Background—Percutaneous access for mitral interventions is currently limited to transapical and transseptal routes, both of which have shortcomings. We hypothesized that the left atrium could be accessed directly through the posterior chest wall under imaging guidance.

Methods and Results—We tested percutaneous transthoracic left atrial access in 12 animals (10 pigs and 2 sheep) under real-time magnetic resonance imaging or x-ray fluoroscopy plus C-arm computed tomographic guidance. The pleural space was insufflated with CO₂ to displace the lung, an 18F sheath was delivered to the left atrium, and the left atrial port was closed using an off-the-shelf nitinol cardiac occluder. Animals were survived for a minimum of 7 days. The left atrial was accessed, and the port was closed successfully in 12/12 animals. There was no procedural mortality and only 1 hemodynamically insignificant pericardial effusion was observed at follow-up. We also successfully performed the procedure on 3 human cadavers. A simulated trajectory to the left atrium was present in all of 10 human cardiac computed tomographic angiograms analyzed.

Conclusions—Percutaneous transthoracic left atrial access is feasible without instrumenting the left ventricular myocardium. In our experience, magnetic resonance imaging offers superb visualization of anatomic structures with the ability to monitor and address complications in real-time, although x-ray guidance seems feasible. Clinical translation seems realistic based on human cardiac computed tomographic analysis and cadaver testing. This technique could provide a direct nonsurgical access route for future transcatheter mitral implantation. (Circ Cardiovasc Interv. 2015;8:e002538. DOI: 10.1161/CIRCINTERVENTIONS.114.002538.)

Key Words: catheterization • endovascular procedures • heart valve prosthesis implantation • magnetic resonance imaging, interventional • mitral valve

Transcatheter mitral valve-in-valve or valve-in-ring implantation is feasible using prostheses designed for the aortic valve. Implantation in the native mitral annulus presents distinct challenges: available aortic prostheses are too small, valve fixation is difficult because the annulus is elastic, and the subvalvular apparatus, which plays an important role in left ventricular function, should not be disrupted. At least 4 dedicated devices have undergone early human testing. These are bulky and require large caliber access ports (up to 32F), mostly transapical.

Whether transapical access is associated with higher mortality than transfemoral remains unclear. The higher mortality reported in some studies may reflect inclusion of higher risk patients or operator experience. Nonetheless, magnetic resonance imaging (MRI) and echocardiography detect apical wall motion abnormalities after transapical access, particularly in patients with increased left ventricle (LV) diameter, which can lead to long-term reduction in global LV function. In the Placement of Aortic Transcatheter Valves (PARTNER) trial quality-of-life assessment, transcatheter aortic valve replacement via transapical approach demonstrated no benefit compared with conventional surgery. Morbidity and mortality are likely even higher in patients with mitral valve disease because of pre-existing LV dysfunction. Truly percutaneous transapical access using nitinol devices for closure is possible, but complications do occur, including pneumothorax, cardiac tamponade, LV pseudoaneurysm, and hemothorax related to coronary or intercostal vessel laceration or bleeding from the LV puncture site.

Alternative approaches have been explored for mitral valve interventions: direct transatrial via minithoracotomy.
WHAT IS KNOWN

- Transcatheter mitral valve replacement requires a large caliber sheath and coaxiality between the delivery system and the mitral valve.
- Transapical access may not be an option in all patients, so alternative approaches are needed.

WHAT THE STUDY ADDS

- Fully percutaneous transhyo-branchio-atrial access and closure is feasible in large animal models and affords superb coaxiality with the mitral valve.
- The procedure can be guided using x-ray fluoroscopy or real-time MRI.
- Cardiac computed tomographic analysis and human cadaver feasibility testing indicate that the left atrium can be accessed with a large caliber sheath through the posterior chest wall in humans.

transjugular transseptal,16,17 and transfemoral transseptal.18 However, a minithoracotomy still confers surgical morbidity. Transeptal delivery of large mitral implants has been demonstrated, but achieving coaxiality with the mitral valve can remain challenging. A straight shot to the mitral valve that permits large sheath access but does not violate the LV myocardium would be desirable and could reduce the engineering constraints of miniaturization, reduce procedural complexity, and improve patient outcomes.

Percutaneous left atrial (LA) access was first performed in the 1950s using long needles through the posterior chest wall to sample pressure.19,20 At first glance, delivering large sheaths in children with no alternative access, through the anterior transthoracic cardiac catheterization has also been performed via this approach seems challenging because of interposed lung, but there is extensive surgical evidence that temporarily collapsing a lung to perform an intrathoracic intervention is safe.21 In fact, diagnostic thoracoscopic with iatrogenic lung deflation is commonly performed in awake patients and confers extremely low morbidity and mortality.22 Percutaneous transthoracic cardiac catheterization has also been performed in children with no alternative access, through the anterior chest into the pulmonary venous atrium and through the lower back into the inferior vena cava.23,24

We hypothesized that with imaging guidance and percutaneous techniques, it is possible to access the LA directly through the posterior chest wall by first displacing a lung with gas, then delivering a large sheath, and finally closing the LA port using off-the-shelf nitinol cardiac occluder devices. Compared with percutaneous transapical LV closure, we think that closing a port in the lower pressure LA may be preferable. Because of anatomic differences between large mammals and human, we tested this hypothesis in 2 different large animal models (porcine and ovine) and then explored feasibility of clinical translation with human cardiac computed tomographic (CT) analysis and human cadaver testing. We also explored different image guidance modalities, MRI and x-ray fluoroscopy, to simplify translation into patients.
After insufflation, the ventilation rate was increased and tidal volumes reduced to keep airway pressure low.

**Transthoracic LA Trajectory Planning and Access**

Three-dimensional MRI or x-ray (C-arm CT and biplane fluoroscopy contrast angiograms) of the LA was acquired at baseline and after pleural insufflation. For x-ray guidance, we used a superimposed C-arm CT of LA and LV angiograms (syngo InSpace EP, Siemens). Swine and sheep were positioned respectively on the right side or prone to optimize working angles. A 20-cm needle was used to puncture through the posterior or lateral chest wall, pass through the empty pleural space, and enter the LA posteriorly (Figures 3 and 4).

Needle tip position was confirmed by atrial pressure waveform and contrast injection. A stiff nitinol guidewire (Nitrex, Covidien) was introduced through the mitral valve to the LV apex, over which a 18F sheath (outer diameter, 7 mm; Large Check-Flo, Cook) and a custom-shortened dilator were advanced into the LA without predilatation. Sheath position and relation to the mitral valve were confirmed using MRI or biplane contrast angiography.

**LA Closure**

The LA port was closed with an off-the-shelf 5- or 6-mm nitinol atrial septal occluder (St Jude Medical, MN; Lepu Medical, Beijing, China). The distal disc was deployed within the LA, and the sheath and delivery catheter were withdrawn in tandem until the disc was in apposition with the LA wall. The proximal disc was deployed outside the heart within the pleural space, and the device was released.

**Human Cadaver Study and Human CT Analysis**

To explore feasibility for humans, we tested percutaneous transthoracic LA access and closure in 3 human cadavers (1 under MR and 2 under x-ray guidance). After femoral access, the cadavers were rolled prone and all procedural steps were identical to those previously described for animal procedures, using a larger sheath (Ascendra, Edwards Lifesciences, 26F/30F inner/outer diameter).

We also examined 10 random cardiac CT angiograms having full chest wall coverage among patients with mitral valve disease, dilated LA, or previous sternotomy in the National Heart, Lung, and Blood Institute anonymized and delinked database. This does not constitute human subjects research under US 45CFR§46.102(f). Each CT was examined for potential trajectories to the LA.

**Statistical Analysis**

Hemodynamic data are reported in the Table as median with first and third quartiles (Q1–Q3). Each hemodynamic parameter was analyzed in a linear mixed model with autoregressive–moving-average (1,1) correlation structure assumed within each animal. The model fit mean levels of each parameter at each of the 4 postbaseline follow-up measurements with baseline as the reference. Because there were 4 follow-up measures for each of 3 hemodynamic parameters, we used a Bonferroni correction factor of 12 to account for multiple comparisons. A multiplicity corrected P value ≤0.05 was considered statistically significant.

**Results**

**Pericardial Access for Autotransfusion Catheter Placement**

Transatrial pericardial access with a 2.8F microcatheter, insufflation of the pericardial space with CO2, placement of a subxiphoid 8.3F drain, and withdrawal of the transatrial microcatheter was uncomplicated in all 12 animals.

**Pleural Insufflation**

Pleural access and left lung deflation with CO2 was uncomplicated in all 12 animals. 600 to 900 mL of CO2 was required to displace the lung sufficiently to establish an unobstructed trajectory to the LA in both species. Pleural pressures remained low (8–10 mmHg) and, despite lung displacement, ventilation was well tolerated with no increase in expired CO2 or evidence of hemodynamic compromise (Table). Reductions in mean arterial pressure and heart rate were observed after pleural insufflation, which were likely caused by an increase in the inhaled anesthetic agent concentration required to allow for the reduction in ventilator tidal volumes. However, these changes were not statistically significant.

![Images](http://circinterventions.ahajournals.org/Downloaded from)
In swine, pleural insufflation caused the heart to rotate, displacing the long axis of the LV by 7° (6°–14°) compared with baseline. A direct trajectory to the LA, avoiding important anatomic structures was achievable in all animals. Distance from skin to LA was 10 cm (9–11 cm) in swine and 11 cm in both sheep.

Trajectory Planning
In swine, pleural insufflation caused the heart to rotate, displacing the long axis of the LV by 7° (6°–14°) compared with baseline. A direct trajectory to the LA, avoiding important anatomic structures was achievable in all animals. Distance from skin to LA was 10 cm (9–11 cm) in swine and 11 cm in both sheep.

Transthoracic LA Access and Closure
The LA was successfully accessed in 10/10 swine, including 8 under MR guidance (Figure 3; Movie I in the Data Supplement) and 2 under x-ray guidance (Figure 4; Movie II in the Data Supplement). All succeeded in a single needle pass except in 1, wherein a custom needle that had become dull required a second pass. The stiff nitinol guidewire was positioned in the LV apex, over which the 18F sheath was advanced without predilation. Sheath advancement displaced the LA wall by 25 mm (20–30 mm; under x-ray guidance), but the wall recoiled as soon as the sheath tip entered the LA. No pericardial or pleural effusions developed during LA puncture or while the large sheath remained in place. Three-dimensional and cine MRI confirmed that the sheath trajectory was offset relative to the long axis of the LV by an angle $\alpha$ of $\leq 30^\circ$ (Figure 3).

The LA port was successfully closed with a single nitinol cardiac occluder device in all animals. During sheath withdrawal and LA port closure, accumulated blood was autotransfused intermittently using the prepositioned pericardial and pleural drains. Median pericardial and pleural autotransfusion volumes were 55 mL (40–73 mL) and 10 mL (10–75 mL), respectively. Animals were stable hemodynamically throughout, and no arrhythmias were observed (Table).

The LA was successfully accessed with a single pass and closed under MRI guidance in 2/2 sheep. One animal had minimal pericardial effusion (50 mL). The second required higher than expected intraprocedural autotransfusion (300 mL) without any hemodynamic compromise. Pleural effusion was negligible in both animals (10 and 20 mL). There was no procedural mortality and all animals recovered uneventfully. At the end of the procedure, the pericardial and pleural spaces were aspirated to dryness, any remaining pleural CO$_2$ was aspirated, and the drains were withdrawn.
Follow-Up
No complications were observed during the follow-up period of 7.5 days (7–8.5 days). Follow-up MRI confirmed stable position of the LA occluder device in all animals. Twelve of 12 animals had no pleural effusion. Eleven of 12 animals had no detectable or trace pericardial effusion (0 mL (0–6 mL)). One pig, in which the LA was punctured twice, had a large but hemodynamically insignificant pericardial effusion (660 mL) at 7 days follow-up. No other complications were observed in any animal and all skin incisions healed well. On necropsy, the nitinol cardiac occluder device was well seated and fibrosed to the LA wall in all animals (data not shown).

Human CT Analysis
Cardiac CT angiograms from 10 patients (age 68 years [59–73 years], 8/10 male) with full chest wall coverage were examined. A direct trajectory to the LA through the right posterior chest wall was achievable in all (Figure 5; Movie III in the Data Supplement). The right lung would need to be displaced by pleural insufflation, but the trajectory avoided important structures, including descending aorta and esophagus. The mean angle \( \alpha \) between the achievable trajectory and the true long axis of the LV was 5° (4°–7°). Mean intercostal distance at the point of entry through the chest wall was 12 mm (11–15 mm).

We also tested whether there was a trajectory to the mitral valve from a right minithoracotomy incision, entering the right atrium, and passing through the interatrial septum. In all 10 patients this was achievable, but the offset angle between the trajectory and the true long axis of the LV was 56° (51°–58°).

Human Cadaver Study
In the prone position, right pleural insufflation and deflation of the right lung were straightforward whether under MR or x-ray guidance. This exposed a direct trajectory to the posterior wall of the LA avoiding other important structures, such as aorta and esophagus, in all 3 cadavers. The LA was successfully entered and a large 26F sheath was delivered. Pleural insufflation did not cause the heart to shift orientation within the thorax. As a result, the sheath trajectory remained well aligned with the long axis of the LV. The LA port was closed using a nitinol cardiac occluder device, and the right lung was reinflated by aspirating the pleural CO\(_2\) (Figure 6; Movie IV in the Data Supplement).

Discussion
We describe a novel percutaneous technique to access the left heart to deliver interventional devices. The technique combines several innovations: (1) fully percutaneous transthoracic LA access with a needle followed by a large sheath; (2) pericardial autotransfusion catheter placement; (3) pleural...
Pleural Insufflation to Create Unobstructed Trajectory to LA

Thoracoscopy to inspect the pleura, perform biopsies, or deliver therapy is an established technique usually performed under moderate sedation. More advanced procedures, for example, lobectomy or management of spontaneous pneumothorax, are typically performed under general anesthesia with dual-lumen endotracheal tube to facilitate single lung ventilation and have excellent perioperative outcomes. However, there is evidence that such interventions can be well tolerated in conscious nonintubated patients even for long procedures and in older sicker patients. Based on this extensive clinical experience, there is reason to expect that single lung deflation for the purpose of transthoracic LA access may be tolerated in patients.

Choice of Imaging Modality to Guide LA Access

The superior soft tissue visualization and multiplanar viewing capabilities of MRI are appealing to guide minimally invasive interventions, particularly interventions that violate vascular boundaries, in which every anatomic structure traversed must be visualized. MRI provides this capability. In this study, we demonstrated that LA access and closure could be safely performed using real-time MRI guidance. MRI also permitted easy access to the pleural space and titration of pleural insufflation to displace lung. Crucially, MRI afforded continuous monitoring for development of pericardial and pleural effusions during LA puncture and closure. Any accumulation of blood in the pericardial or pleural space was immediately identified and autotransfused.

Nonetheless, we explored whether the procedure could be performed using x-ray fluoroscopy. A transseptal pigtail catheter was positioned in the LA. Biplane contrast angiography and pericardial iodinated contrast delineated LA anatomy adequately. This enabled a trajectory to the LA to be planned in orthogonal x-ray projections. It was difficult to definitely establish adequate lung displacement using fluoroscopy only, but C-arm CT provided clear visualization of lung tissue and assurance of satisfactory lung displacement. In humans, where the preferred LA puncture site should be posterior and midway between left and right pulmonary vein ostia, dual transseptal guidewires in left and right pulmonary veins could offer a precise fluoroscopic target for LA puncture. Echocardiography could provide a substitute for real-time MRI to monitor for pericardial blood accumulation and guide autotransfusion.

We also explored using color overlays of the LA and LV, segmented from contrast-enhanced C-arm CT using software designed to guide electrophysiology procedures. The fusion images enhanced our ability to predict trajectories and determine optimal LA puncture location (Figure 4). In addition, the overlays aided in selecting optimal x-ray projection angles and may have reduced overall iodinated contrast usage.

Closure of LA Port

There is clinical precedent for the use of off-label nitinol cardiac occluder devices to seal large holes in vascular structures, including the LV apex or abdominal aorta. Even in the high-pressure LV, hemostasis was rapidly achieved with reversal of anticoagulation. Hemostasis should be easier to achieve in the LA because the pressure is much lower than in the LV or systemic arteries, even in patients with mitral valve disease. In some animals, blood did accumulate in the pericardial or pleural space, but was easily managed by aspiration and autotransfusion, akin to standard surgical blood salvage technique. After aspirating to dryness, all drains were removed post procedure for animal comfort—although in humans they would be left in overnight. Only 1 large but hemodynamically insignificant pericardial effusion was observed at follow-up, in the 1 animal in which 2 LA punctures were made because a custom needle...
had become dull. The animal recovered uneventfully and the effusion would not have accumulated had the pericardial drain remained in place post procedure.

Feasibility of Clinical Translation
We tested LA access and closure in 2 large animal models to determine whether the approach was feasible in different anatomies. The trajectories for unobstructed access to the LA were different in the 2 species but easily achievable by deflating the left lung. Importantly, all animals were hemodynamically stable with a large sheath in the LA. This approach could circumvent many of the risks associated with transapical access in patients with advanced mitral valve disease, in particular, acute hemodynamic instability and late LV pseudoaneurysm, ventricular arrhythmias, and decrement in LV function.

Human cardiac CT angiogram analysis confirmed that a theoretical trajectory exists in humans. In swine, pleural insufflation rotated the heart in the thorax, which resulted in an offset between the long axis of the heart and the achieved trajectory (Figure 3). Because the orientation of the heart in the human mediastinum is different, the trajectory is different from that in swine or sheep. In humans, the right lung would be deflated to puncture the LA posteriorly between the pulmonary veins (Figure 5). In this configuration, right lung deflation would deflect the right pulmonary veins away from the needle trajectory, exposing the posterior wall of the LA. This trajectory avoids other important structures, such as the aorta and esophagus. The mean intercostal distance at the point of entry through the chest wall was sufficient to accommodate a sheath 32F or larger.

To demonstrate that this trajectory was feasible, we accessed the LA in human cadavers and delivered a large sheath under either MRI or x-ray guidance (Figure 6). Pleural insufflation did not shift the orientation of the heart within the thorax in cadavers. We then closed the LA port with a nitinol cardiac occluder device and re-expanded the right lung.

Limitations
There are anatomic differences between humans and swine. For example, the descending aorta and esophagus vary in position within the thorax. Procedural tomography (such as C-arm CT and real-time MRI) is therefore recommended for trajectory planning. Pulmonary disease or chronic heart failure could increase the risk of single lung ventilation. Clotting disorders could increase bleeding. Off-label nitinol cardiac occluder devices may not assure hemostasis. Prior cardiothoracic surgery may cause pleural adhesions, which could impede lung displacement. Because our technique involves 2 points of fixation (chest wall and LA wall), sheath maneuverability is constrained. However, because excellent alignment with the LV long axis can be achieved by careful trajectory planning, we do not anticipate that excessive sheath manipulation would be required to achieve coaxial alignment to perform a mitral valve intervention.

Technical Considerations for Clinical Translation
To perform this procedure in patients under x-ray fluoroscopy guidance, we envision the following provisions: (1) The procedure would be performed under general anesthesia with a dual lumen endotracheal tube and bronchial blockers to facilitate intentional right lung collapse and single lung ventilation. (2) The patient would be positioned initially supine for standard percutaneous access and then rolled prone for transthoracic atrial access. (3) A temperature or transesophageal echocardiography probe would be used to identify the esophagus. (4) A pericardial drain may not be required in patients with prior sternotomy and pericardial adhesions. (5) Respiration would be suspended during LA puncture. (6) The guidewire would be advanced through the mitral valve into the LV over a balloon catheter to prevent chordal entrapment. (7) Anticoagulation would be reversed with protamine immediately before cardiac occluder device deployment. (8) A coaxial buddy wire would be used during LA port closure to allow LA access to be reestablished rapidly in case of inadvertent pull through of the nitinol cardiac occluder device. (9) Pleural and pericardial drains would be left in place for a short period after the procedure to drain any effusions.

Conclusions
Fully percutaneous transthoracic LA access is feasible to deliver large interventional devices to the mitral valve without violating the LV myocardium. The procedure can be guided by a variety of imaging modalities, although in our experience MRI guidance offers the greatest visualization of anatomic structures with the ability to monitor and address complications in real-time, for example, pericardial effusion. Clinical translation seems feasible based on human cardiac CT analysis and human cadaver testing. This technique could provide a direct and coaxial access route for transcatheter mitral valve interventions in the future.

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Disclosures
None.

References


Fully Percutaneous Transthoracic Left Atrial Entry and Closure as a Potential Access Route for Transcatheter Mitral Valve Interventions

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http://circinterventions.ahajournals.org/content/8/6/e002538

Data Supplement (unedited) at:
http://circinterventions.ahajournals.org/content/suppl/2015/05/29/CIRCINTERVENTIONS.114.002538.DC1
Supplemental Material

Supplemental Methods

**MR imaging parameters:** Steady-state free precession (SSFP) imaging followed usual parameters: repetition time (TR)/echo time (TE) 2.9/1.2ms; flip angle 57°; bandwidth 930Hz/pixel; field of view (FOV) 340x340mm; matrix 256x256pixels; slice thickness 6mm.

Three-dimensional radial SSFP non-contrast whole heart parameters were TR/TE 3.1/1.56ms; flip angle 115°; bandwidth, 898Hz/pixel; FOV 220x220mm; voxel size 1.1x1.1x1.1mm; base resolution 192; radial views 12360.

Real-time imaging used SSFP (TR/TE 2.9/1.4ms; flip angle 45°; bandwidth 1000Hz/pixel; matrix 192x108; FOV 300x300mm; GRAPPA Factor 2-4) or gradient echo (TR/TE 4.2/1.9ms; flip angle 15°; bandwidth 500Hz/pixel; matrix 192x144; FOV 300x300mm; GRAPPA Factor 2-4).

To assess for and quantify volume of pericardial effusion, contiguous true axial slices were acquired using a steady-state free precession (SSFP) sequence with breath hold and ECG gating. Slices were prescribed to include cardiac anatomy from base to apex to ensure coverage of the entirety of the pericardial space. Acquisition parameters were: repetition time (TR)/echo time (TE), 2.96/1.25msec; number of averages 2; acceleration factor (GRAPPA) 2; flip angle 80°; bandwidth 1157Hz/pixel; field of view 300x300mm; matrix 240x128 pixels; slice thickness 6mm; and slice distance 0mm. Pericardial and cardiac contours were drawn manually on each slice and the pericardial effusion volume was calculated by subtracting the total cardiac volume from the total pericardial volume using *Syngo Argus* MR analysis software (Siemens).

**Interventional devices used in MR:** We used a custom needle and closure device delivery cable, each incorporating a loop antenna for active visualization. This enables the devices to appear highlighted in color in the real-time MR images. To visualize the 18Fr sheath in MR, a passive
marker containing iron oxide particles was added to the tip, which appears as a dark artifact on the real-time MR images.

*DynaCT imaging parameters:* ECG triggered with breath hold, 4 sweeps with 5 second scan time/sweep, 90 kV, 0.80 degrees/frame, total of 4 sweeps.
Supplemental Videos

Video 1. Real-time MR guided left atrial access and closure in swine

Video 2. X-ray fluoroscopy and cone-beam CT guided left atrial access and closure in swine

Video 3. Planning a trajectory for transthoracic LA access in a human using cardiac CT

Video 4. Real-time MR guided left atrial access in a human cadaver