Patch Closure of Muscular Ventricular Septal Defects With a New Hybrid Therapy in a Pig Model

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Objectives
We evaluated a novel technique for hybrid patch closure of muscular ventricular septal defects (mVSDs) without cardiopulmonary bypass (CPB) in a pig model.

Background
So far, surgical and interventional therapies for mVSDs have been associated with significant morbidity, especially in newborns and infants. Thus, it is essential to develop new techniques. Hybrid therapy is an innovative approach for mVSDs that combines the advantages of surgical and interventional techniques.

Methods
Six pigs underwent left anterolateral thoracotomy to expose the left ventricle (LV). The mVSDs were created under echocardiographic guidance with a 7.5-mm sharp punch instrument that was forwarded via an LV incision. A special designed patch system composed of a patch with a Nitinol frame was passed across the carotid artery into the LV and positioned in front of the mVSD. An instrument resembling a stapler was introduced across the LV wall on the beating heart without use of CPB. The patch was fixed with Nitinol anchors on the septum under echocardiographic and fluoroscopic guidance. Finally, the Nitinol frame was detached from the patch.

Results
The locations of the defects were apical (n = 1), midmuscular (n = 3), and anterior muscular (n = 2). Closure of the mVSD was successful in 5 of 6 animals confirmed by echocardiography, hemodynamic measurements, and explantation of the heart. Animals were hemodynamically stable throughout the experiment.

Conclusions
Here, we present a novel technique for hybrid closure of mVSDs without use of CPB. Further development of the patch system is necessary to assess applicability in humans, especially for the target group of newborns and infants. (J Am Coll Cardiol 2008;51:1597–603) © 2008 by the American College of Cardiology Foundation

Ventricular septal defects (VSDs) are one of the most common congenital cardiac defects and account for approximately 30% of all congenital heart diseases (1). They are classified according to their location in the septum (2). Muscular ventricular septal defects (mVSDs) account for approximately 10% to 15% of all VSDs (3).

Until now, therapy for mVSDs beyond the moderator band has been challenging, especially in newborns and infants, and is associated with increased morbidity and mortality. Both surgical and interventional approaches have their limitations. Surgical repair of these defects beyond the moderator band might frequently require left ventriculotomy or the division of multiple important right-sided muscle bands. These procedures are often associated with significant morbidity and mortality (4). Moreover, surgery is associated with prolonged hospital admission, a scar, and patient discomfort (5). Furthermore, surgery requires the use of cardiopulmonary bypass (CPB), which might be associated with various adverse effects, such as impaired neurologic development (6,7) or systemic inflammatory response syndrome (SIRS) (8).

Recently there has been an increase in the use of alternative interventional strategies. These interventions are limited by poor vascular access and low patient weight, especially in young infants (9–11). Currently, the devices used in these interventions are still at an investigational stage. In addition, there are several reports about significant arrhythmias, hemodynamic compromises, valve injuries, or incomplete closure (12,13).

Hybrid cardiac surgery, a combination of interventional and surgical techniques, has been demonstrated as a new,
innovative approach for therapy of mVSDs, because it reduces operation times, complexity, operative trauma, and avoids use of CPB (10,14). Several authors reported off-pump closure of mVSDs with an Amplatzer device via a perventricular approach. Advantages over open repair included avoidance of trans-section of the moderator band or other right ventricular muscle bundles without limitations of vascular access or patient weight (14). Nevertheless, authors also reported valve injuries, device embolization into the aorta, and rhythm disturbances (10).

Thus, new therapeutic strategies have to be developed. Here, we present a new method for closure of mVSDs with a patch delivery device and mini Nitinol anchors in a hybrid technique.

**Methods**

**Animals.** We used 6 German Landrace piglets of either gender (20 to 30 kg), which were purchased from the farm of the university (Oberschleissheim, Germany). The experimental protocol was approved by the local Governmental Commission on the Care and Use of Animals. The animals received care in compliance with the Guide for the Care and Use of Laboratory Animals. All experiments were performed in the laboratory of Surgical Research, Walter-Brendel-Center for Experimental Medicine, at the Ludwig-Maximilians-University of Munich.

**Anesthesia.** First, the piglets were fasted overnight and pre-medicated with an intramuscular injection of 500 mg ketamine, 10 mg/kg body weight azaperone, and 0.5 mg atropine. After cannulating an ear vein, midazolame (0.1 mg/kg body weight intravenously) was administered. The animals were intubated with a 6.5-F (Charriere scale) tube and ventilated with a inspiratory oxygen concentration of 50%. Anesthesia was induced and maintained with propofol (induction 1.5 to 2 mg/kg body weight, maintenance 10 mg/kg body weight/h) and fentanyl (induction 0.02 mg/kg body weight, maintenance 0.045 mg/kg body weight/h). The respiratory rate and tidal volume were adjusted to keep the arterial partial pressure of carbon dioxide (pCO₂) between 35 and 45 mm Hg. Arterial blood samples were obtained for analyses of partial pressure of oxygen (pO₂), partial pressure of carbon dioxide in the arterial blood (PₐCO₂), and pH. Before performing thoracotomy, muscle paralysis was induced with pancuronium bromide, 0.1 mg/kg body weight intravenously; additional doses were administered when necessary.

Intravenous fluids (Ringer solution) were given at a rate of 10 ml/kg body weight/h and increased when necessary. Hydroxy ethyl starch 6% was given in case of relevant blood loss. Oxygenation, electrocardiogram, and temperature were also monitored and recorded continuously. Amiodarone (20 mg/kg body weight/d) and magnesium were administered throughout the procedure to prevent ventricular arrhythmias.

**Device and stapler.** The patch delivery device consisted of a self-expanding frame made of a 0.25-mm × 0.75-mm Nitinol wire (wire 1) covered by a polyethylene tube (1.5 mm in diameter) and a grip. A 0.1-mm polyester patch was appropriately trimmed and then attached to the Nitinol frame by a 0.1-mm Nitinol wire (wire 2) (Fig. 1, upper panel) (15). A custom-designed stapler was used to fix the patch on the septum with mini-anchors made of Nitinol (Fig. 1, lower panel).

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**Figure 1. Basic Construction of the Patch Delivery Device and the Custom-Designed Stapler**

The upper panel shows the polyester patch and the patch delivery device (B). (A and C) Enlargement of B, whereas A shows the back and C the front. The lower panel presents the custom-designed stapler. (E) Enlargement of the front of the custom-designed stapler and a mini Nitinol anchor. (F) Demonstrates how the mini Nitinol anchor is fixated in the plier contained in the stapler.
Imaging. For imaging, 2-dimensional (2D) and 3-dimensional (3D) echocardiography were used. For 2D echocardiography (Sonos 5500, Philips Healthcare, Andover, Massachusetts), a 5-MHz transesophageal echocardiographic probe was placed behind the beating heart via an incision of the 6th intercostal space. The 3D echocardiography was performed epicardially by using the X7-2 matrix transducer of the IE33 Ultrasound System (Philips Healthcare). Additionally, closure of the mVSD was performed under fluoroscopic guidance.

Surgical preparation. All animals were shaved for thoracotomy and neck dissection on the right side. Afterwards, the right-sided external carotid artery and the jugular vein were exposed. The external carotid artery was cannulated with a 9-F and the jugular vein with an 11-F introducer sheath. Arterial pressure and central venous pressure (CVP) were measured continuously.

Animals were placed in dorsolateral recumbency with the left side upward. A left fourth intercostal thoracotomy was performed, and the heart was exposed by incising the pericardium. The following steps were performed without CPB. Two 4-0 polypropylene purse-string sutures on the LV wall were applied for instrument insertion.

Creation of mVSDs. Creation of mVSDs was achieved under 2D and 3D echocardiographic guidance with a special designed punch instrument via an LV incision (7.5 mm) (Fig. 2). Successful creation of an mVSD was confirmed by echocardiography and oxymetric measurement of the shunt volume by the Fick method.

mVSD closure. A 7-F introducer sheath shortened to 2 cm was inserted through the incision in the LV wall, which was also used for creation of the mVSDs in order to minimize LV trauma during the closing procedure. Contrast medium was applied to detect the mVSD in fluoroscopy.

The patch delivery device was inserted into a custom-designed, 30-cm-long 7-F sheath. It was forwarded over a 6-F pigtail catheter via the 9-F introducer sheath across the carotid artery into the left ventricle (LV). The patch was deployed and positioned over the defect under fluoroscopic and echocardiographic guidance.

The custom-designed stapler was introduced through the shortened 7-F sheath inside the lateral LV wall. Then, the patch was fixed with 8 to 10 Nitinol mini anchors (Fig. 1) under echocardiographic and fluoroscopic guidance. After secured fixation the Nitinol frame was detached from the polyester patch by releasing the sutures (pulling the Nitinol wire 2) (Fig. 1) and was drawn back into the long 7-F sheath.

Finally, animals were killed by an intracardial injection of 40 mval potassium chloride.

Autopsy of the hearts revealed the location of the mVSD as well as the position and fixation of the patch.

Measurements and echocardiography. Arterial blood samples were obtained continuously to control appropriate ventilation. Heart rate (HR), arterial pressure, and CVP were measured and recorded. The following hemodynamic parameters were obtained as baseline before performing thoracotomy: CVP, pulmonary arterial pressure, and pulmonary capillary wedge pressure (PCWP). Echocardiography was performed to exclude congenital defects such as septal defects and valve insufficiencies.

After creating the shunt the same hemodynamic parameters as described previously were obtained. Blood samples were taken to measure the shunt volume. Echocardiography was used to assess the diameter of the created VSD.

After closure the residual shunt volume was measured by obtaining the required hemodynamic parameters. Additionally, echocardiography was performed to detect potentially existing residual shunts and valve insufficiencies.

Statistical analysis. Values are presented as mean ± SD. For comparison of paired observations, the paired t-test was used without correction for multiple comparisons. A p value <0.05 was considered statistically significant.

Results

Creation of mVSDs. Echocardiography and hemodynamic measurements before the procedure excluded valve insufficiencies and cardiac defects as well as relevant shunting in all animals. Creation of an mVSD under echocardiographic guidance was successful in all animals (n = 6) (Fig. 3). The mean size of the created mVSD was 6.0 ± 0.7 mm, as determined by 2D echocardiography (Table 1, Fig. 3). Successful creation of the defects was also confirmed by 3D color Doppler echocardiography (Fig. 3). Shunt volumes ranged from 10.2% to 41.3%, mean 20.1%. The defects were located in the apical (n = 1), midmuscular (n = 3), and anterior (n = 2) septum revealed by explantation of the heart at the end of the experiment (Table 1). Animal 6 needed dopamine in a dose of 3 μg/kg/min after creation of the defect, because the LV showed a volume overload.

Ventricular septal defect closure. Figure 4 demonstrates the main principle of our hybrid therapy. The patch delivery device was inserted into the long 7-F introducer sheath and
forwarded across the carotid artery into the LV. Because the patch delivery device consists of Nitinol, the patch expanded easily to its original form after deploying through the end of the sheath. Maneuvering of the patch in the LV and positioning in front of the defect was performed without any difficulties.

Successful closure of the mVSD was completed under echocardiographic and fluoroscopic guidance in 5 of 6 animals (Fig. 5). The absence of residual shunts in these animals was confirmed by 2D and 3D color Doppler echocardiography. No left to right shunt could be detected after closure in 5 of 6 animals. The patch in the sixth animal was positioned too medially. Echocardiography and hemodynamic measurements showed significant residual shunting. None of the animals needed catecholamines at the end of the procedure. However, all animals showed mild tricuspid and mitral valve insufficiency. Additionally, 1 animal had mild to moderate aortic valve insufficiency.

**Examination of the explanted hearts.** Examination of the explanted hearts revealed substantial mVSDs. The diameters of the mVSDs were in accordance with the echocardiographic measurements in all investigated hearts (Table 2).

Furthermore, appropriate position and fixation of the patch could be confirmed in 5 of 6 animals (Fig. 6). In the sixth animal the patch did not cover the defect completely, and a residual defect of 3 mm remained.

No structures of the mitral and tricuspid valve apparatus were injured during patch closure. No damage was seen at the side of the aortic valve even in the animal with the mild to moderate aortic insufficiency.

**Hemodynamic measurements.** Pigs were hemodynamically stable throughout the whole experiment (Fig. 7). Dopamine was administered in only 1 animal (Table 1). All hemodynamic data did not show any significant difference. Although not statistically significant, pulmonary arterial pressure and PCWP measurements showed a tendency to increase after creation of the mVSD. At the end of the patch closure there was no additional increase of these values.

### Table 1 Relevant Data About Animals 1 to 6

<table>
<thead>
<tr>
<th>Animals</th>
<th>VSD (mm)</th>
<th>VSD Location</th>
<th>Need of Catecholamines</th>
<th>Successful Implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.0</td>
<td>Anterior muscular</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>6.0</td>
<td>Midmuscular</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>5.1</td>
<td>Anterior muscular</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>6.3</td>
<td>Midmuscular</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>6.7</td>
<td>Midmuscular</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>6.0</td>
<td>Apical</td>
<td>Dopamine (3 µg/kg/min after creation of the mVSD and during closure)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

mVSD = muscular ventricular septal defect; VSD = ventricular septal defect.

**Discussion**

We present a new technique for hybrid closure of mVSDs without using CPB. In general, hybrid therapy, a combination of interventional and surgical techniques, seems to be a new innovative approach for therapy of mVSDs (10). So far, both surgical and interventional therapies for mVSDs have their limitations.
Surgical repair of these defects continues to represent a significant challenge. Incidence of residual mVSDs still remains high after surgery (4). Reoperation rates up to 10% have been reported (16). Owing to technical difficulties, for many mVSDs below the moderator band pulmonary artery banding (PAB) is the preferred therapy in order to postpone corrective surgery. Interventional therapies are often limited by poor vascular access, low patient weight, and rhythm disturbances (10).

First hybrid procedures for other cardiac defects have already been described in the 1980s, such as intraoperative balloon occlusion of the Blalock Taussig shunt and intraoperative balloon dilation of critical aortic stenosis in neonates and infants (17,18). Newer hybrid procedures are pulmonary valve replacement or duct stenting combined with bilateral PAB as an alternative first-step approach for children with hypoplastic left heart syndrome (19,20). Recently, several authors reported off-pump closure of mVSD with an Amplatzer device via a perventricular approach (10,21). Besides the advantages, they also had to deal with a set of complications, such as valve injuries, device embolization into the aorta, and rhythm disturbances (10). But the authors believe children will profit from improving hybrid therapy, especially patients with complex defects beyond the moderator band.

Because previous therapeutic strategies for mVSD closure have had their limitations, we performed a pilot study to

**Table 2** Hemodynamic Data Throughout the Experiment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After Creation of mVSD</th>
<th>After Closure of mVSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>80.0 ± 13.3</td>
<td>74.5 ± 20.8</td>
<td>71.5 ± 13.9</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>8.0 ± 2.7</td>
<td>9.6 ± 4.6</td>
<td>8.6 ± 3.7</td>
</tr>
<tr>
<td>Systolic PAP (mm Hg)</td>
<td>27.3 ± 4.2</td>
<td>33.83 ± 6.1</td>
<td>34.5 ± 9.4</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>7.75 ± 1.2</td>
<td>15.2 ± 4.7</td>
<td>14.0 ± 3.2</td>
</tr>
</tbody>
</table>

CVP = central venous pressure; MAP = mean arterial pressure; mVSD = muscular ventricular septal defect; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure.

**Figure 5** Implantation and Fixation of the Patch

(A) Fluoroscopic images before (left panel) and after (right panel) pulling the Nitinol wire 2. (B) Three-dimensional (3D) echocardiography of the patch and the patch delivery device put on the muscular septum. (C) Three-dimensional echocardiography of the patch and the mini Nitinol anchors after the patch delivery device was drawn back into the 7-F sheath.

**Figure 6** Explanted Heart of Animal 2

Appropiate position and fixation of the patch. The ellipse points to the location of the muscular ventricular septal defect.

**Figure 7** Hemodynamic Stability During the Whole Experiment

Mean arterial pressure (red circles) and central venous pressure (black circles) during the course of the experiment. Application of catecholamines was not necessary. 1 = skin cut; 2 = creation of the muscular ventricular septal defect; 3 = implantation of the patch; 4 = fixation of the patch.
evaluate a new hybrid therapy for mVSD closure. The construction of the patch delivery system and the custom-designed stapler have been described recently (15). In principle, a patch with a Nitinol frame was delivered across the carotid artery into the LV and positioned over the defect. Afterwards, it was fixed with a custom-designed stapler. Finally, the Nitinol frame was detached from the patch and could be easily drawn back into a 7-F sheath, so that only the patch with the mini Nitinol anchors remained in the muscular septum. The mVSDs were successfully closed in 5 of 6 animals without a residual shunt.

Our method combines surgical and interventional advantages, because it can be performed without the use of CPB. First of all, the use of an LV approach might have some advantages over repair from the right ventricular side. Many mVSDs are very difficult to detect from the right ventricular side, because of muscular trabeculations. The margins of an mVSD are much easier to define from the LV side, owing to the smooth surface of the septum. Furthermore, the pressure gradient between left and right ventricular side supports the patch alignment to the muscular septum. But until now, LV approaches were rarely undertaken because of the risk of development of impaired LV function. In our proposed hybrid therapy, a minimal LV incision, approximately 2 mm, has to be made for fixation of the patch by the custom-designed stapler. Thus, the approach proposed in this report might offer the benefits of closure of a VSD through the LV without the complications of a large LV incision. We believe that the risk of development of LV dysfunction will be significantly reduced.

Combination of echocardiography and fluoroscopy in our new technique is reasonable, because the exposure to radiation can be reduced. Recently, several therapeutic strategies proposed implantation of the Amplatzer device as a hybrid technique (9,15). The Amplatzer device is quite stiff and inflexible. There is a potential risk of damage for adjacent anatomical structures, especially valves and the conduction system (9,22,23). Thus, we believe implantation of a patch in hybrid technique is an innovative approach, because a patch shows a high flexibility and has a lower risk of hurting adjacent anatomical structures.

In the future, a chronic setting of these experiments is needed to evaluate how the patch will integrate with the myocardium and whether LV dysfunction or pulmonary hypertension develops. In this set of experiments, PCWP doubled at the end of the experiment after VSD procedure. This effect was not statistically significant, but we believe this is due to the small sample size. This indicates stress to the ventricles due to the VSD creation. After the patch implantation no additional increase of the PCWP was seen. A future chronic investigation must address whether there is a considerable, long-term depression of the myocardium. Furthermore, it is important to observe whether the valve insufficiencies we have seen at the end of the procedure will accelerate, level off, or deteriorate. Insufficiencies of the atrioventricular valves were mostly seen after mVSD creation. An additional negative effect due to the implantation procedure could not be seen. The mild aortic valve insufficiency observed in 1 animal is probably related to the extension of the valve by the implantation sheath. A damage of the valve itself could not be seen in the autopsy.

Some might argue that we used the external carotid artery as peripheral vascular access instead of the femoral artery, which would be the typical access in humans. We believe that the implantation can also be done from the femoral artery. Thus, further experiments are needed to evaluate the feasibility of patch implantation across the femoral artery.

**Study limitations.** In our study, we used animals weighing 20 to 30 kg. Large arterial and venous sheaths were required. For this first feasibility study we decided to use large patches, carrier systems, anchors, and application systems in order to evaluate a general applicability of this system. We plan to modify this system to 5-F in order to make it usable in smaller piglets weighing approximately 5 to 10 kg. We are aware that only a minimized working system will allow us to treat newborns and avoid a primary PAB.

Shunt measurements sometimes were unexpectedly small, although echocardiographic assessment of the mVSD and explantation of the heart revealed moderate to large VSDs. We believe that swelling of the surrounding area of the created mVSD could be responsible for quite small shunt volumes. Nevertheless, explantation of the heart revealed that we created substantial defects. Thus, myocardial swelling is a problem of this acute animal model. Conversely, we believe that creation of bigger mVSDs could have resulted in the death of the animal, because an acute creation of VSDs is associated with a large hemodynamic compromise. However, the explanted heart revealed that the mVSDs were covered by the patch completely in 5 of 6 animals. Therefore, without swelling, closure of the defects would have also been successful.

Appropriate imaging was essential for this study. To date, implantation is mainly done under guidance of fluoroscopy and 2D transesophageal echocardiography. Epicardial 3D echocardiography might be theoretically beneficial, because an on-face view of the VSD and patch can be produced. However, simultaneous epicardial echocardiography and fixation of the patch is challenging at this time. Therefore, imaging has to be developed further. We believe that a 3D transesophageal probe placed behind the heart will improve implantation significantly. There is a potential risk of embolization of the Nitinol anchors. This might be dangerous for patients. In this series, of 49 Nitinol anchors, 3 embolizations occurred. For this reason, further development of the application device is a major issue and the staplers will be modified. We plan to incorporate a stop mechanism before the anchors are released. Besides, we believe angled staplers will facilitate implantation significantly.
Conclusions

In conclusion, we present a novel hybrid technique for mVSD closure without using CPB and with a minimal LV incision, which might be an alternative therapeutic option for newborns instead of PAB. However, further evaluation and development of the patch delivery device and the custom-designed stapler is necessary to assess their applicability in humans, especially in newborns and infants.

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