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PROGNOSTIC OF NT-PROBNP IN HEART FAILURE PATIENTS WITH PRESERVED, MID AND REDUCED EJECTION FRACTION

Pronóstico de NT-proBNP en insuficiencia cardíaca con fracción de eyección preservada, media y reducida

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Resumen

Objective. The prognostic value of N-terminal procerebral natriuretic peptide (NT-proBNP) in patients with heart failure (HF) is well established. In contrast, its role as an early predictor of mortality in patients hospitalized for heart failure with preserved ejection fraction (HF-EF) and heart failure with reduced ejection fraction (HF-EF) is less well documented. Therefore, the objective of this study is to evaluate the usefulness and prognostic value of plasma NT-proBNP in these patients.

Method. This retrospective observational study included 620 patients admitted for acute heart failure, classified into 3 groups according to their left ventricular ejection fraction (LVEF): HF-EF (LVEF ≥ 50%), HF-mEF (heart failure with ejection fraction mean) (LVEF 35-49%) and

Abstract

Objetivo. El valor pronóstico del péptido natriurético procerebral N-terminal (NT-proBNP) en pacientes con insuficiencia cardíaca (IC) está bien establecido. En cambio, su papel como predictor temprano de mortalidad en pacientes hospitalizados por insuficiencia cardíaca con fracción de eyección conservada (IC-FEc) e insuficiencia cardíaca con fracción de eyección reducida (IC-FEr) está menos documentado. Por tanto, el objetivo de este estudio es evaluar la utilidad y valor pronóstico del NT-proBNP plasmático en estos pacientes.

Método. Este estudio observacional retrospectivo incluyó a 620 pacientes ingresados por insuficiencia cardíaca aguda, clasificados en 3 grupos según su fracción de eyección del ventrículo izquierdo (FEVI): IC-FEc (FEVI ≥ 50%), IC-FEm (insuficiencia cardíaca con fracción de eyección media) (FEVI 35-49%) e IC-FEr (FEVI <40 %), cuyos niveles plasmáticos de NT-proBNP y datos clínicos se

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HF-rEF (LVEF <40%), whose plasma levels of NT-proBNP and clinical data were determined at hospital admission. Univariate and multivariate logistic regression was used to perform prognostic values of NT-proBNP levels for 3.4 years of all-cause mortality in each group.

Results: The mean plasma levels of NT-proBNP in patients with HF-cEF (35%) and borderline HF-cEF (43%) was 1001-5000 pg / ml; patients with HF-rEF were similarly distributed between the groups 1001-5000pg / ml (30%), 5001-15000pg / ml (31%) and> 15001pg / ml (30.6%). The mortality rate increased significantly in patients with NT-proBNP concentrations > 15001 pg / ml (40%) and decreased with NT-proBNP levels <250 pg / ml (4%), compared to the other NT-proBNP groups. The mortality rate increased proportionally to elevated baseline NT-proBNP, regardless of LVEF.

Conclusion. In patients hospitalized for an acute decompensated event with HF-cEF (LVEF ≥50%) and HF-mEF (LVEF 35-49%), plasma levels of NT-proBNP are a useful tool to predict early mortality, as for HF -FEr (LVEF <40%).

Keywords: NT-proBNP, heart failure, mortality, prognostic, cardiovascular

determinaron al ingreso hospitalario. Se utilizó regresión logística univariada y multivariante para realizar los valores pronósticos de los niveles de NT-proBNP para 3.4 años de mortalidad por todas las causas en cada grupo.

Resultados. Los niveles plasmáticos medios de NT-proBNP en pacientes con IC-FEc (35%) y IC-FEc limítrofe (43%) fue de 1001-5000 pg / ml; los pacientes con IC-FEr se distribuyeron de manera similar entre los grupos 1001-5000pg / ml (30%), 5001-15000pg / ml (31%) y > 15001pg / ml (30. 6%). La tasa de mortalidad aumentó significativamente en pacientes con concentraciones de NT-proBNP >15001 pg / ml (40%) y disminuyó con niveles de NT-proBNP <250 pg / ml (4%), en comparación con los otros grupos de NT-proBNP. La tasa de mortalidad aumentó proporcionalmente a los valores basales elevados de NT-proBNP, independientemente de la FEVI.

Conclusión. En pacientes hospitalizados por evento agudo desestabilizado con IC-FEc (FEVI ≥50%) y IC-FEm (FEVI 35-49%) los niveles plasmáticos de NT-proBNP son una herramienta útil para predecir la mortalidad temprana como lo es para la IC-FEr (FEVI <40%).

Palabras clave: NT-proBNP, insuficiencia cardíaca, pronóstico de mortalidad.

Introduction

Heart failure (HF) is one of the greatest causes of death worldwide. It is estimated that approximately 37.7 million people are currently suffering from HF and that this growing epidemic was the cause of death of 17.3 million people in 2013[1,2]. The average population of America has a 20% risk of developing HF at the age of 40 and approximately 5.1 million people present with symptoms related to such; these statistics are expected to increase in the future. According to AHA, HF is defined as having "a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood"; said syndrome is classified based on patient left ventricular ejection fraction (LVEF). HF with preserved ejection fraction (HFpEF) is determined by an LVEF ≥50% and an HF with reduced ejection fraction (HFrEF) is determined by an LVEF ≤40%. If the LVEF is between these two digits, it is classified as borderline HFpEF. Patients that can recover from a reduced ejection fraction fall into the clinical subset classified as improved HfpEF[3,4].

HF can be recognized by its common manifestations such as fatigue, dyspnea, and fluid retention. The gold standard diagnostic test for evaluating HF is the echocardiogram; this tool provides relevant information on the mechanical heart function. A limitation being that this useful diagnostic machine needs a specialized personal and it isn't commonly available in the emergency department[3,5]. In contrast, the clinical use of NT-proBNP has become very important in recent years and is a fast and cost-effective mechanism for early HF detection and prognosis. The ProBNP forms part of the natriuretic peptide family, just as its counterpart proANP. These proteins are encoded by different genes but share a similar structure. The main stimulus for the release of these hormones is cardiomyocyte stretch and

overload; both molecules needing to be processed to form their respective active metabolites: ANP and BNP. NT-proBNP is defined as the inactive N-terminal portion that is cleaved before the active peptide is processed[6,7,8].

Nowadays, one of the most reliable markers for diagnosing and prognosis HF is the BNP and NT-proBNP. In patients with HF, several studies have conducted the same conclusions about this useful protein. In the cohort by deBoer *et al.* The risk of HFpEF increased in asymptomatic patients with elevated BNP levels[9,10]. Likewise, elevated levels of NT-proBNP were able to predict patient mortality in patients with decompensated acute HfpEF[11]. All over the world, numerous studies have been developed about the clinical use of NT-proBNP. However, the relationship between HF and NT-proBNP in the Mexican population hasn't yet been studied. From this perspective, our investigation team conducted a retrospective study, with the aim of determining the prognostic value of NT-proBNP in patients with heart failure in dependence of their ejection fraction.

Main text

Methods

Study design and population

This is a retrospective observational study conducted at the National Institute of Cardiology Dr. Ignacio Chávez in Mexico City, Mexico, during the time period of June 2010-October 2013; aiming to determine the prognostic value of NT-proBNP in patients with heart failure in dependence of their ejection fraction. The inclusion criteria for this study were: 1) 18 years of age or older; 2) patients who received urgent care due to symptoms like the debut of dyspnea or angina; 3) NYHA class >2; 4) first time being hospitalized for cardiovascular reasons; 5) measurement of serum NT-proBNP levels during hospitalization; 6) transthoracic echocardiogram to register cardiovascular pathology and an ejection fraction of left ventricle. Patients with known cardiovascular diseases, receiving treatment for such, or who have been previously hospitalized by the nephrology or rheumatic departments were excluded; this because of increased difficulty for data recollection. 636 individuals were identified during this time frame, of which 16 were excluded due to the absence of echocardiogram during hospitalization; therefore, 620 patients were enrolled in this study. Data collection from the hospital's database was carried out with the use of a data recollection instrument composed of multiple-choice questions and fill out questions for lab/diagnostic results. There was no patient follow up thanks to the nature of this study.

Statistical analysis

The data was statistically analyzed utilizing the SPSS V. 16.0 software. Multifactorial logistic regression analysis was performed for the presented variables. Univariate analysis for quantitative variables was performed by using central tendency and dispersion methods. The rest of the variables were analyzed by bivariate and multivariate analysis, controlled by the Bonferroni correction method. To verify the independence of the variables and to measure the discrepancy between the observed and theoretical distribution, Pearson's Chi-square test was used, while normality was assessed using the Kolmogorov-Smirnov test. For categorical variables with abnormal distribution, Kruskal-Wallis test was used. Statistical significance was sought using the ANOVA test. A value of $p<0.05$ was taken as the point of significance.

Results

The general characteristics of the studied population are shown in Table 1, based upon their left ventricular ejection fraction % (LVEF %). The screened variables include age, sex, systolic and diastolic BP, heart rate, hemoglobin, sodium, creatinine clearance, NT-proBNP, LVEF, tobacco usage, atrial fibrillation, diabetes, hypertension, COPD, cerebrovascular infarct and thyroid function.

A total of 620 patients participated in this study; 72.9% being composed of males and a mean age of 61.25 ± 13.85 years. Left ventricular ejection fraction (LVEF) >50% was seen in 190 patients (30.6%), 35-49% in 234 patients (37.8%) and <34% in 196 patients (31.6%); with male predominance in all groups. Upon admission, the generalized population had a mean systolic blood pressure of 124± 31 mmHg; sodium levels of 137± 9 mmol/L; hemoglobin levels of 13.8± 0.20 g/dl; creatinine clearance of 70.9± 38.4ml/min, lowest clearance being present in the LVEF >50% group.

The comorbidities prevalent in these patients are listed in Table 1. The LVEF <34% group had the highest prevalence of COPD and diabetes mellitus in comparison to the other groups (62% and 43%, respectively); while the LVEF>35-49% group had a higher prevalence of hypertension (40%). The etiology of heart failure in these patients was predominantly of undetermined causes (74%).

Serum NT-proBNP was measured in all patients (Table 2), the cut off level being 250 pg/ml; of which 3.9% of patients was found below this range. The majority of individuals from all EF groups had NT-proBNP concentrations of 1001-5000 pg/ml (37.1%), followed by concentrations of 5001-15000 (27.9%). Table 3 shows the mortality rate in association with LVEF and levels of NT-proBNP. Depending on the LVEF classification, patients predominate with a specific NT-proBNP concentration: the greatest percentage of individuals in the LVEF >50% and LVEF 49-35% groups both present with NT-proBNP levels in the 1001-5000 pg/ml range (35% and 43%, respectively); while in the LVEF<34% group, NT-proBNP levels are similarly distributed between the 1001-5000pg/ml, 5001-15000pg/ml and >15001pg/ml groups (30%, 31% and 30.6%, respectively).

The lowest mortality rate was presented by individuals belonging to the NT-proBNP <250 pg/ml group (4%); a relative increase in mortality can be visualized as NT-proBNP levels rise. Patients in the NT-proBNP >15001 pg/ml group presented the highest mortality rate in comparison to all other NT-proBNP groups (40%); there is also a correlation between decrementing LVEF and increasing mortality rate in this group of individuals: LVEF>50% with 24%, LVEF 35-49% with 28%, LVEF<34% with 57%.

Discussion

HF is currently the most common cause of death in cardiovascular diseases, and it is the end stage of various pathological cardiac conditions[12]. Nowadays, the guidelines of HF in several countries recommend NT-proBNP as a convenient biomarker in the diagnostic and prognostic assessment of HF. The Canadian Cardiovascular Society guidelines and European Society of Cardiology guidelines[13] recommend threshold for NT-proBNP is 125 pg/mL; the National Heart Foundation of Australia/ Cardiac Society of Australia and New Zealand the corresponding value is of 300 pg/mL[13,14,15]. The American College of Cardiology/American Heart Association/ Heart Failure Society of America doesn't stipulate a particular threshold; Similarly, this study presents a median threshold of 250 pg/mL[16].

Almost 50% of patients with HFpEF and borderline HFpEF had an NT-proBNP concentration <5000 pg/mL and 60% of patients with HFrEF had an NT-proBNP concentration >5000 pg/mL. The pathophysiological interpretation of these values is related to the primary stimulus of NT-proBNP release: left ventricular wall stress, which is explained by the interrelated components of LaPlace's Law (transmural pressure gradient, ventricular internal dimensions, wall thickness)[17]. Therefore, patients with HFpEF are more likely to have lower NT-proBNP levels. These findings validate and extend the observations of numerous studies where natriuretic peptide levels in patients with HFpEF are below the levels of HFrEF patients[18,19,20].

Variation in plasma concentrations related to certain patient variables, particularly age and renal dysfunction, has been used as an argument for thresholds adapted to the patient, recommendations suggest age-stratified NT-proBNP thresholds. Januzzi *et al.* evaluated the diagnostic capacity of NT-proBNP by using distinct cutoffs for the age groups of < 50 years, 50 to 75 years, and > 75 years[21]; the recommended thresholds being 450,900 and 1800 pg/mL, respectively (15). Our report included a narrow range of age (mean age of 61.25 ± 13.85 years), referring to the subgroup of 900 pg/mL cutoff in the age category. Interestingly, this age category also approaches the average age presented in the meta-analysis of Geng Z *et al.,* where the prognosis value of NT-proBNP in cardiovascular and all-cause mortality risk was shown to be higher for participants with a mean age ≥ 70 years than those with a mean age < 70 years, in particular for cardiovascular mortality (RR 5.10 vs. 3.40)[22].

As reported previously, NT-proBNP plasmatic levels depend on renal function due to its renal metabolism and excretion. Mean serum concentrations of this peptide progressively increase with renal impairment[23,24]. This fact suggests that lower levels of circulating NT-proBNP are correlated with increased renal function in HFpEF patients and inversely in patients with HFrEF. Our study used creatinine clearance (CrCl) as an indicator of kidney function, and contrary to the expected, patients with HFpEF presented a lower creatinine clearance (CrCl) rate (67.49±39.0 ml/min) compared with HFrEF patients (71.38±36.7 ml/min). These results do not bring into doubt the association between serum and urinary natriuretic peptide levels, nor the role of urinary NT-proBNP as a prognostic marker of HF (considering it as a simple, non-invasive test in specific conditions and primary care settings), but perhaps the utility of GFR and CrCl in plasma concentrations of NT-proBNP[25].

For the prognostic ability of NT-proBNP during admission, actual research reveals that mortality rate increased proportionally to the elevated NT-proBNP baseline values, independently of the LVEF (Table 3). These findings are in line with other studies, where mortality was similar between HFpEF and HFrEF patients following acute cardiac hospitalization[26,27]. The relation between natriuretic peptides and the detrimental outcome is mainly thought to be a reflection of increased filling pressure due to ischemic events or diastolic dysfunction[28]. In addition, we found that individuals with the highest NT-proBNP concentrations (>15001 pg/mL) significantly increased 1.80-fold mortality in patients with HFrEF compared to those with HFpEF. In this respect, we confirm previous studies that have reported equal prognostic hazard in patients within the highest quartile of NT-proBNP levels[18,29].

Interestingly, as presented in the proportional hazard curve (Figure 1), patients with HFpEF that exhibited higher levels of NT-proBNP at admission were those with higher mortality rates. This result underscores the prognostic utility of this biomarker in a homogeneous population with a HFpEF, suggesting the independent predictive value for all-cause death and cardiac deaths of NT-proBNP. Indeed, the data suggest that even if the NT-proBNP levels are lower than average, there seems to be a chance of cardiovascular problems and mortality[30].

This outcome is particularly important in HFpEF and borderline HFpEF patients since its treatment represent an actual challenge. NT-proBNP levels is an attractive alternative as an early predictor of mortality, due to its feasibility in daily clinical practice in comparison with echocardiographic tests or other invasive techniques, and therefore proving data on the characteristics that the therapeutic intervention must possess.

Conclusion

In conclusion, NT-proBNP serum levels is an effective alternative tool to assess mortality prognostic in hospitalized patients secondary to an acute destabilized event, independently of functional class. Patients

with elevated baseline serum levels of such biomarker presented higher mortality rates, proportional with increased NT-proBNP concentrations range.

Conflict of interest statement

None.

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Statement of ethics

All subjects provided written informed consent authorizing the data presented in this study on a protocol approved by the National Institute of Cardiology Dr. Ignacio Chávez office of Human Research Protection.

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