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Absence of significant aortic regurgitation seven years after closure of patent foramen ovale☆

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ABSTRACT

Background: It has been suggested that there is an increase in aortic regurgitation (AR) in the short and medium term after percutaneous closure of patent foramen ovale (PFO). The aim of this study is to determine the long-term effect of percutaneous closure of PFO on the prevalence of AR.
Methods: Patients with cryptogenic stroke or transient ischemic attack who had undergone percutaneous closure of PFO more than five years before the study were invited to an echocardiographic examination.
Results: Out of 83 invited patients, 64 accepted the invitation and were examined with echocardiography. Mild AR was found in one patient (2%), but this was already evident in the patient's echocardiographic result before PFO closure. Trace AR was detected in 11 patients (17%). No case of moderate or severe AR was detected. Patients with AR were more often hypertensive (six out of 12 patients with AR, compared to nine of the 52 without AR, $p = 0.025$), and the indexed sinus of Valsalva was larger in patients with AR (18.6 mm/m^2, SD 1.6, as compared to 17.3 mm/m^2, SD 1.6, $p = 0.02$).
Conclusion: In this long-term study with a minimum follow-up of 5.6 years and a mean of 7.1 years, we found negligible levels of AR. Where present, AR was associated with hypertension and mild dilatation of the aortic root, but there was no indication that device closure per se increased the risk of developing AR.

1. Introduction

Patent foramen ovale (PFO) is associated with cryptogenic stroke, and non-randomized studies suggest a reduction in stroke recurrence after percutaneous closure [1–4]. In contrast, randomized trials showed no significant reduction in primary endpoints [5–7], but a secondary per-protocol analysis of the RESPECT trial suggested a benefit of PFO closure [6]. Nonetheless, many patients in recent years have received an occluder as a prophylactic measure after cryptogenic stroke. Short- and medium-term follow-ups show a low risk, about 1%, of serious adverse events, such as atrial perforation and thrombus formation on the device [3,8]. An increased prevalence of aortic regurgitation (AR) has also been reported [9,10]. Echocardiography up to one year after closure showed a 10% increase in new or worsened AR, of which 92% were mild AR and 8% were moderate AR. However, the long-term effects of closure are not known. Therefore, we performed an echocardiographic follow-up, focusing on the presence or absence of AR at a mean of 7.1 years after percutaneous closure of PFO.

2. Methods

Between 1997 and 2006, 85 patients underwent percutaneous closure of a PFO at Sahlgrenska University Hospital/Östra, Gothenburg, Sweden. An Amplatzer occluder (AGA Medical Corporation, MN, USA) was used in all patients and the size and model of device was chosen after balloon sizing. In 82 patients, a 25 or 35 mm Amplatzer PFO occluder was used. It has a thin waist and the right atrial disk diameter is the full size of the occluder. To ensure a better fit, the left atrial disk diameter is smaller, 18 or 25 mm. The Amplatzer atrial septal defect (ASD) occluder, with a waist diameter corresponding to the stretched balloon diameter of the defect, was used in three patients.

The following indications for PFO closure were applied: (1) first-ever cryptogenic stroke or transient ischemic attack combined with high-risk morphology, such as atrial septal aneurysm, or (2) PFO with low-risk morphology in patients with recurrent cryptogenic stroke or TIA events. A single event was not considered to be an indication for closure of a PFO with low-risk morphology [3]. The diagnosis of cryptogenic stroke

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was made by a specialist in neurology or internal medicine experienced in stroke medicine. The majority of patients were referred by neurologists. During this time period, the closure decision was made by the interventional cardiologist. Atrial septal aneurysm was defined as at least 10 mm bulging into one of the atria, beyond the plane of atrial septum secundum [11]. All PFOs were diagnosed with contrast transesophageal echocardiography before catheterization [12,13]. The characteristics of the total population at the time of closure are shown in Table 1. Hypertension was defined according to medical treatment for hypertension at follow-up. One patient with moderate carotid stenosis suffered cortical blindness deemed as cryptogenic stroke, due to splinter thrombosis, since CT showed bilateral infarction.

2.1. Echocardiography

A standard transthoracic echocardiogram was performed with commercially available echo machines (Vivid 7 or Vivid 9, General Electric, Fairfield, CT, USA). Special attention was paid to visualizing any AR, thrombus formation on the device, atrial erosion or interatrial shunting. Color Doppler imaging of the aortic valve was performed in the parasternal long and short axis and in apical five-chamber and long-axis views. In apical views, continuous and pulsed wave Doppler was also registered. Classification of aortic regurgitation was analyzed independently by two physicians on offline images, using the EchoPAC PC software (General Electric), and disparities were settled by consensus. Investigators were blinded to clinical information, size and model of device, and to the degree of AR before closure. AR was classified as mild, moderate, or severe, according to recent guidelines [14]. In addition, trace AR was defined as any visible regurgitation with a color Doppler vena contracta less than 1 mm. Mild AR was defined as vena contracta at least 1 mm but less than 3 mm. The aortic root diameters were measured by MJ according to guidelines [15] and indexed for body surface area [16]. Pre-closure echocardiographic images and reports from patients with any AR at follow-up were used to establish the presence or absence of AR before closure. When the cusp morphology was ambiguous on the transthoracic images, the transesophageal images during closure and six months after closure were used to classify the valve as tricuspid or not tricuspid.

The study was approved by the human research regional ethical review board in Gothenburg and all patients gave written informed consent. The patients received reimbursement only for travel expenses.

2.2. Statistics

The independent-samples t test was used for comparing age and sinus Valsalva diameter in relation to AR and for comparing sinus Valsalva diameter in relation to hypertension. For the analysis of hypertension, atrial septal aneurysm and age groups in relation to AR, Fisher's exact test was used. The PFO 35 mm occluder was compared with all the other sizes combined in relation to AR and in relation to atrial septal aneurysm with Fisher's exact test. The baseline and follow-up prevalence of any AR were compared with McNemar's test. A p-value < 0.05 was considered significant and tests were two-sided. The inter-observer variability of the presence/absence of AR was assessed in all follow-up patients. The intra-observer reproducibility of aortic sinus diameter measurements was assessed in 30 patients with the intraclass correlation coefficient (ICC). All statistical analyses were performed with IBM SPSS Statistics version 19 (Armonk, NY: IBM Corp., USA).

Table 1
Population characteristics at the time of PFO closure.

Characteristics	
Number of patients	85
Men, n (%)	47 (55)
Age in years, mean (SD)	48.7 (10.7)
BMI, kg/m^2, mean (SD)	26.3 (6.3)
Current smoker or ex-smoker, n (%)	18 (21)
Hypertension, n (%)	14 (17)
Diabetes, n (%)	2 (2)
Hyperlipidemia, n (%)	15 (18)
Carotid stenosis >50%, n (%)	1 (1)
Atrial septal aneurysm, n (%)	58 (68)

Table 2
Aortic regurgitation at baseline and at long-term follow-up.

Aortic regurgitation	Baseline n = 64	Long-term follow-up n = 64
None, n (%)	56 (87)	52 (81)
Trace, n (%)	7 (11)	11 (17)
Mild, n (%)	1 (1.6)	1 (1.6)
Moderate or severe, n	0	0
Any AR, n (%)	8 (13)	12 (19)

3. Results

Information on survival was available for all 85 patients, of whom two had died, both from lung cancer. Medical records with clinical information were available and were reviewed in all the other patients. Out of 83 invited patients, 64 (77%) agreed to visit the clinic and undergo an echocardiographic examination. Among the other 19 patients, 14 were living far away and five patients could not attend our center and thus were interviewed by telephone. The mean time from closure to follow-up was 7.1 years, SD 1.5, with a minimum of 5.6 years and maximum 12.4 years. The mean age at follow-up was 55.9 years, SD 10.0 (25–75). Information on survival and recurrent stroke or TIA has been reported previously [17].

Some degree of AR was detected in 12 (19%) of the 64 examined patients, as shown in Table 2. There were no patients with moderate or severe AR. Of the 12 cases of AR, 11 (17%) were trace AR, and only four (6%) of these cases represented new trace AR; the remaining patient (2%) had mild AR that was also evident in the baseline echocardiographic result. Thus, AR was already present at baseline in eight (12%) of the patients. Patients with AR showed three distinguishing features regarding morphology, hypertension and age (Table 3). First, the aortic root diameter was larger at the level of sinus Valsalva but with the same aortic annulus diameter; however, the magnitude of dilatation was mild, with only one patient showing a diameter over the normal limit of 21 mm/m^2 body surface area [16]. Second, hypertension was more common in patients with AR and the aortic sinus diameter was slightly, but non-significantly, larger in patients with hypertension at follow-up, as compared to those without hypertension (18.2 mm/m^2, SD 1.9 vs. 17.4 mm/m^2, SD 1.6, $p = 0.19$). Third, patients with AR were older than those without AR, but the difference did not reach statistical significance; the youngest patient with AR was 44 years of age, as shown in Fig. 1. There was a non-significant trend toward more frequent AR with the PFO 35 mm occluder than with the smaller sizes; this occluder was more often used in the presence of atrial septal aneurysm (36 out of 42 compared to 10 out of 21, $p = 0.02$).

Table 3
Comparison of patient characteristics in relation to the presence/absence of aortic regurgitation at long-term follow-up.

	No AR N = 52	AR N = 12	p
Sinus Valsalva, mm/m^2 BSA, mean ± SD	17.3 ± 1.6	18.6 ± 1.6	0.015
Age in years, mean ± SD	55.3 ± 10.4	59.8 ± 8.3	0.17
Hypertension, n (%)	9 (17)	6 (50)	0.025
Atrial septal aneurysm, n (%)	35 (67)	11 (92)	0.16
ASD occluder, n	2	0	
PFO occluder 25 mm, n	18	2	
PFO occluder 35 mm, n	32	10	0.19*

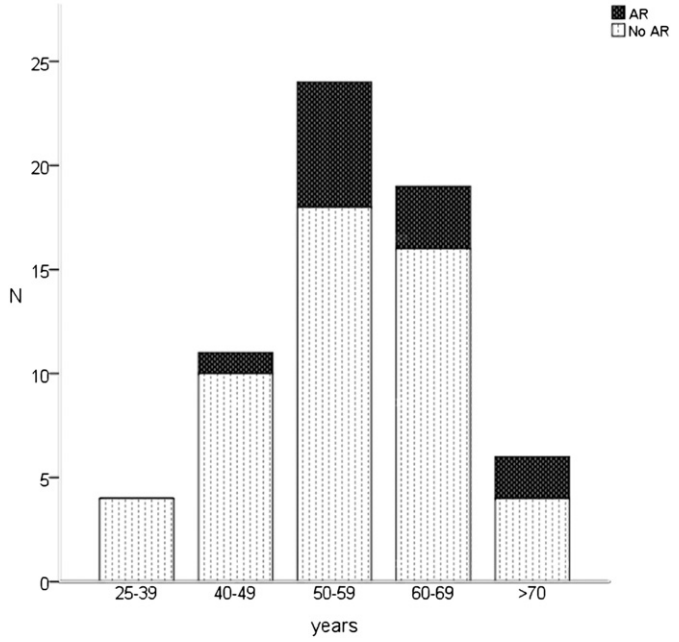

Fig. 1. p > 0.2 for the comparison of AR prevalence according to age group. AR = aortic regurgitation.

The aortic valve was tricuspid and without fibroid calcification in all patients. The device was visualized in the expected position without any signs of the device impinging on the aortic root. No residual shunt was visualized with color Doppler. No serious adverse events e.g. pericardial effusion, perforation or fistulas occurred during the procedure or at long-term. There was agreement between observers regarding the presence/absence of AR in all but one of the follow-up exams and this was resolved by consensus, corresponding to an inter-observer reproducibility of 98.4%. The intra-observer reproducibility for aortic sinus diameter was excellent (ICC = 0.952).

4. Discussion

In this long-term follow-up study of more than seven years after PFO closure, no patients with significant AR were found. The mild AR that was found in one patient (2%) was already evident before closure. A distinguishing feature of the current study is that the follow-up time is longer than in other studies. The current study thus adds new information on the long-term safety of percutaneous closure of PFO. Our results are in contrast with some other studies reporting on new AR after closure [9,10], as shown in Table 4, where we compare details of the other studies. The study that reported as much as 10% new or worsened AR used the Cardia device in 98% of PFOs [9], and this device is no longer in use. In the current study, the Amplatzer occluder was exclusively used. The Amplatzer ASD occluder has a self-centering waist that should correspond to the balloon-sized diameter of the defect. When oversized, it overstretches the defect and may thereby predispose to AR [10]. There is also another model of the Amplatzer ASD occluder: the Amplatzer multi-fenestrated "cribriform" occluder, thus named because it is designed to cover multiple small defects in one location. It has a thin waist and the two disks have the same diameter. Both these models are designed for ASD closure and approved for use in the USA. In the current study, on the other hand, the Amplatzer PFO 25 or 35 mm occluder was used in 97% of the patients. Like the cribriform occluder, it has a thin waist, but the diameter of the left atrial disk is smaller: 18 and 25 mm. In our experience, this makes the left side of the occluder fall into place abutting on the aorta. The disks will be positioned closer and more parallel to each other, instead of straddling the aorta, which often happens with the cribriform occluder.

Trace AR was found in 11 of 64 patients, 17%. However, trace AR in a morphologically normal valve is considered to be within the normal range for the age group in this study. A large population survey in the age range 40–60 years found AR in 6.2% of a healthy population [18]. The population survey also showed an increase with age, from 3.8% in the age range 40–49 years to 8.1% in 50–59 year olds. Therefore, due to normal aging during the average follow-up period of 7.1 years in our study group, there ought to be about two new cases of AR at follow-up. The Doppler technique is highly sensitive to small leakages, so these regurgitations may be only a few milliliters [19]. In a recent follow-up study after percutaneous closure, the presence of trace AR was not regarded as AR [20]. With this approach, the current study thus shows AR in only one patient (2%) and no new AR after closure. In concordance with our results, a magnetic resonance imaging study found no significant difference in AR before versus after PFO closure [21]. With that technique, the volume of backward flow in the aorta was calculated to be 1.9 ml (0.9–3.6) before closure and 2.9 ml (1.5–4.1) (p = 0.108) after closure, but the presence of trace AR might have been missed. A striking feature of two recent studies on PFO closure is a high prevalence of AR before closure, 19% and 16%, most of which was mild [9,10]. Another novel finding of our study is the relation between dilatation of the aortic root and the presence of AR. Dilatation of the aortic root, often associated with increasing age and hypertension, will predispose to both AR [22] and more aneurysmatic atrial septum [23–25]. A wide aortic root may induce tenting of the aortic valve, which reduces the area of coaptation between the cusps and predisposes for regurgitation [26]. In general, dilatation of the aortic root will also shorten the distance between the aortic wall and the atrial free wall, which is the distance covered by the atrial septum. Any reduction in this distance will thus make the atrial septum redundant and more likely to be aneurysmatic [24]. In the presence of a PFO, increased septal mobility is associated with increased right-to-left shunting [3]. A recent study showed aortic sinus of Valsalva diameter to be larger in PFO patients with cryptogenic cerebrovascular events, as compared to healthy controls (34 mm, SD 4 versus 31 mm, SD 3) [25].

Table 4
Studies reporting aortic regurgitation after percutaneous closure of interatrial shunts.

	Sadiq [27]	Schoen [9]	Loar [20]	Wohrle [21]	Krasniqi [10]
Type, no. of patients	ASD, 205	PFO, 170 ASD, 70	PFO, 204 ASD, 118	PFO, 102	PFO, 177
Population	Children and adults	Adults	Children and adults	Adults	Adults
Follow-up time (range)	5.2 years (6 months–10.3 years)	1 year	1.2 years (2 months–5 years)	1 year	6 months
Device (% of PFOs)	Amplatzer ASD, 100%	Cardia, 98% Amplatzer, 2%	Amplatzer, 88% Helex, 12%	Cardia, 63%, Premere, 1% Amplatzer, 36%	Amplatzer, 100%
Method	TTE	TEE Trace AR reported as AR	TTE/TEE Trace AR reported as no AR.	MRI Regurgitant volume and fraction	TTE/TEE Trace AR reported as AR
Conclusion	New AR in 1%, thought to be due to oversizing of the device	New or worsened AR in 10% of patients	New mild AR in 0.6% of patients	No change in regurgitation volume	New or worsened AR in 9% of patients

5. Limitations

In this single center study, the Amplatzer occluder was used in all patients, so other brands were not tested. All the patients were selected for closure and there was no non-closed control group. The follow-up examination was not performed in 23% of study participants. There are also some obvious limitations regarding the analysis of pre-closure images, since this is a retrospective analysis; the baseline AR prevalence might therefore be underestimated.

6. Conclusion

In this long-term study with follow-up of a minimum of 5.6 years and a mean of 7.1 years, mild AR was found in 2% of patients but was already evident before PFO closure. No moderate or severe AR was found. Trace AR was seen in 17% of patients and the presence of AR was associated with hypertension and mild dilatation of the aortic root. There was no indication that device closure per se increased the risk of developing AR.

Conflict of interest

Johansson: Honoraria from AGA medical. Mirzada and Ladenvall: None.

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