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Clinical Research

Growth Differentiation Factor-15 Is a Useful Prognostic Marker in Patients With Heart Failure With Preserved Ejection Fraction

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See editorial by Putko et al., pages 264-266 of this issue.

ABSTRACT

Background: Circulating growth differentiation factor 15 (GDF-15) levels correlate with heart mass and fibrosis; however, little is known about its value in predicting the prognosis of patients with heart failure with preserved ejection fraction (HFpEF).

Methods: We measured serum GDF-15 levels in 149 consecutive patients with left ventricular diastolic dysfunction (LVDD) and normal LV ejection fraction (>50%) and followed them for cardiovascular events. LVDD was defined according to the European Society of Cardiology guidelines.

Results: The New York Heart Association functional class and circulating B-type natriuretic peptide (BNP) levels were significantly higher in the high–GDF-15 group (n = 75; greater than or equal to the median value [3694 pg/mL]) than in the low–GDF-15 group (n = 74). Patients were divided into HFpEF and LVDD groups according to the

RÉSUMÉ

Introduction : Les concentrations circulantes du GDF-15 (*growth differenciation factor 15*) corrèlent avec la masse cardiaque et la fibrose. Cependant, on en connaît peu sur sa valeur pour prédire le pronostic des patients ayant une insuffisance cardiaque à fraction d'éjection préservée (IC-FEP).

Méthodes : Nous avons mesuré les concentrations sériques du GDF-15 de 149 patients consécutifs ayant une dysfonction diastolique du ventricule gauche (DDVG) et une fraction d'éjection du VG normale (> 50 %), et avons suivi les événements cardiovasculaires subis. Le DDVG a été défini selon les lignes directrices de la Société européenne de cardiologie.

Résultats : La classification fonctionnelle et les concentrations circulantes du peptide natriurétique de type B (PNB) selon la New York Heart Association ont été significativement plus élevées dans le

Growth differentiation factor-15 (GDF-15), a member of the transforming growth factor–β superfamily, has emerged as a promising cardiovascular biomarker.[1] Serum GDF-15 levels correlate positively with left ventricular (LV) mass in elderly individuals,[2] and a high plasma GDF-15 level is an independent predictor of LV hypertrophy in hypertensive patients.[3] We have recently shown that circulating GDF-15 is a useful biomarker for differentiating hypertrophic cardiomyopathy from hypertensive LV hypertrophy.[4] In patients with end-stage nonischemic dilated cardiomyopathy, serum GDF-15 level correlated with the severity of myocardial fibrosis.[5] Because cardiac hypertrophy and interstitial fibrosis are histologic hallmarks of heart failure with preserved ejection fraction (HFpEF),[6] we hypothesized that circulating GDF-15 reflects disease severity and predicts mortality in patients with HFpEF. In the present study, we evaluated serum GDF-15 levels in patients with HFpEF to determine whether GDF-15 could be used as a prognostic biomarker in these patients.

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See page 343 for disclosure information.

Materials and Methods

Study population

We recruited 149 consecutive patients with LV diastolic dysfunction (LVDD) scheduled to undergo coronary angiography

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presence or absence of HF. Serum GDF-15 levels were significantly higher in the HFpEF group (n = 73) than in the LVDD group (n = 76) (median, 4215 [interquartile range, 3382-5287] vs 3091 [interquartile range, 2487-4217 pg/mL]; $P < 0.0001$). Kaplan-Meier curve analysis showed a significantly higher probability of cardiovascular events in the high−GDF-15 group than in the low−GDF-15 group for data of all patients (log-rank test $P = 0.006$) and data of patients in the HFpEF group only ($P = 0.014$). Multivariate Cox hazard analysis identified age (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.87-0.98; $P = 0.008$), atrial fibrillation (HR, 7.95; 95% CI, 1.98-31.85, $P = 0.003$), lnBNP (HR, 3.37; 95% CI, 1.73-6.55; $P < 0.0001$), and GDF-15 (ln [GDF-15]) (HR, 4.74; 95% CI, 1.26-17.88, $P = 0.022$) as independent predictors of primary end points.

Conclusions: GDF-15 is a potentially useful prognostic biomarker in patients with HFpEF.

groupe ayant un GDF-15 élevé (n = 75; plus grand ou égal à la valeur médiane [3694 pg/ml]) que dans le groupe ayant un GDF-15 faible (n = 74). Les patients ont été divisés en deux groupes : le groupe ayant une IC-FEP et le groupe ayant un DDVG selon la présence ou l'absence d'IC. Les concentrations sériques du GDF-15 ont été significativement plus élevées dans le groupe ayant une IC-FEP (n = 73) que dans le groupe ayant un DDVG (n = 76) (médiane, 4215 [intervalle interquartile, 3382-5287] *vs* 3091 [intervalle interquartile, 2487-4217 pg/ml]; $P < 0{,}0001$). L'analyse de la courbe de Kaplan-Meier a montré une probabilité significativement plus élevée d'événements cardiovasculaires dans le groupe du GDF-15 élevé que dans le groupe du GDF-15 faible quant aux données de tous les patients (test logarithmique par rangs $P = 0{,}006$) et aux données des patients du groupe IC-FEP seul ($P = 0{,}014$). L'analyse multivariée selon le modèle de Cox a déterminé l'âge (rapport de risque [RR], 0,92; intervalle de confiance [IC] à 95 %, 0,87-0,98; $P = 0{,}008$), la fibrillation auriculaire (RR, 7,95; IC à 95 %, 1,98-31,85, $P = 0{,}003$), le lnBNP (RR, 3,37; IC à 95 %, 1,73-6,55; $P < 0{,}0001$) et le GDF-15 (ln[GDF-15]) (RR, 4,74; IC à 95 %, 1,26-17,88, $P = 0{,}022$) comme des prédicteurs de critères de jugement principaux.

Conclusions : Le GDF-15 est un biomarqueur pronostique potentiellement utile chez les patients ayant une IC-FEP.

for stable or suspected coronary artery disease or a diagnostic workup for HF at Kumamoto University Hospital between February 2009 and December 2011. The diagnoses of HFpEF and LVDD were based on the European Society of Cardiology guidelines.[7] HF was diagnosed according to the presence of either 2 major or 1 major plus 2 minor Framingham diagnostic criteria.[8] Patients with acute coronary syndrome, malignant tumours, current infection, inflammatory disease, or a serum creatinine level > 2.0 mg/dL were excluded from the study. After blood sampling, patients were followed in the outpatient clinic. The study end point was a composite of all-cause mortality, nonfatal myocardial infarction (MI), stroke, and hospitalization for HF decompensation. Mortality and cardiovascular events were identified by searching the medical records and confirmed by direct contact with the patients/relatives and their physicians. The study was conducted in accordance with the guidelines approved by the ethics committee of our institution, and written informed consent was obtained from each patient.

Procedures

Blood samples to assess GDF-15 level were drawn from the femoral vein while the patient was in the supine position at rest and analyzed by enzyme-linked immunosorbent assay (Biovendor, Asheville, NC). The intra-assay and interassay variability of GDF-15 were 5.6% and 9.6%, respectively. Echocardiography was conducted in all study participants using an Aplio XG (Toshiba, Tokyo, Japan) or a Vivid 7 (GE Vingmed Ultrasound, Horton, Norway) ultrasonography system, and the images were evaluated by 2 independent investigators who were blinded to the clinical data.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. However, the values of GDF-15, B-type natriuretic peptide (BNP), high-sensitivity C-reactive protein, and high-sensitivity cardiac troponin T (hsTnT) showed skewed distribution and were expressed as median values (interquartile range) and were log transformed before using Pearson correlation and Cox regression analysis. Categorical variables were expressed as numbers (percentages). Continuous and categorical variables were compared using the Student *t*-test and Mann-Whitney *U* and Fisher exact tests, respectively. Correlations between levels of circulating GDF-15 and BNP, or LV mass index (LVMI) were evaluated using the Pearson correlation. The Kaplan-Meier method, log-rank test, and simple and multiple Cox regression analyses were used to assess prognostic associations. A 2-tailed P value < 0.05 denoted the presence of a statistically significant difference. All data were analyzed statistically using SPSS, version17.0J for Windows (SPSS Japan Inc, Tokyo, Japan).

Results

Table 1 shows the clinical characteristics of the study participants. Using the median value (3694 pg/mL), patients were divided into the high−GDF-15 group and the low−GDF-15 group. Patients in the high−GDF-15 group were older than those in the low−GDF-15 group. Patients in the high−GDF-15 group presented with more severe symptoms than did those with low GDF-15 levels (New York Heart Association [NYHA] functional class (I/II/III/IV): 48/23/3/0 vs 25/41/8/1; $P < 0.0001$). Circulating levels of BNP were significantly higher in the high−GDF-15 group than in the low−GDF-15 group. Serum BNP levels were positively correlated with GDF-15 in all study participants (Fig. 1A). Conversely, LVMI was not correlated with GDF-15 in the study participant shown in Figure 1B.

We also divided the patients into HFpEF or LVDD groups according to the presence or absence of HF. Table 2 shows the clinical characteristics of the LVDD and HFpEF groups. Serum GDF-15 levels were significantly higher in the HFpEF