Development and Testing of the Helex Septal Occluder, a New Expanded Polytetrafluoroethylene Atrial Septal Defect Occlusion System

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Background—A variety of transcatheter atrial septal defect (ASD) occluders are currently in use around the world. Although for the most part effective, all of these devices lack features that would be desirable in a “perfect” device. The Helex septal occluder is a new type of device designed to improve the results of transcatheter ASD closure. This study was designed to examine the effectiveness and safety of this occluder in an animal model.

Methods and Results—The Helex was implanted into 24 dogs with surgically created ASDs. Procedural details focusing on deployment, removal, and early closure rates were examined. Follow-up consisted of sequential transesophageal echocardiography and fluoroscopy as well as epicardial contrast echocardiography and angiography at the time of death. Specimens were examined grossly and histologically, and devices were tested for metal fatigue. All animals had successful ASD closure. Implantation was uncomplicated (mean fluoroscopy time 11.7 minutes), and removal or repositioning was always possible. Closure rate as judged by transesophageal echocardiography was 88% initially and 100% at 2-week follow-up. Devices rapidly became infiltrated with connective tissue without inflammation and were endothelialized over time. There were no instances of thromboembolism. A single wire-frame fracture occurred secondary to a prototype delivery system malfunction.

Conclusions—The Helex septal occluder proved safe and effective for ASD closure. Several advantages over currently available devices were evident in this model. Controlled prospective clinical trials are needed. (Circulation. 2001;104:711-716.)

Key Words: heart septal defects • catheterization • pediatrics • shunts

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Since the 1970s, investigators have been searching for improved techniques to achieve transcatheter closure of atrial septal defects (ASDs). Although a number of devices have undergone investigation, the ideal device does not exist. Such a prosthesis would be simple to implant and easy to remove, provide 100% closure, maintain a low profile on the atrial septum, have an atraumatic contour, and be composed of materials with proven mechanical integrity and long-term biocompatibility. In 1995, we began to design an occlusion system that would incorporate these features. This study reports the results of tests of this new device in an animal model.

Methods

Device and Delivery System

The Helex occluder is composed of a single piece of nickel-titanium (nitinol) wire with a patch of microporous expanded polytetrafluoroethylene (ePTFE; W.L. Gore & Associates, Inc) attached along its length. The superelastic property of nitinol is used to form the wire frame into 2 equal-size opposing disks that bridge and occlude the septal defect (Figure 1). The wire frame is easily visible with fluoroscopy and contains 3 clearly marked “eyelets” that facilitate proper placement. The occluder is fixed in place by a unique locking mechanism that passes through the center of the device from the left to the right atrial disk, thereby securing it in place. The ePTFE is specially designed to facilitate rapid cell penetration, thereby promoting rapid tissue ingrowth, resulting in permanent defect closure and device stability.

The delivery system is a coaxial catheter assembly consisting of a 9F preshaped outer delivery catheter, an inner 6F control catheter used for deployment and/or withdrawal of the device, and a central mandrel used to configure the device and deploy the locking mechanism (Figure 2). An ePTFE retention suture anchored to the tip of the control catheter loops through the right atrial eyelet and is exteriorized to the operator. This suture allows for removal of the device after complete deployment and release from the catheter delivery system if desired.

Delivery Procedure

The occluder comes premounted on the delivery system. After irrigation with heparinized saline, the system is introduced through a standard 9F femoral venous sheath. The delivery catheter is designed to facilitate direct passage across the ASD, obviating the need for placement of a guidewire and delivery sheath in the left atrium (Figure 3). Once positioned in the left atrium, incremental advance-
ment of the control catheter and retraction of the mandrel result in constitution of the left atrial disk. The appearance of the center eyelet marks the completion of left atrial disk deployment. Gentle retraction of the entire system then results in apposition of this disk to the atrial septum. The right atrial disk is then delivered in a similar fashion. Before the device is locked in place, repeated repositioning of either disk and/or complete device removal via the delivery catheter is possible. Withdrawal of the mandrel into the control catheter results in deployment of the lock and separation of the device from the catheter. Once this occurs, the device and atrial septum are free of all distortion associated with the delivery system, and a true assessment of device position and leak status can be made. Even at this late stage of delivery, if device removal is desired, traction on the retention suture unlocks the device and allows it to be withdrawn back into the delivery catheter. If the result is acceptable, however, the retention suture is removed, completing the procedure.

Animal Implantations

Implantations were performed in 24 mature dogs cared for in accordance with the “Position of the American Heart Association on Research Animal Use.” Before this study, extensive laboratory and computer analysis of all device and delivery system components was performed. Animals were given oxymorphone (0.05 mg/kg SC) and atropine (0.04 mg/kg IM) before the induction of general anesthesia with diazepam (0.2 mg/kg IV) and ketamine (5 to 10 mg/kg IV) and were maintained with isoflurane and vecuronium (0.1 mg/kg IV). Septal defects were created surgically via a left lateral thoracotomy. A 6-mm punch was passed via a purse-string suture from the left to the right atrium as previously described by Das et al.8 Defect creation was followed by device closure from a right femoral venous approach. Preclosure evaluation consisted of transesophageal color Doppler echocardiography (TEE), left atrial angiography, and static balloon sizing (Nitinol Medical Technologies). During the study period, devices were available in 15-, 20-, and 25-mm diameters. After device placement, results were assessed by TEE and right atrial angiography. Antiplatelet therapy (aspirin 81 mg/d) began 2 days before the procedure and continued until the dog was euthanized or for a maximum of 6 months. Animals received heparin 100 U/kg IV and antibiotic prophylaxis (cefazolin 22 to 44 mg/kg IV) during the procedure.

Follow-Up and Explants

TEE and fluoroscopy were performed 2 weeks after implantation and monthly thereafter. Animals were euthanized at 1, 3, 6, or 12 months after implantation. At the time of device explantation, TEE was performed, followed by lateral thoracotomy and placement of a large-bore catheter into the left atrium. Epicardial color Doppler and bubble contrast echocardiography (left and right atrial injections) and right and left atrial angiography were then performed. Heart, lungs, brain, and kidneys were examined grossly and microscopically for evidence of thromboemboli.

Results

Implantation

Twenty-six dogs (mean weight 23.6 kg) were used for the study. Two died after ASD creation before catheterization. Twenty-three of the remaining 24 animals had left-to-right shunting at the atrial level demonstrated by TEE after the surgical procedure. In 1, no ASD was identified, and a transseptal puncture and static dilation of the atrial septum were used to create a defect. Mean static and balloon-sized defect diameters were 7.9 ± 2.3 and 10.4 ± 2.4 mm, respectively. In 23 of 24, the ASD was crossed with the delivery system alone. For the animal that required transseptal puncture, a guidewire and long sheath were used to cross the ASD.

Device placement was successful in all animals, and repositioning of the device was always possible before lock deployment. Mean fluoroscopy time for single device implantations was 11.7 ± 6.2 minutes. There were 4 instances of device removal (withdrawal of the deployed device back into the delivery catheter before lock deployment) and 3 instances...
of device retrieval (snare-assisted recapture of a completely released device). Indications for removal or retrieval included prototype delivery system failure (n=4), operator error (n=2), or a combination of both (n=1). Delivery system failure was a result of high friction between the mandrel and the control catheter that resulted in poor coordination of the deployment sequence. All 3 instances requiring snare-assisted removal occurred early in the study and involved failure of the suture retrieval cord related to the friction issue mentioned above. After this design issue was addressed, this problem disappeared. Retrieval was performed with a commercially available Amplatz gooseneck snare (Microvena) and was achieved without incident in the aorta and right and left atria. The helical design and smooth contour of the device made snare capture and removal through the bloodstream easy and atraumatic.

**Efficacy–Closure Rate**

Twenty-one animals (88%) had immediate complete ASD closure as determined by TEE and right atrial angiography. Three were noted to have trivial residual shunts immediately after device placement. At 2-week follow-up, all had complete ASD closure as judged by TEE. One animal was subsequently found to have a 2- to 3-mm residual shunt seen only with left atrial angiography and epicardial contrast echocardiography before euthanasia 3 months after implantation. No other animal had evidence of a residual shunt by angiography, TEE, epicardial contrast echocardiography, or autopsy examination (Figure 4). The overall complete closure rate was 95%, with 1 small residual shunt that was not detectable by standard noninvasive imaging methods.

**Device Performance and Appearance**

Because of the relatively small chamber size and prominent crista terminalis found in the canine heart, 11 of 24 devices had a somewhat flared, rather than parallel, appearance immediately after implantation. Interestingly, follow-up fluoroscopy demonstrated progressive realignment of the disks in 7 of these animals, resulting in a parallel orientation of the disks over time. This phenomenon suggests that the nitinol frame adapted to the unfavorable topography of the crowded atria in this model for a period of time after implantation.

In 1 case, the flared disk appearance became more pronounced with time. A fracture of the wire frame was detected 120 days after implantation. A review of the procedure and examination of the frame at explantation suggested that the
fracture was secondary to kinking of the device within the delivery catheter before implantation, coupled with the large size (25 mm) of the device for the small canine atrium. This combination led to excessive stress forces placed on the wire frame that exceeded the known tolerance limits, resulting in fracture. Importantly, at explantation, there was neither any evidence of thrombosis on the device surface nor microscopic evidence of distant thromboembolism. There was no residual leak, and the device posed no threat to the surrounding cardiac structures.

Device Mechanical Integrity Testing
After enzymatic digestion of the atrial septum, scanning electron microscopy was performed examining the nitinol frame for evidence of excessive wear or fatigue (Figure 5). Other than the fractured device discussed previously, we found no evidence of wear or fatigue at any time after implantation.

Nickel Assay
Five tissue samples were obtained from 8 dogs (3 test samples in close proximity to the device and 2 control samples obtained >1 cm from the device perimeter) and analyzed for nickel content at 3-, 6-, and 12-month intervals with inductively coupled plasma/mass spectrometry. Analysis was performed with a split ANOVA plot. No statistical difference was found between test and control samples taken at any time interval (the lower test limit was 0.025 ppm), nor was any difference between the average nickel concentrations found at 3, 6, or 12 months.

Pathology
Pathological examination of the heart and distal organs was performed at 1, 3, 6, and 12 months after implantation. Microscopic evaluation was performed on the organs of all dogs at each time frame and on the devices of 5 dogs at 1 month, 1 dog at 3 months, 4 dogs at 6 months, and 3 dogs at 12 months after placement. Devices used for mechanical integrity testing were not available for microscopic evaluation.

There was no gross evidence of thrombosis on the device surface or within any of the cardiac chambers at any time after implantation (Figure 6). At 1 and 6 months, resolving microthrombi were observed on the surface of each device. Microthrombi were not visible grossly, occurred in low numbers, and appeared to be part of the healing process. Microthrombi were not visible at 1-year follow-up. In no animal was there any gross or microscopic evidence of new or old thromboembolism in the brain, lungs, or kidney.

By 1 month after implantation, all devices were nearly completely covered by a thin layer of fibrous connective tissue that deeply infiltrated the interstices of the ePTFE (Figure 7). A layer of spindle-shaped endothelium-like cells covered the luminal surfaces of the device. Areas not covered by fibrous connective tissue were generally located at the margins of the device, associated with areas of separation between the device and the septal surface. These areas appeared to be a result of the topography and small size of the dog atrium. Further development and maturation of the device covering was observed over time. At 6-month follow-up, 2 small nodules of fibrous connective tissue were attached to the atrial septum, immediately adjacent to a device in 1 dog. They appeared to be the result of the device margin abrading the septum. Similar nodules were observed in 2 dogs at 1-year follow-up. All nodules were firmly adherent to the myocardium and were of no hemodynamic significance.

Discussion
Cardiac surgery is a relatively safe and time-tested method for closing secundum atrial septal defects. As with all open surgical procedures, however, certain aspects of this therapy,
such as the risks of cardiopulmonary bypass, postoperative pain, incisional scarring, and psychological trauma, are unavoidable. Even in the so-called “modern era” of cardiac surgery, morbidity related to ASD surgery continues to be important.10 Transcatheter septal occlusion devices have been in various stages of development and testing for more than a quarter of a century. Although the newer generation of occluders are more effective than those used in the past, several problems remain, including complicated loading and delivery techniques, frame fracture, damage to intracardiac structures, large bulk, and with certain designs the requirement to stent and distort the atrial septum. In addition, although all currently used devices are said to be removable, this is possible only as long as the device is attached to the catheter elements of the delivery system. After release of the device, recapture is required, which typically results in device distortion that often complicates removal and is potentially damaging to the heart and vascular system. On the basis of these concerns, we set out to design a new septal occlusion system that would possess the following features: (1) simple loading and implantation; (2) soft, circular, atraumatic design; (3) low septal profile; (4) minimal septal distortion; (5) consistent complete defect closure; (6) being removable during all stages of delivery (including after deployment); (7) benign, rapid biological response; and (8) long-term biocompatibility and device integrity.

After completion of rigorous bench testing, the Helex was studied in the present model to assess these features. The front-loading delivery method successfully allowed for direct device delivery into the left atrium in all but 1 animal, obviating the need for a long, large-diameter sheath as currently required for the delivery of all other septal occlusion devices. Placement of these long sheaths in the left atrium places the patient at risk for air embolism and thromboembolism. This important design feature should lessen or completely eliminate this potentially devastating complication. In addition, the relatively small delivery catheter (9F) and circular, atraumatic, low-profile contour of Helex will allow for extension of this therapy to smaller patients. The atraumatic design was confirmed by the minimal abrasive injury observed in surrounding atrial tissue compared with that described for more rigid, rectangular devices.10 Although the incidence is low, several of the newer occluders have been noted to result in late (postprocedural) cardiac perforation. The nonabrasive, rounded design of the Helex may completely abolish the potential for this devastating complication. The ability to repeatedly and easily withdraw this device back into the delivery catheter during any stage of deployment should improve outcomes by allowing suboptimally positioned devices to be correctly repositioned rather than left in place because of fear of a difficult retrieval. Although some current designs allow for repositioning during certain stages of deployment, the ability to easily remove a device even after release from the delivery catheter is an important advance. It is well accepted that the determination of the final position of any septal occluder is difficult when the device is still attached to a relatively rigid delivery system that causes significant, albeit temporary, distortion of both the device and the atrial septum. The retention suture of this device allows complete separation of the Helex from the delivery catheter but maintenance of control of the device if it should embolize or need to be removed. Thus, an assessment of the true final device position with no tension on either the device or the septum is part of the normal deployment process. This feature introduces a new level of control that is currently unavailable with existing systems. Although the suture removal technique was not used in this series, it has been shown to be simple and reliable both in earlier animal studies and more recently in human implantations. The high incidence (13%) of snare retrieval required during the initial part of this study was a result of high friction between the mandrel and control catheter, which made consistent smooth deployment and locking of the device difficult. The fact that snare retrieval was not necessary after this design flaw had been corrected supports this notion. Furthermore, early human implantation data from more than 100 patients suggests that the need for device retrieval in the clinical setting will be <2% and primarily related to poor patient selection rather than device failure. Importantly, device embolizations are known to occur to various degrees with every transcatheter device. The fact that the Helex is low profile (all retrievals were performed through the 9F delivery catheter), is malleable, and has rounded contours made snare capture of this device and its passage through the vasculature safe, simple,

Figure 7. Low-power (×2) and high-power (×100) microscopy of Helex occluder 30 days (a) and 12 months (b) after implantation (Paragon stain). One month after implantation, there is no evidence of inflammation, and device disks are completely covered by a thin layer of fibrous connective tissue (arrows). Twelve months after implantation, fibrous connective layer has become vascularized, with a surface covering of neoendothelial cells (arrowheads). D indicates device; F, fibrous connective tissue; L, lumen; S, atrial septum; and V, vessels within connective tissue layer.
and atraumatic. These same characteristics may allow for successful ASD closure with smaller device/defect ratios, thereby further extending the age and size of patients in whom it may be used. Although not specifically addressed in this study, it appears that device/defect ratio as small as 1.5:1 to 1.6:1 may be ideal with this device. Coupled with the minimalist design, the amount of implanted material associated with Helex ASD closure will be considerably less than with other devices. Although implantation of large, bulky devices into growing children has not proved to be hazardous, intuitively one would think the less intravascular material implanted the better. Although the Helex possesses a nickel-titanium frame, the small amount of metal is nearly completely covered by ePTFE. The normal levels of nickel found in adjacent tissue during this study suggest that nickel leaching will not be a problem with this device. The lack of any evidence of thromboembolic events, early appearance of a benign tissue response, and neoendothelial covering of the device support long-term biocompatibility. Furthermore, the major component of the Helex, ePTFE, has been used in cardiac surgery for decades and has a proven record of safety and durability. Although a single instance of wire fracture was observed, it appears to have been related to excessive forces placed on that particular device as a result of a faulty prototype delivery system coupled with oversizing of the device for the small canine atrium. If the delivery system is modified and the device properly sized, frame fractures should not occur. The initial nonparallel appearance of the disks in 46% of the implantations reflects the malleable nature of this low-profile device, which can adapt to varying atrial topography compared with more rigid devices, which must distort the atrial septum and surrounding structures to assume their designed configurations. The ability to adjust to the atrial terrain is most likely advantageous. For example, in the common case involving absence of the anterior/superior septal rim, where the posterior wall of the aorta composes this margin of the ASD, the Helex disks can splay around the aorta, providing atraumatic, improved closure rates. Finally, the high closure rates observed both initially and in follow-up suggest that the Helex occluder is very effective for complete early closure of secundum ASD, thus predicting a very low requirement for reintervention of any kind.

Study Limitations

The canine atrial anatomy differs significantly from that of humans, which makes it an imperfect model. The right atrium possesses a very prominent crista terminalis, and the septal surfaces on both sides are quite small compared with the human (even that of a small child). This resulted in less direct contact between the device and septal surface than we expect will occur in the human heart. Surgically created atrial septal defects cannot duplicate the noncircular shape and variable position of secundum atrial septal defects seen in humans. In particular, we were unable to assess device performance when a portion of the defect rim is deficient.

Conclusions

The new Helex occluder appears to offer a number of advantages over currently existing transcatheter occlusion devices. The ease of implantation, atraumatic design, high closure rate, simple removal technique, and compatible biological profile shown in this animal study suggest that this device will be a useful addition to the therapy already available for treatment of ASD. The data reported here support the initiation of multicenter controlled human clinical trials.

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