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Flow ejection dynamics as echocardiographic diagnostic parameters of severity in aortic stenosis

Utilidad de la dinámica de eyección como parámetros ecocardiográficos diagnósticos de la severidad de la estenosis aórtica

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ABSTRACT. Introduction: Aortic stenosis (AS) is a progressive disease whose final stage results in an inadequate cardiac output and death from cardiovascular causes. Its severity can be assessed by non-invasive methods such as echocardiography; however, discrepancies have been observed between severity estimated by the continuity equation and transvalvular gradients in up to a third of patients with preserved LVEF when compared with hemodynamic parameters obtained by cardiac catheterization. Recent studies have evaluated the usefulness of ejection dynamics, such as acceleration time (AT) and acceleration time/ejection time (AT/ET) ratio, as diagnostic and prognostic parameters. **Objective:** To assess whether AT and AT/ET ratio measured in the continuous Doppler curve of aortic flow have a direct relationship with severity of AS. **Material and methods:** Cross-sectional, analytical and predictive study. Patients with AS (aortic peak velocity >2m/s) were included. General characteristics, clinical presentation and echocardiographic parameters were analyzed in different stages of AS. A ROC curve was plotted to determine the best cutoff value of AT, ET and AT/ET ratio to identify severe AS. **Results:** 75 patients were included (mean age 64.7±16.7 years, 48% women); of whom 8 had mild AS (10.7%), 16 had moderate AS (21.3%) and 51 had severe AS (68%). A cutoff value of 104.5ms for AT had a sensitivity of 92.2% and a specificity of 83.3% for severe AS; a cut-off value of 323.5ms for ET had a sensitivity of 80.4% and a specificity of 70.8%, and a cut-off value of 0.345 for AT/ET ratio had a sensitivity of 84.3% and a specificity of 91.7%. **Conclusion:** AT, ET and AT/ET ratio are useful to identify severe AS.

Key words: Aortic stenosis, acceleration time, ejection time, acceleration time/ejection time ratio.

RESUMEN. Introducción: *La estenosis aórtica (EAo) es una enfermedad progresiva cuyo estadio final resulta en un gasto cardiaco inadecuado y muerte por causas cardiovasculares. Su severidad puede evaluarse por métodos no invasivos como la ecocardiografía; sin embargo, se han observado discordancias entre la severidad estimada por ecuación de continuidad y los gradientes transvalvulares hasta en una tercera parte de los pacientes con FEVI conservada cuando se compara con cálculos hemodinámicos durante el cateterismo. Estudios recientes han evaluado la utilidad de la dinámica de eyección, como lo es del tiempo de aceleración (TA) y el índice tiempo de aceleración/tiempo de eyección (TA/TE), como parámetros diagnósticos y pronósticos.* ***Objetivo:*** *Evaluar si el TA y el índice TA/TE medidos en la curva Doppler continuo del flujo aórtico tienen una relación directa con la severidad de la estenosis aórtica.* ***Material y métodos:*** *Estudio transversal, analítico y predictivo. Se incluyeron pacientes con EAo de válvula nativa (velocidad máxima del jet aórtico >2m/s). Se analizaron las características generales, presentación clínica y parámetros ecocardiográficos en los diferentes estadios de la EAo. Se realizó una curva ROC para determinar el mejor valor de corte del TA, TE e índice TA/TE para identificar la EAo severa.* ***Resultados:*** *Se incluyeron 75 pacientes con diagnóstico de EAo (edad media de 64.7±16.7 años, 48% mujeres); 8 de grado ligero (10.7%), 16 moderado (21.3%) y 51 severo (68%). El mejor valor de corte para la detección de EAo severa para el TA fue de 104.5ms (S 92.2%, E 83.3%), para el TE fue de 323.5ms (S 80.4%, E 70.8%) y para el índice TA/TE fue de 0.345 (S 84.3%, E 91.7%).* ***Conclusión:*** *El TA, TE y el índice TA/TE son útiles para identificar la EAo severa.*

Palabras clave: *Estenosis aórtica, tiempo de aceleración, tiempo de eyección, índice tiempo de aceleración/tiempo de eyección.*

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INTRODUCTION

Aortic stenosis (AS) is the most frequent native valve disease followed by mitral regurgitation.[1] Anatomic, genetic and clinical factors contribute to the pathogenesis of AS.[2-4] It has three main causes: a congenital bicuspid valve with overlapping calcification, a progressive calcification of a normal trileaflet aortic valve and rheumatic diseases.[2,5]

Echocardiography is the gold standard method to assess the severity of AS.[6] Although current American guidelines recommends specific parameters for the diagnosis,[7,8] discrepancies have been observed between the severity of AS estimated by the continuity equation and the transvalvular gradients in up to 30% of patients with preserved left ventricular ejection fraction (LVEF), when compared with catheterization.[7,9]

Clinical practice guidelines recommend the use of ejection dynamics parameters in the assessment of obstruction of prosthetic aortic valves;[10,11] however, few studies have evaluated these parameters in native aortic valve disease.[12,13] It has been observed that the length of acceleration time (AT) and ejection time (ET) have a significant relationship with the severity of AS, with prolongation of its duration and therefore of AT/ET ratio (not flow dependent parameter). In addition, a change in the aortic waveform shape is described, being more rounded in the case of a severe AS *(Figure 1)*.[10,12] Moreover, AT/ET ratio has shown utility as a prognostic marker.[9]

Therefore, these parameters can be useful to confirm the diagnosis of severe AS when there are discrepancies in the usual measurements. Our objective was to assess whether AT and AT/ET ratio have a direct relationship with severity of AS.

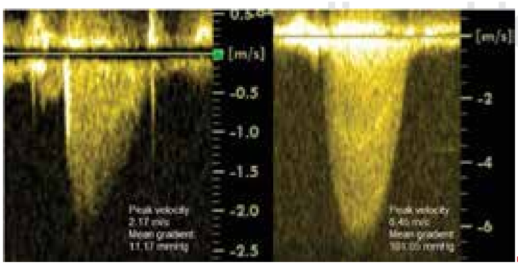

Figure 1:

Aortic waveform shape measured by continuous Doppler and its relationship with the severity of aortic stenosis.

MATERIAL AND METHODS

A cross-sectional, analytical and predictive study was conducted. We prospectively included 75 patients between January and October 2018, both genders, age ≥18 years and valvular native AS (peak velocity >2m/s) diagnosed by transthoracic echocardiogram (TTE). The exclusion criteria were subvalvular or supravalvular AS, moderate or severe aortic regurgitation, ascending thoracic aorta diameter <25 mm, mitral or tricuspid valvular disease more than mild, hyperdynamic states and suboptimal window.

2D and Doppler TTE was performed using a General Electric Healthcare Vivid S6 version 12.2 equipment. All tests were performed by one experienced cardiologist. The parasternal long-axis view was used to measure aortic annular diameter in early systole. The time-velocity integral (TVI) was obtained by using pulsed Doppler in the LVOT, placing the sample volume 0.5 cm below the aortic valve. Stroke volume was calculated assuming a circular shape of the LVOT. Maximal and mean pressure gradients through aortic valve was performed from the five-chamber windows, using the modified Bernoulli equation. Effective orifice area (EOA) was calculated using the continuity equation, and then indexed by body surface area. Doppler velocity index (DVI) was calculated as the TVI of the LVOT divided by the TVI of the aortic jet. All measurements were made in an average of 3 cardiac cycles for patients with sinus rhythm and 6 for patients with a rhythm other than sinus rhythm. The inclusion of an extrasystolic heartbeat was avoided. The Doppler records were made at a scanning speed of 100mm/s.

No patient required a dobutamine echocardiogram, because no patient with aortic stenosis included during the study period met the criteria to carry out said evaluation.[8]

The ejection dynamics parameters were measure using the velocity curve of the continuous Doppler recording in the apical 5-chambers axis. The ET was measured as the time from beginning to the end of systolic flow. The AT was obtained as the time interval between the onset of systolic flow to its maximum velocity. Finally, the AT/ET ratio was calculated as well as the DVI.

The aortic waveform shape measured by continuous Doppler was performed by an by an expert echocardiography cardiologist, classifying it as rounded or triangular.

Statistical management of the information was analyzed with the IBM SPSS Statistics version 20 program. Quantitative variables are presented as mean and standard deviation (SD), and were compared using Kruskal-Wallis or ANOVA one-way. Categorical variables are reported as percentages and were compared using the χ^2 test or the Fisher's exact test. A ROC curve was plotted to determine the best cutoff value of AT, ET and AT/ET ratio that identified severe AS. Comparison between ejection dynamics parameters and other echocardiographic parameters was calculated by Pearson or Spearman correlation. Analysis of the aortic waveform shape was performed using a χ^2 test and subsequent subanalysis with Fisher's exact test. Differences were considered significant at p values <0.05 with a confidence interval (CI) of 95%.

RESULTS

A total of 75 patients were included with a mean age 64.7±16.7 years (48% women), of whom 10.7% had mild AS, 21.3% had moderate AS and 68% had severe AS. General patient characteristics are summarized in *Table 1*. 37.9% of the patients presented other diseases such as Parkinson's disease, hypothyroidism, COPD, rheumatoid arthritis, epilepsy and depressive disorder. Two patients were carriers of a definitive pacemaker, 5 patients had atrial fibrillation and one patient had a history of EVC.

Clinical presentation is shown in *Table 2*. Of the symptomatic patients (n=53), the average in

Table 1: General patient characteristics.[¥]

	Mild AS (n = 8)	Moderate AS (n = 16)	Severe AS (n = 51)	p
Age (y)	69.0 ± 16.6	68.6 ± 16.6	62.8 ± 16.7	NS
Women (%)	62.5	37.5	49.0	NS
Weight (kg)	69.0 ± 9.9	76.5 ± 11.1	72.6 ± 13.4	NS
BMI (kg/m^2)	27.10 ± 3.63	29.16 ± 3.27	28.03 ± 4.64	NS
BSA (m^2)	1.72 ± 0.15	1.81 ± 0.16	1.76 ± 0.18	NS
HR (bpm)	71.0 ± 10.7	70.4 ± 13.8	66.8 ± 13.0	NS
SBP* (mmHg)	125.1 ± 20.3	123.1 ± 19.0	126.2 ± 20.4	NS
DBP* (mmHg)	72.9 ± 9.5	79.0 ± 9.8	80.3 ± 11.0	NS
MBP* (mmHg)	90.3 ± 10.4	93.7 ± 12.2	95.6 ± 13.5	NS
Physical inactivity* (%)	85.7	69.2	91.3	NS
Smoking* (%)	57.1	53.8	47.8	NS
Hypertension* (%)	85.7	69.2	69.6	NS
Diabetes* (%)	71.4	30.8	26.1	NS
Dyslipidemia* (%)	42.9	46.2	34.8	NS
IHD* (%)	42.9	30.8	8.7	0.024[§]
CKD* (%)	28.6	15.4	2.2	0.024[§]
Other* (%)	57.1	38.5	34.8	NS

[¥] Data are expressed as mean ± SD or as percentages.
* Data of 9 patients were not included because they were not recorded during the study.
[§] Mild AS vs. severe AS.
AS = aortic stenosis; BMI = body mass index; BSA = body surface area; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; IHD = ischemic heart disease; CKD = chronic kidney disease; NS = not significant.

months of the onset of symptoms was 23.53±22.47, without statistically significant difference.

As expected, a statistically significant difference was observed between the usual echocardiographic parameters and the severity of AS, with the exception of the indexed stroke volume and LVEF *(Table 3)*. 70.7% patients presented mild aortic insufficiency.

It can be observed that ejection dynamics parameters were higher in patients with more severe AS. ROC curve analysis shows the best cutoff value to detect severe AS for AT (104.5ms), ET (323.5ms) and AT/ET ratio (0.345), with good sensitivity and specificity *(Table 4)*. The largest AUC was for AT (0.968), followed by AT/ET ratio (0.944), and finally by ET (0.726) *(Figure 2)*.

Table 2: Clinical presentation of patients.[¥]

	Mild AS	Moderate AS	Severe AS	p
Heart failure	42.9	46.2	69.6	NS
NYHA I-II	66.7	16.7	31.3	
NYHA III-IV	33.3	83.3	68.7	
Syncope	14.3	15.4	19.6	NS
Angor pectoris	14.3	38.5	60.9	0.041[§]
CCS I-II	100.0	40.0	32.2	
CCS III-IV	0.0	60.0	67.8	
Asymptomatic	57.1	30.8	10.9	0.009[§]
Other	0.0	7.7	10.9	NS

[¥] Data are expressed as percentages. Data of 9 patients were not included because they were not recorded during the study.
[§] Mild AS vs. Severe AS.
AS = aortic stenosis; NYHA = New York Heart Association; CCS = Canadian Cardiovascular Society; NS = not significant.

Table 3: Echocardiographic parameters in the different stages of AS.[¥]

	Mild AS	Moderate AS	Severe AS	p
Peak velocity (m/s)	2.50 ± 0.47	3.22 ± 0.46	4.94 ± 0.71	< 0.001[‡*]
Mean gradient (mmHg)	14.61 ± 6.19	23.64 ± 7.15	63.96 ± 21.19	< 0.001[‡*]
Maximal gradient (mmHg)	26.04 ± 9.04	41.99 ± 11.58	99.64 ± 30.53	< 0.001[‡*]
EOA (cm^2)	1.66 ± 0.16	1.30 ± 0.19	0.69 ± 0.19	< 0.001
Indexed EOA (cm^2/m^2)	0.98 ± 0.13	0.72 ± 0.11	0.40 ± 0.10	< 0.001
DVI	0.47 ± 0.14	0.35 ± 0.08	0.20 ± 0.05	< 0.001
Indexed stroke volume (ml/m^2)	46.29 ± 14.06	50.47 ± 12.45	48.83 ± 9.92	NS
LVEF (%)	61.0 ± 6.0	59.4 ± 10.6	62.9 ± 7.3	NS
AT (ms)	86.38 ± 14.81	90.06 ± 14.65	135.49 ± 22.30	< 0.001[‡*]
ET (ms)	304.13 ± 51.61	311.06 ± 51.16	343.37 ± 35.92	0.021[‡], 0.038*
AT/ET ratio	0.29 ± 0.04	0.29 ± 0.04	0.40 ± 0.05	< 0.001[‡*]
Indexed ventricular mass (g/m^2)	86.44 ± 25.59	102.10 ± 42.04	126.06 ± 49.30	0.025

[¥]Data are expressed as mean ± SD or as percentages. (To evaluate the differences between the groups, the Tukey *post hoc* test was used).
[‡]Severe AS vs. mild AS.
*Severe AS vs. moderate AS.
AS = aortic stenosis; EOA = effective orifice area; DVI = Doppler velocity index; LVEF = left ventricular ejection fraction;
AT = acceleration time; ET = ejection time; NS = not significant.

Table 4: Diagnostic tests: optimal cutoff values of AT, ET and AT/ET ratio to differentiate severe AS.

Variable	AUC	Optimal cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
AT	0.968	104.5 ms	92.2	83.3	89.3	92.2	83.3
ET	0.726	323.5 ms	80.4	70.8	77.3	85.4	63.0
AT/ET ratio	0.944	0.345	84.3	91.7	86.6	95.6	73.3

AT = acceleration time; ET = ejection time; AS = aortic stenosis; AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value.

Table 5: Correlation between AT and AT/ET ratio with usual echocardiographic measures to evaluate the degree of AS.

Variable	AT	p	AT/ET ratio	p
Peak velocity	r = 0.735	< 0.001	r = 0.719	< 0.001
Mean gradient	r = 0.718	< 0.001	r = 0.744	< 0.001
Maximal gradient	r = 0.705	< 0.001	r = 0.699	< 0.001
EOA	r = -0.732	< 0.001	r = -0.666	< 0.001
Indexed EOA	r = -0.767	< 0.001	r = -0.704	< 0.001
DVI	r = -0.754	< 0.001	r = -0.724	< 0.001

AT = acceleration time; ET = ejection time; AS = aortic stenosis; EOA = effective orifice area; DVI = Doppler velocity index.

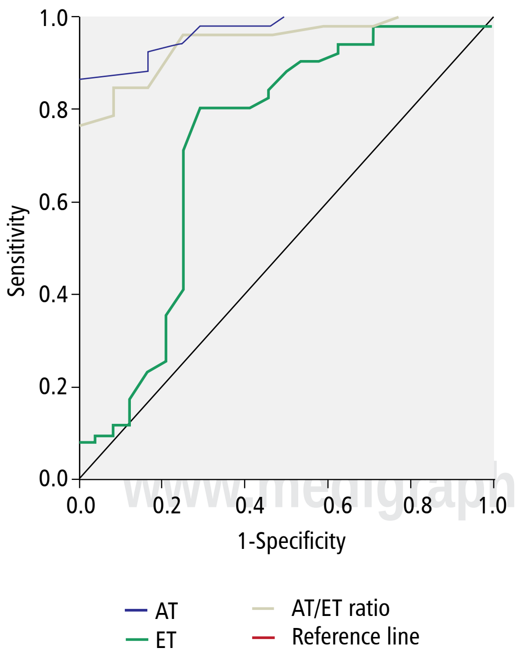

Figure 2:

ROC curve to detect severe AS based on AT, ET and AT/ET ratio.

ROC = receiver operating characteristics; AS = aortic stenosis; AT = acceleration time; ET = ejection time.

We found high correlations between AT and AT/ET ratio with usual echocardiographic measures to evaluate the degree of AS *(Table 5)*. There were no correlations respect these measures and ET. Similarly, there was also no correlation between indexed stroke volume, LVEF and indexed ventricular mass with ejection dynamics parameters.

Respect the aortic waveform shape, we found that a redound contour of the Doppler jet velocity profile is more related to severe AS compared with moderate AS (p<0.001) and mild AS (p<0.001), stages in which it is more frequent to find a triangular spectrum.

DISCUSSION

Despite the fact that echocardiography remains the cornerstone in the diagnosis of AS, there is sometimes a discrepancy between clinical evaluation and echocardiographic data. The main limitations in calculating the valvular area by the continuity equation, lie in their complexity, variability in the measurement of aortic valve annulus, flow dependence, state of volume and in some cases ventricular function. Therefore, it's considered necessary to find new parameters that demonstrate greater independence and reproducibility, in order to confirm the diagnosis, stratify the pathology, predict the outcomes and/or the evolution of the disease to choose appropriate treatment on time.

Study groups such as those of Hatle et al[14] and Nakamura et al, have previously reported a good correlation between the prolongation of AT and AT/ET ratio with the peak and mean transvalvular gradient evaluated by catheterization. Only works from a group of researchers in Spain,[12,13] France[15] and South Korea[6] have been published, who report a direct relationship between the duration of AT and AT/ET ratio with the severity of AS, and a strong association with high risk of death during follow-up. After adjusting variables of prognostic importance, such as the mean pressure gradient or indexed stroke volume, patients with a AT/ET ratio >0.36 and a AT >112ms presented an increased risk of global mortality.[15] So, both groups suggest to include these measurements in all echocardiograms of patients with AS.

The above has not been studied yet in the Mexican population, until this moment. The AT was significantly higher in patients with severe AS compared to the group of moderate and mild AS. We found that the best cutoff value to detect severe AS was 104.5ms, compared to Gamaza-Chulian et al, whose cut point reported was lower (94ms), with lower sensitivity and specificity.

The AT/ET ratio was significantly increased in the group of severe AS with respect to the other groups. Our optimal cutoff point was 0.345, while our reference study[12] found a slightly higher cut-off point (0.35), with lower sensitivity and specificity.

When we performed the correlation between the traditionally used parameters for the evaluation of the severity of the AS with the AT, ET and AT/ET ratio, a high correlation was found only with the AT and the AT/ET ratio. In concordance with previous reports,[12] we found no significant correlation with ET.

Our work group similarly found no correlation between the indexed stroke volume and the LVEF with AT nor with the AT/ET ratio. The above is of great importance, since it shows us that such parameters are independent of transvalvular flow and ventricular function.

Finally, regarding aortic waveform shape, coinciding with the other study groups,[13,16] we found that severe AS significantly presented a more rounded spectrum or with a later maximum peak compared to moderate or mild AS.

These novel measurements are obtained in a simpler and more reproducible way, with the advantage of being independent from ventricular function, flow and volume status, unlike most of the traditional parameters, which are subject to a greater margin of error besides increased inter and intra-observer variability. Our study confirms in our population that AT, ET and AT/ET ratio are useful parameters to identify the severity of AS and its usefulness is not limited only to cases in which there is disagreement with the usual measurements.[17]

CONCLUSIONS

The AT and the AT/ET ratio measured in the continuous Doppler curve of the aortic flow have a direct relationship with the severity of the aortic stenosis.

Limitations

The principal limitation of this trial was that it did not include patients with severe low-flow/low-gradient AS with reduced LVEF or paradoxical low-flow severe AS, which would help us confirm the validity of the parameters of the ejection dynamics when there is left ventricular dysfunction. Furthermore, we do not assess intra- and inter-observer variability as in other studies. In any way, to our knowledge until the writing of this work, we are the first group to study the parameters of ejection dynamics in Mexican population and also obtain a cut-off point for severe AS, not only with AT and the AT/ET ratio, but also with ET. A tool that can be easily measured, which helps to corroborate the diagnosis of severe AS when there are discrepancies with the usual measurements.

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