Original Article

Intermittent Systolic Overload Promotes Better Myocardial Performance in Adult Animals

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Abstract

Background: Corrected transposition of great arteries often evolves with right ventricular dysfunction. The ventricular preparation for anatomic correction in adult patients has produced disappointing results.

Objective: To assess right ventricular hypertrophy (RV) induced by conventional and intermittent pulmonary banding (PB) in adult animals.

Methods: Nineteen adult goats were divided into three groups: conventional (six animals), intermittent (six animals) and control (seven animals). The Conventional group underwent fixed PB with cardiac tape, while the intermittent group received PB adjustable device, which generated systolic overload for 12 hours, alternated with 12 hours of rest of RV. The pressures of the RV, pulmonary artery and aorta were measured throughout the study. Echocardiography was performed weekly. After four weeks, the animals were euthanized for morphological evaluation of the ventricles. The Control group was put to euthanasia for analysis at baseline.

Results: Pressure overload was lower in the intermittent group ($p = 0.001$), compared to the conventional group. There was an increase in the thickness of the RV of the Intermittent group measured by echocardiography compared to their baseline values ($p < 0.05$). The myocardial performance index in the RV group was better in the Intermittent group ($p = 0.024$), compared to the Conventional group. The groups stimulated showed increased muscle mass compared to the Control group ($p = 0.001$). There was no difference in myocardial water content.

Conclusion: The intermittent BP developed hypertrophy of better performance, suggesting this protocol as the preferred method of ventricular preparation. (Arq Bras Cardiol 2010; 95(3): 364-372)

Key words: Ventricular dysfunction, right; hipertrophy, right ventricular; animals; transposition of great vessels/surgery.

Introduction

Late right ventricular dysfunction (VD) is a complication of relative frequency in patients with transposition of the great arteries (TGA) operated at the atrial level or in those with corrected transposition of the great arteries (c-TGA)[1-4]. Since the late 1980s, several authors have reported satisfactory results by performing an operation aimed at the anatomic correction of these diseases through arterial switch (the Jatene procedure)[5], associated with atrial inversion[6-9]. Such procedure was named Double Switch, i.e., a double replacement surgery. This approach aims to prevent the natural evolution of systemic RV failure, and thus avoid the adoption of more drastic measures in these patients, such as heart transplantation, since it functionally rescues the morphological left ventricle (LV) for the systemic circulation, relieving pressure overload on the RV, significantly improving its function. In approximately one third of these cases, it is necessary to prepare the LV through pulmonary banding (PB), adjusting it to work as a systemic pressure pump[6,10,11]. However, ventricular preparation through PB in these patients produces unsatisfactory results[8,11-14], especially when performed in adolescence and adulthood. The main problems relate to the long time needed to obtain hypertrophy, development of early and late ventricular dysfunction, difficulty of preparation in elderly patients and need for reinterventions to fit the banding. Some authors have reported alternative strategies to traditional preparation even in clinical studies, primarily through adjustable banding of pulmonary trunk[8], or promoting intermittent pressure overload, mimicking the skeletal muscle training of athletes[15,16]. Hence, we hypothesized that a protocol of intermittent PB could promote a more suitable preparation, with greater preservation of ventricular functions.

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Original Article

Methods

This study was approved by the Ethics Committee for Analysis of Research Projects of HC - FMUSP (protocol 621/05) and performed in the Division of Applied Physiology of InCor - HC - FMUSP, according to the standards of animal use in teaching and research of Cofipa (Audit Committee of Animal Research).

The study employed 19 adult goats divided into three groups: Control (n=7, weight = 28.74 ± 4.13 kg, no surgical procedure), Conventional (n=6, weight = 26.33 ± 2.32 kg, PB with continuous systolic overload of the RV) and Intermittent (n=6, weight = 25.17 ± 2.48 kg, PB with adjustable device and 12 hours/day of intermittent systolic overload of the RV).

Preoperative evaluation

The animals were weighed and examined by a veterinarian to rule out preexisting conditions. Baseline echocardiographic assessment was performed to certify the absence of anatomical or morphological abnormalities prior to the procedure.

Anesthesia

The pre-anesthetic drug used was xilazina 2% at a dose of 0.1 mg/kg, intramuscular (IM). Anesthesia was induced with propofol 1% (7 mg/kg) intravenous (IV) for orotracheal intubation. The animals were maintained on mechanical ventilation (Takaoka Fuji Maximus, São Paulo, SP) with oxygen 60% - 100%, tidal volume of 10 ml/kg and inhalation of isoflurane (1-2%). The goats were positioned in right lateral position monitored with continuous electrocardiogram (ECG) and continuous invasive blood pressure line measured by catheterization of the left atrial artery with Introcath 22G catheter (BD, Juiz de Fora, MG). Postoperative analgesia was obtained on the first three days with administration of tramadol chloridrate (2 mg/kg, intramuscular, 12/12h).

Surgical procedure

The goats were prepared for sterile procedure (antisepsis with povidone-iodine). We performed left thoracotomy in the 4th intercostal space and implanted intracath catheters 17G (BD, Juiz de Fora, MG) in the descending thoracic aorta (Ao), at the outflow of the RV and in the pulmonary trunk (PT), as described previously[15]. Then, the PT was dissected to implant PB. In the animals of the Conventional group, the TP banding was performed with cardiac tape cotton (Polysuture, São Sebastião do Paraíso, MG), positioned about 10 mm above the valve. In the animals of the Intermittent group, an adjustable banding device was implanted immediately above the pulmonary valve and fixed to the adventitia of the PT, to prevent migration. Both groups were subjected to a systolic overload of the RV around 70% of systemic systolic pressure. Heparin was administered at a dose of 5,000 IU twice a day subcutaneously until the end of the protocol.

Description of the adjustable banding device

The device was developed in collaboration with SILIMED, *Indústria de Silicone e Instrumental Médico-Cirúrgico e Hospitalar* Ltda., Rio de Janeiro, RJ. It consists of three parts: banding ring, extension tube and inflation button (Fig. 1).

Protocol of RV systolic overload

Conventional group

The RV training was initiated in the banding implant surgery. The animals remained under continuous systolic overload of the RV for a period of four weeks with conventional fixed banding adjusted on the day of surgery. With the animal conscious and immobilized on a special stretcher, the pressures of RV, PT and Ao were recorded twice a week. The pressure gradient between RV and pulmonary trunk and the pressure ratio between RV and Ao were obtained by measuring their respective systolic pressures.

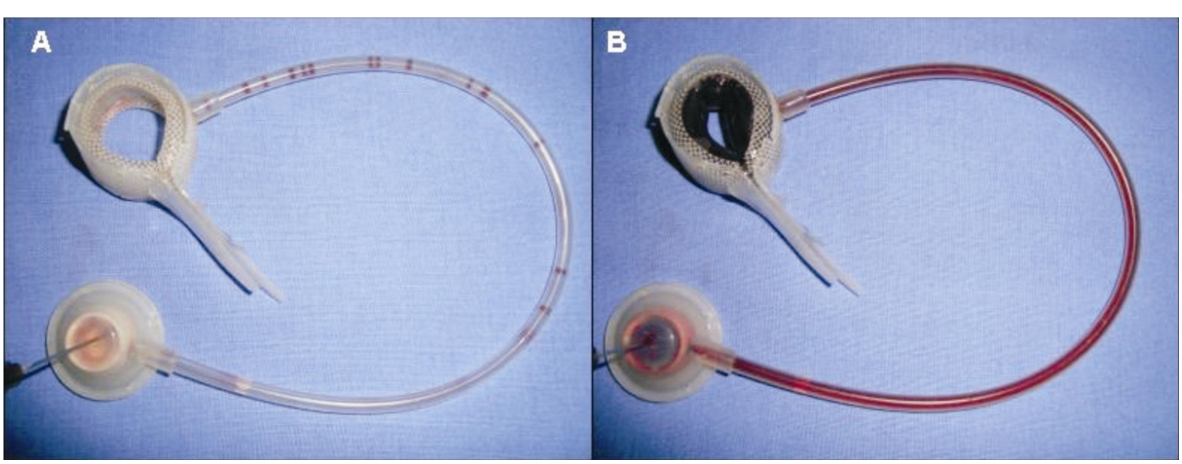

Figure 1 - PT adjustable banding device for use in adult animals. Panel A - device deflated; Panel B - device inflated with 2 ml.

Intermittent group

The RV training was initiated after full recovery from surgery (approximately 60 hours of convalescence). As in the Conventional group, the basal pressures of RV, PT and Ao were recorded with the animal conscious, immobilized on a special stretcher and the device completely deflated. After reading the basal pressures, the adjustable banding device was inflated with 0.9% saline in order to reach an RV systolic pressure of approximately 70% of systemic systolic pressure, provided that it did not cause a decrease of systolic pressure of more than 10%, as described in previous studies[15,17,18]. Then, the pressures were measured again. The RV systolic overload was maintained for a period of 12 hours, after which the animal was again placed on a special stretcher for hemodynamic monitoring. After the reading of pressures, the device was deflated and, again, the pressures were measured. The procedure to inflate and deflate the device was performed daily for four weeks, and the pressures were measured three days a week. On alternate days, the injected volume corresponded to the same volume calculated on the last day of hemodynamic measurements.

Echocardiographic study

All animals underwent echocardiographic evaluation before the protocol, and weekly after surgery to evaluate the adaptation of the RV during the four weeks of study. For the exams, the goats were sedated with ketamina (10 mg/kg intramuscular) and maintained in the left lateral position during the examinations. We used ACUSON Cypress echocardiography machine (Siemens, Munich, Germany) and multifrequency sector transducer (1.8 to 3.6 MHz) to obtain the images and flow analyses. The thicknesses of the interventricular septum (IVS) and LV posterior wall were measured in two-dimensional echocardiogram at the end of diastole through the longitudinal parasternal section at the height of the mitral valve cusps[19]. The thickness of the RV free wall was obtained in the cross-sectional parasternal section (at the height of the great vessels and at the level of the papillary muscles) and in the longitudinal four-chamber section in the region where its boundaries are more easily viewed. Then, we obtained the arithmetic mean of these values. Also in the longitudinal four-chamber section, we measured the end diastolic diameter (EDD) and end diastolic volumes (EDV) and end systolic volumes (ESV) of the RV through the modified Simpson method[19], and from the latter, we obtained the calculation of the RV ejection fraction (RVEF)[20], according to the formula:

$$\mathbf{RVEF = (EDVRV - ESVRV) \times EDVRV^{-1}}$$

Normal values of RVEF were considered at or above 55%[21]. As the most reliable parameter of RV performance, we calculated the myocardial performance index of the RV myocardial (MPI_{VD}) according to the formula:

$$\mathbf{MPI_{RV} = (TCIV + TRIV) \times ET^{-1}}$$

where TCIV is the isovolumetric contraction time, TRIV, isovolumetric relaxation time and ET, ejection time. The values were obtained in longitudinal four-chamber section, positioning the sample volume at the center of the tricuspid valve annulus, measuring the time interval between the onset of valve closure to the beginning of the next diastole (time a). The RV ejection time was calculated with the sample volume located in the RV outflow (time b) through the parasternal short axis. Subtracting the time a for b, we obtain TCIV + TRIV. This value was then divided by the TE, producing MPI_{VD}[22].

Cardiac masses

After euthanasia, the heart were then removed from the thorax and the ventricular and septal walls were separated according to the technique of Fulton et al[23]. Then, the RV, LV and IVS were weighed in a digital scale METTLER AE-200 (Mettler-Toledo AG, Greifensee, Switzerland). Due to variations in animal weight, measurements were standardized by means of indexation of weight of heart muscle mass according to animals' body weight, as suggested by Bishop and Cole[24].

Water content of tissues

After weighing, samples were collected from each of the cardiac walls for evaluation of water content (WC). The initial weight (IW) of each sample was determined. Then, they were wrapped in aluminum foil and properly identified before being placed in an incubator (temperature: 55-60°C). After about 70 hours of dehydration, each sample was weighed again to determine the dry weight (Wd). The water content percentage was then determined through the following formula, assuming that the water distribution was homogeneous in the septum and ventricles:

$$\mathbf{WC\ (\%) = 100 - (Wd \times IW^{-1} \times 100)}$$

The water contents of heart muscle mass of Conventional and Intermittent groups were compared to the Control group, in order to clarify whether the RV weight gain was associated with myocardial edema or actual acquisition of muscle mass.

Statistical analysis

The normal distribution of each variable was assessed using the Kolmogorov-Smirnov test. The mean hemodynamic and echocardiographic variables were compared between groups and throughout the protocol through two-factor analysis of variance (ANOVA) for repeated measures followed by Bonferroni multiple comparisons. The values of mass and water content of the RV, LV and IVS were compared by means of one-way ANOVA, followed by Bonferroni multiple comparisons. The systolic overload imposed on the RV of the Continuous and Intermittent groups was assessed by calculating the areas under the curve (trapezoidal method). The comparison between these areas was performed through unpaired Student's t test. The values are presented as mean ± standard deviation (SD). For all cases, the significance level was 5%. Statistical analyses were performed with software applications using the program GraphPad Prism v.4 (San Diego, CA - USA) and SigmaStat v.3.11.0 (Systat Software, Inc., San Jose, CA, USA).

Results

Hemodynamic measures

Pressure gradient RV/PT

Systolic overload generated by the PT banding in the Conventional and Intermittent groups, throughout the protocol, is shown in Figure 2, panel A. Panel B shows the comparison of areas under the curves of global systolic overload imposed on the RV throughout the study. In the Intermittent group, after the period of postoperative recovery of 72 hours, we found peak systolic gradients RV/PT greater than those generated in the Conventional group, alternating with periods of "rest" of the RV. In the Conventional group, there was a virtually continuous gradient, with small decreases in gradient between surgery and the first week and between the fourth week and the time of euthanasia (Figure 2, panel A). When the areas under the curves were compared between stimulated groups (Fig. 2, panel B), we observed a lower systolic overload imposed on the RV in the Intermittent group ($p = 0.002$).

Pressure ratio RV/Ao

The baseline pressure ratio RV/Ao was similar in study groups. As intended with the surgery, it was possible to achieve a pressure ratio between RV and Ao of 0.7. However, we noted a significant decrease in the ratio of this Conventional group, from the first week ($p < 0.05$), which was maintained throughout the study period. In the Intermittent group, facing the possibility of daily adjustment of banding, the maximum RV/Ao ratio remained around 0.7 throughout the study period, unlike the Conventional group ($p < 0.05$), except for a significant reduction in the fourth week, with recovery of the relationship at the time of euthanasia (Figure 3).

Echocardiographic findings

Thickness of cardiac walls

The preoperative evaluation of the thickness of the RV free wall revealed no differences between stimulated groups and the Control group. From the second week of study, the Intermittent group presented a 37.2% increase of the RV thickness compared to baseline values ($p < 0.05$), whereas in the Conventional group, no change was observed in this wall during the four weeks of continuous overload (Table 1). The thicknesses of the IVS and LV posterior wall did not vary in both stimulated groups.

RV ejection fraction

The RV ejection fraction in both groups remained constant, with no statistical difference by two-factor analysis of variance ($p = 0.45$).

RV diastolic diameter

Similar to the ejection fraction, there was no significant variation of the RV end diastolic diameter over time or between groups in four weeks ($p = 0.42$).

RV end-diastolic volume

In addition to the RV end diastolic diameter, there were also no differences in RV end-diastolic volume during the systolic overload protocol in relation to the preoperative echocardiographic assessment, in none of the groups or among them ($p = 0.70$).

RV myocardial performance index (MPI_{VD})

Figure 4 shows that the groups started from similar baseline MPI_{VD}. However, the Intermittent group presented a better stimulated ventricle performance represented by lower values of MPI_{VD} over the overload protocol when compared to the

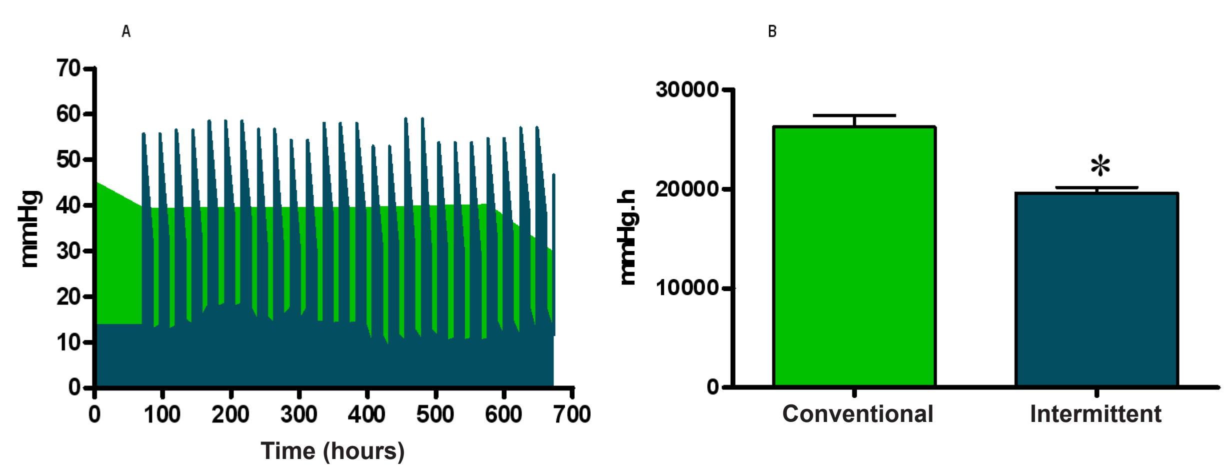

*Figure 2 - Area of pressure overload imposed by banding in the groups. Conventional and Intermittent, over the period of the protocol. Panel A - Graphic Illustration; Panel B - Comparison between the areas under the curves. * p = 0.0002: Intermittent x Conventional.*

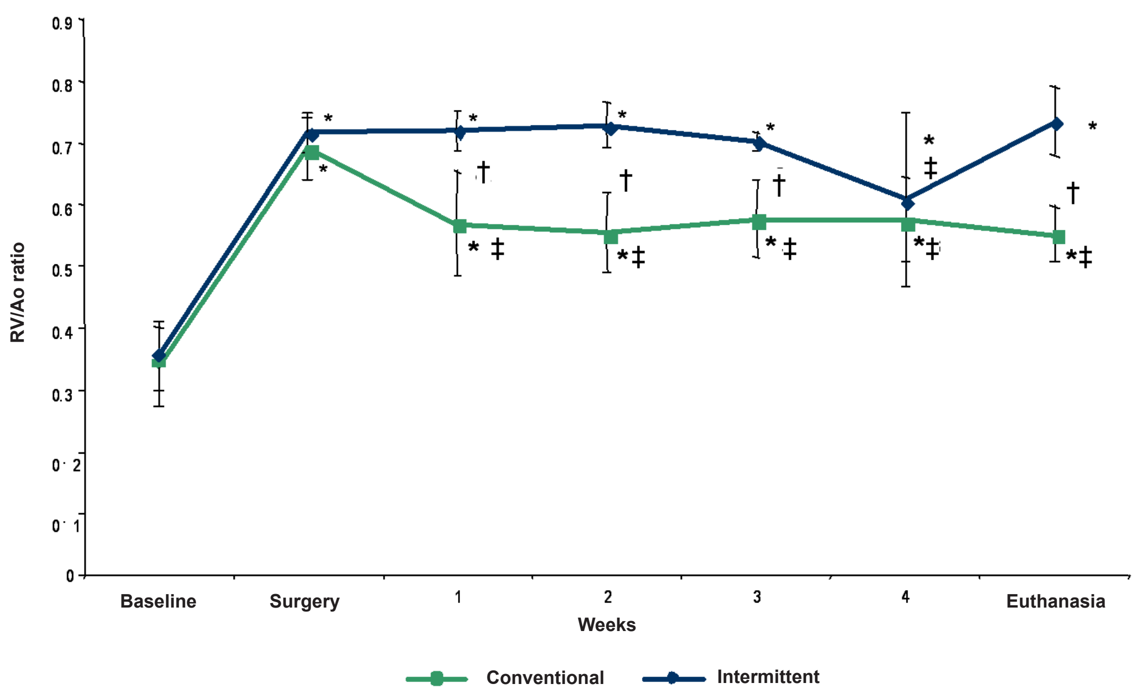

*Figure 3 - Development of RV/Ao ratio over the protocol in the Conventional and Intermittent groups. * P <0.05 comparing to the baseline of the group itself. † p < 0.05 comparing Intermittent and Conventional groups for the moment. ‡ p < 0.05 comparing the time of the surgery of the group itself.*

Table 1 - RV Thickness in RV systolic overload (conventional and intermittent) measured by echocardiogram

Time	Conventional	Intermittent
Basal	0,48 ± 0,03	0,43 ± 0,03
1st week	0,53 ± 0,09	0,53 ± 0,06
2nd week	0,52 ± 0,07	0,59 ± 0,05*
3rd week	0,53 ± 0,07	0,54 ± 0,05*
4th week	0,52 ± 0,07	0,57 ± 0,05*

*Conventional - fixed and continuous systolic overload group (n = 6). Intermittent - adjustable and intermittent systolic overload group (n = 6). Values (cm) - average ± standard deviation. *p < 0.05 compared to the baseline.*

Conventional group (p = 0.024).

Morphological findings

Weighing of cardiac masses

Weight data of ventricular cavity masses indexed to the weight of each animal are shown in Figure 5. The Intermittent group (1.24 g/kg ± 0.15 g/kg) and the Conventional group (1.08 g/kg ± 0.17 g/kg) showed increased muscle mass of RV of 67.57% and 45.95%, respectively (p = 0.001) compared to the control group (0.74 g/kg ± 0.07 g/kg). There were no weight differences of LV IVS between the study groups, The index of RV mass by the area of systolic overload is shown in Figure 6. There was a more significant increase in this ratio in the Intermittent group, i.e., for variations of the same magnitude of systolic overload imposed on the RV, the mass gain observed in the Intermittent group was higher (p = 0.0006).

Water content

Table 2 shows water content data of the groups. There was no significant difference in water content between the groups in any of the myocardial segments studied.

Discussion

This study has was clearly attested the easiness in handling pressure gradients using adjustable banding, and, consequently, higher pressure gradients were achieved, which could reduce many of the setbacks reported in myocardial preparation in adults, such as inaccurate adjustments of banding and the need for re-interventions[11,12]. Although it has been subjected to a smaller area of systolic overload, the Intermittent group was found to be more likely to gain ventricular mass, which was approximately 75% of the gain observed in young animals subjected to the same systolic overload protocol, but with a training time seven times smaller[15]. That corroborates the differences found between infants and adults in ventricular preparation studies, with great variability in time and increased risk of early and late ventricular failure in adults[25-27]. Moreover, traditional banding confirmed the difficulties faced in surgeries in adolescents,

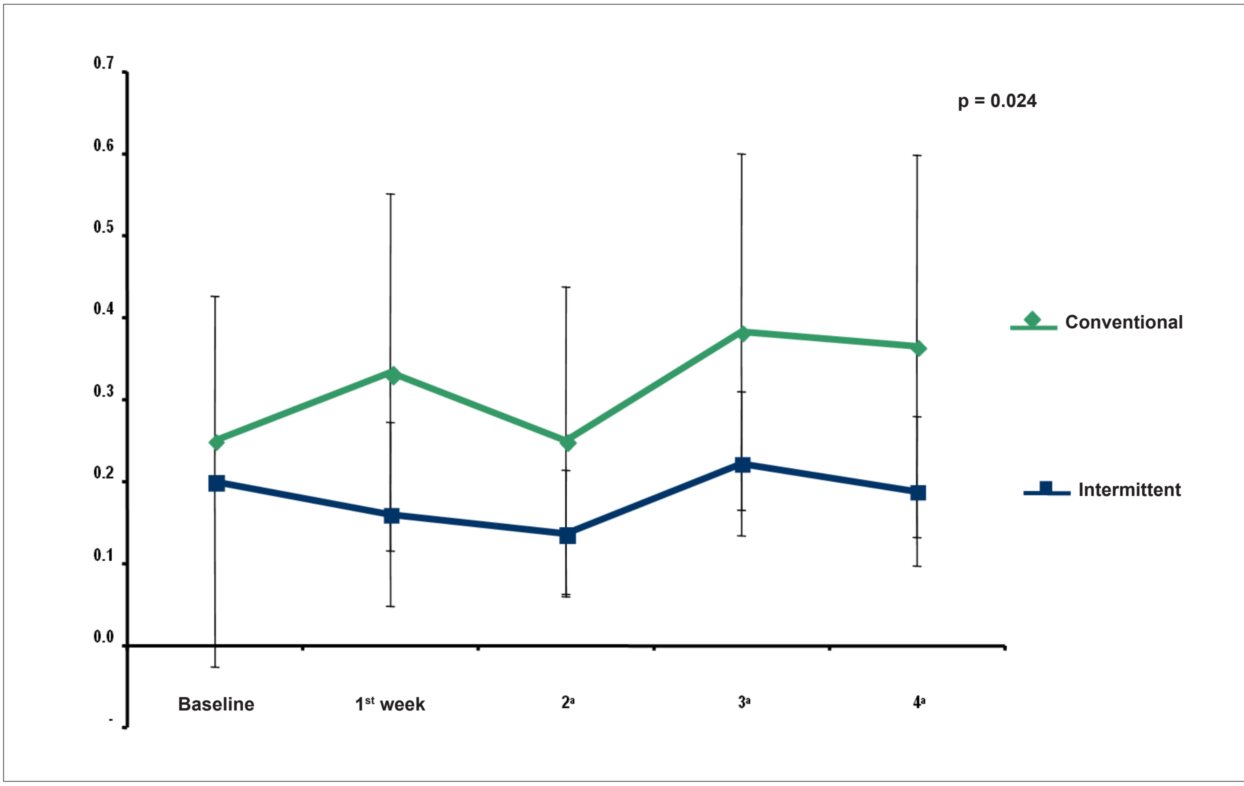

Figure 4 - Development of the MPI_{VD} in the Conventional and Intermittent groups, in the four weeks of study.

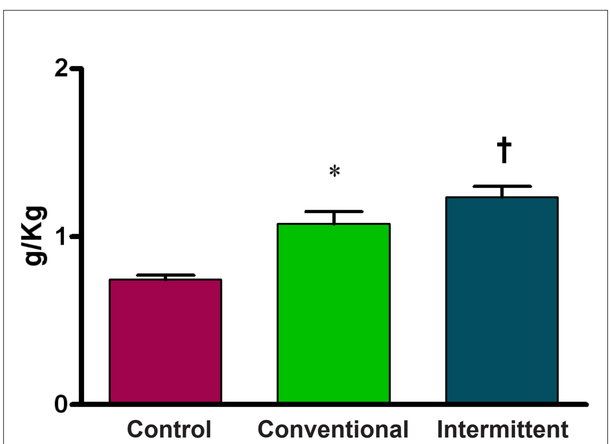

*Figure 5 - Indexed weights of the RV (g/kg) of Control, Conventional and Intermittent Groups. * p < 0.01: Control x Conventional; † p < 0.001: Control x Intermittent.*

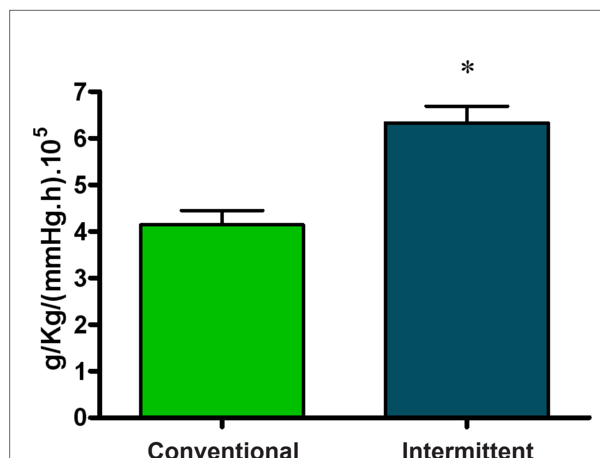

*Figure 6 - RV mass indexed by the area of systolic overload of Conventional and Intermittent groups. * p = 0.0002: Conventional x Intermittent.*

Table 2 - **Water content of muscle masses of Control, Conventional and Intermittent groups**

Water content	Control	Conventional	Intermittent	p value
RV	78,33 ± 1,50	79,67 ± 1,25	80,61 ± 1,87	**0,06**
LV	78,23 ± 0,95	79,25 ± 1,80	79,98 ± 2,30	**0,22**
IVS	78,46 ± 0,61	78,74 ± 1,95	79,47 ± 1,55	0,46

Control - Control Group (n = 7); Conventional - fixed and continuous systolic overload of RV (n = 6); Intermittent - adjustable and intermittent systolic overload of RV (n = 6); Values (%) - average ± standard deviation.

when small banding adjustments caused severe hemodynamic instability in animals, determining repeated adjustments and a time-consuming and hard surgical procedure, in line with clinical studies. Despite the difficulties faced with conventional banding, it was possible to reach the RV/Ao ratio desired in all animals in the Conventional group during surgery. However, the intraoperative adjustment was less accurate after anesthetic recovery, with a drop in the RV/Ao ratio, as reported in several clinical and experimental studies, incurring loss of the gradient intended along the desired protocol, either by dilation or dysfunction of subpulmonary chamber[28,29].

Echocardiographic parameters

The 33% increase observed in the RV free wall thickness in the Intermittent group corresponded to about 25% of the increase found in the study of young animals, corroborating the findings of a smaller increase in ventricular mass in adult animals, over a longer time of hypertrophic stimulus[15]. The most evident RV free wall thickness appeared as early as in the second week and remained constant thereafter. It is difficult to say that the ventricular hypertrophic process in humans would be the same, given the differences between species. However, there is a remarkable tendency to reduce the preparation time with the intermittent banding. Concerning the functional assessment of the RV preparation, the ejection fraction showed no differences at rest. However, the MPI_{VD} has proven to be a valuable tool for assessing right ventricular function[22,30]. The analysis of this parameter revealed the functional supremacy of the ventricular preparation observed in the animals of the Intermittent group, over its lower indexes of MPI_{VD}. This finding may be due to the benefit of resting periods interspersed with intermittent pressure overload. As in young animals, perhaps these resting intervals over the protocol may optimize the subendocardial coronary flow and consequently a larger input of substrates for myocardial hypertrophic process, thereby limiting the severity of systolic stress imposed on the RV of the continuous group[31,32]. As athletic training promotes a physiological ventricular hypertrophy without myocardial dysfunction[33], we tried to implement in ventricular preparation some principles already adopted for some athletes. Among them, periods of intense training interspersed with periods of rest, which would allow the replacement of intracellular muscle stores, gradually adapting the muscles to the new pressure condition.

Morphological parameters

Before the finding of mass gain of the RV in stimulated groups, we tried to analyze potential morphological substrates to justify such increase. Initially, we measured the water content in myocardial tissues to identify a potential edema, which would increase weight and thickness of muscle masses, which did not occur significantly. This study consistently demonstrates the hypertrophy ability in the mature myocardium by means of increased weight and thickness of the RV, with a trend toward superiority over the Intermittent group. French researchers evaluated the retraining of the myocardium of adult sheep, identifying foci of fibrosis in animals subjected to conventional banding, as opposed to those undergoing intermittent banding[16], which may be one of the substrates for a worse functional performance. Vida et al[34] compared the ventricular adaptive process of young and adult rats undergoing pulmonary trunk banding. The authors found a greater accumulation of collagen in adult hearts. The intermittent stimulation of this study promoted hypertrophy with less imposition of ventricular overload. With this, it would be natural to propose such a pressure system as a healthier alternative to the traditional model of preparation. Perrino et al[35] studied the LV from mice undergoing physiological stimuli of hypertrophy, such as running and swimming, compared with fixed intermittent pressure overload by aortic banding. The authors demonstrated that the fixed overload triggered ventricular dysfunction, while the intermittent overload maintained the ventricular function, similar to physiological stimuli (running and swimming). However, when molecular markers of hypertrophy were analyzed, it was noticed that there were pathological signs in both types of artificial overload, both fixed and intermittent, unlike physiological stimuli.

Clinical implications

In the clinical setting, assessment of LV preparation in adult patients takes into account some factors: pressure ratio of morphological LV/proper systemic pressure with good ventricular function, good inotropic response and hypertrophy triggered by systolic overload of the banding. However, not infrequently, patients have left ventricular dysfunction after anatomic correction, even requiring cardiac transplantation. Some clinical studies have reported an inability to perform ventricular preparation in patients who have reached adolescence, due to the difficulty to obtain ventricular hypertrophy without causing dysfunction in these patients[8,11]. Other authors conclude that age is a major risk factor for the development of adaptive changes[34]. Hence, in the future, protocols of intermittent overload, similar to those tested in this study, could be suggested for these patients, in order to promote an effective hypertrophy, without any damage to the myocardial tissue, preventing the development of ventricular dysfunction.

Study limitations

This study has the limitations inherent to an experimental study, and the main one lies in the fact that PB in experimental animals promotes upgrading of the RV, while in patients with TGA and c-TGA, PB promotes the preparation of the LV. The observation of the trend towards smaller hypertrophy in the Conventional group may reflect the difficulty in preparing mature myocardium in clinical practice, as well as the need for longer periods of stimulation to achieve that end. Although magnetic resonance imaging is currently the standard for morphological and functional assessment of RV[36,37], in this study, we could not rely on such examination, which would certainly enrich the findings. Despite this, RV function was estimated by the same observer (MCDA), using the same method for all animals, which minimizes the variability between the two diagnostic approaches. Histological and energy metabolism studies in these animals are underway in our laboratory to support the functional evidence found in this study.

Conclusions

The banding of the pulmonary trunk promoted RV hypertrophy in both study groups of adult goats, either conventionally or intermittently over the four weeks with no significant accumulation of water. Despite the lower RV systolic overload imposed on the Intermittent group, this group presented larger systolic peak gradients, greater variation in thickness of the RV free wall and greater muscle mass per unit of overload. The hypertrophy promoted by the intermittent overload provided better performance of the right ventricle during the study. Probably the most physiological ventricular preparation of adolescents with TGA or c-TGA with systemic ventricle failure would benefit from intermittent systolic overload to promote an effective hypertrophy, with preservation of left ventricular function.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References

1. Wilson NJ, Clarkson PM, Barratt-Boyes BG, Calder AL, Whitlock RM, Easthope RN, et al. Long-term outcome after the mustard repair for simple transposition of the great arteries. 28-year follow-up. J Am Coll Cardiol. 1998; 32 (3): 758-65.
2. Sarkar D, Bull C, Yates R, Wright D, Cullen S, Gewillig M, et al. Comparison of long-term outcomes of atrial repair of simple transposition with implications for a late arterial switch strategy. Circulation. 1999; 100 (19 Suppl): II176-81.
3. Puley G, Siu S, Connelly M, Harrison D, Webb G, Williams WG, et al. Arrhythmia and survival in patients > 18 years of age after the mustard procedure for complete transposition of the great arteries. Am J Cardiol. 1999; 83 (7): 1080-4.
4. Oechslin E, Jenni R. 40 years after the first atrial switch procedure in patients with transposition of the great arteries: long-term results in Toronto and Zurich. Thorac Cardiovasc Surg. 2000; 48 (4): 233-7.
5. Jatene AD, Fontes VF, Paulista PP, de Souza LC, Neger F, Galantier M, et al. Successful anatomic correction of transposition of the great vessels: a preliminary report. Arq Bras Cardiol. 1975; 28 (4): 461-64.
6. Mee RB. Severe right ventricular failure after Mustard or Senning operation. Two-stage repair: pulmonary artery banding and switch. J Thorac Cardiovasc Surg. 1986; 92 (3 Pt 1): 385-90.
7. Reddy VM, McElhinney DB, Silverman NH, Hanley FL. The double switch procedure for anatomical repair of congenitally corrected transposition of the great arteries in infants and children. Eur Heart J. 1997; 18 (9): 1470-7.
8. Devaney EJ, Charpie JR, Ohye RG, Bove EL. Combined arterial switch and Senning operation for congenitally corrected transposition of the great arteries: patient selection and intermediate results. J Thorac Cardiovasc Surg. 2003; 125 (3): 500-7.
9. Imamura M, Drummond-Webb JJ, Murphy DJ Jr, Prieto LR, Latson LA, Flamm SD, et al. Results of the double switch operation in the current era. Ann Thorac Surg. 2000; 70 (1): 100-5.
10. Padalino MA, Stellin G, Brawn WJ, Fasoli G, Daliento L, Milanesi O, et al. Arterial switch operation after left ventricular retraining in the adult. Ann Thorac Surg. 2000; 70 (5): 1753-7.
11. Winlaw DS, McGuirk SP, Balmer C, Langley SM, Griselli M, Stumper O, et al. Intention-to-treat analysis of pulmonary artery banding in conditions with a morphological right ventricle in the systemic circulation with a view to anatomic biventricular repair. Circulation. 2005; 111 (4): 405-11.
12. Mavroudis C, Backer CL. Arterial switch after failed atrial baffle procedures for transposition of the great arteries. Ann Thorac Surg. 2000; 69 (3): 851-7.
13. Poirier NC, Mee RB. Left ventricular reconditioning and anatomical correction for systemic right ventricular dysfunction. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2000; 3: 198-215.
14. Poirier NC, Yu JH, Brizard CP, Mee RB. Long-term results of left ventricular reconditioning and anatomic correction for systemic right ventricular dysfunction after atrial switch procedures. J Thorac Cardiovasc Surg. 2004; 127 (4): 975-81.
15. Assad RS, Abduch MC, Valente AS, Andrade JL, Krieger JE, et al. Adjustable pulmonary trunk banding: comparison of two methods of acute subpulmonary ventricle hypertrophy. Braz J Cardiovasc Surg. 2006; 21 (4): 418-28.
16. Le Bret E, Lupoglazoff JM, Borenstein N, Fromont G, Laborde F, Bachet J, et al. Cardiac "fitness" training: an experimental comparative study of three methods of pulmonary artery banding for ventricular training. Ann Thorac Surg. 2005; 79 (1): 198-203.
17. Dias CA, Assad RS, Caneo LF, Abduch MC, Aiello VD, Dias AR, et al. Reversible pulmonary trunk banding. II. An experimental model for rapid pulmonary ventricular hypertrophy. J Thorac Cardiovasc Surg. 2002; 124 (5): 999-1006.
18. Muraoka R, Yokota M, Aoshima M, Nomoto S, Kyoku I, Kobayashi A, et al. Extrathoracically adjustable pulmonary artery banding. J Thorac Cardiovasc Surg. 1983; 86 (4): 582-6.
19. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005; 18 (12): 1440-63.
20. Snider AR, Serwer GA, Ritter SB. Methods for obtaining quantitative information from the echocardiographic examination. In: Snider AR, Serwer

GA, Ritter SB, editors. Echocardiography in pediatric heart disease. 2nd ed. Missouri: Mosby; 1997. p. 133-234.

21. Morhy SS, Andrade JL, Soares AM, Ribeiro ZV, Wilberg TM, Mathias W Jr, et al. Non-invasive assessment of right ventricular function in the late follow-up of the Senning procedure. Cardiol Young. 2005; 15 (2): 154-9.

22. Tei C, Nishimura RA, Seward JB, Tajik AJ. Noninvasive Doppler-derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echocardiogr. 1997; 10 (2): 169-78.

23. Fulton RM, Hutchinson EC, Jones AM. Ventricular weight in cardiac hypertrophy. Br Heart J. 1952; 14 (3): 413-20.

24. Bishop SP, Cole CR. Production of externally controlled progressive pulmonic stenosis in the dog. J Appl Physiol. 1969; 26 (5): 659-63.

25. Takahashi Y, Nakano S, Shimazaki Y, Kadoba K, Taniguchi K, Sano T, et al. Echocardiographic comparison of postoperative left ventricular contractile state between one- and two-stage arterial switch operation for simple transposition of the great arteries. Circulation. 1991; 84 (5 Suppl): III180-6.

26. Benzaquen BS, Webb GD, Colman JM, Therrien J. Arterial switch operation after Mustard procedures in adult patients with transposition of the great arteries: is it time to revise our strategy? Am Heart J. 2004; 147 (3): E8.

27. Quinn DW, McGuirk SP, Metha C, Nightingale P, de Giovanni JV, Dhillon R, et al. The morphologic left ventricle that requires training by means of pulmonary artery banding before the double-switch procedure for congenitally corrected transposition of the great arteries is at risk of late dysfunction. J Thorac Cardiovasc Surg. 2008; 135 (5): 1137-44, 1144 e1-2.

28. Corno AF, Bonnet D, Sekarski N, Sidi D, Vouhe P, von Segesser LK. Remote control of pulmonary blood flow: initial clinical experience. J Thorac Cardiovasc Surg. 2003; 126 (6): 1775-80.

29. Bonnet D, Corno AF, Sidi D, Sekarski N, Beghetti M, Schulze-Neick I, et al. Early clinical results of the telemetric adjustable pulmonary artery banding FloWatch-PAB. Circulation. 2004; 110 (11 Suppl 1): II158-63.

30. Takeuchi D, Nakanishi T, Tomimatsu H, Nakazawa M. Evaluation of right ventricular performance long after the atrial switch operation for transposition of the great arteries using the Doppler Tei index. Pediatr Cardiol. 2006; 27 (1): 78-83.

31. White FC, Sanders M, Peterson T, Bloor CM. Ischemic myocardial injury after exercise stress in the pressure-overloaded heart. Am J Pathol. 1979; 97 (3): 473-88.

32. Carroll SM, Nimmo LE, Knoepfler PS, White FC, Bloor CM. Gene expression in a swine model of right ventricular hypertrophy: intercellular adhesion molecule, vascular endothelial growth factor and plasminogen activators are upregulated during pressure overload. J Mol Cell Cardiol. 1995; 27 (7): 1427-41.

33. Oliveira EM, Krieger JE. Hipertrofia cardíaca e treinamento físico: aspectos moleculares. Hipertensão. 2002; 5: 73-8.

34. Vida VL, Angelini A, Ausoni S, Bilardi A, Ori C, Vlassich F, et al. Age is a risk factor for maladaptive changes in rats exposed to increased pressure loading of the right ventricular myocardium. Cardiol Young. 2007; 17 (2): 202-11.

35. Perrino C, Prasad SV, Mao L, Noma T, Yan Z, Kim HS, et al. Intermittent pressure overload triggers hypertrophy-independent cardiac dysfunction and vascular rarefaction. J Clin Invest. 2006; 116 (6): 1547-60.

36. Horton KD, Meece RW, Hill JC. Assessment of the right ventricle by echocardiography: a primer for cardiac sonographers. J Am Soc Echocardiogr. 2009; 22 (7): 776-92; quiz 861-2.

37. Sade LE, Gulmez O, Ozyer U, Ozgul E, Agildere M, Muderrisoglu H. Tissue Doppler study of the right ventricle with a multisegmental approach: comparison with cardiac magnetic resonance imaging. J Am Soc Echocardiogr. 2009; 22 (4): 361-8.