REVERSIBLE PULMONARY TRUNK BANDING WITH A BALLOON CATHETER: ASSESSMENT OF RAPID PULMONARY VENTRICULAR HYPERTROPHY

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Objective: We sought to assess the rapid hypertrophy of the right ventricle of young goats submitted to progressive pressure load by a balloon catheter.

Methods: The hearts of 6 young goats were assessed by means of echocardiography and cell morphology during and after right ventricular hypertrophy had been produced by a balloon catheter. Myocardial samples of the right ventricular outflow tract were harvested for microscopic studies. The external diameter of longitudinally sectioned myocytes was measured at the nucleus level. The volume density of mitochondria was also determined. A balloon catheter was then placed through the right ventricular outflow tract in the pulmonary trunk and progressively inflated every 2 days. Postoperative serial echocardiography was performed at intervals of 1 to 2 days. The animals were killed after 2 to 3 weeks of right ventricular training for morphologic analysis.

Results: Under optical microscopy, there was a 20.5% increase in the mean diameter of the myocyte of the trained right ventricle. However, under electron microscopy, there was no significant change in the mean volume density of mitochondria from the trained right ventricle. Serial echocardiography showed equalization of the ventricular thickness over a short interval of 6 to 10 days of progressive balloon inflation.

Conclusions: The balloon catheter permits the manipulation of the pressure load over the right ventricle, causing rapid hypertrophy in a 6- to 10-day period. This study suggests that nonsurgical preparation of the "pulmonary ventricle" in patients with transposition of great arteries with intact ventricular septum beyond the neonatal period could probably be accomplished within a very few days. (*J Thorac Cardiovasc Surg* 2000;120:66-72)

The rapid 2-stage approach remains an interesting alternative for neonates with transposition of the great arteries (TGA) with intact ventricular septum (IVS) referred beyond the neonatal period.¹

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Nevertheless, preliminary banding of the pulmonary trunk may cause the following problems: (1) Imprecision of optimal occlusion may occur at the time of banding; (2) additional palliative procedures may be necessary to increase pulmonary blood flow; (3) anatomic distortion of the pulmonary trunk, pulmonary arteries, or both may occur.

A balloon catheter designed to induce rapid pulmonary ventricular hypertrophy was developed at the Bioengineering Division of The Heart Institute (InCor), University of São Paulo Medical School. The purpose of this study is to assess, by means of echocardiography and cell morphology, the behavior of the right ventricle (RV) of young goats submitted to progressive pressure load imposed by the new balloon catheter.

Methods

Anesthesia. Six young goats aged 30 to 60 days (average weight, 5.3 kg) were studied. Anesthesia was induced with intramuscular ketamine (50 mg/kg). A jugular venous line was placed for drug infusions. Each animal was sedated with

pentobarbital sodium (Nembutal, 5-10 mg/kg administered intravenously) and then ventilated through a tracheal tube with 100% oxygen (Harvard 708, South Natick, Mass). A femoral artery line was placed for blood gas samples (Nova Biomedical, SP Ultra C, Waltham, Mass). Electrocardiogram and blood pressure measurements were taken through computer software (ACQknowledge 3.01; Biopac Systems, Inc, Goleta, Calif). The goat was then prepared for a sterile surgical procedure.

The goats received cefazolin 500 mg and gentamicin 10 mg intramuscularly every 12 hours, beginning just before the operation.

The balloon catheter. A modified Swan-Ganz catheter (Baxter Healthcare Corp, Edwards Division, Santa Ana, Calif) was used for this purpose, in which the temperature probe was removed and the respective port was annulled. The length of the catheter was shortened so that the distal orifice was placed 30 mm away from the original proximal orifice. The original balloon was replaced by a manufactured balloon made with segmented polyether polyurethane copolymer, diluted in *N,N*-dimethylacetamide. Some characteristics of this copolymer are shown in Table I.

The balloon was fixed between the two orifices with 6-0 polypropylene sutures and biocompatible glue. The catheter ended up with three ports (one for the balloon and two for pressure measurements) proximal at the level of the RV and distal at the pulmonary trunk. So that the quality of the catheters could be assessed, each one was inflated and placed in an aqueous environment for 15 days under a pressure of 120 mm Hg. If no leak was observed, the catheter was then released and prepared for sterile use.

Procedure. The chest was opened at the fourth left intercostal space to expose the right ventricular outflow tract (RVOT). A purse-string suture (6-0 polypropylene) was placed in the RVOT to insert the balloon catheter. Before the insertion, an intravenous dose of heparin, 500 U/kg, was given to the goat, followed by 2500 U subcutaneously every 12 hours. The balloon catheter was then inserted through the RVOT so that the balloon was kept just above the pulmonary valve level. The catheter was then fixed in position and exteriorized through the chest wall. The ribs were approximated after placing a small drainage catheter in the left pleural space, and the soft tissues were closed. After 4 to 6 hours of postoperative care, the pleural catheter was then removed.

Echocardiographic studies. All examinations included 2-dimensional and M-mode echocardiographic imaging of the ventricles from the right parasternal view with 2.5- and 5 MHz-transducers (Ultramark 4; Advanced Technology Laboratories, Bothell, Wash). Initial evaluation confirmed a diminished RV muscle mass as compared with the left ventricle (LV) and the position of the balloon before starting the protocol. Postoperative evaluation of induced hypertrophy was performed with intervals of 1 to 2 days.

Protocol. Digoxin was given to all goats ($0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ administered intramuscularly). RV training was begun after full surgical recovery. The balloon was initially inflated with

Table I. Characteristics of the polyether polyurethane copolymer, according to the American Society for Testing and Materials

Hardness (shore)	75 A-65 D
Specific gravity (g/cm^3)	1.09-1.17
Tensile strength (psi)	4500-6640
Elongation at break (%)	390-650

psi, Pounds per square inch (1 ATM = 760 mm Hg = 14,696 psi); *shore*, scale for hardness measurement in polymer (shore A = softest material; shore D = hardest material).

0.5 mL of distilled water and progressively incremented with the same volume at intervals of 2 days, according to the tolerance of the animal to the pressure load. If systemic hypotension, respiratory distress, or both developed after balloon inflation, it was deflated to the previous volume compatible with RV tolerance and maintenance of goat hemodynamics. RV training was carried out for 9 to 20 days. The animals were then killed for morphologic evaluation of the heart.

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health.

Morphologic studies. Baseline myocardial samples (3-mm maximal diameter) from the subepicardial layer of the RVOT were collected for optical and electron microscopic studies just before catheter insertion. The animals were killed at different postoperative times (1-3 weeks of RV training). Another myocardial sample from the RV wall was taken for electron microscopy just before the animals were killed. After removal of the hearts from the thorax, the position of the catheter was checked in the pulmonary trunk. The hearts were then fixed in 10% buffered formalin for 24 hours.

Optical microscopy. A transverse cut of the ventricular mass was made 1 cm below the level of the atrioventricular junction. Sections from the ventricular septum, RV, and LV were obtained. After routine histologic processing, 5- μ sections were stained with hematoxylin and eosin. The external diameter of 50 longitudinally sectioned cardiomyocytes and their respective nuclei were measured in the short axis at the level of the nucleus by means of an image-analysis system (Quantimet-Leica; Leica Cambridge Ltd, Cambridge, United Kingdom) at a magnification of 400 $\times$ (Fig 1).

Electron microscopy. Myocardial samples for transmission electron microscopy were fixed in 3% glutaraldehyde, and after routine processing, 1- μ sections were examined with the electron microscope (Philips EM 301, Eindhoven, The Netherlands).

Random photographs were taken from baseline and trained RVs (10 for each condition) at a magnification of 1600 $\times$. Morphometric estimation of the area occupied by mitochondria relative to the total myocyte area was determined by a transparent test system sheet containing 340 regularly spaced points applied over each photograph.

Fig 1. Photograph of longitudinally sectioned cardiomyocytes, indicating measurement of external diameter and the respective nucleus (*arrows*). (Original magnification 400 $\times$.)

The number of hits (points incident) over the mitochondria and over the other myocyte components allowed the determination of the volume density of mitochondria in each photograph, as follows: Volume density = (No. of hits over mitochondria/Total No. of hits over entire myocyte).

The relative standard error associated with the volume density estimation was less than .05 for both the samples before and after ventricular training.

Statistical analysis. Values are expressed as means $\pm$ SD. Differences between the baseline value and post-RV training data were analyzed by the Student *t* test. A paired *t* test was used to compare RV thickness measured by means of echocardiography and volume density of mitochondria before and after RV training.

Results

The systolic gradient achieved during the protocol varied from 25 to 133 mm Hg, with a mean of 62 ± 41 mm Hg. There was no migration or balloon rupture. The balloon catheter tip was found touching the pulmonary trunk bifurcation in goat 506. This caused a problem in measuring distal balloon pressure. The same goat had fever on the 19th postoperative day, despite antibiotic therapy.

Morphologic findings

Gross findings. Two animals (Nos. 409 and 1206) had pleural effusions. All goats had adequate balloon positioning, with some fibrin deposit at the tip of the catheter. No damage to the tricuspid or pulmonary valves was noticed. Three goats (Nos. 409, 506, and 1206) had vegetations on the catheter tip, which is sug-

gestive of infection. However, only in animal 409 was a bacterial endocarditis (Gram-positive cocci) identified. In the other two animals vegetations represented an organizing thrombus. Transverse sections of the ventricles showed increased RV muscle thickness in all cases.

Optical microscopy. Table II shows the mean diameters of myocardial fibers measured before and after preparation of the RV. A 20.5% increase in the mean diameter of trained RV myocytes was observed. The magnitude of this increase, however, was not significant ($P = .13$).

Regarding the nucleus, Table III shows no difference between the mean nuclear diameter of cells belonging to the trained RV ($P = .43$).

There was no edema or myocardial fibrosis in either ventricle of any of the animals.

Electron microscopy. When the mean volume density of the mitochondria was compared before (0.25 ± 0.06) and after (0.21 ± 0.06) RV training, there was no significant difference ($P = .43$). When volume density was related to the length of the training period (Table IV), we observed that goat 2205, submitted to the longest training period (20 days), was the only one noted to show an increase in volume density of mitochondria compared with what would be baseline levels in the other animals. That animal, however, had a fairly low baseline value before training (Fig 2). All others subjected to a lesser time of overloading (8-13 days) have exhibited a decrease in volume density of mito-

Table II. Diameters of longitudinally sectioned myocardial fibers measured at the level of the nucleus (Quantimet-Leica image analysis system, magnification of 400×, values = μ)

Condition of the heart	RV	LV	Interventricular septum
Baseline RV (n = 4)	6.62 $\pm$ 0.27*	NO	NO
Trained RV (n = 6)	7.98 $\pm$ 1.58*	7.58 $\pm$ 0.70	7.80 $\pm$ 0.87

Values are presented as means $\pm$ SD. NO, Not obtained.

* $P = .13$.

chondria. We were not able to detect any signs of degeneration, interstitial fibrosis, or edema in these samples.

Echocardiographic findings. Table V shows echocardiographic data of muscle thickness before and after RV training. It is noteworthy that a short period of 6 to 10 days was necessary to make the thickness of the RV free wall equal to that of the LV free wall and septum. It is also important to emphasize that in two animals (Nos. 2205 and 2711), RV thickness surpassed that of the septum and LV free wall in only 6 days.

The mean RV thickness after training (4.83 ± 1.17 mm) was significantly higher than the one before training (2.67 ± 0.52 mm, $P = .001$). The LV and septum thickness did not change during the study.

Although a mild pericardial effusion was found in one animal (No. 2711) during the trial, LV contractility of all animals remained normal during the entire protocol.

Discussion

This catheter may provide a new clinical tool for the rapid 2-stage approach in the treatment of dextro-TGA with IVS. It was designed to manipulate the pulmonary artery blood flow by reducing the effective lumen through the balloon inflation, creating a progressive and reversible pulmonary ventricle overload. The balloon size and pressure gradient can be adjusted, allowing a precise assessment of the patient's hemodynamic condition.

Critique of the preparation. Although this represents a nonsurgical approach in the clinical setting, in the experimental animal we placed the balloon catheter through a thoracotomy to guarantee a steady-state systolic overload of the RV. The main reason for this was that the goats were ambulatory during the protocol. In pilot studies the animals often caused dislodgment of the catheter with body and neck movements during RV training when a percutaneous approach was used. Nevertheless, percutaneous placement of the catheter

Table III. Diameter of cardiomyocyte nucleus measured in the longitudinally sectioned myocardial fibers (Quantimet-Leica image analysis system, magnification of 400×, values = μ)

Condition of the heart	RV	LV	Interventricular septum
Baseline RV (n = 4)	3.85 $\pm$ 0.28*	NO	NO
Trained RV (n = 6)	4.08 $\pm$ 0.50*	4.09 $\pm$ 0.56	4.18 $\pm$ 0.61

Values are presented as means $\pm$ SD. NO, Not obtained.

* $P = .43$.

would be more likely to be used in a patient continuously monitored and sedated in an intensive care unit environment.

Furthermore, this model of RV hypertrophy assessment does not reflect clinical reality in patients with TGA and IVS, where independent regulation of systemic and pulmonary blood flow is present. Thus, the balloon inflation may not be tolerated in a patient without a shunt and with severe limitation of pulmonary blood flow.

In addition, pressure load imposed on the RV could stimulate general myocardial hypertrophy rather than just RV hypertrophy. It would be important to observe whether baseline LV and septal myocyte measurements changed with RV training. However, in our pilot project, baseline biopsy specimens taken from the septum and LV caused increased morbidity and mortality.

Historical notes. The idea of partially obstructing the pulmonary trunk with a balloon catheter was initially reported by Tatroles and Kittle² and Simpson and colleagues³ in 1968. They have suggested this approach in infants with ventricular septal defect.

The balloon catheter was first applied clinically by Rashkind and colleagues⁴ in 1969 as an adjunct in evaluating the pulmonary arteriolar reactivity in children with ventricular septal defects. In 1975, Barbero-Marcial and colleagues⁵ used a Swan-Ganz catheter in the pulmonary trunk of a patient with a large ventricular septal defect for temporary relief of pulmonary hypertension, resulting in improvement of pulmonary congestion before the surgical treatment.

In 1992, the first clinical application of a balloon catheter as a rapid approach as the first stage of the Jatene operation was reported with success.⁶ This success emphasizes the feasibility of this maneuver.

In 1997, Bonnet and colleagues⁷ presented a balloon catheter similar to our prototype. They suggested this technique as a means of assessing afterload reserve of the tested ventricle before surgical banding of the pulmonary trunk.

Fig 2. Photographs of RV myocardium of goat 2205, with training period of 20 days, presenting a significant increase in volume density of the mitochondria. (Original magnification 1600 $\times$.) **A**, Before training; **B**, after training. Mitochondria are indicated by *arrows*.

Implications. Our data demonstrated that a gradual increase of the RV overload allowed for better tolerance of the pulmonary trunk stenosis. Therefore, the systolic stress generated by the pulmonary ventricle was less abrupt and had less effect on the myocardial mass, which in turn allowed for early development of the desired pressure increase (6-10 days). The trained RV was able to eventually obtain and surpass pressure generated by the LV.

Boutin and colleagues⁸ have demonstrated that late LV dysfunction observed in a group of patients subjected to the rapid 2-stage approach was inversely proportional to the rapid degree of hypertrophy at the time of pulmonary trunk banding. It seems that the extreme acute load appears to adversely affect late outcome. However, it is not clear whether such hypertrophy represents an abnormal state of the myocardium or a reprogrammed normal ventricle associated with ventricular dysfunction.

Taquini,⁹ Vlahakes,¹⁰ and their colleagues have demonstrated that a sudden increase in the RV afterload results in an inability to generate systolic pressure over 60 mm Hg, without a corresponding increase in the muscular mass.

Table IV. Volume density of the mitochondria before and after RV training ($n = 5$)

	Animal No.				
	409	2205	2711	1206	2805
Baseline RV	0.26	0.17	0.3	0.21	0.31
Trained RV	0.12	0.28	0.24	0.19	0.24
Time of training (d)	13	20	13	12	8

Ilbawi and colleagues¹¹ described the combination of pressure plus volume overload as the best method to generate ventricular hypertrophy. However, pressure overload was considered the most important factor to achieve increments in ventricular mass.¹² The mortality rates of 30% to 40% reported for aortic banding in animals are a direct consequence of the limited tolerance of the ventricle when confronted with acute obstruction of the outflow tract.¹³ In addition, there is an associated change in coronary vascular responsiveness. Our model of RV hypertrophy is more comparable with the rapid 2-stage approach because it does not promote coronary artery hypertension.

Table V. Echocardiographic findings

Goat No.	RV thickness		Septum thickness	LV thickness	Period of training	Period of muscle equality
	Before	After				
2205	3	5	4	4	20	6
506	2	4	4	4	15	7
409	2	3	3	3	13	8
2711	3	6	4	4	13	6
1206	3	5	5	5	12	10
2805	3	6	6	6	8	7

Values of muscle thickness are given in millimeters. *Period of training*, Duration of balloon inflation (d); *Period of muscle equality*, time required for equality among the muscle thicknesses of the RV free wall, septum, and LV (d).

A Berman angiographic catheter (a balloon catheter with only proximal side holes) has been used for this purpose.^{14,15} Nevertheless, the ability of continuous distal pressure measurement with our prototype gives important information. Together with oximetry, an optimized pulmonary blood flow can be achieved. Thus, the degree of systolic overload can be sufficient to stimulate the acute hypertrophy of the pulmonary ventricle without impairing pulmonary blood flow. The potential effects of balloon inflation over pulmonary blood flow and desaturation can be minimized, preventing the need for a shunt.

Morphologic aspects. Myocyte hypertrophy results in an increment in the use of oxygen, which in turn requires an increased number of mitochondria responsible for oxygen consumption and energy supply for the muscle. This phenomenon has been clearly demonstrated in long-term ventricular hypertrophy studies.¹⁶ The increment in the myocyte and nuclear diameter, as well as the volume density of mitochondria, are histologic parameters that indicate myocardial hypertrophy. Other morphologic evidence that was not quantified in the present work includes increased amounts of myofilament and free or membrane-bound ribosomes.

In the present study, the trend of increased diameter of the myocytes from the prepared RV may suggest that the RV is more apt to support a pressure equal to or greater than that of the LV. Similarly, parallel changes in nuclear diameters of the myocytes suggest that the nucleus is undergoing an increase in genetic transcription to attend to a larger protein synthesis demand of the trained RV. Thus, the pulmonary ventricle would be able to handle an increased afterload (ie, the peripheral vascular resistance).

Considering that an increase in the cardiomyocyte diameter and RV thickness was observed in the trained RV, we would expect a parallel increase in volume density of mitochondria responsible for oxygen consump-

tion and adenosine triphosphate synthesis. However, this finding was observed in only a single preparation (goat 2205), in which progressive pressure afterload was maintained for 20 days. That animal had the lowest baseline volume density of mitochondria. Therefore, this observation would not be statistically reliable for the whole group. Actually, there is an opposite trend in the other animals, in which the training time was inferior (8-13 days). This finding could be related to intracellular edema, which was not observed in any of the samples. Alternatively, we could speculate that the initial stimulus of hypertrophy has determined the increase of other cellular components not evaluated in the present study. In this context the increased number of mitochondria could be a marker of long-standing hypertrophy and not remarkable during the initial phase of rapid ventricular preparation.

It has been demonstrated that a significant increase of mitochondrial components in the first 24 hours after pressure induced hypertrophy.¹⁷ However, 3 to 10 days after LV pressure load, there is a reduction of the volume density of mitochondria in ventricular hypertrophy caused by an acute pressure stimulus, which corroborates the trend in a similar period of RV training in our protocol.^{18,19}

Ongoing studies from our laboratory are being carried out at comparable periods aimed at distinguishing such temporal differences to elucidate this point.

Conclusions

This study demonstrates the feasibility of manipulating the pulmonary trunk effective lumen with the use of the balloon catheter, with the possibility of adjusting the degree of obstruction to the clinical status of the subject. The reversible pulmonary trunk banding with a balloon catheter applied in goat hearts has permitted rapid RV hypertrophy in a 6- to 10-day period. This catheter could probably allow the nonsurgical rapid preparation of the pulmonary ventricle for the definitive treatment of patients with dextro-TGA with IVS beyond the neonatal period.

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