Published in final edited form as:

Catheter Cardiovasc Interv. 2013 April ; 81(5): 888–895. doi:10.1002/ccd.24458.

Impact of Differential Right-to-Left Shunting on Systemic Perfusion in Pulmonary Arterial Hypertension

Timo Weimar, MD, Yoshiyuki Watanabe, MD, Toshinobu Kazui, MD, Urvi S. Lee, PhD, Alessandro Montecalvo, MD, Richard B. Schuessler, PhD, and Marc R. Moon, MD
Division of Cardiothoracic Surgery, Washington University School of Medicine, Barnes-Jewish Hospital, St. Louis, Missouri

Abstract

Objectives—This study aimed at identifying the ideal right-to-left shunt-fraction to improve cardiac output (CO) and systemic perfusion in pulmonary arterial hypertension (PHT).

Background—Atrial septostomy has been a high-risk therapeutical option for symptomatic drug-refractory patients with PHT. Results have been unpredictable due to limited knowledge of the optimal shunt-quantity.

Methods—In 9 dogs, an 8-mm shunt-prosthesis was inserted between the superior vena cava (SVC) and the left atrium. With pulmonary artery banding, mean ($\pm$ SEM) systolic right ventricular pressure increased from 37 ± 1 mmHg at baseline to 44 ± 1 mmHg (moderate PHT, $P=0.005$) and 50 ± 2 mmHg (severe PHT, $P<0.001$). Shunt-flow was adjusted by total (forcing all flow through the shunt) or partial occlusion of the SVC and partial or total clamping of the shunt. Caval-, shunt- and aortic-flow were measured by ultrasonic flow-probes. Blood gases were drawn from the aortic root and pulmonary artery.

Results—At severe PHT, a shunt-flow of $11\pm 1\%$ of CO (253 ± 90 mL/min) increased CO significantly by 25% (1.8 ± 0.1 to 2.4 ± 0.2 L/min, $P=0.005$) causing an increase of systemic oxygen delivery index (DO_2I) by 23% (309 ± 23 to 399 ± 32 mL/min/ M^2 , $P=0.035$). Arterial O_2 -saturation did not change significantly until a shunt-flow of $18\pm 2\%$ was exceeded, causing a drop from $96\pm 1\%$ to $84\pm 4\%$ ($P=0.013$). At moderate PHT, CO or DO_2I did not improve significantly at any shunt-flow.

Conclusions—In severe PHT, a shunt-flow of 11% of CO represented the ideal shunt-fraction. Augmentation of CO compensated for declined O_2 -saturation due to right-to-left shunting and improved DO_2I . In moderate PHT, atrial septostomy is less promising.

Keywords

Atrial Septostomy; Shunt; Cardiac Output; Oxygen Delivery

Introduction

Beyond medical therapy consisting mainly of prostacyclin analogues and PDE-5 inhibitors, atrial septostomy (AS) has been employed as a high-risk therapeutic option in symptomatic,

Corresponding Author: Marc R. Moon, MD, Division of Cardiothoracic Surgery, Washington University School of Medicine, Barnes-Jewish Hospital, Suite 3108 Queeny Tower, 1 Barnes-Jewish Hospital Plaza, St. Louis, MO 63110, Telephone: (314) 362-0993, Fax: (314) 747-0917, moonm@wudosis.wustl.edu.

Disclosures

The authors have nothing to disclose.

drug-refractory patients with pulmonary hypertension [1–13]. However, the precise role of AS in the treatment of pulmonary hypertension remains uncertain because only small series have been reported. Results are still unpredictable due to the fine balance that likely exists between amelioration of right ventricle pressure (RVP) overload, increased cardiac output, augmented systemic oxygen delivery, and inevitable arterial desaturation. While symptoms of right ventricular failure seem to improve immediately after AS, early reports from Sandoval and colleagues noted a median survival of only 19.5 months after the intervention [14,15]. Over the last decade, results have improved but remain modest with a 5-year survival of less than 50% following AS in patients with a mean age of only 35 years [11,16]. A better understanding of the appropriate shunt quantity seems crucial to improve cardiac performance and augment systemic perfusion while avoiding critical levels of desaturation with falling systemic oxygen delivery [17].

Our laboratory previously demonstrate that low-flow right-to-left shunting (15% of cardiac output) consistently improved right atrial mechanics and systemic perfusion in dogs with chronic pulmonary arterial hypertension (PHT), while high-flow shunting (29% of cardiac output) clearly exceeded the ideal with a drop of oxygen delivery below baseline [18]. However, the model did not allow for the differential determination of the optimal shunt fraction based on the degree of RV pressure overload with regards to hemodynamic performance and oxygen delivery. The purpose of the present experimental study was to identify the ideal right-to-left shunt fraction in relation to cardiac output that would generate optimum systemic perfusion in two different severities of PHT in an acute dog model.

Methods

Nine adult mongrel dogs of either sex weighing 20 – 23 kg were used in this study. All animals received humane care in compliance with the “Guide for the care and use of laboratory animals” published by the National Institutes of Health (NIH publication no. 85-23, revised 1985). The study was approved by the Washington University School of Medicine Animal Studies Committee and conducted according to Washington University policy.

Controlled Surgical Model of Atrial Septostomy

Animals were anaesthetized with propofol (5 –7 mg/kg, iv), intubated and ventilated with supplemental inhalational 2% to 4% isoflurane using a standard protocol as previously described by our laboratory [18–20]. Pulse oximetry, surface electrocardiogram (ECG), and arterial blood gases were monitored throughout the experiment. A median sternotomy was performed to access the heart. The animals were heparinized (100 U/kg, iv) and the activated clotting time was maintained at greater than 250 seconds throughout the study. Two 7-Fr pressure catheter (MPC-500, Millar Instruments, Houston, TX) were zeroed in a 37 °C water bath for 30 minutes and inserted into the right ventricle and the ascending aorta to measure right ventricular pressure (RVP) and central arterial pressure. Ultrasonic flow probes (8 to 14 mm perivascular probes with a T402 Flowmeter; Transonic Systems, Ithaca, NY) were placed around the superior (SVC) and inferior vena cava (IVC) approximately 0.5 cm from the caval-atrial junction to obtain accurate measurement of right atrial (RA) inflow as well as around the ascending aorta to determine cardiac output (CO). A tourniquet was placed around the SVC to allow for transient superior caval occlusion. Through purse string sutures in the SVC (cranial to the tourniquet) and at the left atrial (LA) wall at its junction with the right superior pulmonary vein, a custom-made composite metallic shunt with 8-mm tubing was implanted to allow diversion of RA inflow from the SVC to the LA. To measure continuous flow through the shunt, a custom-made ultrasonic flow-probe (Transonic Systems, Ithaca, NY) was calibrated specifically for this setting and placed around the shunt tubing. An inflatable silastic band (16-mm diameter, Access Technologies, Skokie, IL) was

placed and secured around the distal main pulmonary artery (PA) to allow for continuous PA-banding by injecting saline into the band and thus narrowing the diameter.

Data Acquisition

After determining baseline systolic RVP, two states of PHT were created by pulmonary banding: 1) “Severe PHT” was defined as the maximum RVP that was hemodynamically tolerated (i.e., a drop of systemic systolic pressure 80 mmHg but not lower), and 2) “Moderate PHT” was defined as the approximate midpoint between baseline systolic RVP and maximum RVP during severe PHT for each animal.

To create five different shunt fractions (at each level of PHT), data were obtained during 1.) SVC open and shunt totally clamped (No-Shunt), 2.) SVC totally occluded by the tourniquet and shunt open, thereby forcing all SVC flow through the shunt (Maximum-Shunt), 3.) SVC partially occluded and shunt open (High-Shunt), 4.) SVC open and shunt open (Medium-Shunt), and 5.) SVC open and shunt partially clamped (Low-Shunt) during moderate and severe PHT. The order of data acquisition for the five different levels of atrial shunting was randomized to avoid time-related interference with cardiac performance during PHT. During each data-acquisition run, aortic pressure, RVP, SVC flow, IVC flow, aortic flow, and shunt flow were recorded. After steady state of five minutes, blood gases were drawn and analyzed from the pulmonary artery and the aortic root for each hemodynamic state. At the conclusion of the study, the animals were euthanized using pentothal sodium (1 g iv) followed by potassium chloride (80 meq iv).

Data Analysis

To calculate the body surface area (BSA) for dogs, the following equation was used: $BSA = (K_m \cdot BW^{0.67}) / 100 [M^2]$, where the constant, K_m , for dogs is 10.1 and body weight (BW) is measured in kg. Parameters obtained by mixed venous and arterial blood gas analyses were used to calculate the following contents and indices:

$$\begin{aligned} \text{Arterial Oxygen Content (CaO}_2\text{)} &= (\text{Hb} \cdot 1.34 \cdot \text{SaO}_2) + (0.0031 \cdot \text{PaO}_2) \text{ [mL/dL]} \\ \text{Mixed Venous Oxygen Content (CvO}_2\text{)} &= (\text{Hb} \cdot 1.34 \cdot \text{SvO}_2) + (0.0031 \cdot \text{PvO}_2) \text{ [mL/dL]} \\ \text{Systemic Oxygen Delivery Index (DO}_2\text{I)} &= \text{CaO}_2 \cdot \text{CI} \cdot 10 \text{ [mL/ min /M}^2\text{]} \\ \text{Systemic Oxygen Uptake Index (VO}_2\text{I)} &= (\text{CaO}_2 - \text{CvO}_2) \cdot \text{CI} \cdot 10 \text{ [mL/ min /M}^2\text{]} \\ \text{Systemic Oxygen Extraction Index (O}_2\text{EI)} &= ((\text{SaO}_2 - \text{SvO}_2) / \text{SaO}_2) \cdot 100 \text{ [\%]} \end{aligned}$$

where Hb is hemoglobin, SaO_2 is arterial O_2 -saturation, PaO_2 is the partial pressure of oxygen in the arterial blood, SvO_2 is mixed venous O_2 -saturation, PvO_2 is the partial pressure of oxygen in the mixed venous blood, CI is Cardiac index calculated as cardiac output divided by BSA.

Statistical Analysis

All data are reported as mean $\pm$ SEM. Categorical data were expressed as absolute numbers and proportions. Comparisons were made with the unpaired t-test. Data recorded from the different hemodynamic phases (No-Shunt, Low-Shunt, Medium-Shunt, High-Shunt, Maximum-Shunt for moderate and severe PHT, respectively) were compared using repeated-measures ANOVA. All statistical analyses were performed using Systat v13 (Systat Software, Inc., Chicago, IL).

Results

Hemodynamics

With pulmonary artery banding, systolic RVP was elevated significantly from 37 ± 1 mmHg at baseline ($42 \pm 2\%$ of systemic pressure) to 44 ± 1 mmHg ($60 \pm 3\%$ of systemic pressure) during moderate PHT ($P = 0.005$) and to 50 ± 2 mmHg ($68\% \pm 2\%$ of systemic pressure) during severe PHT ($P < 0.001$). There were also significant falls in CO and cardiac index (CI) from 2.9 ± 0.2 L/Min and 3.8 ± 0.2 L/min/M² to 1.8 ± 0.1 L/min and 2.3 ± 0.1 L/min/M² in severe PHT, respectively ($P < 0.001$, respectively) and to 1.8 ± 0.2 L/min and 2.4 ± 0.2 L/min/M² in moderate PHT, respectively ($P < 0.001$, respectively. Table 1).

Severe PHT—Figure 1 illustrates the changes in CO during the five shunt fraction states in severe PHT. Shunt flows were $8 \pm 1\%$ of CO (170 ± 20 mL/min) during Low-Shunt, $11 \pm 1\%$ (250 ± 30 mL/min) during Medium-Shunt, $18 \pm 2\%$ (370 ± 40 mL/min) during High-Shunt, and $28 \pm 3\%$ (540 ± 40 mL/min) of CO during Maximum-Shunt. Both CO and CI improved significantly by 25% at Medium-Shunt compared to No-Shunt state (No-Shunt CO: 1.8 ± 0.1 L/min, Medium-Shunt CO: 2.4 ± 0.2 L/min, $P = 0.005$; No-Shunt CI: 2.3 ± 0.1 L/min/M², Medium-Shunt CI: 3.1 ± 0.2 L/min/M², $P = 0.009$). However, when exceeding Medium-Shunt levels, CO and CI fell continuously back to No-Shunt values (Table 2).

Moderate PHT—Shunt flows were $8 \pm 1\%$ of CO (140 ± 20 mL/min) during Low-Shunt, $12 \pm 1\%$ (240 ± 30 mL/min) during Medium-Shunt, $21 \pm 2\%$ (410 ± 50 mL/min) during High-Shunt, and $26 \pm 3\%$ (520 ± 70 mL/min) of CO during Maximum-Shunt which were similar to the shunt fractions obtained during severe PHT ($P > 0.30$ at all degrees of shunting). There was a trend to an increase in CO and CI peaking also at the Medium-Shunt level of 12%; however, those changes were not significant at moderate PHT (Table 3).

Systemic Perfusion and Oxygen Behavior

Severe PHT—Systemic oxygen delivery reflected by DO₂I declined significantly by 45% after pulmonary banding compared to baseline (No PHT) (559 ± 37 mL/min/M² to 308 ± 23 mL/min/M², $P < 0.001$). Figure 2 illustrates the changes in systemic DO₂I for the different hemodynamic states in severe PHT. With the Medium-Shunt fraction of 11% of CO, systemic DO₂I increased significantly by 23% from 309 ± 23 mL/min/M² to 399 ± 32 mL/min/M² when compared to No-Shunt state ($P = 0.035$). When exceeding a shunt fraction of 11% of CO, DO₂I declined again and even reached a level below No-Shunt state when approaching the Maximum-Shunt fraction of 28% of CO (291 ± 27 mL/min/M², Table 2). The systemic oxygen uptake reflected by VO₂I was reduced as well by 42% in severe PHT when compared to baseline (No PHT) ($P = 0.008$, Table 1). A shunt fraction of 8%, 11% and 18% of CO all increased VO₂I. However, improvement peaked with a shunt fraction of 11%, at which VO₂I could be significantly increased by 33% from 121 ± 15 mL/min/M² to 180 ± 9 mL/min/M² ($P = 0.005$, Figure 2). With higher shunt fractions, VO₂I declined continuously back to No-Shunt level. Systemic oxygen extraction reflected by O₂EI did not significantly change with pulmonary artery banding and was not influenced by different shunt fractions either. SaO₂ did not change significantly until a shunt flow of 18% of CO was exceeded, causing a drop from $96\% \pm 1\%$ to $84\% \pm 4\%$ ($P = 0.013$), which reflects increasing desaturation with increasing right-to-left shunt (Figure 3).

Moderate PHT—Although DO₂I and VO₂I decreased as well significantly by 46% ($P < 0.001$) and 30% ($P = 0.037$), respectively, with pulmonary banding, both parameters did not improve significantly at any shunt fraction in moderate PHT (Table 1 and 3). However,

SaO₂ declined significantly after exceeding a shunt fraction of 21% of CO, causing a drop from 94% ± 2% to 82% ± 4%, $P = 0.022$; Table 3).

Discussion

Idiopathic pulmonary hypertension is characterized by a progressive elevation of pulmonary artery pressure that is followed by right ventricular failure, declined cardiac output, decreased systemic oxygen transport, and ultimately death [21]. Even with aggressive medical approaches survival in those patients is only approximately 63% at 3 years [22,23]. Patients with PHT and a patent foramen ovale who were awaiting transplantation were observed to have a survival advantage over those without such a defect [24,25]. For patients with Eisenmenger syndrome, yielding an anatomic right-to-left shunt, a better prognosis was reported as well [26]. Atrial septostomy was first reported in 1983 for PHT [27] in an attempt to provide similar benefits in selected patients with recurrent syncope or significant right heart failure refractory to medical therapy [4,28–30]. Reported beneficial effects included prolonged survival with deferral of transplantation, a reduction of symptoms and an improved quality of life by increasing left ventricular preload, preserving systemic output and improving systemic perfusion and oxygen delivery [1,3,4,6,14,27,30,31]. However, if the interatrial communication is oversized, massive right-to-left shunting may result in inadequate pulmonary blood flow, severe hypoxemia and possibly left ventricular failure [17]. This fine balance that likely exists between intended improvement of hemodynamics and desaturation may account for the high risk that is associated with atrial septostomy. Morbidity and mortality occurred more frequently with the initially applied blade balloon septostomy, which was similar to the Rushkind procedure. The uncontrolled shunt was immediately life threatening and most likely explained the unacceptable high intra- and post procedural mortality rate of up to 30% [1,2,6]. Although results improved with the introduction of controlled balloon dilatation and new recommendations with regards to the indication and time of intervention, they are still far from being satisfactory [3,4,6,11,16,32,33].

Limited studies exist addressing the appropriate degree of shunting that should be produced for different levels of PHT [18,34–37]. In 1964, Austen and associates found improved hemodynamics and exercise capacity after right-to-left shunting in dogs, but their model could not control or quantify the shunt fraction [34]. Kawaguchi and colleagues reported improved systemic oxygen uptake following interatrial shunting in rats with PHT, but again, the degree of shunting could not be quantified [36]. Our group previously demonstrated in dogs with chronic PHT that low-flow shunting (15% of CO) could improve RA compliance and cardiac output while high-flow shunting (29% of CO) reversed those beneficial effects [18]. However, although this controlled shunt model could quantify the shunt flow, it could not determine the cross-over point that identifies the shift from the ideal to excess shunting.

In the present study, a shunt fraction of 11% of CO significantly improved cardiac output by 25% in severe PHT. The increase in stretch of cardiac muscular fibers (increased left ventricular preload) caused by shunting improved contractility, according to the Frank-Starling mechanism. However, augmentation of contractile force likely occurred at the expense of increased myocardial oxygen consumption. This becomes important if shunt fractions are increased beyond the ideal. When arterial desaturation, caused by an oversized shunt, becomes critical, oxygen delivery decreases, limiting left ventricular myocardial oxygen supply. This balance between CO and oxygen delivery was consistent with the findings of the current experiment. Increased CO compensated for arterial desaturation, caused by right-to-left shunting. Both CO and oxygen delivery reached their optimum ($P = 0.005$ and $P = 0.035$, respectively) at the identical shunt-fraction of 11%. In addition, our findings of an increase in oxygen delivery (DO₂I) resulting in an increase in oxygen

consumption (VO_2I) indicates that oxygen demand was not previously being met in PHT, because otherwise, a plateauing VO_2I would have been expected. This reflects and emphasizes the importance of oxygen behavior in PHT. At the point where DO_2I no longer meets oxygen demand (i.e. caused by decline in CO), oxygen consumption becomes supply dependent, but oxygen supply is critical in patients with PHT, leading to a vicious circle. Importantly, these findings were only present when PHT was severe. When right ventricular pressure was only mildly elevated, there were no beneficial effects from right-to-left shunting. Thus, the current report suggests that atrial septostomy is indicated only as a palliative treatment for drug-refractory severe, not moderate, PHT that results in limited pulmonary flow followed by insufficient left ventricular filling and systemic output.

Potential Limitations

The goal of the present experimental study was to identify the ideal right-to-left shunt fraction that would generate optimum systemic perfusion in two different severities of PHT. To achieve a controlled model of two different degrees of PHT, we chose to elevate right ventricular pressure in the acute setting. Although the present findings might not be directly transferable to the clinical setting of slowly developing chronic PHT, the focus of this investigation was on the changes of peripheral perfusion and oxygen behavior with differing right-to-left shunt fractions rather than long-term alterations of right atrial and ventricular function. This model was felt to be most suitable to identify the optimal shunt fraction in both moderate *and* severe PHT. However, our data is consistent with our earlier reports using a chronic model of PHT with regard to improved mechanical properties of the right atrium and the right ventricle as well as oxygen delivery at a shunt fraction of about 15% [18]. The data were very consistent through all our animals and provide a valid basic concept to corroborate these findings in chronic models of severe PHT. Mid- and long-term changes in mechanical properties following altered loading conditions for the right and left ventricle after implementing a shunt might change under these conditions and are rather difficult to predict. Moreover, this might change the shunt fraction itself over time. Adjustable devices, as recently introduced for annuloplasty in mitral valve surgery, that can change their diameter by induction applied from the body's surface and thus increase and decrease the shunt fraction dependent on the actual development of hemodynamic conditions might be able to cope with this problem in the future. We therefore considered using an intracardial adjustable device to create an interatrial shunt that may have been more similar to the clinical application of atrial septostomy; however, such devices are limited in the capacity to facilitate direct and accurate measurements or to alter the degree of shunting in a magnitude as needed for this study [13,17]. Finally, the valid calculation of peripheral perfusion with regard of oxygen delivery and consumption is highly dependent on, and influenced by, parameters such as hemoglobin and PaO_2 . Thus, changes in DO_2I and VO_2I could be caused rather by alterations in those parameters during the time-course of the study (i.e. by bleeding or adjustments in ventilation) than by the shunt-fraction. However, hemoglobin levels were not significantly different during varying hemodynamic states and ventilation settings were not changed during the experiment with no differences in PaO_2 before or after conclusion of the experiment. Furthermore, the applied model created a right-to-left shunt from SVC to LA, which might have caused different O_2 saturation levels than expected for a classical interatrial shunt due to a physiologically higher O_2 saturation in the IVC compared to SVC. Since our data suggest that the alteration of left ventricular loading condition is the main reason for benefits seen in oxygen delivery, the absolute value of right-sided saturation seems to be less relevant in identifying the optimal shunt fraction. This would rather result in an upward-shift of the oxygen delivery curve than in a sideward-shift of the shunt fraction.

Summary

In severe PHT, with a RVP of 68% of systemic arterial pressure, a right-to-left shunt fraction of 11% of CO represented the ideal shunt fraction. In this setting, augmentation of CO compensated for a decline in arterial O₂-saturation and was associated with a significant improvement of systemic oxygen delivery. Lower shunt fractions underachieved the ideal balance between hemodynamic improvement and observed desaturation and oxygen delivery. Higher shunt fractions exceeded optimal shunting and reversed the beneficial effects, often beyond baseline. In moderate PHT, right-to-left shunting did not significantly improve both hemodynamics or oxygen delivery and does not appear to be an appropriate treatment option in this setting. The present data suggest that atrial septostomy is most beneficial in severe PHT when it yields a shunt fraction of approximately 10 to 15% of cardiac output.

Acknowledgments

Grants

This study was funded by grants from the NIH National Heart, Lung and Blood Institute R01 HL92088, R01 HL085113, and T32 HL07776.

References

1. Kerstein D, Levy PS, Hsu DT, Hordof AJ, Gersony WM, Barst RJ. Blade balloon atrial septostomy in patients with severe primary pulmonary hypertension. *Circulation*. 1995; 91:2028–2035. [PubMed: 7534664]
2. Rich S, Dodin E, McLaughlin VV. Usefulness of atrial septostomy as a treatment for primary pulmonary hypertension and guidelines for its application. *Am J Cardiol*. 1997; 80:369–371. [PubMed: 9264443]
3. Reichenberger F, Pepke-Zaba J, McNeil K, Parameshwar J, Shapiro LM. Atrial septostomy in the treatment of severe pulmonary arterial hypertension. *Thorax*. 2003; 58:797–800. [PubMed: 12947142]
4. Doyle RL, McCrory D, Channick RN, Simonneau G, Conte J. Surgical treatments/interventions for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004; 126:63S–71S. [PubMed: 15249495]
5. Klepetko W, Mayer E, Sandoval J, Trulock EP, Vachiery JL, Darteville P, Pepke-Zaba J, Jamieson SW, Lang I, Corris P. Interventional and surgical modalities of treatment for pulmonary arterial hypertension. *J Am Coll Cardiol*. 2004; 43:73S–80S. [PubMed: 15194182]
6. Kurzyna M, Dabrowski M, Bielecki D, Fijalkowska A, Pruszczyk P, Opolski G, Burakowski J, Florczyk M, Tomkowski WZ, Wawrzynska L, Szturmowicz M, Torbicki A. Atrial septostomy in treatment of end-stage right heart failure in patients with pulmonary hypertension. *Chest*. 2007; 131:977–983. [PubMed: 17426198]
7. Law MA, Grifka RG, Mullins CE, Nihill MR. Atrial septostomy improves survival in select patients with pulmonary hypertension. *Am Heart J*. 2007; 153:779–784. [PubMed: 17452153]
8. O'Byrne ML, Rosenzweig ES, Barst RJ. The effect of atrial septostomy on the concentration of brain-type natriuretic peptide in patients with idiopathic pulmonary arterial hypertension. *Cardiol Young*. 2007; 17:557–559. [PubMed: 17868499]
9. Ciarka A, Vachiery JL, Houssière A, Gujic M, Stoupel E, Velez-Roa S, Naeije R, van de Borne P. Atrial septostomy decreases sympathetic overactivity in pulmonary arterial hypertension. *Chest*. 2007; 131:1831–1837. [PubMed: 17400672]
10. Barst RJ, Gibbs JS, Ghofrani HA, Hooper MM, McLaughlin VV, Rubin LJ, Sitbon O, Tapson VF, Galie N. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009; 54(1 Suppl):S78–84. [PubMed: 19555861]

11. Keogh AM, Mayer E, Benza RL, Corris P, Darteville PG, Frost AE, Kim NH, Lang IM, Pepke-Zaba J, Sandoval J. Interventional and surgical modalities of treatment in pulmonary hypertension. *J Am Coll Cardiol*. 2009; 54(1 Suppl):S67–77. [PubMed: 19555860]
12. Corris PA. Atrial septostomy and transplantation for patients with pulmonary arterial hypertension. *Semin Respir Crit Care Med*. 2009; 30:493–501. [PubMed: 19634088]
13. Lammers AE, Derrick G, Haworth SG, Bonhoeffer P, Yates R. Efficacy and long-term patency of fenestrated amplatzer devices in children. *Catheter Cardiovasc Interv*. 2007; 70:578–584. [PubMed: 17896406]
14. Sandoval J, Gaspar J, Pulido T, Bautista E, Martinez-Guerra ML, Zeballos M, Palomar A, Gomez A. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension. A therapeutic alternative for patients nonresponsive to vasodilator treatment. *J Am Coll Cardiol*. 1998; 32:297–304. [PubMed: 9708453]
15. Sandoval J, Rothman A, Pulido T. Atrial septostomy for pulmonary hypertension. *Clin Chest Med*. 2001; 22:547–560. [PubMed: 11590848]
16. Sandoval J, Gaspar J, Peña H, Santos LE, Córdova J, Del Valle K, Rodríguez A, Pulido T. Effect of Atrial Septostomy on the Survival of Patients with Severe Pulmonary Arterial Hypertension. *Eur Respir J*. 2011 Feb 24. [Epub ahead of print].
17. Baglini R, Scardulla C. Reduction of a previous atrial septostomy in a patient with end-stage pulmonary hypertension by a manually fenestrated device. *Cardiovasc Revasc Med*. 2010; 11:264.e9–264.e11. [PubMed: 20934666]
18. Zierer A, Melby SJ, Voeller RK, Moon MR. Interatrial shunt for chronic pulmonary hypertension: differential impact of low-flow vs. high-flow shunting. *Am J Physiol Heart Circ Physiol*. 2009; 296:H639–644. [PubMed: 19136607]
19. Gaynor SL, Maniar HS, Bloch JB, Steendijk P, Moon MR. Right atrial and ventricular adaptation to chronic right ventricular pressure overload. *Circulation*. 2005; 112(suppl I):I-212–I-218. [PubMed: 16159819]
20. Maniar HS, Prasad SM, Gaynor SL, Chu CM, Steendijk P, Moon MR. Impact of pericardial restraint on right atrial mechanics during acute right ventricular pressure load. *Am J Physiol Heart Circ Physiol*. 2003; 284:H350–357. [PubMed: 12388317]
21. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med*. 1991; 115:343–349. [PubMed: 1863023]
22. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation*. 2002; 106:1477–1482. [PubMed: 12234951]
23. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, Rainisio M, Simonneau G. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol*. 2002; 40:780–788. [PubMed: 12204511]
24. Glanville AR, Burke CM, Theodore J, Robin ED. Primary pulmonary hypertension. Length of survival in patients referred for heart-lung transplantation. *Chest*. 1987; 91:675–681. [PubMed: 3105966]
25. Rozkovec A, Montanes P, Oakley CM. Factors that influence the outcome of primary pulmonary hypertension. *Br Heart J*. 1986; 55:449–458. [PubMed: 3707785]
26. Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. *J Heart Lung Transplant*. 1996; 15:100–105. [PubMed: 8820089]
27. Rich S, Lam W. Atrial septostomy as palliative therapy for refractory primary pulmonary hypertension. *Am J Cardiol*. 1983; 51:1560–1561. [PubMed: 6189385]
28. Barst RJ. Role of atrial septostomy in the treatment of pulmonary vascular disease. *Thorax*. 2000; 55:95–96. [PubMed: 10639523]
29. Haworth SG. Pulmonary hypertension in the young. *Heart*. 2002; 88:658–664. [PubMed: 12433912]
30. Rothman A, Sklansky MS, Lucas VW, Kashani IA, Shaughnessy RD, Channick RN, Auger WR, Fedullo PF, Smith CM, Kriett JM, Jamieson SW. Atrial septostomy as a bridge to lung

- transplantation in patients with severe pulmonary hypertension. *Am J Cardiol.* 1999; 84:682–686. [PubMed: 10498139]
31. Thanopoulos BD, Georgakopoulos D, Tsaousis GS, Simeunovic S. Percutaneous balloon dilatation of the atrial septum: immediate and midterm results. *Heart.* 1996; 76:502–506. [PubMed: 9014798]
 32. Allcock RJ, O'Sullivan JJ, Corris PA. Palliation of systemic sclerosis-associated pulmonary hypertension by atrial septostomy. *Arthritis Rheum.* 2001; 44:1660–1662. [PubMed: 11465717]
 33. Allcock RJ, O'Sullivan JJ, Corris PA. Atrial septostomy for pulmonary arterial hypertension. *Heart.* 2003; 89:1344–1347. [PubMed: 14594898]
 34. Austen WG, Morrow AG, Berry WB. Experimental Studies of the Surgical Treatment of Primary Pulmonary Hypertension. *J Thorac Cardiovasc Surg.* 1964; 48:448–455. [PubMed: 14218643]
 35. Nihill MR, O'Laughlin MP, Mullins CE. Effects of atrial septostomy in patients with terminal cor pulmonale due to pulmonary vascular disease. *Cathet Cardiovasc Diagn.* 1991; 24:166–172. [PubMed: 1722434]
 36. Kawaguchi AT, Kawashima Y, Ishibashi-Ueda H, Yanase M, Murakami T, Yagihara T, Kunieda T. Right-to-left interatrial shunt in rats with progressive pulmonary hypertension. *J Thorac Cardiovasc Surg.* 1993; 106:1072–1080. [PubMed: 8246541]
 37. Diller GP, Lammers AE, Haworth SG, Dimopoulos K, Derrick G, Bonhoeffer P, Gatzoulis MA, Francis DP. A modelling study of atrial septostomy for pulmonary arterial hypertension, and its effect on the state of tissue oxygenation and systemic blood flow. *Cardiol Young.* 2010; 20:25–32. [PubMed: 20144254]

Cardiac Output for Severe Pulmonary Arterial Hypertension

Figure 1. Changes of cardiac output (CO) in severe pulmonary arterial hypertension (PHT_{max}, right ventricular pressure, 68% ± 2% of systemic systolic pressure) for different right-to-left shunt fractions as percent of cardiac output. Parameters are expressed as mean ± SEM.

DO₂I and VO₂I for Severe Pulmonary Arterial Hypertension

Figure 2. Changes of systemic oxygen delivery index (DO₂I) and systemic oxygen uptake index (VO₂I) in severe pulmonary arterial hypertension (PHT_{max}, right ventricular pressure of 68% ± 2% of systemic systolic pressure) for different right-to-left shunt fractions as percent of cardiac output. Parameters are expressed as mean ± SEM.

SaO₂ for Severe Pulmonary Arterial Hypertension

Figure 3.

Changes of arterial oxygen saturation (SaO₂) in severe pulmonary arterial hypertension (PHT_{max}, right ventricular pressure of 68% ± 2% of systemic systolic pressure) for different right-to-left shunt fractions as percent of cardiac output. Parameters are expressed as mean ± SEM.

Table 1

Hemodynamics and Systemic Oxygenation in Moderate and Severe Right Ventricular Outflow Obstruction.

Parameters	Baseline	No PHT	PHT moderate	P value	PHT severe	P value
Systemic systolic BP (mmHg)	90.9 ± 3.9	74.7 ± 4.1	0.011	72.6 ± 1.2	0.001	
Mean systemic BP (mmHg)	56.5 ± 4.5	42.4 ± 2.7	0.019	43.5 ± 1.4	0.021	
Systolic RVP (mmHg)	37.3 ± 1.4	43.7 ± 1.4	0.005	49.6 ± 1.6	<0.001	
Systolic RVP/systemic systolic BP (%)	41.5 ± 1.8	59.7 ± 3.4	<0.001	68.3 ± 2.1	<0.001	
Cardiac Output (L/min)	2.9 ± 0.2	1.8 ± 0.2	<0.001	1.8 ± 0.1	<0.001	
CI (L/min/M ²)	3.8 ± 0.2	2.4 ± 0.2	<0.001	2.3 ± 0.1	<0.001	
SaO ₂ (%)	98 ± 0	94 ± 2	0.070	96 ± 1	0.066	
PaO ₂ (mmHg)	169 ± 23	141 ± 36	0.522	130 ± 18	0.202	
Hb (g/dL)	10.9 ± 0.4	9.9 ± 0.3	0.068	10.0 ± 1.1	0.136	
CaO ₂ (mL/dL)	14.9 ± 0.6	12.9 ± 0.6	0.029	13.3 ± 0.6	0.093	
SvO ₂ (%)	63 ± 2	48 ± 2	<0.001	58 ± 5	0.409	
PvO ₂ (mmHg)	51.4 ± 2.3	43.5 ± 2.3	0.025	50.1 ± 5.1	0.829	
CvO ₂ (mL/dL)	9.3 ± 0.4	6.5 ± 0.3	<0.001	8.0 ± 0.9	0.220	
O ₂ EI (%)	36.2 ± 2.3	48.7 ± 2.2	0.001	40.2 ± 5.3	0.502	
DO ₂ I (mL/min/M ²)	559 ± 37	303 ± 28	<0.001	308 ± 23	<0.001	
VO ₂ I (mL/min/M ²)	210 ± 24	146 ± 11	0.037	121 ± 15	0.008	

Data are expressed as mean ± SEM. RVP, right ventricular pressure. PHT, pulmonary arterial Hypertension (moderate: RVP 60±3% of systemic pressure; severe: RVP 68±2% of systemic pressure). BP, blood pressure. CI, cardiac index. SaO₂, arterial O₂ saturation. PaO₂, partial arterial O₂ pressure. Hb, hemoglobin. CaO₂, arterial O₂ content. SvO₂, mixed venous O₂ saturation. PvO₂, partial mixed venous O₂ pressure. CvO₂, mixed venous O₂ content. O₂EI, systemic O₂ extraction index. DO₂I, systemic O₂ delivery index, VO₂I, systemic O₂ uptake index. *P*-values reflect comparison between PHT moderate vs. baseline and PHT severe vs. baseline, respectively.

Table 2
Hemodynamics and Systemic Oxygenation in Severe Right Ventricular Outflow Obstruction for different Right-to-Left Shunt Fractions.

Parameters	No-Shunt	PHT severe					
		Low (8%) [†] Shunt	P value	Medium (11%) [†] Shunt	P value	High (18%) [†] Shunt	P value
Cardiac Output (L/min)	1.8 ± 0.1	2.1 ± 0.2	0.126	2.4 ± 0.2	0.005	2.2 ± 0.2	0.083
SaO ₂ (%)	96 ± 1	93 ± 2	0.320	96 ± 1	0.862	91 ± 3	0.064
PaO ₂ (mmHg)	130 ± 18	102 ± 8	0.177	104 ± 10	0.236	86 ± 6	0.044
CaO ₂ (mL/dL)	13.3 ± 0.6	12.7 ± 1.0	0.601	12.9 ± 0.6	0.660	12.3 ± 0.7	0.289
SvO ₂ (%)	58 ± 5	52 ± 3	0.356	52 ± 3	0.368	52 ± 3	0.347
PvO ₂ (mmHg)	50.1 ± 5.1	44.2 ± 2.9	0.324	43.8 ± 3.1	0.306	43.4 ± 2.0	0.242
CvO ₂ (mL/dL)	8.0 ± 0.9	7.0 ± 0.6	0.370	6.9 ± 0.6	0.351	7.0 ± 0.5	0.385
O ₂ EI (%)	40.2 ± 5.3	44.6 ± 2.5	0.465	46.1 ± 3.1	0.351	42.8 ± 2.3	0.658
DO ₂ I (mL/min/M ²)	308.5 ± 23.2	341.6 ± 31.8	0.414	399.3 ± 31.6	0.035	348.1 ± 37.0	0.380
VO ₂ I (mL/min/M ²)	120.8 ± 15.1	149.2 ± 10.2	0.140	179.6 ± 8.5	0.005	147.9 ± 14.1	0.207

Data are expressed in mean ± SEM.

[†]Shunt fractions as % of cardiac output. PHT, pulmonary arterial hypertension (severe: right ventricular pressure 68±2% of systemic systolic pressure). SaO₂, arterial O₂ saturation. PaO₂, partial arterial O₂ pressure. CaO₂, arterial O₂ content. SvO₂, mixed venous O₂ saturation. PvO₂, partial mixed venous O₂ pressure. CvO₂, mixed venous O₂ content. O₂EI, systemic O₂ extraction index. DO₂I, systemic O₂ delivery index, VO₂I, systemic O₂ uptake index. P-values reflect comparison between the different shunt-fractions vs. No-Shunt state.

Table 3
Hemodynamics and Systemic Oxygenation in Moderate Right Ventricular Outflow Obstruction for different Right-to-Left Shunt Fractions.

Parameters	PHT moderate									
	No-Shunt	Low (8%) [†] Shunt	P value	Medium (12%) [†] Shunt	P value	High (21%) [†] Shunt	P value	Maximum (26%) [†] Shunt	P value	P value
Cardiac Output (L/min)	1.8 ± 0.2	1.8 ± 0.2	0.921	2.1 ± 0.3	0.418	2.0 ± 0.2	0.552	2.0 ± 0.2	0.514	
SaO ₂ (%)	94 ± 2	92 ± 2	0.555	89 ± 3	0.242	87 ± 4	0.105	82 ± 4	0.022	
PaO ₂ (mmHg)	141 ± 36	96 ± 12	0.261	101 ± 12	0.318	82 ± 5	0.140	68 ± 9	0.079	
CaO ₂ (mL/dL)	12.9 ± 0.6	11.2 ± 0.8	0.101	11.1 ± 0.9	0.125	10.7 ± 0.9	0.059	10.0 ± 0.9	0.019	
SvO ₂ (%)	48 ± 2	44 ± 4	0.389	47 ± 5	0.820	44 ± 4	0.400	44 ± 2	0.166	
PvO ₂ (mmHg)	43.5 ± 2.3	41.2 ± 3.0	0.561	42.5 ± 3.9	0.831	39.6 ± 3.0	0.316	39.0 ± 2.2	0.176	
CvO ₂ (mL/dL)	6.5 ± 0.3	5.3 ± 0.6	0.092	5.8 ± 0.8	0.446	5.5 ± 0.6	0.158	5.3 ± 0.5	0.049	
O ₂ EI (%)	48.7 ± 2.2	51.8 ± 4.3	0.522	47.8 ± 4.5	0.865	48.9 ± 4.2	0.958	46.8 ± 2.8	0.597	
DO ₂ I (mL/min/M ²)	303.2 ± 28.0	264.4 ± 35.4	0.403	310.6 ± 59.6	0.912	277.1 ± 42.5	0.616	256.9 ± 31.1	0.284	
VO ₂ I (mL/min/M ²)	146.3 ± 11.5	131.6 ± 14.5	0.441	134.9 ± 17.5	0.595	126.6 ± 14.4	0.301	119.0 ± 16.4	0.194	

Data are expressed in mean ± SEM.

[†]Shunt fractions as % of cardiac output. PHT, pulmonary arterial hypertension (moderate: right ventricular pressure of 60±3% of systemic systolic pressure). SaO₂, arterial O₂ saturation. PaO₂, partial arterial O₂ pressure. CaO₂, arterial O₂ content. SvO₂, mixed venous O₂ saturation. PvO₂, partial mixed venous O₂ pressure. CvO₂, mixed venous O₂ content. O₂EI, systemic O₂ extraction index. DO₂I, systemic O₂ delivery index, VO₂I, systemic O₂ uptake index. P-values reflect comparison between the different shunt-fractions vs. No-Shunt state.