7 MitraClip® system design and history of development

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OVERVIEW OF THE MITRACLIP SYSTEM

The MitraClip® system consists of four major components: (*i*) the delivery catheter, (*ii*) the steerable sleeve, (*iii*) the MitraClip device, and (iv) the steerable guiding catheter (Fig. 7.1).

The MitraClip system is composed of a triaxial catheter delivery system. The outermost catheter is a steerable guiding catheter (guide), which includes a tapered dilator and a knob on the handle that controls deflection of the distal tip. The clip delivery system is inserted into the guide and has an outer steerable sleeve with two knobs that control the medial-lateral (ML) and anterior-posterior (AP) deflection of the sleeve. The MitraClip device is attached to the distal end of the innermost catheter called the delivery catheter, which has controls on its handle that enable opening, closing, and deployment of the device. The MitraClip device (Clip) is a cobalt/chromium implant with two arms that are opened and closed via controls on the delivery catheter handle. The Clip includes a gripper adjacent to each arm to secure the leaflets as they are captured during grasping and while closing the arms of the Clip. Each leaflet is therefore independently secured between an arm and a gripper. Once the leaflets are grasped and the Clip arms are closed, the leaflets are permanently coapted at the location of the regurgitant flow resulting in the reduction of the mitral regurgitation. The MitraClip device has a locking mechanism to maintain the implanted Clip in a closed position, and the arms and grippers are covered with a polyester fabric to promote tissue ingrowth.

STEERABLE GUIDING CATHETER

The steerable guiding catheter (Fig. 7.2) serves as a conduit for the introduction of the clip delivery system and consists of a distal shaft (22 French) and a proximal shaft (24 French). The length of the catheter is constructed with braided stainless steel wire to provide axial stiffness and torque transmission. A radiopaque ring on the distal tapered tip allows fluoroscopic alignment with radiopaque markers on the steerable sleeve catheter and provides an echogenic atraumatic tip. The steerable guide catheter is delivered over a tapered dilator, which also has echogenic markings at the distal tip. A knob on the guide handle allows the distal tip to be straightened during introduction into the femoral vein and, once positioned in the left atrium, the rotation of the knob provides substantial curvature of the distal end to precisely position the MitraClip device. The central lumen of the steerable guide catheter allows for aspiration of air and the infusion of fluids through a hemostasis valve located on the handle.

CLIP DELIVERY SYSTEM

Steerable Sleeve

The steerable sleeve aids in positioning and orienting the MitraClip device above the mitral valve leaflets. The steerable sleeve provides the physician with the means to position the Clip along the AP and ML axes, relative to the mitral valve anatomy.

The steerable sleeve is a long, flexible multilumen catheter with a handle at the proximal end (Fig. 7.3). The shaft has one central thru-lumen surrounded by six smaller lumens designed to house cables that are used to steer the distal tip. The steerable sleeve is designed to provide a mechanism for translation and rotation of the Clip delivery catheter, which lies within the thru-lumen. Three pairs of control cables lie within the six smaller lumens and serve to deflect the distal end of the steerable sleeve. The distal tip of the steerable sleeve is radiopaque to provide for visualization under fluoroscopy. An introducer on the shaft of the sleeve is used to introduce the MitraClip implant into the steerable guide catheter.

The handle on the steerable sleeve has two control knobs for ML and AP steering (Fig. 7.4). Two control knobs allow the operator to adjust the curvature of the distal end of the steerable sleeve by applying tension to the control cables located inside the shaft.

A hemostasis valve facilitates air management of the thru-lumen of the steerable sleeve and provides a flush port for the introduction of fluids during the implant procedure.

The system includes a mechanism for alignment of the steerable sleeve within the steerable guide (Fig. 7.5). A stainless steel key near the distal end of the steerable sleeve mates with channels on the inner wall of the steerable guide catheter to maintain the two catheters in a fixed rotational orientation. This prevents the steerable sleeve from rotating relative to the guide and maintains its stability during deflection. A longitudinal alignment marker on the proximal shaft of the steerable sleeve ensures proper alignment with a corresponding mark on the steerable guide catheter.

The distal region of the steerable sleeve is deflectable to facilitate the precise position of the MitraClip device. A stainless steel radiopaque tip ring at the distal tip provides the attachment point for the control cables. When tension is applied to the control cables via the control knobs, the radiopaque tip ring is pulled, which deflects the distal region of the sleeve in the desired direction. Two additional radiopaque alignment markers are embedded into the distal shaft to allow the positioning of the steerable sleeve relative to the distal tip of the steerable guide (Fig. 7.6).

Delivery Catheter

The delivery catheter consists of a handle and a multilumen shaft and provides the operator with the means to actuate and deploy the MitraClip device. The delivery catheter resides inside the steerable sleeve thru-lumen and is free to translate

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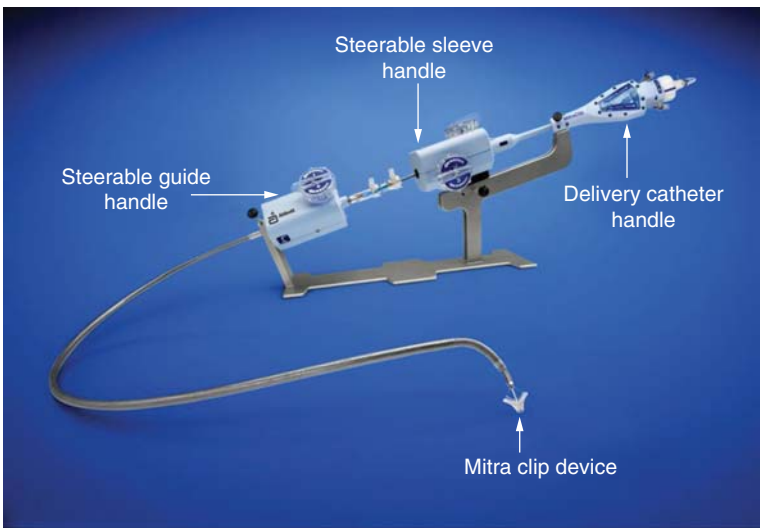


Figure 7.1 MitraClip system: major components.

Figure 7.2 Steerable guiding catheter.

and rotate. The MitraClip device is located at the distal tip of the delivery catheter. The delivery catheter handle consists of a fastener, lock lever, actuator knob, arm positioner, release pin, gripper lever, and two flush ports (Fig. 7.7). The fastener is used to temporarily secure the delivery catheter position relative to the sleeve, to prevent inadvertent manipulation of the MitraClip device once the leaflets have been grasped. The lock lever is used to lock and unlock the locking mechanism of the MitraClip device and the gripper lever is used to repeatedly raise and lower the grippers. The arm positioner opens, closes, and inverts the clip arms by advancing and retracting the actuator mandrel which is threaded onto the clip. Rotation of the arm positioner causes translation of the actuator mandrel, which controls the opening and closing of the clip arms. The flush ports allow for aspiration of air and infusion of liquids (e.g., heparinized saline) into the thru-lumens of the delivery catheter.

At the completion of the implant procedure, the double-length lock line and gripper line are removed from the delivery catheter. The release pin is removed; then the actuator knob is rotated to unthread the actuator from the clip, resulting in the deployment of the clip from the delivery catheter.

The delivery catheter's multilumen shaft (Fig. 7.8) consists of a stainless steel braided polymer jacket; a support coil that encapsulates the four gripper and lock line lumens; a compression coil that holds the actuator mandrel, and a tension cable to prevent elongation.

MitraClip Device

The MitraClip device is a percutaneously implanted, mechanical clip designed to reduce mitral regurgitation (Fig. 7.9). The MitraClip device grasps and coapts the mitral valve leaflets, resulting in fixed approximation of the mitral leaflets throughout the cardiac cycle and a functional double-orifice mitral valve.

MitraClip Components and Material

The MitraClip device is made of cobalt-chromium and nickel-titanium metallic components and covered with polyester fabric to enhance the healing response. Each component has been carefully designed to complement the overall function and integrity of the MitraClip device.

MitraClip Functions

The MitraClip device performs three primary functions:

1. Arm control: opening, closing, and inverting the arms for MitraClip device to grasp and release the mitral valve leaflets.
2. Arm locking: locking of the clip arms in a closed position to coapt the leaflets and prevent opening of the MitraClip device.

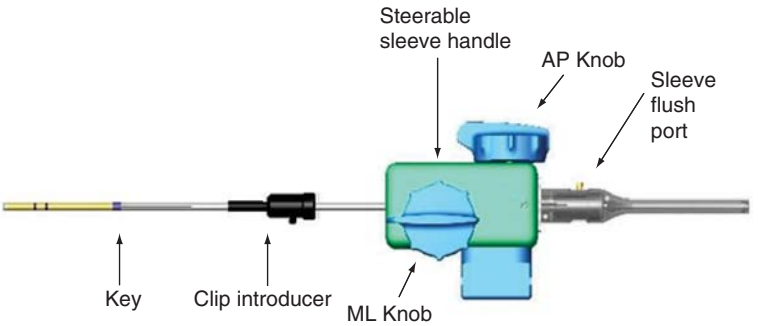


Figure 7.3 Steerable sleeve catheter assembly.

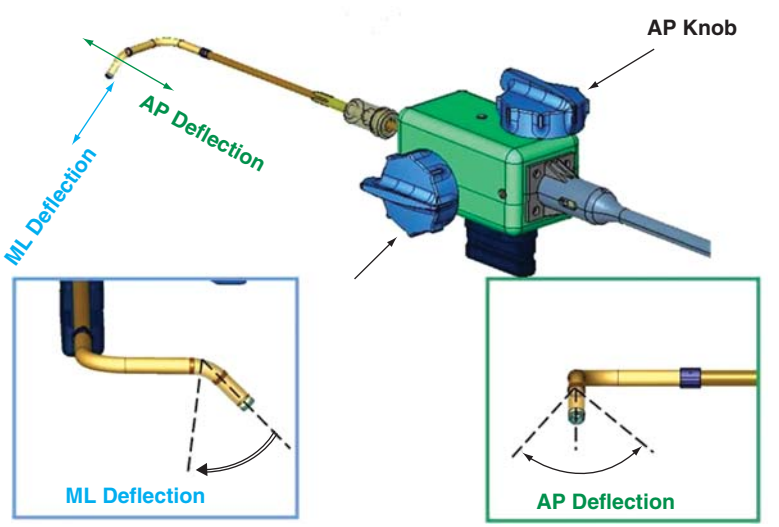


Figure 7.4 Steerable sleeve handle assembly. AP, anterior posterior, ML, medial lateral.

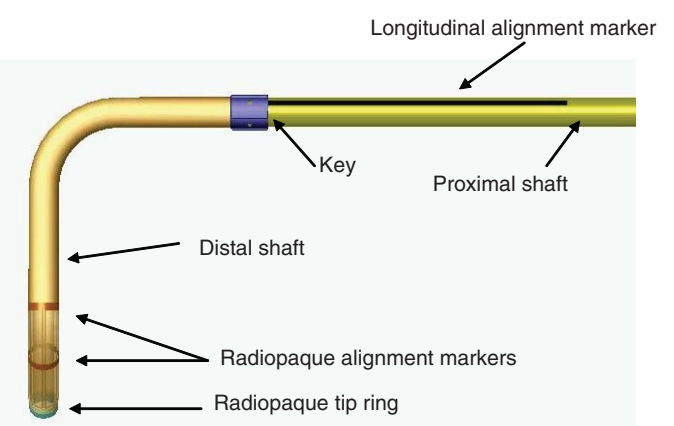


Figure 7.5 Distal end of the steerable sleeve.

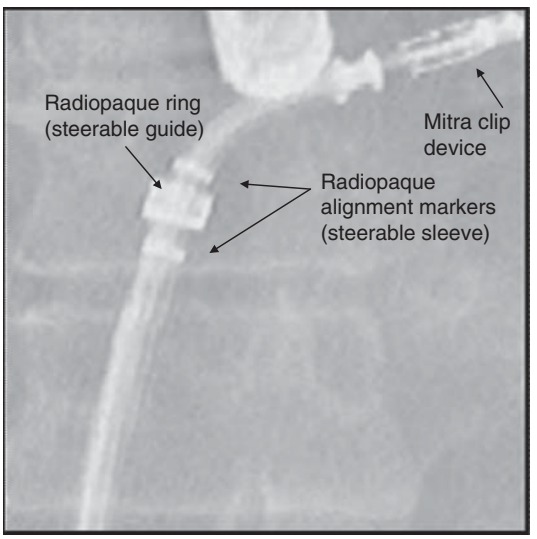


Figure 7.6 Fluoroscopic image of steerable sleeve inside the steerable guide.

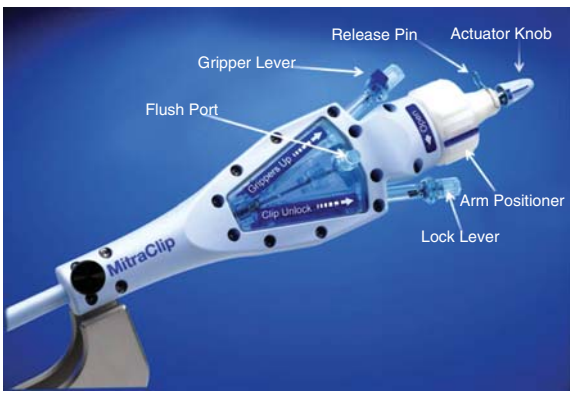


Figure 7.7 Delivery catheter handle.

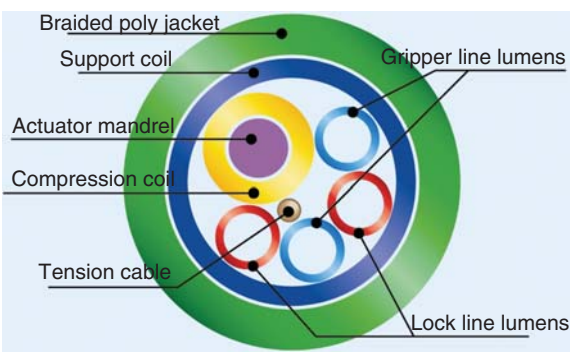


Figure 7.8 Delivery catheter, multi-lumen shaft cross-section.

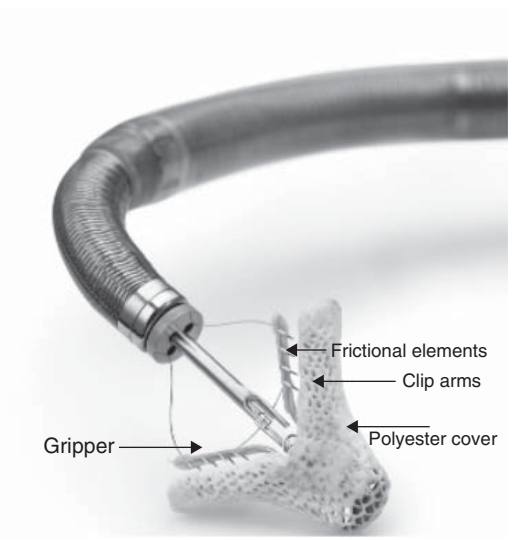


Figure 7.9 MitraClip device.

3. Gripper control: raising and lowering of the grippers relative to the arms to secure the valve leaflets in the MitraClip device.

The MitraClip device arms can be adjusted to various positions (Fig. 7.10) such as closed, open, and inverted. These positions are designed to allow the MitraClip device to grasp and approximate the leaflets of the mitral valve, using controls on the Delivery Catheter Handle. The MitraClip device can be unlocked using the Lock Lever on the delivery catheter handle. The MitraClip device can be repeatedly opened and closed using the Arm Positioner. The gripper can be raised or lowered repeatedly using the Gripper Lever.

Locking Mechanism

The MitraClip device is locked by default. In this condition, the Binding Plate binds between the Threaded Stud and the Connector. Pressure from the Leaf Spring initiates the wedging of the binding plate onto the threaded stud. The threaded stud can always be retracted, even though the MitraClip device is locked, allowing the MitraClip arms to close. However, advancement of the threaded stud is restricted when the MitraClip device is locked. Therefore, the arms of the device cannot open when the device is locked (Fig. 7.11).

To unlock the MitraClip device and allow the arms to open, tension is applied to the lock line by retracting the lock lever on the delivery catheter handle. This action raises the harness and the binding plate. The lifting binding plate compresses the leaf spring, unwedging the binding plate. The threaded stud is now able to move freely in both directions, allowing the arms to be opened and closed.

Deployment of the MitraClip device from the delivery catheter requires three separate steps. First, the lock lines are

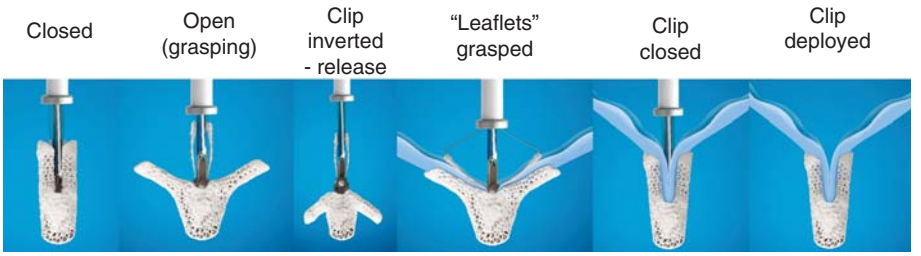


Figure 7.10 Various arm positions of the MitraClip device.

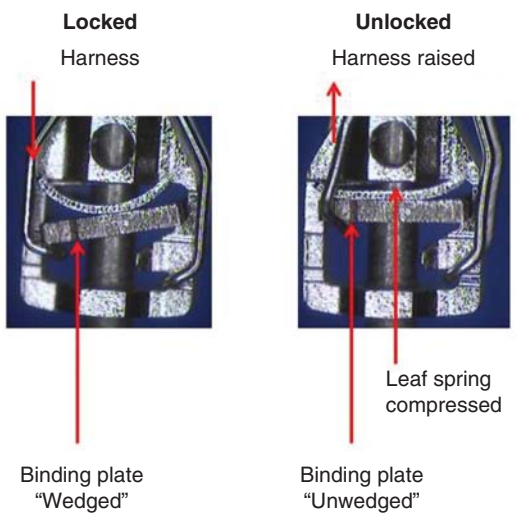


Figure 7.11: Locked vs. unlocked MitraClip device.

removed by removing the lock lever cap exposing both ends of the double-length lock line, then pulling on one end to remove the lock line. Second, the release pin is removed and the actuator is unthreaded from the clip by turning the actuator knob, which decouples the distal tip of the delivery catheter from the clip. The third step is the removal of the gripper line.

HISTORY OF DEVELOPMENT AND KEY DESIGN FEATURES

Mitral Valve Access

Devising a method to grasp the mitral leaflets on a beating heart proved to be a challenge. Early prototype device concepts were developed to accomplish grasping of the leaflets from the inferior (ventricular) side, but the desire to minimize manipulations within the ventricle to avoid the chordae tendinae resulted in the decision to approach the mitral valve from the superior (atrial) side of the leaflets. Subsequent designs approached the mitral valve via femoral vein access to the right atrium then transseptal access to the left atrium. This pathway allowed grasping of the mitral leaflets "from above" the valve.

Suture Design

The early concepts for replicating the surgical edge-to-edge mitral valve repair using a percutaneous catheter system involved placing sutures in the leaflets (Fig. 7.12). Early prototypes of grasping catheters used retractable, angled wire loops, positioned perpendicular to the line of coaptation to immobilize the leaflets from the ventricular side. Once grasped, a hollow needle was advanced to puncture each leaflet. A pledget made of a loop of nitinol wire was then advanced through the needle. A second catheter was used to fasten the sutures together using a "suture lock." Because of the risk of the suture cutting through the leaflet, as well as the inability of this design to allow multiple, atraumatic grasping attempts, the design complexity increased significantly and therefore alternate design concepts were pursued.

Butterfly Design

The creation of the suture prototypes with angled wire loops led to a breakthrough concept: The same component of the device that was used for grasping could also be used to coapt the leaflets as a permanent implant. This led to the butterfly design concept (Fig. 7.13), where a pair of nitinol wire loops was used to independently grasp and hold each leaflet. The superior loop included frictional elements to increase the grip of each leaflet. Once the leaflets were grasped, the loops were retracted into a barrel on the inferior side of the leaflets to bring the loops together to coapt the leaflets. This design concept was important in that it resulted in the invention of "grippers" with "frictional elements" and "arms" used to grasp the leaflets, which are key features of the final MitraClip device design.

Final MitraClip Design

Early animal studies indicated that an optimal design would include rigid arms, ability to close the clip to a low profile, and polyester covering to enhance the healing response. This resulted in the development of a clip with rigid arms that could be opened to a grasping position and closed to a low profile position multiple times. This design was implanted surgically onto porcine mitral valves to test the feasibility of this clip design. The clips were implanted using a short, rigid delivery catheter via direct access into the left atrium. These feasibility studies provided the first evidence that a mechanical clip could be safely attached to the beating mitral valve to permanently

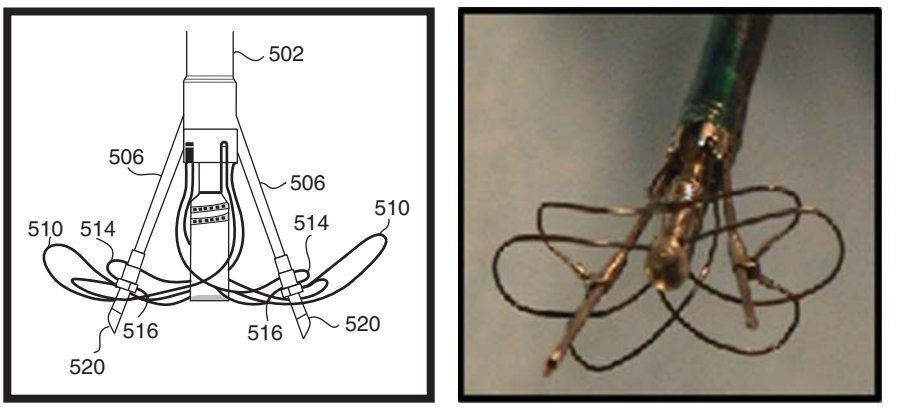


Figure 7.12 Early concept and prototype of the suture design.

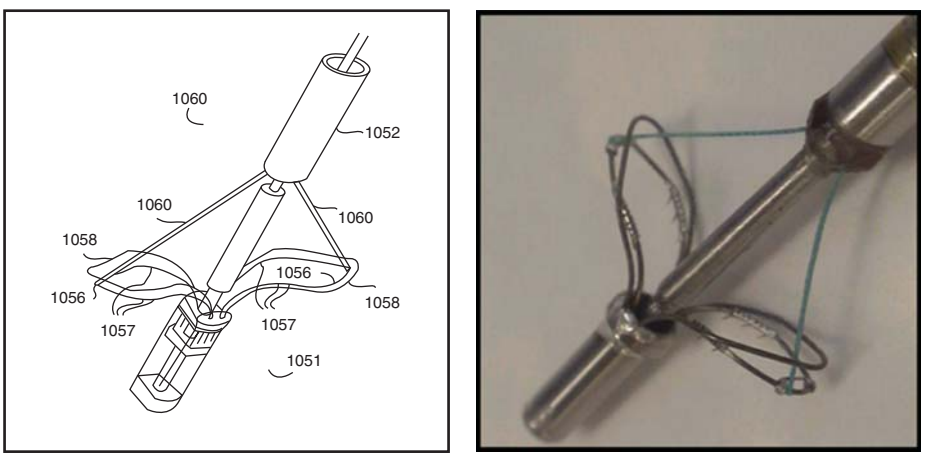


Figure 7.13 Early concept and prototype of the butterfly design.

coapt the mitral leaflet with a benign healing response. Further development and refinement of the clip concept resulted in two key changes. First was refinement of the "frictional elements" located on the "grippers" as integrated narrow pointed elements to engage and hold on to the leaflets while closing the clip arms. The geometry of the "frictional elements" was designed to not only partially penetrate the thickness of the leaflets to achieve atraumatic grasping, but also secure grasping of the leaflets. Also the frictional elements were angled in a direction that secured the leaflets when the clip was opened, the grippers raised, and the clip was retracted into the left atrium. Second was an important design addition that allowed the arms of the clip to be fully opened to an inverted state to allow for retraction from the ventricle back into the left atrium. These design features allowed atraumatic grasping and releasing of the leaflets multiple times, allowing for optimal clip placement. Another key design feature developed for the final design was a means of locking the clip arms once placed on the leaflets. The locking mechanism required the ability to be cycled between the locked and unlocked state multiple times to allow repositioning of the clip to optimize the reduction of mitral regurgitation. The first-generation lock mechanism was limited to allowing the clip to be locked at only three angles. The final design of the steerable guide (Fig. 7.14) was improved to allow the lock to hold the clip at any arm angle.

IN VIVO CHRONIC ANIMAL STUDIES

Prior to the development of the femoral vein access catheter delivery system, animal studies were performed in a healthy porcine model using direct access into the left atrium to evaluate the chronic healing response. Dr Fann et al. (1) reported progressive healing of the clips with fibrous tissue and collagen over the surface of the clip and evidence of tissue deposition between the arms of the clip by week 4. By week 24 a mature, continuous tissue bridge had formed between the anterior and posterior leaflets between the arms of the clip. Scanning electron microscopy showed full encapsulation of the clip with complete endothelialization of the surface (Fig. 7.15).

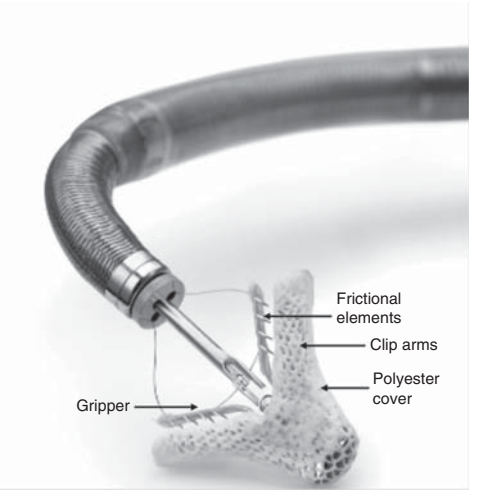


Figure 7.14 Final MitraClip device design.

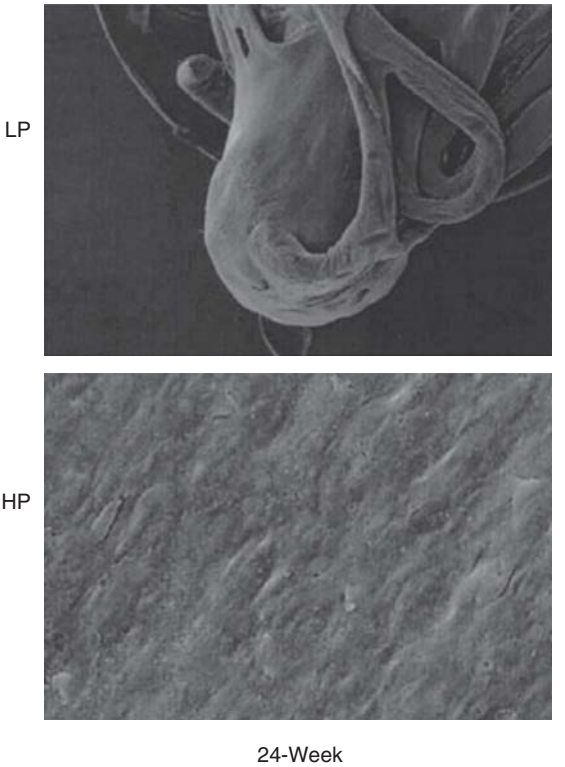


Figure 7.15 Low-power (LP) and high-power (HP) scanning electron microscopy of clip incorporated by surrounding tissue and endothelialization at 12 and 24 weeks.

These early findings in the porcine model were later corroborated by Dr Ladich et al. (2), who reported on the pathologic healing response of MitraClip devices that had been explanted from humans. Histopathologic analysis of long-term human implants showed fibrous encapsulation with extension over the adjacent mitral leaflets and tissue bridge formation between the clip arms and the presence of type I collagen (Fig. 7.16).

Durability Testing and Finite Element Analysis

To develop a permanent implant that is reliable and durable, it was critical to understand the forces acting on the device throughout its lifetime. Forces acting on an edge-to-edge mitral valve repair have been studied and reported in the literature. Nielsen et al. (3) utilized direct measurement of force by attaching a miniature C-ring force transducer to the leaflets in an acute ovine model. The peak load was reported to be 0.46 Newtons. An in vitro model that also used a miniature C-ring transducer was used by Jimenez et al. (4), who reported a peak load of 0.072 Newtons, and a finite element model was developed by Avanzini et al. (5) which showed a resulting peak load of 0.39 Newtons.

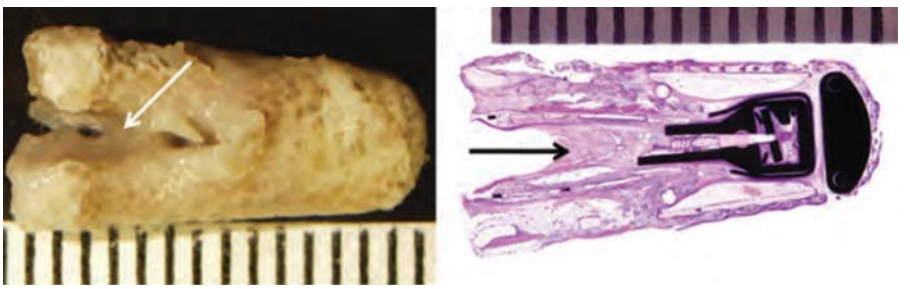
A large safety factor was added to the highest of these reported load values in order to perform accelerated durability testing at loads significantly exceeding these values. Testing was conducted by fixturing clips in an EnduraTEC 3200 fatigue tester and exerting diastolic and systolic loads on the clip arms immersed in a saline bath at 37°C (Fig. 7.17). Accelerated durability testing has been performed on the MitraClip device representing over 15 years of life time, and the results show no fracture, damage, or clip lock failure.

A finite element analysis model (Fig. 7.18) was also developed in order to understand the theoretical fatigue safety factor for each component of the clip. This finite element model was validated by subjecting clips to "dynamic load to failure," where the loads are increased incrementally until a component fracture occurs. The predictions determined from the finite element model for which component would be first to fail concurred with the "dynamic load to failure" test results. The load at which the first failure occurred during "dynamic load to failure" testing was more than seven times the predicted in vivo load.

CATHETER DEVELOPMENT

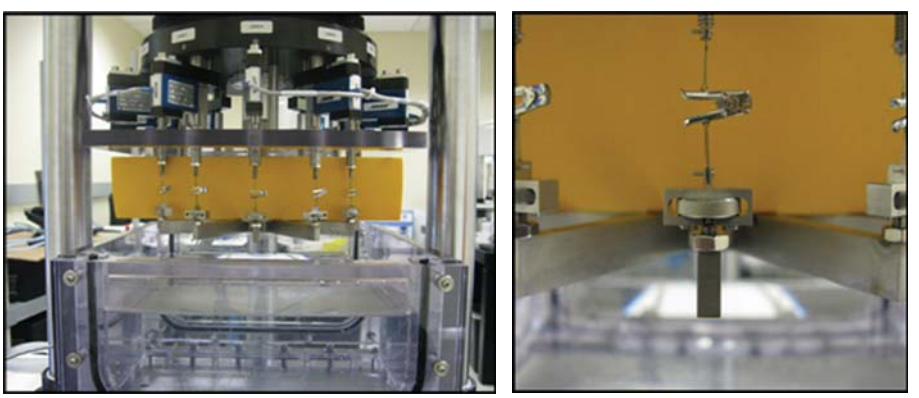
To deliver, actuate, and deploy the clip on the mitral leaflets required the development of sophisticated steerable delivery and guiding catheters. Development of these catheter systems was very challenging. In order to approach the mitral valve from the left atrium and accurately position the clip perpendicular to the plane of the mitral valve, a two-part steerable catheter system was developed: a 16 French steerable sleeve catheter within a 24 French steerable guiding catheter.

The steerable guiding catheter must be straight for femoral vein introduction, yet must curve up to a 90° angle within the left atrium to allow for a wide range of expected transseptal puncture locations and to accommodate anatomical variability. This required a multilayered catheter design incorporating



(A) (B)

Figure 7.16 Chronic human explantation group (91–300 days). (**A**) Gross image demonstrating fibrous tissue bridging the area between the device arms (atrial tissue bridge, arrow). (**B**) Photomicrograph of the histological section of a MitraClip device explanted after 283 days demonstrating the tissue bridge (arrows).



(A) (B)

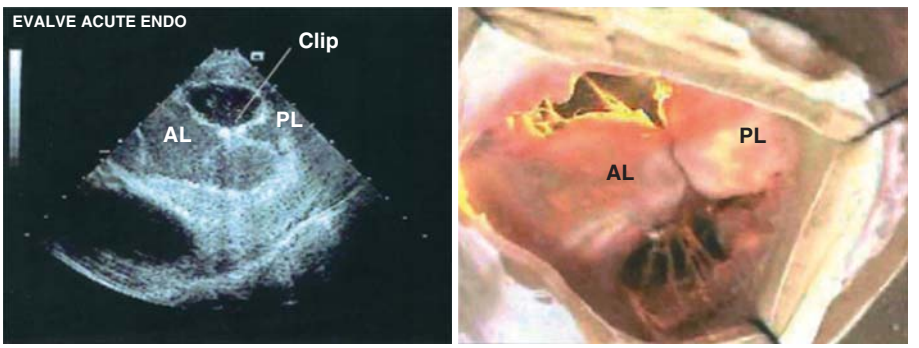
Figure 7.17 Accelerated durability testing.

Figure 7.18 Finite element analysis model.

tension cables to actuate the curves. The steerable sleeve catheter must be able to maintain a plane of curvature roughly 90 degrees to the plane of curvature on the steerable guiding catheter. To maintain the curves of the two catheters in orthogonal planes, a rotational alignment system was devised with a metallic key feature on the steerable sleeve that is mated with channels on the inner wall of the steerable guide. The requirement for steerability in multiple planes to accurately place the MitraClip device was discovered during early animal studies. This led to the final steerable sleeve catheter design with three sets of tension cables incorporated into the wall of catheter. The tension cables allowed the steerable sleeve to be curved in three distinct directions. The final design of the steerable guide and steerable sleeve allow for a wide range of steerability to accommodate significant anatomical variation and provided precision and accuracy for positioning the clip on the mitral leaflets.

The catheter designed to actuate and deploy MitraClip device has multiple functions: opening and closing the arms of the clip, raising and lowering the grippers, locking and unlocking the clip locking mechanism, and deploying the clip. The delivery catheter design also must perform with minimal elongation, minimal axial compressibility, and must maintain straightness when extended from the curved guide and sleeve. These multiple and, in some cases, conflicting design requirements were achieved by developing a composite delivery catheter using several stainless coils, a tension cable inside a braided outer shaft with differential stiffness along its length, and a novel clip deployment mechanism.

Preclinical animal studies in an acute porcine model were used to refine and optimize the steerable guide catheter, the



(A) (B)

Figure 7.19 (**A**) Echo short axis of double orifice after clip deployment. AL indicates anterior leaflet PL, posterior leaflet. (**B**) Ex vivo picture from a similar angle showing well-apposed anterior and posterior mitral valve leaflets viewed from the atrium.

steerable sleeve, and the clip delivery catheter. Dr St Goar et al. (6) reported on 12 postmortem examinations of 12 acute porcine implants, where the clip was able to create a double-orifice mitral valve. In all cases the clip was located in the desired central location on the valve with the clip arms perpendicular to the line of leaflet coaptation (Fig. 7.19).

No clinically significant inferior vena cava, right atrial, atrial septum, left atrial, leaflet, left ventricle, or chordal trauma was observed in any animal. They concluded that the MitraClip device was able to successfully approximate the middle scallops of the anterior and posterior leaflets, creating a functional double-orifice mitral valve.

During the early human feasibility study (EVEREST I, Feldman et al.) (7), several product enhancements and ease of use improvements were identified. For example, the initial angle between the steerable sleeve and steerable guide curve planes was adjusted by rotating the key on the steerable sleeve. Doing this resulted in an insertion position that was closer to the nominal position required for the human anatomy resulting in an easier clip positioning. Also, the steerable guide catheter was simplified by removing one of the steering knobs that was needed for the porcine model but was not necessary for placement of the clip in humans. In addition, the dilator tip was redesigned to be more echogenic to more easily visualize the tip relative to the interatrial septum. Also, the clip-locking mechanism was redesigned to provide greater flexibility in locking the clip at any desired angle. This final MitraClip device and multicatheter system was utilized in the EVEREST II randomized clinical trial and the results of this trial have been reported by Feldman et al. (8).

In summary, the development of the MitraClip system including designing three catheters and the implantable MitraClip device was a significant engineering endeavor. The three catheters had many unique and challenging design requirements to allow accurate positioning of the clip on the mitral valve leaflets of a beating heart. The MitraClip implant also posed many design challenges to ensure atraumatic grasping of the leaflets with a secure locking mechanism to ensure permanent attachment to coapt the leaflets. The final result has been studied in multiple human clinical trials demonstrating a high rate of safe MR reduction that has translated to clinical benefits for patients. These results demonstrate successful achievement of the design requirements for the MitraClip device.

ACKNOWLEDGMENTS

We thank Jan Komtebedde, DVM, Brian Martin, Eric Goldfarb, Sylvia Erickson, Alfred Raschdorf, Jaime Sarabia, Larry Rogers, Kent Dell, Sandra Saenz, Sylvester Lucatero, Francisco Valencia, Steve Dang, Pedro Lucatero, Jessie Garcia, Mheng Heflin, and Rudy Arechiga for their excellent contributions in development of the MitraClip therapy.

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