Surgical palliation of primary pulmonary arterial hypertension by a unidirectional valved Potts anastomosis in an animal model

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Objective: Patients with idiopathic pulmonary hypertension are at risk for right-sided heart failure and sudden death. Despite improvement in pharmacologic management, some still require lung transplantation. Potts anastomosis has been demonstrated as a good palliation in children to alleviate symptoms and medical therapy despite desaturation in the lower part of the body. Young adult patients with pulmonary hypertension and isosystemic pressure remain at risk, particularly at exercise. The goal of this research was to find a palliation for patients in whom suprasystemic pulmonary hypertension developed at exercise. Creating a Potts anastomosis involved a unidirectional valve between the left pulmonary artery and the descending aorta.

Methods: Experimental study was performed on 14 pigs. A prosthetic patch of polytetrafluoroethylene (Gore-Tex; WL Gore & Associates Inc, Newark, Del) was used to create the unidirectional valve and implanted in the Potts anastomosis. Via a left thoracotomy, an aorto-aortic shunt between the aortic isthmus and the distal descending thoracic aorta was instituted, allowing a safe surgical procedure. Intrapulmonary injection of Erciplex glue (Peters Surgical, Bobigny, France), diluted in 70% alcohol, was used to create acute pulmonary hypertension. The right to left shunt across the unidirectional valvular patch was evaluated after clamping the aorta in the acute phase of pulmonary hypertension by echo-pulsed Doppler at the level of the descending thoracic aorta by withdrawal of blood gas (arterial carbon dioxide tension, alveolar carbon dioxide tension) and assessment of peripheral oxygen saturation. Similar reevaluation of the shunt was performed at a mean interval of 13 ± 2.5 weeks.

Results: In the first series, Erciplex glue increased pulmonary artery pressure from 15.3 ± 3.1 mm Hg to 38.7 ± 6.0 mm Hg. Mean peripheral oxygen saturation decreased from 100% to $85\% \pm 1.5\%$. Mean partial pressure of carbon dioxide increased from 31.9 ± 9.1 mm Hg to 46.2 ± 12.5 mm Hg after shunt opening ($P < .01$), and mean peripheral oxygen decreased from 435.1 ± 109.4 mm Hg to 261.9 ± 77.9 mm Hg ($P < 0.05$), indicating right to left shunt through the Potts valve ($P < .013$). Pulsed Doppler showed a mean peak laminar flow of 133.3 ± 35.3 cm/s before aortic clamping, turbulent flow of 234.9 ± 40.1 cm/s after glue injection, and return of laminar flow 128.5 ± 30.1 cm/s after aortic isthmus unclamping. In the second series, the same results were obtained but with a lesser peak flow velocity because of the endothelialization on the valvular patch. Gross analysis of the patch did not show thrombosis, aneurysm, or fissure.

Conclusions: Palliation of exercise suprasystemic pulmonary hypertension was demonstrated by a unidirectional valved Potts anastomosis. This technique can be of help in young adult patients with pulmonary hypertension and isosystemic pressure but with exercise intolerance. (J Thorac Cardiovasc Surg 2011;142:1223-8)

Primary pulmonary hypertension (PPH) may eventually lead to right ventricular failure and death. Without treatment, the mean survival after diagnosis is less than 1 year in children^{1,2} and 2 to 3 years in adults.^{2,3} Patients with severe right-sided heart failure (New York Heart Association class IV) have the worst prognosis, with a median survival of 6 months.⁴ Right atrial pressure, pulmonary artery

pressure, and cardiac index have been shown to correlate with mortality.¹

The introduction of new pharmacologic agents has considerably improved patient survival.⁵⁻⁹ Calcium blockers, prostaglandin E1,¹⁰⁻¹² endothelin receptor antagonists,^{13,14} and nitric oxide are well used in this subset of patients.¹⁵ Patients with PPH who have recurrent syncope, severe right-sided heart failure, or both have a worse prognosis because they generally have an intact interatrial septum.³ Longer survival has been described in patients with PPH who have an interatrial communication.⁴ With sufficient right-to-left shunting through an interatrial communication, cardiac output can be maintained or increased as needed, despite severe pulmonary vascular disease. Furthermore, right-to-left shunting at the atrial level allows decompression of the right atrium and right ventricle, alleviating signs and symptoms of right-sided heart failure.² These hemodynamic changes are

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Abbreviations and Acronyms

LPA = left pulmonary artery
PAH = pulmonary arterial hypertension
PPH = primary pulmonary hypertension

associated with decreased systemic arterial saturation but improved oxygen transport. These findings have prompted several authors to perform an atrial blade septostomy to decompress right-sided heart cavities and to improve systemic output^{1,2}; however, this procedure is associated with a low rate of success in patients with severe right-sided heart failure because of profound systemic desaturation. Finally, double lung or heart lung transplantation is an option, but shortage of organ donors and chronic rejection remain serious drawbacks to this procedure.¹⁶

On the other hand, patients with Eisenmenger syndrome demonstrate a longer survival until 50 years of age,^{1,4} particularly when the cardiac cause is as simple as a patent ductus arteriosus. Therefore, the idea to convert primitive pulmonary hypertension into Eisenmenger's pattern by creating a communication between pulmonary and aortic vascular beds, namely, a Potts anastomosis, should theoretically improve the survival and quality of life. This procedure was recently reported in 2 patients with terminal pulmonary arterial hypertension (PAH), in whom an anastomosis was created between the left pulmonary artery (LPA) and the descending aorta (ie, Potts anastomosis) long after an arterial switch operation for transposition of the great vessels.¹⁷ Both patients recovered, and right and left ventricular pressures were equalized. We also performed this procedure on 9 critically ill children with good early and midterm results.¹⁸ Indications for a standard Potts anastomosis should therefore include patients with suprasystemic intractable pulmonary hypertension. There is, however, a large category of patients with PPH well stabilized by medical treatment who demonstrate isosystemic pulmonary artery pressures at rest that increase for minimal exercise and therefore present an intolerance for minimal exercise.

To palliate this subgroup of patients, we designed an animal model of PPH in which a unidirectional valved Potts anastomosis allows right to left shunting during a suprasystemic pulmonary hypertensive crisis and no shunting when pulmonary arterial pressures are isosystemic.

MATERIALS AND METHODS

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (www.nap.edu/catalog/5140.html). Pigs (n = 9) with a mean weight of 29.3 ± 4.2 kg underwent induction of anesthesia with intramuscular ketamine (10 mg/kg) and atropine (0.04 mg/kg) and were intubated with a cuffed endotracheal tube. Animals were ventilated with a melange of air and oxygen (21%). Anesthesia was

maintained with inhalation of 1% to 2% isoflurane. In addition, pancuronium 0.1 mg/kg and nalbuphine 0.2 mg/kg were administered for muscle relaxation. Antibiotrophylaxis was achieved by cefotaxime 1 g and gentamicin 80 mg twice. A pressure monitoring catheter was placed in the right femoral artery. Pulmonary artery and left thoracic artery pressures were placed under direct vision. Electrocardiogram was recorded, and saturation sensors were placed on the right ear and tail.

Induction of Pulmonary Hypertension

Previous results from our laboratory showed that in situ injection of Erciplex glue (Peters Surgical, Bobigny, France), diluted at a proportion of 2 to 1 in 70% alcohol to obtain less viscosity, 3 times 2 mL with an interval of 7 minutes induces severe pulmonary hypertension for at least 15 minutes. Although the underlying mechanism is not well understood, clear pulmonary hypertension developed.

Construction of Unidirectional Valve

The unidirectional valve was constructed with polytetrafluoroethylene (Gore-Tex; WL Gore & Associates Inc, Newark, Del) patches (expanded polytetrafluoroethylene cardiovascular patch 0.5 mm) by mimicking the membrane of fossa ovalis. The unidirectional valve is made of 2 polytetrafluoroethylene (Gore-Tex) Acuseal or knitted Dacron double patches. One patch is oval and one patch is semi-lunar, half of the circumference of the first patch. The small patch is superposed to the oval one and sutured at its 2 horns. The polytetrafluoroethylene (Gore-Tex) 0.1-mm patch was not used because it was too thin to support such hemodynamic patterns (Figure 1).

Experimental Protocol and Surgical Technique

The animals were placed in the right decubitus position, and a left thoracotomy was made in the fourth intercostal space. The thoracic aorta from the isthmus to diaphragm and the LPA were mobilized and exposed. After heparin administration (300 IU/kg), an aorto-aortic shunt was instituted between the aortic isthmus and the descending aorta close to the diaphragm using right-angle cannulas. During the aorto-aortic shunt, the LPA and descending aorta were crossclamped. An aortopulmonary anastomosis was created between the LPA and the descending aorta, with a diameter of 10 to 12 mm and a length of 18 to 21 mm, and a unidirectional valve of different tissues (Patch Acuseal Gore-Tex, 0.5 mm; tissue patch of knitted polyester [Bard Sauvage Filamentous; Bard Peripheral Vascular, Inc, Tempe, Ariz]; IMPRA [Bard Peripheral Vascular, Inc] expanded polytetrafluoroethylene cardiovascular patch 0.5 mm) with adapted dimensions (mean 18.3 ± 0.8 mm in length and 0.8 ± 0.3 mm in width) was inserted into this Potts anastomosis.

The concave side of the semi-lunar patch is sewed "en sandwich" between pulmonary aortic arteriotomies, and the half circumference of the oval patch is also sewed "en sandwich" between pulmonary and aortic arteriotomies, opposite to the semi-lunar patch. The oval patch is placed on the systemic side, and the semi-lunar patch is placed on the pulmonary side of the anastomosis. Half of the oval patch is therefore free floating in an open position and is applied on the semi-lunar patch in a closed position. Opening and closing of this valve are therefore dependent on the gradient pressure between the aorta and the pulmonary artery (Figure 2).

After completion of the unidirectional valvular Potts anastomosis, the descending aorta and the LPA were deaired and unclamped. Mean aortic clamping time was 47 ± 8.3 minutes, LPA time was 45 ± 4.8 minutes, mean intervention time for the valved Potts anastomosis was 137 ± 26.6 , and aorto-aortic bypass time was 71 ± 12.4 minutes. Hemodynamic parameters (blood pressure, heart rate) were monitored, as well as the oxygen saturation and its changes in the pig's ear and tail.

To induce PAH, Erciplex glue was injected through a number 16 catheter into the LPA according to our previous protocol. One to 2 minutes after the glue injection, the aortic isthmus was clamped completely between the anastomosis and the superior cannula to obtain a suprasystemic pulmonary

FIGURE 1. A, Unidirectional valve is constructed by a double patch. B, Oval patch on the systemic side. Semilunar patch on the pulmonary side.

hypertension. Flow velocity of the right to left shunt across the valved patch during the acute phase of pulmonary hypertension was measured by intra-thoracic pulsed-Doppler ultrasound (1.9-MHz probe, Philips, Bothell, Wash; Hewlett-Packard Sonos 100, Palo Alto, Calif) in the descending aorta (Figure 3). Blood was taken from the descending aorta before and after the aortic clamping to evaluate changes of the arterial carbon dioxide tension and alveolar carbon dioxide tension values. After decannulation of the aorta, chest closure, and extubation, the animals were observed for vital parameters and postoperative management until the reevaluation. No antiaggregant treatment was started. Low-molecular-weight heparin, enoxaparin sodium 0.4 mL (7500 UI) twice per day, was given the first postoperative week and once per day the next week.

After a mean of 12 ± 2.5 weeks, the right to left shunt was reevaluated in the same manner as in the first experimental procedure but without the aorto-aortic shunt. The animals were then killed for valve morphology inspection.

Statistics

Results were calculated and presented as means $\pm$ standard deviation of a minimum of 3 measurements in each animal. Statistical analysis was achieved using the Student *t* test. Differences between the values were calculated using SigmaPlot 11.0 (Systat Software Inc, San Jose, Calif).

RESULTS

Glue injection allowed PAP to increase significantly from a mean of 15.3 ± 3.1 mm Hg before the procedure to 38.7 ± 6.0 mm Hg at the end of the procedure. PAP returned

to the previous values (mean, 18.7 ± 2.7 mm Hg) at the end of the experimental procedure ($P < .01$), showing that the glue injection effectively created conditions of PAH. Systemic pressures, heart rate, and temperature were stable during the aorto-aortic shunt and thoracic aorta crossclamping.

Under experimental conditions of suprasystemic PAH, opening of the unidirectional valve in the Potts anastomosis created a right to left shunt and led to a decrease in peripheral oxygen saturation on the tail to a mean of $85.7\% \pm 1.5\%$. Peripheral oxygen decreased from a mean of 435.1 ± 109.4 mm Hg to 261.9 ± 77.9 mm Hg, and alveolar carbon dioxide tension increased from 31.9 ± 9.1 mm Hg to 46.2 ± 12.5 mm Hg, indicating an effective right to left shunt ($P < .01$).

By provoking PAH after the glue injection and clamping the aortic isthmus, the pressure in the descending aorta decreased, permitting a turbulent flow at a higher velocity from the LPA into the descending aorta across the unidirectional valve of the Potts anastomosis, reflecting the sudden augmentation of the pulmonary pressures. Maximum shunt flow velocity in the descending aorta accelerated from a mean of 133.3 ± 35.5 cm/s before glue injection to a mean of 234.9 ± 40.1 cm/s after injection under aortic clamping conditions ($P < .001$), and then returned to the

FIGURE 2. Flow through the unidirectional valved Potts anastomosis. A, Open position of unidirectional valve when pulmonary pressures is suprasystemic. B, Focus on unidirectional valve. Ao, Aorta (descending); LPA, left pulmonary artery; UdV, unidirectional valve; RLF, right to left flow; OvP, oval patch; SLP, semilunar patch.

FIGURE 3. Gross view of the explanted unidirectional valve from the LPA (A) and the aortic side (B) with a 7 Hegar probe through the valve.

previous values after unclamping the aorta with a mean of 128.5 ± 30.1 cm/s.

When the aortic isthmus was unclamped again, the pressure in the descending aorta increased again, which diminished the shunt through the valved Potts anastomosis. Subsequently, the flow velocity across the shunt decreased progressively, once again becoming laminar after total unclamping of the aortic isthmus.

Early complications included inferior paraplegia in 1 animal 24 hours after the operation. The animal had to be killed to examine the valved Potts anastomosis, which was found to be undamaged. Another animal presenting with signs of mesenteric microembolism died 36 hours post-surgery. In the absence of any other cause, these findings were correlated to a non-dissolving glue that was used in our experiments. The other animals survived. We observed no complications due to pulmonary thrombosis, no distal or visceral embolism, and no PAH.

At reintervention, mean PAP increased significantly from a mean of 15.9 ± 2.8 mm Hg before to 46.7 ± 11.4 mm Hg after the glue injection and returned to the previous values (mean, 20.3 ± 2.8 mm Hg) at the end of the procedure ($P < .01$), showing that the glue injection can effectively create iterative PAH.

Reevaluation of the Permeability of the Valved Potts Anastomosis

Maximum shunt flow velocity in the descending aorta accelerated from a mean of 109.9 ± 38.0 cm/s before glue injection to a mean of 171.0 ± 30.2 cm/s after glue injection under aortic clamping conditions ($P < .001$), and then returned to previous values after unclamping the aorta with a mean of 116.2 ± 38.4 cm/s. Maximum velocities are less elevated in the reintervention series compared with those in the first series.

Comparison of the Shunt Flow Between First and Second Series

In both groups, the velocity of the right to left shunt showed highly significant differences ($P < .001$) before and after glue injection under clamping and unclamping

conditions, respectively. There was no significant difference between the velocities before the glue injection and after aortic unclamping, indicating that the flow changes in the descending aorta were exclusively due to the flow shunt through the unidirectional valve opening under the conditions of PAH and in the presence of systemic arterial hypotension due to the clamping of the aortic isthmus. The differences in the peak velocity after glue injection were significant in the 2 series (first series and reexaminations: 234.9 ± 40.1 cm/s vs 171.5 ± 30.2 cm/s, respectively; $P < .002$). There were no differences between the peak flow velocity before injection and after unclamping in either of the groups.

Surgical Evaluation of Valved Potts Anastomosis After Reintervention

The morphologic examination of the valved anastomosis at the end of the second series showed a preserved device with no perforations, tearing, false aneurysms, or thrombosis. A layer of intima or fibrin had formed progressively, making the valve patch less flexible and therefore less permeable for the right to left shunt with a less wide orifice of the unidirectional valve in some animals. This phenomenon may be responsible for the decreased peak flow velocity of the right to the left shunt in the reintervention series. The effective mean orifice size for shunting was 6.6 ± 1.3 mm (Figure 3).

DISCUSSION

Primary PAH often has a fatal outcome because there is no effective therapy. As a surgical palliative solution, creation of a right to left shunt has been proposed to relieve the overload on the right ventricle, which allows a ventricular septal shift from left to right, increasing the systemic left ventricle filling and optimizing coronary perfusion. Such a shunt has been proposed as an intracardiac right to left shunt, created by perforation of the interatrial septum or an extracardiac right to left shunt in the form of a Potts anastomosis between the LPA and the descending aorta. Whereas the interatrial shunt may be disadvantageous because of uncontrolled desaturation of the upper body and

coronary and brain circulation, the Potts anastomosis bears the risk of turning the right to left shunt from the pulmonary artery into the aorta under PAH conditions into a left to right shunt from the aorta into the pulmonary artery under conditions of normal pressure conditions, thus being responsible for a volume overload of the pulmonary circulation and increasing pulmonary artery pressures and a steal phenomenon from systemic to pulmonary circulation. Descriptions of either method have been made rather sporadically in the clinical field without illuminating the basic pathophysiologic processes. We therefore considered it necessary to create an experimental animal model to outline the pathophysiology and surgery of the Potts anastomosis in the field of PAH.

Adult pigs weighing approximately 30 kg were preferred to create the valved Potts anastomosis because they have sufficient LPA dimensions (0.8–1.3 cm) to enable implantation of the unidirectional valve. Also, a bigger animal can tolerate the experimental PAH created by the Erciplex glue. The left thoracotomy at the fourth intercostal space permits the best access to the vascular structures to be connected. For the purpose of our protocol, which includes clamping and unclamping the aorta to test the function of the valve, to ensure a reproducible surgical technique, and to maintain stability of systemic hemodynamics, an aorto-aortic shunt was used. However, with increasing experience and in clinical conditions of PAH, a simpler approach avoiding aorto-aortic shunt should be possible.

It was important to find out the ideal dose and dilution of the injected glue to avoid acute and irreversible right-sided heart failure induced by massive PAH and at the same time allow sufficient PAH to initiate the right to the left shunt through the anastomosis. Dilution of the glue was also necessary to avoid embolism of the systemic arteries of the inferior body by overly large glue particles. The valve inserted into the Potts anastomosis was created of double patches sutured symmetrically into the LPA and the aorta at the same time, and their dimension depended on the dimension of the LPA.

In preliminary studies, it was found that Gore-Tex Acuseal was the better material for constructing the patch because it was the thinnest and smoothest, therefore guaranteeing a longer flexibility and functionality. The exact installation of the unidirectional valve in the Potts anastomosis was important to avoid an inversed shunt from the aorta into the LPA after the creation of the anastomosis. The valved Potts anastomosis should be placed as close as possible to the pulmonary arterial bifurcation because the wider dimensions of the artery allow an easier valved anastomosis and the more central location of the anastomosis allows the pulmonary arterial blood to drain correctly into the descending aorta.

When the descending aorta is completely clamped on the level of the aortic isthmus, the right to left shunt starts to work immediately under the conditions of PAH; subse-

quently, the pulmonary pressure decreases immediately while the shunt is working. This guarantees stable hemodynamics of the systemic circulation. Our experiments show that the unidirectional valve in the Potts anastomosis allows desaturated blood to drain from the LPA into the descending aorta for discharge of the right ventricle under the conditions of PAH, with left ventricle filling shown by stable invasive blood pressure measurements, flow measurements across the Potts shunt by pulsed Doppler, desaturation, and increasing partial pressure of carbon dioxide in the inferior body. As soon as the aortic circulation is stabilized, the valve closes and normal conditions are reestablished without shunt inversion.

The reintervention showed that the peak flow acceleration was less marked than in the first series, which may be due to the endothelialization phenomenon of the valve that was covered with intima and fibrin layers, and therefore more rigid and less permeable for the blood passing through the shunt. Fibrin formation may induce platelet aggregation; therefore, antiaggregation treatment may help to avoid thrombosis of the valve in the long-term, especially when the valve opens less frequently. Reduction of the effective orifice of the valve may be due to the closed position of the valve during the interim period of 12 weeks. Indeed, during this period the animals were in a normal hemodynamic status with low pulmonary artery and high aortic pressures. In the clinical field, one could anticipate that such a device will open several times daily at any minimal exercise, therefore maintaining a satisfactory effective orifice.

The advantage of the intervention with a valved Potts anastomosis is the immediate decompression of the overload of the right ventricle by creating a right to left shunt on the arterial level that will not create cyanosis in the upper half of the body. The desaturation caused by the right to left shunt will be controlled automatically by the unidirectional valve at the level of the anastomosis when the systemic pressure increases again to values superior to those in the pulmonary artery, without inversion of the shunt because of the valve in the anastomosis. This intervention can thus be applied in young patients with primary PAH and an intact interatrial septum and suprasystemic exertional PAH. The method also can be used in patients with so-called Eisenmenger's syndrome and profound cyanosis after intracardiac repair as a means to reduce upper-body cyanosis.

CONCLUSIONS

In the acute phase of PH, the unidirectional valve of the Potts anastomosis opens when pulmonary arterial pressures become suprasystemic and then creates a right to left shunt at the arterial level, allowing discharge of the pulmonary circulation into the descending aorta. The valve closes when pulmonary arterial pressures return to isosystemic or infrasystemic levels.

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