 1.63	20.95 ± 1.22	20.66 ± 1.94	0.273
Device compression ratio (%)	16.29 ± 4.51	16.28 ± 4.04	16.91 ± 5.42	14.7 ± 1.72	17.55 ± 7.55	15.99 ± 5.01	0.893

Group 1: No gap all the time; Group 2: No gap at procedure, but new gap developed at 45-day follow-up; Group 3: Intraprocedural gap that closed at 45-day and 12-month follow-up; Group 4: Intraprocedural gap closed at 45-day but reopened at 12-month follow-up or new gap develop at 12-month follow-up; Group 5: Gap noted at procedure, and continued at 45-day and 12-month follow-up.
LVEF = left ventricular ejection fraction; LAA = left atrial appendage; BMI = body mass index; INR = international normalized ratio; TEE = trans-esophageal echocardiogram.

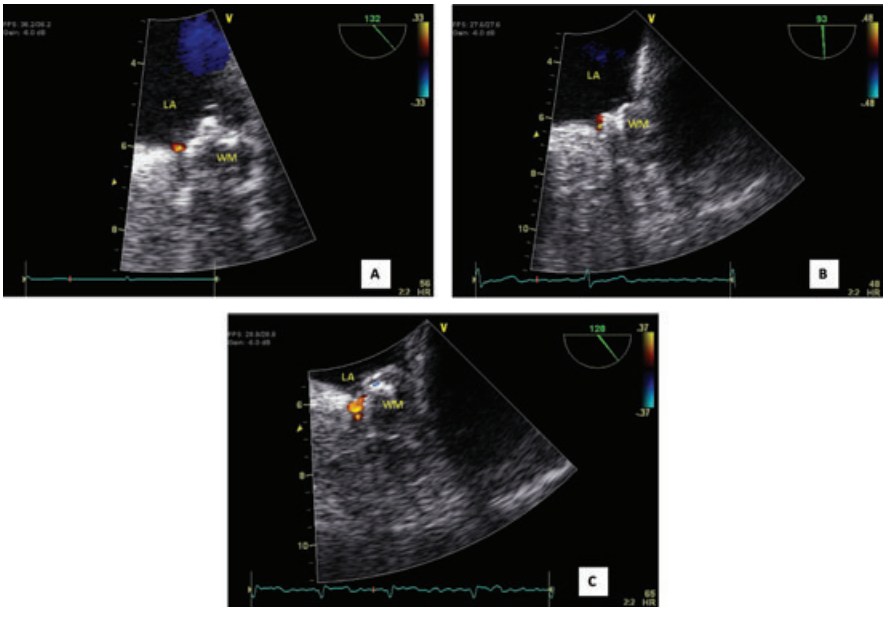

Figure 2. *An example of TEE Colored-Doppler image of persistent peridevice gap with blood leak (star) in a same patient. A: Intraprocedural; B: 45-day follow-up; C: 12-month follow-up.*
LA = left atrium; TEE = transesophageal echocardiogram; WM = WATCHMAN device.

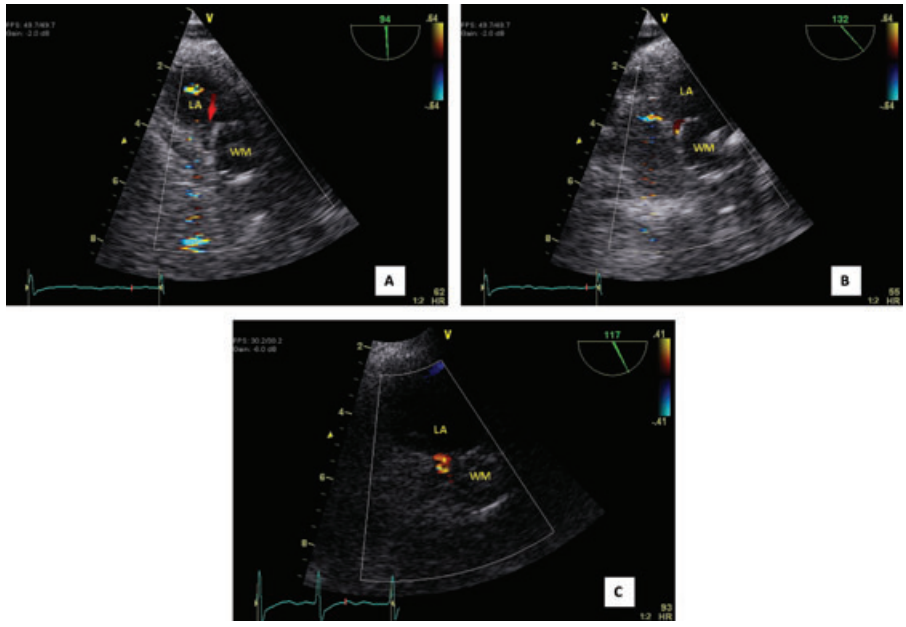

Figure 3. *Pictures of the patient who developed a stroke 4.7 months after WATCHMAN device implant. Intraprocedural TEE showed a peridevice gap (A, red arrow) with intermittent blood leak (B, star). This gap persisted at the 45-day TEE evaluation and became enlarged in size with a blood jet size of 4 mm (C, star). Patient underwent surgical removal of the entire LAA with the WATCHMAN device. On the dissected gross specimen, no niche between the device surface and the LAA wall was noted. LA = left atrium; LAA = left atrial appendage; TEE = transesophageal echocardiogram; WM = WATCHMAN device.*

WATCHMAN group and 4.9/100 patient-year in the warfarin group, which met a greater than 99% probability of noninferiority. Eighty-six percent of the patients who receive a WATCHMAN device could stop taking warfarin at 45th day based on the criteria of study protocol[3,4]; however, the rate of stroke was 50% higher in the WATCHMAN group compared to the warfarin group (3% vs 2%).[8] The safety event rate for occurrence of procedure related complications was also high in the LAA occlusion group.[3]

The WATCHMAN device is always placed distal to the ostium of the LAA, optimally with the shoulder of device at the same level of LAA orifice. It is designed to occlude blood flow and prevents the migration of thrombus forming in the appendage. The fixed circular-shaped device is available in 5 sizes from 21 to 33 mm in diameter. To ensure sufficient and stable positioning of the device, the device size is chosen according to it being 20% larger than the diameter of the LAA body.[6] However, bearing in mind the geometric complexity and individual variation of the morphology of the LAA,[9,10] one may expect that an incomplete occlusion could be present. In other words, even though the device is well anchored inside the LAA at implant, there is the possibility of a gap between the LAA wall and the device surface. In our series, gap with blood leak was demonstrated by serial TEEs in more than 40% of patients who underwent WATCHMAN implant, either immediately after the device was deployed or during the follow-up period. An 8–20% compression ratio was also recommended as a criterion to release the device. When a bigger size WATCHMAN device is deployed in the LAA, it may not fully (100%) expand because of the restriction by a relatively smaller LAA. So this measurement (compression ratio) reflects, to some extent, how tightly the LAA wall is attached with the device. However, we found no association between the completeness of LAA closure and

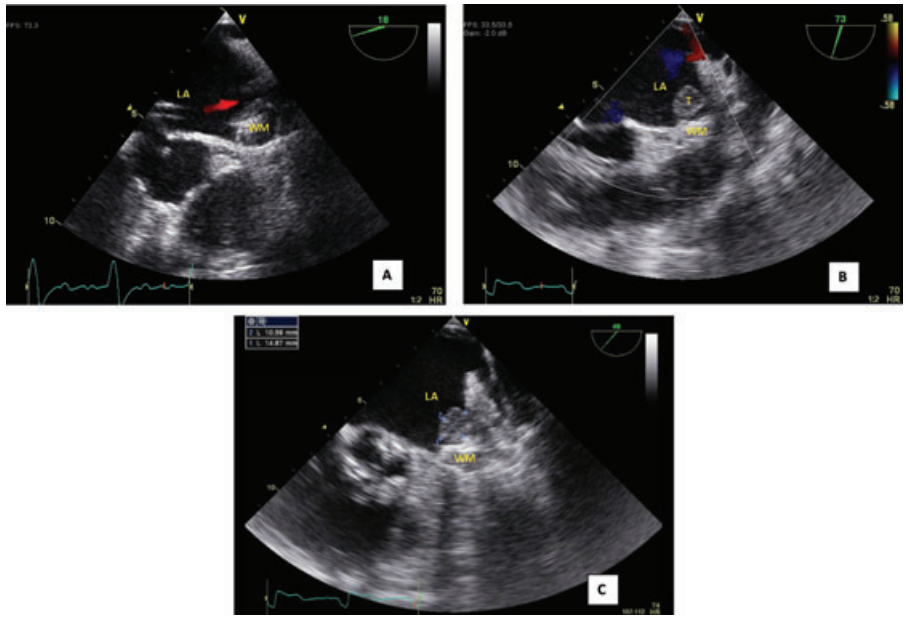

Figure 4. *TEE images of the patient who developed an LA thrombus 21.6 months after WATCHMAN device implant. Intraprocedural TEE showed a peridevice gap (A, red arrow). At the 21.6-month follow-up, a large thrombus (T) was noted over the WATCHMAN device (LA-facing surface; B). This thrombus measured 10.98 × 14.87 mm (C). LA = left atrium; LAA = left atrial appendage; TEE = transesophageal echocardiogram; WM = WATCHMAN device.*

the level of WATCHMAN device compression. It indicates that the presence of intraprocedural gap/leak was mainly due to the mismatch between the device shape and LAA morphology, as well as the position of device within the LAA.

The pathophysiological consequence after the implant and the interaction between the WATCHMAN device and the LAA are poorly understood thus far. In our series, we observed that an intraprocedural gap could persist, close or close and reopen during the follow-up period. In 7 patients the LAA was perfectly sealed by the WATCHMAN device at the end of procedure, but a new gap was detected at 45-day TEE. Of interest, all these 7 gaps persisted through 1 year. What is happening after WATCHMAN implantation is a complex process that may include 1 or more of the following changes in the same patient: (1) The LAA might shrink and become more tightly anchored with the device if the LAA ostium was completely blocked by the device; (2) Progressive LA/LAA remodeling occurs over time in persistent AF, which might be associated with a dilation or deformation of these structures. Because the LAA myocardium has a higher distensibility than the LA myocardium, the disconcordance may lead to splitting of the device struts from the LAA wall[11]; (3) Under a fluid-dynamical effect of blood flow antegradely or/and retrogradely passing through the gap, the size of gap may become larger over time; (4) With the force of LA and LAA contraction, the relative position of the device inside LAA may slightly change, which generates a mechanical stretch to the LAA wall; and (5) During the period time of endothelialization, the endothelial proliferation, organization of microthrombus and fibrotic tissue may fill up a gap, partially or fully. These could explain the different situations we found in our patients after WATCHMAN device implantation. Our findings also suggested that a newly developed gap after implant is less likely to spontaneously close during follow-up.

A peridevice gap with mild blood leak may not affect the stability of the WATCHMAN device inside LAA, as evidenced by the fact that no device dislodgement occurred in our patients. We also did not see any significant difference of the incidence of AF in the study population over time or correlation between the size of LA and the variation of gap size during follow-up period. However, whether an incomplete LAA occlusion is associated with more thromboembolic event remains unclear. It has been reported that in patients with incomplete surgical ligation, 50% had spontaneous echo smoke or thrombus in the LAA, whereas 22% developed thromboembolic events.[12,13] In fact, thrombus formation after implantation has been associated with both PLAATO (ev3 Inc., Plymouth, MN, USA) and AMPLATZER (AGA Medical Corp., Minneapolis, MN, USA) device,[11,14] another 2 transcatheter LAA closure systems in addition to the WATCHMAN device. Theoretically a small communication between the LA and the LAA may (1) result in higher blood velocity at the LAA os, which might actually increase the risk of stroke[15]; and (2) produce stagnation of low velocity blood flow within the LAA that would then be a milieu of thrombus formation and continue to serve as a potential source of embolization because a port of entry into the systemic circulation still exists.[11] In one of our patients who had a stroke 4.7 months after the WATCHMAN device implantation, the intraprocedural gap persisted and became slightly larger at the 45-day TEE. Warfarin therapy was discontinued because the gap size still remained in the "safe limits" suggested by previous publications.[4-6] However, the gap in this patient was detected only by TEE, but it did not show on the dissected gross specimen of the LAA and the WATCHMAN device. Stöllberger reported a similar case with thrombus formation from delayed incontinence of a PLAATO device. They detected on TEE a thrombus and blood flow jet in the niche between the LAA wall and the PLAATO device, which were not visualized by cardiac MRI. Both cases supported our hypothesis that this kind of small peridevice gap could behave in an "intermittent open and close" pattern—becoming manifested only with a dynamic force (e.g., contraction of the heart) but collapsed in a standstill condition. Another patient from our center with intraprocedural peridevice gap developed a large LA thrombus over the WATCHMAN device as late as 21.6 months postprocedure. Since that the presence or persistence of gap/leak might not be really "benign," our data raise concerns about whether it is appropriate to discontinue warfarin as early as 45 days after WATCHMAN device implantation, because new gaps may occur or initially closed gaps may reopen after 45 days. Necessity and length of warfarin therapy after WATCHMAN device implantation need to be determined by further studies. Furthermore, even though animal studies have shown that complete endothelialization (endocardial lining) on WATCHMAN device surface can be achieved in approximately 30–45 days,[16] the possibility of clot formation still exists, especially on the LA-facing surface. In addition, given the extent of comorbidities in some AF patients and the possible presence of a systemic coagulation and platelet dysfunction, an approach that only targets LAA occlusion may not be sufficient.[15]

Study Limitation

We have a small population; therefore, this study has limited power to determine a statistically significant association between the presence of peridevice gap or its size and clinical events. This is a retrospective analysis. However, data were prospectively entered into a database.

Conclusion

Peridevice gap with blood leak is common after WATCHMAN device implantation. Most of the intraprocedural gaps may persist through 12 months while new gaps also occur during the follow-up. The size of gap shows no significant association with the device compression level or with the time when it develops; however, if persistent, the size of the gap may increase over time. Whether the presence, the persistence or the variation of gap size are markers of the risk of thromboembolic event needs to be verified by large, controlled clinical trial with long-term follow-up.

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