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# Adjustable Pulmonary Artery Banding

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## 1. Introduction

Pulmonary trunk banding is a technique of palliative surgical therapy. It has been used as a staged approach to operative correction for children born with cardiac defects characterized by left-to-right shunting or in need for ventricle retraining. This technique can be used to somehow diminish pulmonary overcirculation or to promote myocardial hypertrophy until subsequent total repair be possible. It consists of placing a band well proximal to the pulmonary artery (PA) bifurcation. The band is tightened and secured by suture to narrow the main PA, until the pressure distal to the band is one-third to one-half that of the aorta. Excessive blood flow to the lungs is therefore diminished by constricting the PA circumference, thereby achieving the desired limitation of the pulmonary flow and a balance with aortic blood flow. Nevertheless, skill and accuracy of the surgery, supplemented by good fortune are most likely to assure success in this imprecise conventional procedure. In addition, the band commonly used is fixed and unchanged in the postoperative course. It means that adjustment of the traditional band is unpredictable and empiric, performed under artificial conditions, different from the postoperative period. Since mid-80's, early definitive intracardiac repair has largely replaced palliation with PA banding. This trend has evolved because many centers have demonstrated improved outcomes with primary corrective surgery as an initial intervention in the neonate with congenital heart disease. Although the use of PA banding has recently decreased significantly, it continues to maintain a therapeutic role in certain subsets of patients with congenital heart disease. PA banding may be applicable to the very sick and small infants with torrential pulmonary blood flow, commonly producing heart failure beyond age one to two months, when diminished pulmonary vascular resistance allows substantial left-to-right shunting. Babies usually have feeding difficulties and failure to gain weight and grow. Multiple muscular ventricular septal defects with a "Swiss cheese" septum, single or multiple ventricular septal defects with coarctation of the aorta or interrupted aortic arch, single ventricle type of defects with increased pulmonary blood flow, are among the lesions in which

the use of PA banding may allow time for recovery until the patient can be submitted to definitive surgery.

PA banding has also played a role in the preparation and “training” of the left ventricle (LV) in patients with d-transposition of the great arteries (TGA) that are evaluated for a delayed arterial switch procedure (Jatene procedure). It has also been applied in patients with congenitally corrected TGA (CCTGA) or after Senning or Mustard operations with right ventricular (RV) failure. It is now recognized that the arterial switch operation can be done only with a LV conditioned to pump against systemic resistance. After birth, the LV starts pumping blood against the progressive low-resistance pulmonary vasculature, while the RV assumes the systemic function, and also the necessary muscle mass, to overcome a higher vascular resistance. These significant differences in LV and RV muscle mass progress over time and may assume considerable importance if the LV is suddenly required to perform against systemic vascular resistance, as in the arterial switch operation. For the majority of the patients with TGA referred beyond the neonatal period, who presents with an intact (or virtually intact) ventricular septum, the LV cannot retain pressure close to systemic levels. It is important to take advantage of these anatomic features during the neonatal period, in which LV is still adequate to handle systemic circulation, to carry out the arterial switch operation in a “safe” period. A number of circumstances can arise, causing postponement of surgery beyond the neonatal period. For example, a neonate may be seriously ill with necrotizing enterocolitis, renal or hepatic failure, or a hemorrhage in the central nervous system. Also, the neonate may be geographically distant from a center offering the arterial switch operation.

The establishment of the arterial switch operation as the best option for the surgical treatment of TGA, as well as the well-studied concept about the RV’s inability to maintain appropriate performance as a long-term systemic ventricle in atrial inversion operations or in CCTGA, led many centers to retrain the hypotrophied LV, aiming to surgically recruit it for systemic circulation. Therefore, arterial switch operation must be performed after preliminary PA banding, with or without a systemic to PA shunt, to stimulate the development of LV muscle mass, followed by an arterial switch operation later on, a concept introduced by Yacoub et al. in 1977. The retraining period between the two stages will allow the LV to function as a systemic pump. Some years later, the Boston Children’s Hospital group introduced the concept of rapid, two-stage arterial switch operation for TGA, limiting the interval between the first and the second operation to an average of seven days. However, one of the greatest limitations of this technical approach was related to the lack of adjustability of the PA banding. The degree of PA banding may be inadequate or imprecise and can cause an important acute systolic overload of the LV. That trial succeeded in their objective, once there was significant cardiac mass acquisition in about 7 days, reducing the risks of complications resulted from the primary repair of TGA in a patient with unprepared LV. However, the “rapid approach” produced some degree of unsatisfactory myocardial contractile performance in the late follow-up of about one fourth of the patients. In addition, other centers have reported a high morbidity and mortality rates associated to that 2-stage approach. Experimental studies have demonstrated myocardial edema and necrosis in hearts that experience abrupt systolic overload, followed by late ventricular failure. That is why the use of an adjustable PA banding system for LV

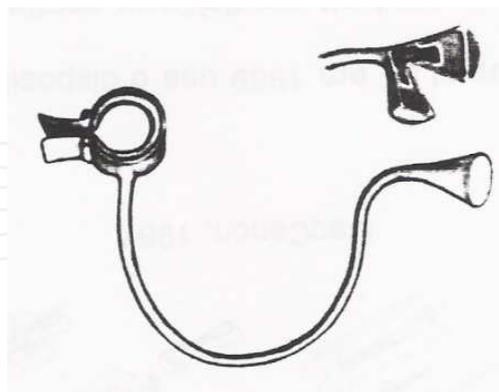
retraining to this subset of patients became of interest to many investigators. Since then, several studies have been carried out to achieve the most physiologic way to obtain LV retraining.

In developing countries, the number of patients with TGA presenting beyond the neonatal period is still considerable. The rapid 2-stage approach remains an interesting alternative for that population with late referral. Nevertheless, preliminary traditional 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. (4) The degree of abrupt acute systolic overload on the left ventricle may impair late ventricular function.

Said that, it sounds like traditional PA banding, used to treat the above-mentioned heart lesions, is inconvenient in that it does not allow late and fine adjustment according to the patient's clinical condition over time, and therefore sometimes requiring new interventions to achieve that.

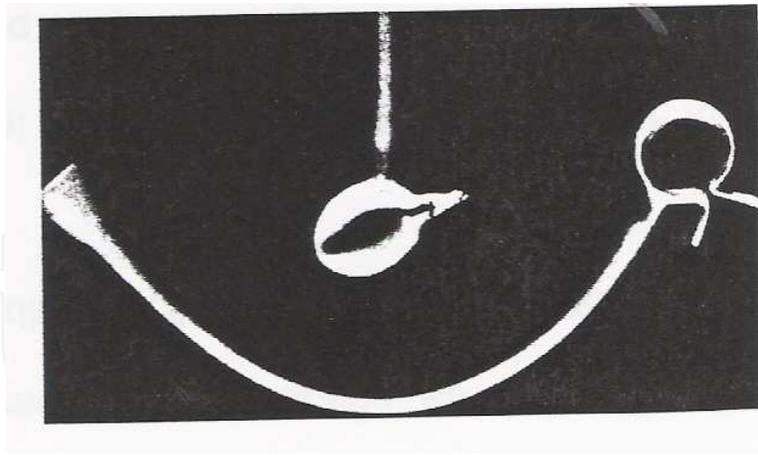
## 2. Historical notes of adjustable PA banding systems

The idea of adjustable banding device composed of a hydraulic cuff and a self-sealing button was first proposed in 1957. In fact, Jacobson & McAllister proposed a device consisted of a rubber cuff, with a lateral opening, and connected to a reservoir protected by self-sealing rubber (Figure 1). It was used on the great vessels of dogs, aiming a congestive heart failure model. Complications in handling the device were observed.



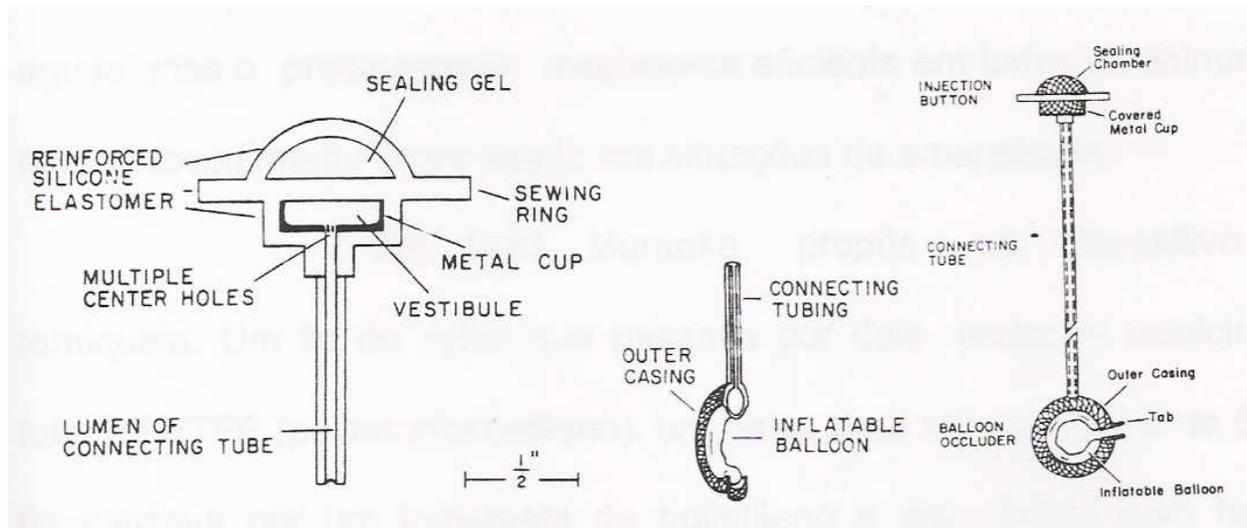
**Figure 1.** Jacobson & McAllister proposed in 1957 a device consisted of a rubber cuff, with a lateral opening, and connected to a reservoir protected by self-sealing rubber

In 1969, Bishop & Cole improved Jacobson & McAllister device by covering the cuff with silicone, with the aim of reducing local tissue reaction (Figure 2). They induced RV hypertrophy and congestive heart failure in a dog model.



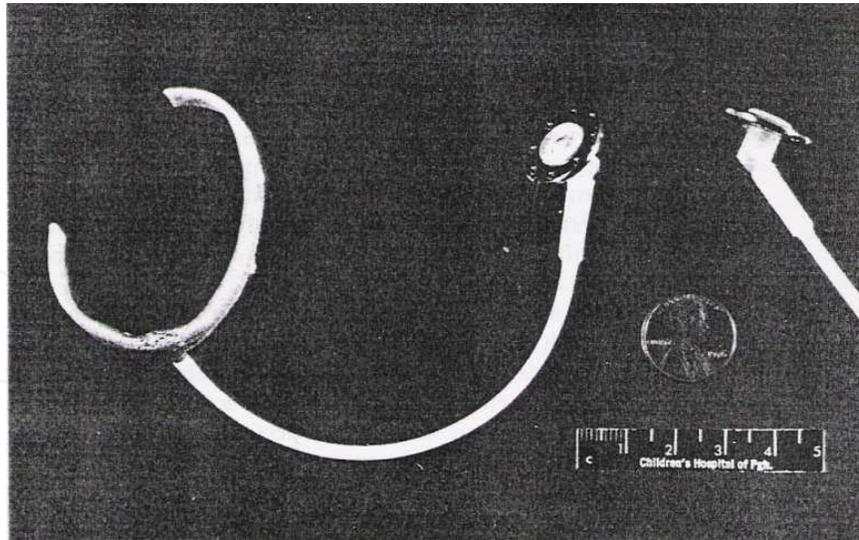
**Figure 2.** In 1969, Bishop & Cole device was covered with silicone to reduce tissue reaction

In 1972, Edmunds et al introduced two main changes: an external, non-deformable layer on the hydraulic cuff and silicone, instead of rubber (Figure 3). However, they observed asymmetric inflation or rupture of the cuff, and leakage of the injected material prevented from clinical use.



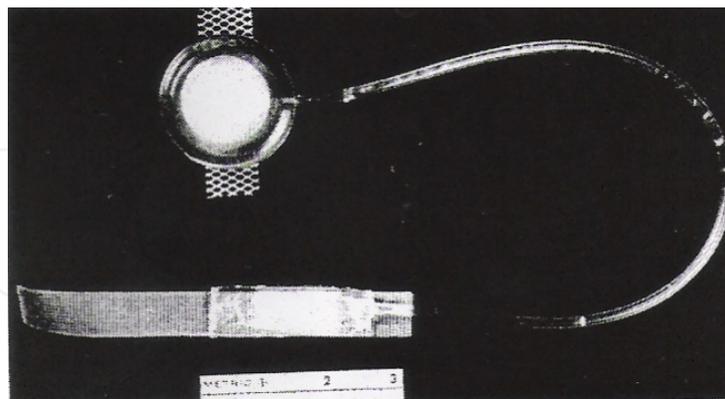
**Figure 3.** In 1972, Edmunds prototype presented an external, non-deformable layer on the hydraulic cuff and silicone, instead of rubber

In 1985, a new device made of biologically stable material (medical grade silicone) was introduced by Park et al. (Figure 4) The cuff was covered with reinforced braid and coated with silicone. The self-sealing button has a silicone diaphragm which did enable repeated needle puncture, avoiding leaking through the button. The device implanted in dogs and lambs was easily and effectively adjusted.



**Figure 4.** In 1985, Park introduced a prototype made of medical grade silicone. The cuff was covered with reinforced braid and coated with silicone. The self-sealing button had a silicone diaphragm which did enable repeated needle puncture.

During that same year, Solis et al. proposed a similar device to the previous one, intended to prepare the subpulmonary ventricle for the two-stage Jatene operation for the first time in the literature (Figure 5). Nevertheless, when the system was submitted to a high pressure gradient, as in the systemic circulation, dilation of the reservoir and the connecting tube occurred. In addition, there was a tendency of the cuff to bulge laterally under high pressure.



**Figure 5.** For the first time in the literature, Solis proposed in 1985 a similar device to prepare the subpulmonary ventricle for the two-stage Jatene operation.

In another study, the same group improved the strength of the material by reinforcing the cuff and the connecting tube with a spiral of 4-0 silk to withstand systemic arterial pressure. Again, they experienced bulging of the cuff due to a losing silk.

### 3. Adjustable PA banding system for ventricle retraining

We have begun this research line for more than two decades ago, using a balloon catheter to induce rapid pulmonary ventricular hypertrophy. We developed an experimental model of young goats, designed to adjust PA banding percutaneously. The main idea is that systolic overload might be less acute and intense using such a device than a traditional PAB, in which no changes are possible during ventricular retraining. We have assessed, by means of echocardiography and cell morphology, the behavior of the right ventricle (RV) submitted to progressive pressure load imposed by a balloon catheter positioned above the pulmonary valve. The catheter is a modification of the Swan-Ganz catheter, 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 (Figure 6).



**Figure 6.** Balloon catheter prototype, modified from the Swan-Ganz catheter and used for subpulmonary ventricle retraining.

A rapid RV hypertrophy was achieved in a short period of six to 10 days. It has been demonstrated that nonsurgical preparation of the “pulmonary ventricle” for the 2-stage arterial switch operation could be probably accomplished non-invasively with a balloon catheter within a very few days.

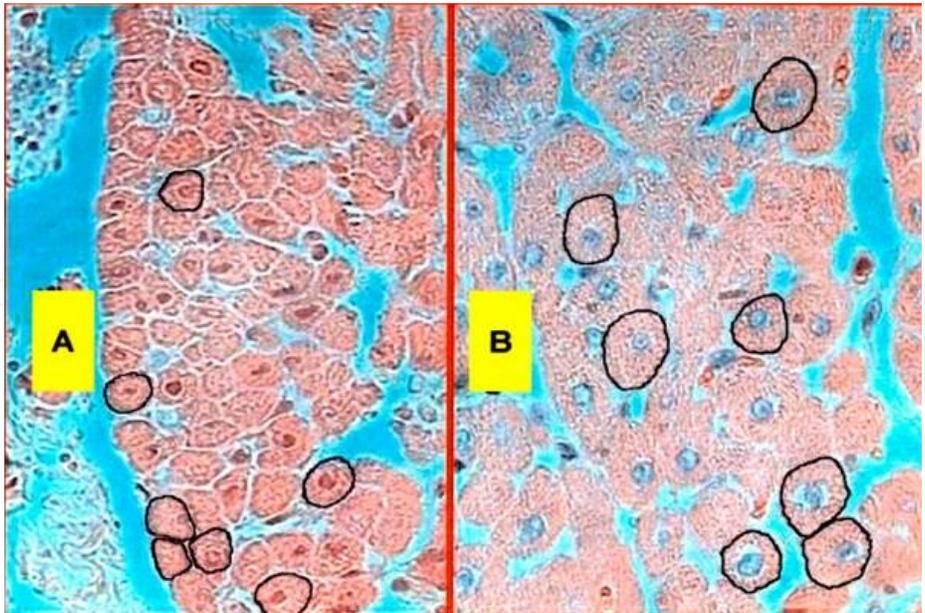
In mid-90's, we started to study experimentally an extravascular adjustable PA banding device, with a hydraulic cuff system, connected to a self-sealing button for percutaneous systolic overload adjustment (Figure 7). The banding ring (Hazen Everett Co) is a C-shaped hydraulic cuff with a 10-mm internal diameter and a 5-mm width. Its outer layer consists of 1-mm-thick rigid silicone, which keeps it from deforming. The inner surface has a deformable layer of silicone, which expands, compressing the lumen of the vessel according to the volume injected into the inflation button. At the 2 ends of the cuff, there are small orifices that are used for securing the ring to the PA. The extension tube, also made of silicone, links the banding ring with the insufflation button. It has a 2-mm inner diameter and is 25 cm long. The inflation button (Bard Access System) is a circular reservoir made of self-sealing silicone, the base of which includes a metal plate. The reservoir has a port, which is connected to the extension tube. This button is implanted subcutaneously, thus permitting percutaneous inflation or deflation of the banding ring.



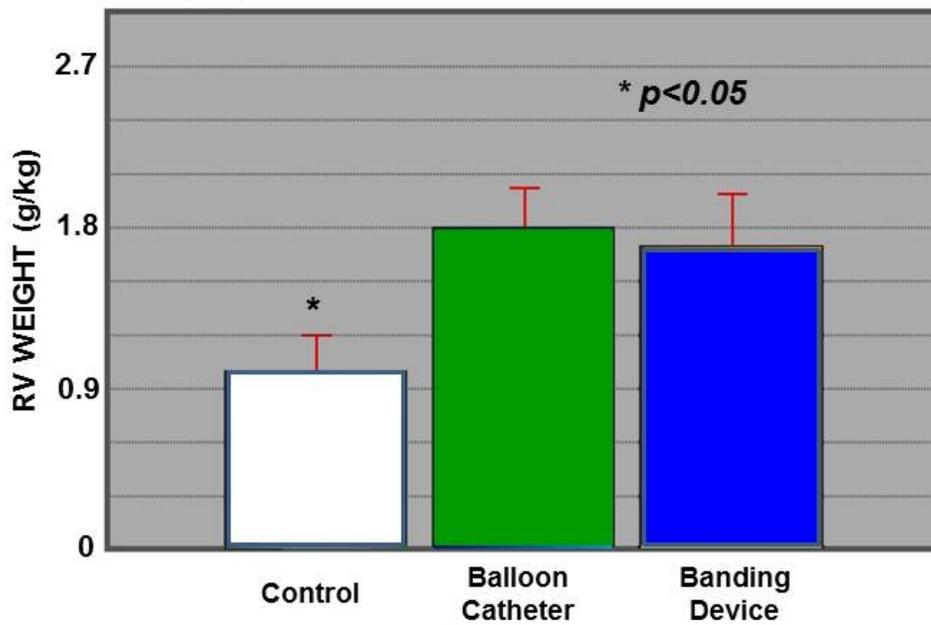
**Figure 7.** Adjustable banding device consisting of 3 parts: banding ring (hydraulic cuff), extension tube, and self-sealing inflation button (reservoir).

The device was implanted on the pulmonary trunk of young goats and inflated so that a 0.7 RV to LV pressure ratio was achieved. Continuous systolic overload was maintained during a 96-hour period. The study group showed a 74% increase in RV mass when compared with the control group, while a 66% increase in RV wall thickness was found by serial 2-D echocardiography. There was a 24% increase in the mean myocyte perimeter, and the myocyte area increased 61% (Figure 8).

This extravascular device was further compared to the endovascular approach (balloon catheter), during a 96-hour protocol of continuous systolic overload. Both approaches were able to induce rapid RV hypertrophy of similar magnitude (Figure 9).



**Figure 8.** Microphotography of RV cardiac myocytes of animal 6 sectioned transversely at the level of the nucleus, indicating their perimeters and respective areas: A, baseline samplings; B, samplings after 96 hours of systolic overload. (Original magnification 400x)



**Figure 9.** Both devices are able to induce a similar degree of RV hypertrophy during a 96-hour study period.

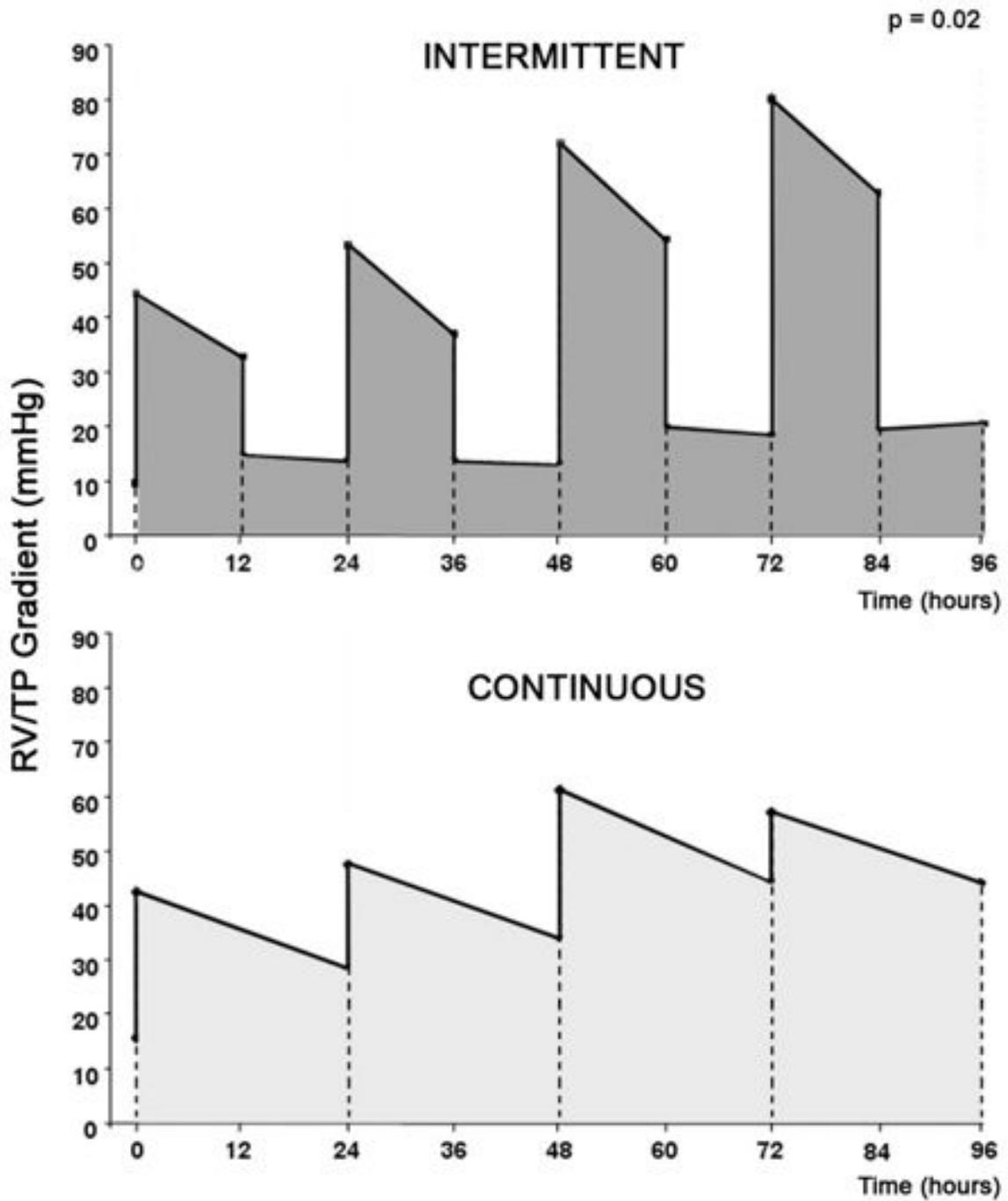
#### 4. Intermittent systolic overload

Heart hypertrophy is the main adaptive response of a heart submitted to physiological or pathological overload. At present, there is great concern about the quality of ventricular

hypertrophy, leading to questions regarding the most efficient and physiologic training program and the adaptive mechanisms involved in the process. On the other hand, the hypertrophy of an athlete's heart, characterized by normal or increased capillary density with little or no fibrosis, is a consequence of physiologic stresses like endurance exercise, intermittent by nature. It is interesting to note that the acquisition of LV mass during physical conditioning of athletes who practice swimming for example, reaches a peak in about only one week of training. Then the LV mass remains relatively constant. Based on the fact that both the cardiac and the skeletal muscles are striated, it has been proposed that a fitness program similar to that developed by athletes would lead to an acquired muscular mass with better performance. Besides that, the knowledge that the myocardium is a postmitotic organ, which means that cardiomyocytes are capable of proliferating after the neonatal period, leads to the hypothesis that myocyte hyperplasia may be an important feature in mass acquisition, although it has not been clarified to what extent it occurs. Trying to improve the rapid hypertrophic process without causing injury to the myocardium of the subpulmonary ventricle, we tried to find an analogy between the physiological hypertrophic processes with intermittent PA banding, where periods of systolic overload were alternated with resting periods of the subpulmonary ventricle. We formed a hypothesis that submitting the RV to daytime systolic overload, paired with nighttime resting period, could cause a more beneficial hypertrophic process, similar to a fitness program of athletes. We then carried out an experimental study designed to evaluate two protocols of PA banding (continuous and intermittent) and to analyze histologically the structural phenotype changes (hypertrophy and/or hyperplasia) of the contractile (cardiomyocytes) and noncontractile cells (vascular and interstitial) from the stimulated ventricle of young goats (Figure 10).

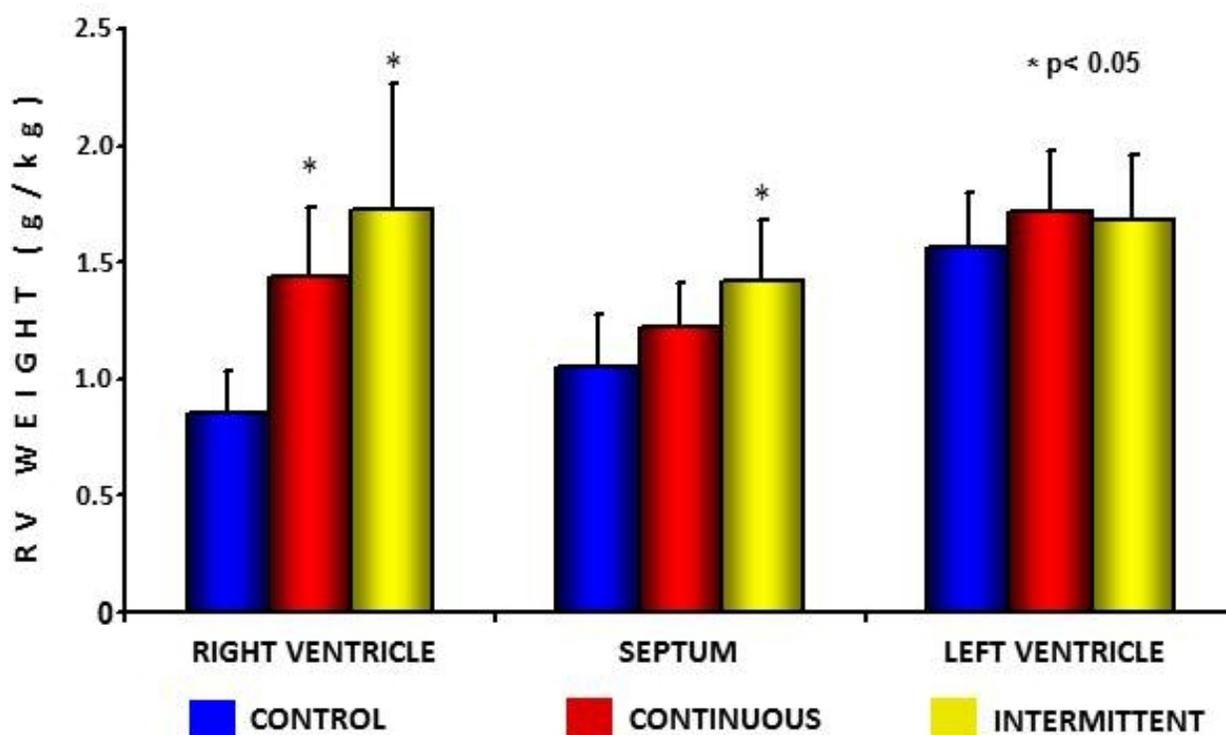
An interesting finding in this study was that both groups presented with significant increase in the RV free wall thickness. Nevertheless, this increase was significantly greater in the Intermittent Group (132.1%), compared to a 63.7% increase of in the Continuous Group. Regarding RV mass, there was a significant increase in the both groups, as compared to the Control Group (55.6% for the Continuous Group and 88.9% for the Intermittent Group), while only the Intermittent Group developed a significant increase of septal mass (40%), when compared to the Control Group (Figure 11). That study has demonstrated that intermittent systolic overload was more efficient in promoting the increase in RV mass than in the Continuous Group, considering the greater septal hypertrophy.

Morphometric analysis revealed that for both stimulated groups, hypertrophy and hyperplasia of cardiomyocytes occurred (Figure 12). Nevertheless, it is well recognized that interstitial cell proliferation is also a feature in myocardial hypertrophy caused by other factors. The interstitium has important functions, such as support for cardiomyocytes, blood and lymphatic vessels; acting as a defense mechanism against microorganisms; facilitating myocardial nutrient exchanges; and aiding in cell contraction. However, when interstitium enlargement is excessive, it may cause early diastolic dysfunction and, in the final stages, also jeopardizes systolic function. In that study, no significant difference existed in RV collagen area fraction among the three groups (Continuous, Intermittent, and Control groups). We cannot rule out the possibility that the observation time (96-hour protocol) was not sufficient to demonstrate an increase in the interstitial component.

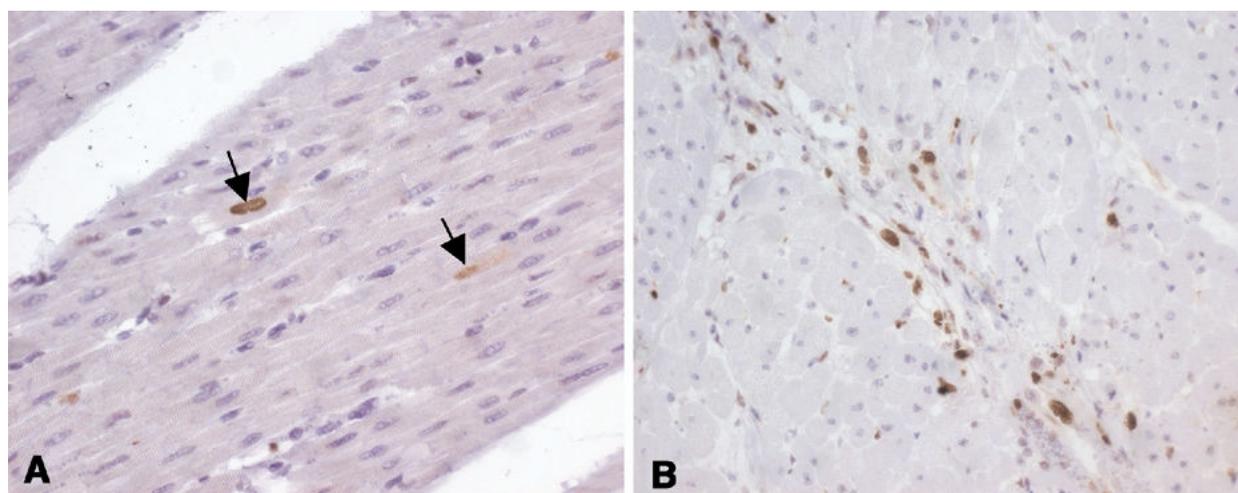


Lower graph: RV to Pulmonary trunk (PT) gradient (mmHg) of group submitted to continuous RV systolic overload (\*p=0.02).

**Figure 10.** Diagram of RV systolic overload. Upper graph: RV to Pulmonary trunk (PT) gradient (mmHg) of the group submitted to 12-hour RV systolic overload paired with 12-hour resting period.



**Figure 11.** Cardiac masses Weight of Control, Continuous and Intermittent Groups. Similar increase in the RV masses of both stimulated groups was observed, as compared to Control Group ( $p < 0.05$ ). Only Intermittent Group had a significant increase of septal mass ( $p < 0.03$ ), when compared to Control Group. No significant changes were seen in the LV mass of the three groups ( $p = 0.53$ ).



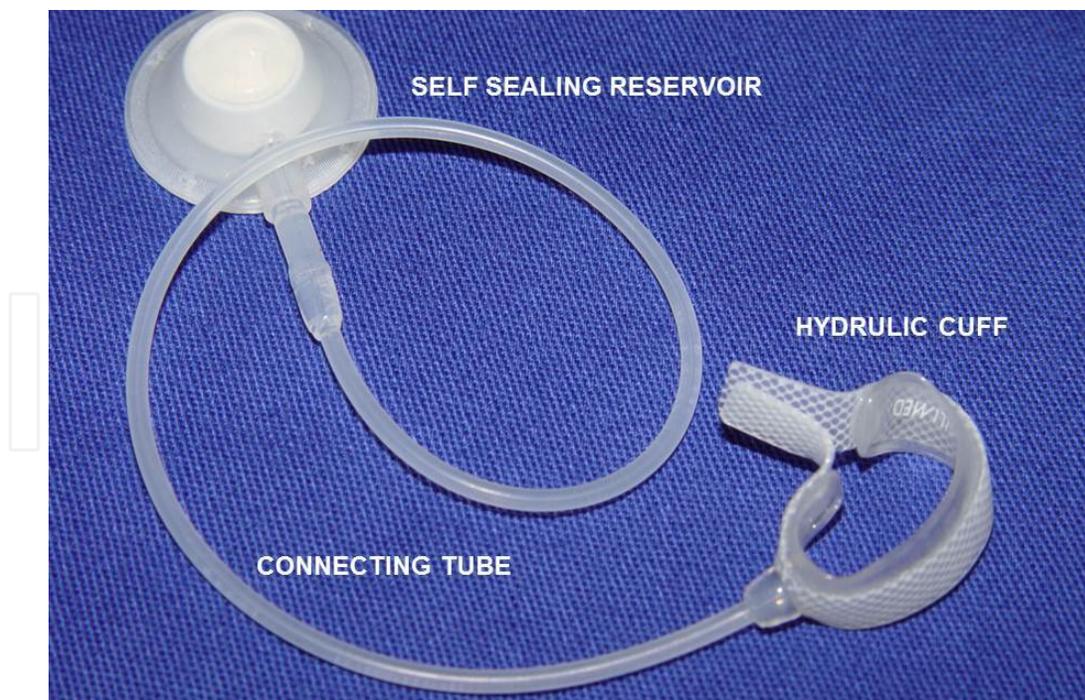
**Figure 12.** Histologic aspect of Ki-67-labeled cardiomyocytes. Higher indexes of proliferating cells were found in the RV of both stimulated groups (Continuous group, 1.13%; Intermittent group, 0.68%) when compared with the corresponding LV and ventricular septum.

This hypothesis is corroborated by the studies of Le Bret et al. They have demonstrated in adult animal model that only two hours per day of RV systolic overload was capable of inducing

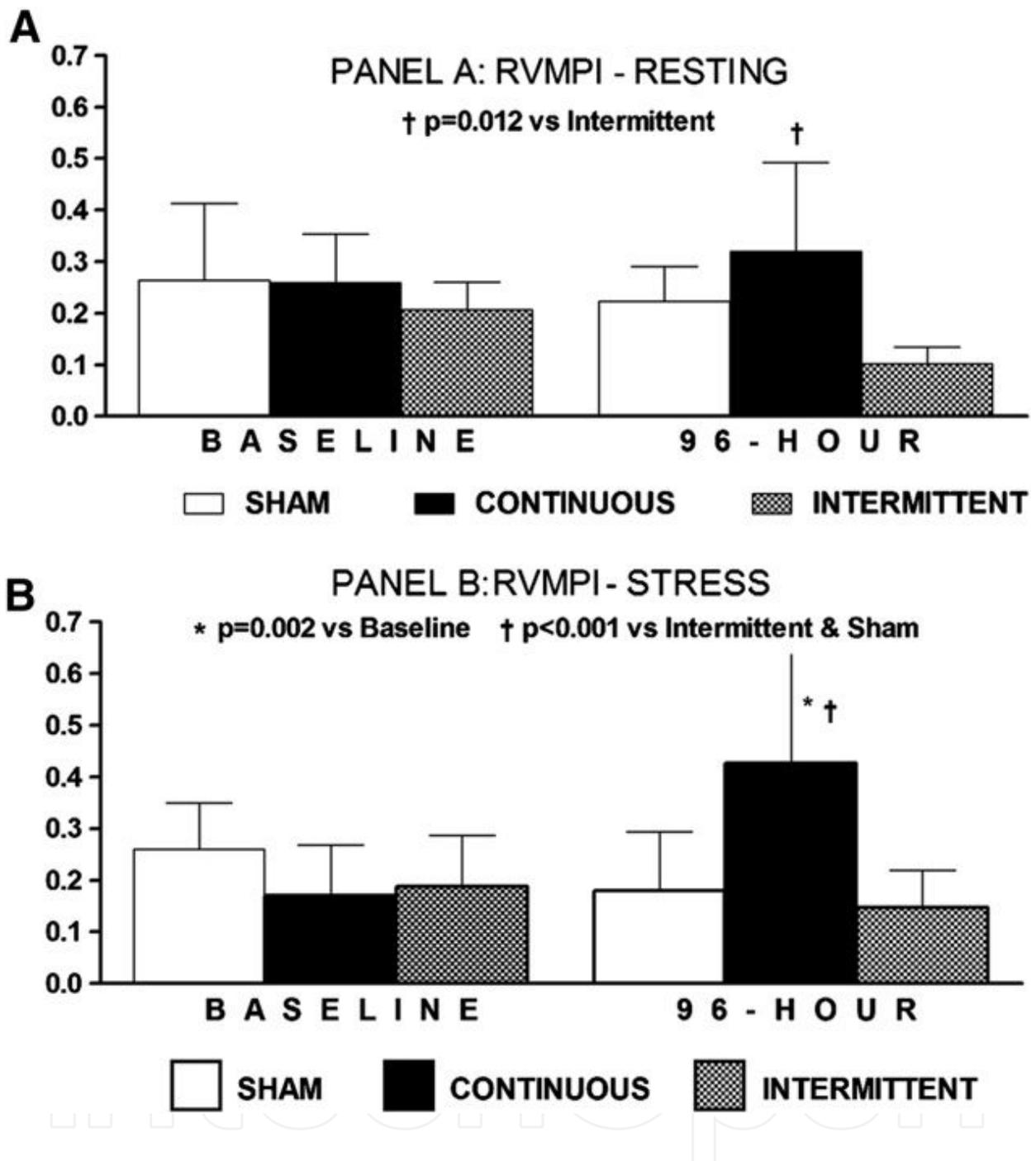
RV hypertrophy during a period of five weeks. On the other hand, fibrosis was observed only in animals submitted to traditional PA banding protocol, when compared to intermittent group. Therefore, it seems that the duration of the training period is important as an inductor of myocardial fibrosis, responsible for late heart failure.

## 5. Intermittent systolic overload and heart function

Evaluation of RV function is difficult to image because of its complex morphology. Although cardiac magnetic resonance imaging is currently considered the reference technique for RV volumetry and calculation of the ejection fraction, various echocardiographic parameters can provide reliable information on RV dimensions and RV systolic and diastolic function in daily clinical practice. Therefore, the myocardial performance index (MPI) has been proposed as a relatively simple method to assess the combined systolic and diastolic performance of the right ventricle simultaneously. Focusing on a more sensitive method to detect early disturbances in ventricular function during the process of rapid RV hypertrophy, we have compared subpulmonary ventricular function of intermittent versus continuous systolic overload, using MPI and a pharmacologic stress technique. The combination of these techniques resulted in greater sensitivity in assessing ventricular function in that protocol. A new adjustable pulmonary artery banding system, made by SILIMED Inc. (Rio de Janeiro, Brazil), was implanted just beyond the pulmonar valve (Figure 13).



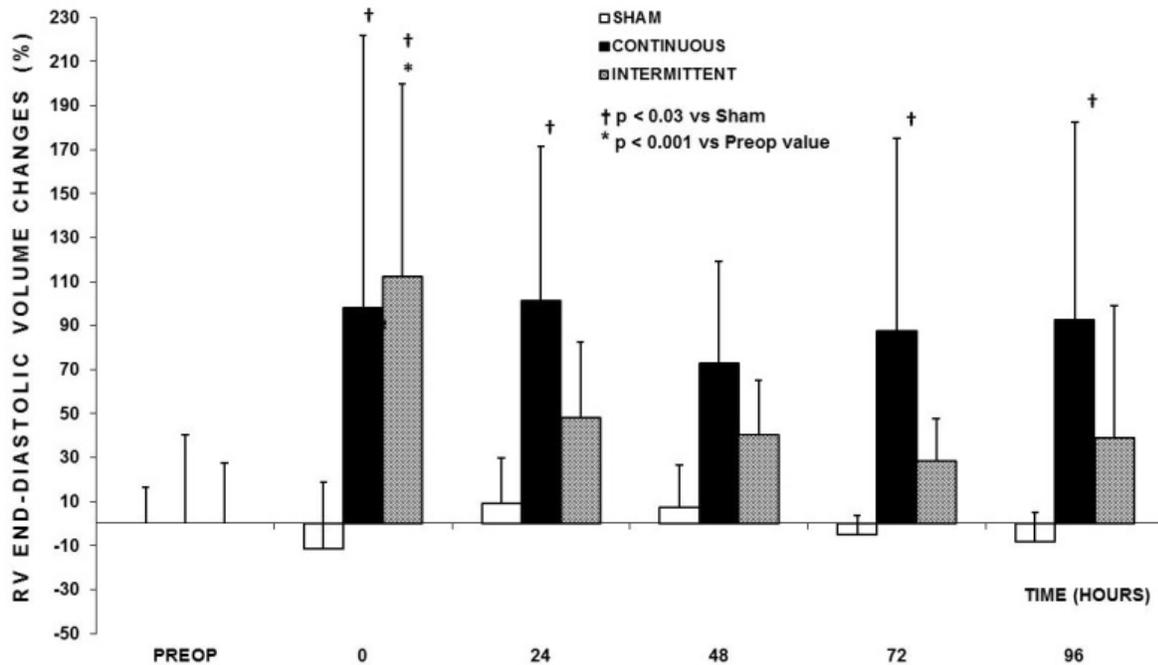
**Figure 13.** The adjustable pulmonary artery banding system, made by SILIMED Inc., Rio de Janeiro. The prototype has three parts: an insufflating button that includes a self-sealing silicone diaphragm at a top, a banding ring comprising a hydraulic cuff and an extending tube connecting both hermetically.



**Figure 14.** Right ventricular myocardial performance index (RVMPI) of sham, continuous, and intermittent groups, under dobutamine stress. A, Resting condition († p=0.012 compared with that in intermittent group at the same moment) and, B, dobutamine stress (\* p=0.002 compared with baseline value; † p<0.001 compared with that in intermittent and sham groups at the same moment).

It has been demonstrated that intermittent systolic overload promoted a functionally superior hypertrophy at rest and under dobutamine stress, and that MPI enhances diagnostic confidence in ventricular retraining (Figure 14).

Regarding RV end diastolic volume, continuous systolic overload resulted in persistent dilation throughout the protocol (Figure 15). This could also reflect worse ventricular adaptation in the continuous group. On the other hand, the 12-hour resting periods of intermittent systolic overload might have optimized subendocardial coronary flow in the intermittent group, limiting the severity of systolic overload. It would probably provide a better adaptation and consequent preservation of ventricular function in the intermittent group at periods of systolic overload.

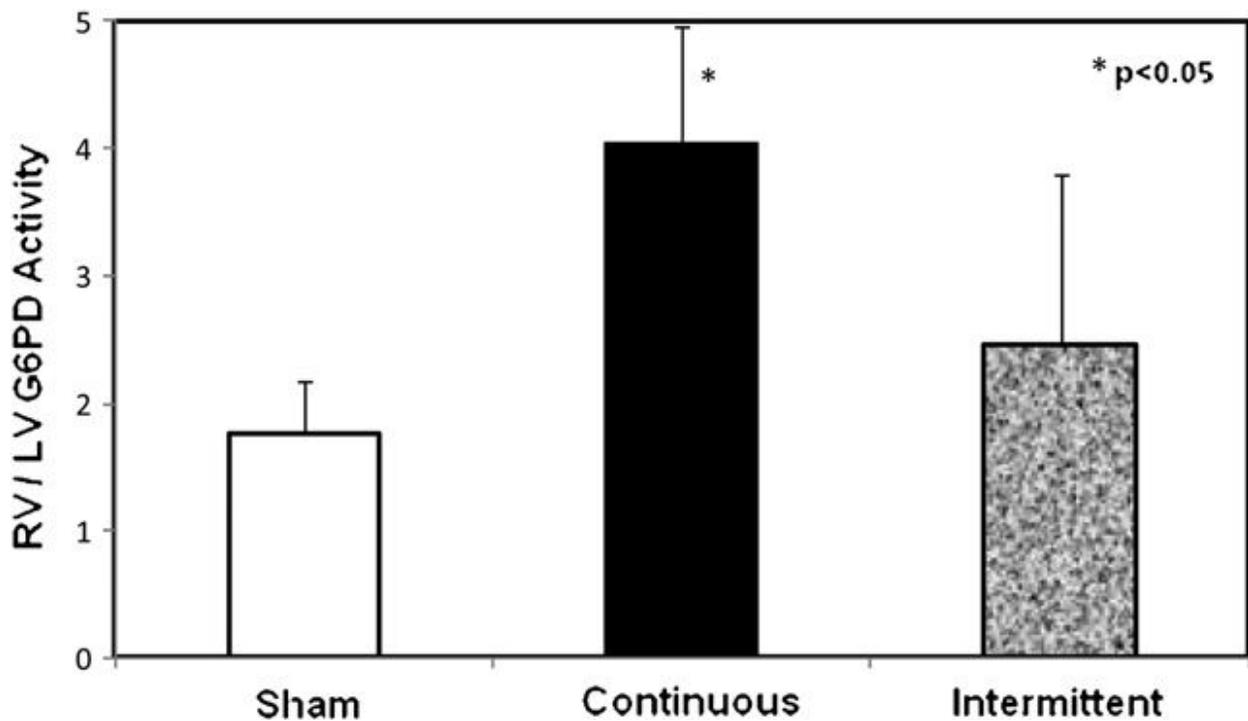


**Figure 15.** Right ventricular end diastolic volume changes of Sham, Continuous and Intermittent groups. †  $p < 0.001$  compared with that of the sham group. \*  $p < 0.001$  compared with its respective baseline value.

## 6. Intermittent systolic overload and energetic metabolism

It is essential to understand the molecular mechanisms involved in PAB-induced myocardial hypertrophy to establish training protocols that lead to a desirable “physiologic hypertrophy” versus a deleterious “pathologic hypertrophy.” Because a known shift occurs in energy substrate use in favor of glucose in pathologic conditions, energy metabolism might be altered in PAB ventricular retraining protocols. In addition, recent experimental studies have linked an unbalanced oxidative and reductive process to a variety of diseases, such as atherosclerosis and heart failure. Glucose 6-phosphate dehydrogenase (G6PD), the rate limiting enzyme that commits glucose to the pentose phosphate pathway, is mainly responsible for the generation of nicotinamide adenine dinucleotide phosphate (NADPH) and ribose 5-phosphate, an

essential precursor of the de novo synthesis of RNA and DNA. G6PD-derived NADPH, a cofactor for glutathione and thioredoxin reductase, preserves reducing potentials and protects the cell from oxidative stress in normal conditions. In human diseases, G6PD can be either activated or inhibited; however, evidence has emerged that the overexpression and activation of G6PD enhances NADPH oxidase-derived superoxide generation and increases oxidative stress in diseases like diabetes, heart failure, and hypertension. In regard to rapid ventricular training, it is of great interest to evaluate myocardial energy metabolism in response to different cardiac hypertrophy models and its relationship to heart function. We have compared the myocardial G6PD activity of young goats in 2 RV training protocols, continuous versus intermittent systolic overload (Figure 16).



**Figure 16.** RV/LV ratio of G6PD activity in the sham, continuous, and intermittent groups. \* $p < 0.05$  compared with that in the sham and intermittent groups.

The continuous group presented a series of deleterious effects during rapid subpulmonary ventricle retraining. Persistent RV dilation was followed by impaired RV function and increased G6PD activity. Because the pentose phosphate pathway is one of the major sources of NADPH in cardiac myocytes, this is an important finding, and it may indicate an unbalanced redox, with the occurrence of oxidative stress and generation of reactive oxygen species related to NADPH oxidase. The final consequence of this cascade of events would be the cardiomyopathy related to protein aggregation owing to reductive stress. It has been demonstrated that either G6PD activation or inhibition is associated with diseases. However, growing evidence has emerged that G6PD overexpression correlates with oxidative and reductive stress, and new investigational drugs are currently under development to suppress its action. For instance, diabetic patients had upregulation of G6PD with high NADPH levels, and that was

linked to inhibition of nitric oxide synthesis and endothelial dysfunction. Although the mechanisms underlying the increased production of reactive oxygen species in the heart are not completely understood, it has been proposed that the high rate of glucose oxidation increases mitochondrial membrane potential, which enhances production of superoxide anion. The latter would be a modulator in diabetic vasculopathy and precede the development of diabetic cardiomyopathy. We speculate that, in case of persistent systolic overload, upregulation and hyperactivity of myocardial G6PD observed in the continuous group strongly suggest that the pentose phosphate pathway enhances cytosolic NADPH availability, thus fueling free radical production by NADPH oxidase and uncoupled nitric oxide synthase. Therefore, it may induce superoxide anion myocardial injury, as well as protein aggregation, and subsequently heart failure. We postulate that intermittent systolic overload promotes the desirable effects of myocardial hypertrophy without its adverse effects. We would argue that the 12-hour resting period allowed the myocardium to replenish energy substrates and reestablish subendocardial perfusion owing to a lower ventricular wall tension. That would probably provide better hemodynamic performance at periods of systolic overload.

It is difficult to make definitive conclusions about a hypertrophic process based on a single enzyme activity. Nevertheless, it is essential to correlate these biochemical findings with production of superoxide anions and apoptosis to better understand the role of oxidative stress in hypertrophy training protocols. Previous studies have demonstrated that the oxidative branch of the pentose phosphate pathway, which produces NADPH and ribulose 5-phosphate, is essentially irreversible, being controlled primarily by G6PD activity and, hence, the NADPH/NADP ratio. NADPH oxidase preferentially uses NADPH derived from the pentose phosphate pathway, and that, in the failing heart, more glucose is oxidized through the pentose phosphate pathway, with a consequent increase in electron donors available to fuel  $O_2$  generating enzymes. Maybe that is the way NADP<sup>+</sup> is upregulated. Although this is a non-specific pathway of free radical production, we have found a concordance of impaired RV function of continuous group and increased G6PD. Nevertheless, it would be more objective if oxygen-derived free radicals or tissue injury markers related to their production had been measured. Therefore, it is somehow difficult to assume and interpret a whole metabolic pathway based on the activity of a single enzyme. The hyperactivity in myocardial G6PD, together with RV dilation and dysfunction, may be related to an unbalanced redox determined by a constant and pathologic systolic overload. Given that pentose phosphate pathway enhances cytosolic NADPH availability, this altered energy substrate metabolism can elevate levels of free radicals by NADPH oxidase, an important mechanism in the pathophysiology of heart failure. On the other hand, intermittent systolic overload has promoted a more efficient RV hypertrophy than the continuous one, with better preservation of myocardial performance and smaller G6PD activity.

## **7. Mature ventricle retraining**

Although the survival of patients with CCTGA is dictated largely by the associated defects, life expectancy is diminished for patients even with the isolated form of the condition. A

number of studies have confirmed that life expectancy is substantially diminished even for patients who have reached adulthood. The most common cause of death is congestive heart failure secondary to morphologically right (systemic) ventricular dysfunction, often associated with regurgitation of the tricuspid valve. The traditional surgical approach to the treatment of patients with CCTGA maintains the morphologically RV and tricuspid valve in the systemic circulation. However, dysfunction of the systemic (morphologically right) ventricle or systemic atrioventricular (tricuspid) valve tends to develop and worsen with time, which may lead to significant morbidity and mortality. Tricuspid regurgitation can be addressed by valvuloplasty or replacement of the systemic atrioventricular valve. Nevertheless, this procedure is often unsuccessful in preventing or reversing right ventricular dysfunction. There are indeed anatomical and physiological considerations that support the assumption that the LV is more suitable than the right to serve the systemic circulation. First of all, LV (with its cylindrical shape, its concentric contraction pattern, and both the inlet and outlet orifices situated in close proximity) seems ideally adapted to work as a pressure pump, whereas the RV (with its crescent-shaped cavity, its large internal surface area-to-volume ratio, its bellows-like contraction pattern, and its more separated inlet and outlet segments) seems better suited to serve as a low-pressure volume pump chamber. Also, the LV has two coronary arteries (left anterior descending and circumflex), while the RV has only one (right coronary). Furthermore, the papillary muscles of the RV are small and numerous, originating both from the septum and from the right ventricular free wall, in contrast to the two papillary muscles of the LV. This architecture allows the tricuspid valve to be pulled apart as the RV dilates, leading to tricuspid regurgitation. In long-term, patients with CCTGA begins to dilate RV and the tricuspid annulus (which is the systemic valve), allowing RV blood regurgitation during ventricular contraction and, consequently, pulmonary congestion and dyspnea. The high late mortality associated with the traditional approach has stimulated a number of groups to propose a more anatomic repair on the basis of the hypothesis that establishment of atrioventricular and ventriculoarterial concordance would improve the long term survival of patients with this anomaly. This approach has been named as double switch operation, i.e., atrial level circulation switch by the Senning procedure and arterial switch operation at the same time. This strategy has the appealing theoretic advantage of recruiting the morphologically LV and mitral valve to sustain systemic pressure and resistance, thus relieving the hemodynamic burden on the RV and tricuspid valve. Many of these patients are older and are seen because of right ventricular failure, usually with tricuspid valve regurgitation and often without associated defects. As would be expected in these cases, the LV is physiologically unprepared to sustain systemic pressure and resistance, because it has been working as the pulmonary ventricle. Therefore, double switch procedure must be performed after a preliminary PA banding procedure to recondition the LV. Although PAB appears to be capable of providing adequate LV training when done at an early age, it is not always suitable for mature myocardium, with disappointing results in older patients. Because of the high degree of variability among these patients, optimal band tightness is not always achieved on the first effort and is often limited by the onset of LV dysfunction. The retraining process of the LV, especially in older patients, may take months before obtaining the necessary LV hypertrophy to sustain systemic pressure and vascular resistance. According to Mavroudis and Backer, in patients

with TGA and failed atrial inversion, aged from 1.9 to 23 years, it took an average of 15.6 months to retrain the subpulmonary ventricle for the two-stage Jatene operation. In addition, it has been described in the literature the need for subsequent reoperations to readjust PA banding in cases where patient cannot achieve adequate LV hypertrophy. The difficulties in retraining adult myocardium with the traditional approach has stimulated several groups to propose a more physiologic protocol based on the hypothesis that intermittent systolic overload would improve the quality of subpulmonary ventricle hypertrophy. Such an approach has the appealing advantage of ventricular retraining with no collagen formation, providing a more physiologic hypertrophy. However, the time necessary to retrain these ventricles and the best way to achieve a more physiologic hypertrophy and assess the specific histologic changes involved in this process are still required. We have compared the histomorphometric changes of PAB-induced RV hypertrophy of adult goats, with the emphasis on a detailed analysis of the myocardium adaptation process (Table 1).

	Sham N = 6	Traditional N = 6	Intermittent N = 6	p value
Mass (g/kg)	0.79 ± 0.15	1.08 ± 0.17 *	1,24 ± 0.16 †	<0.05
Water Content (%)	79.16 ± 1.28	79.67 ± 1.25	80.61 ± 1.87	0.27
Cardiomyocyte diameter (µm)	11.54 ± 0.89	12.96 ± 1.35	13.76 ± 1.68 †	<0.05
Nuclei diameter (µm)	3.86 ± 0.14	4.40 ± 0.48	4.74 ± 0.71 †	<0.05
Collagen percentage area (%)	2.94 ± 0.65	5.82 ± 1.91 *	3.44 ± 1.24 #	<0.05
Cardiomyocyte Ki67 <sup>+</sup> cells (cells/ field)	0.33 (0.08-0.75)	0.33 (0.08-0.83)	0.25 (0.08-0.58)	0.89
Interstitial/Vessel Ki67 <sup>+</sup> cells (cells/field)	2.67 (1.00-3.58)	2.83 (1.25-8.50)	2.17 (1.75-4.75)	0.68

Values: means ± SD or medians (limits)

\* p<0.05 compared Traditional and Sham groups;

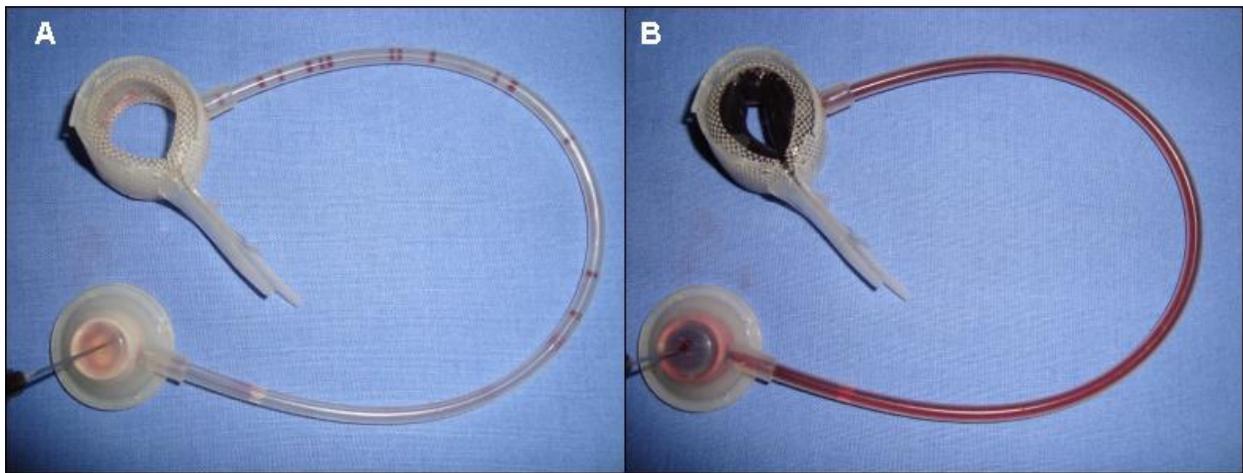
† p<0.05 compared Intermittent and Sham groups;

# p<0.05 compared Intermittent and Traditional groups.

**Table 1.** Gross and histomorphometric RV findings in Sham, Traditional and Intermittent groups

The prototype used in this study (SILIMED, Rio de Janeiro, Brazil) represents the adult version of the small adjustable PAB system used previously in young animals (Figure 17). Its dimensions were planned to support higher pressure gradients in adolescents and adults patients considered for subpulmonary ventricle retraining. All parts of the Adjustable Banding System are made of biologically stable material (medical grade silicone).

The banding ring is a C-shaped hydraulic cuff that has three layers. The inner wall of the banding ring is formed by a very thin and flexible silicone that allows centripetal distension. Differently from the young animal prototype, the outer layer is divided in two parts, both

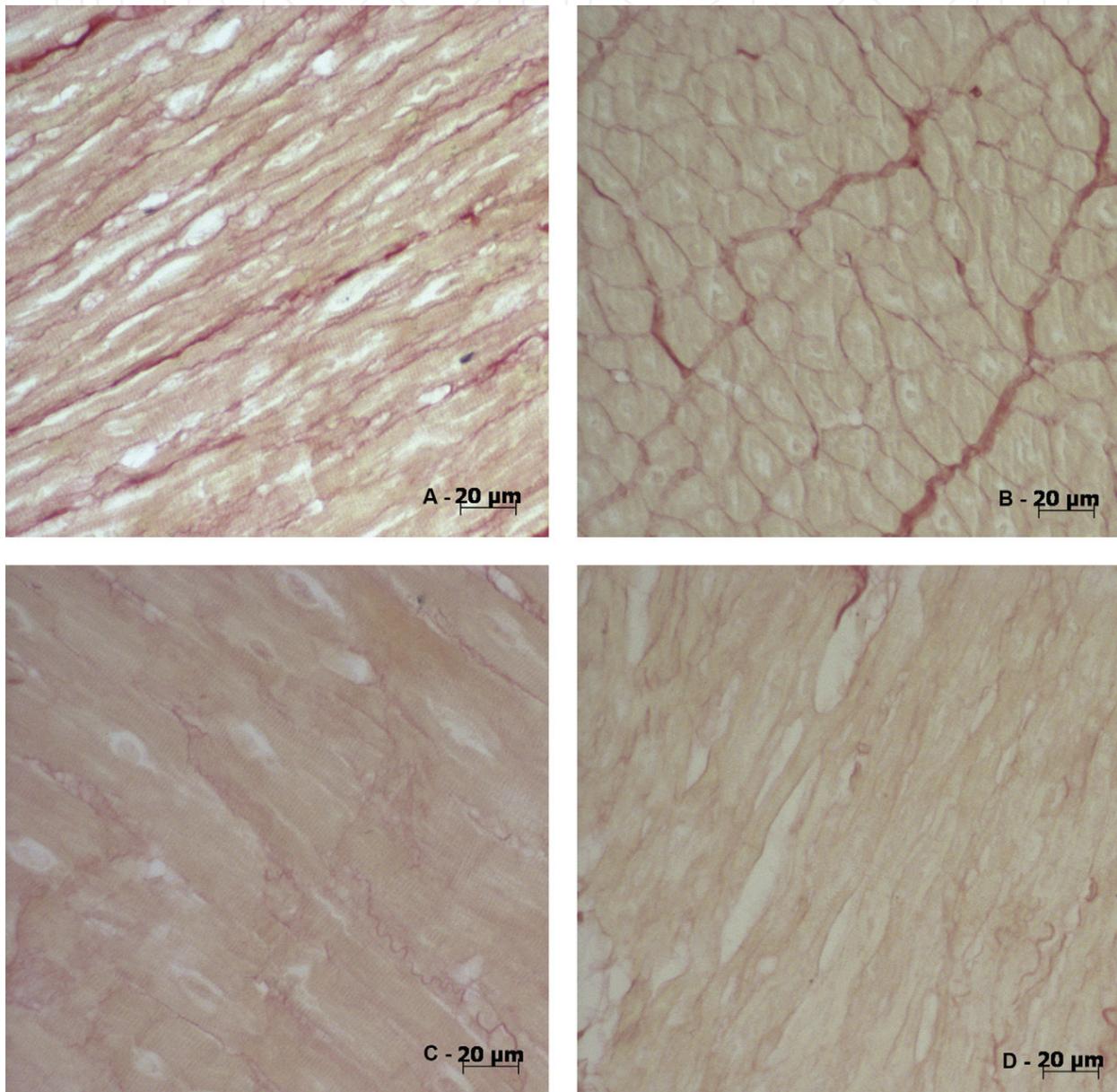


**Figure 17.** The adult banding device consists of an inflatable C-shaped hydraulic cuff (24-mm diameter) and an inflation reservoir connected hermetically to each other by a 2.0-mm diameter tube (SILIMED, Rio de Janeiro, Brazil).

consisting of 1.0-mm-thick rigid silicone each, reinforced with a polyester mesh. The outer external layer presents some small holes along the non apart borders, which are used for securing it firmly with sutures to the adventitia of the artery. This keeps the adjustable banding system from migrating distally and impinging on the pulmonary artery bifurcation. The external layer prolongs with two apart ends, planned for further adjustment of the hydraulic cuff, when placed around the artery, by suturing together the ends. The inner external layer prolongs alongside the cuff as a canoe, to keep it from deforming. The connecting tubing has 1.0 mm inner diameter. The inflation reservoir used to pump fluid to the hydraulic cuff consists of a ceramic cylindrical reservoir, with a self-sealing silicone diaphragm at the top, which keeps the banding system leak proof after repeated needle puncture of the reservoir.

The two regimens of ventricular training, traditional and intermittent, have promoted different degrees of myocardial hypertrophy. However, it was less intense and longer in adult animals than that observed previously in young goat hearts. Histomorphometric and echocardiographic data indicated that intermittent RV systolic overload promoted a harmless RV hypertrophy in adult goats during a 4-week study period. On one hand, the primary mechanism of RV mass acquisition was probably related to increased protein synthesis and cell hypertrophy rather than myocardial hyperplasia or edema. On the other hand, the traditional PAB group evolved with greater collagen production, which is one of the important mechanisms of late ventricular failure. The absence of myocardial edema and significant cell proliferation observed in that study suggests that the mass acquisition was probably related to enhanced protein synthesis, both intracellular (contractile proteins) and extracellular (matrix proteins). In the adult heart of mammals, it is generally believed that almost none of the cardiomyocytes proliferate and that the hypertrophy process functions as the fundamental adaptive response. The magnitude of cardiomyocyte hypertrophy then depends on the age at which the stimulus is produced. As predicted in an adult model, no significant cellular proliferation was observed in any cardiac segment, contrary to the findings of similar experimental studies in young animals, in which RV responds not only with hypertrophy of the myocardial fibers but also with hyperplasia of the contractile and interstitial myocardial cells.

Although the intermittent group was the one least exposed to systolic overload, a more efficient RV hypertrophy was observed, just as documented previously by our studies in young goat hearts. Similarly, the hemodynamic results showed that the intermittent group could achieve greater RV-to-PA pressure gradients than the traditional group during the 4-week study period. Intermittent systolic overload mimics exercise training, which can benefit the trained myocardium with improved subendocardial perfusion. On one hand, it is likely that the mechanism of this hypertrophic process may be developed during the resting periods with ideal oxygen transport and, hence, without the collagen deposition resulting from continuous



**Figure 18.** Photomicrographies of the right ventricular myocardium from four representative animals, two from the Traditional (A and B) and two from the Intermittent (C and D) group, after four weeks of systolic overload. Panels A and B show a higher density and intensity of collagen staining (red fibers around individual cardiomyocytes- endomyocardial fibrosis) than that in panels C and D. Sirius-red staining, objective magnification-20X.

relative diastolic hypoperfusion. On the other hand, the traditional group had deleterious effects at the end of the protocol, with more collagen deposition in the RV interstitium. The mean RV collagen area fraction of the Traditional group was significantly greater than in the Sham group (98% increase;  $p < 0.01$ ), and greater than that in the Intermittent group (69.2% increase;  $p < 0.05$ ). The histological distribution of collagen in representative animals from trained groups is demonstrated in Figure 18. This collagen deposit may be the key determinant of the impaired RV function previously observed on the same protocol. Accordingly, Le Bret and colleagues reported myocardial fibrosis associated with continuous overload and no fibrosis in their "fitness" group, during a 5-week period in adult sheep. Although the results with adjustable intermittent PAB are encouraging, it is premature to assume this as the definitive solution for adult myocardium retraining.

## 8. Adjustable PA banding and hypoplastic left heart syndrome

More recently, bilateral PA banding has been applied to hypoplastic left heart syndrome (HLHS). The mitral and aortic valves present either with atresia or hypoplasia. This results in a situation where the left side of the heart is completely unable to support systemic circulation, though the right side of the heart is typically normally developed. Blood returning from the lungs to the LA must pass through an atrial septal defect to the right side of the heart. The RV must then pump blood both to the lungs (via the pulmonary trunk) and out to the body (via a patent ductus arteriosus). The patent *Ductus Arteriosus*, a normal structure in the fetus, is often the only pathway through which blood can reach the body from the heart. When the *Ductus Arteriosus* begins to close, as it typically does in the first days of life, the blood flow to the body will severely diminish, resulting in dangerously low blood flow to vital organs and leading to shock. Without treatment, HLHS is uniformly fatal, often within the first hours or days of life. The most commonly pursued treatment for HLHS is "staged reconstruction" in which a series of operations, usually three, are performed to reconfigure the child's cardiovascular system to be as efficient as possible, despite the lack of an adequate LV. The first operation in the staged approach is the Norwood operation and is typically performed in the first week of life. With the Norwood operation, the RV becomes the systemic or main ventricle pumping to the body, and a systemic-to-pulmonary shunt aims redirectioning circulatory pathways to protect the pulmonary vasculature from excessive blood flow and optimize systemic organ flows. However, some overloading of the systemic right ventricle still persists after this operation. Also, such major surgical procedure is usually performed in the neonatal period (sometimes in a low-birth weight patient and unfavorable anatomy), which may result in sub-optimal neurological outcomes in the long-term. Because of the extensive reconstruction of the aorta that must be done, this operation is one of the most challenging heart surgeries in Pediatrics. This traditional surgical approach of newborns with HLHS is complex and continues to have significant mortality compared with other neonatal cardiac operations.

An alternative approach for palliation of hypoplastic left heart in the neonatal period has been stenting the arterial duct in combination with branch PA banding and atrial septostomy, as needed. The so called hybrid stage I palliation has been considered the preferred therapeutic

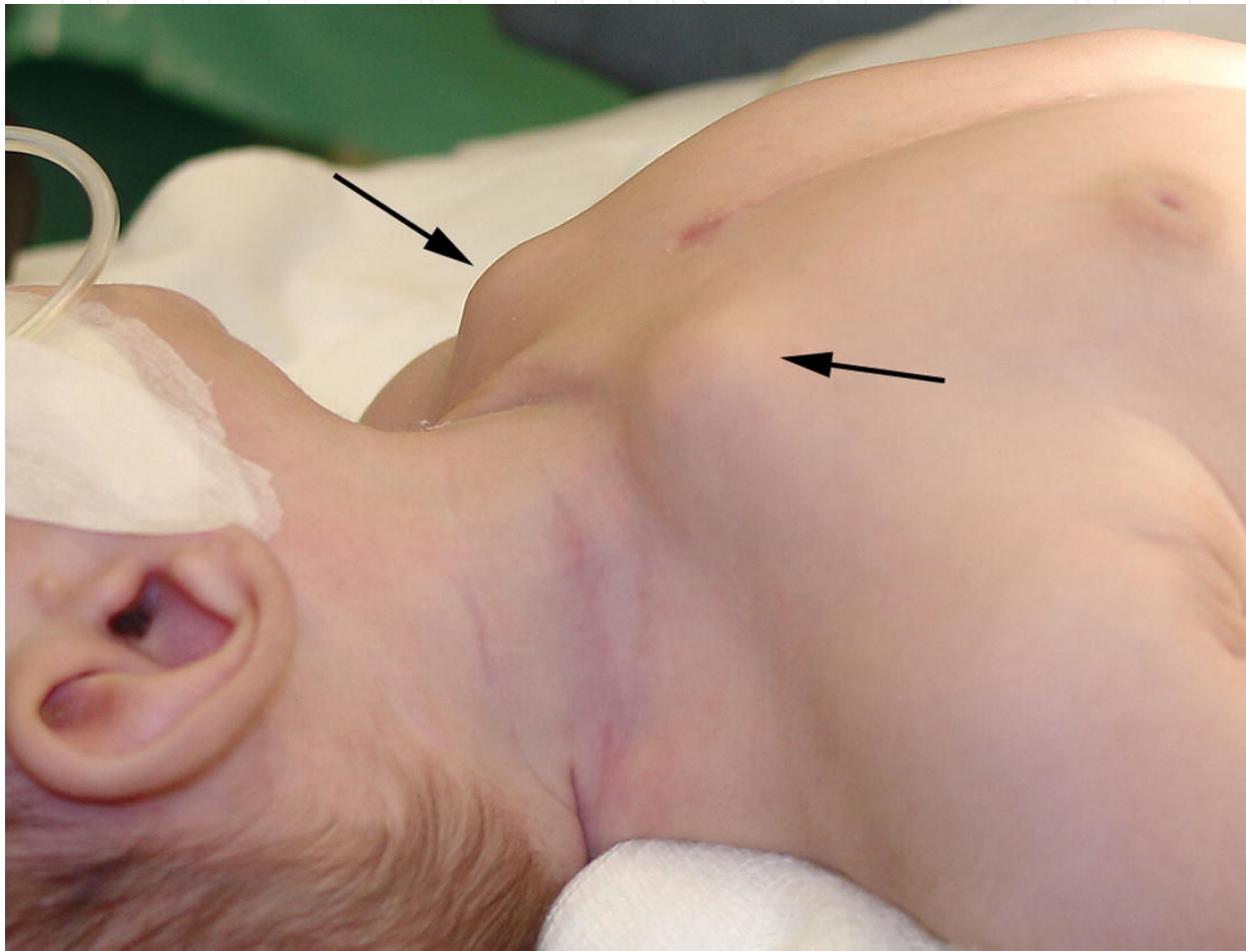
approach in high-risk neonates. However, fine adjustments of the amount of pulmonary blood flow, which is a critical issue, has proved to be a particularly difficult aspect of the procedure. This can be readily explained when it is recalled that Poiseuille's law predicts that blood flow is related to the fourth power of the radius of the vessel. Therefore, a minor alteration in diameter will have a large impact on flow and pressure gradient across the band site. Generally, the bands are surgically adjusted (tighten or loosened), based on pressure measurements and the arterial oxygen saturation monitoring. A systolic pressure in the distal pulmonary artery less than half of the systemic pressure and an arterial oxygen saturation of 75%-85% usually reflect an adequate balance between the pulmonary and systemic blood flow. This may be readily achieved in the operating room, with an open chest and under artificial conditions. However, in the postoperative period, which may be quite unpredictable, the fixed pulmonary bandings do not allow for fine adjustments according to the underlying clinical needs of the patient. Moreover, in order to avoid hypoxemia as the infant rapidly grows up, the balance between the pulmonary and systemic blood flows should be adjusted, which is impossible with the fixed bands. To deal with these problems, we devised a mini banding device that allows for fine percutaneous adjustments of the pulmonary blood flow in the neonate (Figure 19). The banding ring is a C-shaped hydraulic cuff, with 5 mm width, and a rigid outer layer, reinforced with a polyester mesh, which keep it from deforming centrifugally. It can be used in pulmonary arteries varying from 3 mm to 6 mm internal diameter range.



**Figure 19.** The adjustable pulmonary artery banding system (SILIMED, Rio de Janeiro, Brazil) used for Hybrid Stage I palliation for HLHS.

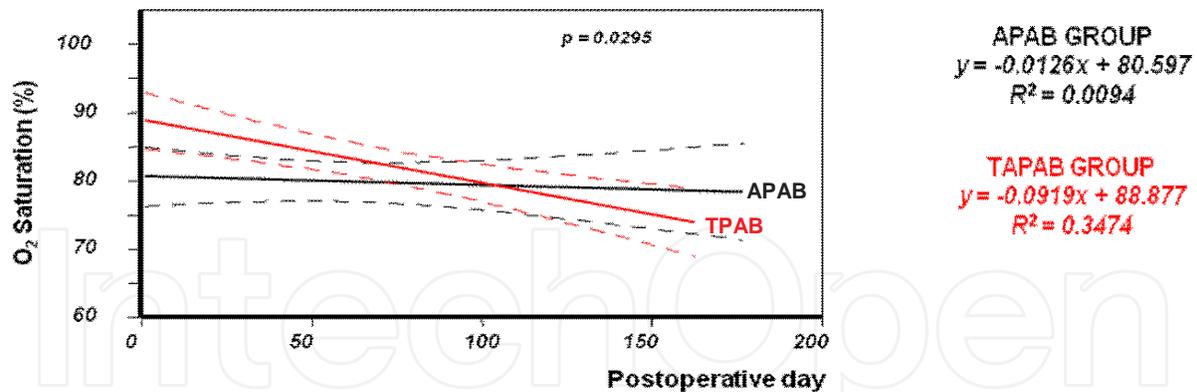
This innovative percutaneous mini adjustable banding system permits a fine control of the pulmonary blood flow by increasing or decreasing accurately the cross-sectional diameter of the pulmonary arteries. Therefore, it is adjusted according to the underlying clinical conditions

of the patients: hypoxemia is, for instance, managed by unfastening the pulmonary artery banding circumference. Once the adjustable banding ring is placed around the PA's and the inflation reservoirs left in the infraclavicular subcutaneous tissue, the degree of banding rings constriction is adjusted after sternal closure (Figure 20). Each band is inflated with saline solution to decrease arterial oxygen saturation to the 75%-85% range, while breathing under a 30% inspired oxygen fraction.



**Figure 20.** Inflating reservoirs positioned in the infraclavicular area (arrows), one for each pulmonary artery for independent percutaneous blood flow adjustment.

We have performed Hybrid Stage I palliation for HLHS using the adjustable PA band (APAB group) in 3 patients (1.8 kg - 2.8 kg) and traditional bands (TPAB group) in 3 patients (2.0 kg - 3.3 kg). The babies were followed closely with serial echocardiographic assessment every week. During inter-stage 1-2, several additional percutaneous adjustments of the PA's banding systems were necessary to maintain the arterial oxygen saturation in the recommended range according to somatic growth. Figure 21 shows the O<sub>2</sub> saturation behavior of both groups during interstage 1-2 period.



**Figure 21.** Traditional PA banding group evolved with progressive decrease of oxygen saturation during interstage 1-2, while the group using adjustable PA bands maintained more stable arterial oxygen saturation according to somatic growth.

In the APAB group, all patients reached stage 2 operation, and one of them has already completed Fontan circulation at 2 years of age, while in the TPAB group, two cases underwent the stage 2 operation and one patient died just before stage 2 operation (pulmonary infection). This small series of HLHS cases demonstrated that customization of the pulmonary blood flow seemed to result in a more precise balance between the pulmonary and systemic circulations during the interstage 1-2 period. The use of adjustable PA bands in the stage-1 hybrid procedure for HLHS can provide a more stable clinical condition, according to the rapid somatic growth and underlying clinical needs of the patient. However, the calibration of the banding cuffs was sometimes difficult to achieve, due to the extreme complexity of the continuously changing relationship between systemic and pulmonary vascular resistance, with the dependency upon several inter-related variable such as the values of the arterial pO<sub>2</sub>, pCO<sub>2</sub>, pH, hemoglobin, cardiac output, level of sedation, use of peripheral and/or pulmonary vasodilators, etc. Nevertheless, fine and reversible adjustments could be performed as many times as needed, both in acute and ambulatory settings, avoiding further surgical interventions. The use of this innovative banding system seemed to result in a more predictable postoperative course, and in a more stable patient, which is highly desirable for the comprehensive phase II operation. A concern with any PAB technique or device, including ours, is the possibility of causing vessel distortions or stenoses, which may have a deleterious impact for subsequent cavo-pulmonary operations. Fortunately, the scar tissue surrounding the banding devices was minimal in our patient and did not result in any of these complications. The cases electively submitted to the “comprehensive” stage II surgical palliation showed the anatomy of the pulmonary arteries well preserved with no distortions.

In summary, the use of our innovative mini PAB system allowed for a fine control of the pulmonary blood flow in neonates with HLHS undergoing phase I palliation. This customization of the pulmonary blood flow according to the underlying clinical needs of an infant with rapid somatic growth seemed to result in a more precise balance between the pulmonary and systemic circulations during the inter-stage period.

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