

Causes of Exercise Intolerance in Pectus Excavatum: a Study of 111 Cases and 20 Controls

Causas de intolerancia al esfuerzo en el pectus excavatum: estudio en 111 casos y 20 controles

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ABSTRACT

Background: Despite several studies have reported lower exercise capacity in patients with pectus excavatum, none of them could demonstrate a clear pathophysiology.

Objective: The aim of this study was to evaluate cardiac hemodynamics and systolic and diastolic function at rest and during exercise in patients with pectus excavatum and compare it with healthy controls.

Methods: Stress echocardiography was performed in 111 subjects with pectus excavatum and 20 healthy controls.

Results: Patients with pectus excavatum had lower right ventricular inflow minimum diameter: 1.29 ± 0.26 cm/m² versus 1.89 ± 0.25 cm/m² ($p < 0.01$).

Peak exercise capacity was lower in patients with pectus excavatum: 8.3 ± 1.4 METs versus 15 ± 4.5 METs ($p < 0.0001$).

Left ventricular diastolic dysfunction was observed in 34.6% of the patients with pectus excavatum and in 5% of the healthy controls ($p = 0.007$), while 40% of the subjects with pectus excavatum and 15% of the healthy controls presented right ventricular diastolic dysfunction ($p = 0.04$).

Medium tricuspid pressure gradient during exercise was higher in patients with pectus excavatum: 6.21 ± 2.29 mm Hg versus 4.8 ± 1.17 mm Hg in healthy controls ($p = 0.01$).

The tricuspid valve area remained fixed during exercise in patients with pectus excavatum: 1.48 ± 0.57 cm²/m² versus 2.11 ± 0.88 cm²/m² in healthy controls ($p = 0.0001$).

Conclusions: Patients with pectus excavatum present functional abnormalities, probably due to external compression of the heart, which are evident by a small tricuspid annulus, a higher diastolic tricuspid pressure gradient during exercise, tricuspid area that remains fixed at exercise and rest, and signs suggestive of diastolic dysfunction of both ventricles. Such abnormalities contribute to explain the lower exercise performance.

Key words: Pectus excavatum - Echocardiography, Stress - Exercise Tolerance

RESUMEN

Introducción: En múltiples estudios se ha determinado menor capacidad de esfuerzo en pacientes con pectus excavatum, pese a lo cual no se ha logrado demostrar claramente un mecanismo fisiopatológico que la explique.

Objetivo: Evaluar la hemodinamia cardíaca y la función sistodiastólica en reposo y en esfuerzo en pacientes con pectus excavatum, comparándolos con controles sanos.

Material y métodos: Se estudiaron con eco estrés 111 sujetos portadores de pectus excavatum y 20 controles sanos.

Resultados: El diámetro mínimo a nivel del tracto de entrada del ventrículo derecho fue menor en los pacientes con pectus excavatum: $1,29 \pm 0,26$ cm/m² versus $1,89 \pm 0,25$ cm/m² ($p < 0,01$).

La capacidad de esfuerzo máxima fue menor en los pacientes con pectus excavatum: $8,3 \pm 1,4$ MET versus $15 \pm 4,5$ MET ($p < 0,0001$).

Se observaron signos de disfunción diastólica del ventrículo izquierdo en el 34,6% de los pacientes con pectus excavatum y en el 5% de los controles sanos ($p = 0,007$), y de disfunción diastólica del ventrículo derecho en el 40% de los portadores de pectus excavatum y el 15% de los controles sanos ($p = 0,04$).

El gradiente tricuspídeo medio en el esfuerzo fue mayor en los pacientes con pectus excavatum: $6,21 \pm 2,29$ mm Hg versus $4,8 \pm 1,17$ mm Hg en los controles sanos ($p = 0,01$).

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El área tricuspídea en el esfuerzo se mantuvo fija en los portadores de pectus excavatum: $1,48 \pm 0,57 \text{ cm}^2/\text{m}^2$ versus $2,11 \pm 0,88 \text{ cm}^2/\text{m}^2$ en los controles sanos ($p = 0,0001$).

Conclusiones: Los pacientes con pectus excavatum presentan alteraciones funcionales, probablemente producto de la compresión cardíaca externa, que se evidencian por un diámetro del anillo tricuspídeo menor, un gradiente diastólico tricuspídeo mayor en el esfuerzo, un área tricuspídea fija en reposo y en esfuerzo, y signos que sugieren disfunción diastólica del ventrículo izquierdo y el ventrículo derecho. Dichas alteraciones contribuyen a explicar la menor performance en el esfuerzo.

Palabras clave: Pectus excavatum - Ecocardiografía de estrés - Tolerancia al ejercicio

Abbreviations

PA	Pulmonary artery	LVOT	Left ventricular outflow tract.
ASE	American Society of Echocardiography	IVC-RA	Inferior vena cava-right atrium
TAD	Tricuspid annulus diameter	RV	Right ventricle
RVDD	Right ventricular diastolic dysfunction	TRV	Tricuspid regurgitation velocity
LVDD	Left ventricular diastolic dysfunction	LV	Left ventricle
DTG	Diastolic tricuspid pressure gradient	CO	Cardiac output
PE	Pectus excavatum	PV	Pulmonary valve
TAPSE	Tricuspid annulus plane systolic excursion		

INTRODUCTION

Pectus excavatum (PE) is a deformity of the chest wall characterized by an inward depression of the sternum, below the level of the anterior costal arch which produces displacement of the thoracic organs. The depression may affect only one portion (upper portion, lower portion or mid portion) of the sternum, two portions or the entire sternum. The sternum may “sink” toward the left or the right (tilting of the sternum), producing different geometric abnormalities in the three-dimensional distribution and configuration of the thoracic organs. Several studies have reported lower exercise capacity in patients with PE. (1, 2) Other manifestations related to PE are syncope, (3), arrhythmias (4) and hypercapnia. (5) Although no respiratory abnormalities have been demonstrated, lower stroke volume index and lower maximal oxygen consumption during exercise stress test, among other abnormalities have been reported in these patients. (6) Numerous studies reported improvement after corrective surgery. (6-10) Baseline lung function has not shown abnormalities, either before or after corrective surgery. (11) Several studies using different methods (magnetic resonance imaging, computed tomography) have demonstrated anatomic anomalies in relation to the three-dimensional arrangement of the internal thoracic organs of patients with PE. (12-15)

However, we have not found any study using stress echocardiography in these patients to evaluate anatomic parameters as tricuspid annulus diameter (TAD), or functional parameters as left ventricular (LV) or right ventricular (RV) diastolic function, pressure gradients, cardiac output (CO) and biventricular systolic function.

The aim of this study was to prospectively evaluate these parameters using supine bicycle stress echocardiography in patients with PE and compare them with healthy controls.

METHODS

From March 2013 to December 2015, 111 consecutive patients with different levels of pectus excavatum and 20 healthy controls underwent stress echocardiography. The control group consisted of subjects < 35 years, with normal baseline echocardiogram, who attended the echo laboratory for routine assessment. Patients with PE had to be capable of undergoing a stress test on a bicycle in the supine position.

The presence of baseline conduction disturbances in the electrocardiogram was reported.

The baseline echocardiogram included measurement of the following parameters from the apical 4-chamber view: RV inflow minimal diastolic diameter, equivalent to TAD; LV CO estimated at the LV outflow tract (LVOT) and RV CO at the level of the pulmonary valve (PV) using pulsed wave Doppler; diastolic tricuspid pressure gradient (DTG) with continuous Doppler; S-wave, e-wave and a-wave with tissue-Doppler at the level of the tricuspid annulus and interventricular septum; tricuspid annulus plane systolic excursion (TAPSE) by M-mode; and E-wave and A-wave of the tricuspid and mitral valves using pulsed Doppler echocardiography. All these measurements were used to determine the diastolic function of both ventricles using the normal reference values reported by the American Society of Echocardiography (ASE), and analyzing diastolic function as a qualitative variable.

Right ventricular diastolic dysfunction (RVDD) was qualitatively considered as an e/a ratio <0.6 or an E/A ratio <0.8 according to ASE criteria. (16) Due to the lack of definition of these parameters during exercise, the same cutoff points used at rest were considered if there was a difference compared with baseline values (inverted E/A ratio or e/a ratio). Left ventricular diastolic dysfunction (LVDD) at rest was qualitatively considered as $e < 7 \text{ cm/s}$, E/e ratio >15, and tricuspid regurgitation velocity (TRV) >2.8, according to the 2009 ASE criteria, when the protocol was designed. (17) The inversion of the E/A ratio or e/a ratio during peak exercise was arbitrarily considered a sign of LVDD.

Diastolic tricuspid valve area was estimated by the continuity equation using the PV and the LVOT as reference.

Then, the patients underwent a maximal stress test on a supine bicycle using the Astrand protocol. During the last

exercise stage, all the parameters were measured again, except for the pulmonary artery (PA) diameter and the LVOT diameter which were assumed as constant.

All patients with PE underwent a computed tomography scan and the Haller index (ratio of the transverse diameter, maximum internal laterolateral diameter, and the narrowest antero-posterior diameter of the chest) was calculated. The normal Haller index is 2.5. Significant PE has an index >3.25 , representing the standard for determining candidacy for repair.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation and were compared with the t test or with non-parametric tests, as applicable. Categorical variables were expressed as percentages and were compared using the chi square test. A two-tailed p value < 0.05 was considered statistically significant.

Ethical considerations

All the patients signed an informed consent form before participating in the study.

RESULTS

Table 1 shows baseline characteristics of controls and patients with PE.

The baseline echocardiogram showed normal LV diastolic function in all the patients, with E/A ratio of 1.7 ± 0.5 , e/a ratio of 2 ± 0.8 and E/e ratio of 6.9 ± 1.8 . Systolic function was also normal, with mean LV ejection fraction of $67.2\% \pm 6.6\%$.

The analysis of RV diastolic function showed an E/A ratio of 1.5 ± 0.4 , e/a ratio of 2 ± 0.9 and E/e ratio of 4.7 ± 1.9 . At least one parameter of diastolic dysfunction was present in 16.5% of the patients at rest (p=ns versus controls).

The pressure gradient between the inferior vena cava and the right atrium (IVC-RA) measured from the subcostal view, did not evidence differences between controls and patients with PE.

Sixteen percent of the patients presented some degree of non significant tricuspid regurgitation (TR).

Right ventricular inflow minimum diameter (TAD) was significantly lower in patients with PE (Table 2).

The tricuspid valve area (TVA) was estimated using the continuity equation with the PA and was indexed by body surface area; the average value was

Table 1. Baseline characteristics of patients with pectus excavatum and controls

	<i>Pectus excavatum</i>	Controls	p
Age, years	20.4 $\pm$ 8	22.2 $\pm$ 7.5	ns
Haller*	5.7 $\pm$ 4.4	ND	
Men, %	86	90	ns
RVDD, %	16	0	ns
TAPSE	21.5 $\pm$ 4.4	24.8 $\pm$ 4.0	ns

* Haller index, measured by computed tomography scan, an anatomic indicator of sternal depression severity. RVDD: Right ventricular diastolic dysfunction. TAPSE: Tricuspid annulus plane systolic excursion. ND: Not determined. ns: Non-significant.

Table 2. Measurements of patients with pectus excavatum and controls at rest

	<i>Pectus excavatum</i>	Controls	p
TAD, cm/m ²	1.29 $\pm$ 0.26	1.89 $\pm$ 0.25	0.0001
TVA, cm ² /m ²	1.47 $\pm$ 0.43	1.55 $\pm$ 0.7	ns
DTG, mmHg	1.3 $\pm$ 0.59	1.09 $\pm$ 0.9	ns
RBBB, %	85.6	35	<0.0001

TAD: Tricuspid annulus diameter. TVA: Tricuspid valve area. DTG: Diastolic tricuspid gradient. RBBB: Right bundle branch block. ns: Non-significant.

similar in patients with PE and in controls.

Mean DTG at rest was not different between both groups (Table 2).

The presence of right bundle branch block was more frequent in patients with PE compared with controls (85.6% vs. 35%; p < 0.0001)

Exercise stress test

Although 32% of the patients with PE complained of some degree of exercise intolerance in everyday life, there was no correlation with the exercise performed during the stress test.

The exercise stress test was maximal in all the patients. The average exercise capacity was significantly lower in patients with PE (8.3 ± 1.4 MET) compared with controls (15 ± 4.5 MET) (p <0.0001).

Diastolic function

Left ventricular diastolic dysfunction (inversion of the E/A ratio or e/a ratio) was observed in 34.6% of the patients and 5% of controls (p=0.007). According to the 2016 guidelines, none of the patients reached the criteria of definite diastolic dysfunction during exercise stress test (E/e' ratio >15 , septal e' velocity <7 cm/sec and TRV >2.8 m/sec). (18)

Forty percent of the patients presented at least one sign of RVDD (inversion of the E/A ratio or e/a ratio) versus 15% of controls (p = 0.04).

The pressure gradient IVC-RA was not significantly different between patients with PE and controls.

Tricuspid regurgitation was seen in 7.2% of the patients and all presented a TRV <2.8 m/sec. None of the controls presented TR during exercise.

Systolic function

Left and right ventricular systolic indexes were normal in both groups, without significant differences.

Tricuspid pressure gradient

Mean DTG was significantly greater in patients with PE compared with controls (PE 6.21 ± 2.29 mmHg vs. controls 4.8 ± 1.17 mmHg; p <0.01) (Table 3).

Tricuspid valve area

During exercise, TVA was significantly lower in pa-

Table 3. Measurements of patients with pectus excavatum and controls during exercise

Exercise stress test	<i>Pectus excavatum</i>	Controls	p
MET	8.3±1.4	15±4.5	<0.0001
TAPSE	25.7±5.2	35.1±3.7	<0.0001
LVEF, (%)	81.5	80.9	ns
RVDD, %	40	15	0.04
LVDD, %	34.6	5	0.007
Mean DTG, mmHg	6.21±2.29	4.8±1.17	0.01
TVA, cm ² /m ²	1.48±0.57	2.11±0.88	0.0001

MET: Metabolic equivalent. TAPSE: Tricuspid annulus plane systolic excursion. LVEF: Left ventricular ejection fraction. RVDD: Right ventricular diastolic dysfunction. LVDD: Left ventricular diastolic dysfunction. DTG: Diastolic tricuspid gradient. TVA: Tricuspid valve area. ns: Non-significant.

tients with PE compared with controls (Table 3) and similar to the area estimated at rest. Tricuspid valve area increased in controls during exercise (2.11 ± 0.88 cm²/m²) compared with the value measured at rest (1.55 ± 0.7 cm²/m²).

This finding suggests that controls are capable of increasing TVA during exercise, while the patients with PE cannot do so and TVA remains fixed at rest and during exercise.

DISCUSSION

Despite several previous studies have reported lower exercise capacity in patients with PE, none of them could demonstrate a clear pathophysiological mechanism or changes in respiratory function. (19, 20) In this study, we observed that the baseline differences between patients with PE and controls are minimal and limited to anatomical features (TAD) without functional expression, since pressure gradients and biventricular systolic and diastolic function are preserved. However, exercise induces differences between both groups. These differences are consistent between each other, as a greater DTG is observed, with a significantly lower area and impossibility of increasing it. A higher CO with a fixed area will necessarily increase the pressure gradient. In turn, the higher rate of signs of diastolic dysfunction implies another functional abnormality, probably due to the three-dimensional geometrical distortion of the heart, particularly of the RV. These distortions are present at birth and could generate functional changes; however, the presence of fibrosis could also produce intrinsic abnormalities in cardiac walls.

Why do not all the patients present similar changes? Probably, because not all the patients have tissues with identical elasticity; in turn, the Haller index gives a broad idea of PE severity, but does not take into account other important anatomical details, as which portion of the sternum is depressed or tilted (depression towards the right or the left). Our group is working to develop more accurate indexes for a bet-

ter characterization of patients with PE. (21)

The changes demonstrated (lower TAD, greater DTG, signs suggestive of diastolic dysfunction, fixed TVA at rest and during exercise) seem be subclinical, yet, they could have functional impact and might identify those patients that could obtain benefit with surgical PE repair or by other techniques. This hypothesis is currently being evaluated by our group and others. (21, 22)

Why do they appear to be subclinical? Because most of the patients develop a normal life and do not feel limitations; however, they do not know their real exercise capacity, which is significantly reduced as this study and many others have demonstrated. An significant training level and other adaptive mechanisms may explain why patients may not notice any difference.

The fact that we did not measure strain, as we lack the necessary technique, is an important limitation of our study. We think that strain would reflect the intrinsic abnormalities of the tissues as a consequence of the three-dimensional geometric distortion since birth. The low number of controls was due to difficulty in finding healthy volunteers of equivalent age for this type of complex studies.

Another difficulty is related to the fact that exercise-Doppler echocardiography requires a supine bicycle, an equipment with the capability of storing images in digital format and off-line analysis. Although not all the curves are achieved in all the cases, feasibility was over 98% in our study. Moreover, most measurements are performed from the apical view, which is suboptimal in patients with PE.

CONCLUSIONS

Patients with PE present functional abnormalities, probably due to external compression of the heart, which are evident by a significantly lower TAD, higher DTG during exercise, TVA that remains fixed at exercise and rest, and signs suggestive of biventricular diastolic dysfunction. Such abnormalities may contribute to explain the lower exercise performance.

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Conflicts of interest

None declared. (See authors' conflicts of interest forms in the website/Supplementary material).

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