


## Echocardiographic assessment of systemic cardiac output in pulmonary atresia with intact ventricular septum

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### ARTICLE INFORMATION

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### Competing interests

The authors declare no competing interests

### Acronyms

**IVCT:** isovolumetric contraction time

**IVRT:** isovolumetric relaxation time

**LVEF:** left ventricular ejection fraction

**LVVI:** left ventricular volume index


**PAIVS:** pulmonary atresia with intact ventricular septum

**SI:** systemic index

**VET:** ventricular ejection time

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### ABSTRACT

**Introduction:** In the study of pulmonary atresia with intact ventricular septum, not enough attention has been paid to the dual nature of the left ventricle as a circulatory receptor, and its impact on systemic hemodynamics.

**Objective:** To identify, by echocardiography, the pathophysiological elements that characterize the disease and that determine its basic hemodynamic performance, influencing cardiac output and generating potential conditions for short-term prognosis.

**Method:** A descriptive, prospective and applied study was conducted. It included 43 patients who were referred to the William Soler Pediatric Cardiology Hospital from January 1992 to November 2011 with a diagnosis of the disease. In each subject, the profiles of eight echocardiographic variables were assessed, as well as the heart rate profile. Their level of association and mutual dependence were statistically assessed by simple regression models.

**Results:** There are considerable variations in heart rate, in the volume index and in the ejection fraction of the patients' left ventricle compared with those in the reference control group.

**Conclusions:** The increased size of the atrial septal defect and the prolongation of transmitral diastasis favor left ventricular volume increment. Heart rate, the restrictive nature of the left ventricular myocardium and its ejection fraction are regulatory factors of cardiac output in this disease.

**Key words:** Pulmonary atresia, Cardiac output, Heart rate, Diastasis

### *Evaluación ecocardiográfica del gasto cardíaco sistémico en la atresia pulmonar con septo interventricular intacto*

### RESUMEN

**Introducción:** El estudio de la atresia pulmonar con septo interventricular intacto no ha prestado suficiente atención al carácter dual del ventrículo izquierdo como receptor circulatorio y su repercusión sobre la hemodinámica sistémica.

**Objetivo:** Identificar, mediante la ecocardiografía, los elementos fisiopatológicos propios de esa enfermedad que perfilan su actuación hemodinámica de base, influyen sobre el gasto cardíaco y generan condiciones potenciales para el pronóstico a corto plazo.

**Método:** Se realizó una investigación con carácter descriptivo, prospectivo y aplicado, donde se estudiaron 43 pacientes con diagnóstico de la enfermedad remitidos al Cardiocentro Pediátrico "William Soler" desde enero de 1992 a noviembre de 2011. Se evaluaron, en cada sujeto, los perfiles de ocho variables ecocardiográficas y de la frecuencia cardíaca. Se analizaron los niveles de asociación y dependencia entre ellas mediante la aplicación estadística de modelos de regresión simple.

**Resultados:** Existen variaciones considerables en la frecuencia cardíaca, en el índice volumétrico y en la fracción de eyección correspondientes al ventrículo izquierdo de los pacientes respecto al grupo control de referencia.

**Conclusiones:** El mayor tamaño de la comunicación interauricular y la prolongación de la diastasis transmitral favorecen el incremento volumétrico del ventrículo izquierdo. La frecuencia cardíaca, el carácter restrictivo del miocardio ventricular izquierdo y su fracción de eyección son factores reguladores del gasto cardíaco en esta enfermedad.

**Palabras clave:** Atresia pulmonar, Gasto cardíaco, Frecuencia cardíaca, Diastasis

## INTRODUCTION

The functional status of the left ventricle and its dynamic implications are important for a proper diagnostic approach, planning a therapeutic strategy and making a prognosis in any heart disease<sup>1,2</sup>. The broad spectrum of abnormalities linked to the field of congenital heart disease is included in the above mentioned statement, which applies to those diseases in which the ventricular cavity receives both pulmonary venous circulation and systemic circulation<sup>3</sup>.

Pulmonary atresia with intact ventricular septum (PAIVS) is part of this group of diseases<sup>4</sup>. The attention of researchers has been focus on characterizing the type of atresia, conducting a structural analysis of the right ventricle and detecting anomalies in the coronary circulation, to the detriment of the study of pathophysiological characteristics that impact on cardiac output, and help to determine the vital status of patients<sup>5</sup>.

Although they have been ignored, these characteristics are worthy of consideration and analysis.

The comprehensive and harmless character of transthoracic echocardiography make it the ideal tool to screen newborns with PAIVS and conduct this research, whose main objective is to identify the pathophysiological aspects, typical of this disease, that outline its basic hemodynamic performance, influence on cardiac output and create potential conditions for the short-term prognosis.

## METHOD

### Patients and type of study

The William Soler Pediatric Cardiology Hospital re-

ceived 43 patients of both sexes with PAIVS, confirmed by echocardiography, from the national pediatric cardiology network in the period from January 1992 to November 2011. This population of children was used to structure this research, which is classified as a descriptive, prospective and applied study.

A reference group was formed through the technique of systematic probability sampling in order to conduct the contrasting process. It was formed by supposedly healthy children of age and weight similar to the patients with PAIVS. They had been sent to the hospital's outpatient echocardiography laboratory for assessment, due to clinical symptoms of innocent murmurs. In order to ensure an adequate statistical power, this group of subjects, used as a control group, quadrupled the size of the population of patients with heart disease<sup>6</sup>.

The echocardiographic examinations of all the elements involved in the investigation were performed by a single observer; therefore, in order to prevent bias, the masking methodology was used according to the characteristics that are inherent in a triple-blind study<sup>7</sup>.

### Echocardiogram

The preoperative and prospective transthoracic echocardiographic examination was performed in left lateral decubitus position. Machines Aloka SSD-860®, Aloka SSD-5500 Prosound® and Philips IE 33® were used for the investigation; all of them included electromagnetic transducers. The two-dimensional scanning (B-mode) included the use of the apical four-chamber approach and left anterior oblique view at

atrial level. The transmitral diastolic flow profile was studied by pulsed-wave Doppler echocardiography. From the apical window, in four-chamber two-dimensional approach, the sample volume was located, with a three-millimeter range, inside the left ventricular cavity at the edges of the leaflets. Acquired modal velocity corresponded to the darkest central region of the inscribed spectrum at a scanning rate of five centimeters/second. A continuous electrocardiographic monitoring was established during the study of each case, and the figures obtained from each variable measured in six consecutive cardiac cycles were averaged out.

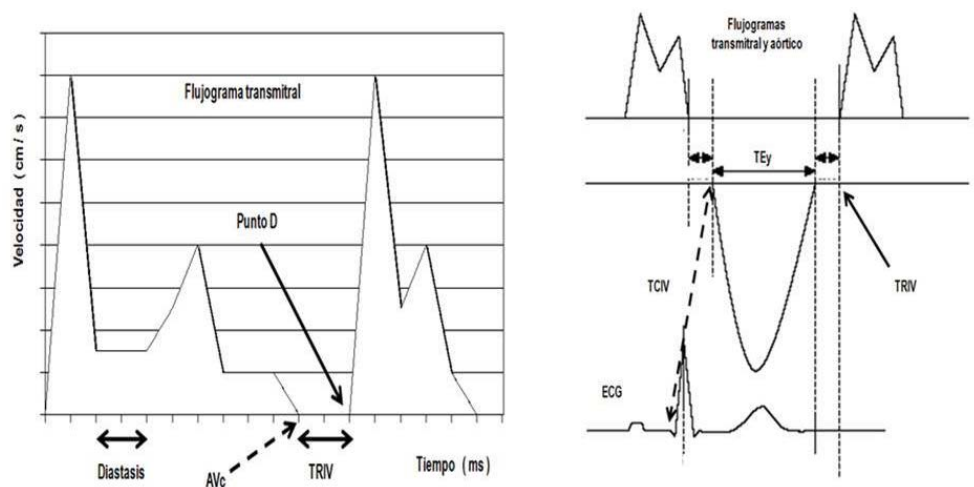
### Variables

The study included the assessment of nine variables, most of them represented in figure 1:

- Isovolumetric contraction time (IVCT): Also called pre-ejection period. It includes the time interval from the mitral valve closure to the opening the sigmoid aortic valve. It was measured considering, as reference points, the beginning of the QRS complex recorded on the simultaneous electrocardiogram and the onset of ventricular ejection recorded by Doppler echocardiography<sup>8</sup>. It was expressed in milliseconds (ms).
- Ventricular ejection time (VET): time interval that indicates, by assessment of Doppler echocardiographic spectrum in the ascending aorta, the initiation and termination of left ventricular ejection phase in the cardiac cycle<sup>8</sup>. Expressed in ms.
- Isovolumetric relaxation time (IVRT): Time interval, measurable by Doppler echocardiography, ranging from the closure of the sigmoid aortic valve (AVC artifact) to mitral opening (point D)<sup>9</sup>. It was expressed in ms.
- Transmitral diastasis: Also called slow ventricular filling phase. It begins at the end of the ventricular early diastolic filling period and ends with atrial systole. During transmi-

tral diastasis, the flow velocity, detected by Doppler echocardiography, takes a plateau configuration due to existing pressure balance. Under normal circumstances, it is a brief phase of the cardiac cycle; it depends on the amount of pulmonary venous flow, and is inversely proportional to heart rate<sup>9</sup>. It was expressed in ms.

- Heart rate (HR): It is the quantification of cardiac cycles per unit of time<sup>8</sup>. Expressed in beats/minute (beats/min).
- Left ventricular ejection fraction (LVEF): It is the quantification of the end-diastolic blood volume of the left ventricle that is ejected into the aorta in each systole. It was calculated by one-dimensional echocardiography (M-mode), according to rules established by the American Society of Echocardiography (ASE)<sup>10,11</sup>. The postulates of the International System of Units suggest measuring this variable in centesimal notation<sup>12</sup>.
- Systemic index (SI): Systemic cardiac output calculated according to echocardiographic methodology, which is established and standardized considering the body surface area<sup>13,14</sup>. Its units are liters/minute/square meter (l/min/m<sup>2</sup>).
- Left ventricular volume index (LVVI): left ventricular end-diastolic volume calculated using the biplane Simpson's method and normalized considering the body surface area<sup>14,15</sup>. It was expressed in milliliters/square meter (ml/m<sup>2</sup>).



**Figure 1.** Joint schematic representation of mitral and aortic flow charts. AVc: artifact on Doppler spectrum indicating the time of aortic valve closure. Diastasis: transmitral diastasis. Point D: mitral valve opening time. TCIV: isovolumetric contraction time. TEy: ventricular ejection time. TRIV: isovolumetric relaxation time. Source: Database. Echocardiography Laboratory. William Soler Cardiology Hospital.

- Dimension of the native atrial septal defect: two-dimensional echocardiographic measurement, recorded in millimeters (mm), of the atrial septal defect (ASD) in patients with PAIVS. No post-atrioseptostomy measurements of subjects undergoing the surgical procedure were included.

### Processing and statistical analysis

The information was stored in a database that was configured and processed with MedCalc® software, version 12. All variables were quantitative. In those variables with normal distribution, the mean and standard deviation were adopted as summary measures; in those with asymmetric distributions the median and interquartile range were used for the same purpose.

In order to assess the degree of difference between the calculated averages from two independent groups, the parametric t test of Student – Fisher was used in those quantitative variables with normal distribution. When the distributions did not meet that condition, the analysis was performed by using the nonparametric Mann – Whitney U test, replacing the means by medians.

Simple linear regression models were built and applied to pairs of continuous quantitative variables. The coefficient of determination ( $R^2$ ), standard error (SE) and the residual standard deviation (RSD) of the dependent variable (y), with the corresponding regression equation, were calculated in each case.

The significance level that was adopted in order to statistically validate the results was less than 5% ( $p < 0.05$ ), for the degrees of freedom previously fixed in each of the circumstances. In simple linear regression models, the lines for confidence interval and prediction in-

terval were drawn, both set at 95%.

### Ethical Considerations

This study was conducted under strict adherence to ethical regulations in force at national level and in line with the Declaration of Helsinki, issued by the World Medical Association, as useful principles to guide health professionals who conduct medical research in human beings<sup>16</sup>.

### RESULTS

The comparative assessment of factors associated with systemic hemodynamics in the population of subjects with PAIVS and the control group of supposedly healthy children is shown in Table 1. The LVVI (PAIVS,  $54.00 \pm 3.00$  ml/m<sup>2</sup>; control group,  $42.00 \pm 10.00$  ml/m<sup>2</sup>;  $p = 0.0001$ ) and LVEF (PAIVS, median 0.71 – interquartile range 0.67 to 0.75; control group, median 0.68 – interquartile range 0.64 to 0.71;  $P = 0.01$ ) increased significantly in the group of sick infants. In this group, the HR decreased significantly (PAIVS,  $135.18 \pm 10.27$  beats/min; control group,  $151.88 \pm 8.57$ ;  $p = 0.0001$ ). The IVCT ( $p = 0.39$ ), the VET ( $p = 0.12$ ), the IVRT ( $p = 0.12$ ) and the SI ( $p = 0.70$ ) showed no remarkable changes.

**Table 1.** Factors associated with systemic hemodynamics in pulmonary atresia with intact ventricular septum.

Variables	Groups				p
		PAIVS (n = 43)		Control group (n = 175)	
IVCT (ms)	$\mu \pm SD$	$45,00 \pm 5,57$	$X \pm SD$	$44,00 \pm 4,63$	0.39 <sup>¶</sup>
VET (ms)	$\mu \pm SD$	$70,88 \pm 6,84$	$X \pm SD$	$73,22 \pm 6,41$	0.12 <sup>¶</sup>
IVRT (ms)	$\mu \pm SD$	$42,00 \pm 3,83$	$X \pm SD$	$43,25 \pm 3,29$	0.12 <sup>¶</sup>
HR (beats/min)	$\mu \pm SD$	$135,18 \pm 10,27$	$X \pm SD$	$151,88 \pm 8,57$	0.0001 <sup>¶</sup>
LVEF	Median IR	0,71 <sup>¥</sup> (0,67 a 0,75)	Median IR	0,68 <sup>¥</sup> (0,64 a 0,71)	0.01 <sup>§</sup>
SI (l/min/m <sup>2</sup> )	$\mu \pm SD$	$2,41 \pm 0,12$	$X \pm SD$	$2,40 \pm 0,10$	0.70 <sup>¶</sup>
LVVI (ml/m <sup>2</sup> )	$\mu \pm SD$	$54,00 \pm 3,00$	$X \pm SD$	$42,00 \pm 10,00$	0.0001 <sup>¶</sup>

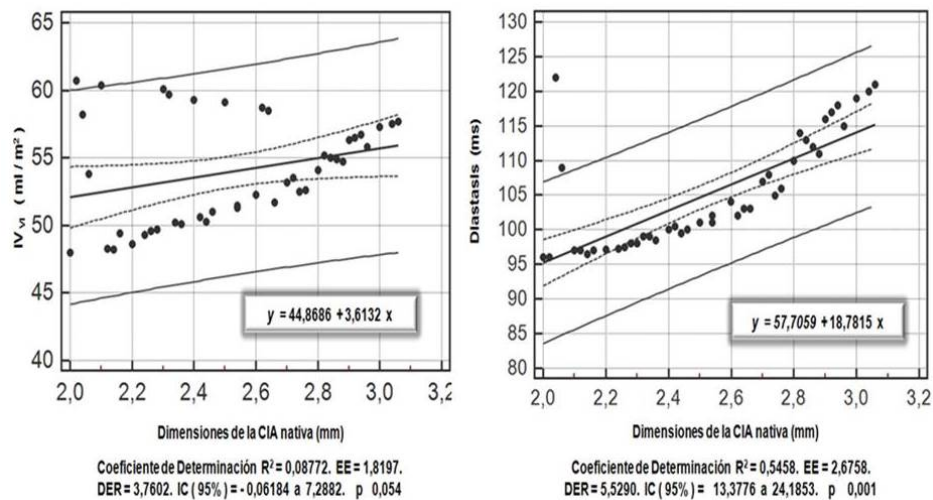
¶ Student-Fisher t test. § Mann-Whitney U test. ¥ Asymmetric distribution.

Legend: SD: standard deviation. HR: heart rate. LVEF: left ventricular ejection fraction. SI: systemic index. LVVI: left ventricular volume index. IR: interquartile range. IVCT: isovolumetric contraction time. VET: ventricular ejection time. IVRT: isovolumetric relaxation time.

Figure 2 shows that the LVVI ( $R^2 = 0.08772$ ; SE = 1.8197; RSD = 3.7602;  $p = 0.054$ ) and transmitral diastasis ( $R^2 = 0.5458$ ; SE = 2.6758; RSD = 5.5290;  $p = 0.001$ ) showed an increase in their values as the size of the existing atrial septal defect increased in PAIVS patients.

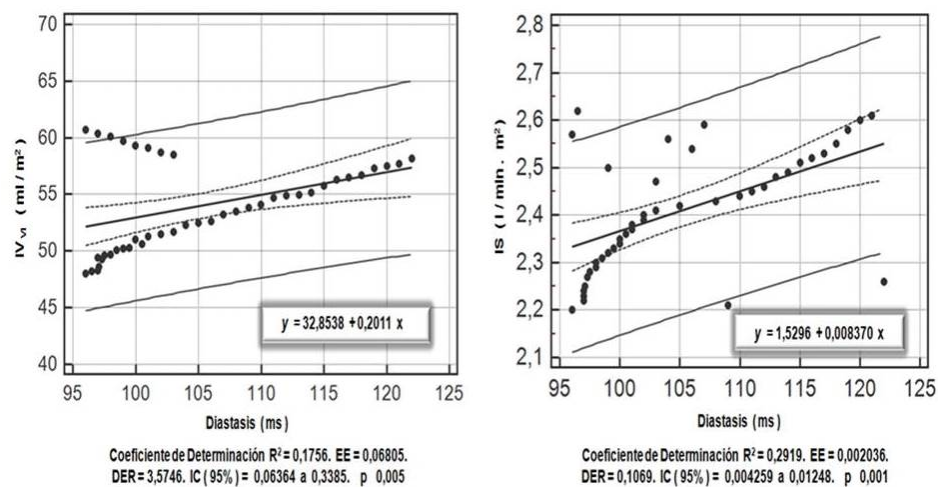
The level of dependence of the systemic and left ventricular volume indices with respect to transmitral

diastasis in the population suffering from PAIVS is seen through the simple linear regression models included in Figure 3. They show how the increasing trend occurred in LVVI ( $R^2 = 0.1756$ ; SE = 0.06805; RSD = 3.5746;  $p = 0.005$ ) and SI ( $R^2 = 0.2919$ ; SE = 0.002036; RSD = 0.1069;  $p = 0.001$ ) with the prolongation of diastasis.



**Figure 2.** Behavior of transmitral diastasis and left ventricular volume index regarding the dimensions of the atrial septal defect in pulmonary atresia with intact ventricular septum. CIA: atrial septal defect. IV<sub>VI</sub>: left ventricular volume index. Diastasis: transmitral diastasis.

Source: Database. Echocardiography Laboratory. William Soler Cardiology Hospital.

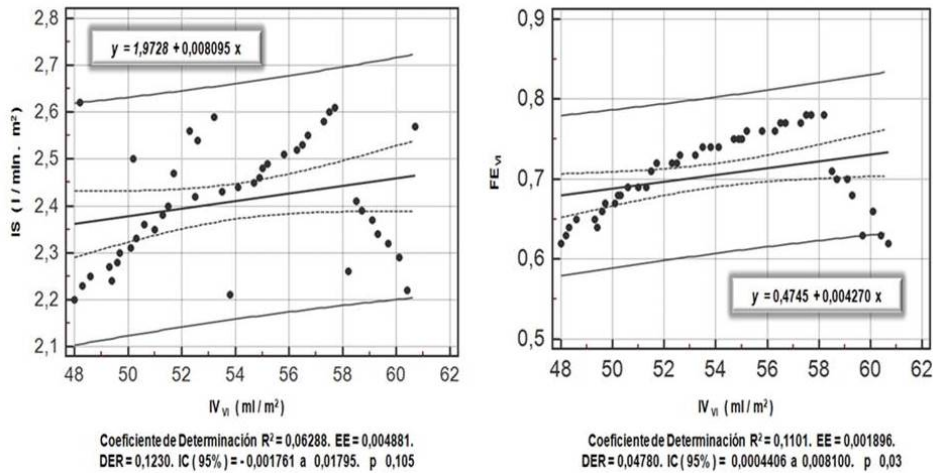


**Figure 3.** Level of dependence of systemic and volume indices on left ventricular transmitral diastasis in pulmonary atresia with intact ventricular septum. Diastasis: transmitral diastasis. IV<sub>VI</sub>: left ventricular volume index. SI: systemic index.

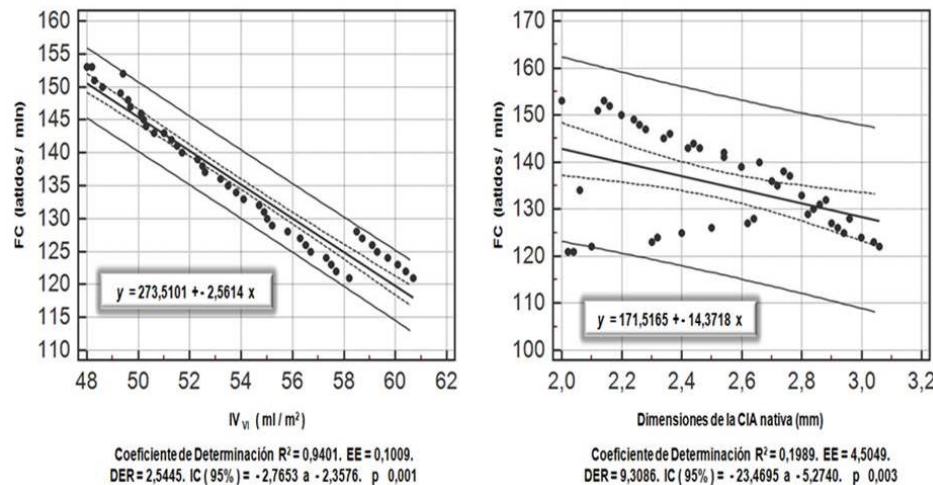
Source: Database. Echocardiography Laboratory. William Soler Cardiology Hospital.

Figure 4 illustrates the finding of low levels of association of SI ( $R^2 = 0.06288$ ; SE = 0.004881; RSD = 0.1230;  $p = 0.105$ ) and the high degree of dependence of LVEF ( $R^2 = 0.1101$ ; SE = 0.001896; RSD = 0.04780;  $p = 0.03$ ) with respect to variations in the left ventricular volume index in patients with the disease.

Figure 5 shows the close and directly proportional relationship between HR and LVVI ( $R^2 = 0.9401$ ; SE = 0.1009; RSD = 2.5445;  $p = 0.001$ ) and the native size of the atrial septal defect in PAIVS ( $R^2 = 0.1989$ ; SE = 4.5049; RSD = 9.3086;  $p = 0.003$ ).



**Figure 4.** Level of association of systemic index and ejection fraction index with left ventricular volume index in pulmonary atresia with intact ventricular septum. IVVI: left ventricular volume index. IS: systemic index. FEVI: left ventricular ejection fraction. Source: Database. Echocardiography Laboratory. William Soler Cardiology Hospital.



**Figure 5.** Heart rate dependence and association with respect to left ventricular volume index and with the size of atrial septal defect in pulmonary atresia with intact ventricular septum. FC: heart rate. IVVI: left ventricular volume index. CIA: atrial septal defect. Source: Database. Echocardiography Laboratory. William Soler Cardiology Hospital.

## **DISCUSSION**

The intracardiac pathophysiology of PAIVS has been studied by several authors in different times, but the analysis of its impact on the left ventricle and major circulation has been repeatedly neglected<sup>4,5</sup>.

The characterization of the left ventricle as a recipient of total circulation is not an isolated event and has peculiarities and implications likely to be identified and assessed by a diagnostic tools, such as transthoracic echocardiography, whose possibilities on seriously ill neonatal patients turn it into an indispensable tool for such cases<sup>3,8,9,11,13,15</sup>.

The results of the echocardiographic assessment of various factors that are associated with systemic hemodynamics show the presence of significant variations in the population of patient with PAIVS, when compared with a control group composed of supposedly healthy children. The LVVI ( $p = 0.0001$ ) and LVEF ( $p = 0.01$ ) increased; the HR shows a significant downward trend within the range that is considered as normal according to age ( $p = 0.0001$ ). These facts, reported in Table 1 are not random and are linked with other events of interest.

Figure 2 shows the direct proportional relationship between variations of LVVI ( $p = 0.054$ ), transmitral diastasis ( $p = 0.001$ ) and the native dimensions of the ASD in patients with PAIVS. In normal conditions, the time interval of transmitral diastasis is inversely proportional to heart rate, and its amplitude depends on the amount of pulmonary venous flow entering the left atrium<sup>9</sup>; the pathophysiological circumstances of PAIVS explain the impossibility of the influence of the last mentioned aspect, due to the tiny amount of blood supplied by the ductus arteriosus, that returns to the above mentioned atrial cavity<sup>4</sup>. The systemic venous flow that is directed toward the left cardiac cavities through the atrial septal defect becomes the determining factor in left ventricular volume overload, and is associated with the prolongation of transmitral diastasis. This view is reinforced in Figure 3, as it shows the degree of dependence of LVVI on transmitral diastasis ( $p = 0.005$ ) which, when prolonged, causes an increase in the time of the interatrial shunt, increases the systemic flow volume entering the left heart chambers and favors its positive and indirect association with SI ( $p = 0.001$ ).

The simple linear regression model shown in Figure 4 shows the lack of dependence of SI on LVVI in PAIVS patients ( $p = 0.105$ ). This controversial finding may

have a hypothetical explanation in the existence of a functional restriction of the left ventricular myocardium due to the pathological SI increase and due to increased LVVI<sup>5,17</sup>. Laplace's law provides the necessary theoretical foundation to justify the genesis of myocardial hypertrophy with the existing volume overload<sup>18</sup>. This secondary myocardial thickening must be the element that promotes the above mentioned restriction. The dependence shown by the LVEF, regarding LVVI variations found in patients with PAIVS ( $p = 0.03$ ), is a manifestation of the known heart muscle response to increased ventricular volume, and has an adequate foundation in the Frank-Starling law of the heart<sup>19</sup>.

The level of association between HR and LVVI ( $p = 0.001$ ) and with the native size of the ASD ( $p = 0.003$ ) in the population of children with PAIVS is the indirect manifestation of what has been stated in the discussion (Figure 5). The HR is seen as one of the main factors that, in its interaction, participate in the regulatory process of cardiac output in these patients. The HR figures found in subjects with the disease, which are much lower than those recorded in the control group but always fluctuate within the normal range for the age, lend credence to that idea<sup>20</sup>.

## **CONCLUSIONS**

The morphological abnormalities that are typical of the PAIVS favor the existence of peculiar pathophysiological conditions, with implications for systemic hemodynamics. The increase in the size of the native atrial septal defect and the prolongation of transmitral diastasis help increase the volume of the left ventricle, which is a dual recipient of intracardiac blood circulation in this disease. Heart rate, the restrictive nature of the left ventricular myocardium and its ejection fraction must play an important role as cardiac regulatory elements. Future multicenter studies are necessary to delve into the issue and determine the true role of each of the assessed aspects, and their interaction in the genesis of the systemic circulation in patients with PAIVS.

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