

# Explantation of Patent Foramen Ovale Closure Devices

## A Multicenter Survey

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**Objectives** The aim of this study was to examine the frequency and causes of surgical explantation of patent foramen ovale (PFO) closure devices.

**Background** PFO has been linked with cryptogenic strokes, recurrent transient neurologic deficits, sleep apnea, decompression illness, and migraines. Several randomized trials are in progress to determine whether PFO closure is preferable to medical management in the treatment of patients with cryptogenic strokes or migraine. The majority of PFO closures are performed off-label, because there is no U.S. Food and Drug Administration approval for use of any device to close a PFO. As data are accumulating on the benefits of implanting PFO closure devices, it is also important to examine complications that might occur.

**Methods** We performed a database review to identify the frequency and causes of PFO device explantation, examining 18 PFO closure centers in Europe and the United States.

**Results** Of the 13,736 percutaneous PFO device implantations performed over the past 9 years at these 18 institutions, 38 devices (0.28% [95% confidence interval: 0.20% to 0.37%]) required surgical removal. There were a wide range of causes cited for these removals. The most common cause for explantation was chest pain (n = 14), often determined to be secondary to nickel allergy to the PFO device. Other causes for explantation included persistence of a residual shunt (n = 12), the presence of thrombus on the device (n = 4), pericardial effusion (n = 2), perforation of the atrium or aortic root (n = 2), recurrent strokes (n = 1), the development of endocarditis (n = 1), and undocumented reasons (n = 2).

**Conclusions** The vast majority of PFO closure procedures are performed safely with minimal complications. However, there is a small (0.28%) incidence of severe long-term problems associated with PFO closure that might require surgical removal of the device. In addition, the frequency of surgical explantation was found to be device-dependent; some of these devices seem to be safer than others. (J Am Coll Cardiol Intv 2011;4: 579–85) © 2011 by the American College of Cardiology Foundation

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Patent foramen ovale (PFO) is associated with cryptogenic strokes, recurrent transient neurologic deficits, sleep apnea, decompression illness, and migraines (1). Approximately 20% of adults have a PFO (2), and it is estimated that 8,000 PFO closure procedures are performed each year in the United States, with various devices (3).

Percutaneous closure of PFO is very effective, with nearly 90% of patients displaying complete closure of their PFO after 1 year (4). Multiple observational studies describe the apparent safety of PFO closure with percutaneous devices (5). Several randomized trials are in progress to determine whether PFO closure is preferable to medical management in the treatment of patients with cryptogenic strokes or migraine, with respect to efficacy as well as safety (6,7).

As data are accumulating on the benefits of implanting PFO closure devices, it is important to also examine complications that might occur. Currently, there is no U.S. Food and Drug Administration approval for any PFO closure indication; nevertheless, PFOs are being closed off-label without a clear understanding of the relative frequency of complications. There have been isolated reports of patients that needed to have their device removed. Because extraction of a

PFO device requires open heart surgery, we wanted to determine the relative frequency of this untoward event.

#### Abbreviations and Acronyms

**ASD** = atrial septal defect  
**CI** = confidence interval  
**PFO** = patent foramen ovale  
**TEE** = transesophageal echocardiogram

#### Methods

A retrospective survey was performed to identify the frequency and causes of PFO device ex-

plantation by examining 18 PFO closure centers in Europe and the United States. The total number of PFO device implantations was obtained from each institution. The number of patients who underwent surgical explantation of their device was determined. The information was obtained from each institution as an aggregate total number of explants and total number of implants without personal identifiers attached. This study was approved by the research review board of each institution. The time period covered was different for each institution but includes all cases that were performed at that institution. Because this was a retrospective, self-reporting study, underreporting has to be assumed.

Data were obtained on the type of device used for implantation, type of device that was explanted, and the causes for explantation. Information was also obtained with regard to patients who had prolonged chest pain (>1 year) but who did not undergo device explantation. This registry did not address device closure of atrial septal defects (ASDs), which might have a higher rate of surgical explantation.

#### Results

There were 13,736 devices implanted among the 18 centers over the past 3 to 9 years. Amplatzer (AGA Medical Corporation, Golden Valley, Minnesota) devices were used in 9,109 (66%) of the procedures. CardioSEAL (NMT Medical, Boston, Massachusetts) devices were implanted in 2,023 (15%) patients. Helex (W.L. Gore and Associates, Flagstaff, Arizona) devices were employed in 1,201 (9%) implantations, and 1,403 (10%) other devices were used, including Sideris (Custom Medical Devices, Amarillo, Texas), PFO Star (Cardia, Inc., Burnsville, Minnesota), Occlutech (International Occlutech AB, Helsingborg, Sweden), Solysafe (Swissimplant AG, Solothurn, Switzerland), Premere (St. Jude Medical, Maple Grove, Minnesota), FigullaFlex (International Occlutech), Cierra (Cierra, Redwood City, California), Coherex (Coherex, Salt Lake City, Utah), Angelwings (Microvena Corporation, White Bear Lake, Minnesota), SeptRX (SeptRX, Fremont, California), or BioStar (NMT Medical).

There were a total of 38 devices explanted at these institutions. The 19 Amplatzer devices accounted for 50% of the explanted devices, and the 16 CardioSEAL devices accounted for 42%, but the frequency of explantation is device-dependent. There were 2 (5%) Helex devices that were surgically excised. There was also 1 (3%) incident of 1 of the lesser-used devices (Sideris) that was explanted. A summary of the results from this self-reporting survey are provided in Tables 1, 2, and 3.

Among the 38 total explantations, 14 (37%) patients underwent surgical excision of their device for chest pain, and of these, 7 (18%) had nickel allergy, 12 (32%) devices were explanted because of the persistence of a residual shunt; 4 (11%) patients had the device removed secondary to thrombus formation on the device, and 2 (5%) devices were taken out because of pericardial effusion. Erosion was responsible for 2 (5%) devices being explanted. Recurrent stroke accounted for the removal of 1 (3%) PFO closure device, 1 (3%) device was excised secondary to development of an infection stemming from the device, and 1 (3%) was removed due to the persistence of migraine symptoms. There was 1 (3%) device taken out due to an unspecified cause. In addition to the 38 patients who underwent explantation, there were 3 patients with prolonged chest pain (>1 year) who did not

**Table 1. Type of Device, Number of Implants and Explants Reported**

	CardioSEAL	Amplatzer	Helex	Other	Total
Implantations	2,023	9,109	1,201	1,403	13,736
Explantations	16	19	2	1	38
% explanted	0.79%	0.21%	0.17%	0.07%	0.28%

Amplatzer (AGA Medical Corporation, Golden Valley, Minnesota); CardioSEAL (NMT Medical, Boston, Massachusetts); Helex (W.L. Gore and Associates, Flagstaff, Arizona). The difference between the frequency of explanted Amplatzer and CardioSEAL devices is statistically significant (chi-square = 17.9,  $p < 0.00003$ ).

**Table 2. Implantations and Explantations/Device by Institution**

Institution	Implantations					Explantations				
	AMP	CS	HX	Other	Total	AMP	CS	HX	Other	Total
Brescia, Italy	750	0	0	110	860	2	0	0	0	2
Columbia University	4	1,104	73	2	1,183	0	3	1	0	4
Emory University	225	0	5	20	250	0	0	0	0	0
Evanston Hospital	42	0	53	3	98	0	0	0	0	0
Intermountain Medical Center, SLC	1,529	246	250	0	2,025	4	1	0	0	5
Mayo Clinic, Rochester	660	3	32	0	695	0	0	0	0	0
Rush University	600	0	150	0	750	0	0	0	0	0
Sankt Katharinen, Frankfurt, Germany	1,635	27	485	1,128	3,275	1	0	0	0	1
Swedish Medical Center	35	211	0	0	246	1	3	0	0	4
UCLA	150	35	45	0	230	3	2	1	0	6
UMDNJ, Cooper University Hospital	125	40	0	0	165	0	0	0	0	0
University Hospital, Bern, Switzerland	1,350	20	5	125	1,500	0	0	0	1	1
University of Colorado	425	25	0	0	450	0	0	0	0	0
University of Milan, Italy	348	0	0	15	363	0	0	0	0	0
University of Pennsylvania	115	105	5	0	225	1	1	0	0	2
University of Utah	484	35	91	0	610	3	0	0	0	3
University of Washington	92	112	7	0	211	1	0	0	0	1
Washington University, St. Louis	540	60	0	0	600	1	2	0	0	3
Total	9,109	2,023	1,201	1,403	13,736	19	16	2	1	38

Explantations were not necessarily performed at the same institution where the devices were implanted.

AMP = Amplatzer; CS = CardioSEAL; HX = Helex; SLC = Salt Lake City; UCLA = University of California at Los Angeles; UMDNJ = University of Medicine and Dentistry of New Jersey.

undergo surgical excision of their device, but surgery was discussed with the patient. In 1 patient, the symptoms resolved gradually after 1 year, and another patient was lost to follow-up.

Of the 14 cases of chest pain, 10 (71%) patients had Amplatzer devices, 2 (14%) patients had CardioSEAL devices, and 2 (14%) patients had Helex devices. Nickel allergy was present in 7 of these 14 patients with chest pain, as documented by a reaction to the TRUE (Allerderm, Phoenix, Arizona) skin patch test. All 7 of these patients had Amplatzer devices in place, and treatment was attempted with clopidogrel, steroids, and/or non-steroidal anti-inflammatory drugs before undergoing surgical explantation of their device. Of the 14

patients with chest pain, there were 7 who were not tested for nickel allergy and therefore were designated as having refractory chest pain of unknown etiology. Of the 7 patients who were not tested for nickel allergy, 3 had Amplatzer devices, including an individual determined to have coronary sinus obstruction. This patient began experiencing chest pain on exertion 1 month after the procedure. The 35-mm Amplatzer PFO Occluder (the largest available size) was explanted 6 months after the closure procedure. CardioSEAL devices were placed in 2 of the patients. There was also 1 case of a 25-mm Helex device that was removed 3 weeks after implantation, for intractable chest pain. There was 1 other case of a Helex device

**Table 3. Reasons for Explantation/Device**

	Amplatzer (n = 9,109)	CardioSEAL (n = 2,023)	Helex (n = 1,201)	Other (n = 1,403)	Total (n = 13,736)
Chest pain	10 (0.11%)	2 (0.10%)	2 (0.17%)	0	14 (0.10%)
Residual shunt	4 (0.04%)	8 (0.40%)	0	0	12 (0.09%)
Thrombus	1 (0.01%)	3 (0.15%)	0	0	4 (0.03%)
Perforation	1 (0.01%)	1 (0.05%)	0	0	2 (0.01%)
Pericardial effusion	2 (0.02%)	0	0	0	2 (0.01%)
Recurrent stroke	0	1 (0.05%)	0	0	1 (0.01%)
Infection	0	1 (0.05%)	0	0	1 (0.01%)
Other	1 (0.01%)	0	0	1 (0.08%)	2 (0.01%)
Total	19 (0.21%)	16 (0.79%)	2 (0.17%)	1 (0.08%)	38 (0.28%)

Percentages represent the number of specific devices explanted/specific devices implanted.

n = number of implantations performed, with respect to each specific device.

being explanted 6 months after closure for complaints of chest pain and new onset atrial fibrillation.

In addition to the 14 individuals who had their devices removed because of chest pain, there were 2 other patients that had their devices taken out for a large residual shunt (1 Amplatzer, 1 CardioSEAL) who also complained of chest pain. The chest pain symptoms resolved in all 16 patients who underwent surgical explantation of their device.

There were 12 (0.09%) instances of explantation secondary to residual shunt, relative to the 13,736 implantations; 8 of these procedures were for CardioSEAL devices (0.40% of such devices), and 4 were for Amplatzer devices (0.04%). In all of these cases, there were indications of device malposition or new atrial tears that directed the operators to choose explantation instead of placement of a second device.

Thrombus formation on the device was the justification for surgical excision in 4 (0.03%) of the 13,736 device implants. Of the 4 devices explanted with thrombus in the current study, 3 were CardioSEAL devices (0.15% of such devices) and 1 was an Amplatzer device (0.01%).

Of the 13,736 individuals who underwent implantation of PFO closure devices, there were 2 (0.01%) patients found to have perforations; 1 occurred just hours after a CardioSEAL device was implanted. This could have been due to the implantation procedure or trauma from the device itself. The second patient had an Amplatzer PFO 25-mm device removed for a late erosion, without any symptomatic complaints. There were 2 (0.01%) patients with Amplatzer devices explanted for effusion and concern for possible erosion. Pericardial effusion has been observed in patients with nickel allergy, but testing for nickel allergy was not performed on either of these patients.

There was only 1 (0.01%) patient who had the device removed because of a recurrent stroke after the device was in place. This CardioSEAL device was noted on transesophageal echocardiogram (TEE) to be distorted, and the recurrent stroke was suspected to be secondary to the persistence of a right-to-left shunt after the closure procedure, but a residual thrombus on the device could not be excluded.

In this study of over 13,000 patients, there was only 1 (0.01%) patient who developed endocarditis around the device, which led to surgical explantation of a CardioSEAL device.

There were 2 (0.01%) other patients that had their device removed; 1 was an Amplatzer device removed because of exacerbation of migraine symptoms. Testing for nickel allergy was not performed on this patient. The other was a lesser-used, Sideris device, explanted for an undocumented reason.

Amplatzer devices were removed in a total of 19 (0.21% [95% confidence interval (CI): 0.13% to 0.33%]) of the 9,109 patients who received the Amplatzer device. CardioSEAL devices were explanted in 16 (0.79% [95% CI: 0.49% to 1.28%]) of the 2,023 patients who had this device implanted. The difference between the frequency of explanted Amplatzer and CardioSEAL devices is statistically significant (chi-square = 17.9,  $p < 0.00003$ ). Two of the 1,201 (0.17% [95% CI: 0.02%

to 0.46%]) Helex devices were taken out, which is a significantly lower rate than the CardioSEAL devices (chi-square = 7.2,  $p < 0.008$ ). The CardioSEAL implant was removed with a frequency that is 4 times as high as the Amplatzer and 5 times the frequency of the Helex device.

A representative case example might be useful to understand the reasoning behind the decisions to perform open-heart surgery in these patients.

**Case example.** A 49-year-old woman presented with history of episodic migraine headaches with visual aura since age 7. At age 45, she had a transient neurologic deficit consisting of an altered state of consciousness, total global amnesia, dizziness, and apraxia. The clinical evaluation revealed a PFO with no evidence of atherosclerotic disease. An Amplatzer 25-mm Cribiform ASD closure device was implanted without difficulty.

Within 3 months after the procedure, there was an increase in the frequency (3 per month) and intensity of her migraines. The patient also developed intermittent chest discomfort around the xiphoid area that occurred at rest and was exacerbated by lying on her left side or by exertion. She also experienced episodes of shortness of breath and palpitations, usually lasting a few minutes. The chest pain progressed in severity and became constant.

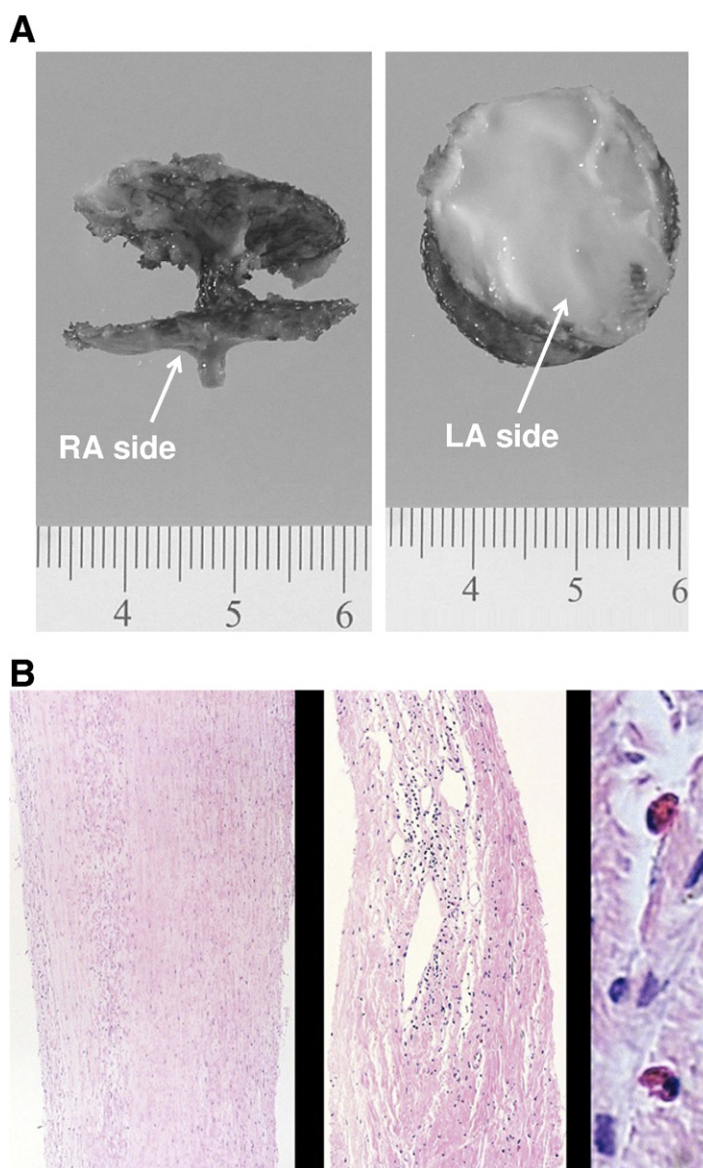
One year after PFO closure, the patient moved to another city and was diagnosed with a nickel allergy, manifested by a significant blister reaction to a TRUE skin patch test. A transcranial Doppler study revealed a grade 4/5 right-to-left shunt. A course of clopidogrel and prednisone was attempted. Severe chest pain persisted, requiring emergency department visits for pain control. Medical therapy was unsuccessful for her chest pain or headaches and she underwent surgical excision of the Amplatzer device (Fig. 1) with insertion of a bovine pericardial patch. A small fenestration in the atrial septum was observed inferior to the Amplatzer device, which accounted for the persistent right-to-left shunt. Pathological examination revealed extensive fibrosis with scattered eosinophils and inflammatory cells. After the explantation, the chest pain resolved, and the migraines were reduced to 2 episodes in 6 months.

The residual shunt might have accounted for her recurrent headache but not the chest pain. By contrast, nickel allergy could explain both recurrent headache as well as severe chest pain due to excessive inflammation. This device was implanted at another institution, so it is unknown whether this small hole was a fenestration that was originally there. The fenestration was not immediately adjacent to the Amplatzer device, and so it did not seem at surgery to be due to erosion.

## Discussion

The various PFO devices can be inserted percutaneously with a high degree of success and a low complication rate. Although the randomized trials are not completed yet, the observational reports of the effect of PFO closure have been





**Figure 1. Amplatzer 30-mm Cribriform ASD Occluder and H and E Stain**

**(A)** Amplatzer 30-mm Cribriform ASD Occluder (AGA Medical Corporation, Golden Valley, Minnesota). The explanted 30-mm Cribriform atrial septal defect (ASD) occluder reveals extensive fibrosis especially on the left atrial (LA) side. **(B)** Hematoxylin and eosin (H and E) staining demonstrate intense fibrosis with mild inflammatory cells with occasional eosinophils.

very positive. Therefore, many PFO devices are implanted each year off-label despite the absence of U.S. Food and Drug Administration approval. However, it is important to understand the potential risks associated with this procedure. One of these risks is the possibility of the need for open-heart surgery to remove these implanted devices. Indications for surgical removal might include perforation of the atrial wall, intracardiac thrombosis, device embolization, deformation of the device umbrellas, fatigue fractures of the metal struts, presence of post-procedural shunts,

prolonged chest pain, and allergic reactions to nickel within the device. Although there are a variety of reasons that might lead to explantation of a PFO device, there are only a small percentage of cases that eventually need to have the device removed. In this survey of 13,736 cases from 18 centers in Europe and the United States, there were 38 (0.28% [95% CI: 0.20% to 0.37%]) cases that required surgical removal of the PFO device.

It is possible that nickel allergy could have been an underlying cause in almost one-half of the patients who underwent

explantation, because many of those patients who had chest pain or effusion were not tested for nickel allergy. There is disagreement as to the optimal method of testing for nickel allergy, which occurs in 10% to 15% of the population, and whether a cutaneous reaction to a patch test corresponds to an allergic reaction within the bloodstream (8–10). Some studies also suggest that the rise of nickel levels in the blood can only be observed for a few weeks after implantation; therefore, associated symptoms persisting for several months cannot reliably be linked to nickel allergy (11–13). However, the mechanism of nickel allergy to an indwelling device is not well-understood and might not depend only on the solubility of nickel ions. Although there does not seem to be a perfect correlation, the TRUE patch test in our experience seems to identify those patients who have a higher incidence of an exaggerated inflammatory reaction to the Amplatzer devices manifested by chest pain and migraine headaches after implantation (14).

Residual shunt was the second-most-common cause for explantation of PFO closure devices in our study. Although a small residual shunt is not uncommon immediately after the procedure, most of the shunts disappear in the subsequent 3 to 6 months as fibrous tissue develops around the device allowing for complete closure of the PFO. However, some devices report a high incidence of large residual shunts; for example, the CardioSEAL is reported to have a large residual shunt in 15% of cases (15). In some instances, another device has been implanted adjacent to the original apparatus, resolving the residual shunt (16). The cases described in this series were large shunts that the operators felt were not amenable to a second percutaneous device for various reasons. The decision to explant the devices was left up to the individual operators.

Some patients underwent explantation of their device after thrombus was visualized on the device during follow-up echocardiography. Most of these cases resolve with medical therapy and do not require surgical removal. Thrombus formation is seen in 0% to 7% of patients who undergo percutaneous PFO closure but is variable and depends on the type of device (e.g., thrombus has been observed by TEE in 7% to 23% of CardioSEAL cases) (17,18). Because post-procedure TEE was not performed routinely at these centers, the incidence of thrombus on the different devices in this survey is not known. Only those patients who had very large thrombus and/or embolic phenomenon were likely to undergo surgical explantation of the device.

Perforation of the atrium or aortic root has been associated with the Amplatzer ASD device, but there are only 5 case reports of perforation due to the PFO closure device (19–23). Pericardial effusion can also be a sign of the inflammatory response from nickel allergy; therefore, the presence of a pericardial effusion does not necessarily indicate that erosion has occurred.

The persistence of symptoms after implanting the PFO closure device can indicate device malposition or a possible

second defect in the atrial wall. This is sometimes seen in patients who continue to complain of migraines, have recurrent strokes, or transient neurologic deficits. This might be resolved by placing a second device into the heart, but it was noted as one of the causes for explantation. The decision to proceed with surgical explantation is variable, depending on the practice of the physician and the subjective level of discomfort of the patient.

**Study limitations.** It should be emphasized that this is a self-reporting, retrospective survey that could lead to several biases. The true prevalence of device explantation is probably underestimated because of underreporting. With this type of retrospective analysis, follow-ups might not have been complete (e.g., patients might have moved). Patients who underwent surgical explantation might not have had their device implanted at the same institution. One of the biases in this study is that it focused on selected centers that were willing to participate and had a database of patient follow-up and does not attempt to encompass all the devices that have been implanted worldwide. However, it is unlikely that a prospective trial will ever be performed with the number of cases that is described in this paper. Therefore, this retrospective survey provides the best chance to estimate the frequency of explantation for the various PFO devices.

## Conclusions

The vast majority of PFO closure procedures are performed safely with minimal complications. However, there is a small incidence (0.28% [95% CI: 0.20% to 0.37%]) of severe adverse reactions associated with PFO closure devices that require surgical removal. In this compilation of over 13,000 cases from 18 clinical centers, the most common reason given for explantation was severe persistent chest pain, which might be related to nickel allergy in some patients. Other causes for explantation included recurrent stroke, persistence of a residual shunt, the presence of an intracardiac thrombus, erosion of the device with perforation of the atrium or aortic root, and the development of endocarditis.

Only randomized clinical trials can provide unbiased data as to the relative benefit of PFO closure with a device compared with medical therapy. Surgical removal of PFO closure devices is rare (1 in 361 cases in this series) but requires open-heart surgery. However, the frequency of removal seems to be device-dependent: in this survey the rate of explantation was 1 in 126 for CardioSEAL devices, 1 in 480 for Amplatzer devices, and 1 in 600 for the Helex device. Patients should be made aware of the possibility of device explantation when informed consent is obtained. This retrospective analysis provides practical information for the patient and physician about the approximate frequency of these complications that can result in surgical explantation.

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**Key Words:** adult congenital heart disease ■ device closure ■ explantation ■ patent foramen ovale ■ PFO closure.