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Patent Foramen Ovale

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ISBN 978-1-4471-4986-6 ISBN 978-1-4471-4987-3 (eBook)
DOI 10.1007/978-1-4471-4987-3
Springer London Heidelberg New York Dordrecht

Library of Congress Control Number: 2014957317

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Part I

Background and Anatomy

Historical Perspective and Importance of PFO

1

John F. Rhodes Jr. and Amanda Green

Abstract

Patent foramen ovale (PFO) is a commonly recognized structure in the heart with many references to a relationship to neurologic and paradoxical embolic events. The following is a historical timeline of this relationship.

Keywords

Patent foramen ovale • Stroke • TIA • Paradoxical event • Migraine headache • Decompression sickness

Patent foramen ovale (PFO) was first described by Galen in the early sixteenth century, and presently is a commonly recognized structure in the heart, felt to be found in about 25–30 % of the normal population [1].

1490 – Leonardo da Vinci began drawing sketches of the heart and circulation. These drawings were primarily made from his studies of the circulatory system and organs in pigs and oxen, it was only much later that he had access to study the cardiac anatomy in humans. Di Vinci made significant advances in the understanding of blood flow and of the heart itself. He demonstrated that the heart was indeed a muscle, that it was not responsible for warming the blood, found that it had four chambers, and was able to connect the pulse in the wrist to the contraction of the left ventricle. Given his artistic abilities, Di Vinci took what he had seen and drew sketchings of the heart and circulation. In some of his descriptions and drawings he described a "communication between the auricles".

1561 – Falloppio and Vesalius, who both described the foramen ovale.

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1564 – Dr. Leonardo Botallo, an Italian surgeon, again described the patent foramen ovale, naming it "Botallo's foramen" in 1564.

1570 – Bartholomaeus Eustachius, a professor of medicine in Rome, was the first to describe the presence and purpose of the patent foramen ovale in the fetus. He also described that it closed at birth by "thin valvular layer", which often had an "imperfect upper margin". His works and drawings remained unprinted and forgotten until 1714, when they were published along with the work of the famous physician Lancisi. Eustachius is also credited as being one of the founders of modern anatomy, discovering the Eustacian tube, thoracic duct, the adrenals, and the abducens nerve. He also gave the first accurate description of the uterus.

1805 – A report published by Spry, describing two cases. The first a girl, aged 7 years, with no history of cyanosis during her lifetime, and a finding of a foramen ovale patent to 15 mm. The second case was that of a 21 year old woman who had symptoms of cyanosis, palpitations, and dyspnea, since she was 3 months of age with a finding of a patent foramen ovale to 25 mm.

1846 – Rudolf Virchow, a German pathologist who is recognized as the father of modern pathology, described a phenomenon of simple embolism of particulate matter through the vascular system.

1877 – Julius Friedrich Cohnheim, a German pathologist and a protégé of Virchow, described how the patent foramen ovale could act as a suitable means of by-passing the pulmonary

Z. Amin et al. (eds.), *Patent Foramen Ovale*,
DOI 10.1007/978-1-4471-4987-3_1, © Springer-Verlag London 2015

vascular system. It was 4 years later that this theory was substantiated with a finding of an embolus into the frontal lobe, in a 35 year old woman, as well as a thrombus in the lower extremity veins. Upon inspection of the heart, a very large foramen ovale, "through which I could pass three fingers with ease". He stated that after this discovery, he could "no longer ignore the fact that a torn-off piece of thrombus arising from the inferior vena cava, while traveling through the heart (passed) out of the right atrium into the left atrium and to the frontal lobe."

1881 – F.W. Zahn first used the term "paradoxical embolus" to describe a branched thrombus from a uterine vein caught in a PFO on a postmortem examination.

1930–1933 – Thompson and Evans/Saphir, reported cases of paradoxical coronary embolism from the venous system across the foramen ovale. The classical feature described in the cases of coronary embolism was sudden death.

1939 – Blakemore, began the initial attempts at surgical closure of atrial septal defects using simple inversion of the atrial appendage.

1948 – G. Murray performed the first surgical ASD closure on a 12 year old girl. The follow up catheterization demonstrated only partial closure of the ASD.

1951 – B.J. Johnson, did a review of the literature which found 41 cases of embolus lodged in the PFO. He defined "presumptive" paradoxiacal emobolism when there was venous thrombosis, an open foramen ovale but no embolus in the PFO, and a reversal of pressure gradient between the atria.

1952 – Nolton Bigelow, a physician in Albany, New York, published a case report of a 69 year old man who had underwent a right nephrectomy 2 years earlier for renal calculi, presented with left flank pain secondary to a renal calculus, for which he underwent ureterolithotomy. On post-operative day 7, he developed a DVT in his right calf. On the 13th post-operative day, he became suddenly pale, sweaty, dyspneic, and tachycardic. He died precipitously. The post-mortem evaluation revealed multiple pulmonary emboli as well as a conical 3.5 cm length (4×9 diameter) embolus lodged in the PFO.

1966 – William Rashkind, a pediatric cardiologist in Philadelphia, PA, described the life-saving technique to open the foramen ovale for patients with transposition of the great arteries using a balloon atrial septostomy technique.

1972 – King and Mills described a transcatheter technique for closure of atrial defects. This was done in an animal model with 5 of 13 animals successfully closed.

1975 – King and Mills performed the first transcatheter ASD closure in a 17 year old girl at the Ochsner Clinic in New Orleans. The ASD was measured at 25 mm with a 2:1 shunt.

1986 – The first reported incidence of decompression illness in a diver with ASD, which was hypothesized to be caused by a paradoxical gas embolism across the atrial septum.

1987 – Jim Lock, a pediatric cardiologist at Boston Children's Hospital used the first Clamshell device to close an atrial septal defect.

1988 – P. Lechat, published the first case control study showing a high prevalence of PFO in young patients with cryptogenic stroke. He published 60 stroke patients less than 55 years old and 100 control patients. Of the young stroke patients, 50–60 % of them had a patent foramen ovale vs 25 % of patients in the control group [2].

1988 – M. W. Webster published a study looking at the incidence of patent foramen ovale in young stroke patients vs an age and sex matched control group. He found that right to left shunting was found in 50 % of the stroke patients (20 out of 40 patients), and in 15 % of the controls (6 out of 40 patients). This study suggested that PFO may be an under recognized cause of stroke in young adults [3].

1989 – Lesley Newson published his theory that a "hole in the heart brings on the bends". This was the first two case control studies, which confirmed the link between PFO and decompression illness [4].

1992 – Jim Lock – The first publication demonstrating that patent foramen ovale closure can be accomplished with little morbidity and reduce the risk of recurrent stroke events [5].

1994 – D Brogno published a case study on a patient where a embolus was found to be lodged in the foramen ovale with a portion of the clot in both the right and left atriums.

1995 – Jean-Louis Mas, a French physisician published that patients who have a patent foramen ovale with aneurysmal motion of the atrial septum may be an indicator of a higher risk for recurrent stroke.

1995 – Mike Landzberg, in Boston, described Platypnea-Orthodeoxia in a series of six patients who had undergone surgical resection of a thoracic carcinoma, who had symptoms of positional dyspnea and desaturation. All of the patients were treated with transcatheter device closure of the PFO, with resulting increase in oxygen saturations from 70 to 85 % to 95 % following PFO closure [6].

1996 – Lausanne Study – Demonstrated that the first brain event in patients with patent foramen ovale may be devastating, as ½ of the patients suffered a severe initial stroke. Ultimately, making recommendations for risk stratification of patent foramen ovale [7].

2000 – J.R. Overall – Published that prevalence of PFO was 40–70 % in patients with cryptogenic stroke, and five-fold higher incidence of PFO prevalence in young patients with cryptogenic stroke patients [8].

2002 – HDE approval obtained for CardioSEAL Occlusion system and the Amplatzer PFO Occluder.

2003 – RESPECT clinical trial, first PFO stroke trial approved by the US FDA. This trial randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care.

2003 – CLOSURE I clinical trial began. Randomizing patients with neurologic events and PFO to medical therapy or device closure of the PFO.

2004 – The MIST study was the first prospective, randomized, double-blinded study to obtain approval in the UK for evaluation of transcatheter device closure of the PFO using the STARFlex septal occluder for patients with migraine headaches.

2006 – The HDE for both the CardioSEAL and Amplatzer PFO Occluder Devices were removed.

2008 – The results of the MIST clinical trail were published. Confirming the high prevalence of right to let shunt in patients with migraine headache with aura, but did not meet primary or secondary endpoints [9].

2008 – The REDUCE clinical trial for PFO and stroke began enrollment. This trail is randomizing patients with imaging confirmed stroke and PFO to either device closure of PFO or anti-platelet therapy.

2010 – The results of the CLOSURE 1 clinical trial were presented at the AHA, and described "No overall benefit, no reduction in stroke or TIA with PFO closure" [10].

2012: The RESPECT and PC trials were presented as late breaking trials at the AHA, with both failing to meet their endpoint.

2013 – The RESPECT clinical trial results were published and demonstrated no significant benefit associated with closure of the PFO in adults with crypogenic stroke in the intent-to-treat analysis. However, in the as-treated analysis, PFO closure was superior to medical therapy alone, and with a low rate of associated risks [11].

Over the past centuries we have learned a lot about the anatomy, physiology, and incidence of patent foramen ovale, but in some aspects we are no closer to fully understanding all of the intricacies and implications of this anatomic structure.

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Embryology, Neonatal Circulation and Anatomy of PFO

2

John L. Bass

Abstract

Patent foramen ovale (PFO) is a normal fetal communication. The opening closes after birth in the majority of people, but may remain in up to 20 % of adults. The embryology of the PFO shapes the anatomy of the communication. This influences the shape of the communication after birth, and the best method of transcatheter closure.

Keywords

Contrast • Embolism • Patent foramen ovale • Patent foramen ovale closure • Shunts • Transesophageal echocardiography

Abbreviations

AV	Atrioventricular
IVC	Inferior vena cava
PFO	Patent foramen ovale
TCD	Transcranial Doppler
TEE	Transesophageal echocardiography
TTE	Tranthoracic echocardiography

The foramen ovale is a natural and necessary part of fetal cardiac development. The anatomy results from a complicated series of developmental changes resulting in a channel uniquely designed to allow blood flow to the left side of the heart in utero. After birth, this opening is no longer needed. Through the decades of life, the opening gradually seals shut in the majority of people. But this does not occur immediately at birth, and the foramen ovale remains patent into later life in a significant number of people. Persistent patency becomes important under conditions that allow blood to pass from the right atrium to the left, bypassing the filtering of the pulmonary circulation, and in some cases enough desaturated blood enters the systemic circulation to produce clinical cyanosis. In these circumstances eliminating the opening may be desirable. Surgical closure of the patent foramen ovale (PFO) is a simple procedure. Surgeons are able to vary the technique at the time of closure to deal with variations in PFO anatomy. Transcatheter closure can also be simple, but does not have the same flexibility to alter technique that direct exposure provides to the surgeon. The details of the anatomy of a PFO are therefore critical to the success of transcatheter closure, including choice of device and the risk of complications such as erosion. Understanding the embryology and fetal hemodynamics help in understanding the anatomy.

Embryology

The septum primum arises from the posterior superior wall of common atrium and grows towards atrioventricular (AV) valves [1, pp 239–240]. Fenestrations develop in the septum primum and coalesce superiorly and anteriorly maintaining a communication as fusion occurs inferiorly with the endocardial cushions. The septum secundum then arises to the right atrial side of septum primum and grows towards the AV valves leaving an inferior posterior communication by the inferior vena cava, the fossa ovale. The septum secundum forms the superior and anterior margins of the foramen ovale.

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Z. Amin et al. (eds.), *Patent Foramen Ovale*,
DOI 10.1007/978-1-4471-4987-3_2, © Springer-Verlag London 2015

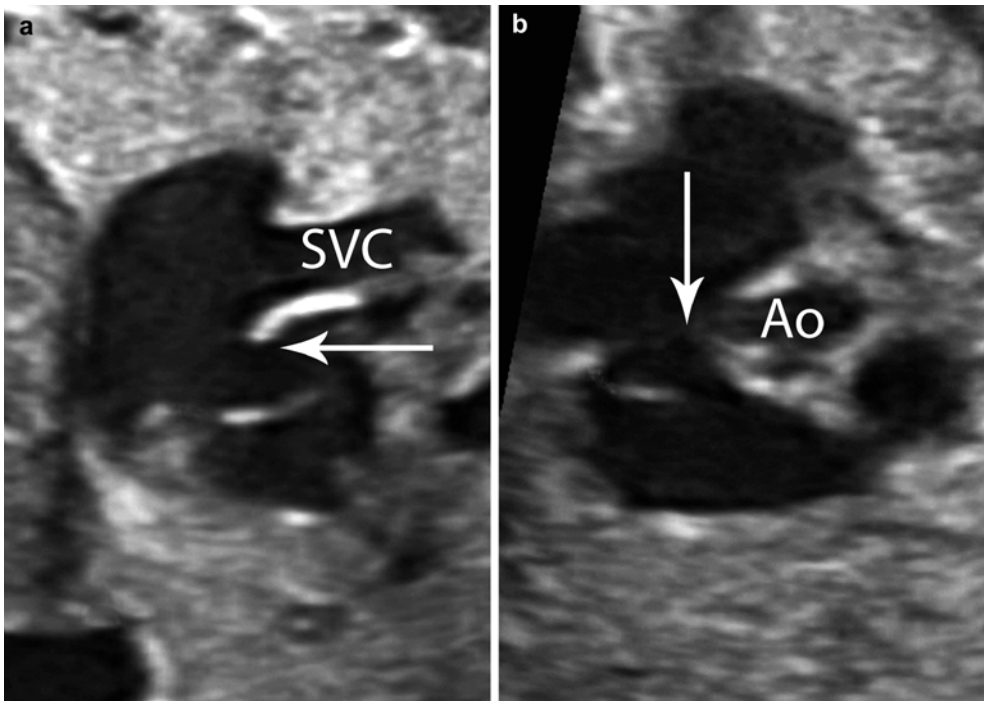

Fig. 2.1 Fetal Echocardiograms at 20 weeks gestation demonstrating the inferior and posterior attachment of the flap of the foramen ovale leaving it free to open anteriorly and superiorly allowing inferior caval blood to cross the atrial septum. In (**a**), a bicaval view shows the superior opening (*arrow*) by the superior vena cava (*SVC*). In (**b**), a short axis view shows the anterior opening behind the ascending aorta (*Ao*)

The residual septum primum forms the valve of the foramen ovale with posterior and inferior attachments. These keep the valve of the foramen from interfering with blood flow from the pulmonary veins entering the left atrium, or that flowing across the mitral valve. This development leaves a right atrial opening opposite the inferior vena cava (IVC), and a left atrial opening in the anterior, superior atrial septum (Fig. 2.1). These relationships are critical to the anatomy of the future patent foramen ovale.

Fetal Circulation

Studies in fetal sheep show that in intrauterine life the IVC carries 65–70 % of blood returning to the heart (from the lower half of the body and the placenta) [1, pp 8–9]. The location of the right atrial opening, the Eustachian valve, and the large inferior venal caval flow keep the valve of the foramen ovale open, and between 36 and 43 % of this blood crosses the foramen ovale into left atrium where it joins the 5–10 % of venous return to the heart that comes from the lungs [1, pp 8–9]. This volume of blood flow is necessary for normal development of the left ventricle.

Postnatal Circulation

At birth, loss of the placenta decreases inferior vena caval return and increases systemic resistance [1, pp 19–20]. Pulmonary resistance falls and pulmonary venous return increases as all systemic venous return passes through the right ventricle. Increased pulmonary venous return causes an increase in left atrial pressure and functionally closes the valve of the foramen ovale.

Natural Closure

Once the valve of the foramen ovale is in apposition to the former septum secundum, the valve becomes adherent over several months resulting in permanent closure. Patency may, however, persist into adult life. This was described over 400 years ago. In a review of the literature, Patten noted in 1938 [2] that the foramen ovale was not completely closed in 21.2 % of adults. The process of closure is gradual, and the percentage of persistent patency falls gradually from 34 % between 1 and 9 years of life to 20 % in adults over age 80 (Fig. 2.2) [3].

Consequences of Persistent Patency

As long as the foramen ovale remains patent after birth, shunting of blood may occur through the potential opening. A small amount of blood flowing from the left atrium around the valve of the foramen ovale into the right atrium is often seen in newborn infants. Lesions that elevate left atrial pressure and enlarge the left atrium (e.g. ventricular septal defect or patent ductus arteriosus) may make the valve incompetent resulting in left to right flow. Conditions that elevate right

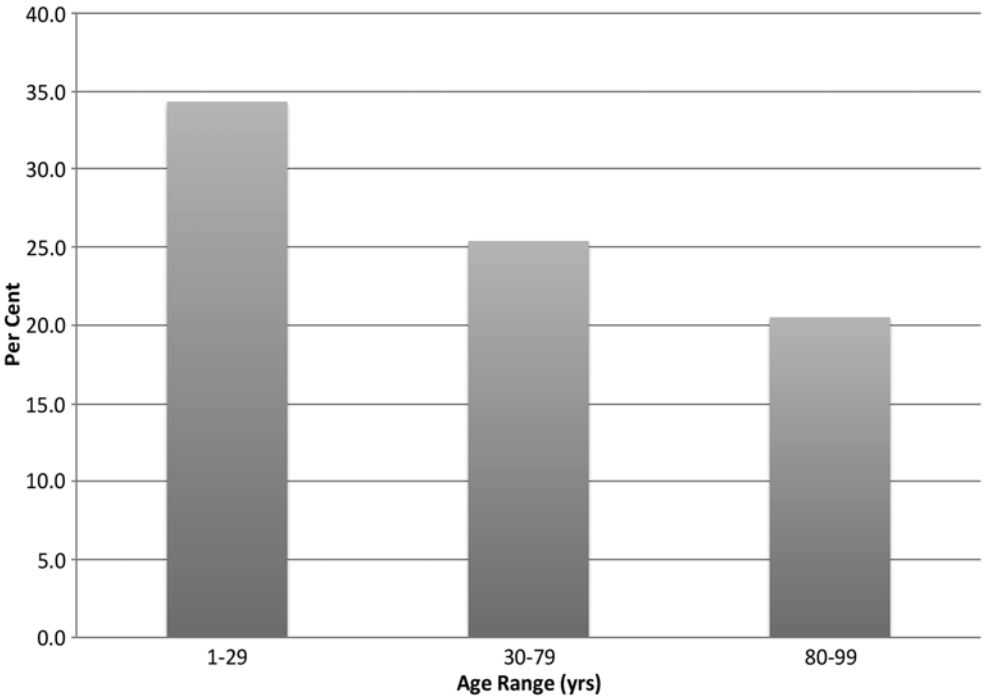

Fig. 2.2 Graph depicting the frequency of a patent foramen ovale from autopsy at different ages (Adapted from Hagen et al. [3])

atrial pressure above that of the left may cause loss of apposition of the valve to the atrial septum and right to left flow across the atrial septum. Some congenital heart defects (tricuspid atresia, total anomalous pulmonary venous connection) require the foramen ovale to allow blood from the right atrium to enter the left side of the heart. Non-cardiac problems such as severe pulmonary disease or pulmonary hypertension can elevate right atrial pressure resulting in a right to left shunt through a patent foramen ovale. Right atrial pressure can be transiently elevated above left atrial pressure in normal individuals. Crying, breath holding, or straining will elevate intrathoracic pressure decreasing systemic venous return. With release, the transiently detained systemic venous return rushes back to the right atrium elevating right atrial pressure. When the foramen ovale is still patent, there may be a transient right to left shunt. The Eustachian valve and location of the right atrial opening encourage channeling of inferior vena caval return through the foramen ovale as they did in intrauterine life. In rare conditions such as orthodeoxia/platypnea there may be flow of desaturated right atrial blood into the left atrium across the foramen ovale under baseline conditions with no obvious cause of elevated right atrial pressure.

Normally all systemic venous blood returns to the lungs where any thrombi are filtered out. When the foramen ovale remains patent, a passing thrombus may be caught in any right to left atrial shunt bypassing the lungs (paradoxical embolus). If this thrombus arrives in a critical area (the coronary or cerebral circulation), there may be disastrous consequences. There are a significant number of adults who have a stroke and no definitive cause can be found (cryptogenic stroke). When a patent foramen ovale is identified in these patients, it may be assumed that an inducible right to left shunt is a smoking gun, with the possibility of a paradoxical embolus. Since there are a large number of these patients, there has been significant interest in developing a transcatheter mechanism of eliminating persistent patency and avoiding a lifetime of anticoagulation.

Anatomic Variations

Transcatheter closure of atrial septal defects, patent ductus arteriosus and ventricular septal defects have taught us that failure to consider the human anatomy of these forms of congenital heart disease can result in unexpected complications, from erosion through the walls of the heart to protrusion of the device into the circulation. To develop a device that will safely close a patent foramen ovale, it is important to consider the anatomy of the defect. For the foramen ovale, this can be complex. Understanding the anatomy of the foramen ovale in utero helps to understand the anatomy of the persistently patent foramen. In the fetus, the valve of the foramen is attached posteriorly and inferiorly [2]. This allows blood to enter the left atrium through the residual anterior/superior communication. Persistent patency of the foramen ovale results from failure of fusion across this superior/anterior margin (Fig. 2.3).

Four primary variations of a persistently patent foramen ovale result from differences in the extent of fusion,

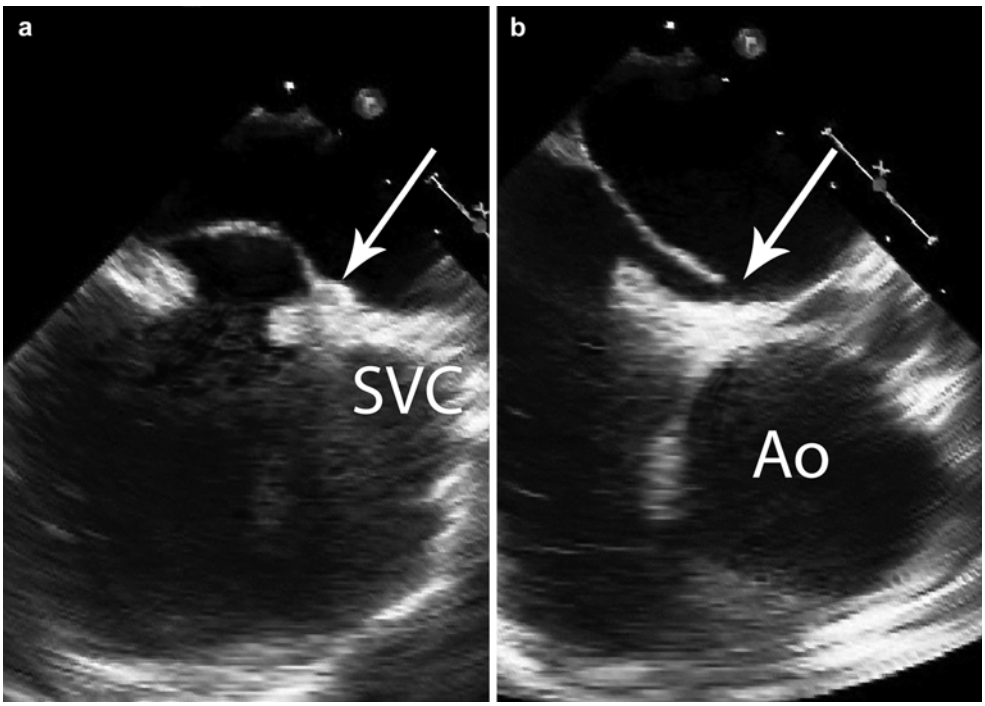

Fig. 2.3 Transesophageal echocardiographic images demonstrating the relationship of the valve of the foramen ovale to the anterior and superior septum secundum. In (**a**), the attachment of the valve to the superior rim of septum secundum is indicated by an *arrow*. In (**b**), the valve of the foramen ovale (*arrow*) has failed to attach to the anterior septum secundum along the aorta. *Ao* aorta, *SVC* superior vena cava

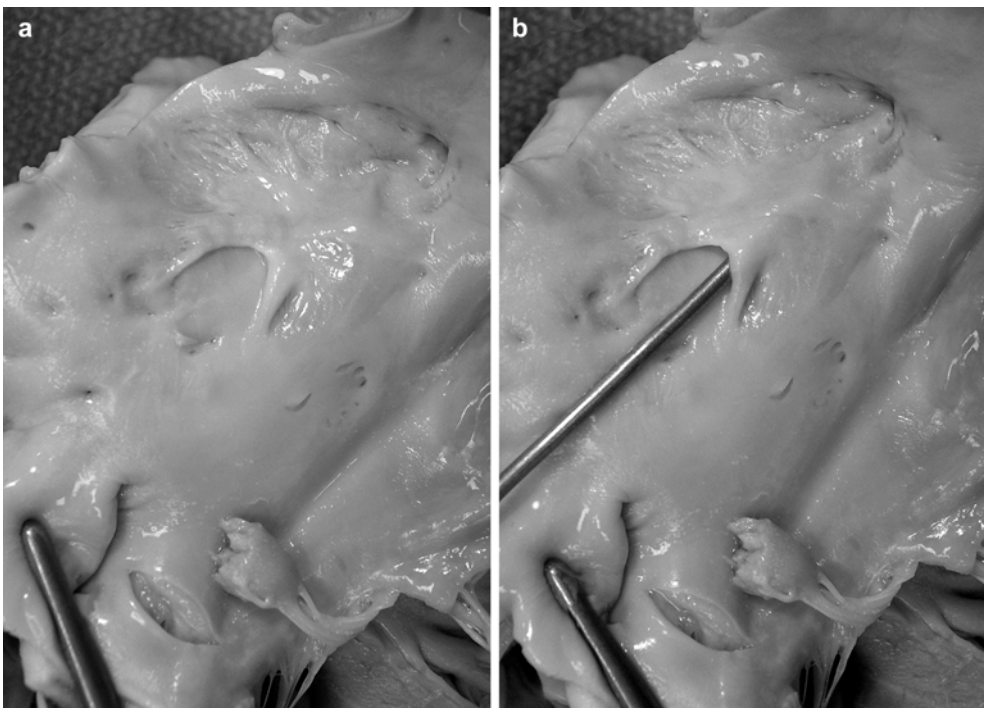

Fig. 2.4 Pathological specimen with a probe patent foramen ovale from the right atrial aspect. In (**a**), the septum secundum can be seen as a rim superior and anterior to the valve of the foramen ovale. In (**b**), a probe is inserted through the residual communication demonstrating the anterior superior course of the communication

and the character of the valve of the foramen ovale. These include lack of fusion only at the most anterior superior margin (the classic "probe patent" foramen ovale), failure of fusion across the entire anterior superior margin, fenestrations of the flap of the foramen ovale, and excessive mobility of the flap (aneurysm of the atrial septum).

The probe patent foramen ovale (Fig. 2.4) occurs superiorly and anteriorly above the aortic valve and may be short or create a tunnel of variable length depending on the length of the flap. The particularities of the length of the connection have major implications for selection of a device to occlude the defect. Since the communication has a small diameter,

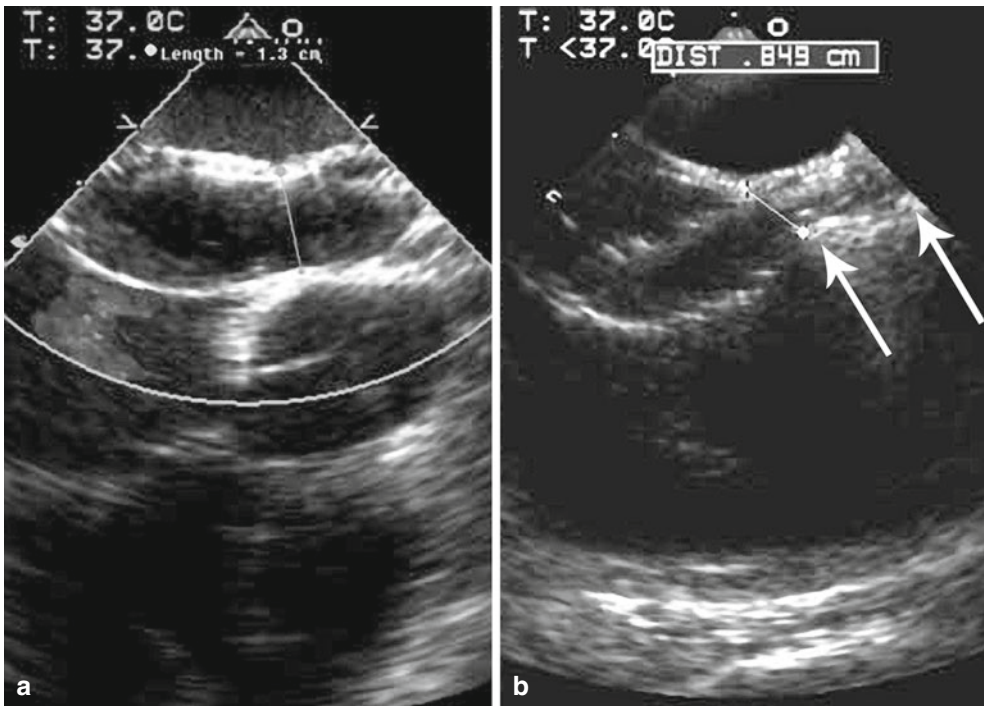

Fig. 2.5 Transesophageal echocardiographic images of a sizing balloon across the foramen ovale demonstrating the difference between complete compliance of the valve, and a tunnel communication. In (**a**), there is a discrete waist in the balloon that measures 1.3 cm in diameter. In (**b**), there is a tunnel communication that extends over some length (*between arrows*). The diameter of the tunnel is 0.9 cm

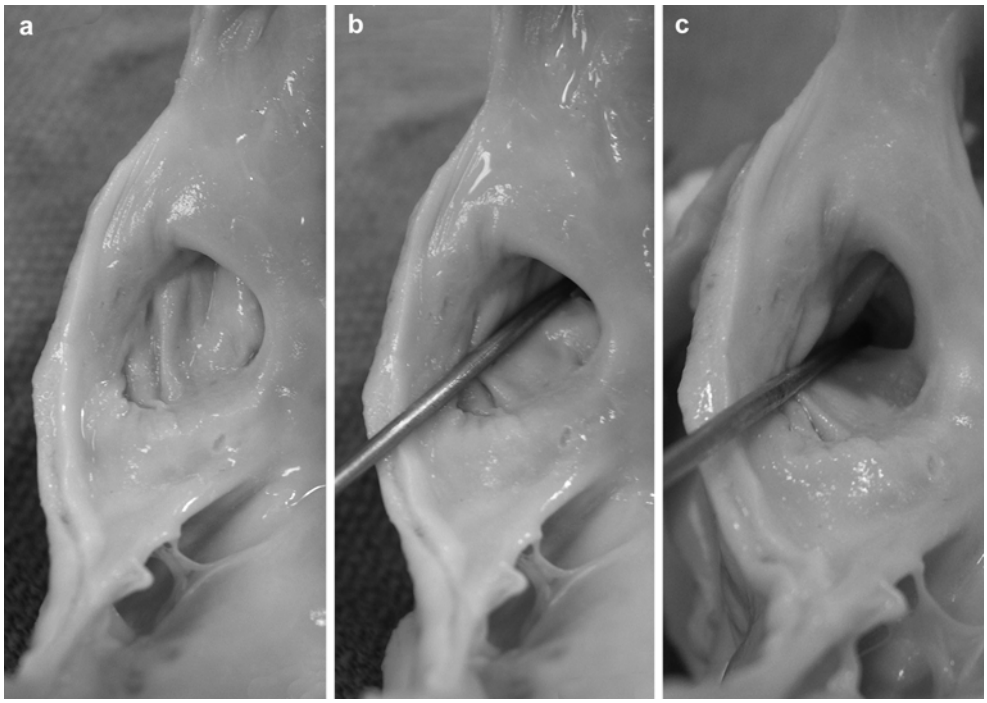

Fig. 2.6 Pathological specimen with a larger failure of fusion of the valve with septum secundum. In (**a**), the valve guards the foramen. In (**b**, **c**), a large potential communication is opened as a probe progressively folds the pliable valve of the foramen. This results in a large defect similar to a true atrial septal defect

it is ideal for a center post device. If the tunnel has a great length, a device that can accommodate extending over that length is ideal. A "self-centering" device with a waist that expands to fill a defect may not seat appropriately in this type of opening. The inability of a self centering device to shorten and fully expand will distort the device. This type of defect can be recognized by the response to a guidewire or sheath passing across the defect, or to an inflated balloon sizing catheter across the defect (Fig. 2.5b). An inflated sizing balloon in particular will reveal the diameter of the communication, and the length of any tunnel.

When fusion of the foramen ovale does not occur at any point, the flap is able to fold away, held in place by its posterior, inferior attachments (Fig. 2.6). This leaves an opening

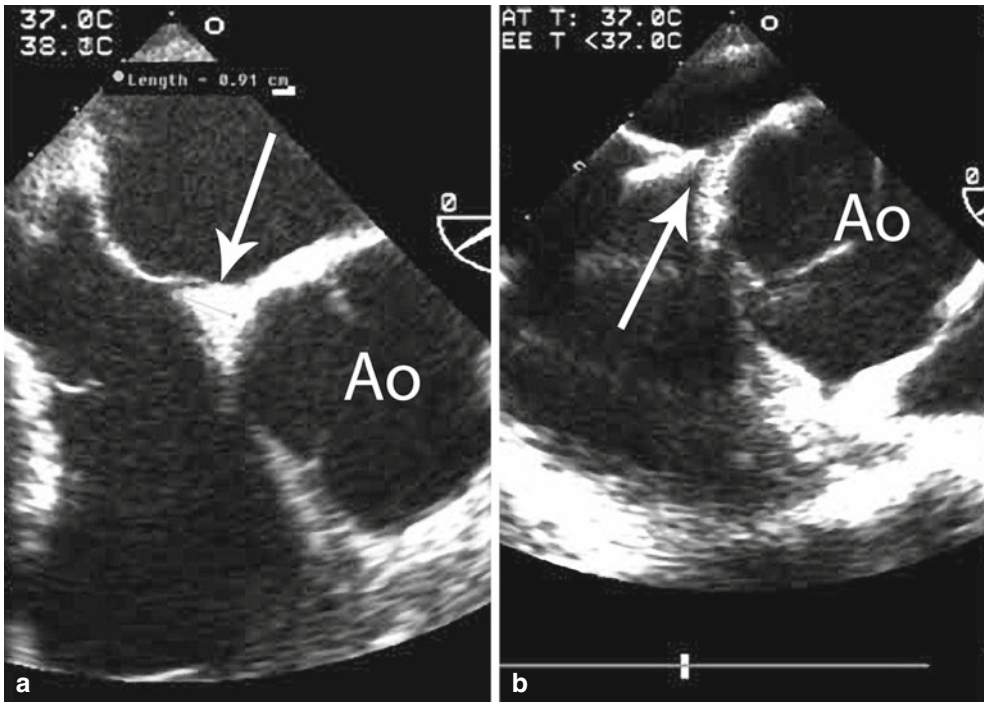

Fig. 2.7 Transesophageal echocardiographic images demonstrating the "anterior superior" rim of the foramen ovale. In (**a**), there is a 9 mm rim (*arrow*) formed by the septum secundum along the posterior ascending aorta. A centerpost device with 18 mm discs will just reach the ascending aorta in this setting. In (**b**), there is no anterior superior rim with a guidewire crossing the communication (*arrow*). Any device implanted in the foramen ovale will be in contact with the ascending aorta

similar to the intrauterine position, almost a true atrial septal defect. A center post device can move within this type of patent foramen ovale. If the radius of the center post device is less than the diameter of the potential defect, it could embolize. A self-centering device whose waist fills the space will keep the device in place and stable. This type of defect is easily defined by inflating a balloon sizing catheter across the defect (Fig. 2.5a). It is immediately apparent that the defect has no length and the true potential diameter is defined so that an appropriate self-centering device can be chosen.

Both the probe patent/tunnel type of PFO and the larger communication communicate anteriorly and superiorly on the left atrial side. This portion of the communication is bounded by the anterior superior rim formed from the septum secundum and the flap of the foramen ovale. The Amplatzer atrial septal occluder devices have been associated with erosion through the anterior superior wall of the right and left atria [4]. The amount of rim of atrial septum in this area may be associated with the risk of erosion [4]. The amount of rim can vary from almost complete absence to a centimeter or more (Fig. 2.7). If the length of this rim is less than half the diameter of the proposed Amplatzer PFO device, this is considered an exclusion criterion. In one study, only 2–31 % of patients with a PFO were appropriate candidates for closure with this device based on the length of their anterior superior rim [5].

Fenestrations of the valve of the foramen ovale may also occur (Fig. 2.8). Technically these are not persistent patency of the foramen ovale, but provide the same potential for right to left shunting. Fenestrations may occur together with a PFO. Careful evaluation of the entire atrial septum prior to closure is necessary to exclude multiple communications. The potential for a residual right to left shunt after PFO closure can occur with additional communications if they are not closed. A small residual left to right shunt could be accepted with an atrial septal defect if the size of the shunt is not clinically significant. With a PFO, however, all communications must be completely closed to eliminate the risk of a paradoxical embolus. Attention must be paid to localizing all atrial septal communications at closure.

An aneurysm of the atrial septum (Fig. 2.9) is caused by redundancy of the valve of the foramen ovale. When this occurs with a patent foramen ovale, it has been associated with an increased risk of embolic events. Many feel that eliminating the aneurysm by clasping it between discs of a device placed to occlude the foramen is important to reduce risk. Exactly how the aneurysm increases the risk of embolism is not clear, although roughening of the surface has been reported [6]. The echocardiographic definition of an aneurysm in adults is at least a 15 mm excursion of the aneurysm with a base of at least 15 mm [7].

Contrast Echocardiography

While the anatomy of the PFO is critical to technique of closure, detection of the right to left shunt depends on demonstrating the passage of an "echo contrast agent" from the right atrium to the left with ultrasound [8]. Right atrial pressure must exceed that of the left atrium for a right to left