Left Ventricular Elastance With Resting Volumetric Transthoracic Echocardiography Identifies Different Phenotypes in Heart Failure With Preserved Ejection Fraction: A Retrospective Analysis of a Multicenter Prospective Observational Study

Yi Wang, MD, PhD, Quirino Ciampi, MD, PhD, Lauro Cortigiani, MD, Angela Zagatina, MD, Ratnasari Padang, MD, PhD, Garvan C. Kane, MD, PhD, Hector R. Villarraga, MD, Jesus Peteiro Vazquez, MD, Elena Kalinina, MD, Alla Boshchenko, MD, Tamara Ryabova, MD, Fiore Manganelli, MD, Hugo Rodriguez-Zanella, MD, Jelena Celutkiene, MD, Elisa Merli, MD, Clarissa Borguezan-Daros, MD, Jorge Lowenstein, MD, Rosina Arbucci, MD, Diego M. Lowenstein Haber, MD, Sofia Marconi, MD, Pablo M. Merlo, MD, Karina Wierzbowska-Drabik, MD, Ayten Safarova, MD, Tatiana Timofeeva, MD, Ariel Saad, MD, Francesca Bursi, MD, Jaroslaw D. Kasprzak, MD, Ana Djordjevic-Dikic, MD, Sergio Kobal, MD, Dimitrios Soulis, MD, Nicola Gaibazzi, MD, Nithima Chaowalit Ratanasit, MD, Rodolfo Citro, MD, PhD, Albert Varga, MD, Marco Fabio Costantino, MD, Fausto Rigo, MD, Aleksandra Nikolic, MD, Giovanni Benfari, MD, Miguel Amor, MD, Ana Cristina Camarozano, MD, Rosangela Cocchia, MD, Attila Palinkas, MD, Antonello D'Andrea, MD, Miodrag Ostojic, MD, Tamara Kovačević Preradović, MD, Iana Simova, MD, Federica Re, MD, Paolo Colonna, MD, Maria Grazia D'Alfonso, MD, Fabio Mori, MD, Claudio Dodi, MD, Filipa Xavier Valente, MD, Giovanni Tripepi, MD, Lixue Yin, MD, Mauro Pepi, MD, Scipione Carerj, MD, Patricia A. Pellikka, MD, and Eugenio Picano, MD, PhD, on Behalf of the Stress Echo 2030 Study Group, *Chengdu, China; Benevento, Lucca, Avellino, Faenza, Milan, Parma, Salerno, Campobasso, Potenza, Venice, Verona, Naples, Nocera Inferiore, Rome, Bari, Florence, Piacenza, Reggio Calabria, and Messina, Italy; Saint Petersburg, Tomsk and Moscow, Russian Federation; Rochester, Minnesota; La Coruna and Barcelona, Spain; Mexico City, Mexico; Vilnius, Lithuania; Criciuma and Curitiba, Brazil; Buenos Aires, Argentina; Lodz, Poland; Belgrade, Serbia; Beer Sheva, Israel; Athens, Greece; Bangkok, Thailand; Szeged and Hódmezővásárhely, Hungary; Banja Luka, Bosnia and Herzegovina; Pleven, Bulgaria*

From the Department of Cardiovascular Ultrasound and Noninvasive Cardiology, Sichuan Provincial People's Hospital, Chengdu, China (Y.W., L.Y.); Division of Cardiology, Fatebenefratelli Hospital, Benevento, Italy (Q.C.); Cardiology Department, San Luca Hospital, Lucca, Italy (L.C.); Cardiology Department, Research Cardiology Center "Medika", Saint Petersburg, Russian Federation (A.Z., E.K.); Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota (R.P., G.C.K., H.R.V., P.A.P.); Complexo Hospitalario Universitario A Coruna, University of A Coruna, La Coruna, Spain (J.P.V.); Cardiology Research Institute, Tomsk National Research Medical Centre of the Russian Academy of Sciences, Tomsk, Russian Federation (A.B., T.R.); Cardiology Division, Ospedale Moscati Avellino, Avellino, Italy (F. Manganelli); Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico (H.R.-Z.); Centre of Cardiology and Angiology, Clinic of Cardiac and Vascular Diseases, Faculty of Medicine, Institute of Clinical Medicine, Vilnius University, State Research Institute Center for Innovative Medicine, Vilnius, Lithuania (J.C.); Cardiology Unit, Ospedale per gli Infermi, Faenza, Italy (E.M.); Cardiology Division, Hospital San José, Criciuma, Brazil (C.B.-D.); Cardiodiagnosticos, Investigaciones Medicas, Buenos Aires, Argentina (J.L., R.A., D.M.L.H., S.M., P.M.M.); Department of Internal Diseases and Clinical Pharmacology, Medical University, Lodz, Poland (K.W.-D.); Department of Internal Medicine With a Course in Cardiology and Functional Diagnostics at the Medical Institute of the People's Friendship University of Russia, Moscow, Russia (A. Safarova, T.T.); División de Cardiología, Hospital de Clínicas José de San Martín, Buenos Aires, Argentina (A. Saad); Cardiology Division, Department of Health Sciences, University of Milan, ASST Santi Paolo e Carlo, Milan, Italy (F.B.); I Department of Cardiology, Bieganski Hospital, Medical University, Lodz, Poland (J.D.K.); Cardiology Clinic, University Center Serbia, Medical School, University Clinical Center Serbia, University of Belgrade, Belgrade, Serbia (A.D.-D., E.P.); Cardiology Department, Soroka University Medical Center, Beer Sheva, Israel (S.K.); Kosmoiatriki Medical Center, Athens, Greece (D.S.); Cardiology Department, University of Parma, Parma, Italy (N.G.); Division of Cardiology, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand (N.C.R.); Cardiology Department and Echocardiography Lab, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy (R. Citro); Department of Medicine and Health Science, Cardiology Institute Research Responsible University Hospital, University of Molise, Campobasso, Italy (R. Citro); Institute of Family Medicine, University of Szeged, Szeged, Hungary (A.V.); Cardiology Division, San Carlo Hospital, Potenza, Italy (M.F.C.); Villa Salus Foundation/IRCCS San Camillo Hospital, Venice, Italy (F. Rigo); Department of Noninvasive Cardiology, Institute for Cardiovascular Diseases Dedinje, School of Medicine, Belgrade, Serbia (A.N.); Section of Cardiology, Department of Medicine, University of Verona, Verona, Italy (G.B.); Hospital Echocardiography Laboratory, Ramos Mejia Hospital, Buenos Aires, Argentina (M.A.); Hospital de Clinicas UFPR, Medicine Department, Federal University of Paranà, Curitiba, Brazil (A.C.C.); Azienda Ospedaliera Rilevanza Nazionale A. Cardarelli Hospital, Naples, Italy (R. Cocchia); Internal Medicine Department, Elisabeth Hospital, Hódmezővásárhely, Hungary (A.P.); Department of Cardiology, Umberto I Hospital, Nocera Inferiore, Italy (A.D.); Clinic of Cardiovascular Diseases, University of Banja Luka University Clinical Centre of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina (M.O., T.K.P.); Heart and Brain Center of Excellence, University Hospital, Pleven, Bulgaria (I.S.); Ospedale San Camillo, Cardiology Division, Rome, Italy (F. Re); Cardiology Hospital, Policlinico University Hospital of Bari,

Background: Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous entity including different phenotypes of near normal, normal, and supernormal left ventricular (LV) function. The aim of this study was to assess the value of resting LV elastance (also known as force) using transthoracic echocardiography to identify HFpEF phenotypes.

Methods: In a prospective, observational, multicenter study, 2,380 patients with HFpEF were recruited from July 2016 to May 2024. Systolic blood pressure (SBP) was measured. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV ejection fraction, force (SBP/LVESV), stroke volume (SV), arterial elastance, ventricular-arterial coupling, and left atrial volume index were assessed. Global longitudinal strain was available in 1,164 patients (48.9%). Six hundred eighty patients finished follow-up with a composite endpoint of major adverse cardiac events (MACEs). Patients were divided into three groups: group 1, low force (<25th percentile, <3.24 mm Hg/mL); group 2, intermediate force (≥25th percentile and ≤75th percentile, 3.24-5.48 mm Hg/mL); and group 3, high force (>75th percentile, >5.48 mmHg/mL).

Results: The three groups showed a gradient with descending values (group 3 > group 2 > group 1) for SBP, LV ejection fraction, global longitudinal strain, arterial elastance, and ventricular-arterial coupling, with the opposite gradient (group 1 > group 2 > group 3) for LVEDV, LVESV, SV, and left atrial volume index values ($P < .01$ for all). After a median follow-up period of 16 months, 205 MACEs occurred in 138 patients. The cumulative MACE rate was lowest in group 2 (14.7% person-years) and higher in groups 1 (16.1% person-years) and 3 (22.9% person-years; log-rank $P = .036$).

Conclusions: Patients with HFpEF present with different LV contractile phenotypes, easily identified with resting LV force and volumetric transthoracic echocardiography. The dominant hemodynamic feature of hypocontractile phenotype is a preload recruitment with larger LVEDV and normal SV, while the hypercontractile phenotype is characterized by a small left ventricle with reduced SV. The hypercontractile and hypocontractile phenotypes are associated with a higher risk for subsequent events. (J Am Soc Echocardiogr 2025;38:409-20.)

Keywords: Heart failure with preserved ejection fraction, Left ventricular, Echocardiography, Contractility, Phenotype

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous condition that includes varying phenotypes of left ventricular (LV) function, characterized by near normal, normal, and supernormal LV ejection fraction (LVEF). Generally, good LV systolic function, clinically identified as preserved LVEF, accelerates LV relaxation via LV elastic recoil and may alleviate heart failure (HF) symptoms. However, HF symptoms frequently occur even in patients with higher LVEFs but impaired ventricular-arterial coupling (VAC).[1,2] Furthermore, LVEF is not synonymous with LV contractility. Previous studies have demonstrated a poor correlation between LVEF and changes in LV contractility when using LV end-systolic elastance, also known as force, as a load-independent measurement of cardiac contractility, particularly in cases of altered afterload.[3] The concept of LV elastance was introduced to cardiology in the seminal studies of Suga and Sagawa in the early 1970s[4] and was first applied in the noninvasive stress echocardiography laboratory a decade later by Ginzton *et al.*[5] Force can be measured noninvasively with a single-beat technique as the ratio of LV end-systolic pressure, estimated through its surrogate of systolic blood pressure (SBP) measured by cuff sphygmomanometer, to LV end-systolic volume (LVESV), offering a simplified means of assessing LV contractility.[6,7] In its simplified, single-beat, and completely noninvasive surrogate form used in the present study, LV force has been extensively evaluated in various cardiovascular conditions, both at rest and during stress, by Bombardini and colleagues,[8,9] starting 20 years ago. This method for measuring LV elastance requires only a cuff sphygmomanometer to assess SBP and transthoracic echocardiography (TTE) to estimate LVESV. It is more sensitive than LVEF in identifying both subnormal and supernormal LV contractility, identified as reduced or increased values of force, despite LVEF in the normal range.[6,7] The aim of this study was to assess the value of resting LV elastance (also known as force) using TTE to identify HFpEF phenotypes.

The study design was prospective, as the protocol was defined a priori, and data collection commenced prospectively. This study is

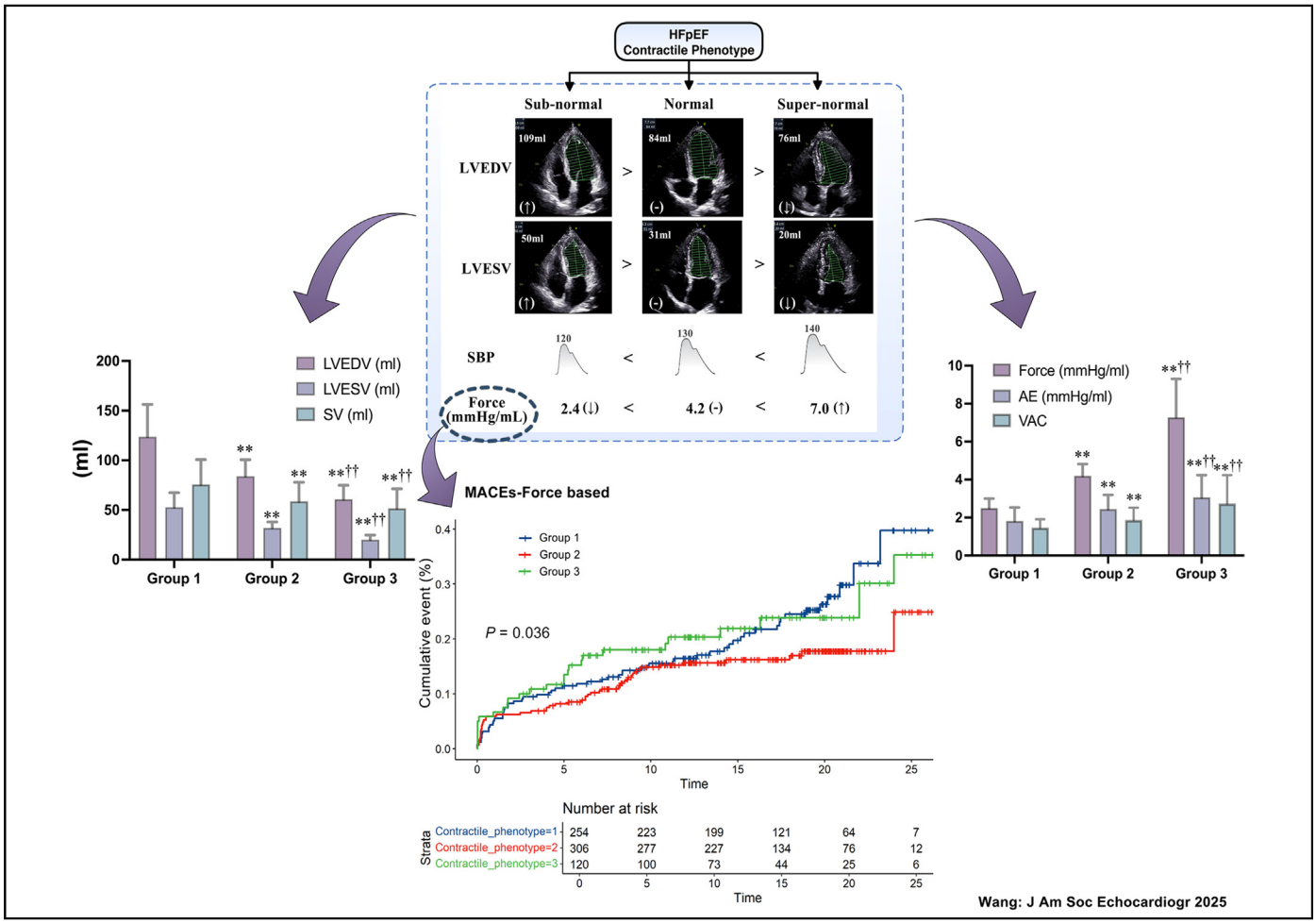
Bari, Italy (P.C.); Cardiology Department, Careggi University Hospital, Florence, Italy (M.G.D., F. Mori); Cardiology Division, San Antonino Clinic, Piacenza, Italy (C.D.); the Department of Cardiology, Hospital Universitario Vall d'Hebron, Institut de Recerca, Universitat Autònoma de Barcelona, Barcelona, Spain (F.X.V.); CNR, Institute of Clinical Physiology, Reggio Calabria, Italy (G.T.); Centro Cardiologico Monzino, IRCCS, Milan, Italy (M.P.); and Cardiology Division, University Hospital Policlinico G. Martino, University of Messina, Messina, Italy (S.C.).

This research was supported by unrestricted funding from Società Italiana di Ecocardiografia e Cardiovascular Imaging. Dr. Yi Wang is the recipient of a grant from Regione Campania for the China-Italy cultural exchange and is presently spending 6 months as visiting research fellow in Salerno, Italy.
Kian Keong Poh, MD, served as guest editor for this report.

Reprint requests: Yi Wang, MD, PhD, Department of Cardiovascular Ultrasound and Noninvasive Cardiology, Sichuan Provincial People's Hospital, #32, Xierduan, 1st Ring Road, Chengdu 610072, China (E-mail: *wangyihdl@126.com*).

0894-7317

https://doi.org/10.1016/j.echo.2024.12.012



Central Illustration Patients with HFpEF with different LV contractile phenotypes can be easily identified using resting LV force and volumetric TTE. The dominant hemodynamic feature of hypocontractile phenotype is preload recruitment with larger LVEDV and normal SV, whereas the hypercontractile phenotype is characterized by a small left ventricle with reduced SV. Both the hypercontractile and hypocontractile phenogroups are associated with higher risk compared with the normal function phenogroup.

part of a larger project evaluating the value of comprehensive rest and stress echocardiography in various cardiovascular conditions.[10] The study protocol, known as Stress Echo 2020, was established in 2016 and was in place at the time of data acquisition and storage. Quality control procedures were completed by all recruiting centers before patient recruitment began. The enrollment of patients with known or suspected HFpEF was a prespecified subproject of the study, designated as SEDIA (Stress Echocardiography in Diastolic Heart Failure).

However, the identification of a hypercontractile phenotype using resting force was not a prespecified study hypothesis; this concept emerged only after evidence accumulated over the past 5 years highlighting the potential clinical and prognostic significance of supernormal LV function.[7] Although the study design and data acquisition were prospective, hypothesis testing involved a retrospective analysis of data that had been prospectively acquired from 2,380 patients with HFpEF, who were recruited from July 2016 to May 2024 by 35 certified laboratories across 16 countries.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The study protocol was reviewed and approved by the institutional ethics committees, as a part of the more comprehensive Stress Echo 2020 study (148-Comitato Etico Lazio-1, July 16, 2016; ClinicalTrials.gov identifier NCT03049995) and Stress Echo 2030 study (291/294/295 Comitato Etico Lazio-1, March 8, 2021; ClinicalTrials.gov identifier NCT05081115). No support from industry was received. The study was officially endorsed by the Italian Society of Echocardiography and Cardiovascular Imaging (SIECVI), and all data were stored in a dedicated data bank property of SIECVI. Written informed consent was obtained from all patients.

Study Population

In this retrospective analysis of prospectively acquired data, we initially screened 2,558 patients with HFpEF recruited from July

Abbreviations

BSA = Body surface area

GLS = Global longitudinal strain

HF = Heart failure

HFpEF = Heart failure with preserved ejection fraction

LAVI = Left atrial volume index

LV = Left ventricular

LVEDV = Left ventricular end-diastolic volume

LVEF = Left ventricular ejection fraction

LVESV = Left ventricular end-systolic volume

MACE = Major adverse cardiac event

MI = Myocardial infarction

NT-proBNP = N-terminal pro–brain natriuretic peptide

OR = Odds ratio

RWT = Relative wall thickness

SBP = Systolic blood pressure

SIECVI = Italian Society of Echocardiography and Cardiovascular Imaging

SV = Stroke volume

TTE = Transthoracic echocardiography

VAC = Ventricular-arterial coupling

2016 to May 2024 by 35 certified laboratories across 16 countries (Argentina, Bosnia and Herzegovina Republic of Srpska, Brazil, Bulgaria, China, Hungary, Italy, Israel, Lithuania, Mexico, Poland, Russian Federation, Serbia, Spain, Thailand, and the United States) (Supplemental Table 3). The initial inclusion criteria were (1) age > 18 years; (2) referral for known HFpEF; (3) no severe valvular or congenital heart disease or presence of prognosis-limiting comorbidities, such as advanced cancer, reducing life expectancy to <1 year; (4) echocardiography of acceptable quality at rest; and (5) willingness to give written informed consent allowing the scientific use of observational data, respectful of privacy rights. HFpEF was diagnosed according to the European Society of Cardiology guidelines, which included patients with LVEFs ≥50% with dyspnea and noncardiac reasons or other cardiac reasons for dyspnea.[11-13]

Of these initial 2,558 patients, 100 patients (3.9%) without recorded blood pressure at the time of TTE and 78 patients without complete measurements of LV volume (3.0%) were excluded (Figure 1). The final study population included 2,380 patients (mean age 68 ± 11 years, 1,173 men [49.3%]) with known HFpEF. All patients underwent resting TTE as part of a clinically driven evaluation and according to the referring physician's indications.

Rest TTE

We used commercially available high-end ultrasound machines. All patients underwent comprehensive TTE at rest. All measurements were taken or approved by certified cardiologists according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[14] SBP was measured at the time of TTE without averaging. We assessed semiquantitatively wall motion score index using a 4-point score ranging from 1 (normal/hyperkinetic) to 4 (dyskinetic) in a 17-segment model of the left ventricle. B-lines were assessed using lung ultrasound and the four-site simplified scan, from the midaxillary to midclavicular lines on the third intercostal space, with each site scored from 0 (normal horizontal A-lines) to 10 (white lung with coalescent B-lines),[15,16] with a cumulative score per patient ranging from 0 (normal) to 40 (severely abnormal). A value ≥2 was considered abnormal. The modified biplane Simpson method was used to quantitatively measure LV end-diastolic volume (LVEDV), LVESV, and LVEF. Stroke volume (SV) was calculated from volumetric echocardiography as LVEDV − LVESV. Force (SBP/LVESV), arterial elastance (SBP/SV), VAC (SV/LVESV), cardiac output (SV × heart rate), SV index (SV/body surface area [BSA]), and cardiac index (cardiac output/BSA) were then derived. LVEDV index and LVESV index were the ratios of the corresponding volume to BSA. The same readers (one from each center) accredited for regional wall motion analysis also underwent quality control for LVESV and LVEDV assessment, as detailed elsewhere.[17] Many derived parameters, such as AE and VAC, contain either SBP or LVESV, and therefore collinearity occurs, but they are also unique in describing cardiovascular response that none of the constituent parameters may provide. Relative wall thickness (RWT) was measured as 2 × LV posterior wall thickness/LV end-diastolic diameter. Left atrial volume was measured using biplane method and indexed to BSA as left atrial volume index (LAVI). Peak blood inflow velocity from the left atrium to the left ventricle during early diastole (E) was acquired using pulse Doppler. Peak tricuspid regurgitant velocity was acquired in the apical four-chamber view using the continuous-wave Doppler method. Systolic pulmonary artery pressure was calculated as 4 × (tricuspid regurgitant velocity)^2 + right atrial pressure. Right atrial pressure was estimated according to inferior vena cava diameter and collapse.[18] In the same plane, the velocity profiles of mitral annular movement were acquired using the same method at both the medial and lateral annulus. The peak mitral annular velocity during early diastole (e′) was obtained as the averaged values from both sides. The E/e′ ratio was also calculated. Tricuspid annular plane systolic excursion was measured. Global longitudinal strain (GLS) was available in 1,164 patients (48.9%). In 271 patients (11.4%), N-terminal pro–brain natriuretic peptide (NT-proBNP) was assessed. In 1,153 patients (48.4%), estimated glomerular filtration rate was assessed. Left anterior descending coronary artery velocity was available in 1,522 patients (63.9%).

Data Storage and Analysis

The results for each test were entered in the data bank at the time of testing by each recruiting center and sent monthly to the coordinating institution of SIECVI, with the electronic case report form that included clinical data. After checking for internal consistency by trained technical staff members and double-checking with the center for data verification on possibly inconsistent input, the data were added to the data bank and locked. Starting in March 2021, data were directly entered by centers in a dedicated REDCap program in the framework of the Stress Echo 2030 study. The collection of echocardiographic data was performed at peripheral sites by accredited cardiologists who passed the web-based quality control reading of the main echocardiographic variables under study. The accepted accreditation criterion was <10% interobserver variability and <5% intraobserver variability as previously described.[19,20] Data were analyzed by statisticians who had no role in data acquisition.

Outcome Data Analysis

This is the interim analysis of the prespecified evaluation of long-term outcomes, to be completed by the end of 2030.[10] Outcome data were considered for patients recruited at 21 centers with structured follow-up programs. Deaths were identified from the National Health Service database. Nondeceased participants were contacted directly. Follow-up data were obtained from a review of each patient's hospital record, personal communication with the

HIGHLIGHTS

- HFpEF is a heterogeneous entity with different phenotypes of LV function.
- Different phenotypes show distinctive hemodynamic and echocardiographic features.
- Hyper- and hypocontractile phenotypes are associated with unfavorable outcomes.

patient's physician, a review of the patient's chart, a telephone interview with the patient or a close relative conducted by trained personnel, and a staff physician visiting the patient at regular intervals in the outpatient clinic. To avoid misclassification of the cause of death, overall death was considered. Major adverse cardiac events (MACEs) included all-cause death, nonfatal myocardial infarction (MI), increase of diuretic dose, new onset of atrial fibrillation, revascularization, and incident HF rehospitalization. Assessors were blinded to clinical and transthoracic echocardiographic results. If patients had more than one event, only the first event was counted.

Statistical Analysis

We divided patients into three groups because the entity of HFpEF is currently understood to have a heterogeneous LV contractile substrate, with a subset with normal, one with reduced, and a third with supernormal LV resting function.[21] This statistical handling of data was considered more likely to provide an adequate sample size and expose intergroup differences. Categorical data are expressed in terms of the number of subjects and percentage, while continuous data are expressed as mean ± SD when normally distributed or as median (interquartile range) when not normally distributed. For continuous variables, differences among groups were tested using a one-way analysis of variance followed by Bonferroni post hoc tests for between-group comparisons or the Kruskal-Wallis test followed by the Mann-Whitney test using the Bonferroni correction, as appropriate. The χ^2 test or Fisher exact test was used to compare the distributions of categorical variables among groups. As NT-proBNP values are not normally distributed, log-transformed data were used for NT-proBNP concentrations. Univariable and multivariable linear regression analysis assessed independent factors associated with log NT-proBNP. Receiver operating curve analysis was used to derive optimal cutoffs for each continuous variable to differentiate the high rest force group from the other groups. Univariable and multivariable logistic regression analysis assessed independent factors associated with the high-force group. Thereafter, stepwise likelihood ratio backward selection procedure was conducted to screen the variables: variables with P values $<.10$ were allowed to enter, and those with P values $\geq.10$ were eliminated. Odds ratios (ORs) with corresponding 95% CIs were estimated. Variables predicting high-force group independently in the multivariable logistic regression analysis were used to build the noninvasive prediction score according to the strength of association by β coefficients.[22] Specifically, the regression coefficient of each of these variables was divided by the smallest coefficient in the model and allocated a weight accordingly. The overall prediction score was obtained by summing the weights obtained from all coefficients. The effect of contractile phenotypes on cumulative events was demonstrated using a Kaplan-Meier curve. Cumulative curves were compared by means of the log-rank test. Univariate Cox proportional-hazards models were used to identify candidate predictors for selected end points. All variables with P values $<.10$ in univariate analysis were considered for inclusion in the multivariate Cox proportional-hazards model. Collinearity was verified for all models. We used variance inflation factors to check for the presence of collinearity and, for the multivariable model containing the positivity components, the values of all the variables were <5. Statistical significance was set at $P < .05$. All analyses were performed using Stata release 14 (StataCorp) or R (R Foundation for Statistical Computing).

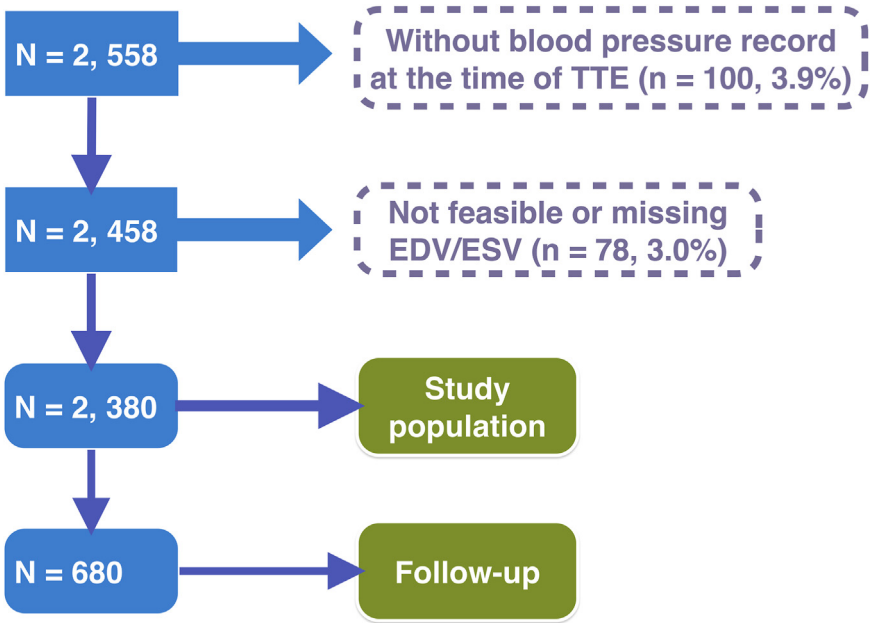


Figure 1 Study flowchart. *EDV*, End-diastolic volume; *ESV*, end-systolic volume.

RESULTS

Patients were divided into three groups: group 1, low force (<25th percentile, force < 3.24 mm Hg/mL); group 2, intermediate force (≥25th percentile and ≤75th percentile, force 3.24-5.48 mm Hg/mL); and group 3, high force (>75th percentile, force > 5.48 mm Hg/mL; Table 1). Examples of patients from groups 1 (subnormal force), 2 (normal force), and 3 (supernormal force) are shown in Figure 2.

Clinical and Echocardiographic Characteristics

Three hundred thirty patients (13.9%) presented with ischemic regional wall motion abnormalities on resting TTE. Patient characteristics overall and for the three subgroups are shown in Table 1. The percentage of women was higher in group 3, while patients in group 3 had lower percentages of obesity, prior MI, prior coronary artery disease, previous revascularization, and use of β-blockers ($P < .05$ for all). The three groups showed a gradient with descending values (group 3 > group 2 > group 1) for SBP, LVEF, RWT, GLS, AE, and VAC, with the opposite gradient (group 1 > group 2 > group 3) for LVEDV, LVESV, SV, cardiac output, and cardiac index values ($P < .01$ for all; Figure 3). Patients in group 3 had higher NT-proBNP levels ($P < .05$) and lower estimated glomerular filtration rates ($P < .01$) compared with those in groups 1 and 2. The three groups were similar for values of E/e′ ratio, left anterior descending coronary artery velocity, systolic pulmonary artery pressure, and tricuspid annular plane systolic excursion (Table 1). LAVI and LV mass index were lower in group 3 ($P < .01$ for both). Group 3 patients showed a higher prevalence of B-lines.

In the 271 patients with available NT-proBNP, log NT-proBNP was weakly related to force ($r = 0.271$, $P < .001$; Supplemental Table 1, Supplemental Figure 1).

Clinical Parameters Associated With High Force in HFpEF

In the multivariable logistic regression model, high rest force was associated with female sex (OR, 2.39; 95% CI, 1.73-3.32; $P < .001$), no history of MI (OR, 1.84; 95% CI, 1.11-3.11; $P = .020$), and higher SBP (OR, 2.40; 95% CI, 1.76-3.28; $P < .001$; Table 2).

On the basis of the results of the multivariable analysis, a simple composite score was built with the following variables according to the strength of association by β coefficients: female sex (one point), SBP > 137 mm Hg (one point), and no previous MI (one point). Each variable with values other than those reported received a score of zero. The percentage of high rest force on the basis of composite clinical score was 5.8% for score 0 ($n = 173$), 14.2% for score 1 ($n = 782$), 27.8% for score 2 ($n = 1{,}025$), and 47.3% for score 3 ($n = 400$) (Figure 4).

Follow-Up Events and Outcome Prediction

The follow-up was completed in 680 patients. During a median follow-up period of 16 months (interquartile range, 12-20 months), 36 deaths, 52 HF rehospitalizations, eight nonfatal MIs, 34 increases of diuretic dose, 64 revascularizations, 11 instances of new-onset atrial fibrillation, and 205 MACEs occurred in 138 patients altogether. There were no significant differences in mortality and HF rehospitalization among the three groups (log-rank $P = .23$ and $P = .34$, respectively). The cumulative MACE rate was lowest in group 2 (14.7% person-years) and higher in groups 1 (16.1% person-years) and 3 (22.9% person-years; log-rank $P = .036$; Figure 5). If patients were divided into three groups according to LVEF (50% ≤ LVEF < 60%, 60% ≤ LVEF ≤ 65%, and LVEF > 65%) on the basis of a previous study,[23] no significant difference in cumulative MACE rate was observed (Supplemental Figure 2). On multivariable Cox analysis, male sex (hazard ratio, 1.62; 95% CI, 1.12-2.33; $P = .010$), prior coronary artery disease (hazard ratio, 2.73; 95% CI, 1.90-3.94; $P < .001$), SBP (hazard ratio, 1.02; 95% CI, 1.01-1.03; $P = .036$), low rest force (hazard ratio, 1.35; 95% CI, 1.05-2.02; $P = .038$), and high rest force (hazard ratio, 1.40; 95% CI, 1.04-2.27; $P = .049$) were independently associated with the MACE composite end point (Table 3). The lowest risk for MACEs was associated with a rest force value of 3.7 mm Hg/mL (Figure 5). Of note, the distribution of the main demographic and clinical data of 680 patients with available follow-up information (see Supplemental Table 2) did not materially differ from the overall population (see Table 1). Even though there were statistical differences in some LV volume parameters, the volume index of the follow-up group did not differ from that of the overall population.

DISCUSSION

Our study demonstrated that patients with HFpEF with different LV contractile phenotypes can be identified by using resting LV force and volumetric TTE. A hypercontractile phenotype of LV in patients with HFpEF was associated with clinical predictors including female sex, higher SBP, and no previous MI. By TTE, the dominant hemodynamic feature of hypocontractile phenotype was preload recruitment with larger LVEDV and normal SV, while the hypercontractile phenotype was characterized by a small left ventricle with reduced SV. Signs of pulmonary congestion indicated by B-lines and increased values of AE and VAC were more prevalent in group 3, while group 1 patients showed higher values of LAVI and lower values of GLS. Both subnormal and supernormal force were associated with a higher rate of adverse events.

Heterogeneity of Contractile Phenotype in HFpEF

HFpEF is a heterogeneous condition with rising incidence and few available treatment options.[24] Contrary to the LVEF cutoffs used to define HFpEF in current HF guidelines, recent epidemiologic data indicate that mortality risk follows a U-shaped pattern relative to LVEF, with the lowest risk at an LVEF of 60% to 65% in routine clinical practice, further highlighting the variations in HFpEF phenotypes across different LVEF ranges.[23] In this study we investigated whether stratification of patients with HFpEF according to rest LV force identifies differential morphologic and functional subphenotypes, which might provide novel insights into the pathophysiologic heterogeneity of the disease. From a clinical perspective, there was a higher prevalence of smoking, obesity, prior MI, and prior revascularization in group 1. From the morphologic and functional perspectives, the three groups showed a gradient with descending values (high rest force group > intermediate rest force group > low rest force group) for SBP, RWT,LV EF, GLS, AE, and VAC, while with the opposite gradient (low rest force group > intermediate rest force group > high rest force group) was seen for LVEDV, LVESV, SV, cardiac output, and cardiac index values. Patients with HFpEF with different rest LV contractility showed different kinds of morphologic and functional characteristics. In addition, the hypercontractile group was associated with clinical predictors including female sex and high SBP. Increased central stiffness and heightened adrenergic drive in patients with high SBP are possible mechanisms leading to

Table 1 Clinical characteristics, hemodynamics, and rest echocardiographic findings

Parameter	Overall (*n* = 2,380)	Low rest force (*n* = 599)	Intermediate rest force (*n* = 1,186)	High rest force (*n* = 595)	*P*
Clinical characteristics					
Sex, male	1,173 (49.3)	408 (68.1)	585 (49.3)*	180 (30.2)*,†	<.0001
Age, y	68 ± 11	65 ± 12	67 ± 12*	70 ± 11*,†	<.0001
BSA, m^2	1.87 ± 0.22	1.99 ± 0.24	1.87 ± 0.19*	1.77 ± 0.18*,†	<.0001
BMI, kg/m^2	28.86 ± 9.10	30.10 ± 8.07	28.76 ± 9.23*	27.82 ± 4.48*	<.0001
Hypertension	1,908 (80.2)	480 (80.1)	945 (79.7)	483 (81.2)	.749
Diabetes	607 (25.5)	159 (26.5)	291 (24.5)	157 (26.4)	.613
Smoking	577 (24.2)	194 (32.4)	266 (22.4)*	117 (19.7)*	<.0001
Dyslipidemia	1,740 (73.1)	448 (74.8)	876 (73.9)	416 (70.0)	.074
Obesity	805 (33.8)	260 (43.4)	369 (31.1)*	176 (29.6)*	<.0001
History of AF	191 (8.0)	41 (6.8)	101 (8.5)	49 (8.2)*,†	.445
Prior MI	394 (16.6)	150 (25.0)	185 (15.6)*	59 (9.9)*	<.0001
Previous revascularization	530 (22.3)	191 (31.9)	242 (20.4)*	97 (16.3)*	<.0001
No CAD	1,707 (71.7)	380 (63.4)	876 (73.9)*	451 (75.8)*	<.0001
One-vessel	248 (10.4)	65 (10.9)	125 (10.5)	58 (9.7)	.532
Multivessel	425 (17.9)	118 (19.7)	223 (18.8)	69 (11.6)*,†	<.0001
NYHA functional class I	349 (14.7)	96 (16.0)	183 (15.4)	70 (11.8)*,†	.003
NYHA functional class II	1,612 (67.7)	386 (64.4)	816 (68.8)‡	410 (68.9)‡	.038
NYHA functional class III	363 (15.3)	99 (16.5)	173 (14.6)	91 (15.3)	.257
NYHA functional class IV	56 (2.4)	18 (3.0)	14 (1.2)*	24 (4.0)†	.001
β-blocker	1,326 (55.7)	355 (59.3)	663 (55.9)	308 (51.8)‡	.032
ACE inhibitor/ARB	1,546 (64.9)	380 (63.4)	775 (65.3)	391 (65.7)	.613
CCB	645 (27.1)	185 (30.9)	310 (26.1)‡	150 (25.2)‡	.037
Nitrate	110 (4.6)	31 (5.2)	44 (3.7)	35 (5.9)	.086
Statin	1,505 (63.2)	387 (64.6)	746 (62.8)	372 (62.5)	.661
Diuretic	867 (36.4)	228 (38.1)	438 (36.9)	201 (33.8)	.269
Serum creatinine, mg/dL	0.97 (0.80-1.14)	1.02 (0.88-1.20)	0.95 (0.80-1.14)*	0.91 (0.79-1.09)*	<.0001
eGFR, $mL/min/1.73\ m^2$	79.33 ± 33.23	87.23 ± 39.56	79.53 ± 30.97*	69.55 ± 26.40*,†	<.0001
NT-proBNP, pg/mL	231 (95-787)	231 (70-682)	218 (97-699)	420 (123-1,499)	.031
Hemodynamic and rest echocardiographic findings					
HR, beats/min	71 ± 14	68 ± 12	70 ± 12*	72 ± 13*,§	<.0001
SBP, mm Hg	132 ± 23	126 ± 17	132 ± 17*	139 ± 18*,†	<.0001
DBP, mm Hg	77 ± 12	76 ± 12	78 ± 11*	78 ± 11*	.0001
WMSI	1.04 ± 0.21	1.10 ± 0.23	1.04 ± 0.16*	1.01 ± 0.06*,†	<.0001
B-lines ≥ 2	475 (20%)	92 (15.5%)	241 (20.3%)‡	143 (24.0%)*,§	.048
LVEDV, mL	87.6 ± 25.5	123.7 ± 32.5	83.9 ± 16.7*	60.8 ± 14.0*,†	<.0001
LVEDVi, mL/m^2	46.8 ± 9.7	62.2 ± 13.9	45.2 ± 8.9*	34.6 ± 7.8*,†	<.0001
LVESV, mL	33.9 ± 11.2	52.7 ± 14.7	32.0 ± 6.0*	20.1 ± 4.6*,†	<.0001
LVESVi, mL/m^2	18.2 ± 4.5	26.5 ± 6.4	17.3 ± 3.4*	11.5 ± 2.8*,†	<.0001
SV, mL	61.2 ± 20.6	75.8 ± 24.9	58.7 ± 19.2*	51.7 ± 19.6*,†	<.0001
SVi, mL/m^2	31.7 ± 11.3	38.1 ± 11.6	31.6 ± 10.3*	29.5 ± 11.3*,†	<.0001
LVEF, %	61.6 ± 5.7	57.2 ± 4.7	61.3 ± 5.4*	66.3 ± 6.5*,†	<.0001
Cardiac output, mL	4.41 ± 2.23	5.21 ± 1.83	4.24 ± 1.51*	3.93 ± 1.57*,†	<.0001
Cardiac index, mL/m^2	2.38 ± 0.97	2.83 ± 1.11	2.29 ± 0.91*	2.12 ± 0.92*,†	<.0001
Force, mm Hg/mL	4.54 ± 1.87	2.50 ± 0.50	4.20 ± 0.62*	7.28 ± 2.02*,†	<.0001
AE, mm Hg/mL	2.45 ± 0.98	1.82 ± 0.71	2.45 ± 0.74*	3.07 ± 1.16*,†	<.0001
VAC	1.99 ± 0.83	1.47 ± 0.44	1.87 ± 0.65*	2.74 ± 1.49*,†	<.0001
LAD velocity, cm/s	27.9 ± 11.2	29.2 ± 12.4	27.3 ± 10.2	28.2 ± 10.1	.053

(*Continued*)

Table 1 (*Continued*)

Parameter	Overall (*n* = 2,380)	Low rest force (*n* = 599)	Intermediate rest force (*n* = 1,186)	High rest force (*n* = 595)	*P*
RWT	0.44 ± 0.12	0.41 ± 0.09	0.44 ± 0.11*	0.48 ± 0.14*,†	<.0001
LVMI, g/m^2	92.5 ± 31.5	98.2 ± 28.0	91.4 ± 29.2*	88.3 ± 30.9*	<.0001
LAVI, mL/m^2	31.3 ± 13.3	34.2 ± 15.4	30.5 ± 13.8*	29.9 ± 12.2*	<.0001
E, cm/s	76.0 ± 23.3	72.2 ± 22.5	76.9 ± 22.9*	78.2 ± 24.3*	.0003
e′, cm/s	8.62 ± 2.70	8.62 ± 2.61	8.70 ± 2.52	8.46 ± 2.43	.406
E/e′ ratio	9.31 ± 3.72	9.15 ± 4.12	9.25 ± 3.56	9.60 ± 3.85	.305
SPAP, mm Hg	30.23 ± 8.98	30.61 ± 10.46	29.63 ± 9.02	30.94 ± 9.51	.128
LV GLS, %	16.93 ± 4.21	16.16 ± 3.37	16.89 ± 3.81‡	17.57 ± 4.08*,§	<.0001
TAPSE, mm	22.6 ± 4.8	22.7 ± 4.3	22.7 ± 4.3	22.6 ± 4.4	.937

ACE, Angiotensin-converting enzyme; *AE*, arterial elastance; *AF*, atrial fibrillation; *ARB*, angiotensin receptor blocker; *BMI*, body mass index; *BSA*, body surface area; *CAD*, coronary artery disease; *CCB*, calcium channel blocker; *DBP*, diastolic blood pressure; *eGFR*, estimated glomerular filtration rate; *HR*, heart rate; *LAD*, left anterior descending coronary artery; *LVEDVi*, LVEDV index; *LVESVi*, LVESV index; *LVMI*, LV mass index; *NYHA*, New York Heart Association; *SPAP*, systolic pulmonary artery pressure; *SVi*, SV index; *TAPSE*, tricuspid annular plane systolic excursion; *WMSI*, wall motion score index.

Data are expressed as number (percentage), mean ± SD, or median (interquartile range).

*P < .01 vs low rest force group.

†P < .01 vs medium rest force group.

‡P < .05 vs low rest force group.

§P < .05 vs medium rest force group.

hypercontractile phenotype. Increased afterload can induce an uncoupling of ventricular-arterial elastance, with a compensatory increase in LV contractility to restore the ideal match. However, there is a threshold at which increased contractility can no longer offset the increased central stiffness, leading to reduced SV, which indicates insufficient compensatory capability of the left ventricle.[25-27] Studies have shown that women with supranormal LVEFs experience greater microvascular dysfunction and higher sympathetic tone, driven by estrogen-induced sympathetic hyperactivity and parasympathetic impairment.[28-30] Earlier experimental studies indicate that cardiomyocyte hypertrophy, resulting from increased aortic stiffness and elevated afterload in older women, may explain their significant age-related increase in LVEF.[31] This supports our study that older women are more prone to developing the hypercontractile

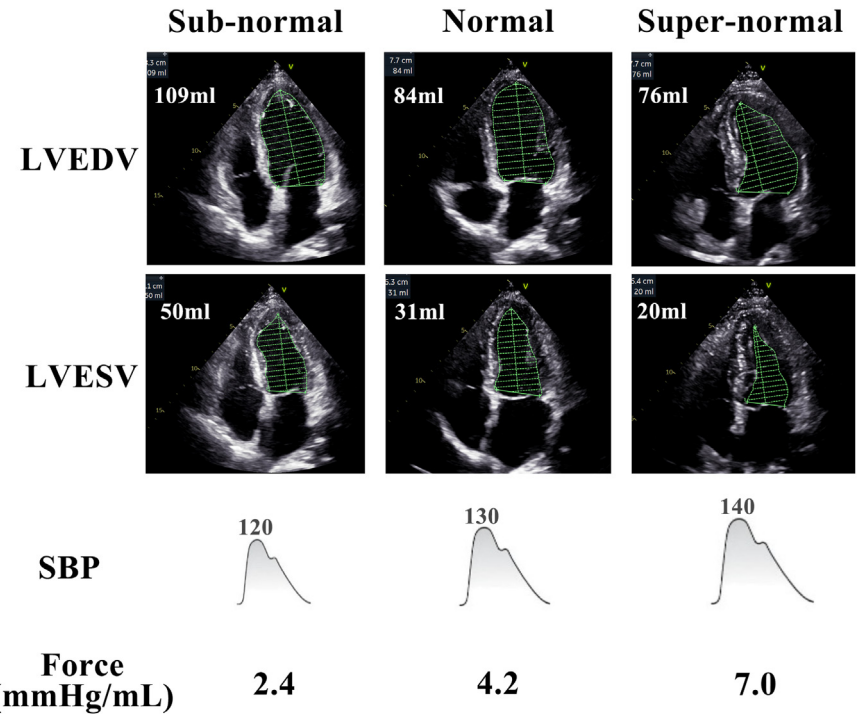


Figure 2 The characteristics of different contractile phenotypes in patients with HFpEF.

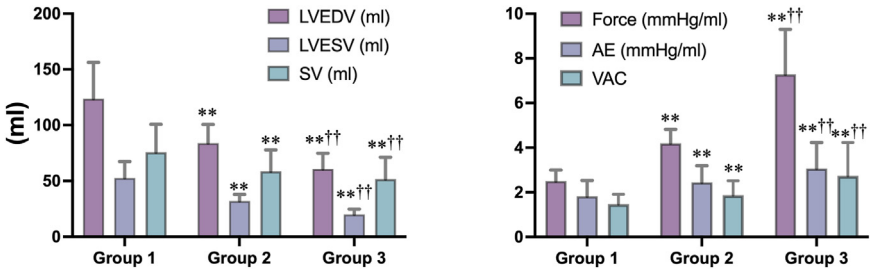


Figure 3 LVEDV, LVESV, and SV *(left)* and force, AE, and VAC *(right)* in the three groups. $^{**}P < .001$ vs group 1; $^{\dagger\dagger}P < .001$ vs group 2.

phenotype. However, LV mass index was lower in higher force group, which might be due to the smaller LV chamber. Additionally, RWT in this group was much higher, indicating the concentric remodeling.

Comparison With Previous Studies

The hypercontractile phenotype has been identified in patients with acute or chronic coronary syndromes, characterized by a supernormal LVEF (>65% or >70%). This phenotype is associated with a detrimental systemic hemodynamic profile and a worse prognosis compared with patients with normal LVEFs.[23,32] The identification of force in the highest quartile of distribution in group 3 (mean, 7.28 mm Hg/mL) corresponds to values exceeding 1 SD of the force distribution (4.0 ± 1.9) in 103 normal, healthy subjects, as previously demonstrated by Merli *et al.*[33] from our study group. Patients with HFpEF and higher LVEFs may exhibit supernormal LV elastance, which is associated with increased VAC and lower event-free survival.[2] These data suggest that resting assessment of LV contractility can be instrumental in identifying heterogeneous subsets with mildly impaired, truly preserved, and supernormal LV function. This classification, typically based on LVEF but potentially refined using force measurements, has important therapeutic and prognostic implications. In our population, the high-force group was characterized by smaller LVEDV (a sign of reduced preload reserve) and greater prevalence of B-lines (a direct sign of pulmonary congestion and an indirect sign of elevated pulmonary artery capillary wedge pressure).[15] This finding is consistent with the emerging concept that patients with supernormal LV function may have increased LV filling pressures, despite the frequent normality of conventional biomarkers such as resting LVEF or cardiac natriuretic peptides.[34]

Clinical Implications

The findings in this study emphasize the significant clinical, morphologic, functional, and prognostic differences among the three distinct HFpEF contractile phenotypes. On the contrary, no significant differences in the cumulative rates of MACEs were observed among LVEF-based phenotypes, which was different from previous studies.[1] LVEF, as the most widely used biomarker of LV systolic function, is not synonymous with LV contractile function. Compared with LVEF, force serves as a more precise parameter for evaluating contractility. However, it remains to be determined if these different phenogroups are separate entities or may reflect different disease stages over time, with an initial hypercontractile stage later progressing to pseudonormal and then at a final stage of hypocontractile phenotype. Furthermore, patients with the hypercontractile phenotype of

Table 2 Clinical parameters associated with high force in HFpEF

	Univariate logistic regression		Multivariable logistic regression		
Variable	OR (95% CI)	*P*	OR (95% CI)	β	*P*
Sex, female	2.94 (2.41-3.59)	<.001	2.39 (1.73-3.32)	0.87	<.001
Age > 68 y	1.81 (1.50-2.19)	<.001			
BMI < 27 kg/m^2	1.39 (1.15-1.67)	.003			
No smoking	1.29 (1.04-1.62)	.081			
No obesity	1.24 (1.02-1.52)	.082			
No history of CAD	1.32 (1.07-1.64)	.047			
No prior MI	2.13 (1.59-2.88)	.001	1.84 (1.11-3.11)	0.61	.020
No prior coronary revision	1.70 (1.35-2.16)	.001			
Absence of β-blocker	1.24 (1.03-1.49)	.051			
Absence of CCB	1.11 (0.90-1.37)	.454			
SBP > 137 mm Hg	2.28 (1.89-2.75)	<.001	2.40 (1.76-3.28)	0.87	<.001
HR > 73 beats/min	1.57 (1.31-1.91)	<.001			
eGFR < 72 mL/min/1.73 m^2	1.95 (1.48-2.56)	<.001			

BMI, Body mass index; *CAD*, coronary artery disease; *CCB*, calcium channel blocker; *eGFR*, estimated glomerular filtration rate; *HR*, heart rate.

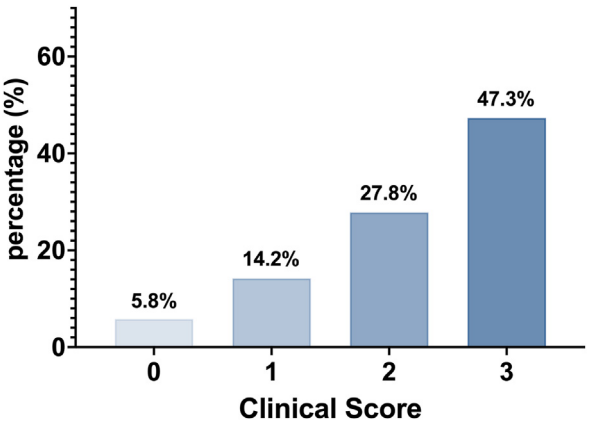


Figure 4 Percentages of high rest force in different clinical score groups.

HFpEF exhibit higher levels of NT-proBNP and a higher percentage of New York Heart Association functional class IV but a lower percentage of β-blocker treatment. These findings indicate that the current attention paid to the treatment of patients with the hypercontractile phenotype is insufficient. In this study, the different clinical and hemodynamic features suggest that their response to therapy can also be different, standard therapy for HF with reduced ejection fraction might be more effective in the hypocontractile phenotype, and different therapies such as β-blockers might be more effective in the hypercontractile phenotype subset.[13,35,36] Therefore, a one-size-fits-all approach is likely ineffective for managing HFpEF. The identification of different contractile phenotypes is crucial for developing targeted therapeutic strategies.

Study Limitations

We used the standard and universally accepted two-dimensional method for volumetric echocardiography. However, artificial intelligence–assisted real-time three-dimensional echocardiography provides more objective, reliable, and operator-independent data.[37] The study recruitment period is quite lengthy, spanning from July 2016 to May 2024, which may have influenced the study results. However, the COVID-19 pandemic significantly slowed the recruitment rate for the Stress Echo 2020 study, as well as for all studies worldwide. During the forced pause due to the pandemic (2020-2021), the study was refreshed, updated, and expanded, transitioning from Stress Echo 2020[38] to Stress Echo 2030.[39] The database was migrated to REDCap, which is owned by SIECVI. Additionally, the original project was scaled up to include new countries, such as the United States and China, and data collection was refined and updated to incorporate new clinical, echocardiographic, and follow-up data. For example, in the original 2016 data set, we lacked systematic information on the use of sodium-glucose cotransporter 2 inhibitors, which are now recognized as a disease-modifying therapy capable of reducing mortality, as demonstrated in breakthrough randomized controlled trials, and have been included in guidelines starting in 2021.[40] Soft end points were incorporated into the interim analysis of outcomes. The final data analysis will focus an all-cause death after the recruitment of 5,000 patients followed for 5 years until 2030, according to the prespecified study protocol. All centers passed quality control, and we accepted their contributions even if they recruited only one or two patients, which was often due to their later enrollment in the study. Some centers began recruiting in 2016, while others joined as late as 2024. We specified a priori that once quality-controlled centers had entered their data into the database, the data could not be modified or excluded to prevent any form of data contamination. No core laboratory reading was available, and this may have affected the reliability of some measurements, such as GLS, as different vendors were used in the recruiting centers and even within the same center at different time points.[41] NT-proBNP analysis was available only in a small subgroup of patients, preventing us from drawing clear conclusions about level differences among the three phenotypes. Further research with larger sample sizes is needed. No core laboratory reading was available in this study, but all sites entered the data into the database following preliminary strict quality control.[39] This approach significantly reduced the economic resources and manpower needed for this curiosity-driven study while facilitating the acquisition of real-world data. The data, collected from different institutions (both academic and hospital based), using different vendors and enrolling diverse ethnic groups (from 16

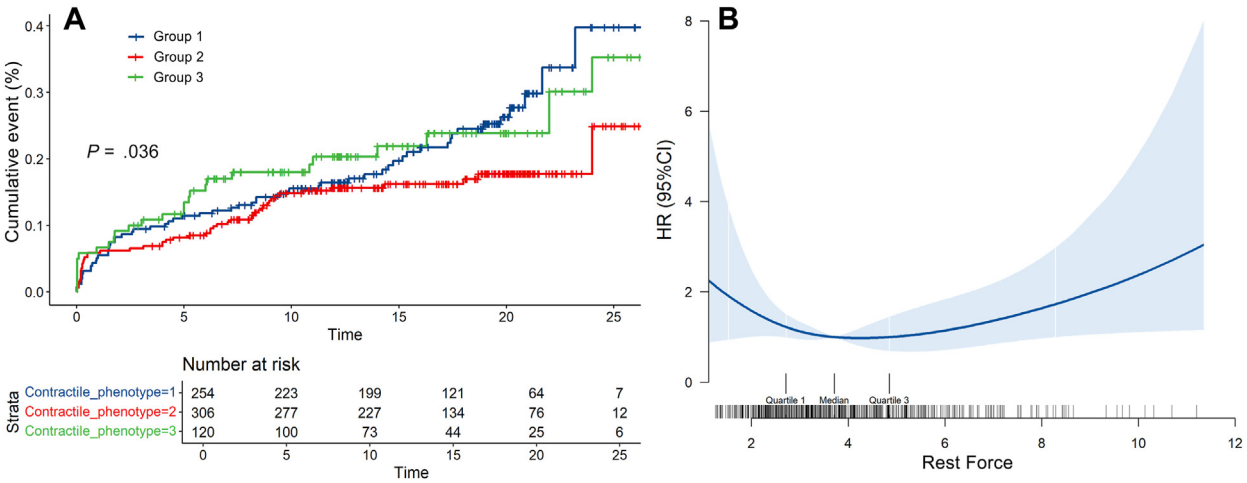


Figure 5 **(A)** Cumulative event curves according to the three phenogroups with subnormal (group 1), normal (group 2), and supernormal (group 3) resting LV function. **(B)** Hazard ratio of MACEs plotted against rest force value. The *blue line* and range indicate the hazard ratio with the 95% CI. Lines on the x axis represent individual study subjects.

Table 3 Predictors of MACEs

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.02 (1.01-1.03)	.031		
Sex	1.76 (1.24-2.51)	.002	1.62 (1.12-2.33)	.010
BMI	1.00 (0.97-1.03)	.941		
Hypertension	1.42 (0.88-2.28)	.153		
Diabetes	1.52 (1.05-2.22)	.028		
Dyslipidemia	1.54 (1.01-2.35)	.044		
Smoking	1.11 (0.77-1.59)	.586		
Prior CAD	2.84 (2.01-4.03)	<.001	2.73 (1.90-3.94)	<.001
β-blocker	1.69 (1.18-2.41)	.004		
Contractile phenotype (intermediate rest force as reference)				
Low rest force	1.41 (1.07-2.05)	.031	1.35 (1.05-2.02)	.038
High rest force	1.47 (1.12-2.34)	.042	1.40 (1.04-2.27)	.049
HR	1.00 (0.99-1.02)	.592		
SBP	1.02 (1.01-1.03)	.010	1.02 (1.01-1.03)	.036
LVMI	1.01 (1.01-1.02)	.097		
LAVI	1.01 (0.98-1.02)	.937		
WMSI	0.93 (0.71-1.20)	.562		
B-lines	1.01 (0.94-1.09)	.822		
LVEDVi	1.01 (1.00-1.02)	.250		
LVESVi	1.01 (0.99-1.03)	.408		
LVEF	1.02 (0.99-1.05)	.242		
Cardiac index	1.07 (0.88-1.30)	.500		
Force	1.05 (0.96-1.16)	.260		
E/e′	1.03 (0.97-1.10)	.301		

BMI, Body mass index; *CAD*, coronary artery disease; *HR*, heart rate; *LVEDVi*, LVEDV index; *LVESVi*, LVESV index; *LVMI*, LV mass index; *WMSI*, wall motion score index.

nations across four continents), are more generalizable. The assessment was performed at rest, and many alterations in diastolic and systolic LV function, valve competence, pulmonary hemodynamics, and right ventricular–pulmonary artery uncoupling may be more apparent during stress.[42] However, the phenotype characterization with resting TTE is simpler and hazard free and requires no additional expertise or stress laboratory infrastructure, as resting TTE is an obligatory first-line imaging test in these patients. The multivariable analysis for high-force prediction and the clinical score incorporates SBP, which is not surprising and may even appear tautological, as SBP is a determinant of force. However, it directly conveys the concept that the assessment of contractility is inextricably linked with the simultaneous assessment of LV volumes and SBP.

CONCLUSION

Patients with HFpEF with different LV contractile phenotypes can be easily identified using resting LV force and volumetric TTE (Central Illustration). The dominant hemodynamic feature of hypocontractile phenotype is a preload recruitment with larger LVEDV and normal SV, whereas the hypercontractile phenotype is characterized by a small left ventricle with reduced SV. The hypercontractile phenotype in patients with HFpEF is associated with clinical predictors including female sex, higher SBP, and absence of prior MI. Both the hypercontractile and hypocontractile phenogroups are associated with higher risk compared with the normal function phenogroup. The therapeutic implications of this distinct echocardiographic phenotype need further investigation.

REVIEW STATEMENT

Given her role as *JASE* Editor-in-Chief, Patricia A. Pellikka, MD, had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to guest editor Kian Keong Poh, MD.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICTS OF INTEREST

None.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2024.12.012.

REFERENCES

1. Ohte N, Kikuchi S, Iwahashi N, et al. Unfavourable outcomes in patients with heart failure with higher preserved left ventricular ejection fraction. Eur Heart J Cardiovasc Imaging 2023;24:293-300.
2. Ohte N, Kikuchi S, Iwahashi N, et al. Distinctive left ventricular-arterial and right ventricular-pulmonary arterial coupling observed in patients with heart failure and a higher left ventricular ejection fraction range. Eur Heart J Cardiovasc Imaging 2024;25:774-81.
3. Walley KR. Left ventricular function: time-varying elastance and left ventricular aortic coupling. Crit Care 2016;20:270.
4. Suga H, Sagawa K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. Circ Res 1974;35:117-26.
5. Ginzton LE, Laks MM, Brizendine M, et al. Noninvasive measurement of the rest and exercise peak systolic pressure/end-systolic volume ratio: a sensitive two-dimensional echocardiographic indicator of left ventricular function. J Am Coll Cardiol 1984;4:509-16.
6. Picano E, Bombardini T, Kovačević Preradović T, et al. Left ventricular contractile reserve in stress echocardiography: the bright side of the force. Kardiol Pol 2019;77:164-72.
7. Wang Y, Yin L. Noninvasive identification and therapeutic implications of supernormal left ventricular contractile phenotype. Explor Cardiol 2024;2:97-113.

8. Bombardini T, Correia MJ, Cicerone C, et al. Force-frequency relationship in the echocardiography laboratory: a noninvasive assessment of Bowditch treppe? J Am Soc Echocardiogr 2003;16:646-55.
9. Bombardini T. Myocardial contractility in the echo lab: molecular, cellular and pathophysiological basis. Cardiovasc Ultrasound 2005;3:27.
10. Picano E, Ciampi Q, Arbucci R, et al. Stress Echo 2030: the new ABCDE protocol defining the future of cardiac imaging. Eur Heart J Suppl 2023;25(Suppl C):C63-7.
11. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
12. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J 2019;40:3297-317.
13. Borlaug BA, Sharma K, Shah SJ, et al. Heart failure with preserved ejection fraction: JACC scientific Statement. J Am Coll Cardiol 2023;81:1810-34.
14. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
15. Scali MC, Zagatina A, Ciampi Q, et al. Lung ultrasound and pulmonary congestion during stress echocardiography. JACC Cardiovasc Imaging 2020;13:2085-95.
16. Scali MC, Zagatina A, Simova I, et al. B-Lines with lung ultrasound: the optimal scan technique at rest and during stress. Ultrasound Med Biol 2017;43:2558-66.
17. Bartolacelli Y, Barbieri A, Antonini-Canterin F, et al. Imaging quality control, methodology harmonization and clinical data management in stress echo 2030. J Clin Med 2021;10:3020.
18. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-731.
19. Ciampi Q, Zagatina A, Cortigiani L, et al. Functional, anatomical, and prognostic correlates of coronary flow velocity reserve during stress echocardiography. J Am Coll Cardiol 2019;74:2278-91.
20. Ciampi Q, Zagatina A, Cortigiani L, et al. Prognostic value of stress echocardiography assessed by the ABCDE protocol. Eur Heart J 2021;42:3869-78.
21. Popovic D, Alogna A, Omar M, et al. Ventricular stiffening and chamber contracture in heart failure with higher ejection fraction. Eur J Heart Fail 2023;25:657-68.
22. Sullivan LM, Massaro JM, D'Agostino RB. Sr. Presentation of multivariate data for clinical use: the Framingham study risk score functions. Stat Med 2004;23:1631-60.
23. Wehner GJ, Jing L, Haggerty CM, et al. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? Eur Heart J 2020;41:1249-57.
24. Ho JE, Enserro D, Brouwers FP, et al. Predicting heart failure with preserved and reduced ejection fraction: the international collaboration on heart failure subtypes. Circ Heart Fail 2016;9:10.1161/CIRCHEARTFAILURE.
25. Chantler PD. Arterial ventricular uncoupling with age and disease and recoupling with exercise. Exerc Sport Sci Rev 2017;45:70-9.
26. Kass DA. Ventricular arterial stiffening: integrating the pathophysiology. Hypertension 2005;46:185-93.
27. Chirinos JA, Segers P, Hughes T, et al. Large-artery stiffness in health and disease: JACC state-of-the-art review. J Am Coll Cardiol 2019;74:1237-63.
28. Maredziak M, Bengs S, Portmann A, et al. Microvascular dysfunction and sympathetic hyperactivity in women with supra-normal left ventricular ejection fraction (snLVEF). Eur J Nucl Med Mol Imaging 2020;47:3094-106.
29. Kaski JC. Cardiac syndrome X in women: the role of oestrogen deficiency. Heart 2006;92(Suppl 3):iii5-9.
30. Gulli G, Cemin R, Pancera P, et al. Evidence of parasympathetic impairment in some patients with cardiac syndrome X. Cardiovasc Res 2001;52:208-16.
31. Anversa P, Palackal T, Sonnenblick EH, et al. Myocyte cell loss and myocyte cellular hyperplasia in the hypertrophied aging rat heart. Circ Res 1990;67:871-85.
32. Rosch S, Kresoja KP, Besler C, et al. Characteristics of heart failure with preserved ejection fraction across the range of left ventricular ejection fraction. Circulation 2022;146:506-18.
33. Merli E, Ciampi Q, Scali MC, et al. Pulmonary congestion during exercise stress echocardiography in ischemic and heart failure patients. Circ Cardiovasc Imaging 2022;15:e013558.
34. Packer M. A reclassification of heart failure based on recognition of heart failure with normal to supernormal ejection fraction, a clinically common form of cardiac contracture, with distinctive pathophysiological and therapeutic features. Eur J Heart Fail 2023;25:669-72.
35. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. Circulation 2022;145:e895-1032.
36. Campbell P, Rutten FH, Lee MM, et al. Heart failure with preserved ejection fraction: everything the clinician needs to know. Lancet 2024;403:1083-92.
37. Sveric KM, Botan R, Dindane Z, et al. Single-site experience with an automated artificial intelligence application for left ventricular ejection fraction measurement in echocardiography. Diagnostics (Basel) 2023;13:1298.
38. Picano E, Ciampi Q, Citro R, et al. Stress echo 2020: the international stress echo study in ischemic and non-ischemic heart disease. Cardiovasc Ultrasound 2017;15:3.
39. Picano E, Ciampi Q, Cortigiani L, et al. Stress echo 2030: the novel ABCDE-(FGLPR) protocol to define the future of imaging. J Clin Med 2021;10:3641.
40. Mahmood A, Dhall E, Primus CP, et al. Heart failure with preserved ejection fraction management: a systematic review of clinical practice guidelines and recommendations. Eur Heart J Qual Care Clin Outcomes 2024;10:571-89.
41. Ünlü S, Mirea O, Bézy S, et al. Inter-vendor variability in strain measurements depends on software rather than image characteristics. Int J Cardiovasc Imaging 2021;37:1689-97.
42. Harada T, Naser JA, Tada A, et al. Cardiac function, haemodynamics, and valve competence with exercise in patients with heart failure with preserved ejection fraction and mild to moderate secondary mitral regurgitation. Eur J Heart Fail 2024;26:1616-27.