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TITULO: DIAGNOSTIC UTILITY OF CLINICAL CRITERIA FOR THE DETECTION OF LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC DYSFUNCTION COMPARED WITH ECHOCARDIOGRAPHY AND NT-proBNP LEVELS.

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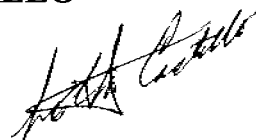
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ASUNTO: Autorización del trabajo de investigación del Dr. José Fidel Baizabal Carvallo.

DR. ISIDRO AVILA MARTÍNEZ
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Presente.

Estimado Dr. Avila Martínez:

Me permito informar a usted que el **Dr. José Fidel Baizabal Carvallo,** alumno del curso de especialización en **Medicina Interna** en el **Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán",** presenta el trabajo de investigación intitulado ***"Diagnostic utility of clinical criteria for the detection of left ventricular systolic and diastolic dysfunction compared with echocardiography and NT-proBNP levels".***

De conformidad con el artículo 23 capítulo 5º. de las Normas Operativas del Plan Unico de Especializaciones Médicas (PUEM) se considera que cumple con los requisitos para validarlo como el trabajo formal de Investigación que le otorga el derecho de la diplomación como especialista.

Sin otro particular de momento, reciba un cordial saludo.

Atentamente
"POR MI RAZA HABLARÁ EL ESPÍRITU"
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JEFE DE LA SUBDIVISIÓN

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Diagnostic utility of clinical criteria for the detection of left ventricular systolic and diastolic dysfunction compared with echocardiography and NT-proBNP levels

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RESUMEN

Antecedentes: debido a que la disfunción ventricular por lo general ocurre en pacientes sin enfermedad cardiovascular conocida esta alteración puede mantenerse asintomática y tratarse cuando los síntomas ya están presentes y la función ventricular está gravemente deprimida.

Objetivo: evaluar la importancia de algunos factores clínicos como indicadores tempranos de disfunción ventricular.

Pacientes y métodos: se estudiaron 178 pacientes mediante un cuestionario que incluía los factores que a menudo se asocian con disfunción ventricular sistólica o diastólica. También se realizaron ecocardiogramas transtorácicos y determinación de la porción N-terminal del propéptido natriurético tipo B (NT-proBNP) en todos los pacientes.

Resultados: se identificaron 27 pacientes con disfunción sistólica y 54 con disfunción diastólica del ventrículo izquierdo. Cuando hubo más de tres factores de riesgo (cardiopatía isquémica, marcapasos, tabaquismo, género masculino y edad mayor de 70 años) existió 70% de probabilidad de detectar disfunción sistólica. Cuando se detectaron tres o más factores de riesgo existió más del 50% de probabilidad de haber disfunción diastólica.

Conclusiones: se sugiere que en los pacientes con tres o más factores de riesgo se realice un ecocardiograma para evaluar la función ventricular.

Palabras clave: disfunción diastólica, disfunción sistólica, diagnóstico clínico.

ABSTRACT

Background: As left ventricular dysfunction often occurs in the absence of a known cardiovascular disease, this condition may go unrecognized and treated when symptoms already exist and ventricular functions are severely depressed.

Objective: To evaluate several clinical factors as early detectors of ventricular dysfunction.

Patients and methods: We studied 178 patients with a clinical questionnaire that included factors usually associated with ventricular systolic and diastolic dysfunction. Transthoracic echocardiograms as well as a determination of NT-proBNP in each patient were performed.

Results: We identified 27 patients with left systolic and 54 patients with left diastolic ventricular dysfunction. When more than three risk factors were present, there was a 70% of probability of finding a systolic dysfunction (risk factors included: ischemic heart disease, pacemaker, tobacco use, male gender and age older than 70 years). When three or more risk factors were present for diastolic dysfunction (systemic hypertension, snoring and age older than 70 years), there was more than 50% of possibilities of finding it.

Conclusions: Our model suggests that for patients with three or more risk factors an echocardiogram should be performed in order to evaluate the left ventricular function.

Key words: diastolic dysfunction, systolic dysfunction, clinical diagnosis.

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Heart failure is a very common clinical syndrome, with 5 million people suffering from it in the United States.[1] So far, there is not precise information regarding developing countries.

This clinical syndrome has special relevance because of its high prevalence and mortality and economic burden. From 1948 to 1988, the Framingham study showed a median survival time of 1.7 years in men and 3.2 years in women after the diagnosis of congestive heart failure was made, only 25% of men and 38% of women were alive after 5 years.[2]

American College of Cardiology and the American Heart Association (ACC/AHA) guidelines have emphasized the asymptomatic nature of the disease in its early stages, making difficult an early diagnosis.[3] This has generated a new interest for early detection of left ventricular systolic dysfunction[4] and increased left ventricular mass,[5] especially in patients at risk such as those with hypertension.[6]

There is no clear data about the prevalence of left ventricular systolic dysfunction, and community based studies report prevalence that range from 1.8 to 14% with heart failure symptoms, and 0.9 to 12.9% with no symptoms, depending on the ejection fraction criteria considered (< 0.30% to 0.54%).[7] Mild diastolic dysfunction was found in 20.6% of persons without symptoms of heart failure and in 6.8% of persons with moderate or severe symptoms in a community based study in Minnesota.[8]

Although echocardiogram and natriuretic peptides have proved to be useful and necessary for the diagnosis of heart failure, these methods are not readily available for use in open population, and lack of cost-effective studies make uncertain their use in this setting.

Many clinical criteria have also been used to diagnose heart failure. Framingham, Duke and Boston criteria have been validated with quantitative assessment of systolic function with radionuclide ventriculography, however these criteria consider only symptomatic patients,[9] but there are not clinical criteria based on history and related diseases that allow us an early stage diagnosis.

Because of this reason we studied a group of patients referred to the department of cardiology of our Hospital to perform an echocardiogram. We researched among them for risk factors in medical history, we measured levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) searching for a correlation between clinical characteristics in the questionnaire and echocardiography abnormalities suggestive of systolic and/or diastolic ventricular dysfunction in our population.

PATIENTS AND METHODS

We studied a group of 178 consecutive patients with heart failure risk factors, referred for cardiovascular evaluation and echocardiogram, from March 2003 to August 2003. All of them were asked to answer a multiple choice questionnaire before they underwent a trans-thoracic echocardiogram and quantitative NT-proBNP determination.

Clinical assessment

We considered three main aspects: 1) History of cardiac and non-cardiac diseases related to heart failure; 2) Symptoms suggestive of heart failure or cardiac disease; and 3) Demographic data that included height, weight, exercise practice, alcohol and drug consumption, and other usual habits. (Appendix)

Echocardiography

The echocardiographist was a cardiologist blinded to the clinical evaluation and results of NT-proBNP. Wide angle, two dimensional echoes were videotaped on a ¾ inches videocassette recorder with patients in left lateral position, using HP sonos ultrasound 5000 imaging system. Apical four chambers and apical two chambers were the views selected for left ventricular long axis at the end diastole and at the end systole to calculate ejection fraction, and stroke volume. All these parameters were estimated according to the recommendations of the American Society of Echocardiography.

Ventricular dysfunction was diagnosed following the echocardiographic criteria of the American Heart Association, American College of Cardiology and European Society of Cardiology. Systolic ventricular dysfunction was considered when the ejection fraction was ≤ 45% and/or shortening fraction was ≤ 28%, severe dyscinesia or dilatation of left ventricle. Diastolic dysfunction was diagnosed when the ejection fraction was ≥ 45%, and shortening fraction ≥ 28%, without severe segmental dyscinesia of the left ventricle, left atrial enlargement, or increased thickness of posterior wall, interventricular septum, and cardiac mass index, with an abnormal transmitral flow pattern.[10,11]

NT-proBNP analysis

A 10 mL sample of venous blood was collected from each patient into a tube containing potassium EDTA after the patients answered the clinical questionnaire, and were sitting for 15 minutes. The samples were centrifuged and plasma was stored in a -70° C freezer, for later analysis.

Determination of NT-proBNP was made with the electrochemoluminescence immunoassay (ECLIA) with the immunoanalyzer (Roche Elecsys 1010/2010 and Modular Analytics E170). Lower detection limit of NT-proBNP was < 5 pg/mL (< 0.6 pmol/L) and the interassay coefficient of variation at levels 175 and 1068 pg/mL were 2.7% and 1.8% respectively.

Statistical analysis

Continuous data are presented as means ± SD and categorical data as percent. Group comparisons of

continuous variables were made by analysis of variance (ANOVA), using Scheffe post hoc test. *Chi square* or Fisher exact test were performed for categorical variables; p values < 0.05 were considered significant. Concentrations of NT-proBNP were not normally distributed and were log-transformed before analysis. All statistical calculations were performed using SPSS 12.0 software (SPSS Inc., Chicago, Illinois). We used stepwise multivariate logistic regression to determine the significant independent variables associated with systolic and diastolic dysfunction. From this logistic regression models we estimated the probabilities of systolic and diastolic dysfunction according to the number of risk factors present with the following natural log equation:

$$Probability = 1 / (1 + exp - \text{(a+bx+cy...)})$$

Where "a" is the intercept, "b" and "c" are regression coefficients and "x" and "y" are the values for the variables found to be significant associated with disease.

RESULTS

Ventricular dysfunction was echocardiographically established in 81 of the 178 studied patients (45%). Diastolic dysfunction was found in 54 patients (30%) and systolic dysfunction in 27 patients (15%); variables associated with these groups are presented in table 1. Age was significantly higher for patients with diastolic and systolic dysfunction.

Male gender, diabetes, systemic arterial hypertension, alcohol and tobacco use, history of heart attack and heart surgery were associated with systolic dysfunction. Obesity, diabetes, arterial hypertension, snoring, history of heart attack and heart surgery were significantly associated with diastolic dysfunction. The mean ejection fraction calculated was 27.4% for patients with systolic dysfunction and 59.7% for patients with diastolic dysfunction. Interventricular septum measurement was significantly higher in patients with diastolic (mean 13.2 ± 2.5 mm) compared to those with systolic dysfunction (mean 11.1 ± 1.5 mm, table 2).

Log NT-proBNP levels were higher in patients with systolic dysfunction compared with patients with diastolic dysfunction and subjects without left ventricular dysfunction (figure 1).

In the multivariate analysis we obtained that the significant independent risk factors associated with diastolic dysfunction were: systemic hypertension, snoring and age older than 70 years (table 3); and for systolic dysfunction they were: ischemic heart disease, use of pacemaker, tobacco, male gender and age older than 70 years (table 4).

In cases with diastolic dysfunction, the presence of 3 or more of the risk factors had a sensitivity of 61.1%, specificity: 91.7%, positive predictive value: 80.5%, and negative predictive value: 80.9% (table 5).

In cases with systolic dysfunction three or more of these factors had low sensitivity (55.5%), but high specificity (98.9%), positive predictive value (93.7%) and high negative predictive value (88.9%, table 6).

Table 1. General characteristic of studied patients

Variables	Normal (n = 97)	Diastolic (n=54)	Systolic (n=27)	p value
Age (years)§	48.5 ± 18	61.2 ± 15.7*	66.4 ± 17.6**	*0.003 **<0.0001
Sex (male), n (%)	30 (31.3)	24 (44.4)	19 (67.9)**	**<0.0001
Body mass index (kg/m²)§	27.6 ± 8.2	30.6 ± 10.5*	25.7 ± 4.9	*0.01
Obesity (BMI > 30), n (%)	39 (40.6)	33 (62.3)*	8 (29.6)	*0.01
Diabetes, n (%)	26 (27.1)	27 (50.9)*	13 (48.1)**	*0.004 **0.04
Hypertension. n (%)	31 (32.3)	43 (81.1)*	14 (51.9)**	*<0.0001 **<0.05
Hypercholesterolemia, n (%)	20 (20.8)	15 (28.3)	7 (25.9)	NS
Alcohol consumption, n (%)	14 (15.4)	7 (14.3)	9 (33.3)**	**0.03
Tobacco consumption, n (%)	14 (14.6)	12 (22.6)	8 (29.6)**	**<0.05
Heart attack, n (%)	9 (9.4)	12 (22.6)*	11 (40.7)**	*0.03 **<0.0001
Snoring, n (%)	51 (53.1)	37 (69.8)*	9 (34.6)	*0.047
Heart surgery or pacemaker, n (%)	5.0 (5.2)	4 (7.3)	7 (25.9)**	**0.047

§Data are expressed as mean ± standard deviation.
* Statistically significant p values between diastolic dysfunction and normal group.
** Statistically significant p values between systolic dysfunction and normal group.

Table 2. Echocardiographic characteristics of studied patients

Variables	Normal	Diastolic	Systolic	p value
LVDD (mm)	43.8 ± 5.1	43.2 ± 7.7	56.6 ± 8.1*	*<0.0001
LVSD (mm)	27.5 ± 4.2	26.7 ± 6.2	44.6 ± 10.1*	*<0.0001
IVS (mm)	10.1 ± 1.7	13.2 ± 2.5**	11.1 ± 1.5	**<0.0001
PWD (mm)	9.6 ± 1.5	12.0 ± 2.1**	10.3 ± 1.2	**<0.0001
Fractional shortening (%)	36.8 ± 5.1	37.1 ± 6.2	22.8 ± 4.6*	*<0.001
Ejection fraction (%)	60.5 ± 6.7	59.7 ± 8.1	27.4 ± 14.2*	*<0.0001
PAP (mmHg)	39.4 ± 13.1	55.4 ± 20.2**	51.2 ± 18.8*	*0.04; **<0.001
LAD (mm)	37.7 ± 7.4	41.3 ± 7.4**	44.1 ± 9.3*	*0.001. ** 0.007

LVDD: left ventricle diastolic diameter; LVSD: left ventricle systolic diameter; IVS: interventricular septum: PWD: posterior wall diameter
PAP: pulmonary artery pressure; LAD: left atrium diameter.
* Statistically significant p values between diastolic dysfunction and normal group.
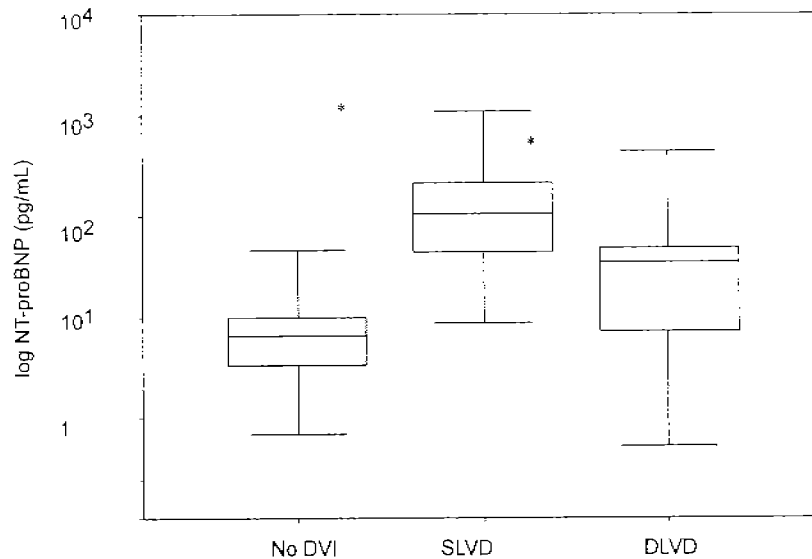** Statistically significant p values between systolic dysfunction and normal group.

Figure 1. Log NT-proBNP in patients without left ventricular dysfunction (No LVD), systolic (SLVD) and diastolic (DLVD) ventricular dysfunction. Boxes are median and interquartile ranges. Lines are ranges of concentrations. *p < 0.001 compared with No LVD group.

DISCUSSION

The main finding of the present study was that persons with 3 or more of the following risk factors: age, older than 70 years, body mass index over 30, arterial hypertension, previous heart attack and snoring have great possibilities to find functional and structural abnormalities and therefore, it could be necessary to perform an echocardiographic examination because the probability of diastolic dysfunction is over 50% in our model.

For those persons with 3 or more risk factors (table 4), the probability to have systolic dysfunction is over 70% with our model. Patients with less than 3 factors have a wider range of probability (table 6), so there is uncertainty about the usefulness of an echocardiogram, and maybe these patients should be referred to measure quantitative levels of B type natriuretic peptide which is a faster and less expensive test than echocardiogram. Unfortunately quantitative measure of NT-proBNP is usually not available in many hospitals or medical centers in Mexico.

After the new classification of chronic heart failure proposed in 2001[3] clinicians have realized that although the natural history of asymptomatic left ventricular dysfunction is still unknown, it could represent an increased morbidity and mortality. In fact, some studies have shown different prevalence in men, elderly persons and patients

Table 3. Logistic regression analysis using significant variables associated with diastolic dysfunction

Included variables	Regression coefficient	OR (95% CI)	p value
Age > 70 years	1.1817	3.26 (1.2-8.7)	0.02
Obesity (BMI > 30)	0.6675	1.9 (0.8-4.5)	0.04
Hypertension	2.0177	7.5 (3.2-17.6)	<0.0001
Heart attack	1.3067	3.7 (1.2-11.2)	0.02
Snoring	0.8829	2.4 (1.1-5.8)	<0.05
Intercept	-3.0475		<0.0001

Table 4. Logistic regression analysis using significant variables associated with systolic dysfunction

Included variables	Regression coefficient	OR (95% CI)	p value
Age > 70 years	2.9865	19.82 (4.2-93.6)	0.002
Sex (male)	1.5386	4.6 (1.2-17.6)	0.02
Tobacco use	1.6437	5.22 (1.1-24.9)	0.04
Heart attack	2.4181	11.31 (2.6-49.2)	0.0013
Heart surgery or pacemaker	2.3497	10.6 (1.5-71.1)	0.016
Intercept	-4.6738		

Table 5. Probability according to independent risk factors and median levels of NT-proBNP of suffering diastolic left ventricular dysfunction

Risk factors	Probability %	Patients with diastolic dysfunction n (%)	Normal n (%)	NT pro-BNP (pg/mL)*
3-5	50-95	33 (60)	8 (8.3)	396 (103-561)
0-2	4-50	21 (40.2)	89 (91.7)	62.8 (23.4-120.1)

*Median values (25th-75th percentile)
Sensitivity: 61%; specificity: 91.7%; positive predictive value: 80.5%; negative predictive value: 80.9%.

with coronary heart disease (4.8%-8.5%),[11,12,13] some of them have shown higher prevalence in black persons.[14,15] We lack data in Hispanic population so far. Clinical factors to screen theses populations should be different to enhance sensitivity.

Asymptomatic left systolic and diastolic dysfunction imply high probabilities for these patients to develop symptomatic forms of heart failure which usually is associated to more extensive hystologic myocardial damage and thus a worst prognosis.

One special problem in patients without symptoms is that no specific echo criterion exists to define which of them have diastolic ventricular dysfunction.[7]

NT-proBNP and N-terminal pro-atrial natriuretic peptide have proved to be useful for the detection of patients with depressed left ventricular ejection fraction,[6] and have a good correlation with the functional status of the patients and their prognosis.[17,18] Some studies have also reported its usefulness to detect patients with asymptomatic left ventricular systolic dysfunction and left ventricular hypertrophy[19-22] although the measure of these peptides

did not prove to be useful in a community based study.[23] Our results show that different levels of NT-proBNP can be found among patients with more than 2 risk factors for systolic and diastolic dysfunction evidenced by echocardiogram, as other studies have shown.[24]

According to our results, even asymptomatic patients with several co-morbidities (≥ 3 risk factors) should have a type B-BNP determination and among than those with high levels, perform an echocardiogram, in order to detect preclinical forms of ventricular dysfunction. Such an early detection allows a prompt specific treatment of ventricular dysfunction and an improvement of prognosis.

Limitations of the study

Because this study was made in a third level hospital, the use of our model with high specificity and positive and negative predictive values, it is possible that we have overestimated its usefulness as a screening method in an open population. Because of its low sensitivity, it should be carefully evaluated before a recommendation to use it for community based detection of heart failure could be emitted.

Table 6. Probability according to independent risk factors and median levels of NT-proBNP of suffering systolic left ventricular dysfunction

Risk factors	Probability %	Patients wit systolic dysfunction n (%)	Normal n (%)	NT pro-BNP (pg/mL)*
3-5	70-99	15 (55.6)	1 (1)	516 (193.8-1737.0)
0-2	<1-67	12 (44.4)	96 (99)	93.5 (35.2-342.2)

* Median values (25th-75th percentile).
Sensitivity: 55.5%; specificity: 98.9%; positive predictive value: 93.7%; negative predictive value: 88.9%.

Appendix. Questionnaire for detection of left ventricular

Please answer all the questions   Date_____

I. Identification card
Name: _____ Age:_____ years Sex: M   F
Height: _____m. Weight: _____kg.
Do you make exercise? Yes___ No___ How often? _____
Do you consume alcohol Yes____ No_____ How often? _____ How much?_____
Do you consume drugs Yes_____ No_____ Which one(s)?_____How often?_____

II. Diseases related to heart failure
Do you have diabetes? Yes_____ No_____ Treatment_____
Do you have high blood pressure? Yes___ No___ Treatment_____
Do you have high cholesterol (>200mg/dL)? Yes___ No___ Treatment_____
Do you smoke? Yes____ No_____ Cigarettes per day_____ Years_____
Have you ever had heart attacks? Yes___ No___ Date(s)_____
Do you have heart surgeries? Yes___ No___ Date(s)_____
Have you had a cardiac procedure? (Angioplasty. stent placement, etc.) Yes___ No___ Dates(s)_____
Do you have another cardiac disease? Yes___ No___ Which one?_____
Do you have a heart pacing? Yes___ No____ Date of placement_____

III. Symptoms
Have you had chest pain or discomfort? Yes___ No____ Duration_____
Chest pain or discomfort is associated with physical effort? Yes___ No____
Chest pain or discomfort stops with: Medications _____ Spontaneously _____ Both_____
Do you have air breathless (dyspnea)? Yes____ No_____
Related with effort? Yes____ No____
Do you use pillows to sleep because of air breathless? Yes__No__ How many?_____
Do you wake up at night because of air breathless? Yes___ No___
Do you have palpitations? Yes___ No____ How often_____
Do you have associated symptoms with palpitations? Yes___ No____Which one(s)?_____(breathless. chest discomfort, death feeling. etc.)
Do you have body swelling? Yes____ No_____ Which part_____
Swelling is painful? Yes____ No____
Have you lost consciousness? Yes____ No_____ How many times?_____
Are you fatigue? Yes____ No____
If you are fatigue, how much time: All day_____ Half a day_____ Few hours_____
Do you snore? Yes___ No___
Do you have day sleepiness? Yes____ No____
Do you stop breathing at night? Yes___ No____

However, the combination of clinical parameters and type B-natriuretic peptide, should allow a screening of patients who need an echocardiogram to define if they have ventricular dysfunction, with or without symptoms suggestive of heart failure.

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