Cardiac Septal Defects: Treatment via the Amplatzer® Family of Devices

37

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Abstract

The majority of patients with congenital heart disease present with defects resulting from vascular narrowing or absence (such as interruption or coarctation of the aorta or pulmonary arteries) or failure of structures to fuse or separate during development (total anomalous pulmonary venous connection, septal defects, fusion of valve cusps). Correction of these defects initially began with open-heart surgery, but now many of these repairs can be performed through catheter-delivered closure devices (e.g., Amplatzer closure devices). This chapter will present a brief history of defect repairs and provide information on the design, development, and preclinical animal testing of such systems.

Keywords

Interventional cardiac catheterization • Atrial septal defect • Transcatheter closure • Patent ductus arteriosus • Muscular ventricular septal defect • Perimembranous ventricular septal defect

37.1 Introduction

Congenital heart disease affects eight of every thousand live births. Correction of these defects initially began with open-heart surgery and was originally limited to repairs that could be performed without stopping the patient's circulation (patent ductus arteriosus or coarctation of the aorta). The subsequent development of cardiopulmonary bypass allowed the surgeon to safely visualize the inside of the heart, and more complex repairs were successful developed. This was the true beginning of caring for children with congenital heart disease, dramatically extending and improving the quality of their lives. However, with these advances, the art of diagnosis by physical examination was no longer sufficient to provide details of anatomy needed by the surgeon. Cardiac catheterization and X-ray visualization during the 1950s and 1960s also underwent a similar clinical explosion as the primary diagnostic tool. Still, surgeons had to be prepared to deal with the unique individual anatomies found during a given operation, i.e., as some details were unexpected. This surgical license to make plans "on the fly" is critical to a successful operation and explains the historical liberation of surgery from restrictions by the Food and Drug Administration (FDA) and Institutional Review Boards.

Next, echocardiography developed to the point where it began to replace cardiac catheterization as the primary diagnostic tool for congenital heart disease (see Chap. 22). Thus, the number of cardiac catheterizations diminished. On the other hand, interventional cardiac catheterization, pioneered by Dr. Gruntzig's coronary angioplasty, became an important clinical tool; these techniques were applied to relieve congenital narrowing of the pulmonary arteries and aorta. Experimental testing preceded the use of these techniques in children with congenital heart disease [1, 2]. Importantly, it was observed that no foreign materials were left behind while performing these angioplasty procedures. Interventional cardiac catheterization further expanded

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with Dr. Porstmann's use of an Ivalon plug to close the persistent patent ductus arteriosus (PDA) [3], as well as Dr. King's [4] and Dr. Rashkind's [5] devices for closure of secundum *atrial septal defects* (ASDs). Nevertheless, technical difficulties (i.e., limited retrievability and large delivery systems) and residual shunts plagued the early development of these devices and their application remained limited.

Two companies in particular—NuMED, Inc. (Hopkinton, NY, USA) and the former AGA Medical Corporation (now St. Jude Medical, St. Paul, MN, USA)—focused their efforts on developing devices aimed at correcting congenital cardiac defects. In 2001, the Amplatzer Septal Occluder became the first device to receive FDA approval for closure of secundum ASDs, followed in 2003 by the Amplatzer Ductal Occluder. This, along with development of stents that could be applied to the larger vascular narrowings of congenital heart diseases, opened the floodgates for interventional cardiac catheterization in children. We consider that both Allen Tower (NuMED, Inc.) and Kurt Amplatz (AGA Medical Corporation) deserve special recognition for choosing to focus their innovative efforts on improving care for children with congenital heart disease, instead of the larger volume and remuneration of fixing adult problems with coronary artery stents or patent foramen ovale closure devices.

37.2 Amplatzer Devices

The Amplatzer devices designed to close congenital cardiac defects are all quite similar; basically, they all are self-expanding stents shaped to fit a specific anatomical defect. These devices are primarily composed of a closed nitinol wire frame fashioned with a waist containing polyester fabric baffles or stuffing to fill the defect, as well as retention discs. The shapes of the wire frames are tailored to fit the various abnormal vascular or intracardiac communications. In other words, the retention discs fix the device against vascular or cardiac walls. The central waist further holds the device in place by placing radial forces against the margins of the communications, i.e., providing stable fixation of the device. Most available devices are concentric and designed to fill defects that are centrally located and thus are surrounded by cardiac structures that will not be injured by the edges of these devices. In general, subsequent occlusion occurs through thrombosis within the polyester baffles or stuffing inside of the wire frame. Importantly, within approximately 3 months, these devices are considered to be covered with protein and cellular layers, reducing the potential for forming a surface thrombus and eliminating the risk of infective endocarditis [6].

Historically, the development of Amplatzer devices began when thin wire technologies reached a point that allowed for the unique construction of frames employing nontoxic nitinol wires. Like all stents, the collapsed device is required to be long and narrow to fit through the delivery sheath. Uniquely, nitinol metal has shape memory such that, as it exits the sheath, the device expands and assumes its original shape at body temperatures. Each device has a microscrew fixed to the proximal end allowing attachment to a delivery cable. Thus, these devices can be retrieved with the cable after deployment and then either removed or repositioned. Finally, the Amplatzer devices can be detached via unscrewing once an optimal, secure, and effective position is confirmed.

37.2.1 Safety

Nickel-containing alloys, such as stainless steel, have been employed in human medicine for over 100 years. They have been used in surgical instruments as well as implants such as pacemaker wires, vascular clips, mechanical cardiac valves, orthopedic prostheses, Harrington rods, and inferior vena cava filters. This demonstrates the relative lack of toxicity of nickel-containing metallic implants; no systemic effects were observed or have been reported. Local fibrotic reactions surrounding stainless steel implants were thought to be due to passivation of nickel ions into surrounding tissue, despite the absence of microscopically visible corrosion. Interestingly, the US Navy developed the new nickel-containing metal, nitinol, in the 1960s. This alloy of nickel and titanium displayed superior corrosion resistance, and it still carries the name of its heritage—NIckel TItanium-Naval Ordnance Laboratory.

Nitinol has numerous properties besides corrosion resistance that make it desirable for use in medical devices, including: (1) super elasticity (pseudo-elasticity), (2) thermal shape memory, (3) high resiliency, and (4) fatigue resistance. Originally, thin wire technology, more specifically the development of the *diamond-drawn* wire, provided a shape that could be used in endodontic appliances. The tendency for nitinol to return to its nominal shape when deformed was especially useful in this application. This property also made nitinol a valuable material in the production of endoluminal devices. Importantly, a nitinol device can be stretched for introduction through a small delivery catheter, and then it expands back to its original shape when deployed. This new alloy replaced most stainless steel devices, especially self-expanding stents. Furthermore, nitinol's fatigue resistance properties prevent wire fractures and extend device durability. The absence of ferromagnetic properties is compatible with magnetic resonance imaging.

To date, all Amplatzer devices have proven to be nontoxic [7]. In addition, such devices performed well in fatigue testing, and when immersed in a saline bath, they did not corrode. A patient's serum nickel levels may rise immediately after insertion of an Amplatzer device, but return to normal over 3 months. Furthermore, devices examined 18 months

post implantation in humans and animals have not revealed any detectable surface corrosion. It should be noted that the incidence of cutaneous nickel allergy is approximately 10 % in humans. Yet, with over 100,000 current implants of Amplatzer devices worldwide over the past 13 years, no definitive case of a reaction has been reported in the literature.

37.3 Animal Models Mimicking Congenital Defects

Originally, the diagnosis of an ASD was established solely by typical findings on physical examination, electrocardiogram, and chest roentgenogram [8]. Surgical repair of cardiac defects, such as those of the atrial or ventricular septa, specifically required the surgeon to evaluate the shape and surrounding structures on an individual basis. Associated abnormalities, such as anomalous pulmonary venous connection, could be identified and dealt with by the surgeon at the time of the operative repair.

Animal models created to test experimental devices may not always account for associated anatomic details encountered in human congenital defects. For most congenital heart defects, an exact animal model is not readily available. Nevertheless, devices can be tested for ease of use, reliability, and efficacy, i.e., by creating an experimental defect by dilating a thin septum, sewing in an artificial vascular connection, or removing a portion of the thicker muscular septum. It should be noted that the concept of these "defects" is chosen from imaging and/or examination of pathological specimens, but may not always mimic the actual defect in humans.

37.4 Atrial Septal Defects

37.4.1 History

Atrial septal defects are congenital deficiencies in the wall separating the systemic and pulmonary venous returns as they enter the heart. These ASDs allow blood from the lungs to flow through the defect and increase the volume of blood passing through the pulmonary arteries. In most patients, after 2 decades of life with this flow pattern, this defect can permanently damage the pulmonary vasculature. Therefore, to prevent this and other problems such as associated cardiac arrhythmias, closure of an ASD is recommended during the first few years of life [9].

The University of Minnesota performed the first surgical closure of an ASD in 1952 [10] (see Chap. 25). This successful operative approach for correction of a congenital intracardiac defect remains as one of the safest open-heart operations performed, with a mortality rate under 0.5 % [9]. Nevertheless, surgical closure may include morbidity from the median sternotomy (or a right thoracotomy), the risk of exposure to blood products, insertion of a chest tube, a 3–5-day hospitalization, convalescence of 4–6 weeks, and/or the chance of postpericardiotomy syndrome. Hence, the potential consequences of these procedures spurred attempts to develop a safe and less invasive method of transcatheter closure.

It is generally accepted that transcatheter closure to treat secundum ASDs is an ideal procedure. These types of ASDs are typically surrounded by rims of tissue that a device can clasp, with no borders formed by or thus impeding the valves or the walls of the heart. King and Mills reported the first attempted transcatheter closure of a secundum ASD in 1974 [4]. This was followed by development of the Clamshell/CardioSEAL (NMT Medical, Inc., Boston, MA, USA) [11], Sideris button (Custom Medical Devices, Inc., Gainesville, FL, USA) [12], ASDOS (Sulzer Osypka, Rheinfelden, Germany) [13], and Angel Wings (Das et al.) [14] devices. Each of these devices provided an alternative to surgical closure, but also resulted in a number of new challenges. For example, large devices were required with the central post design, yet most of these early designs were not self-centering, and the center post could move within the defect. Further, these early devices required large delivery systems, and, additionally, some were plagued by unwanted embolization (e.g., unbuttoning) [15]. It was also found that frame fatigue and arm fracture occurred in up to 10 % of some of these designs, with asymptomatic wire embolization observed in several patients. It was concluded that most of these designs were difficult or impossible to recapture or retrieve after deployment. Hence, surgical removal was required if they were deployed in an improper position, and residual shunt rates were significant [16].

37.5 Amplatzer Device Designs

An ideal septal closure device should be: (1) easily delivered and implanted, (2) self-centering, (3) able to pass through a small delivery system, (4) recapturable and redeployable, (5) highly resilient (without fracturing), and (6) highly effective (without significant residual shunts). The materials used in the construction of such devices should also be biocompatible and nontoxic. It should be emphasized that durability is important, for the majority of patients are children and there is a long device "lifetime" after implantation.

The Amplatzer ASD devices were designed to fulfill these requirements. For example, the Amplatzer Septal Occluder is a woven mesh of 72 nitinol wires 0.003–0.008 in. in diameter with shape memory. There are two retention discs with a central waist that is placed within the defect (Fig. 37.1); the

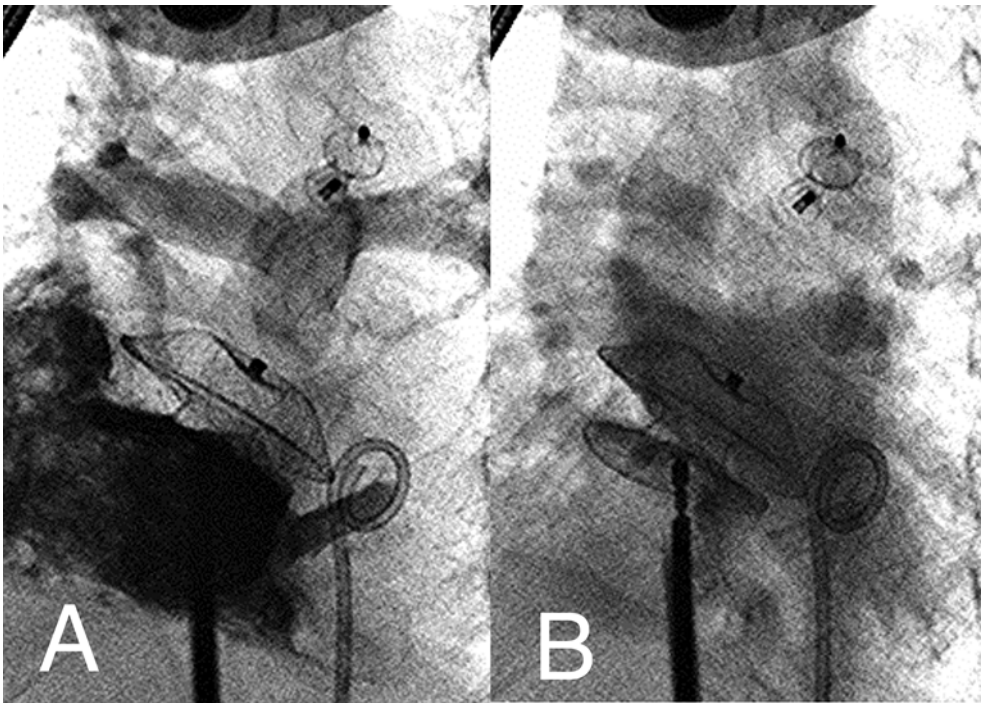

Fig. 37.1 Amplatzer Septal Occluder device. (**A**) Right atrial angiogram performed after deployment of the device in a secundum atrial septal defect, but before release. The right atrial disc is obscured by contrast with the waist within the atrial septal defect. (**B**) The levophase of the right atrial angiogram opacifying the left atrium. Contrast outlines the left atrial disc completely within the left atrium

left atrial disc is 12–14 mm larger than the waist. The stenting action of the waist and the retention discs clasps the atrial septum, thus holding the device stable and in place. Additionally, fabric baffles sewn inside the discs and waist promote thrombosis and thus the overall occlusive ability of the device. Importantly, the delivery systems are also relatively small (6–12 Fr delivery sheaths). In addition, these devices are recapturable and redeployable with microscrew/cable attachments. Available waist diameters range from 4 to 40 mm, thus allowing closure of relatively large defects [16].

37.5.1 Animal Testing of the Amplatzer Device Designs

The Amplatzer Septal Occluder device was originally designed for occlusion of a secundum ASD. Initial animal studies focused on reproducibly creating such atrial septal communications, as a natural model of a secundum ASD did not exist. To do so, nonsurgically the flap of the foramen ovale in the experimental animal was perforated and dilated with a balloon to induce an atrial communication [6]; subsequently, devices were implanted, and, in most cases, there were no complications or residual leaks. It was important to show that no thrombus formed on the devices. Afterwards, human clinical trials confirmed that no retroaortic rim was required for stable device position and complete closure. Importantly, patients could be discharged the morning after device placement, and they remained on low dose aspirin and endocarditis prophylaxis for 6 months after closure [16].

37.5.2 Required Testing for FDA Approval

An FDA-approved study to provide clinical evidence of the effectiveness of the Amplatzer Septal Occluder was originally initiated, based on the prior success of animal studies and European trials in humans. Yet, the clinical study design for this device was considered difficult. In general, patients and their families wanted to avoid surgery, despite the long history of safe surgical closure and the lack of long-term follow-up with this new device. Therefore, a blinded randomization was unsuccessful, as many patients and families that were chosen for the surgical group simply opted out of the trial, preferring to wait for final FDA approval. The overall study design was subsequently modified to allow device closure at some institutions with patients recruited to designated surgical centers. This is not true randomization, but is representative of the difficulty of study design in the real world.

Later, the results of Phase II of the FDA trial also showed that the Amplatzer Septal Occluder was an effective and safe therapy as compared to the surgical group. Importantly, at the end of 12 months, there was complete closure or a small (<2 mm) residual shunt in 98.5 % of device patients, compared to 100 % of surgically closed patients. Furthermore, there were no differences between groups in the incidence of major complications. Minor complications were more common in surgical patients (27/442, 6.1 % versus 29/154, 18.8 %); however, one needs to consider that all patients were not truly randomized. There were differences between groups, with the surgical patients being younger (18.1 ± 19.3

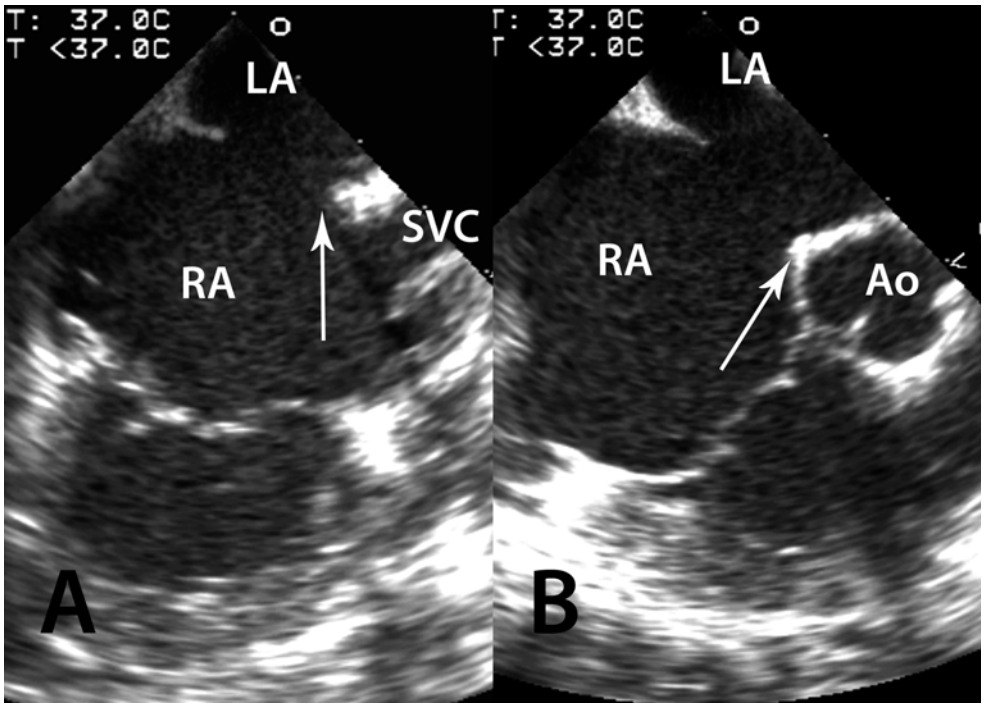

Fig. 37.2 Transesophageal images of an atrial septal defect with minimal superior and anterior (retroaortic) rims. (**A**) A bicaval view is recorded with almost no rim (*arrow*) by the superior vena cava (SVC). (**B**) A short axis view of the aorta (Ao) is recorded with minimal retroaortic rim (*arrow*). Atrial septal defects with minimal rims in these two areas are likely to bring the edges of right or left atrial retention discs in contact with the right or left atrial wall against the ascending aorta and may have a higher risk of cardiac perforation. *LA* left atrium, *RA* right atrium

versus 5.9 ± 6.2 years, $p < 0.001$) and smaller (42.3 ± 27.3 kg versus 20.6 ± 15.2 kg, $p < 0.001$) [16]. In December 2001, the FDA granted premarket approval of the Amplatzer Septal Occluder, the first ASD closure device with such an approval.

37.5.3 Continued Animal Research and Translation to Humans

After extensive successful clinical use, several reports of perforation of the heart by the device began to appear in a small number of patients with secundum ASDs [17]. Subsequently, a careful review of information from patients suffering from erosion after Amplatzer Septal Occluder placement suggested that individuals with "deficiency" of the superior and anterior rims of the atrial septum were at highest risk of this complication (Fig. 37.2). In fact, the majority of patients with secundum ASDs have very little retroaortic rims, so many patients with ASDs may be at increased risk of erosions of the Amplatzer Septal Occluder through the superior, anterior left, or right atrial walls. This anatomical relationship of the ascending aorta to the anterior rim of the secundum ASD was not fully appreciated until these complications of erosion were reported. It should also be noted that the original animal model studied did not truly mimic the anatomies of many patients with secundum ASDs. More recently, using stop flow to eliminate oversizing of the Amplatzer Septal Occluder device [17] has reduced the frequency of these complications (personal communications with Ken Lock, St. Jude Medical Corporation).

37.6 Patent Ductus Arteriosus

A *patent ductus arteriosus* is a failure of closure of a vascular channel present in the fetus that normally closes within the first few days after birth. When this vessel remains open, overcirculation of the lungs results. This, in turn, can damage the pulmonary vasculature, overwork the heart, and predispose these individuals to infective endocarditis. Closure of this channel is recommended to reduce the workload of the heart, when spontaneous closure is no longer likely (beyond 1–2 years of age) [18]. Much like operative closure of a secundum ASD, surgical closure of a PDA is a low risk procedure that has been used for decades [19]. Therefore, any attempt to employ transcatheter closure methods must carry a procedural risk at least as low as surgery. Furthermore, a PDA is similar to a secundum atrial defect in that the vascular communication is surrounded by normal vessels. It has been shown that concentric devices modified from the design of the Amplatzer Septal Occluder provided the opportunity for transcatheter closure procedures in patients with these defects.

Successful transcatheter closure of a small PDA was available before a specific closure device was developed. More specifically, coil occlusion of a PDA was first performed at the University of Minnesota in 1972. These early procedures included filling the aortic ampulla with stainless steel coils and their attached Dacron fibers, or "hanging" a coil across the narrowest part of a PDA; both procedures produced reliable closure. The first embolization coils were not attached to delivery wires, and the coils sometimes embolized

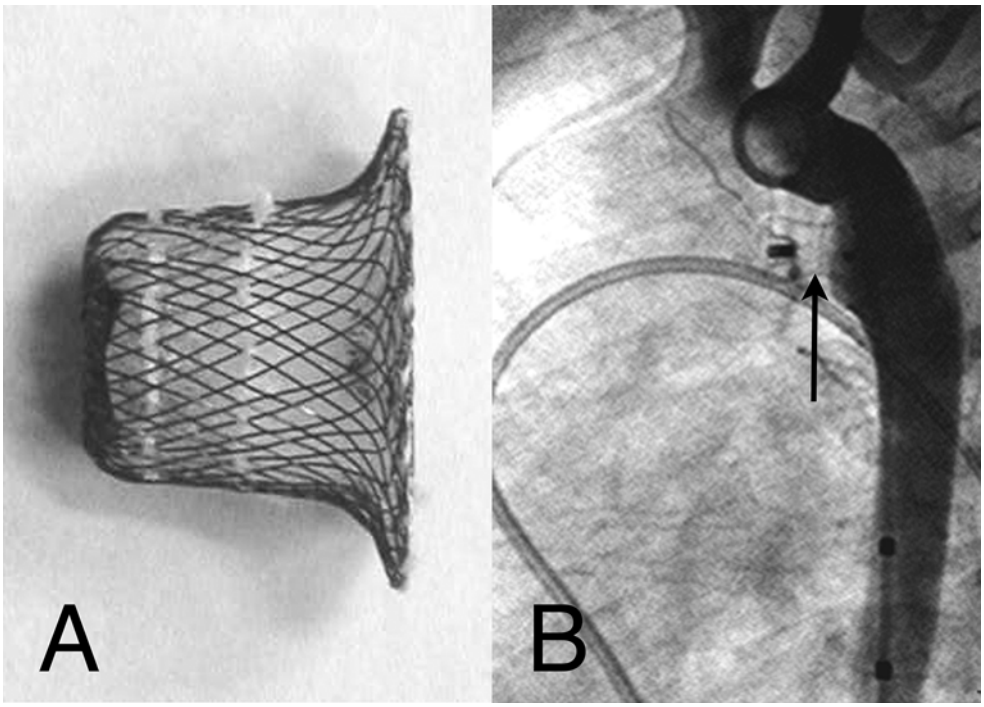

Fig. 37.3 Amplatzer Ductal Occluder device. (**A**) Photograph of the device with clearly visible suturing of the baffle and stuffing to the ductal plug. (**B**) Aortogram immediately after device placement. The aortic disc is flat against the aortic wall with the plug within the ductal lumen. There is no flow through the ductus and no obstruction of the aorta or left pulmonary artery

into the pulmonary circulation. These techniques were most effective when the narrowest diameter of the patent ductus was less than 3 mm [20]. During this period of time, a retrievable device that would occlude larger ductus defects was considered desirable.

The Amplatzer Ductal Occluder is shaped like a plug, sized to the aortic ampulla with an aortic retention disc designed to prevent embolization through the ductus (Fig. 37.3). This device is typically delivered via a venous route, and the delivery catheter is small (5–8 Fr) because of the small collapsed device diameter. This simple modification of a self-expanding stent was found to be extremely successful in producing complete occlusion of even larger PDAs. In the Phase II FDA trial, there was an observed complete closure of over 97 % of PDAs at 6 and 12 months. There was only a 2.3 % incidence of serious or major adverse events (including one embolization that required surgical removal and one death of a child, not device related, with a chromosomal trisomy) [21]. Premarket FDA approval of the Amplatzer Ductal Occluder device was received in January 2003.

37.6.1 Animal Testing of the Amplatzer Ductal Occluder and Translation to Human Use

A persistent PDA does not occur reliably in animals; therefore, a model needed to be created to test the efficacy of the Amplatzer Ductal Occluder. An asynthetic tube was sewn between the descending aorta and the pulmonary artery in animals [22]. The Amplatzer Ductal Occluder device worked well in these animals, completely occluding the surgically created PDA with endothelialization within 3 months. In animal trials, there were no complications, the device was retrievable, and there were no residual hemodynamic abnormalities.

Subsequent to the successful animal studies, clinical trials were undertaken with a high rate of success in occluding various sizes of PDAs in patients [23]. Yet with more extensive clinical use, a few case reports began to surface of partial obstruction of the descending thoracic aorta by the retention disc of the Amplatzer Ductal Occluder device. This was the result of the angle (approximately 65°) of insertion of the naturally occurring PDA with the descending aorta. In these cases, the superior portion of the retention disc was shown to be angled into the aorta by the plug within the PDA (Fig. 37.4), sometimes producing partial aortic obstruction in smaller patients with larger PDAs. It should be noted that the surgically created experimental PDA in the animal model was sewn at a 90° angle to the aorta, so this complication was not predicted by the anatomically inaccurate orientation.

37.6.2 Animal Trials Designed to Test Prototype Angled Amplatzer Ductal Occluder Devices

To reduce the complexity of manufacturing the Amplatzer Ductal Occluder device and, at the same time, address the issues of the angle of the descending aorta with the PDA, a new device was designed with an angled retention disc; the wire

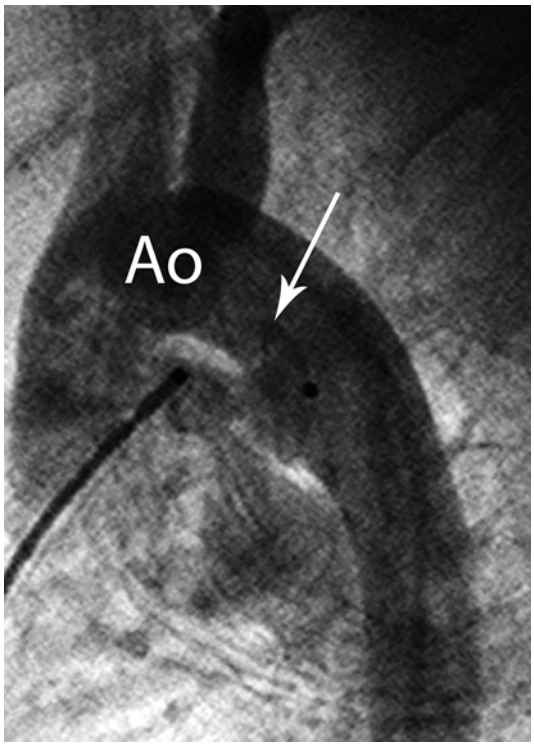

Fig. 37.4 An aortogram recorded in lateral projection after placement of an Amplatzer Ductal Occluder device, fully deployed before release. The aortic retention rim protrudes superiorly (*arrow*) into the aortic lumen (Ao). The angle of the human patent ductus arterosus is at an angle of approximately 65°, instead of 90° in the animal model. This device is oversized and can be retrieved using the delivery cable still attached to the device

count was also increased from 72 to 144 wires, thus eliminating the need for fabric in the device [24]. For animal testing of this new design in next stage trials, a synthetic tube was sewn between the pulmonary artery and aorta at the angle of the more naturally occurring human PDA. Subsequently, in all animals in this preclinical trial, the angled Amplatzer Ductal Occluder device was successful in occluding the created PDA (Fig. 37.5A); however, the initial human use of the device revealed shortcomings with these animal trials. Specifically, an angled Amplatzer Ductal Occluder was successfully placed in a young infant with initial success, which also avoided any protrusion of the device into the aorta; however, after 3 months, the device expanded the PDA resulting in "recanalization" (Fig. 37.5B) [25]. This complication was considered to result from two unanticipated design problems. First, the hoop strength of the angled Amplatzer Ductal Occluder was sufficient to dilate the PDA in a young infant. This, in turn, resulted in an increase in the distance between the radial "spokes" of the device, with less occlusive resistance. In retrospect, the animal model trial used a non-expandable PDA with small diameters that limited the distance between the wires of the device.

37.6.3 Redesign of a Device Without Fabric and Flexible Retention Disc Orientation

The latest iteration of the Amplatzer family of ductal occluder devices (Amplatzer Ductal Occluder device 2—ADO2) is longitudinally symmetrical with retention discs on each end and with flexibility at the connection of the retention discs to the occluding plug (Fig. 37.6). This allows the retention discs to angle and lie smoothly against the aortic or pulmonary wall. To create an animal model for testing this device, infant piglets had balloon dilation of the probe PDA so that an anatomically true defect was available [26]. Subsequently, the size of the discs was further reduced to allow implantation in smaller infants (ADO2-Additional Sizes, ADO2-AS). This device was tested after ductal dilation in newborn piglets weighing 1800–2200 g and implanted under echocardiography to mimic occlusion in a premature infant in the isolette, similar to surgical ligation in this population. The animal testing was successful [27], and there are early positive results in clinical trials of premature infants outside the United States [28].

37.7 Muscular Ventricular Septal Defect

Muscular ventricular septal defects can occur in the lower, thicker ventricular septum. Closure of such defects is clinically recommended for the same indications as ASDs and PDAs—eliminating overwork of the heart and overcirculation of the lungs. However, unlike for the other two defects, surgery to close a muscular ventricular septal defect is generally not a simple or low risk option. More specifically, the surgical closure of muscular ventricular septal defects can be difficult at best, e.g., the right ventricular aspect of the defect can be hidden from the surgeon's view by trabeculations within the right ventricular cavity. This, in turn, can result in a high incidence of residual leaks with a right ventricular approach. On the other hand, directly incising the left ventricle would allow clearer visualization of the defect margins, but left ventricular aneurysms or diminished left ventricular function has resulted in some cases [29]. These surgical difficulties make the transcatheter closure of such ventricular defects an attractive alternative.

In general, the Amplatzer Muscular Ventricular Septal Occluder is very similar to the Amplatzer Septal Occluder. Like a secundum ASD, muscular ventricular septal defects are separated from cardiac valves by myocardium; the obvious difference is the thickness of the ventricular myocardium. Therefore, these devices were designed with greater distances between the discs to accommodate for the differences in myocardial thickness (Fig. 37.7). Greater stability was found to be produced by the radial force applied against

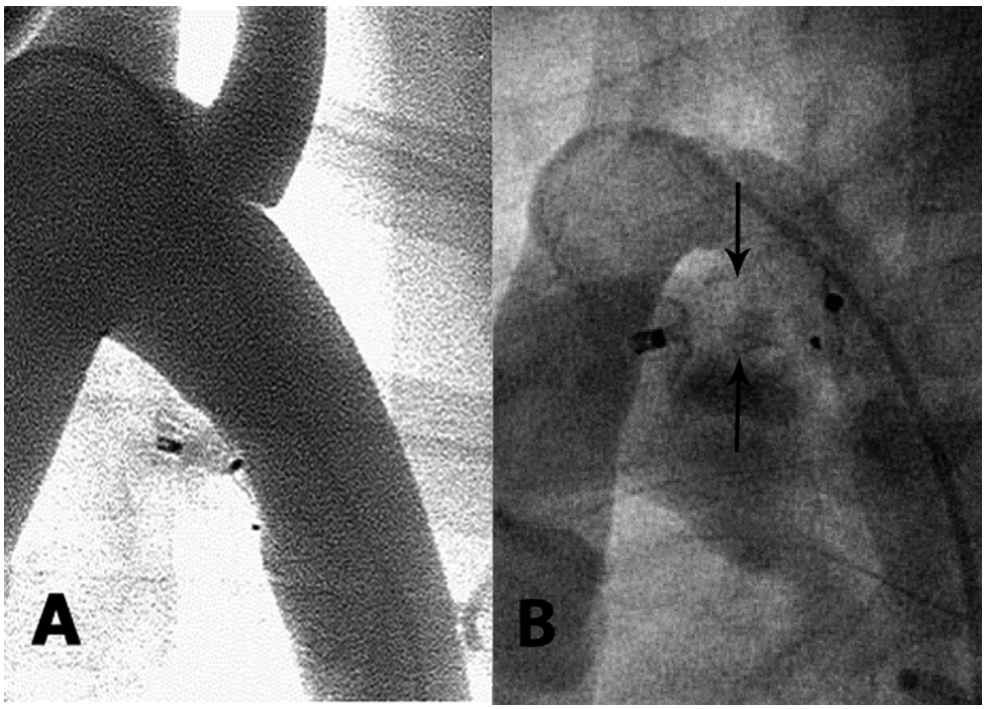

Fig. 37.5 (**A**) An aortogram is performed after placement and release of an angled ductal occluder device in a canine model with the artificial ductus sewn to mimic the natural angle of the human patent ductus arteriosus. The angled aortic retention disc lies flat against the aortic wall with no protrusion into the aortic lumen. The "plug" of the device is compressed with immediate complete occlusion. (**B**) A similar angled patent ductus arteriosus device has been placed in a human infant. The angiogram is recorded 3 months after implantation. The device plug was initially compressed with minimal flow through the middle. After 3 months, the device has expanded the ductus (*arrows*) with increased interwire distance and "recanalization"

the thicker muscular ventricular septum, thus the retention disc diameters were decreased to 6–8 mm larger than the waist. From a design standpoint, it should be noted that initial attempts of transcatheter closure of muscular ventricular septal defects, using the Clamshell/CardioSEAL device, produced a 40 % incidence of residual leaks [30]. These devices have a central post instead of a waist the size of the defect. Therefore, a ventricular "retention" disc had to be sized at least twice the diameter of the defect; residual leaks could result from migration of the central post within the defect. In contrast, the self-centering Amplatzer Muscular Ventricular Septal Occluder is fixed within the defect by its waist. Another advantage of the Amplatzer device is the smaller maximum device diameter required to close a muscular ventricular septal defect, compared with central post devices.

37.7.1 Animal Trials Designed to Test Ventricular Closure Devices

It was the successful animal trials to close surgically created muscular ventricular septal defects [31] that eventually led to human use [32], but once again the clinical use in humans subsequently demonstrated the shortcomings of these preclinical experimental models. In general, naturally occurring muscular ventricular septal defects in humans frequently are not circular (Fig. 37.8); at least 60 % are twice as wide as they are tall [33]. The typical method of sizing muscular ventricular septal defects is to look at the vertical dimension of the defect using either echocardiography or angiography. Angiography, in particular, demonstrates only the vertical dimension, and, because the shunt occurs primarily during systole, the defect is best outlined during contraction when the diameter of the muscular ventricular septal defect is smallest. Measuring the muscular ventricular septal defect from en face or 3D echocardiographic imaging accounts for the oval shape of the defect and can be timed in diastole; note the capability of these imaging modalities has advanced dramatically in the last 5–10 years. The frequency of residual shunts is reduced by using a device with the same circumference as the defect in diastole [33].

37.8 Perimembranous Ventricular Septal Defect

Amplatzer devices designed for closing secundum ASDs, PDAs, and muscular ventricular septal defects are concentrically symmetrical, as there are typically no valves near the edges of the defects they are designed to close. In contrast, in

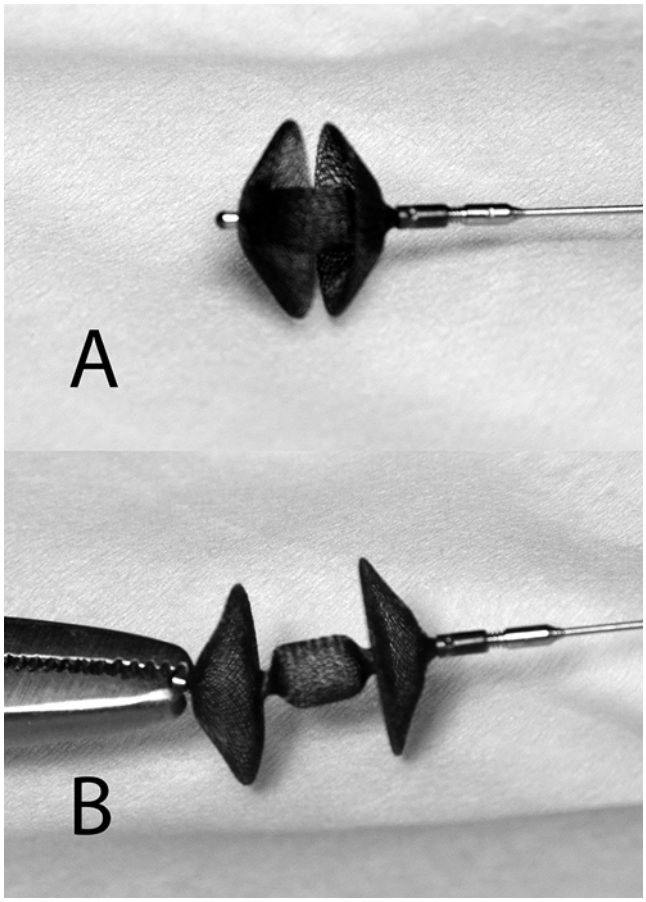

Fig. 37.6 Amplatzer Ductal Occluder II device. The device is longitudinally symmetrical allowing implantation from either the aortic or pulmonary approach. The constriction of the device between the central plug and the retention discs allows the discs to swivel and align against the vascular wall of the aorta and pulmonary artery

perimembranous ventricular septal defects, both the aortic and tricuspid valves can be close to the defect margins. From a historic perspective, early attempts were made to close perimembranous ventricular septal defects with the Clamshell and Sideris button devices. However, it was soon reported that distortions of the aortic valves resulted in aortic insufficiency and, in some cases, the devices were found to have embolized [34]. It was considered that the flexibility of shaping the basic Amplatzer device frames could be advantageous to produce an eccentric, asymmetric device. More specifically, an Amplatzer Perimembranous Ventricular Septal Occluder (Fig. 37.9) was designed with a minimal rim of the left ventricular disc (0.5 mm); to sit beneath the aortic valve, a longer (5.5 mm) inferior left ventricular disc and a short waist (1.5 mm) are needed to keep the right ventricular disc away from the tricuspid valve. In subsequent animal trials, it was shown that an eccentric design protected the aortic and tricuspid valves, yet closed perimembranous ventricular septal defects [35].

However, the difficulty with such systems was in the reliability of delivering the device in the proper orientation. Advancing a pigtail catheter from the pulmonary artery through a patent ductus often results in the curl of the catheter oriented along the lesser curvature of the aorta. Therefore, a sharply curved delivery sheath was designed to deliver these devices to the left ventricular apex, mimicking this property. In addition, simply advancing the asymmetric device through this sheath did not always result in proper device orientation. A sharply curved delivery catheter was designed that forced attachment of the device with the longer left ventricular disc along the lesser curvature of the catheter (Fig. 37.10). Yet, it was determined that when combined

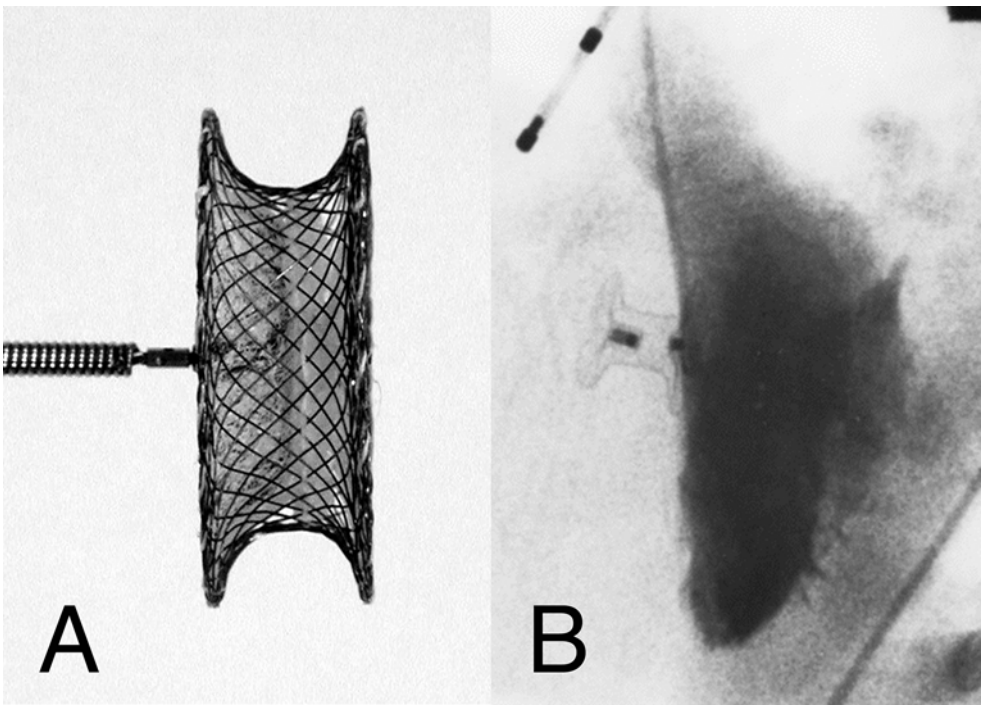

Fig. 37.7 Amplatzer Muscular Ventricular Septal Occluder. (**A**) Photograph of the device; the waist is wider than that of the Amplatzer Septal Occluder to allow for the thicker muscular ventricular septum. (**B**) Left ventricular angiogram 3 months after device placement showing complete occlusion of a mid-muscular ventricular septal defect

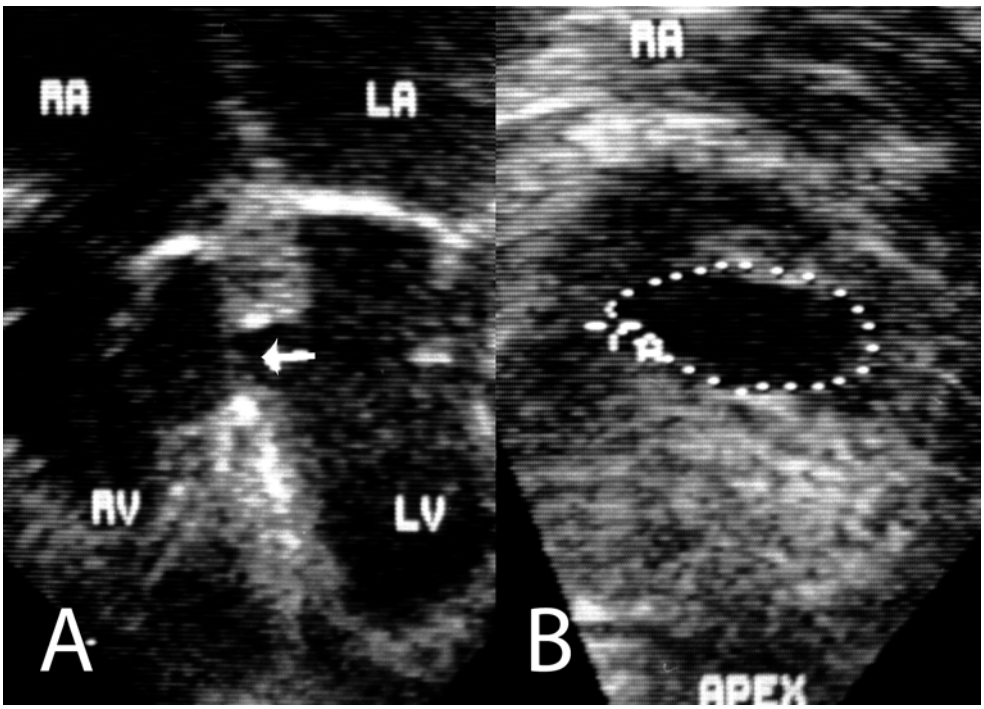

Fig. 37.8 Echocardiographic images of a mid-muscular ventricular septal defect. (**A**) An apical four-chamber view is recorded. There is "dropout" of echoes from the mid septum (*arrow*) with a short vertical dimension. (**B**) An en face view of the right ventricular surface of the ventricular septum is recorded in the same patient. The ventricular septal defect is outlined by the dotted line. The vertical dimension is significantly less than the horizontal one. If only the vertical dimension is considered in choosing the device size, there would be a significant residual shunt, or device embolization might be possible. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

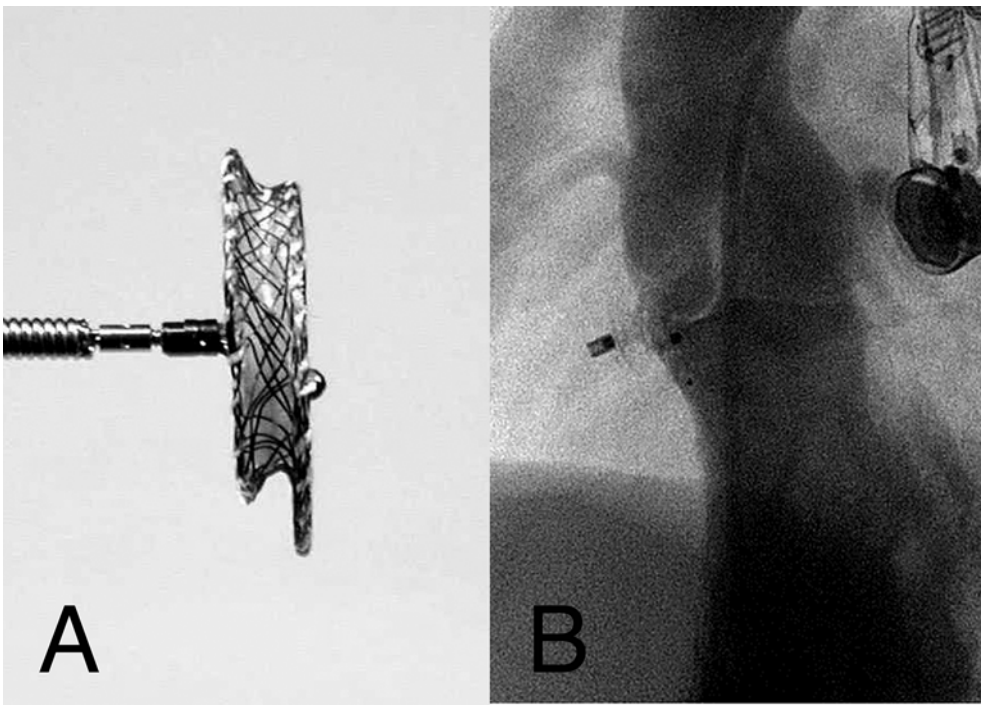

Fig. 37.9 Amplatzer Perimembranous Ventricular Septal Occluder device. (**A**) Photograph of the perimembranous device in which the delivery cable is attached to the right ventricular disc. The asymmetric left ventricular disc is positioned with the minimal rim of the subaortic portion at the top of the device. This prevents interference with the aortic valve. (**B**) Left ventriculogram after device placement. The asymmetric left ventricular disc avoids distortion of the aortic valve. There is no flow through the device immediately after deployment

with the sharply curved delivery sheath positioned in the left ventricular apex, a device advanced to the tip of the delivery sheath assumed proper orientation [35]. This was confirmed in human trials, and complete closures have subsequently been reported to occur in 96 % of patients. In these trials, there were also no serious complications, although the number of patients was notably small [32].

With expanded clinical experience, reports of complete heart block after transcatheter closure of perimembranous ventricular septal defects ranged from 2.1 to 22 % [36–38]. This compared to a contemporary review of surgical closure in patients the same age and size range with an incidence of complete heart block of only 0.8 % [39]. Interestingly, this complication did not occur in the preclinical animal trials or in the

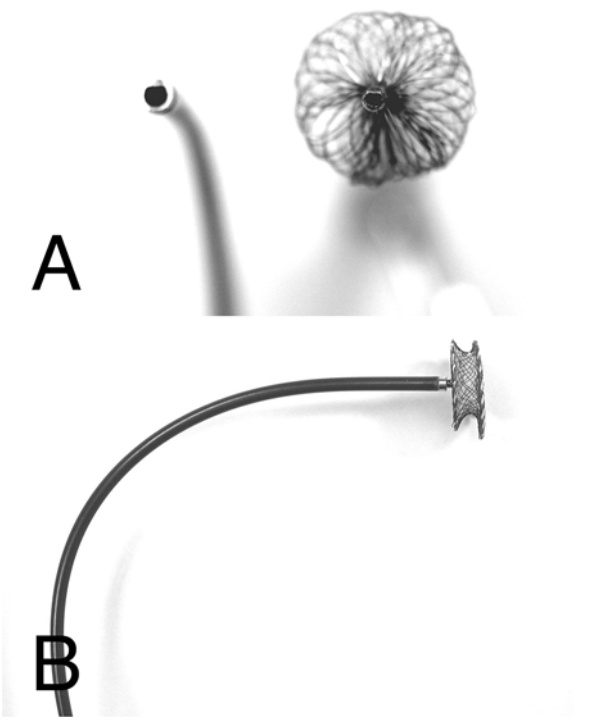

Fig. 37.10 Delivery system for an asymmetric device. (**A**) Photograph of the slot in the delivery catheter, flat at the upper margin. This matches a flattened area at the upper surface of the microscrew. The microscrew will only fit into the slot in the correct orientation. (**B**) The asymmetric perimembranous ventricular septal occluder is attached to the curved delivery catheter. The longer rim of the left ventricular disc is oriented along the lesser curvature of the delivery catheter

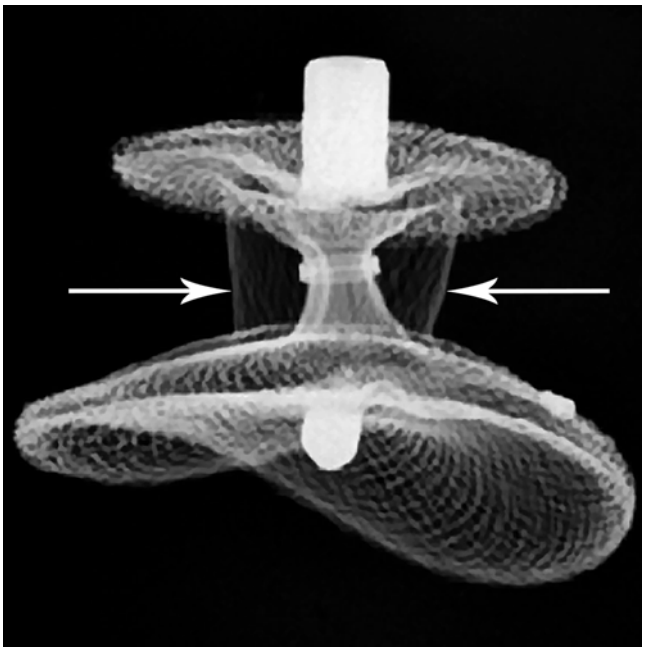

Fig. 37.11 Amplatzer Perimembranous Ventricular Occluder device 2 (pmVSO2). The central device with a narrow waist is made of heavier gauge wire with strength to maintain the device shape. A second softer device surrounding the stiff central device has a wider occluding waist (*arrows*). This significantly decreases the radial force against margins of the defect and the neighboring conduction system. The discs are also further apart than the original design decreasing the "clasping" force of the discs against the septum. The inferior edge of the left ventricular disc has been reduced to decrease possible trauma from contact with the left ventricular side of the septum, while side "wings" improve retention of the device in the defect

initial reported use in humans [32]. Although some investigators continued to implant the pmVSO1 device by avoiding oversizing and aggressive manipulation, they still detected an incidence of heart block around 1 %, thus this complication remained. Possible explanations for this included: (1) trauma to the conduction system from the radial force of the device (exacerbated by oversizing), (2) compression of the conduction system by the short distance between the discs, and (3) abrasion from the elongated inferior left ventricular disc. Accordingly, the device was redesigned with an innovative double-walled construction—a stiff inner layer that maintained device configuration and a softer outer layer with reduced radial force. The interdisc distances were increased slightly to minimize the clamping forces on both the septum and conduction tissue. More specifically, the long, inferior left ventricular disc was reduced to remove a possible source of trauma, while the sideways wings of the left ventricular disc were expanded to maintain stability (Fig. 37.11). Improved control over the orientation of the left ventricular disc was also achieved. Subsequent preclinical animal testing of the new design continued to demonstrate high closure rates, with no trauma to either the aortic or tricuspid valves. As with the original design, there was no occurrence of complete heart block in the animal model [40]. Importantly, initial human experience with 1-year follow-up demonstrated no AV conduction problems in 18 human implants [41]. Validation in humans awaits further clinical trials.

37.8.1 Animal Trials Designed to Test Perimembranous Ventricular Septal Occluders

Unlike all the previously described surgically created animal models of congenital cardiovascular defects, the perimembranous ventricular septal occluder device was tested in a naturally occurring defect animal model (Yucatan mini pig). Morphologically, the porcine defect closely resembles that in humans [42]. It was shown that the device and its unique delivery system were successful in occluding these congenital defects [35]. More specifically, subsequent examination of pathological specimens in this animal model did not show any evidence to explain this complication [43]. It was considered

that this could be a result of minor differences in the conduction system of these mini pigs as compared to humans, or perhaps a consequence of the extremely low incidence of complications associated with these devices. Therefore, caution must be taken when selecting an animal model that mimics a human defect; in this case, it did not foresee a complication when the device was taken to human trials (see also Chaps. 6 and 27). It should be noted that some of these reported problems may have resulted from implanting larger devices, as several European investigators continue to implant this device, minimizing the device size without suffering the complication of complete heart block. Nevertheless, redesigning these devices and carefully avoiding oversizing during implant may aid to further reduce the incidence of complete heart block to acceptable clinical levels.

37.9 Summary

The Amplatzer family of occluder devices has provided for unique minimally invasive methods for the transcatheter closure of congenital cardiovascular abnormalities. In general, the simple underlying device designs allow for easy modification, thus enabling numerous different types and sizes of devices for treating a variety of abnormal cardiac communications. The unique characteristics of these devices include ease of delivery, small delivery systems, retrievability, safety, and effectiveness.

Despite the clinical success of these devices, the transition from an animal trial to the human condition clearly demonstrated the failure of animal model designs to ideally mimic the intricacies of human cardiac anatomies (congenital and adult). Prior to the preclinical studies described here, many of these features had not been appreciated because surgical treatment was easily adjusted to account for them. For example, suture closure of a secundum ASD did not pin the atrial free wall between a stiff device rim and an aorta pulsating with systemic pressure. Likewise, suture ligation of the PDA is not affected by the angle between the PDA and aorta, or the ability of the PDA to expand when internal force is placed against it. Furthermore, surgical patches can be easily and precisely shaped to fit margins of an irregular muscular ventricular septal in a patient's defect. Complete heart block was a known complication of surgical repair of perimembranous ventricular septal defects, and this eventually led to the development of the cardiac pacemaker. The relative occurrence of complete heart block with device closure was not a total surprise due to the proximity of the penetrating bundle to ventricular septal defect margins, although it did not appear in preclinical trials. Therefore, one must consider that there may be minor variations in the relationship of the penetrating bundle and the ventricular septal defect in the porcine perimembranous ventricular septal defect (or even from patient to patient) that account for this variability. On the other hand, one should not consider this as a failure of the animal model design; ASD, muscular ventricular septal defect, and PDA devices are symmetrical, and a central defect was primarily created to test feasibility and efficacy of the device. Thus, these devices functioned perfectly in these designed preclinical models.

It is important to consider that various factors—proximity of a patient's ascending aorta to the anterior margin of a secundum ASD, angle of the PDA to the aorta, expansion of the PDA in younger patients, and frequent occurrence of oval muscular ventricular septal defects—all become significant only under certain treatment conditions. For example, the anatomic details of secundum ASDs and PDAs become more significant when interventional cardiologists tend to oversize devices, either in fear of embolization or due to a perceived lack of previous risk with oversized devices. This is likely also true with perimembranous ventricular septal occluder devices, where a small aortic rim may lead to the risk of embolization. Further, it is likely that an oversized ventricular septal occluder device will increase the pressures against the conduction system in perimembranous ventricular septal defects and thus increase the risk of complete heart block.

There are notable limitations in creating any preclinical animal model for studying therapies for congenital heart disease. For example, tearing the interatrial septum to create an ASD generally does not produce relatively large enough defects, and often there remains an anterior rim of atrial tissue. Furthermore, acutely creating larger communications between systemic and pulmonary circulations (a PDA or ventricular septal defect) is poorly tolerated in these animals, and acute congestive heart failure and pulmonary edema soon develop; long-term animal survival in control groups can be quite low. Likewise, testing the ability of these devices to close large defects in the animal models is also difficult, i.e., even the porcine congenital perimembranous ventricular septal defect is small or moderate in size when the animal is ultimately ready to be used for a closure procedure. Despite these limitations, preclinical testing of any such device is exceedingly valuable to better define device function prior to first use in human procedures.

We consider here that when translating from a given animal model to human use, great care should be taken in defining the specific anatomies of a congenital heart defect to which the devices are to be applied therapeutically. In particular, we suggest that careful review of pathological specimens should be supplemented by 3D imaging (echocardiographic, computed tomographic, or magnetic resonance imaging) to define the proximity of critically important anatomical structures and their relative relationships, such as between the inferior vena cava and interatrial septum or between the aorta and PDA. Critical knowledge of prior surgical experience can also lend important insights to the anatomies of congenital defects, although some surgeons may be a bit reluctant to participate in creating "competitive" treatments.

Finally, devices whose central cores expand to fill an abnormal communication should not be oversized. When possible, device edges should be smooth and rounded rather than sharp, as they may have unanticipated contact with critical cardiac structures. Nevertheless, device closures of congenital cardiovascular defects have revolutionized the care for children with congenital heart diseases. For many transcatheter closures, the Amplatzer devices have been the first successfully employed nonsurgical treatment. Finally, animal testing is an integral part of the process for developing new devices, and the translation to human use requires careful thought.

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