Effects of a localized high-flow anastomosis between the aorta and left lower lobe pulmonary artery on great vessel flow and pulmonary arterial reactivity in the contralateral lung

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Objectives: We sought to assess the effects of a localized anastomosis between the aorta and left lower lobe pulmonary artery on flows through central vessels and on the vascular reactivity of small pulmonary arteries distal or contralateral to the shunt.

Methods: Flow rates in major vessels and tensions from small pulmonary arteries from the left and right lower lobes were determined 48 hours after creation of an end-to-side anastomosis of the left lower lobe pulmonary artery to the aorta.

Results: Anastomoses increased flow through the left lower lobe pulmonary artery from 194 ± 6 to 452 ± 18 mL/min immediately after anastomosis to 756 ± 19 mL/min by the time of harvest ($n = 88$, $P < .05$). Flow rates in main pulmonary arteries from hosts with anastomoses were lower (557 ± 26 vs 1033 ± 244 mL/min), whereas aortic root flows were not different from control values (1370 ± 53 vs 1120 ± 111 mL/min; $P = .07$). Wet/dry weights of both lungs and aortic flow rates were proportional to shunt flow rates. Pulmonary artery rings harvested from the right (unshunted) lobes of high-flow hosts exhibited increased reactivity to the thromboxane agonist U46619 and phenylephrine relative to those of left pulmonary arteries from the same animal or those of control hosts.

Conclusions: Our studies are the first to identify enhanced reactivity of pulmonary arteries in a lung contralateral to a localized high-output shunt between an aorta and pulmonary artery. These observations suggest that patients with localized systemic-to-pulmonary shunt could exhibit modified vascular tone in remote pulmonary arteries. (J Thorac Cardiovasc Surg 2011;141:407-12)

A localized high-flow shunt to the left lower lobe pulmonary artery from the aorta results in substantial increases in flow through the anastomosis over 48 hours and enhanced reactivity of pulmonary arteries contralateral to the shunt relative to ipsilateral or control pulmonary arteries.

Sustained high flow increases pulmonary arteriolar vasomotor activity within hours to days of exposure, presumably through a shift in the balance toward constrictor factors over compensatory relaxants, and ultimately yields vascular remodeling.¹⁻⁶ Very little is known about the subacute (>6 hours but <4 weeks) effects of systemic artery–pulmonary artery (PA) shunts on the relative reactivity of arteries distal to the anastomosis. We are not aware of any

studies of PA reactivity from the lung contralateral to a localized systemic artery–PA shunt. Systematic studies of the effects of a localized anastomosis on flow rates in the connected vessels immediately before and after the procedure, as well as on flow rates through the heart and great vessels of the chest, are similarly lacking.

We developed a model of high flow in an isolated lung lobe of young pigs characterized by neointimal lesions and medial thickening developing within 8 weeks of anastomosis of the left lower lobe artery to the aorta.⁷ We applied the same surgical intervention to characterize physiological changes brought about by high flow after 48 hours. Our first goal was to measure flow in shunted lobar arteries and great vessels to establish the size of the shunt and the effect on flows through the PAs, aortas, and right lung. Second, we measured reactivity of left and right lower lobe pulmonary arteries (LLPAs) in hosts with in vivo exposure to high-flow shunts.

MATERIALS AND METHODS

Materials used were U46619 (catalog no. PG-023; Biomol International, L.P., Plymouth Meeting, Pa) and Transonic Flow Probes (MB-Series Handle Style Catalog no. 3MB; Transonic systems, Inc, Ithaca, NY).

Surgical Anastomosis and Procedures

Weanling infant pigs of either sex 3 to 6 weeks of age and approximately 7 kg in weight underwent creation of an aorto–left LLPA anastomosis, as

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Abbreviations and Acronyms

LLPA = lower lobe pulmonary artery
PA = pulmonary artery

described in our previous publication.⁷ The surgical protocol and postoperative care were in compliance with the "Guide for the care and use of laboratory animals" published by the National Institutes of Health and approved by the Animal Studies Committee of the Zablocki Veterans Administration Hospital and the Medical College of Wisconsin. Sedation was achieved with acepromazine (1.5 mg/kg) and ketamine (30 mg/kg) administered intramuscularly and fentanyl (2 µg/kg) administered intravenously with an isoflurane gas mixture to achieve general anesthesia. Heart rate, end-tidal CO₂ and depth of sedation were monitored during the operation by a veterinarian to ensure hemodynamic stability and adequate pain control.

A left thoracotomy was performed through a midthoracic interspace. The left LLPA was separated posteriorly from the adjacent lower lobe bronchus. The descending PA was ligated just distal to the upper lobe branches and divided. The distal left LLPA was sewn end-to-side to the descending thoracic aorta. Blood loss was consistently less than 20 mL, and therefore no transfusions were required or administered. Intramuscular cefazolin (25 mg/kg) and furosemide (1 mg/kg) were administered postoperatively once to prevent infection and pulmonary edema, respectively.

Definition of 3 Study Groups and Flow Measurements

Measurements of flow through the shunt were obtained with 3-mm probes immediately before and after creation of the shunt, as well as at the time of harvest. For the purposes of these analyses, high flow was defined as flow rates through the anastomoses at harvest that were either twice those of the right LLPA at harvest or twice those of the left LLPA before anastomosis. In some animals flow data and tension measurements in PA rings were obtained without anastomosis; these subjects are referred to as control animals. Similarly, in some animals identified as low-flow control animals, low-flow shunts were deliberately created by narrowing the lumen of the anastomoses between the LLPAs. Harvest flows were less than one half that of the unshunted right or left LLPA before shunt creation in this low-flow group. Only measurements of weight and flow through the anastomotic left lower lobe artery at the time of harvest were obtained in every animal.

Flow Measurements at Harvest

Two days after the creation of the anastomoses, the pigs were sedated with intramuscular acepromazine and ketamine and then pentobarbital (5 mg/kg) to achieve general anesthesia. After intubation, a thoracotomy was performed, and flow probes were placed around the main (8 mm), left, and right PAs (3 mm), as well as the proximal aorta (8 mm), above the anastomoses for determination of flow rates. Pressure measurements in the anastomoses were attempted by positioning a needle connected to a transducer in the anastomosis. These results were highly position dependent, decreasing from systemic pressures at the opening of the anastomosis by greater than 30 mm Hg on advancing the needle 1 cm distally, and were therefore not pursued or reported.

Ring Tension Studies

After flow measurements were obtained, animals were killed by means of exsanguination after achievement of deep anesthesia. The heart and lungs were removed en bloc and transported on ice to the laboratory, where PAs 1 to 2 mm in diameter, 2 to 3 mm in length, and approximately 5 to 7 centimeters distal to the aortopulmonary shunt were microdissected free of adherent lung tissue for tension studies. Tension measurements were

obtained according to methods previously published by us.⁸ PAs were held in ice-cold physiological saline solution (NaCl, 130 mmol/L; CaCl₂, 2.5 mmol/L; NaHCO₃, 15 mmol/L; MgSO₄, 1.2 mmol/L; NaH₂PO₄, 1.2 mmol/L; KCl, 4.7 mmol/L; glucose, 5.5 mmol/L; N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid, 10 mmol/L; and ethylenediamine tetraacetic acid, 0.026 mmol/L, pH 7.4) after dissection until use, generally within 90 minutes. Some rings were denuded by gently scraping the inner endothelial lining with a blunt forcep, followed by rinsing the rings with physiological saline solution. Effective denuding was confirmed by the absence of relaxation to acetylcholine or carbachol.

Rings were mounted on tungsten wires, one connected to a fixed holder and the other to a force displacement transducer (Model FT03E; Grass Instruments Co, West Warwick, RI) for continuously measuring isometric tension. The apparatus was immersed in pH-adjusted, oxygenated physiological saline solution (95% O₂–5% CO₂) at 37°C. Tension data were relayed from transducers to a signal amplifier and acquired and analyzed with CODAS software (DataQ Instruments, Inc, Akron, Ohio). Rings were preloaded with 0.4 g of passive tension based on preliminary studies with PAs from shunted and unshunted lobes to maximize active tension development and then equilibrated for an additional 30 minutes before the studies began. The standard pulmonary vasoconstrictors U46619 (a thromboxane agonist) and phenylephrine were used to increase tension and evaluate the underlying vasoactive state of the PAs. Binding to plasma membrane thromboxane receptors increases inositol phosphate turnover, leading to enhanced activation of smooth muscle. Phenylephrine acts through α receptors to increase the intracellular calcium level, which increases myosin light chain phosphorylation. Viability of all rings was confirmed by measuring the contractile response to the addition of 80 mmol/L KCl in the bath at the end of the experiments. Data from rings that did not show an at least 2-fold increase in tension to KCl were eliminated from the analysis (<20% of those initially dissected and mounted for PAs from both the left and right lower lobes).

Histology and Wet/Dry Lung Weights

Distal sections of lungs from shunted and nonshunted lobes were immersion fixed in neutral formalin for 2 to 4 days, after which samples were embedded in paraffin, sectioned, and reacted with a Movat pentachrome stain.⁹ Digital images were captured at magnifications of 200× or 400× with SPOT Advanced image acquisition software on an inverted Nikon microscope. Randomly selected pieces of left and right lungs were obtained for determination of wet/dry lung weight ratios.⁷

Statistical Analyses

Experimental results for PA rings from the same lobe (typically 4–5 each from the left and right lobes) and the same test conditions (eg, a single dose of U46619 and vehicle pretreatment) were averaged for each "n" value. Hence the "n" values provided in the Results section represent individual animals rather than individual PA rings. Values are expressed as the means ± standard errors from 4 or more animals in each experiment. Least-squares regression analysis was performed to examine the relationship between shunt and aortic flow rates, as well as wet/dry lung weight ratios and shunt flow rates. Comparisons within each group (left vs right) and between control and treated animals were analyzed by means of 2-way repeated-measures analysis of variance, followed by post hoc tests when permitted. Values for paired studies (eg, left LLPA flows immediately before and after anastomoses or maximum contraction to KCl of left vs right LLPAs) were compared by using *t* tests.

RESULTS

Immediate Alterations in Flow by Surgical Anastomosis in High-Flow Subjects

Table 1 contains data regarding the weight and flow rates. In control pigs aortic and main PA flow rates were very

TABLE 1. Weight and aortic, left lower lobe, right lower lobe, and main pulmonary artery flow rates in control pigs, high-flow pigs before anastomosis, high-flow pigs immediately after anastomosis and at harvest, and low-flow pigs at harvest

	Weight (kg)	Aortic flow (mL/min)	LLL flow (mL/min)	RLL flow (mL/min)	Main PA flow (mL/min)
Control pigs (n = 7)	6.5 ± 0.3	1120 ± 111	223 ± 57	207 ± 51	1033 ± 244
High-flow pigs before anastomosis (n = 88)	7.0 ± 0.1		194 ± 6		
High-flow pigs after anastomosis (n = 88)			452 ± 18; <i>P</i> < .001 compared with values before anastomosis and different from control		
High-flow pigs at harvest 48 h after anastomosis		1371 ± 53 (n = 29)	756 ± 19 (n = 88), † <i>P</i> < .01 compared with before and after anastomosis	270 ± 8 (n = 88)	557 ± 26 (n = 29)*
Low-flow pigs at harvest 48 h after anastomosis (n = 9)	7.1 ± 0.18		82 ± 38	380 ± 27*	

Heart rates (mean, 160–170 beats/min), oxygen saturations (96% to 98%), and end-tidal CO₂ values (32–39 mm Hg) during surgical intervention for lung harvest were not different between study groups. Values are presented as means ± standard errors of the mean. **P* value relative to control. †*P* value before and after anastomosis.

similar. Also, flow rates through the left and right LLPAs were not different. In 88 pigs that met the criteria for high flow at the time of lung harvest (48 hours after anastomosis), flow rates through the left LLPA before anastomoses were 194 mL/min. Immediately after the end-to-side anastomosis to the aorta, flows increased to 452 mL/min, which was more than double the baseline value (*P* < .001) and increased over that of left LLPAs in control pigs (223 mL/min, n = 7 control animals, *P* < .005, Table 1).

Harvest Flow Rates in High-Flow Subjects

Forty-eight hours after creation of high-flow anastomoses, the flow in the shunted left LLPA had increased to a mean of 756 mL/min compared with a flow of 270 mL/min in the unoperated right PAs and 452 mL/min immediately after creation of the anastomosis in left LLPAs (both *P* < .001). Therefore the flow through the surgically created shunts increased 1.7-fold over the 2 days between formation of the anastomosis and harvest in high-flow animals.

In the high-flow hosts right LLPA flows at harvest (270 mL/min) were not different from those of the right

lower lobe in control animals. Proximal aortic flow rates in high-flow animals were not different than aortic flows in the control hosts (*P* = .07).

Harvest Flow Rates in Low-Flow Subjects

In 9 pigs that met the criteria for low flow, left PA flow at the time of harvest was 82 ± 38 mL/min compared with 380 ± 27 mL/min in the right LLPA (*P* < .001, Table 1). Low flow was attempted in several additional animals but not achieved because flows at the time of harvest had increased beyond the above-defined thresholds; these animals were eliminated from analysis. Flow rates through the right LLPAs were higher in low-flow than in high-flow animals (Table 1).

Correlation of Flow Rates in the Left Lower Lobe

In all shunted subjects (high and low flow), flow through the shunted left LLPA was directly correlated to cardiac output, as estimated by aortic flow. These data appear in Figure 1, A. The wet/dry weight ratios of lung tissue in

FIGURE 1. A, Aortic flow rates in milliliters per minute as a function of flow rates through the anastomosed left lower lobe pulmonary artery 48 hours after creation of the shunt in 35 pigs. The regression line shows the least-squares fit for these data points, with an *r*² value of 0.60. B, Flow rates through the left or right lower lobe pulmonary artery at the time of harvest are plotted as a function of wet/dry weight ratios of peripheral lungs in 38 samples. The least-squares regression line has an *r*² value of 0.56.

paired samples from right and left lungs from 19 randomly selected high-flow hosts were obtained and appear in Figure 1, B. Wet/dry weight ratios were modestly higher in the shunted lobe compared with those in control lungs (left, 5.83 ± 0.33 ; right, 5.28 ± 0.16 ; $n = 19$ animals; $P < .001$), indicating there was a mild increase in edema, hemorrhage, or both in shunted lobes. There was a positive correlation between the flow rate in the left lower lobe and the wet/dry weight ratios in all hosts (Figure 1, B).

Contractility to U46619 and Phenylephrine Is Higher in Unshunted Than Shunted PAs

Isolated PA rings from the shunted (left) and unshunted (right) lobes, as well as those from control hosts, were tested for reactivity. There was a concentration-dependent increase in tension in all the rings to the thromboxane mimetic U46619 (10^{-10} to 10^{-7} mol/L), as shown in Figure 2. In control hosts there was no difference in reactivity of left and right PAs to U46619 (Figure 2, A). In contrast, PAs from the unshunted right lower lobes of high-flow hosts 48 hours after anastomosis exhibited significantly higher tension to the same concentrations of U46619 as rings from the left lower lobe ($n = 24$; Figure 2, B). Similarly, increased tension to phenylephrine (10^{-8} to 10^{-5} mol/L) in PA rings derived from unshunted right lower lobes compared with those derived from left lower lobes was observed (Figure 2, C).

In contrast to results from high-flow hosts, unshunted right LLPAs from low-flow animals had less tension than PAs from the same hosts harvested from the left lower lobe (Figure 2, D), as well as less than that of control right LLPAs. The tension to U46619 was similar in left LLPAs regardless of whether they derived from high- or low-flow pigs or from control hosts. These data support an effect on tension development in unshunted PAs in this model (Figure 2, E and F).

Denuding Endothelium Eliminates the Difference in U46619 Contractility Between Left and Right PAs

PAs from high-flow hosts denuded of endothelium were equally responsive to U46619 when comparing the left and right lower lobes ($P > .2$, $n = 4$ each in left and right lobes), suggesting that an endothelially derived factor contributes to the increase in contractility of PAs from non-shunted lobes.

High Flow Does Not Alter Depolarization-induced Contraction of the PAs to High Potassium

Rings were constricted with 80 mmol/L KCl to examine nonreceptor or endothelially independent contraction. Contraction to KCl was identical in left and right PAs from lungs exposed to high flow ($n = 34$, $P = .326$). Similarly, contractility of left and right PAs to KCl in control hosts was identical to that of shunted hosts.

High Flow Causes Limited Histologic Changes to Lungs 48 Hours After Anastomoses

There were no differences in the histologic appearance of lungs from control, high-flow, or low-flow animals. Lung sections from both left and right lungs stained with hematoxylin and eosin showed scattered perivascular edema. No vascular occlusions or neointimal hyperplasia characteristic of established pulmonary hypertension,^{3,10} as develops in this model 8 weeks after shunt creation,⁷ were observed. Pleuritis, which is commonly associated with surgical intervention, along the outer surfaces of the lung was observed in many samples from high- and low-flow hosts.

DISCUSSION

To our knowledge, our data are the first to report quantitative flow measurements at the level of the aorta, main PA, and left and right LLPAs 48 hours after creation of an aortopulmonary anastomosis, which substantially increased flow to the left LLPA. Although it is well recognized that sustained exposure to high-pressure/flow shunts in the lung *in vivo* produces characteristic vasculopathic changes,^{2,3,11} little attention has been focused on the short-term vascular effects of this injury. Moreover, there is very limited information regarding the effects of such an anastomosis on cardiac output and flows through the unshunted lung and particularly the effect of flow on reactivity of the unshunted pulmonary vasculature. For example, De Canniere and colleagues¹ reported increased pulmonary vascular resistance and cardiac output 8 weeks after surgical creation of an anastomosis between the aorta and main PA. Therefore the goals of our studies were to characterize flows in the large intrathoracic vessels and reactivity of the small PAs 48 hours after creation of a localized high-flow anastomosis. Low-flow shunts were deliberately created in some pigs to examine the effects of surgical intervention with an anastomosis carrying blood with high oxygen tension but low flow rates.

We observed that flow through the surgical anastomosis increased by 1.7-fold between the initial creation of the connection and 48 hours later at harvest (Table 1). In fact, because of substantial and consistent increments in flow rates through the anastomosed left LLPA between creation of the connection and harvest 48 hours later, experience on the part of the surgical team was required to create an anastomosis that was not so large that it caused death likely as a result of heart failure in this time frame. This evolution is consistent with the development of a high-flow state after the creation of a traumatic arteriovenous fistula,¹² although the rapid time frame and quantitation of these flows in our animal model is new information. Next the creation of high-flow shunts was associated with a modest and insignificant increase in proximal aortic flow rates. Although additional numbers of aortic flows in control pigs would likely

FIGURE 2. Values for pulmonary arteries (PAs) from the right lower lobe are represented by *filled squares*. Those from the left lower lobe are represented by *filled triangles*. Asterisks denote concentration curves that are different one from the other based on 2-way repeated-measures analysis of variance ($P < .05$). A, PAs from the left and right lower lobes from control pigs develop equal tension to U46619 ($n = 4$) in the concentration range of 10^{-10} through 10^{-7} . This concentration range was chosen to develop a full-tension response curve. B, PAs from the right lower lobes of pigs with high-flow shunts developed more tension to U46619 than did PAs from the left lower lobe ($n = 24$, $P < .005$). C, Right lower lobe PAs from pigs with high-flow shunts exhibited increased tension to phenylephrine over left lower lobe PAs from the same pigs ($n = 4$, $P < .05$). D, Left lower lobe PAs from low-flow shunts exhibited very similar tensions to U46619 as those from high-flow pigs but lower tension in PAs from the right lower lobes ($n = 6$, $P < .01$). E, Right lower lobe PAs from high-flow hosts developed higher tension to U46619 than those from control (unoperated) hosts ($n = 24$ high-flow hosts and 6 control hosts). F, Tension to U46619 of left lower lobe PAs from control and high-flow hosts are not different ($n = 24$ high-flow hosts and 6 control hosts).

have resulted in statistically significant increases in aortic flow rates of high-flow pigs over those of control animals, we doubt the physiological significance of a 20% to 25% increase in cardiac output, as determined by proximal aortic flow rates. As expected, aortic flow rates were reasonably correlated to the size of the shunt and flow through the left LLPA at the time of harvest in our model (Figure 1, A).

A key finding from our studies is enhanced reactivity of PAs from the unshunted right lobe over those from the shunted, high-flow left lower lobe of the same hosts. Flow to the right lower lobe in high-flow hosts was not different from that of right LLPAs in control hosts. Because flows to the unshunted right lung were not significantly increased over control values, exposure to increased shear

should not account for the differences in reactivity of right PAs to standard constricting agents. Identical contractility to KCl in shunted and unshunted arteries argues that the contractile apparatus was not affected by the anastomosis. Removal of the endothelium eliminated the differences in contractility. Finally, reactivity of unshunted right PAs appears to be increased over that of right PAs from control (unshunted) hosts. Together these observations suggest that circulating, endothelially derived factors from the shunted lobe might trigger changes in vasoactive endothelial factors in remote PAs (eg, decrease in endothelial nitric oxide synthase activation or expression and blunted prostacyclin production) to result in increased reactivity. High partial pressures of oxygen, pressure (as distinct from flow), or even denervation¹³ in shunted lobes might contribute to differences in reactivity of shunted and unshunted PAs.

With shunt-induced increments in flow to the left lower lobes (and right lobe in low-flow animals), wet/dry weight ratios of lung tissue increased, as anticipated (Figure 1, B). Although statistically significant, these increases were very modest. We speculate that this minimal increase in lung water does not account for differential reactivity in shunted compared with unshunted PAs but cannot completely exclude a contribution of perivascular edema in modifying the contractility of shunted PAs.

In summary, we have induced high flow localized to a single lobe of a lung in juvenile pigs. Flows through these anastomoses increased substantially 48 hours after surgical connection. Enhanced reactivity of PAs in the lung contralateral to the shunt might have clinical implications. Although rare, either traumatic or naturally occurring systemic artery–PA fistulas^{14,15} might be associated with high-flow shunting to a pulmonary lobe. Further studies to better define mechanisms underlying and biochemical perturbations associated with changes in vascular reactivity induced by subacute changes in flow are needed. In the accompanying article¹⁶ we explore the contribution of nitric oxide synthase and eicosanoids to vascular reactivity in this model.

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References

1. De Canniere D, Stefanidis C, Brimioulle S, Naeije R. Effects of a chronic aorto-pulmonary shunt on pulmonary hemodynamics in piglets. *J Appl Physiol*. 1994; 77:1591-6.
2. Botney MD. Role of hemodynamics in pulmonary vascular remodeling: Implications for primary pulmonary hypertension. *Am J Respir Crit Care Med*. 1999;159: 361-4.
3. Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease; a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. *Circulation*. 1958;18:533-47.
4. Steinhorn RH, Russell JA, Lakshminrusimha S, Gugino SF, Black SM, Fineman JR. Altered endothelium-dependent relaxations in lambs with high pulmonary blood flow and pulmonary hypertension. *Am J Physiol Heart Circ Physiol*. 2001;280:H311-7.
5. Storme L, Rairigh RL, Parker TA, Kinsella JP, Abman SH. Acute intrauterine pulmonary hypertension impairs endothelium-dependent vasodilation in the ovine fetus. *Pediatr Res*. 1999;45:575-81.
6. Vititsky EV, Griffin JP, Collins MH, Spray TL, Gaynor JW. Increased pulmonary blood flow produces endothelial cell dysfunction in neonatal swine. *Ann Thorac Surg*. 1998;66:1372-7.
7. Bousamra M 2nd, Rossi R, Jacobs E, Parviz M, Busch C, Nelin LD, et al. Systemic lobar shunting induces advanced pulmonary vasculopathy. *J Thorac Cardiovasc Surg*. 2000;120:88-98.
8. Zhu D, Medhora M, Campbell WB, Spitzbarth N, Baker JE, Jacobs ER. Chronic hypoxia activates lung 15-lipoxygenase, which catalyzes production of 15-HETE and enhances constriction in neonatal rabbit pulmonary arteries. *Circ Res*. 2003; 92:992-1000.
9. Garvey W, Fathi A, Bigelow F, Carpenter B, Jimenez C. Improved Movat pentachrome stain. *Stain Technol*. 1986;61:60-2.
10. Tudor RM, Lee SD, Cool CC. Histopathology of pulmonary hypertension. *Chest*. 1998;114(suppl):1S-6.
11. Fullerton DA, Jones SD, Jaggars J, Piedalue F, Grover FL, McIntyre RC Jr. Effective control of pulmonary vascular resistance with inhaled nitric oxide after cardiac operation. *J Thorac Cardiovasc Surg*. 1996;111:753-63.
12. Bajraktari G, Rexhepaj N, Bakalli A, Shaqiri G, Osmani E, Vokri L, et al. Remission of high-output heart failure after surgical repair of 30-month arteriovenous femoral fistula: Case report. *Heart Surg Forum*. 2005;8:E118-20.
13. Juratsch CE, Jengo JA, Castagna J, Laks MM. Experimental pulmonary hypertension produced by surgical and chemical denervation of the pulmonary vasculature. *Chest*. 1980;77:525-30.
14. Loebl EC, Platt MR, Mills LJ, Estrera AS. Pulmonary resection for a traumatic pulmonary arteriovenous fistula. Case report. *J Thorac Cardiovasc Surg*. 1979; 77:674-6.
15. Yamanaka A, Hirai T, Fujimoto T, Hase M, Noguchi M, Konishi F. Anomalous systemic arterial supply to normal basal segments of the left lower lobe. *Ann Thorac Surg*. 1999;68:332-8.
16. Pfister S, Somberg L, Lowry T, Gao Y, Medhora M, Jacobs ER. Mechanisms underlying increased reactivity of pulmonary arteries contralateral to a localized high-flow anastomosis. *J Thorac Cardiovasc Surg*. 2011;141:425-31.