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ORIGINAL PAPER

# Interactive role of diastolic dysfunction and ventricular remodeling in asymptomatic subjects at increased risk of heart failure

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## Abstract

Diastolic dysfunction (DD) and left ventricular remodeling (LVR) characterize patients at risk for heart failure (HF). To assess the prognostic impact of different diastolic function algorithms and a complex LVR classification (CRC) in asymptomatic subjects with preserved ejection fraction (EF) at risk for HF. We analyzed 1923 asymptomatic patients (male 43%; age 57, 33–76 years) with at least one cardiovascular risk factor and preserved (> 50%) EF. We used three algorithms for LV diastolic function assessment (Paulus et al. in Eur Heart J 28(20):2539–2550, 2007; Nagueh et al. in J Am Soc Echocardiogr 22(2):107–133, 2009, Eur Heart J Cardiovasc Imaging 17(12):1321–1360, 2016), and two algorithms for LVR (classic and CRC). We considered a composite end-point: cardiac death and hospitalization for HF. The highest presence of DD was diagnosed by Nagueh 2009 (211, 11%), while the prevalence according to Nagueh 2016 (63 patients, 3.2%) turned out to be the lowest ($p < 0.001$ vs the other algorithms). According to CRC, 780 (48.6%) patients had normal or physiologic hypertrophy, 298 (15.5%) concentric remodeling, 85 (4.4%) eccentric remodeling, 294 (15.3%) concentric hypertrophy, 39 (2%) mixed hypertrophy, 80 (4.1%) dilated hypertrophy, 73 (3.7%) eccentric hypertrophy and 294 (15.3%) were unclassifiable. After 39-month follow-up (261 events, 13.6%), Cox-regression (adjusted for age, gender, history of stable ischemic heart disease, classic remodeling classification) identified CRC ($p = 0.01$) and Nagueh 2016 ($p < 0.001$) as independent predictors of end-point. The coexistence of an adverse LVR by CRC and DD by Nagueh 2016 was associated with the worst prognosis. A concurrent structural (CRC) and functional (Nagueh Op. Cit) analysis improves prognostic stratification in asymptomatic subjects at risk for HF with preserved EF.

**Keywords** Heart failure · Preserved ejection fraction · Diastolic dysfunction · Cardiac remodeling · Prognosis

## Abbreviations

| | |
|---|---|
| A-dur | A-wave duration |
| A-wave velocity | Pulsed wave trans-mitral flow end-diastolic wave velocity |
| CAD | Coronary artery disease |
| CRC | Complex remodeling classification |

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| | |
|---|---|
| DD | Diastolic dysfunction |
| DT | E-wave deceleration time |
| E/A ratio | Ratio of proto to tele-diastolic trans-mitral flow velocities |
| E/e' ratio | Ratio of proto-diastolic trans-mitral flow velocity to TDI average septal and lateral velocities |
| e' wave velocity | TDI mitral annular proto-diastolic wave velocity |
| EDD | End-diastolic diameter |
| EDV | Left ventricular end-diastolic volume |
| EF | Ejection fraction |
| ESV | Left ventricular end-systolic volume |
| E-wave velocity | PW transmitral proto-diastolic wave velocity |
| HF | Heart failure |
| LAVi | Indexed left atrial volume |
| LV-EDVi | Indexed left ventricular end-diastolic volume |
| LVH | Left ventricular hypertrophy |
| LVMi | Indexed left ventricular mass |
| LVR | Left ventricular remodeling |
| PWT | Posterior wall thickness |
| RWT | Relative wall thickness |
| SIHD | Stable ischemic heart disease |
| TR | Tricuspid regurgitation |

## Background

Heart Failure (HF) involves approximately 1–2% of the adult population in developed countries, rising to ≥ 10% among people > 70 years of age [1]. Pre-clinical abnormalities in left ventricular (LV) structure and function are each independently associated with overt HF.

Adverse LV remodeling (LVR) and diastolic dysfunction (DD) are the main pathophysiological markers of patients with HF and preserved ejection fraction (HFpEF, i.e., EF > 50%), which accounts for up to one-half of cases of HF syndrome [1, 2]. An accurate assessment of diastolic function is a challenge both for a multiplicity of echocardiographic indexes and substantial overlap between values in healthy subjects and patients [3]. Consistently, in sub-studies of randomized controlled trials on HFpEF, diastolic function according to present-day algorithms may result normal, even in the context of elevated natriuretic peptides, and a further 20–30% have only mild or grade I diastolic dysfunction [4–6]. The latest joint task force proposed a new and simpler system for grading diastolic function [7], but the prevalence and outcomes of DD in asymptomatic patients have yet to be studied [8]. LV hypertrophy (LVH) is considered another hallmark of HFpEF [1]. Echocardiography allows an agile and clinically useful analysis of LVR [3]. The universally known 4-group classification of LVR considers the only estimation of LV mass index (LVMi) and relative wall thickness (RWT) as classifying variables [9]. A more complex LVR classification (CRC) includes indexed LV end-diastolic volume (LV-EDVi), adding further phenotypes [10]. How the interplay (and the distribution) of DD and LVR outperform in prognostic stratification of asymptomatic subjects at increased HF risk has largely to be proven.

The integration of a morpho-functional evaluation in pre-clinical stages may offer the appeal of a better prognostic stratification.

We thus designed this study to:

- assess the prevalence of DD using different diastolic function algorithms [7, 11, 12],
- describe the association between DD and CRC,
- evaluate the prognostic impact of a combined structural and functional analysis in a cohort of asymptomatic subjects at risk for HF.

## Materials and methods

### Study population

We retrospectively selected consecutive patients with preserved EF from a multicenter study by the Italian Society of Cardiovascular Echography (SIEC): *Disfunzione Asintomatica del Ventricolo Sinistro (DAVES)* [13]. It included asymptomatic subjects at risk for HF aged more than 18 years admitted to 19 laboratories for transthoracic examination in the presence of ≥ 1 cardiovascular risk factors, from 2003 to 2004. The ethic committees approved the study. All laboratories were selected in agreement with the American Society of Echocardiography (ASE) requirements [14]. The following cardiovascular risk factors were considered: stable ischemic heart disease (SIHD, defined as history of angina or previous coronary revascularization), hypertension (systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mm Hg, or on therapy), diabetes mellitus (fasting glucose > 7.0 mmol/L or on therapy), hypercholesterolemia (total cholesterol > 200 mg/dL or on therapy), family history of cardiovascular disease (including CAD and cardiomyopathy) and smoking (≥ 1 cigarette/day; cessation of smoking < 10 years was considered as smoking). Exclusion criteria were: unstable coronary artery disease (CAD) in the past 6 months, valvular heart disease (moderate/severe), atrial fibrillation, anemia (hemoglobin < 12 mg/dL in women and < 13 mg/dL in men), renal failure (according to estimated glomerular filtration rate, eGFR < 45 mL/min/$m^2$), endocrine disorders. Pericardial disease, pulmonary hypertension, aortic diseases and cardiomyopathy were excluded, as patients with pacemakers. Obese subjects were

also excluded (BMI ≥ 30 kg/m$^2$), since indexing for body surface area (BSA) may result in underestimation biases [3]. All subjects provided written informed consent and medical history.

### Echocardiography

All selected subjects underwent a complete 2-dimensional echocardiographic study to evaluate LV functional and structural findings. Echocardiograms were acceptable when at least 80% of the endocardium was visible. Quantitative analysis was done, for each laboratory, by the same expert operator. All measurements were performed as a mean of three cardiac cycles [3]. We excluded echocardiograms without a comprehensive tissue doppler imaging analysis. A random sample of 5% of patients was centrally re-analyzed by two independent investigators to evaluate intra- and inter-observer variability.

### Diastolic dysfunction assessment

DD assessment was based on the latest recommendations [7], together with 2009 recommendations [11] and 2007 consensus statement [12]. For each classification algorithm, we classified the patients as having normal, abnormal (DD) or undetermined diastolic function. A random sample of 5% of patients was centrally re-analyzed by two independent observers.

According to the inclusion criteria, all patients had preserved EF and were classified accordingly, starting with the Nagueh 2016 algorithm for the diagnosis of LV DD. In the presence of hypertension and pathological LV hypertrophy, we identified a condition of myocardial disease; thus, as suggested by Nagueh, we used the algorithm for estimation of LV filling pressures and grading LV DD in patients with depressed LVEFs and patients with myocardial disease and normal LVEF.

### Left ventricular remodeling

RWT was calculated as the ratio of 2 × posterior wall thickness and End-diastolic diameter (EDD), while LV Mass was calculated according to Devereux formula [15]. Both EDV and LVMi were indexed for BSA. According to the CRC [10], we identified eight LV geometric patterns: normal ventricle, physiological hypertrophy, concentric remodeling, eccentric remodeling, concentric hypertrophy, mixed hypertrophy, dilated hypertrophy, eccentric hypertrophy (no patient with atrophy). We included physiologic hypertrophy as part of normal remodeling pattern, due to its relatively low prevalence in our population. We considered the pattern as undetermined if the LV geometry was unclassifiable by CRC (eight groups in total). A random sample of 5% of patients was centrally re-analyzed by two independent observers.

### Follow-up and outcome events

Follow-up was performed using clinical controls, the hospital database and phone contact. We considered a composite end-point: cardiac death, hospitalization for worsening HF and acute pulmonary edema.

### Statistical analysis

Continuous measures were expressed as the mean value and 95% confidence interval (CI) or median and 95% CI for normally and skewed distributed variables. Categorical variables are presented as percentages and were compared using the Chi square test. We measured intra-observer and inter-observer reproducibility with intra-class correlation coefficient (ICC) and its 95% confidence intervals (CIs). Concordance between diastolic function algorithms and between two raters was assessed using the Kappa statistic. Cox regression analysis was performed to establish independent predictors of outcome (HR and 95% CI), including DD as a dichotomous variable (normal/abnormal) and CRC (considering eight LV remodeling patterns). Variance inflation factor excluded multi-collinearity between selected variables. Time-to-event data were also evaluated with the use of Kaplan–Meier estimates. To confirm the incremental value of proposed classifications for the occurrence of endpoint, we performed a stepwise model of logistic regression analysis. For each step, we tested the differences using the Chi square test. A two-tailed p-value < 0.05 was considered significant. All data were analyzed using SPSS software (version 23.0; SPSS, Inc., Chicago, IL).

## Results

A final population of 1923 patients (male 43%; Age 57, 33–76 years) were suitable for comprehensive assessment of diastolic function analysis and CRC. Table 1 summarizes clinical characteristics, together with risk factors and comorbidities. Echocardiography-derived parameters were summarized in Table 2. We obtained a good intra-observer (all ICCs > 0.8) and a good inter-observer repeatability (all ICCs > 0.8) of all the parameters included in Table 2.

### Left ventricular diastolic function

Diastolic function analysis using three different algorithms revealed the presence of an abnormal pattern in a minority of the population (Table 3): the highest presence of DD was diagnosed by Nagueh 2009 (211, 11%), that

**Table 1** Clinical characteristics of the study population (n = 1923)

| General characteristics | |
|---|---|
| Male gender | 827 (43%) |
| Age (years) | 57 (33–76) |
| Height (cm) | 165 (150–180) |
| Weight (kg) | 70 (50–98) |
| BMI (kg/m$^2$) | 25.9 (20–28.9) |
| BSA (m$^2$) | 1.8 (1.7–1.9) |
| SAP (mmHg) | 135 (105–170) |
| DAP (mmHg) | 80 (70–100) |
| SIHD | 192 (10) |
| Cerebrovascular disease | 58 (3) |
| COPD | 38 (2) |
| PAD | 47 (1.5) |
| CKD | 19 (1) |
| **Risk factors** | |
| Family history heart disease | 630 (32.8) |
| Dyslipidaemia | 1250 (65) |
| Arterial hypertension | 884 (46) |
| Smoke | 423 (22) |
| Diabetes mellitus | 192 (10) |
| **Medications** | |
| Diuretic | 365 (19) |
| ACE-inhibitor | 1000 (52) |
| AT-II antagonist | 231 (12) |
| Dihydropyridine CCBs | 442 (23) |
| Non-dihydropyridine CCBs | 115 (6) |
| Beta-blockers | 635 (33) |
| Alpha-blockers | 96 (5) |
| Nitrates | 308 (16) |
| Anti-platelets | 788 (41) |
| Statins | 808 (42) |

The data are presented as number and (%), mean and 95% confidence intervals if normally distributed or median and 5–95 percentile range if not normally distributed

*ACE* angiotensin-converting enzyme, *AT-II* angiotensin receptor II, *BMI* body mass index, *BSA* body surface area, *CCB* calcium channel blocker, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *DAP* diastolic arterial pressure, *PAD* peripheral artery disease, *SAP* systolic arterial pressure, *SIHD* stable ischemic heart disease (defined as history of angina or previous coronary revascularization)

was nearly equivalent to the frequency of DD based on Paulus 2007 (209, 10.9%; p = ns); the prevalence according to Nagueh 2016 (63 patients, 3.3%) turned out to be the lowest (p < 0.001 vs the other two algorithms). In all the three algorithms, the proportion of DD increased with age, describing the highest frequency of DD in subjects > 60 years of age (p < 0.02; Fig. 1). The proportion of patients with undetermined diastolic function was similar across the three algorithms, with a non-significant higher prevalence in Nagueh 2016 (n = 154, 8%). A significant different distribution of male and female patients was noted in all the three algorithms (p < 0.001), considering a normal diastolic function (42% vs 58% in Nagueh 2009, 41.5% vs 58.5% in Nagueh 2016, and 41.6% vs 58.4% in Paulus 2007), DD (44.2% vs 55.8% in Nagueh 2009, 47% vs 53% in Nagueh 2016, and 45% vs 55% in Paulus 2007) and undetermined diastolic function (54% vs 46% in Nagueh 2009, 57% vs 43% in Nagueh 2016, 67% vs 33% in Paulus 2007). Concordance analysis between three algorithms is reported in the Supplemental Material.

## Left ventricular remodeling

We summarized the distribution of patients according to the classic and CRC in the Supplemental Table 1. Significant different gender distribution was noted in both classifications (p < 0.001). In the classic classification, we observed a higher proportion of women with normal morphology (57% vs 43%), concentric hypertrophy (55% vs 45%) and eccentric hypertrophy (68% vs 32%), while an equal frequency of male and female patients with concentric remodeling was observed. As far as CRC, we described a higher proportion of women with normal morphology (65% vs 35%), concentric hypertrophy (59% vs 41%) and eccentric hypertrophy (70% vs 30%). The frequency of male was higher in patients with eccentric remodeling (63% vs 38%) and mixed hypertrophy (65% vs 35%), while a similar distribution of male and female patients with dilated hypertrophy (52% vs 48%), concentric remodeling (52% vs 48%) or unclassifiable morphology (50% vs 50%) was observed. An age trend was detected only in CRC (p < 0.001), with oldest patients in concentric hypertrophy subgroup (62.7, 60.4–64.7 years) and the youngest ones in the normal pattern (53.5, 51.5–55.8 years). Concordance between two raters was assessed using the Kappa statistic as a measure of agreement: 0.96 for classic LVR classification and 0.91 for CRC.

## Follow-up analysis

During the follow-up (39 ± 9 months), we observed 261 (13.6%) events: 140 (7.3%) hospitalization for HF, 111 (5.8%) cardiac deaths and 10 (0.6%) episodes of acute pulmonary edema. Univariate Cox regression analysis identified CRC (p < 0.001) and the presence of DD according to all the three algorithms (Paulus 2007; Nagueh 2009: p = 0.01; Nagueh 2016: p < 0.001) as independent predictors of composite end-point. In multivariate analysis, adjusted for age, gender, SIHD, and classic LVR classification, we observed CRC (p = 0.01), age (p = 0.006) and DD identified by Paulus 2007 p = 0.01) and Nagueh 2016 (p < 0.001) as independent predictive factors (Table 4). We analyzed the distribution of

**Table 2** Echocardiographic parameters in the overall population (n = 1923)

| Variable | Overall population |
|---|---|
| LV end-diastolic diameter (mm) | 51.2 (45.2–57.7) |
| LV EDVi (mL/m$^2$) | 59.1 (43.2–92.5) |
| EF (%) | 65 (61.8–69.3) |
| Inter-ventricular septum (mm) | 10.5 (8.1–13.1) |
| Posterior wall (mm) | 9.7 (7.7–11.8) |
| Tricuspid reg. max Vel. (m/s) | 2.5–2.9 (2.4–3.1) |
| Estimated sPAP (mmHg) | 31 (23–40) |
| RWT | 0.36 (0.30–0.45) |
| LV Mass indexed (g/m$^2$) | 94.4 (65.2–157.4) |
| E wave velocity (cm/s) | 75.5 (48.4–98.9) |
| E/A ratio | 1.1 (0.8–1.5) |
| Deceleration time (ms) | 195 (170–250) |
| Average e' (cm/s) | 9 (7–12) |
| Average E/e' ratio | 7.5 (6.2–14.9) |
| LAVi (mL/m$^2$) | 29.5 (16.5–43.7) |
| Pulmonary veins S/D ratio | 1.7 (0.8–2.1) |
| TAPSE (mm) | 23 (18–27) |

The data are presented as mean and 95% confidence intervals if normally distributed or median and 5–95 percentile range if not normally distributed

*EDVi* end-diastolic volume indexed, *EF* ejection fraction, *LAVi* left atrial volume indexed, *LV* Left ventricular, *RWT* relative wall thickness, *sPAP* systolic pulmonary artery pressure

**Table 3** Diastolic function distribution in the population (n = 1923) according to three algorithm

| Paulus 2007 | |
|---|---|
| Normal | 1618 (84.1) |
| Diastolic dysfunction | 209 (10.9) |
| Undetermined | 96 (5) |
| **Nagueh 2009** | |
| Normal | 1636 (85.1) |
| Diastolic dysfunction | 211 (11) |
| Grade I | 150 (71) |
| Grade II | 61 (29) |
| Grade III | 0 |
| Undetermined | 76 (4) |
| **Nagueh 2016** | |
| Normal | 1706 (88.7) |
| Diastolic dysfunction | 63 (3.3) |
| Grade I | 45 (71.4) |
| Grade II | 18 (28.6) |
| Grade III | 0 |
| Undetermined | 154 (8) |

The data are presented as number and (%)

population considering both the CRC and diastolic function assessment by Nagueh 2016 classification (Supplemental Table 2). Kaplan–Meier analysis showed a significant different event-free survival distribution (log-rank test: $p < 0.001$) of the remodeling patterns (Fig. 2a): the worst prognosis was reported for patients with concentric hypertrophy, followed by eccentric, mixed and dilated hypertrophy. In the same way, diastolic function demonstrated a significant different event-free survival distribution (log-rank test: $p < 0.001$; Fig. 2b), and the worst prognosis was observed in patients with DD. Then, we subdivided total population according to the coexistence of DD using Nagueh 2016 and adverse hypertrophy pattern (concentric, eccentric, mixed and dilated) based on CRC (Group A, n = 56, 2.9%), the presence of DD or adverse hypertrophy pattern (Group B, n = 437, 22.7%) and the absence of DD and any adverse hypertrophy pattern (Group C, n = 1430, 74.4%). Kaplan–Meier analysis proved a significantly worse prognosis for Group A, followed by Group B and C (Fig. 2c). Survival analysis was also performed in the subgroup of patients with an undetermined diastolic function using Nagueh 2016 (n = 154), confronting the coexistence (n = 77) and the absence (n = 77) of an adverse remodeling pattern (according to CRC), showing a worse prognosis associated with hypertrophy (Fig. 2d).

## Discussion

Main findings of the present paper are:

- The prevalence of DD in asymptomatic subjects at risk for heart failure is low; it is lower with more recent diagnostic algorithms and increases with age;
- A gender difference is reported for DD and CRC;
- CRC and DD have been shown to be outcome predictors;
- The coexistence of DD and adverse remodeling subtend an adverse prognosis.

### Left ventricular diastolic function

HFpEF develops from a complex interplay among several mechanisms, but it has been speculated that DD is probably the critical element beneath it and may also represent the pre-clinical alteration leading to an overt syndrome [16, 17]. In the clinical arena, DD is an echocardiographic, rather than clinical, diagnosis [7, 12]. Unfortunately, the diagnosis of DD is challenging: a recent report found that more than half of consecutive patients coming to the echo laboratory leave with a limited assessment of diastolic function, due to numerous reasons (e.g. tachycardia, E-to-A fusion, atrial fibrillation, valvular dysfunction) [18]. Even after the exclusion of these patients, a substantial proportion of subjects remains unclassifiable (10–17%), with a poor concordance

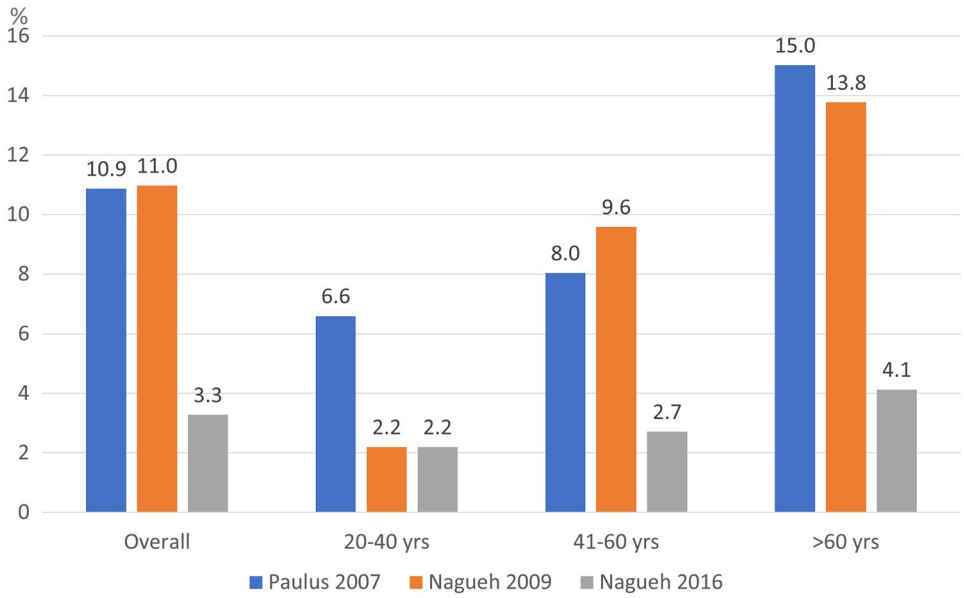


**Fig. 1** Study population stratified by age and classified according to three diagnostic algorithms (Paulus 2007, Nagueh 2009 and Nagueh 2016)

between different algorithms [18, 19]. In this study, we selected a population at Increased risk of HF with preserved EF. Nevertheless, some patients were classified as an undetermined diastolic function (5% with Paulus 2007, 4% with Nagueh 2009, 8% with Nagueh 2016). The presence of DD was associated with a significant age trend, reflecting the progressive myocardial stiffening of ageing [8] The majority of the study population is made up mainly of women (57%), and a significant sex-specific difference was documented in all the algorithms: higher prevalence of female patients with both normal and altered diastolic function, and a higher frequency of male patients in undetermined cases. In accordance with the literature, we ascribed this distribution of DD to gender-related differences in LVR in response to common types of injuries. Indeed, women are more likely associated with DD and low cardiac output syndrome, that are the main foundations of HFpEF [20]. Univariate survival analysis demonstrated a significant association of female gender with adverse prognosis, but diastolic function evaluation, in particular the presence of DD, proved to be a better predictor of poor survival at multivariate analysis, after adjusting for age, gender, SIDH and different LVR patterns. This finding is of utmost importance, because the prevalence of DD was quite low, and only a mild-to-moderate DD was observed, without severe cases of DD. Moreover, the latest classification [7] identified the lowest proportion of DD in comparison with previously proposed algorithms [11, 12], and nevertheless, it performed as the best independent predictor at multivariate analysis. We confirmed in this large sample a relatively limited concordance between the three different diastolic

**Table 4** Cox proportional hazard model: independent predictive factors for composite end-point

| Parameter | Univariate analysis (HR (95% CI) | p-value | Multivariate analysis (HR (95% CI) | p-value |
|---|---|---|---|---|
| Age | 1.009 (1.006–1.011) | <0.001 | 1.007 (1.002–1.012) | 0.006 |
| Gender (male) | 0.891 (0.877–0.983) | 0.03 | 0.992 (0.882–1.117) | ns |
| SIHD | 1.196 (1.092–1.416) | 0.02 | 1.238 (0.995–1.539) | ns |
| Diabetes mellitus | 1.126 (0.839–1.237) | ns | | |
| Arterial hypertension | 1.093 (0.902–1.142) | ns | | |
| Smoke | 1.041 (0.879–1.205) | ns | | |
| CKD | 0.893 (0.754–1.107) | ns | | |
| Paulus 2007 | 1.257 (1.132–1.318) | <0.001 | 1.034 (1.012–1.201) | 0.01 |
| Nagueh 2009 | 1.055 (1.012–1.274) | 0.01 | 0.935 (0.836–1.045) | ns |
| Nagueh 2016 | 1.352 (1.297–1.387) | <0.001 | 1.291 (1.195–1.396) | <0.001 |
| Classic remodeling classification | 1.081 (1.010–1.284) | 0.04 | 0.984 (0.960–1.109) | ns |
| Complex remodeling classification | 1.317 (1.194–1.368) | <0.001 | 1.064 (1.013–1.118) | 0.01 |

*CI* confidence intervals, *CKD* chronic kidney disease, *HR* hazard ratio; *SIHD* stable ischemic heart disease

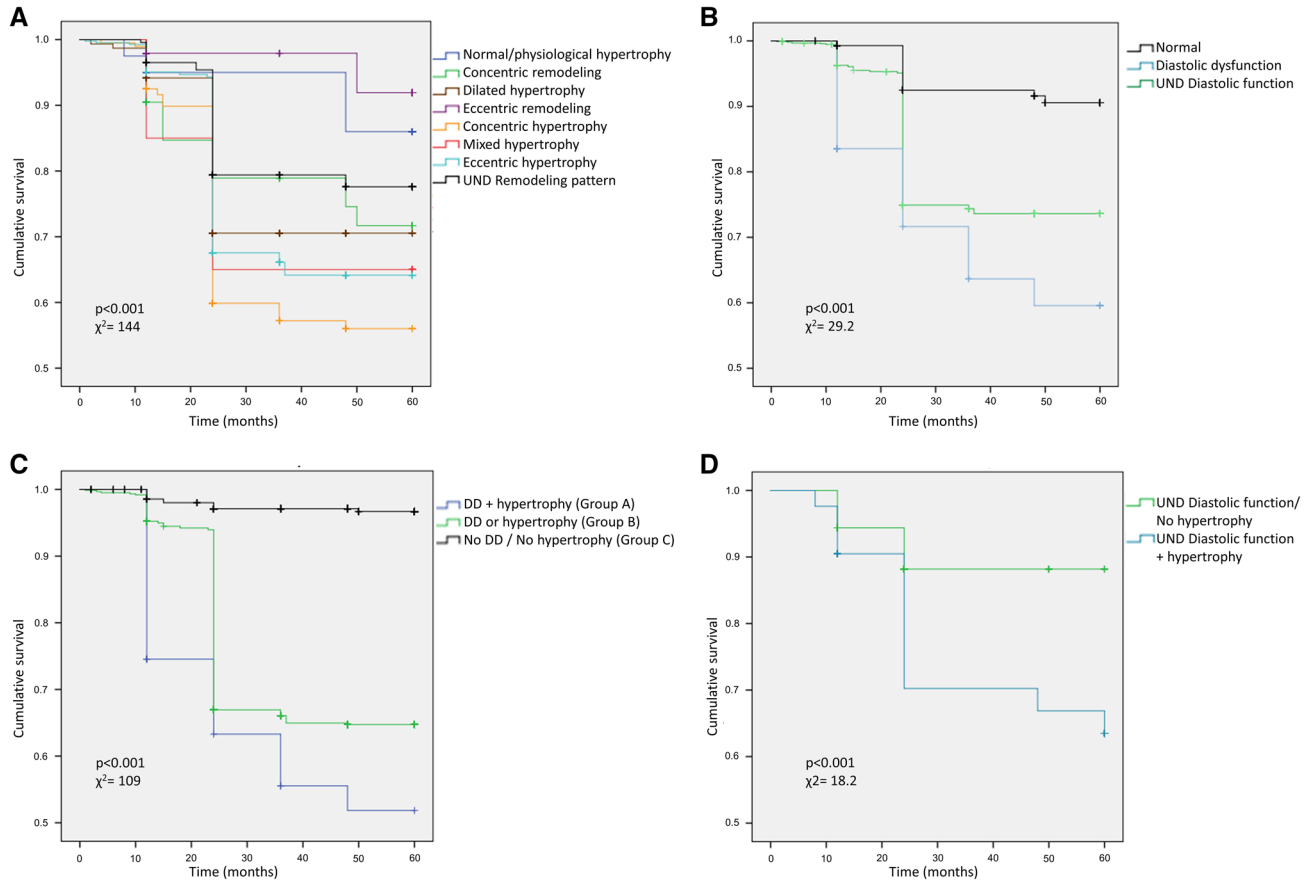


**Fig. 2** Kaplan–Meier event-free survival curves. Patient population (n = 1923), assigned according to the left ventricle (LV) complex remodeling classification (CRC) (**a**) and LV diastolic function evaluation assessed by Nagueh 2016 (**b**). In panel **c**, population was subdivided according to the coexistence of an LV diastolic dysfunction (DD) based on Nagueh 2016 and an adverse LV hypertrophy pattern (concentric, eccentric, mixed and dilated) based on CRC (Group A, n = 56), the presence of DD or adverse hypertrophy pattern (Group B, n = 529) and the absence of DD and any adverse hypertrophy pattern (Group C, n = 1338). In panel **d**, the subgroup of patients with an undetermined (UND) diastole was subdivided according to the presence (n = 77) or absence (n = 77) of an adverse LV hypertrophy pattern

function algorithms [18], except for normal diastolic function. Probably, the higher prognostic accuracy of Nagueh 2016 is related to a redistribution of patients from DD as assessed by previous algorithms to undetermined diastolic function. Indeed, undetermined patients by Nagueh 2016 showed an intermediate survival probability between the presence of DD and normal diastolic function.

## Left ventricular remodeling

LVR is defined as an alteration in heart structure in response to any myocardial injury [21]. LV dilatation or hypertrophy are significantly associated with an increased likelihood of overt HF and adverse events [22, 23]. A renewed and complex classification of LVR demonstrated a better prognostic stratification in comparison with the classic one [10, 24]. In this study, we selected only asymptomatic patients at risk for HF. A normal morphology was observed in the majority of the population, both with classic classification (47%) and CRC (40.6%, including patients with physiological hypertrophy). CRC proved to be a better predictor of adverse prognosis respective to classic classification, even adjusting for age, gender, SIDH and the presence of DD. Noteworthy, significant different gender distribution was noted using CRC, with a female prevalence in patterns characterized by more advanced LVR, in particular concentric (59%) and eccentric hypertrophy (70%). These patterns were associated with the worst prognosis at survival analysis, in agreement with our previous findings [25, 26]. Of interest, former studies focused on HF regardless of EF, revealing a higher prevalence of male patients in all the adverse LVR patterns. In the present study, the higher predominance of female patients in the overall population and more adverse LVR patterns has probably related to the exclusion of subjects with reduced EF.

### The importance of a concurrent structural and functional analysis

Our findings demonstrated even in asymptomatic patients the presence of hypertrophic patterns in a quarter of the population, while only about 3% of the patients presented a DD, using the classifications revealing the best prognostic value (CRC and Nagueh 2016, respectively).

Certainly, structural and functional alterations proved to be strictly connected, because 89% of the patients with DD had an adverse LVR, defined as the development of a hypertrophic pattern. Being pressure overload associated with arterial hypertension one of the most frequent risk factors in the study, it was not surprising concentric hypertrophy was the principal structural alteration. Concentric hypertrophy, together with other hypertrophic patterns (eccentric, mixed and dilated hypertrophy) had the worst outcome invariably. Then, we developed a survival model showing the coexistence of adverse LVR and DD was characterized by the most unfavourable prognosis, while a significantly better survival was observed in the presence of only one alteration (functional or structural) and the lowest number of events was recorded in patients with a normal morphology or low-grade LVR and without DD. Previous pathophysiological studies confirmed DD and adverse LVR independently as typical findings of early stages of HFpEF [27–30] Moreover, we analyzed the behaviour of patients with undetermined diastole (a non-negligible proportion [8%], in line with previous findings in the literature [8, 31]), showing an intermediate prognosis between the presence of DD and normal diastolic function. Interestingly, CRC succeeded in also stratifying this subgroup, proving the coexistence of an adverse hypertrophy pattern is associated with a worse prognosis. On the contrary, almost all patients with an undetermined LVR pattern were characterized by normal diastole (93%), with no cases of DD. Only 18 patients (1% of total population) remained completely undetermined after using both the functional (Nagueh 2016) and the structural (CRC) assessment. To our knowledge, this is the first study showing the concurrent analysis of different diastolic algorithms and LVR classifications in asymptomatic subjects at risk for HF with preserved EF. In this respect, Nagueh 2016 and CRC proved to be reliable assets with incremental prognostic value, in addition to basal clinical evaluation.

### Limitations

The main limitation of the present study is its retrospective nature. However, we excluded as many confounding factors as possible. Moreover, the cohort was relatively young, with an average of 55 years. This is due to strict inclusion criteria, potentially limiting the applicability of our findings in an older patient group. Another study limitation was the use of composite outcomes. The use of standard echocardiographic assessment instead of more sophisticated methods (e.g., strain imaging; three-dimensional echocardiography) could be considered both a limitation and a strength of the study. Anyway, we focused on the utility of currently established and available echocardiographic techniques, this being a real-world study. Another limit of the study is represented by the lack of determination of natriuretic peptide levels. Finally, both Nagueh 2016 and CRC were unable to classify 154 (8%) and 294 (15.3%) patients, respectively, in line with literature [8, 10, 24, 31].

## Conclusions

In asymptomatic subjects at risk for HF with preserved EF, the latest diastolic function algorithm [7] identified a lower prevalence of DD in comparison with previous ones, demonstrating higher prognostic value. CRC retained a better prognostic stratification than classic LVR classification. We, therefore, propose a concurrent functional and structural evaluation of asymptomatic patients at increased HF risk, to improve diagnostic capability and outweigh the potential limitations of both classifications, in particular in cases of undetermined diastolic or LVR assessment.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Research involving animal rights** This article does not contain any studies with animals performed by any of the authors.

## References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al (2016) 2016 ESC guidelines for the diagnosis

and treatment of acute and chronic heart failure. Eur Heart J 37(27):2129–2200
2. Mitter SS, Shah SJ, Thomas JD, Francis GS, Felker GM, Tang WHW (2016) A test in context. J Am Coll Cardiol 67(3):330–337
3. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al (2015) 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 16(3):233–270
4. Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R et al (2011) Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. Circulation 124(23):2491–2501
5. Shah AM, Shah SJ, Anand IS, Sweitzer NK, O'Meara E, Heitner JF et al (2014) Cardiac structure and function in heart failure with preserved ejection fraction: baseline findings from the echocardiographic study of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. Circ Heart Fail 7(1):104–115
6. Persson H, Lonn E, Edner M, Baruch L, Lang CC, Morton JJ et al (2007) Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence. J Am Coll Cardiol 49(6):687–694
7. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T et al (2016) Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American society of echocardiography and the European association of cardiovascular imaging. Eur Heart J Cardiovasc Imaging 17(12):1321–1360
8. Huttin O, Fraser AG, Coiro S, Bozec E, Selton-Suty C, Lamiral Z et al (2017) Impact of changes in consensus diagnostic recommendations on the echocardiographic prevalence of diastolic dysfunction. J Am Coll Cardiol 69(25):3119–3121
9. Huwez FU, Pringle SD, Macfarlane PW (1992) A new classification of left ventricular geometry in patients with cardiac disease based on M-mode echocardiography. Am J Cardiol 70(6):681–688
10. Gaasch WH, Zile MR (2011) Left ventricular structural remodeling in health and disease: with special emphasis on volume, mass, and geometry. J Am Coll Cardiol 58(17):1733–1740
11. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE et al (2007) How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 28(20):2539–2550
12. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth O et al (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 22(2):107–133
13. Carerj S, Penco M, La Carrubba S, Salustri A, Erlicher A, Pezzano A et al (2006) The DAVES (Disfunzione Asintomatica VEntricolare Sinistra) study by the Italian society of cardiovascular echography: rationale and design. J Cardiovasc Med 7(7):457–463
14. Quiñones MA, Douglas PS, Foster E, Gorcsan J, Lewis JF, Pearlman AS et al (2003) ACC/AHA clinical competence statement on echocardiography: a report of the American College of Cardiology/American Heart Association/American College of Physicians-American Society of Internal Medicine Task Force on Clinical Competence. J Am Coll Cardiol 41(4): 687–708
15. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M et al (2015) Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE)†. Eur Heart J Cardiovasc Imaging 16(6):577–605
16. Burke MA, Katz DH, Beussink L, Selvaraj S, Gupta DK, Fox J et al (2014) Prognostic importance of pathophysiologic markers in patients with heart failure and preserved ejection fraction. Circ Heart Fail 7(2):288–299
17. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC et al (2011) Progression of left ventricular diastolic dysfunction and risk of heart failure. JAMA 306(8):856–863
18. Gottbrecht MF, Salerno M, Aurigemma GP (2017) Evolution of diastolic function algorithms: Implications for clinical practice. Echocardiography 35:39–46
19. Rasmussen-Torvik LJ, Colangelo LA, Lima JAC, Jacobs DR, Rodriguez CJ, Gidding SS et al (2017) Prevalence and predictors of diastolic dysfunction according to different classification criteria. Am J Epidemiol 185(12):1221–1227
20. Piro M, Della Bona R, Abbate A, Biasucci LM, Crea F (2010) Sex-related differences in myocardial remodeling. J Am Coll Cardiol 55(11):1057–1065
21. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE (2011) Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. JACC Cardiovasc Imaging 4(1):98–108
22. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS (2003) Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation 108(8):977–982
23. Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA et al (2008) Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research. Circulation 117(19):2544
24. Pugliese NR, Fabiani I, La Carrubba S, Conte L, Antonini-Canterin F, Colonna P et al (2016) Classification and prognostic evaluation of left ventricular remodeling in patients with asymptomatic heart failure. Am J Cardiol 119(1):71–77
25. Pugliese NR, Fabiani I, La Carrubba S, Conte L, Antonini-Canterin F, Colonna P et al (2017) Classification and prognostic evaluation of left ventricular remodeling in patients with asymptomatic heart failure. Am J Cardiol 119(1):71–77
26. Fabiani I, Pugliese NR, La Carrubba S, Conte L, Antonini-Canterin F, Colonna P et al (2017) Incremental prognostic value of a complex left ventricular remodeling classification in asymptomatic for heart failure hypertensive patients. J Am Soc Hypertens 11:412–419
27. Messerli FH, Rimoldi SF, Bangalore S (2017) The transition from hypertension to heart failure. JACC Heart Fail 5(8):543–551
28. Seliger SL, de Lemos J, Neeland IJ, Christenson R, Gottdiener J, Drazner MH et al (2015) Older adults, "malignant" left ventricular hypertrophy, and associated cardiac-specific biomarker phenotypes to identify the differential risk of new-onset reduced versus preserved ejection fraction heart failure. JACC Heart Fail 3(6):445–455
29. Iriarte M, Murga N, Sagastagoitia D, Morillas M, Boveda J, Molinero E et al (1993) Classification of hypertensive cardiomyopathy. Eur Heart J 14(Suppl J):95–101

30. Shah AM, Claggett B, Loehr LR, Chang PP, Matsushita K, Kitzman D et al (2017) Heart failure stages among older adults in the communityclinical perspective. Circulation 135(3):224–240
31. Lancellotti P, Galderisi M, Edvardsen T, Donal E, Goliasch G, Cardim N et al (2017) Echo-doppler estimation of left ventricular filling pressure: results of the multicentre EACVI euro-filling study. Eur Hear J Cardiovasc Imaging 18:961–968