Relief of branch pulmonary artery stenosis reduces pulmonary valve insufficiency in a swine model

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Objective: We sought to determine the impact of relieving branch pulmonary artery stenosis on pulmonary valve insufficiency and right ventricular function. Long-standing pulmonary insufficiency causes progressive right ventricular dilatation, leading to decreased right ventricular function. Adults with pulmonary insufficiency are at risk of decreased exercise tolerance, arrhythmias, and sudden cardiac death. Branch pulmonary artery stenosis frequently occurs in these patients, and the presence of branch stenosis may exacerbate valve insufficiency.

Methods: Neonatal piglets ($n = 7$) underwent surgery to create pulmonary insufficiency and left pulmonary artery stenosis. At 3 months of age, the animals underwent baseline cardiac magnetic resonance imaging followed by stenting of the left pulmonary artery. A repeat magnetic resonance imaging scan was performed 1 week after intervention. Magnetic resonance imaging evaluation included (1) velocity mapping to assess the forward and reverse flow at the main, left and right pulmonary arteries, and aorta; and (2) volumetric assessment of the right ventricle.

Results: Left pulmonary artery flow increased from 14.5% to 36.3% of total net flow after stenting ($P < .01$). Pulmonary regurgitation decreased from 38.7% to 27.4% ($P < .02$). Right ventricular ejection fraction improved from a median of 53.5% to 58.2% after stenting ($P < .01$). Cardiac index improved from a median of 2.7 to 3.5 L/min/m² ($P = .01$).

Conclusion: Relief of branch pulmonary artery stenosis reduces insufficiency and improves right ventricular systolic function in this animal model. This supports the practice of aggressive intervention in patients with branch pulmonary artery stenosis and pulmonary insufficiency.

Pulmonary insufficiency (PI) commonly occurs after surgery for many forms of congenital heart disease, most notably tetralogy of Fallot (TOF). Right ventricle (RV) volume overload secondary to long-standing PI is associated with exercise intolerance, syncope, ventricular arrhythmias, and sudden cardiac death.¹⁻³ The degree of PI has been found to be predictive of adverse events in these patients.^{4,5} Therefore, there has been increased interest in earlier intervention on the RV outflow tract in adults with moderate to severe PI and RV dilation.⁶⁻⁸ Timely intervention, including surgical valve replacement, has been shown to reverse the deleterious effects of RV dilation, to improve symptoms, and to reduce proclivity to arrhythmia in these patients.^{9,10} However, the lifespan of valved conduits is limited secondary to ensuing

conduit valve insufficiency and conduit stenosis, and these patients often undergo multiple repeated operations to revise their RV outflow as a result. Because of the increased morbidity and mortality risk associated with repeat sternotomy, less-invasive interventions to alleviate PI have been sought, including percutaneous valve implantation.¹¹ Unfortunately, only patients with an RV to pulmonary artery (PA) conduit are candidates for such an intervention currently.

Many patients with TOF have significant residual branch PA stenosis after surgical repair.¹²⁻¹⁴ These patients have reduced exercise tolerance compared with other patients with TOF.¹⁵ There has been indirect evidence that branch PA stenosis exacerbates PI.¹⁶ However, the relationship between PI and long-standing branch PA stenosis has not been directly studied. In this study, we measured the impact of relieving left pulmonary artery (LPA) stenosis on PI in a swine model of repaired TOF. Our hypothesis is that relief of unilateral branch PA stenosis alleviates PI by improving antegrade pulmonary arterial flow and enhancing overall hemodynamic efficiency.

MATERIALS AND METHODS

Surgery

Neonatal Yorkshire piglets ($n = 13$) were brought to the operating room at the Laboratory Animal Facility at the Children's Hospital of Philadelphia. The animals were a median of 13 days old (11–17 days) and a median of 3.9 kg (2.8–6.4). The animals were placed under general endotracheal

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Abbreviations and Acronyms

EDV	= end-diastolic volume
ESV	= end-systolic volume
LPA	= left pulmonary artery
LV	= left ventricle
MPA	= main pulmonary artery
MRI	= magnetic resonance imaging
PA	= pulmonary artery
PBF	= pulmonary blood flow
PI	= pulmonary insufficiency
RF	= regurgitant fraction
RPA	= right pulmonary artery
RV	= right ventricle
TOF	= tetralogy of Fallot

anesthesia using 1% to 3% isoflurane. After a dose of intravenous cefazolin (25 mg/kg), a left thoracotomy was performed. After careful blunt dissection, the LPA was identified and isolated. A 2-mm segment of 4.0-mm polytetrafluoroethylene (Gore-Tex; Gore Industries, Newark, DE) shunt material was cut open and wrapped around the proximal LPA and sewn with 6.0 suture. Then a curved clamp was placed across the RV outflow tract, including the valve annulus. Care was taken to ensure that approximately one half of the outflow tract was attained within the clamp. A longitudinal incision was made across the valve annulus onto the main pulmonary artery (MPA). Pulmonary valve tissue was cut away, and a diamond-shaped polytetrafluoroethylene (Gore-Tex) transannular patch was then sewn over the opened outflow tract. After removal of the clamp, the pericardium was closed, the left lung was reexpanded, and the thoracotomy was closed in a layered fashion. After giving a local infusion of bupivacaine (1%) and a single dose of Buprenex (0.1 mg/kg) intramuscularly, the animals were extubated and monitored closely for 48 hours for signs of distress, wound dehiscence, infection, or pain. A fentanyl transdermal patch (25 μ g) was placed for the first 48 postoperative hours. Two additional control animals underwent pulmonary valve resection and transannular patch as described above, but without the band on the LPA. The Institutional Animal Care and Use Committee of the Children's Hospital of Philadelphia approved this protocol.

Cardiac Magnetic Resonance Imaging

Approximately 3 months after surgery, the animals were taken for baseline cardiac magnetic resonance imaging (MRI). The baseline study (MRI 1) was immediately followed by LPA stent placement in the catheterization laboratory (see below). One week later, repeat cardiac MRI (MRI 2) was performed to assess the impact of relief of LPA stenosis. The cardiac MRI study protocol was identical for both pre- and post-intervention studies. The animals were placed under general endotracheal anesthesia and 21% oxygen, using 1% to 3% isoflurane, and then transported to the MRI scanning area. All scans were performed on a 1.5T Siemens Avanto (Siemens Corp, New York, NY) scanner. All scans were reviewed and interpreted by a single observer (M.A.H.).

Phase-Contrast Magnetic Resonance

At both baseline and follow-up MRI studies, phase contrast magnetic resonance acquisition was applied at the main and branch pulmonary arteries and at the aorta for flow quantification. On the post-LPA stent MRI, LPA phase contrast magnetic resonance data was acquired distal to the stent to avoid any stent-produced artifact. The typical imaging parameters included an echo time of 3.5 ms, 3 segments, a temporal resolution of 40 ms, a flip angle of 25 degrees, a matrix of 256 $\times$ 128, and a voxel size of

2.0 $\times$ 1.5 $\times$ 5.0 mm (slice thickness) with a resulting signal-to-noise ratio of approximately 1.0. Four averages were used for improving the signal-to-noise ratio and mitigating respiratory artifact. The velocity limit was set initially at 150 cm/sec and increased as necessary to accommodate increased flow velocities. Phase contrast magnetic resonance data analysis involved contouring regions of interest throughout all phases of the cardiac cycle. Forward, regurgitant, and net flows were then automatically calculated from the resulting flow-time curves. The regurgitant fraction (RF) through a region of interest is defined as follows: RF = (reverse flow/forward flow) $\times$ 100. Fractional branch PA pulmonary blood flow (PBF) distribution is calculated as follows: Fractional branch PA PBF = (net branch PA flow/net total PBF) $\times$ 100. Indexed values were obtained by calculating body surface area based on an accepted conversion formula for swine:¹⁷ body surface area (meters squared) = 0.097 * weight (kilograms)^{0.656}.

Ventricular Volume Analysis

Cine short-axis imaging of the ventricles was acquired from base to apex of the heart using 8 contiguous slices 6 to 8 mm thick, depending on the heart size. The RV systolic function analysis involved contouring the blood pool at end diastole and end systole at each level of the volume data set, thereby quantifying the end-diastolic volume (EDV) and end-systolic volume (ESV). The stroke volume is defined as the difference between the EDV and the ESV, and the ejection fraction is defined as the stroke volume/EDV $\times$ 100.

After MRI 2, the animals were euthanized and the hearts were harvested for gross inspection. Two control animals (5 months of age) without branch PA stenosis also underwent cardiac MRI to evaluate the distribution of flow to the right and left lungs.

Catheterization

The animals were taken directly from the MRI scanner after MRI 1 to the animal catheterization laboratory in the Laboratory Animal Facility. General anesthesia was continued using 1% to 2% isoflurane. The groins were prepped and draped using sterile technique, and a short sheath (7F) was placed in the femoral vein percutaneously. Intravenous doses of cefazolin (25 mg/kg) and heparin (100 U/kg) were given once vascular access was obtained. Hemodynamic evaluation was performed, including measurement of the RV, MPA, right pulmonary artery (RPA), and distal LPA pressures. Pulmonary capillary wedge pressures were measured bilaterally. Angiography was performed at the MPA, and measurements were made of the diameters of the RPA, MPA, and the proximal and distal LPA. The short sheath was then replaced with a 9F to 11F sheath, which was advanced into the distal LPA. A premounted endovascular stent (10 $\times$ 19 mm or 10 $\times$ 29 mm) was deployed across the banded region of the LPA. Care was taken to place the stents distally within the banded region, so that follow-up MRI velocity mapping could be obtained at the proximal RPA with minimal interference from the stent. In 5 animals, the stents were post-dilated with balloons 12 to 14 mm in diameter to achieve a size equal to that of the distal LPA. In 1 animal, a second stent was deployed because of migration of the first stent distal to the region of narrowing. After stenting, angiography was repeated. All vascular lines were removed, and the animals were extubated and monitored closely for 48 hours. The animals received aspirin (325 mg) daily until the day of the follow-up MRI.

Statistics

Values are presented as median (range). During many of the cardiac MRI scans, more than 1 velocity map of the pulmonary arteries was taken. In this situation, a mean value was calculated, and this mean value was used in the analysis. Velocity mapping data were internally verified using Pearson correlation comparing net forward flow at the MPA with the net flow at the ascending aorta, and with the sum of the net flow of the RPA and LPA. Pearson correlation testing was also performed to ensure correlation between net flow measured across the pulmonary and aortic valves, as well

FIGURE 1. Angiography of pulmonary arteries. Angiography performed before (A) and after (B) stenting of LPA in 1 animal subject demonstrates the nature of the stenosis. Pre-stenting, there is moderate proximal stenosis (white arrow) representing the region that was banded during surgery. Distal to this band, the LPA remains smaller than the distal RPA. After stenting (B), there is complete resolution of the narrowing (white arrow). The white asterisk denotes the right pulmonary artery.

as to the RPA and LPA. Finally, correlation was performed in post-stent studies to ensure that LPA flow measured distal to the stent approximated the value calculated by subtracting RPA from MPA flow. Pre- and post-stent MRI data were compared for each animal. Continuous variables were compared using the paired Student *t* test. Dichotomous variables were compared with chi-square and Fisher's exact tests. Statistical analysis was performed using Prism 5.0 (Graphpad Software, Inc, San Diego, CA).

RESULTS

Of the 13 animals, 10 survived the surgical procedure. Three animals survived the surgical procedure but died before completion of the protocol. Nonsurgical causes of death included noncardiac medical problems prompting euthanasia and complications surrounding general anesthesia induction. The 7 animals that completed the protocol underwent baseline MRI and catheterization at a mean of 96 (71–113) days from surgery, at a weight of 32 (23–60) kg.

At the time of catheterization, the LPA at the banded region measured 3.4 (2.9–4.0) mm in diameter, compared with 11.9 (8–15.5) mm distally. The LPA diameter distal to the band was significantly smaller than the distal RPA diameter ($P < .01$) (Figure 1). Hemodynamic data obtained

during catheterization revealed a median LPA systolic pressure of 15 (9–22) mm Hg, with a median gradient to the MPA of 11 (4–22) mm Hg (Table 1). The median transpulmonary gradient on the left was 4 (1–7) mm Hg, compared with 9 (2–16) mm Hg on the right ($P = .03$). After stenting of the banded region of the LPA, the diameter of the proximal LPA increased to a median of 11 (9–12) mm ($P < .01$). There was no pressure gradient between the MPA and the LPA after stenting in each case.

Cardiac MRI velocity mapping demonstrated that at baseline, the LPA received a median of 14.5% (3.2–20) of net flow from the MPA. This improved to 36.3% (11–48) after LPA stenting ($P < .01$) (Figure 2). For the 2 control animals without LPA stenosis, forward flow to the LPA was 40% and 43% of net flow. There was strong correlation among

TABLE 1. Branch pulmonary artery diameters, pressures, and flow

	LPA (range)	RPA (range)	<i>P</i> value
Proximal diameter (mm)	3.4 (2.9–4)	19.3 (16–25)	<.01
Distal diameter (mm)	13.2 (8–15.5)	20.7 (16.5–27)	<.01
Systolic pressure (mm Hg)	15 (9–22)	26 (19–42)	<.01
Mean pressure (mm Hg)	10 (6–15)	16 (10–28)	<.01
Forward flow (%)	14.5 (3.2–20)	85.5 (80–96.8)	<.01
Post-stent			
Systolic pressure (mm Hg)	25 (18–36)	27 (20–39)	NS
Forward flow (%)	36.3 (11–48)	63.7 (52–89)	<.01

LPA, Left pulmonary artery; RPA, right pulmonary artery; NS, not significant.

FIGURE 2. Flow to the LPA before and after stenting. Velocity mapping by cardiac MRI was used to measure flow (%) to the branch pulmonary arteries. Net flow (calculated as total flow–retrograde flow = net flow) to the LPA at baseline was a mean (dashed line) of 14.5%, which improved to 36.3% after stenting ($P < .01$).

FIGURE 3. Velocity mapping of the pulmonary arteries before and after LPA stenting. Velocity mapping by MRI of the MPA, RPA, and LPA was performed before (A) and after (B) LPA stenting. To measure LPA flow after stenting, velocities were sampled distal to the region of the stent to avoid signal dropout (B). The majority of net flow pre-stent (C) was delivered from the MPA to the RPA, with little net flow to the LPA. However, post-stent, net flow to the LPA increased significantly, and RPA net flow decreased. In addition, MPA net flow increased significantly after LPA stenting. *RPA*, Right pulmonary artery; *MPA*, main pulmonary artery; *LPA*, left pulmonary artery.

velocity map measurements of flow among the MPA, LPA, and RPA. At baseline, the sum of net RPA and LPA flow ($RPA_{net} + LPA_{net} = MPA_{net}$) correlated with net flow at the MPA ($R = 0.93$) and net flow ($RPA_{net} + LPA_{net} = Aorta_{net}$) at the aorta ($R = 0.94$). Post-stenting, the RPA and LPA net sum correlated with net flow at the MPA ($R = 0.93$) and at the aorta ($R = 0.90$).

Velocity mapping measurement of net flow after LPA stenting demonstrated that the net flow to the LPA increased ($P < .01$), whereas the net flow to the RPA decreased ($P < .01$) (Figure 3). The net flow at the level of the MPA also increased ($P < .01$). This reflected the decrease in pulmonary RF (Figure 4). The mean RF at the MPA at baseline was 38.7% (21.2–45.8) and decreased to 27.4% (11.3–38.8) after stenting of the LPA ($P = .002$). The branch RF at the level of the proximal RPA ($P = .30$) and LPA ($P = .28$) did not significantly change after LPA stenting.

MRI volumetric assessment was performed on the RV before and after intervention. The RV to left ventricle

(LV) volume ratio at end diastole was 1.4 before stenting, and this did not change 1 week after LPA stenting (Figure 5). The RV EDV did not decrease significantly 1 week after LPA stenting. However, the RV ESV did decrease from a median of 44.9 (35.8–58.3) mL/m² to 39.3 (29.4–49) mL/m² ($P = .03$) (Table 2). The RV ejection fraction improved from 53.5% to 58.2% ($P < .01$). Improved pump function of the RV correlated with the increase in net flow through the MPA.

Finally, cardiac index was assessed by velocity mapping at the MPA and the aorta (Figure 6). The cardiac index improved in all 7 animals, from a median of 2.7 (1.7–3.4) L/min/m² at baseline to 3.5 (2.7–4.4) L/min/m² post-stenting ($P = .01$). To ensure that the increase in cardiac index was not due to an increased inotropic or stressed state, heart rate was compared at time of baseline and follow-up MRI scan. Median heart rate was 93 (74–143) beats/min at baseline and 98 (88–136) beats/min at the time of follow-up MRI scan ($P = .62$).

FIGURE 4. Pulmonary insufficiency before and after intervention. Pulmonary valve insufficiency was measured by velocity mapping at the MPA. Velocity mapping in one subject is shown before (A) and after (B) stenting. Forward flow is represented by the area under the curve *above* the baseline, and reverse flow is represented by the area under the curve *below* the baseline. In this subject, PI decreased after LPA stenting. For the group (C), the mean regurgitant fraction at baseline was 38.7%, and this decreased to 27.4% after LPA stenting ($P = .002$). *RF*, Regurgitant fraction.

FIGURE 5. Relative volumes of the RV and LV at end diastole. Structural MRI scan of the ventricles in short axis demonstrates RV enlargement as a result of volume-loading caused by pulmonary insufficiency. Mean RV:LV end-diastolic volume ratio was 1.4:1. RV, Right ventricle; LV, left ventricle.

DISCUSSION

Among adults with repaired TOF, there is a high prevalence of clinically significant PI. Although this can be well tolerated in the short term, long-standing PI causes RV dilatation and dysfunction.¹⁸ Common clinical practice has been to delay surgical pulmonary valve replacement until the onset of symptoms, signs of RV dilatation, or ventricular arrhythmias. This practice stems from the desire to avoid risks of repeated sternotomy, with the associated morbidities and mortality. In addition, it is recognized that implanted valves, in time, fail on the basis of restenosis and valve incompetence. Thus, even after valve replacement, many patients are left with significant PI. The timing for surgical pulmonary valve replacement remains controversial, because this patient population faces the prospect of multiple operations for pulmonary valve replacement.⁸

A significant number of adults and adolescents with repaired TOF have branch PA stenosis and unequal PBF, most commonly LPA stenosis with corresponding decreased left-sided perfusion, as the result of a combination of developmental anomalies and possibly as a consequence of the

FIGURE 6. Cardiac index measured by velocity mapping. Cardiac index was measured by velocity mapping at the ascending aorta. For all animal subjects, the cardiac index improved after LPA stenting. Mean cardiac index (dashed line) improved from 2.7 to 3.5 L/min/m² (*P* = .01).

surgical approach.^{13,14,19,20} It has been shown that patients with TOF and branch PA stenosis have significantly lower exercise tolerance than other patients with TOF.¹⁵ Exercise intolerance is thought to be due to the ventilation:perfusion mismatch that is seen in these patients.²¹ It has also been postulated that the presence of branch PA stenosis exacerbates PI.^{22,23} Ilbawi and colleagues¹⁶ reviewed the charts of 264 patients with TOF who had undergone catheterization after repair. They found that in the group of patients with moderate-to-severe PI and RV volume overload, both assessed by angiographic methods, branch stenosis was more common. However, the location, distribution, and severity of branch stenosis in these patients were unclear. In another study, Chaturvedi and colleagues²⁴ simulated acute unilateral branch pulmonary atresia in patients with repaired TOF and PI. By using conductance catheter measurement in the RV, they found that PI increased with sudden complete occlusion of a branch PA with a large-caliber balloon. Although this study supports the concept that impedance to antegrade arterial flow exacerbates PI, this does not resemble the clinical scenario of chronic branch pulmonary stenosis in the setting of PI. To our knowledge, the current report is the first study directly evaluating the effects of relief of branch PA stenosis on PI.

We have demonstrated that relief of unilateral branch PA stenosis alleviates PI in an animal model. Cardiac MRI was used to detect changes in RV function and volume after the intervention, because MRI has become the gold standard for RV volumetric analysis.²⁵⁻²⁷ In the current study, mean PI decreased from 38.2% to 27.4% without any intervention on the pulmonary valve itself. This is significant because intervention on branch PA stenosis may provide an opportunity to reduce PI in this challenging patient population. Further, stenting to relieve LPA stenosis is a durable intervention. Stenting of branch pulmonary stenosis has been performed for approximately two decades. Investigators reporting on the intermediate and long-term results have

TABLE 2. Volumetric analysis of the right ventricle before and after left pulmonary artery stent

	Pre-stent (range)	Post-stent (range)	<i>P</i> value
RV EDV (mL/m ²)	96.7 (75.2–122.8)	93.0 (66.8–111.7)	.23
RV ESV (mL/m ²)	44.9 (35.8–58.3)	39.3 (29.4–49)	.01
RV EF (%)	53.5 (47.9–63.4)	58.2 (53.5–61.7)	<.01
RV EDV:LV EDV	1.40 (0.95–1.75)	1.41 (0.89–1.98)	.22
Cardiac index (L/min/m ²)	2.7 (1.7–3.4)	3.5 (2.6–4.4)	.01
Heart rate (beats/min)	93 (74–143)	98 (88–136)	.62

RV, Right ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction.

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shown that stenting is highly effective at durable resolution of branch PA stenosis.²⁸⁻³¹ Thus, although relief of LPA stenosis obviously does not abolish PI, its positive benefits in alleviating PI may be long-lasting. Reduction in PI in this study was associated with increased net flow to the left lung and volume unloading of the RPA. The RV systolic function improved, as indicated by increased ejection fractions. Velocity mapping at the aorta demonstrated an improvement in cardiac index after stenting. The results of this study underscore the importance of continued surveillance and treatment of postoperative branch PA stenosis in patients with TOF. Interventional catheterization in this setting serves an important complementary role to surgical repair by mitigating PI.

Studies in humans with PI have demonstrated that pulmonary valve replacement is associated with a decrease in RV EDV and a decrease in RV EDV:LV EDV ratio. In these studies, follow-up imaging obtained at 6 or 12 months after intervention demonstrates lower RV EDV with no change in RV stroke volume or RV ESV. In the current study, although there was a trend toward lower RV EDV, this decrease was not statistically significant. Although there was no significant change in RV EDV:LV EDV ratio, the repeat evaluation in the current study occurred at 1 week after LPA stenting. Short follow-up time may have limited the ability to detect decreases in RV EDV. RV ejection fraction improved from 53% to 58% in the short follow-up period. This increased systolic performance of the RV may well reflect the increased cross-sectional diameter available for antegrade flow.

The contribution of PI to RV systolic function is complex and has been incompletely explained. Our study, however, demonstrates that RV systolic function can respond, and improve, quickly after relieving branch pulmonary arterial obstruction and thereby reducing PI.

LIMITATIONS

This study used an animal model of PI with unilateral branch pulmonary stenosis. This model was not a true anatomic model of repaired TOF. In addition, the number of animals was relatively small. Finally, the follow-up MRI scans were performed only 1 week after intervention because of protocol constraints. Studies evaluating the long-term effects of LPA stenting on PI and ventricular function are warranted. How these findings relate to human patients born with congenital heart disease is uncertain. Corollary human studies measuring PI and RV function before and after intervention on branch PA stenosis are warranted.

CONCLUSIONS

Relief of unilateral branch PA stenosis reduces PI in this animal model. The improvement in antegrade flow through the MPA after relief of branch stenosis corresponds to improve-

ment in RV systolic performance and cardiac index. Stenting offers the potential to alleviate PI in patients with incompetent pulmonary valves and unilateral branch pulmonary stenosis. In patients with PI, stenting should be strongly considered as a means of nonsurgical palliation. The relationship between alleviation of PI and improved ventricular function remains incompletely explained, and further investigation is warranted.

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