Prevalence of diastolic dysfunction according to the diagnostic guidelines of 2009 and 2016: Relationship with non-invasive hemodynamic assessment

Prevalencia de disfunción diastólica de acuerdo con las guías diagnósticas de 2009 y 2016. Relación con la valoración hemodinámica no invasiva

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Abstract

Objectives: The objectives of the study were to assess the prevalence of developmental disabilities (DD) according to the criteria of the 2009 and 2016 guidelines and its association with systemic arterial compliance (DAS) and peripheral vascular resistance (RVP). **Material and methods:** A total of 306 patients aged ≥ 40 years, with ejection fraction $\geq 50\%$ were analyzed. It was estimated in all DAS and RVP. **Results:** The prevalence of DD was 32.7% and 22.9% according to the 2009 and 2016 guidelines, respectively ($p \leq 0.0001$). Patients with DD according to the 2009 guideline had a lower average of DAS than those with normal function ($p = 0.0001$). Similar with the 2016 guide ($p = 0.0007$). The presence of DD according to the 2009 and 2016 guideline showed higher RVP values than normal values ($p = 0.005$ and $p = 0.018$, respectively). The DD according to both guidelines was a predictor, in the univariate analysis, of $DAS < 0.60 \text{ ml.mmHg}^{-1} \text{ min.l}^{-1}$ and $RVP > 1400 \text{ mmHg.min.l}^{-1}$. The DD according to the 2009 guideline persisted as an independent predictor, in the multivariate analysis, of $RVP > 1400 \text{ mmHg.min.l}^{-1}$. **Conclusion:** The 2016 guide decreases the prevalence of DD. The DD, both from the 2009 and 2016 guidelines, were univariate predictors of $DAS < 0.60 \text{ ml.mmHg}^{-1}$ and $RVP > 1400 \text{ mmHg.min.l}^{-1}$. The DD, according to the 2009 guide, was an independent predictor of $RVP > 1400 \text{ mmHg.min.l}^{-1}$.

Key words: Diastole. Hemodynamics. Doppler. Echocardiography.

Resumen

Objetivos: Evaluar la prevalencia de DD de acuerdo con los criterios de las guías del 2009 y 2016, y su relación con la distensibilidad arterial sistémica (DAS) y la resistencia vascular periférica (RVP). **Material y métodos:** Se analizó a 306 pacientes ≥ 40 años de edad, con fracción de expulsión $\geq 50\%$. Se calcularon en todos DAS y RVP. **Resultados:** La prevalencia de DD fue de 32.7% y 22.9% según las guías de 2009 y 2016, respectivamente ($p < 0.0001$). De acuerdo con las guías del 2009, los pacientes con DD presentaron una media de DAS menor que aquellos con función normal ($p = 0.0001$), de modo similar a las guías del 2016 ($p = 0.0007$). La DD, según las guías de 2009 y 2016, mostró valores más altos de RVP que los normales ($p = 0.005$ y $p = 0.018$, respectivamente). Asimismo, la DD fue predictora, en el análisis univariado, de $DAS < 0.60 \text{ ml.mm Hg}^{-1}$

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y $RVP > 1,400 \text{ mmHg.min.l}^{-1}$ según ambas guías. En el análisis multivariado, la DD, de acuerdo con las guías del 2009, persistió como predictor independiente de $RVP > 1,400 \text{ mmHg.min.l}^{-1}$. **Conclusión:** Las guías del 2016 reducen la prevalencia de DD. Ésta, tanto en las guías del 2009 como en las del 2106, fue predictor univariado de $DAS < 0.60 \text{ ml.mmHg}^{-1}$ y $RVP > 1,400 \text{ mmHg.min.l}^{-1}$. La DD, de acuerdo con las guías de 2009, resultó predictora independiente de $RVP > 1,400 \text{ mmHg.min.l}^{-1}$.

Palabras clave: Diástole. Hemodinamia. Doppler. Ecocardiografía.

Introduction

Diastole is the period of the cardiac cycle whose alteration and consequent dysfunction are critical and necessary for the development of heart failure, especially in patients with preserved systolic function¹, which has implications for prognosis². Non-invasive diastolic function study, through echocardiography, has evolved overtime, and the values and parameters that are used have varied, according to expert guidelines. In 2016, the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) recommendations were published³; these guidelines made an emphasis on the simplification of the parameters to be used and were based on the most feasible and reproducible. In addition, they differed from the 2009 ASE and the European Association of Echocardiography (EAE) recommendations⁴, which use more complex algorithms and parameters.

Non-invasive assessment of hemodynamic parameters, through the determination of systemic arterial compliance (SAC) and peripheral vascular resistance (PVR), was shown to be useful in the assessment and prognosis of patients with aortic valve disease^{5,6}. This work compares the prevalence of diastolic dysfunction (DD) according to the criteria of both these guidelines and its relationship with SAC and PVR, which are parameters that indicate hemodynamic involvement and might establish the prognosis, calculated in a non-invasive manner.

Material and methods

Population

Three-hundred and six 40-year-old or older patients who were referred to the authors' center for Doppler echocardiogram performance and who had an ejection fraction (EF) $\geq 50\%$ were consecutively included. Patients with a history of acute myocardial infarction, sinus tachycardia (heart rate > 110 beats/min), atrial fibrillation or flutter at the time of the study, permanent pacemaker implanted, or worse than mild heart valve disease were included in the study.

Echocardiographic evaluation

All echocardiographic studies were carried out with the Philips Affiniti 50 ultrasound equipment. Chamber quantification and function assessment were carried out according to the 2015 ASE/EACVI guidelines recommendations⁷. The types of ventricular hypertrophy were classified according to EACVI new indications⁸.

DD parameters were quantified in apical views. Mitral filling velocities (E and A peaks) and E peak deceleration time (DTE) were determined with pulsed Doppler, at the level of mitral leaflets distal ends, at mitral valve opening (with an average of three consecutive beats). Using tissue Doppler, lateral and septal (e' and a') mitral annulus velocities were calculated and the corresponding relationships (E/A and E/e') were determined.

Tricuspid regurgitation speed measurement was obtained by continuous Doppler and, using Bernoulli's simplified equation, the right ventriculoatrial pressure gradient was established.

Non-invasive hemodynamic measurements

All patients underwent non-invasive blood pressure measurement with sphygmomanometer during the procedure. Pulse pressure (PP) was calculated with the following operation: systolic blood pressure minus diastolic blood pressure. Mean blood pressure (MBP) was determined by the product of systolic blood pressure by one-third of PP. SAC was calculated with the following equation⁹:

$$SAC = \text{indexed systolic volume}/(PP)$$

PVR was established using the following formula¹⁰:

$$PVR = 80 \times MBP/\text{cardiac output}$$

DD classification

To determine DD using ASE/EAE 2009 guidelines, lateral and septal e' values (> 10 and 8 , respectively) were taken in the first instance, together with the left atrium volume ($> 34 \text{ mL/m}^2$); when these parameters were present, the following parameters were taken into account to determine the degree of DD: E/A ratio, DTE,

and average e/e' ratio. The parameters had to be positive for the degree of DD to be established, and when the parameters were ambiguous, the degree of DD was regarded as indeterminate.

To establish DD using ASE/EACVI 2016 guidelines, four parameters were used: (a) average E/e' ratio > 14 ; (b) septal e' ratio < 7 or lateral e' ratio < 10 ; (c) left atrial volume > 34 mL/m²; and (d) tricuspid regurgitation velocity > 2.8 m/s. More than 50% of the parameters had to be positive, which was possible to attain, for the presence of DD to be determined. If half of the obtained parameters were positive, diastolic function was regarded as indeterminate. To determine the DD grade, the following parameters were used: E/A ratio and E peak velocity. Subsequently, the following parameters were taken into account: (a) left atrial volume > 34 mL/m²; (b) tricuspid regurgitation velocity > 2.8 m/s; and (c) average E/e' ratio > 14 . If two of the latter parameters were positive, the DD grade was determined; if only two criteria were available, both had to be positive. In case one was positive and the other negative, the DD grade was considered to be indeterminate.

Statistical analysis

Continuous variables are presented as the mean $\pm$ standard deviation (SD) and categorical variables, as percentages. Agreement between both classifications was determined with the kappa coefficient. The comparisons between normal individuals and DD with the hemodynamic variables were carried out using the rank-sum test; and the comparison between normal, indeterminate function, or DD of the 2016 ASE/EACVI guidelines with the hemodynamics measurements was carried out using a one-way analysis of variance or Kruskal–Wallis test for continuous variables. The Chi-square test or Fisher's exact test, as appropriate, was used to determine categorical variables' differences. The dichotomous variables that were statistically significant for the prediction of $SAC < 0.60$ mL.mmHg⁻¹ and $PVR > 1400$ mmHg.min.L⁻¹ were subjected to the logistic regression test, for a multivariate analysis. $p = < 0.05$ was considered statistically significant. These statistical analyses were carried out with the STATICTIX 8.0, EPI INFO 6.0™, and MedCalc programs.

Results

Three-hundred and six patients were included in this study, out of which 59.2% were female, with a mean age of 59.6 years (± 10.4) (Table 1). About 85.6% of

Table 1. Clinical and echocardiographic characteristics of the population

Variable	Value
Age (years)	59.6 (± 10.4)
Female gender (%)	59.2
High blood pressure (%)	63.4
Diabetes (%)	16.3
Dyslipidemia (%)	34.3
Body mass index	29.6 (± 5.59)
Obesity (%)	39.9
EF (%)	65.2 (± 5.59)
Left atrial volume (mL/m ²)	35.6 (± 8.02)
Myocardial mass index (g/m ²)	102 (± 29.02)
End-diastolic volume (mL)	85.4 (± 23)
End-systolic volume (ml)	30.9 (± 10.5)
Eccentric hypertrophy (%)	41.8
Concentric hypertrophy (%)	10.8
E/A ratio	0.95 (± 0.34)
DTE (ms)	222 (± 49.9)
Average E/e' ratio	8.62 (± 2.9)
Tricuspid regurgitation velocity (m/s)	2.32 (± 0.34)
Systolic blood pressure (mmHg)	131.38 (± 18.87)
Diastolic blood pressure (mmHg)	73.43 (± 10.1)
SAC (mL.mmHg ⁻¹)	0.73 (± 0.23)
PVR (mmHg.min.L ⁻¹)	1,436.53 (± 352.81)

patients had no symptoms, 2% had New York Heart Association functional class (FC) I dyspnea, 11.6% had FC II, and 0.6% FC III. Of the hypertensive patients, 60.5% were on antihypertensive medication. Out of them, 51.8% were treated with one antihypertensive drug, 41% with two, and 7.2% with three or more. The feasibility of obtaining all four parameters that determine the presence of DD in 2016 ASE/EACVI guidelines was 59.5%, for three parameters, 40.2%, and in 0.3%, only two parameters were obtained. The parameters that assess DD in ASE/EAE 2009 guidelines were obtained in 99.7%. Tricuspid regurgitation velocity determination was not possible in 41.2% of cases.

The prevalence of DD, according to ASE/EAE 2009 guidelines, was 32.7%, while according to the algorithm

Table 2. Agreement between DD criteria (kappa coefficient, 0.56; confidence interval, 0.46-0.66; $p = 0.051$)

	2009 ASE/EACVI diastolic dysfunction		
	Yes	No	
2016 ASE/EACVI diastolic dysfunction			
Yes	58	12	70 (22.9%)
No	42	194	236 (77.1%)
	100 (32.7%)	206 (67.3%)	306

of the 2016 ASE/EACVI guidelines, it was 22.9% (Fig. 1). In patients with DD, according to ASE/EAE 2009 guidelines, the grades were I, 42%; II, 30%; III, 0%; and indeterminate, 28%. When DD was classified according to ASE/EACVI 2016 guidelines, the grades were I, 17.1%; II, 44.3%; III, 1.4%; and indeterminate, 37.2%.

Agreement between both guidelines' DD criteria was moderate (kappa coefficient, 0.56); of the 100 patients with DD criteria based on the ASE/EAE 2009 guidelines, 42 were reclassified as not having DD with ASE/EACVI 2016 guidelines criteria (Table 2). Of these 42 patients, 40 (95%) were reclassified as indeterminate, and 2 (5%), with normal diastolic function.

Mean SAC in subjects with DD, according to ASE/EAE 2009 guidelines, was $0.67 (\pm 0.22) \text{ mL.mmHg}^{-1}$, and in those with normal diastolic function, it was $0.76 (\pm 0.20) \text{ mL.mmHg}^{-1}$ ($p = 0.0001$). Patients with DD, according to ASE/EACVI 2016 guidelines, had a mean SAC of $0.67 (\pm 0.22) \text{ mL.mmHg}^{-1}$, while in those with normal diastolic function, it was $0.75 (\pm 0.24) \text{ mL.mmHg}^{-1}$ ($p = 0.0007$). Mean PVR of patients with normal diastolic function, according to the ASE/EAE 2009 guidelines, was $1403 (\pm 338) \text{ mmHg.min.L}^{-1}$, and in those with DD, $1509 (\pm 366) \text{ mmHg.min.L}^{-1}$ ($p = 0.005$). In individuals with preserved diastolic function, according to ASE/EACVI 2016 guidelines, mean PVR was $1412 (\pm 334) \text{ mmHg.min.L}^{-1}$, and in those with DD, said parameter was $1523 (\pm 390) \text{ mmHg.min.L}^{-1}$ ($p = 0.018$).

Based on ASE/EACVI 2016 guidelines, indeterminate patients had a lower mean SAC than subjects with normal diastolic function ($0.73 \text{ mL.mmHg}^{-1}$ vs. $0.76 \text{ mL.mmHg}^{-1}$, respectively) and better profile in comparison with patients with DD ($p = 0.005$ for all three groups). The same behavior was shown by PVR, which was $1516 \text{ mmHg.min.L}^{-1}$ for patients with DD, $1478.41 \text{ mmHg.min.L}^{-1}$ for indeterminate individuals, and $1385 \text{ mmHg.min.L}^{-1}$ for patients with normal diastolic function ($p = 0.009$).

Figure 1. Prevalence of diastolic dysfunction according to the different guidelines. **Figure 2.** Prevalence of $\text{PVR} > 1400 \text{ mmHg.min.L}^{-1}$ and $\text{SAC} < 0.60 \text{ mmHg.min.L}^{-1}$ according to the presence or absence of DD.

Among the patients with sufficient criteria for DD, according to both guidelines, a larger number of subjects with $\text{PVR} > 1400 \text{ mmHg.min.L}^{-1}$ and $\text{SAC} < 0.60 \text{ mL.mmHg}^{-1}$ were found than among patients without sufficient criteria for DD (Fig. 2).

High blood pressure (HBP) ($p < 0.0001$), dyslipidemia ($p = 0.017$), obesity ($p = 0.015$), smoking ($p = 0.015$), DD according to ASE/EAE 2009 guidelines ($p = 0.003$), and DD according to ASE/EACVI 2016 guidelines ($p = 0.009$) were found to be predictor variables of $\text{SAC} < 0.60 \text{ mL.mmHg}^{-1}$. In the multivariate analysis, HBP persists as the only predictor variable of $\text{SAC} < 0.60 \text{ mL.mmHg}^{-1}$ ($p = 0.0034$) (Table 3).

HBP ($p = 0.001$), diabetes mellitus (DM) ($p = 0.045$), DD according to ASE/EAE 2009 guidelines ($p = 0.0008$), and DD according to ASE/EACVI 2016 guidelines ($p = 0.013$) were predictor variables of $\text{PVR} > 1400 \text{ mmHg.min.L}^{-1}$. In the logistic regression analysis, DM ($p = 0.0395$), HBP ($p = 0.0111$), and DD according to ASE/EAE 2009 guidelines ($p = 0.0263$) persist as predictor variables (Table 4).

Table 3. Logistic regression of predictor variables for $SAC < 0.60 \text{ mL.mmHg}^{-1}$

Variables	Coefficient	Standard error	p
Constant	-2.30540	0.32239	0.0000
Dyslipidemia	0.31155	0.28479	0.2740
Obesity	0.44915	0.27653	0.1043
HBP	0.96627	0.32952	0.0034
Smoking	0.62080	0.40682	0.1270
2009 ASE/EACVI	0.48730	0.34743	0.1607
2016 ASE/EACVI	0.17517	0.37606	0.6414

Table 4. Logistic regression of predictor variables for $PVR > 1400 \text{ mmHg.min.L}^{-1}$

Variables	Coefficient	Standard error	p
Constant	-0.58261	0.20984	0.0055
HBP	0.63987	0.25188	0.0111
2009 ASE/EACVI	0.69768	0.31411	0.0263
2016 ASE/EACVI	0.07684	0.35175	0.8271
DM	-0.68164	0.33102	0.0395

Discussion

Diastolic function evaluation by Doppler echocardiography begins with the measurement of transmitral flow velocities at the level of mitral leaflets distal ends and their changes with age, normality, and different disorders¹¹. The marked dependence on loading conditions made it necessary to have other parameters that more accurately reflected the degree of diastolic compromise and the determination of filling pressures¹². Mitral annular excursion velocity and its quotient with transmitral flow velocity were added to the study of diastolic function¹³. These parameters, together with the left atrial volume measurement and tricuspid regurgitation velocity, emerged as diastolic function core evaluation parameters. Criteria for their use varied from the complexity of the 2009 ASE/EAE guidelines to an attempt at simplification by ASE/EACVI 2016 guidelines.

In this work, a significant decrease ($p \leq 0.0001$) in the prevalence of DD according to ASE/EAE 2009 criteria was identified (32.7%) with regard to the calculations of the 2016 ASE/EACVI guidelines (22.9%). This

prevalence decrease, despite being statistically significant, is of a lower value than that published in the work by Almeida et al.¹⁴, where the prevalence according to ASE/EAE 2009 guidelines was 38.1% and to 2016 ASE/EACVI 1.4%. In the authors' study, agreement between both guidelines was moderate (kappa coefficient = 0.56), which is different from the above-mentioned study, where agreement between both guidelines was poor (kappa coefficient = 0.18). Of note, in the study by Almeida et al., the percentage of feasibility for obtaining all four parameters of ASE/EACVI 2016 guidelines was 98.4%, whereas in the authors' study, it was 59.5%; tricuspid regurgitation velocity was the variable that was less likely to be obtained (58.8% of patients). This work is consistent with population-based studies that have assessed pulmonary artery systolic pressure, where the feasibility of their calculations, through tricuspid regurgitation measurement, ranges from 62 to 69%^{15,16}.

On the other hand, in a recent study¹⁷, a higher prevalence and incidence during DD follow-up was identified by the 2016 ASE/EACVI guidelines in patients with sepsis than with ASE/EAE 2009 guidelines, with not that marked differences both in DD prevalence and incidence between both guidelines, as it occurs in the authors' study, although with antagonistic results; this is probably due to the different clinical context where diastolic assessment was carried out.

Cardiovascular risk factors produce a reduced ability of the arterial wall to adapt to volumes and pressures transmitted from the left ventricle and increase the peripheral resistance (afterload) it has to endure, with a consequent elevation of the left ventricular filling pressures to maintain the cardiac output. Non-invasive hemodynamic parameters (SAC and PVR), which reflect this disturbance, showed altered values in patients with DD according to both studied guidelines, without substantial differences between both. The presence of DD, according to both guidelines, was predictive of $SAC < 0.60 \text{ mL.mmHg}^{-1}$ and $PVR > 1400 \text{ mmHg.min.L}^{-1}$ in the univariate analysis. Only DD established by the ASE/EAE 2009 guidelines was an independent predictor of $PVR > 1400 \text{ mmHg.min.L}^{-1}$. The authors identified differences in the hemodynamic profiles of patients classified as normal, indeterminate, or DD according to 2016 guidelines, which reveal that individuals considered as indeterminate have a poorer hemodynamic profile than normal patients and better non-invasively assessed hemodynamic status in comparison with those with DD. Recent studies showed the capacity of the 2016 guidelines, in terms of sensitivity and

specificity, to predict filling pressures elevation, invasively evaluated¹⁸; in this study, the predictive capacity between both guidelines was not substantially different. This is similar to the authors' study, where both classifications showed predictive capacity for the presence of non-invasively measured hemodynamic alterations, with a slight superiority for the ASE/EAE 2009 guidelines, since the latter were an independent predictor of $PVR > 1400 \text{ mmHg} \cdot \text{min} \cdot \text{L}^{-1}$.

Conclusion

ASE/EACVI 2016 guidelines reduce the prevalence of DD in comparison with AS/EAE 2009 guidelines. Both guidelines predict SAC and PVR alteration. The predictive power for the development of hemodynamic alterations, through SAC and PVR non-invasive measurement, it is slightly higher in the ASE/EAE 2009 guidelines in comparison with those of 2016.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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