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Variability of Pulmonary Regurgitation in Proportion to Pulmonary Vascular Resistance in a Porcine Model of Total Resection of the Pulmonary Valve: Implications for Early- and Long-Term Postoperative Management of Right Ventricular Outflow Tract Reconstruction With Resulting Pulmonary Valve Incompetence

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Abstract

Introduction: Pulmonary regurgitation (PR) is a major concern after right ventricular (RV) outflow tract surgery. We assessed the impact of physiological changes in pulmonary vasculature on hemodynamic severity of PR and RV function and their potential clinical implications for postoperative management using a porcine model with severe PR. **Materials and Methods:** Eight porcine models of acute PR were established by means of resection of pulmonary valve on cardiopulmonary bypass. After separation from bypass and stabilization, blood flow in the main pulmonary artery was measured by a pulsed Doppler flowmeter, and RV systolic function was assessed on the basis of RV segment shortening (RVSS), which was analyzed by sonomicrometry. In the acute PR model, we verified the impact of pulmonary vascular resistance (Rp) on pulmonary regurgitant fraction (PRF) and RV function. Pulmonary vascular resistance was changed by manipulating the level of $PaCo_2$ and by inhalation of nitric oxide (NO). **Results:** After bypass, the mean PRF was 40% $\pm$ 5%, and there was a deterioration of RV function. Under each ventilation condition (high Co_2, low Co_2, and NO 20 ppm), Rp was 836 $\pm$ 207 dyne $\times$ s $\times$ cm^{-5}, 499 $\pm$ 125 dyne $\times$ s $\times$ cm^{-5}, and 340 $\pm$ 102 dyne $\times$ s $\times$ cm^{-5}, respectively, and PRF was 60% $\pm$ 10%, 37% $\pm$ 5%, and 24% $\pm$ 4%, respectively, under each condition. They also showed a positive correlation in all animals. Cardiac output and RVSS were decreased by hypercapnia, while they were significantly improved after NO inhalation. **Conclusions:** This study indicates that low Rp after right ventricular outflow tract reconstruction (RVOTR) resulting in acute PR is advantageous in reducing the severity of PR and RV volume load. These findings may have clinical implications for early and long-term postoperative management of patients subjected to RVOTR with resulting pulmonary valve incompetence.

Keywords

pulmonary regurgitation, right ventricular outflow tract reconstruction, pulmonary vascular resistance, nitric oxide

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Introduction

Many patients with congenital heart disease who underwent right ventricular (RV) outflow tract reconstruction (RVOTR) as children have grown to adulthood and started to suffer from postoperative pulmonary regurgitation (PR) and RV dysfunction. Pulmonary regurgitation will be a major concern until ideal RV outflow patches or conduits used for tetralogy of

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Abbreviations and Acronyms

CO	cardiac output
NO	nitric oxide
PA	pulmonary artery
PR	pulmonary regurgitation
PRF	pulmonary regurgitant fraction
Rp	pulmonary vascular resistance
RV	right ventricular
RVOTR	right ventricular outflow tract reconstruction
RVSS	right ventricular segmental shortening
TOF	tetralogy of Fallot

Fallot (TOF) repair or Rastelli procedures are developed, and PR still has a significant influence on the prognosis after surgery.[1,2] Many surgeons have tried to reduce PR after RVOTR, and our institution has also obtained acceptable mid-term results for transannular patch repair in TOF,[3] but we have also confirmed the functional limitations of monocusp patches in the long term after surgery. The degree of postoperative dilatation of the RV, as well as the severity of PR, is largely variable after RVOTR with a transannular patch even in the same or similar pathologies of pulmonary valves with abolished cusp motion. At present, there are no definitive clinical or experimental data on the impact of the physiological changes in pulmonary vasculature and RV performance on the hemodynamic severity of PR. In this study, we assessed the hemodynamic changes associated with severe acute PR and measured the relationships between pulmonary regurgitant fraction (PRF) and other cardiovascular factors (pulmonary vascular resistance [Rp] and RV function) using a porcine model of total resection of the pulmonary valve cusps.

Materials and Methods

All animals received humane care in compliance with the ''Principles of Laboratory Animal Care'' formulated by the Institute of Laboratory Animal Resources and the ''Guide for the Care and Use of Laboratory Animals'' prepared by the Institute of Laboratory Animal Resources, National Research Council and published by the National Academy Press (revised 1996).

Animal Preparation

Eight white Landrace-Duroc pigs (1 ± 0.4 months, 14 ± 2 kg) were premedicated intramuscularly (ketamine 5 mg/kg and diazepam 0.5 mg/kg) and anesthetized with inhaled sevoflurane of 1.0% to 1.5% throughout the procedure. Support with a volume-controlled ventilator (ACE-300; ACOMA, Tokyo, Japan) was started after endotracheal intubation, and the mean airway pressure was maintained at 10 cm H_2O throughout the experiment. Sterile surgical techniques were used in all animals. Arterial pressure monitoring and central venous access were maintained via a small right branch of the external carotid artery and axillary vein, and arterial blood gases were measured to guide ventilator settings in order to maintain oxygen/carbon dioxide tension and pH values within the normal range. After a median sternotomy, we set up a left atrium pressure monitoring line and an apical solid-state pressure transducer-tipped catheter (MPC-500; Millar, Houston, Texas) to monitor RV and pulmonary artery (PA) pressure. Right ventricular dimension was measured with ultrasonic micro-transducer crystals. One pair of these crystals was placed on the RV free wall at intervals of 2 cm on a parallel line and 10 mm away from the atrioventricular groove. We measured RV segmental shortening (RVSS) with a SonoSOFT recording (Sonometrics, London, Ontario, Canada) and blood flow volume and pattern of the PA using a pulsed Doppler flowmeter (SCPD-10; Transonic Scisense, London, Ontario, Canada). The flowmeter probe consists of silicon rubber integrated with a soft cuff and measurement leads fixed at the same angle (Figure 1). It is easy to maintain a stable position, lead angle, and inner diameter by suturing the cuff around the main PA.

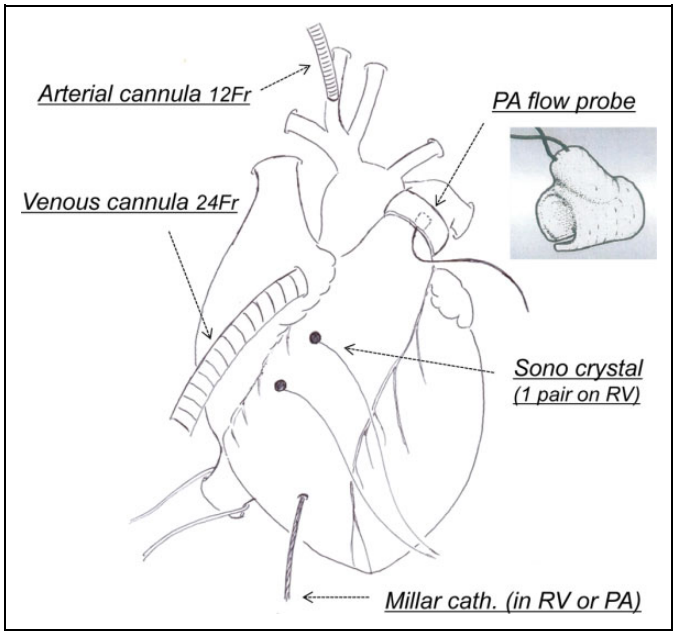

Figure 1. Schema of heart preparation.

Experimental Model

We established a porcine model with severe PR on a beating heart using cardiopulmonary bypass support. After systemic administration of heparin sodium (300 U/kg) and methylprednisolone (30 mg/kg), extracorporeal circulation was achieved using a 12F straight cannula through the right carotid artery and a 24F right angle cannula placed into the right atrium. The bypass circuit included a membrane oxygenator (Capiox SX10; Terumo, Tokyo, Japan) and an extracorporeal pump (Advanced Perfusion System 1, Terumo). Blood oxygen tension was maintained above 100 mm Hg, and bypass flow volume was maintained at around 80% of normal cardiac output (1.5-2.0 L/min) with more than 70% mixed venous oxygen saturation at normothermia. Hematocrit was kept over 20%

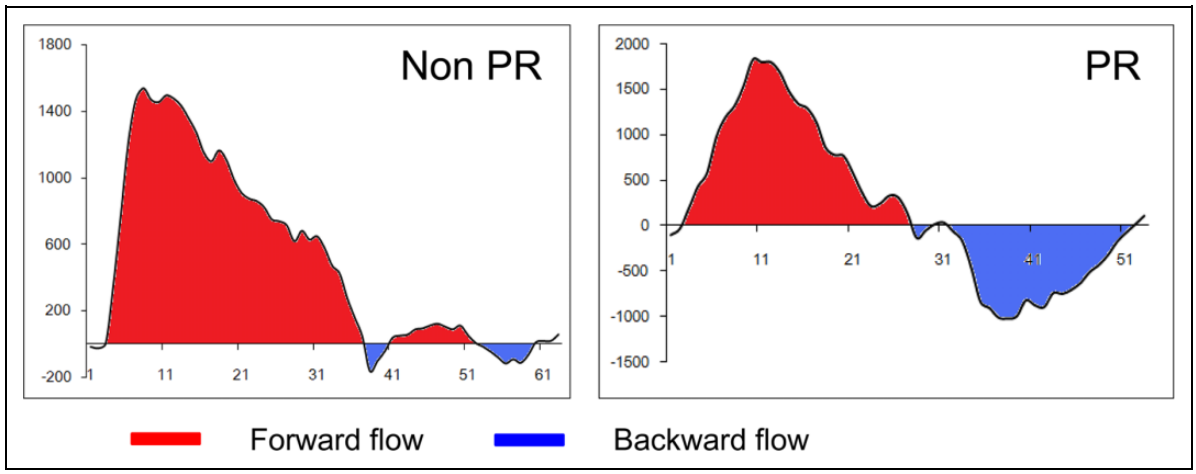

Figure 2. Main pulmonary blood flow volume.

using low-volume Ringer solution priming with no blood. Mean arterial pressure and central venous pressure were maintained at 50 to 70 mm Hg and 0 to 5 mm Hg with no medication during bypass. At first, we made a small incision in the main PA under suction venting and resected all pulmonary valve cusps. After closure of the PA, we weaned the animals from bypass immediately and kept them at rest for 60 minutes to allow for hemodynamic stabilization. A Millar transducer-tipped catheter was used for confirmation of the pressure wave pattern of the PA and RV after valve resection, and the intermittent pressure monitor in the main PA. The animal heart rates were in the range of 80 to 110/min, and there was no significant difference in each animal.

Measurements

Pulmonary blood flow. Using a pulsed Doppler flowmeter attached to the main PA and LabScribe2: LS-20PVL analysis software (iWorx Systems, Dover, New Hampshire), we measured pulmonary blood flow using the following formulas. In addition, we also measured PRF from the antegrade and retrograde pulmonary blood flow volume (Figure 2).

$$\text{Flow speed}: V = (\Delta f_0 \times C)/(2 \times f \times \cos\alpha),$$
$$\text{flow volume}: Q = V \times \pi \times D^2/2 \times 1/10,$$

where Δf_0 is Doppler shift (KHz), C is ultrasonic wave speed (1500 m/s), f is ultrasonic wave frequency, and D is vascular diameter (mm), α is blood flow angle.

RV systolic function. We analyzed RVSS using SonoSOFT under constant preload (CVP = 5 mm Hg), and we assumed RV systolic function as RVSS.

$$\text{RVSS} = (\text{RV end-diastolic wall length} - \text{RV end-systolic wall length})/\text{RV end-diastolic wall length} \times 100\ (\%).$$

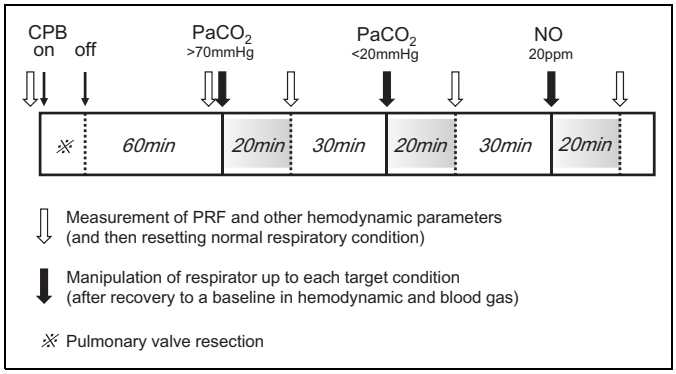

Figure 3. Experimental protocol.

Cardiac output. Cardiac output (CO) = antegrade–retrograde pulmonary flow volume (mL/min).

Pulmonary vascular resistance.

$$\text{Rp} = (\text{mean pulmonary arterial pressure} - \text{left atrial pressure}) \times 80/\text{cardiac output}\ (\text{dyne} \times \text{s} \times \text{cm}^{-5}).$$

Experimental Protocols

1. We measured hemodynamic parameters before and after establishment of severe PR with total resection of pulmonary valve cusps. The influence of the surgical procedure was minimized by using a stabilization period of 60 minutes after bypass.
2. In the steady state after establishing PR, we verified the impact of Rp and RV function on PRF.
3. We changed the Rp by manipulating the level of $PaCo_2$ (>70 mm Hg and <20 mm Hg) using a respirator and inhalation of nitric oxide (No) of 20 ppm under normal $PaCo_2$. After 20 minutes under each condition, we

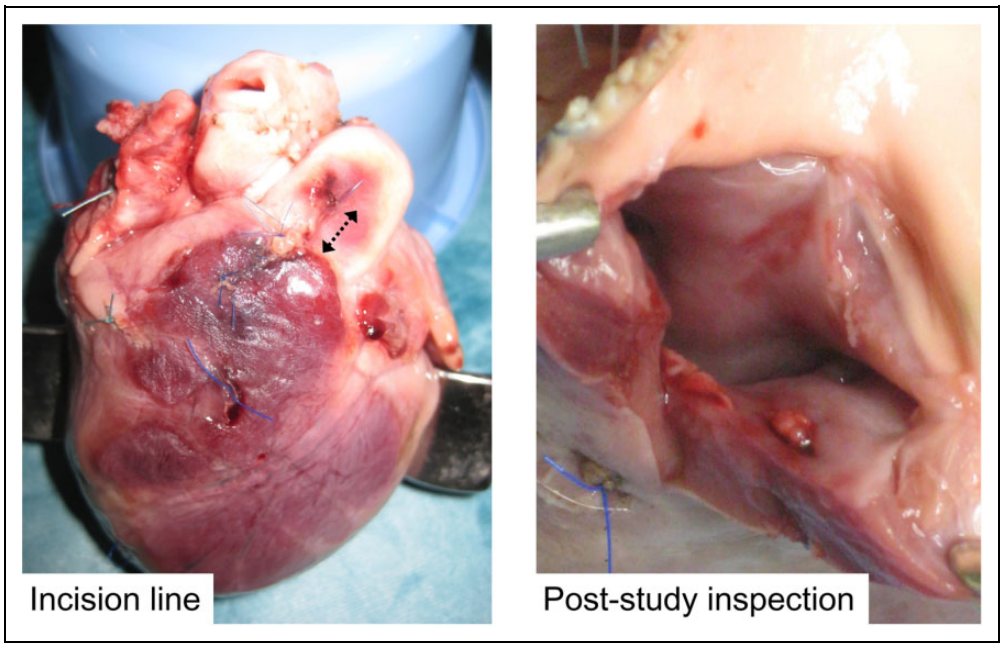

Figure 4. Animal heart after pulmonary valvotomy.

measured PRF and other hemodynamics, and RVSS and Rp were assessed at each measurement (Figure 3).

After the end of each experiment, cardiac specimens were inspected to confirm the total resection of pulmonary valve cusps (Figure 4) and the absence of patent ductus arteriosus and patent foramen ovale that might have affected the measurements.

Statistical Analyses

All data are expressed as mean ± standard deviation. The paired Student *t* test was used for comparison of variables within experimental subjects (non-PR vs PR), and repeated measures analysis of variance was used for interaction effect comparisons. *P* values of <.05 were considered statistically significant.

Results

The mean bypass time for preparation of the PR animal model was 18 ± 4 minutes, and weaning from bypass was easily accomplished without catecholamine support. There was a minimal change in the hematocrit after bypass (pre: 32% ± 3% and post: 28% ± 5%).

Pulmonary Regurgitant Fraction and RV Function in the PR Model

Pulmonary regurgitant fraction was 40% ± 5% in our PR model, and significant deterioration of RV function was shown by CO (baseline: 1.7 ± 0.3 L/min, PR: 1.3 ± 0.2 L/min*) and RVSS (baseline: 22% ± 2%, PR: 18% ± 2%*; Figure 5). Pulse forms of the pulmonary flow in each condition are shown in Figure 6 (*$P < .01$ vs baseline).

Effect of Respiratory Modulation on PR and RV Function

Under each ventilation condition (baseline, high CO_2, low CO_2, and NO 20 ppm) in the PR group, pulmonary vascular resistance was 544 ± 160 dyne × s × cm^{-5}, 836 ± 207 dyne × s × cm^{-5}, 499 ± 125 dyne × s × cm^{-5}*, 340 ± 102 dyne × s × cm^{-5}*$^{\#}$, and PRF was 40% ± 5%, 60% ± 10%, 37% ± 5%*, and 24% ± 4%*$^{\#}$, respectively, under each condition. High Rp and PRF in the hypercapnia condition significantly decreased under hypocapnia and NO inhalation. As for RV function, CO levels were 1.25 ± 0.2 L/min, 1.02 ± 0.15 L/min, 1.33 ± 0.12 L/min*, and 1.44 ± 0.18 L/min*, and RVSS was 17.9% ± 2.0%, 13.6% ± 1.9%, 20.5% ± 1.1%*, and 23.0% ± 3.0%* in each condition (Figure 7). Cardiac output and RVSS were significantly decreased from baseline under hypercapnia, but they were significantly improved after NO inhalation (*$P < .01$ vs $HiCO_2$, $^{\#}P < .05$ vs $LoCO_2$).

Impact of Rp on PRF and CO

In each animal, the coefficient of correlation between Rp and PRF for different ventilation conditions ranged from .874 to .979, and there was a significant positive correlation between Rp and PRF in all animals. There was also a negative correlation between Rp and CO in all animals (Figure 8).

Discussion

In this animal study using an acute PR model, we verified the impact of Rp on PRF and RV function. To the best of our knowledge, this is the first in vivo experimental study to confirm the relationship between Rp, PR, and RV function. Pulmonary regurgitation is generally driven by the diastolic

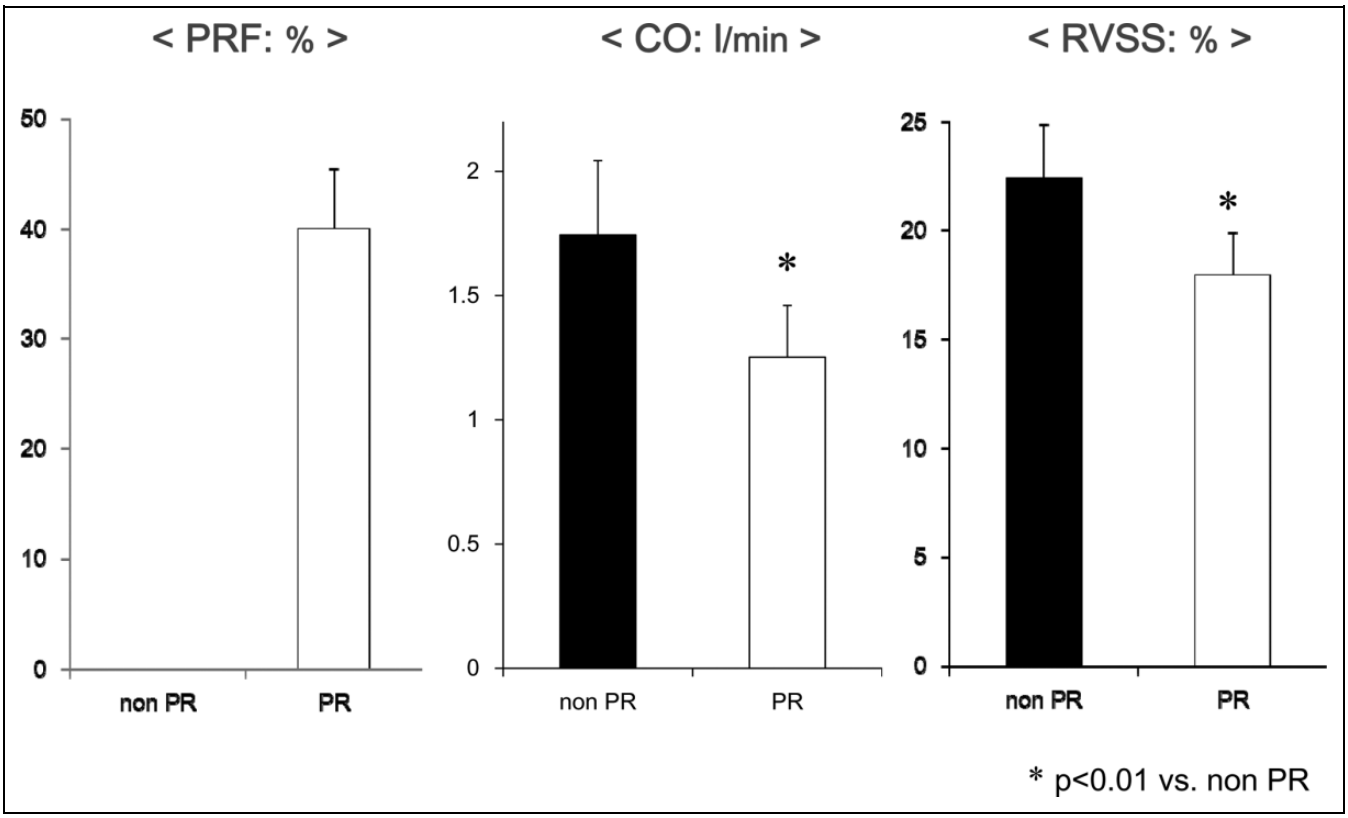

Figure 5. PRF and RV function in non-PR and PR model. PRF indicates pulmonary regurgitant fraction; RV, right ventricular; CO, cardiac output; RVSS, RV segment shortening.

pressure difference between the PA and the RV. On the other hand, we often observe a large variability in the severity of PR after RVOTR, even in stable hemodynamic conditions. Tabayashi et al[4] reported that PRF within 5 years after RVOTR was 5% to 40%, and there was no significant difference between nonvalved and valved transannular patches. In other reports,[5,6] PRFs of chronic PR after RVOTR are very wide ranging. We assume that the hemodynamic characteristics are maintained regardless of PR, as long as there is an adequate level of Rp and RV function. Furthermore, we also confirmed that the degree of PR was remarkably improved by lowering Rp.

Right Ventricular Function Following the Development of PR

Postoperative PR of more than moderate grade generally causes RV volume overload and RV enlargement leading to RV failure with time.[6] Frigiola et al reported that PR reduces both ventricular contractility and function.[7] Subsequently, tricuspid valve regurgitation caused by annular dilatation has been found to lead to further RV enlargement in some cases, and excessive myectomy performed during RVOTR may also result in aneurysm or destruction of RV structures at some point after surgery.[8,9] In this study, the PRF of the PR model was around 40% when the valve competency was totally abolished, and the RV contraction and the CO were significantly impaired, but the hemodynamics reached acceptable levels in a short period. Kuehne et al.[10] also demonstrated impaired RV contractility with preserved RV diastolic function in an animal stenting model. In terms of clinical features, Bouzas et al[11] speculated that postoperative PR is well tolerated after repair of TOF in infancy but poorly tolerated in adults following late primary repairs because of the poor adaptation of a hypertrophied and noncompliant right ventricle in adults. In addition, they posited a physiological mechanism by which the fresh and normal pulmonary microvascular bed takes on some of the role of the pulmonary valve. Actually, many children after TOF repair show preserved RV function and structure until adulthood even if the RV outflow patch has no valve or a fixed open valve. Other than the above, the most important determinants of PR leading to RV dysfunction are persistent RV afterload (pulmonary arterial stenosis, bronchopulmonary disease, and left ventricular dysfunction) and low RV compliance (myocardial hypertrophy or fibrosis) in the chronic stage.

Impact of PVR on PRF and RV Function

Generally, the pressure gradient between the PA and RV at the initial diastolic or end-systolic phase regulates PR. Thus, we think that the PA pressure increases with the Rp and also contributes to increase the PRF. In a similar fashion, Chaturvedi et al[12] demonstrated aggravation of PR by increasing airway

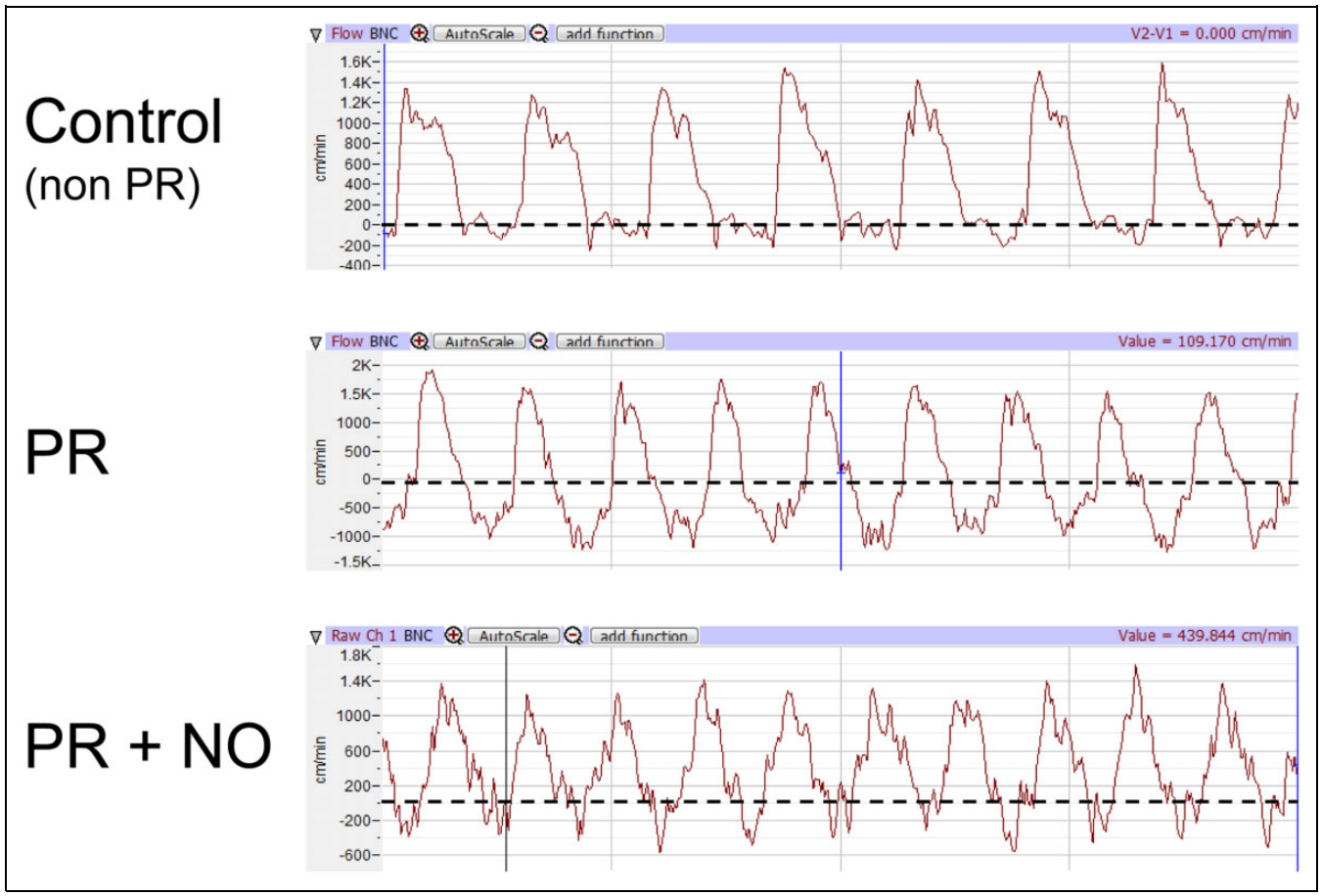

Figure 6. Pulse form of pulmonary blood flow. PR indicates pulmonary regurgitation; NO nitric oxide.

pressure and simulating branch PA stenosis in cases after repair of TOF. The present study also showed that low Rp significantly decreased PRF with the RV volume load reduction and improvement of the CO. In other words, pulmonary vasodilatation in response to hypocapnia or NO inhalation leads to reduction in the RV afterload and the PRF, and it improves pulmonary circulation and CO levels even in the absence of a pulmonary valve. Barbara et al[13] reported that inhaled NO lowered PA pressure and RV end-diastolic pressure and improved stroke volume in a clinical study. We also confirmed a very strong effect of NO on the pulmonary vasculature. Therefore, it may be especially beneficial to apply NO in the acute treatment period after RVOTR resulting in PR. Even in the case of chronic PR, it seems that early induction of pulmonary vasodilators (phosphodiesterase inhibitors or endothelin receptor antagonists) in substitution for NO may delay the progress of RV enlargement and dysfunction.

Clinical Implications

The prognosis after definitive repair of TOF is excellent in recent years. Also, in RVOTR cases where there is a concern about PR in the future, it is preferable to construct pulmonary arteries without any obstruction and preserve the pulmonary valve with or without minimized muscle resection.[14] However, there is still a considerable number of cases (ie, MAPCA, pulmonary atresia, and small annuli) with small pulmonary vasculature or cases that require the use of a transannular patch and RV muscle resection.

Recent trends in TOF operations have been reported in the Society of Thoracic Surgeons Database. According to this source, transannular patches are still used in more than 60% of TOF patients.[15] When a monocusp valve has been incorporated in transannular patch augmentation of the RVOT, some of the handmade pulmonary cusps have been shown to eventually remain fixed in the open position and the valve function completely disappears in the long term after surgery, resulting in progressive RV dysfunction due to PR and RV dilatation. Furthermore, in the acute phase after surgery, we sometimes use a nonvalved conduit for RVOTR in modified Norwood or palliative Rastelli procedures, where acute PR and RV dilatation may be major factors leading to hemodynamic instability.

With the recent sharp increase in adult congenital heart disease cases, it is expected that the need for pulmonary valve replacement after RVOTR will also increase. Pulmonary valve replacement for chronic PR is required in about 12% to 15% of patients with repaired TOF.[16,17] According to a recent report,[18] surgical mortality for pulmonary valve replacement was 4.5%,

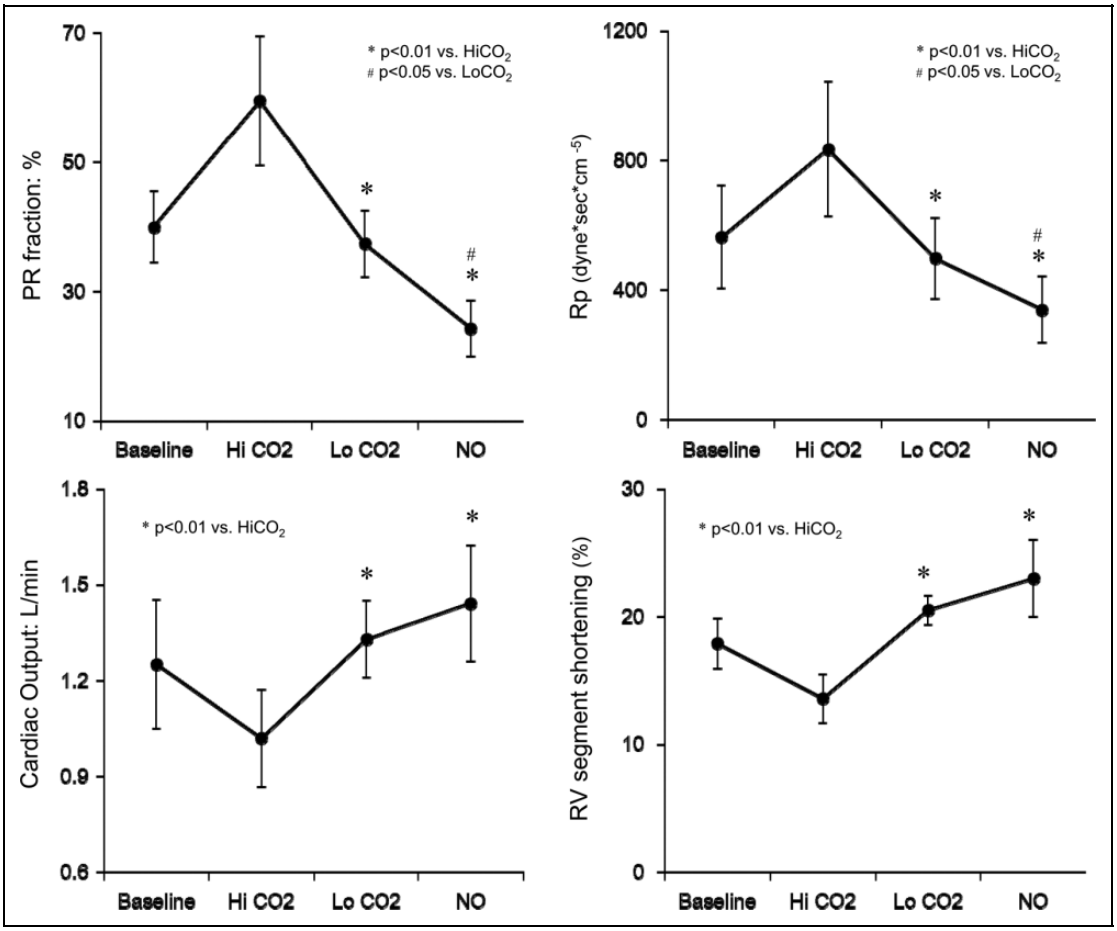

Figure 7. Effect of respiratory modulation on PRF, Rp, CO, and RVSS. PRF indicates pulmonary regurgitant fraction; RV, right ventricular; CO, cardiac output; RVSS, RV segment shortening; Rp, pulmonary vascular resistance.

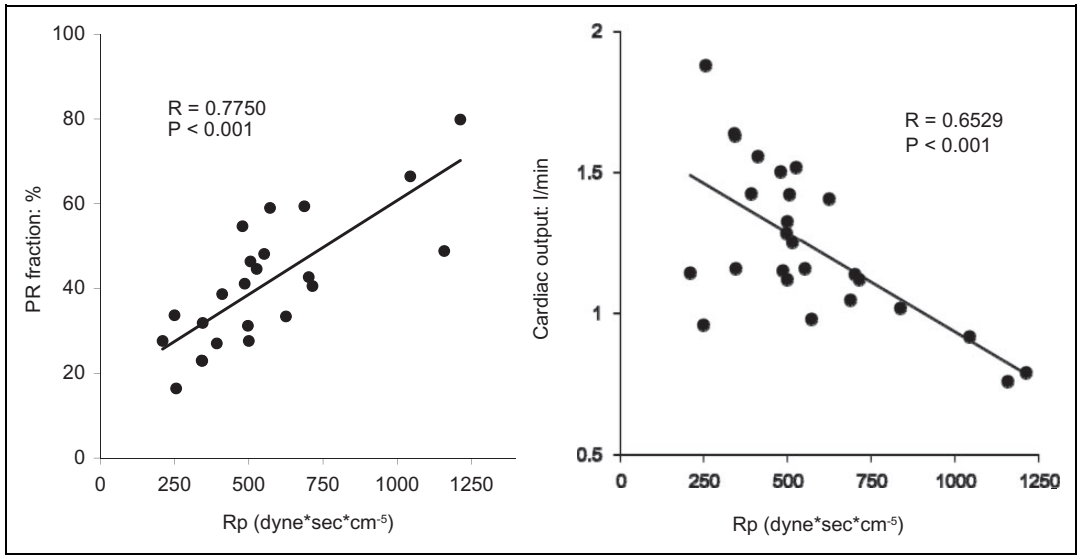

Figure 8. Correlation between PVR and PRF, CO. PRF indicates pulmonary regurgitant fraction; CO, cardiac output.

and the significant risk factors for mortality included age older than 40 years and concomitant surgery. Furthermore, Therrien et al[19] suggested that pulmonary valve replacement in cases with right ventricle end-diastolic volume index >170 mL/m^2 or right ventricle end-systolic volume index >85 mL/m^2 may not contribute to improvement in the RV enlargement and

cardiac dysfunction after surgery. Thus, the appropriate timing and indications for pulmonary valve replacement should be determined carefully based on PRF and RV volume.

The present findings regarding the significant relationship between PR and Rp will provide a basis to verify the feasibility of modulating Rp to minimize the severity of PR in the acute phase of nonvalved RVOTR and may also have implications for the chronic long-term postoperative status after successfully repaired TOF. Furthermore, this study indicates that aggressive utilization of NO and pulmonary vasodilators in the acute recovery phase after surgical RVOTR might be beneficial to avoid acute RV heart failure. In the long term, strategies that result in optimization of the pulmonary vascular resistance may potentially extend the period before pulmonary valve replacement is necessary after RVOTR with resulting PR.

Limitations

This study simulates acute PR condition after RVOTR using an animal normal heart. Right ventricle and pulmonary vascular dynamics in the TOF heart are different from the normal heart, and a chronic experimental model is mandatory to confirm the validity of the relationship between PR and Rp. Nevertheless, a reproducible model of chronic PR with a constant degree may not be easily established in chronic animal studies, while clinical data may be unreliable. The main purpose of this study was to understand the hemodynamics of right-side circulation under PR using a reproducible constant PR model. While further studies are needed, we believe that the relationship between Rp and PR also exists in repaired TOF hearts and chronic PR. In this study, PR was surgically induced with a minimum of influence on hemodynamics and also we did not intend to strongly make a comparison between pre- and postsurgical PR, but we should consider the effects of using bypass. Additionally, we assessed RV function by observing RV wall dimension and cardiac output because it was difficult to measure the exact RV volume. This was minimally invasive and sufficient to extrapolate simple RV function.

Conclusions

This study confirmed that acute severe PR causes deterioration of RV function, and that in the setting of acute PR, the regurgitant fraction and cardiac output vary in response to manipulations that result in changes in pulmonary vascular resistance. Pulmonary regurgitant fraction had a positive correlation with Rp, which indicates that low Rp is advantageous in reducing the severity of PR and the RV volume load after RVOTR with improvement in RV function. These findings may have clinical implications for early and long-term postoperative management of RVOTR with resulting pulmonary valve incompetence.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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