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RESEARCH LETTER

Longitudinal Evolution of Cardiac Dysfunction in Heart Failure and Preserved Ejection Fraction With Normal Natriuretic Peptide Levels

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Heart failure with preserved left ventricular (LV) ejection fraction (HFpEF) is a heterogeneous syndrome caused by abnormalities in cardiac function at rest or with exercise.[1] It was originally believed that all patients with HF displayed elevated plasma natriuretic peptide (NP) levels, but it is now well known that a sizeable proportion of patients have normal NP levels.[2,3] Although individuals with HFpEF and normal NP levels experience lower event rates than those with elevated NP, they still display increased risk compared with patients with normal NP and normal hemodynamics.[3] It is unclear whether patients with HFpEF and normal NP represent a fundamentally different phenotype or are simply identified at an earlier stage of disease progression.[4] To explore this question, we evaluated longitudinal changes in cardiac function in patients with HFpEF on the basis of the presence or absence of elevated NP levels.

The data that support the findings of this study are available from the corresponding author on reasonable request. Patients with invasively verified HFpEF (rest or exercise pulmonary capillary wedge pressure ≥15 or ≥25 mm Hg, respectively) and healthy controls underwent echocardiographic evaluations >1 year apart. Plasma N-terminal pro-brain natriuretic peptide levels were measured at examination 1. Patients with HFpEF were classified as those with normal NP (N-terminal pro-brain natriuretic peptide <125 mg/dL, nNP-HFpEF) or high NP (N-terminal pro-brain natriuretic peptide ≥125 mg/dL, hNP-HFpEF). Sensitivity analyses were performed in subcohorts frequency matched by age, sex, and body mass index (60 controls, 55 nNP-HFpEF, and 66 hNP-HFpEF). The Mayo Clinic Institutional Review Board approved the study protocol and all subjects provided consent for data use.

Cardiac function was assessed by myocardial deformation analyses from 2-dimensional images using commercially available software (Image Arena, TomTec Imaging Systems). Left ventricular global longitudinal strain (LVGLS) was measured using 2-dimensional speckle tracking, determined as the average of the 2 apical views (4- and 2-chamber views). The myocardial reservoir function of the left atrium (LA) was evaluated by the LA strain peak during LA relaxation. Right ventricular free wall strain (RVFWS) was obtained by the value of peak longitudinal systolic strain from the free wall of the right ventricle (RV). LV systolic dysfunction was defined by LVGLS <16%, LA dysfunction was LA reservoir strain <26%, and RV systolic dysfunction was RVFWS <20%. Between-group differences were first compared by 1-way ANOVA or χ^2 test. The Tukey honestly significant-difference test was then used to compare individual groups. Paired within-group differences between examination 1 and examination 2 were assessed using the McNemar test or paired *t*-test. A 2-sided *P* value of <0.05 was considered statistically significant. All data were analyzed using JMP14.0 (SAS Institute Inc).

The sample includes 287 patients: 66 with nNP-HFpEF, 136 hNP-HFpEF, and 85 health controls. Compared with patients with hNP-HFpEF, patients

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Nonstandard Abbreviations and Acronyms

HFpEF	heart failure with preserved ejection fraction
hNP	high natriuretic peptide
LA	left atrium
LV	left ventricle
LVGLS	left ventricular global longitudinal strain
nNP	normal natriuretic peptide
NP	natriuretic peptide
RV	right ventricular
RVFWS	right ventricular free wall strain

with nNP-HFpEF were a decade younger (61±11 versus 71±10 years, $P<0.001$), with higher body mass index (34.9±7.7 versus 31.8±6.9 kg/m^2, $P<0.001$) and lower prevalence of atrial fibrillation (9% versus 59%, $P<0.001$). There were no differences in prevalence of hypertension (88% versus 95%, $P=0.09$) or diabetes (23% versus 27%, $P=0.5$). At examination 1, LVGLS, LA reservoir strain, and RVFWS were higher in nNP-HFpEF than in hNP-HFpEF (Figure). LA reservoir strain was lower in nNP-HFpEF than in healthy controls, but there were no statistically significant differences in LVGLS or RVFWS between nNP-HFpEF and controls at examination 1.

The median time between examinations 1 and 2 was 3.1 (interquartile range, 2.1–5.1) years, with no difference between groups ($P=0.7$). In both nNP-HFpEF and hNP-HFpEF, LVGLS, LA reservoir strain, and RVFWS deteriorated over time (Figure). The prevalence of LV and LA dysfunction increased in nNP-HFpEF. It is noteworthy that there were no differences in the rate of change between nNP-HFpEF and hNP-HFpEF for LVGLS (−0.6%/y versus −0.6%/y, $P=1.0$), LA reservoir strain (−1.2%/y versus −0.6%/y, $P=0.4$), or RVFWS (−1.0%/y versus −1.1%/y, $P=0.9$). Crucially, and in contrast to both HFpEF groups, there was no change in biventricular or LA function in controls over the same time interval (Figure). All group

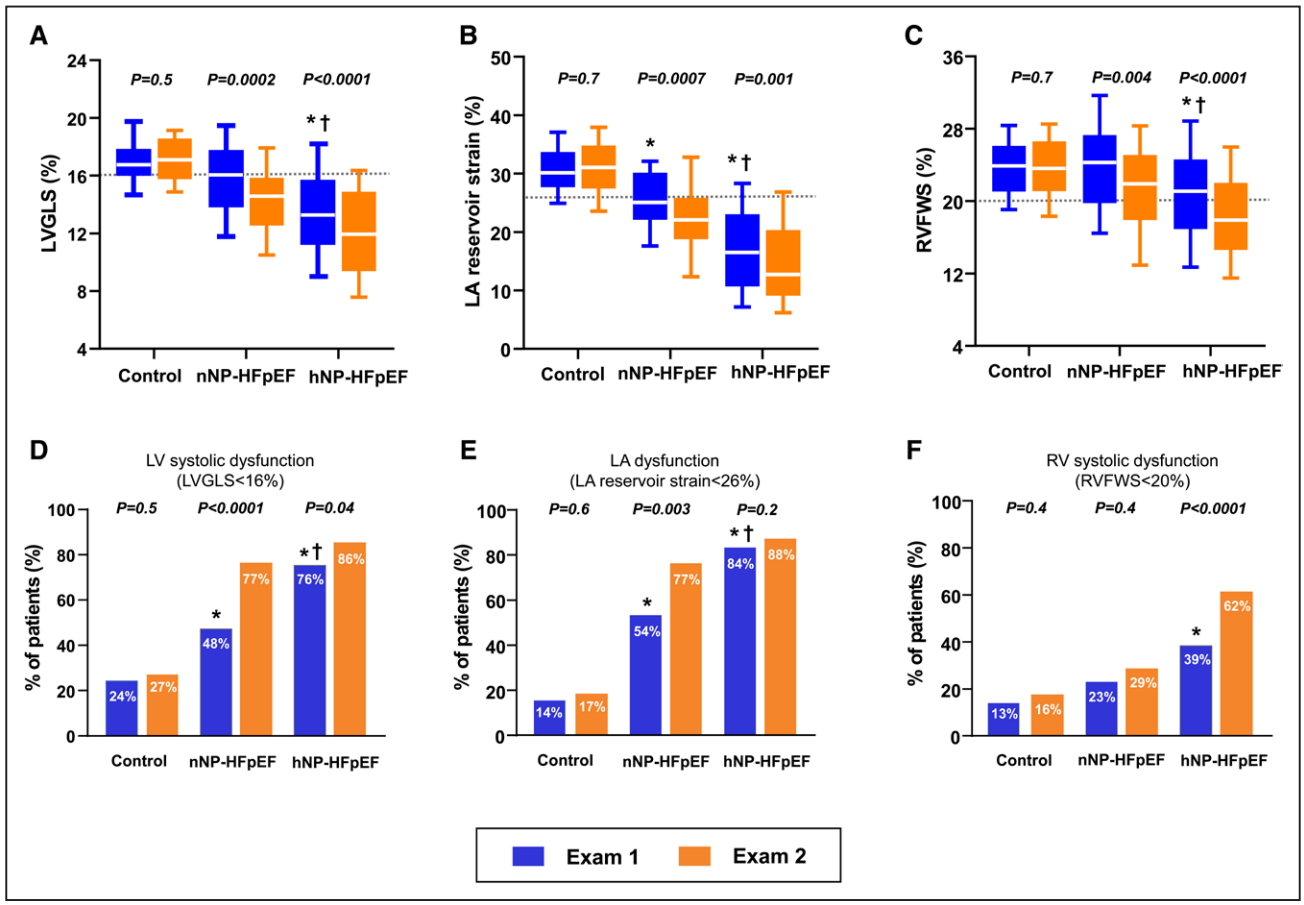

Figure. Longitudinal changes in cardiac structure and function in controls, normal NP HFpEF, and high NP HFpEF. Left ventricular (LV) global longitudinal strain (LVGLS; **A**), left atrial (LA) reservoir strain (**B**), and right ventricular (RV) free wall strain (RVFWS; **C**) deteriorated at the same velocity in HFpEF with normal and high levels of NT-proBNP. **D** and **E**, The prevalence of LV and LA dysfunction increased only in HFpEF with normal and high levels of NT-proBNP over the duration of follow-up. **F**, The prevalence of RV systolic function was to be increased only in HFpEF with high NT-proBNP but did not in HFpEF with normal NT-proBNP and controls. HFpEF indicates heart failure with preserved ejection fraction; hNP, high natriuretic peptide; LA, left atrial; nNP, normal natriuretic peptide; and NT-proBNP, N-terminal pro-brain natriuretic peptide. *$P<0.05$ vs control at examination 1; †$P<0.05$ vs HFpEF with normal NT-proBNP HFpEF at examination 1.

differences in longitudinal changes in cardiac function were similar in age-, sex-, and body mass index–matched sensitivity analysis.

We have previously shown in longitudinal studies that deterioration in RV function over time is a marker of progression to advanced HFpEF.[5] Here, we show for the first time that progression in biventricular and atrial dysfunction over time is similar in patients with HFpEF and normal NP levels to what is observed in patients with HFpEF with elevated NP levels, who are on average a decade older. These data collectively suggest that normal NP-HFpEF is more representative of an earlier stage of HFpEF rather than a fundamentally different phenotype. Because cardiac dysfunction in patients with HFpEF and normal NP is less advanced compared with elevated NP, this cohort may be more responsive to therapeutic intervention to improve clinical outcomes, even as they are often excluded from trials because of normal NP levels.

ARTICLE INFORMATION

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Disclosures

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