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Differential interaction of clinical characteristics with key functional parameters in heart failure with preserved ejection fraction — Results of the Aldo-DHF trial ☆☆

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ABSTRACT

Background: To investigate the interaction of clinical characteristics with disease characterising parameters in heart failure with preserved ejection fraction (HFpEF).

Methods and results

In the multicenter, randomized, placebo-controlled, double-blinded, Aldo-DHF trial investigating the effects of spironolactone on exercise capacity (peakVO2) and diastolic function (E/e′) $n = 422$ patients with HFpEF (age 67 ± 8years, 52% females, LVEF 67 ± 8%) were included. After multiple adjustment, higher age was significantly related to reduced peakVO2, and to increased E/e′, NT-proBNP, LAVI as well as LVMI (all $p < 0.05$). Female gender ($p < 0.001$), CAD ($p = 0.002$), BMI ($p < 0.001$), sleep apnoea ($p = 0.02$), and chronotropic incompetence (CI, $p = 0.002$) were related to lower peakVO2 values. Higher pulse pressure ($p = 0.04$), lower heart rates ($p = 0.03$), CI ($p = 0.03$) and beta-blocker treatment ($p = 0.001$) were associated with higher E/e′. BMI correlated inversely ($p = 0.03$), whereas atrial fibrillation ($p < 0.001$), lower haemoglobin levels ($p < 0.001$), CI ($p = 0.02$), and beta-blocker treatment ($p < 0.001$) were associated with higher NT-proBNP. After multiple adjustment for demographic and clinical variables peakVO2 was not significantly associated with E/e′ ($r = +0.01$, $p = 0.87$), logNT-proBNP ($r = 0.09$, $p = 0.08$), LAVI ($r = +0.03$, $p = 0.55$), and LVMI ($r = +0.05$, $p = 0.37$). The associations of E/e′ with logNT-proBNP ($r = 0.21$, $p < 0.001$), LAVI ($r = +0.29$, $p < 0.001$) and LVMI ($r = 0.09$, $p = 0.06$) were detectable also after multiple adjustment.

Conclusions: Demographic and clinical characteristics differentially interact with exercise capacity, resting left ventricular filling index, neurohumoral activation, and left atrial and ventricular remodelling in HFpEF. Exercise intolerance in HFpEF is multi-factorial and therapeutic approaches addressing exercise capacity should therefore not only aim to improve single pathological mechanisms. Registration: ISRCTN94726526 (http://www.controlled-trials.com), Eudra-CT-number 2006-002605-31.

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1. Introduction

Heart failure is a major health problem in the community [1]. Current data indicate that nowadays, more than 50% of patients with the clinical syndrome of heart failure have a preserved left ventricular ejection fraction (HFpEF) [2–4]. In contrast to earlier reports in which HFpEF was considered to be more benign than heart failure with reduced ejection fraction (HFrEF), recent data suggest that once hospitalized, patients with HFpEF and those with HFrEF have a comparable prognosis in terms of morbidity and mortality [2–4]. Despite increasing clinical and economic relevance, no treatment has yet been shown to convincingly reduce mortality in HFpEF [5–8]. This lack of evidence may in part be founded in an incomplete understanding of the disease. There is some evidence that exercise capacity (peakVO2), left ventricular filling index (E/e′), neurohumoral activation (NT-proBNP) and parameters of left atrial and left ventricular remodelling adequately reflect disease severity and have the potential to serve as prognostic indicators in patients with HFpEF [9,10]. They are part of the diagnostic algorithm for HFpEF recommended by the ESC and they are used, alone or in combination, as clinical endpoints in HFpEF studies [11]. However, it is a matter of debate how demographic and clinical factors such as co-morbidities impact on exercise capacity, diastolic function, neurohumoral activation, and left atrial and left ventricular remodelling in HFpEF and whether these HFpEF characterizing key parameters independent of demographic and clinical factors are correlated with each other.

Therefore, on the basis of HFpEF patients included in the Aldo-DHF study, we aimed to analyse the impact of various demographic and clinical factors on peakVO2, left ventricular filling index, NT-proBNP, left atrial volume index and on left ventricular mass index. We also investigated whether these disease specific key variables were independent of demographic and clinical factors associated among each other.

2. Methods

The rationale and design of the Aldo-DHF trial have previously been described in detail [12]. Aldo-DHF (http://www.controlled-trials.com, ISRCTN94726526/Eudra-CT-number 2006-002605-31) was conducted in the context of the German Competence Network Heart Failure (FKZ 01GI0205) and is funded by the German Federal Ministry of Education and Research- Health Research (DLR Project Management (FKZ 01KG0506).

2.1. Study objectives and primary endpoints of the Aldo-DHF trial

The primary objective of Aldo-DHF was to investigate the effects of the aldosterone receptor blocker spironolactone (25 mg/day vs. placebo) on functional and clinical endpoints in patients with heart failure, a preserved ejection fraction, but echocardiographic evidence of diastolic dysfunction (i.e., diastolic heart failure/DHF), defined as HFpEF with objective evidence of diastolic dysfunction and evidence of impaired exercise capacity as measured by spiroergometry [12]. In the Aldo-DHF trial, the change in exercise capacity (peakVO2 on spiroergometry) and the change in E/e′ (ratio of peak early transmitral ventricular filling velocity to early diastolic tissue Doppler velocity) from baseline to follow-up at 12 months were chosen as co-primary endpoints.

2.2. Trial design and patients

Aldo-DHF is a multicenter, prospective, randomized, placebo-controlled, double-blind, parallel-group study, performed at 9 clinical trial sites in Germany and one trial site in Austria. Patients with symptomatic HFpEF (NYHA II/III, LVEF ≥50%) and objective evidence of diastolic dysfunction by echocardiography were recruited. Exclusion criteria (e.g. relevant anaemia, end stage renal failure or significant obstructive or restrictive pulmonary diseases) were defined to minimise confounding effects and assure recruitment of a true and homogenous heart failure population [12]. Recruitment of 420 patients (210 patients per arm) was planned for statistical analysis, and recruitment goals were reached in April 2011.

The study protocol and amendments were approved by the ethics committees and responsible institutional review boards of all participating centres as well as the Federal Institutes for Drugs and Medical Devices. All patients gave written informed consent before any study related procedure was performed. The study strictly adhered to GCP rules, and data management and monitoring, quality control, and statistical analysis was performed at the Center for Clinical Trials Leipzig, Germany.

2.3. Echocardiography

To ensure high quality and validity of echocardiographic data obtained in Aldo-DHF, two national echo coordinators acted as blinded reference centres for all aspects related to echocardiography. A final Standard Operating Procedure (SOP) for obtaining all echocardiographic parameters was provided and prior to starting recruitment, all participating echocardiographers were trained and certified by the reference centres. The protocol required that 2D and M-mode images and all calculations were in accordance with American Society of Echocardiography (ASE) guidelines [13,14]. Grading of diastolic dysfunction was done as previously described [12,15]. As previously described we noninvasively characterized the ventricular–arterial coupling index: arterial elastance index (Eal)/ventricular elastance index $E_{LV}I$ = end-systolic volume index (ESVI)/stroke volume index (SVI) [16].

2.4. Spiroergometry

The procedure of exercise testing was performed in accordance with recommendations of the European Society of Cardiology [17]. A reference laboratory acted as blinded core lab for all aspects related to cardiopulmonary exercise testing. Before starting recruitment, an SOP for spiroergometry was released by the reference laboratory and all investigators performing exercise testing were trained and certified by the core lab. Validity criteria specify that each exercise test report must be confirmed by the reference centre.

Symptom-limited cardiopulmonary exercise testing on a bicycle ergometer started at a work load of 20 Watts, followed by a stepwise 20 Watt increment every two minutes. Heart rate, ST-segment changes and arrhythmias were continuously monitored via standard 12-lead ECG. Blood pressure was recorded at rest and then every two minutes. Ventilatory exchange (VE), oxygen uptake (VO2) and other cardiopulmonary variables are acquired by averaging breath-by-breath measurements over 10 s intervals. Peak heart rate and work load were recorded immediately upon the end of exercise. PeakVO2 was prospectively defined as the maximum value of the last three 10 s averages during exercise. Ventilatory anaerobic threshold is detected using the V-Slope method [18]. Chronotropic incompetence (CI) was defined as a failure to achieve 80% of the maximum age-predicted heart rate in patients without beta-blockers and to achieve 62% of the maximum age-predicted heart rate in patients with beta-blockers [19,20].

2.5. Laboratory measurements

Blood samples were drawn after 20 min rest in lying position for analysis of laboratory parameters. Samples were immediately cooled, centrifuged and processed for storage at −80 °C. After thawing, N-terminal pro-brain-type-natriuretic-peptide (NT-proBNP) was measured with a commercially available electrochemiluminescence immunoassay on an Elecsys® Analyser (Roche Diagnostics GmbH, Mannheim, Germany).

2.6. Biometry

Data were presented as means and standard deviations or frequencies and percentages as appropriate. Comparisons between patients in NYHA classes II and III were carried out by the *t* test or Fisher's test, respectively (or Kendall's test for ordinal categories). Relationships between predefined general characteristics and peakVO2, E/e′ and NT-proBNP were examined by simple linear regression analyses for each predictor variable, and by multiple regression including all predictors at once. Relationships between peakVO2, E/e′ and NT-proBNP were assessed by Pearson's correlation coefficient and analysis of variance. Partial correlations were controlled for age, sex, coronary heart disease, hypertension, hyperlipidaemia, diabetes mellitus, cerebrovascular diasease, peripheral arterial disease, COPD, atrial fibrillation, history of depression, sleep apnoea, BMI, mean arterial pressure, pulse pressure, heart rate, chronotropic incompetence, ventricular–arterial coupling index, haemoglobin, eGFR, ACE inhibitor/angiotensin receptor blocker, betablocker, and diuretic.

Data for NT-proBNP, were described by medians and inter-quartile ranges, and were analyzed on a logarithmic scale. For the regression analyses of log NT-proBNP, results were transformed back by the exponential function, yielding effect estimates in terms of geometric mean ratios (instead of arithmetic mean differences). A two-sided $p < 0.05$ was considered statistically significant. IBM SPSS version 20 was used as statistical software.

3. Results

Between March 2007 and April 2011, $n = 422$ patients were randomised into the trial. Baseline characteristics, results of exercise testing as well as detailed echocardiographic measurements are shown in Table 1.

Compared to patients with NYHA II, patients in NYHA III were older, more obese, less frequently smoking, and more frequently had a history of hypertension and peripheral artery disease. They were more likely to have peripheral edema and suffer from nycturia, paroxysmal nocturnal dyspnea, and fatigue. Diastolic and pulse pressure were higher in NYHA

Table 1
Characteristics of the study cohort.

Variable	All patients	NYHA class II	NYHA class III	*P*-value
Number of subjects	422	363	59	
Demography				
Age [yr]	67 ± 8	66 ± 7	70 ± 8	0.001
Female sex	221 (52)	178 (49)	43 (73)	0.001
History				
Hospitalisation for heart failure during past 12 months	156 (37)	132 (36)	24 (41)	0.56
Smoking				0.03
Never smoked	223 (53)	186 (51)	37 (63)	
Former smoker	172 (41)	150 (41)	22 (37)	
Current smoker	27 (6)	27 (7)	0 (0)	
Coronary heart disease	170 (40)	144 (40)	26 (44)	0.57
Previous myocardial infarction	67 (16)	58 (16)	9 (15)	1.00
Previous coronary bypass	31 (7)	26 (7)	5 (9)	0.79
Hypertension	387 (92)	329 (91)	58 (98)	0.04
Hyperlipidaemia	273 (65)	236 (65)	37 (63)	0.77
Diabetes mellitus	70 (17)	59 (16)	11 (19)	0.71
Cerebrovascular disease	45 (11)	37 (10)	8 (14)	0.49
Peripheral arterial disease	17 (4)	11 (3)	6 (10)	0.02
COPD	14 (3)	10 (3)	4 (7)	0.12
Atrial fibrillation	22 (5)	19 (5)	3 (5)	1.00
History of depression	47 (11)	40 (11)	7 (12)	0.82
Sleep apnoea	50 (12)	43 (12)	7 (12)	1.00
Physical examination				
BMI [kg/m^2]	28.9 ± 3.6	28.7 ± 3.6	30.2 ± 3.2	0.004
RR systolic [mm Hg]	135 ± 18	135 ± 18	136 ± 21	0.62
RR diastolic [mm Hg]	79 ± 11	80 ± 11	77 ± 11	0.04
MAP [mm Hg]	98 ± 12	98 ± 12	96 ± 13	0.32
Puls pressure [mm Hg]	56 ± 15	55 ± 15	60 ± 17	0.04
Heart rate on ECG [bpm]	65 ± 13	65 ± 13	67 ± 13	0.44
Signs/symptoms				
Peripheral oedema	165 (39)	126 (35)	39 (66)	<0.001
Nocturia	338 (80)	284 (78)	54 (92)	0.02
Paroxysmal nocturnal dyspnoea	67 (16)	49 (14)	18 (31)	0.002
Nocturnal cough	61 (15)	48 (13)	13 (22)	0.11
Fatigue	249 (59)	201 (55)	48 (81)	<0.001
Laboratory				
Sodium [mmol/L]	140 ± 3	140 ± 3	141 ± 3	0.20
Potassium [mmol/L]	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	0.87
Total cholesterol [mg/dL]	195 ± 44	195 ± 45	198 ± 41	0.58
Haemoglobin [g/dL]	13.8 ± 1.2	13.9 ± 1.2	13.5 ± 1.1	0.02
eGFR [mL/min/1.73m^2]	79 ± 19	80 ± 19	73 ± 19	0.006
Uric acid [mg/dL]	6.1 ± 1.6	6.1 ± 1.6	6.2 ± 1.6	0.55
NT-proBNP [ng/L]	158 (83–299)	156 (82–311)	171 (104–286)	0.71
Spiroergometry				
Maximal workload [W]	100 ± 29	103 ± 29	80 ± 20	<0.001
Duration of exercise [s]	540 ± 176	561 ± 174	413 ± 128	<0.001
RR systolic at rest [mm Hg]	122 ± 18	121 ± 18	123 ± 19	0.50
RR systolic at maximal stress [mm Hg]	169 ± 28	170 ± 29	162 ± 25	0.04
RR diastolic at rest [mm Hg]	79 ± 12	79 ± 12	78 ± 13	0.29
RR diastolic at maximal stress [mm Hg]	85 ± 18	86 ± 17	85 ± 19	0.71
Heart rate at rest [bpm]	70 ± 13	70 ± 13	70 ± 13	0.99
Heart rate at maximal stress [bpm]	117 ± 21	118 ± 21	110 ± 18	0.004
Chronotropic incompetence	25 (6)	22 (6)	3 (5)	1.00
V_E at rest [L/min]	8.4 ± 2.4	8.4 ± 2.3	8.5 ± 2.9	0.71
V_E at maximal stress [L/min]	45.7 ± 12.9	46.5 ± 13.0	40.6 ± 11.0	0.001
Peak VO_2 [mL/min/kg]	16.4 ± 3.5	16.7 ± 3.4	14.4 ± 3.4	<0.001
Anaerobic threshold [W]	64 ± 25	66 ± 25	50 ± 19	<0.001
AT VO_2 [mL/min/kg]	11.6 ± 3.2	11.8 ± 3.2	10.4 ± 3.0	0.002
V_E/VCO_2 Slope	30.3 ± 5.2	30.1 ± 4.8	31.8 ± 7.0	0.07
Borg scale	5.4 ± 3.7	5.3 ± 3.9	6.2 ± 2.7	0.07
RQ at rest	0.84 ± 0.07	0.84 ± 0.08	0.85 ± 0.07	0.43
RQ_{max}	1.11 ± 0.12	1.11 ± 0.12	1.11 ± 0.12	0.95
RQ_{max} post	1.38 ± 0.19	1.38 ± 0.19	1.34 ± 0.16	0.12
Six-minute walk test				
Walk distance [m]	530 ± 87	544 ± 73	442 ± 113	<0.001
Terminated before 6 min	8 (2)	2 (1)	6 (10)	<0.001
Borg scale	3.1 ± 1.8	2.9 ± 1.6	4.3 ± 1.9	<0.001
Echocardiography				

Table 1 (*continued*)

Variable	All patients	NYHA class II	NYHA class III	*P*-value
LVEF [%]	67 ± 8	67 ± 8	69 ± 8	0.18
LVD_{ED} diameter (ED) [mm]	46.5 ± 6.2	46.8 ± 6.2	45.1 ± 6.2	0.06
LVD_{ES} diameter (ED) [mm]	25.5 ± 6.4	25.7 ± 6.6	24.3 ± 5.6	0.12
Ventricular-arterial coupling index	0.50 ± 0.17	0.51 ± 0.17	0.47 ± 0.16	0.15
IV septum thickness [mm]	12.2 ± 1.8	12.2 ± 1.9	12.2 ± 1.6	0.96
Posterior wall thickness [mm]	11.5 ± 1.5	11.5 ± 1.5	11.6 ± 1.9	0.57
LV mass index [g/m^2]				
Men	117 ± 31	118 ± 32	110 ± 23	0.22
Women	101 ± 23	100 ± 21	105 ± 27	0.32
LA_{ES} [mm]	44.2 ± 5.7	44.1 ± 5.7	44.9 ± 5.7	0.35
LAVI [mL/m^2]	28.0 ± 8.4	27.8 ± 8.2	29.2 ± 9.7	0.32
E velocity [cm/s]	73 ± 19	73 ± 19	74 ± 20	0.67
A velocity [cm/s]	83 ± 18	82 ± 18	85 ± 18	0.40
E/A	0.91 ± 0.33	0.91 ± 0.32	0.91 ± 0.37	0.99
A duration [ms]	154 ± 32	153 ± 31	158 ± 38	0.42
IVRT [ms]	89 ± 26	88 ± 25	91 ± 28	0.42
Deceleration time [ms]	243 ± 63	242 ± 63	247 ± 59	0.61
Medial e′ velocity [cm/s]	5.9 ± 1.3	5.9 ± 1.4	5.9 ± 1.1	0.88
Medial a′ velocity [cm/s]	9.3 ± 1.8	9.3 ± 1.8	9.2 ± 2.1	0.86
E/e′ (medial)	12.8 ± 4.0	12.8 ± 4.2	12.7 ± 3.0	0.82
PVF systolic [cm/s]	58 ± 12	58 ± 12	58 ± 14	0.82
PVF diastolic [cm/s]	46 ± 14	46 ± 14	47 ± 15	0.79
PVA velocity [cm/s]	33 ± 11	33 ± 11	33 ± 8	0.94
PVA duration [ms]	125 ± 30	125 ± 30	125 ± 30	0.97
Flow propagation time [cm/s]	31 ± 9	31 ± 9	32 ± 11	0.50
Grade of diastolic dysfunction				0.42
I	307 (77)	262 (76)	45 (80)	
II	86 (21)	75 (22)	11 (20)	
III	4 (1)	4 (1)	0 (0)	
IV	3 (1)	3 (1)	0 (0)	
n.d. for atrial fibrillation	22	19	3	
Current medication				
ACEI/ARB	325 (77)	277 (76)	48 (81)	0.51
Betablocker	302 (72)	256 (71)	46 (78)	0.29
Diuretic	227 (54)	186 (51)	41 (70)	0.01
Calcium antagonist	105 (25)	79 (22)	26 (44)	0.001
Anti-platelet agent	221 (52)	188 (52)	33 (56)	0.58
Anticoagulant	58 (14)	48 (13)	10 (17)	0.42
Lipid lowering drug	230 (55)	196 (54)	34 (58)	0.67
Allopurinol	40 (10)	32 (9)	8 (14)	0.24
Antidepressant	30 (7)	22 (6)	8 (14)	0.05
Quality of life				
Responded to questionnaire	388 (92)	334 (92)	54 (92)	0.80
SF-36Physical Functioning scale	63 ± 22	66 ± 21	42 ± 20	<0.001
Symptoms of depression(PHQ-9 sum score)	5.6 ± 4.1	5.3 ± 4.0	7.4 ± 4.1	<0.001

Data are mean ± SD or frequency (percentage), and exceptionally median (IQR) for NTproBNP.
P-values for comparison of NYHA classes II and III from *t*-test (quantities), Fisher's exact test (frequencies), or test for Kendall's tau-b (ordinal variables).

III patients, and laboratory results revealed lower haemoglobin levels as well as worse renal function in the more symptomatic subgroup. We further observed substantial differences in exercise parameters (spiroergometry and six-minute-walk-testing) between the two groups: maximal and submaximal exercise capacity was worse in NYHA III patients and this reduction was accompanied by lower peak heart rate, peak systolic blood pressure, and worse ventilation at peak exercise. They also performed worse in the six-minute-walk test and subjectively felt more exhausted, as measured on the Borg scale. Echocardiographic parameters did not differ between NYHA II and NYHA III patients. Overall, mean LVEF was normal (67 ± 8%) and diastolic dysfunction was present in all patients with sinus rhythm, as per study protocol. The majority of patients were treated with ACEI/ARBs, beta-blockers and diuretics. More than 50% received anti-platelet agents and lipid lowering drugs. Compared to NYHA II, patients with NYHA III were more frequently treated with diuretics, calcium channel antagonists and antidepressants, though prevalence of diagnosed depression did not differ between groups.

3.1. Association of peakVO2 with demographic and clinical characteristics

As shown in Table 2, in unadjusted (simple) regression analyses a lower peakVO2 was significantly related to higher age, female gender, hypertension, diabetes mellitus, atrial fibrillation, and sleep apnoea. Also higher BMI, higher pulse pressure values, disturbed ventricular vascular coupling, lower haemoglobin levels, beta-blocker and diuretics intake were significantly related to lower peakVO2 values. In multiple adjusted regression analyses only higher age, female gender, coronary artery disease, sleep apnoea, chronotropic incompetence, and higher BMI remained significantly related to lower peakVO2 values. The association of peakVO2 with hypertension ($p = 0.06$), diabetes mellitus ($p = 0.05$), and lower heart rate ($p = 0.05$) was still detectable, albeit at borderline statistical significance.

3.2. Association of E/e′ with demographic and clinical characteristics

In unadjusted regression analyses, higher E/e′ values were significantly related to higher age, female gender and to a presence of

Table 2
Cross-sectional relationships of peakVO2 with general characteristics.

Variable	Associated difference in peakVO2 (spiroergometry)			
	Unadjusted (simple regression)		Adjusted (multiple regression)	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Age (per +10 years)	−0.93 (−1.36 to −0.50)	<0.001	−0.90 (−1.33 to −0.48)	<0.001
Female sex	−2.20 (−2.83 to −1.56)	<0.001	−2.47 (−3.14 to −1.80)	<0.001
Coronary heart disease	−0.67 (−1.35 to +0.01)	0.05	−1.13 (−1.83 to −0.43)	0.002
Hypertension	−1.72 (−2.92 to −0.52)	0.005	−1.12 (−2.28 to +0.04)	0.06
Hyperlipidaemia	−0.25 (−0.95 to +0.45)	0.48	+0.21 (−0.47 to +0.89)	0.54
Diabetes mellitus	−1.38 (−2.27 to −0.49)	0.002	−0.79 (−1.59 to 0.00)	0.05
Cerebrovascular disease	+0.50 (−0.58 to 1.58)	0.36	+0.46 (−0.46 to +1.37)	0.33
Peripheral arterial disease	−0.39 (−2.09 to +1.31)	0.65	−0.32 (−1.75 to +1.11)	0.66
COPD	−0.23 (−2.10 to +1.63)	0.81	+0.44 (−1.19 to +2.06)	0.60
Atrial fibrillation	−1.72 (−3.22 to −0.23)	0.02	−0.62 (−2.00 to +0.77)	0.38
History of depression	+0.05 (−1.01 to +1.12)	0.92	−0.29 (−1.20 to +0.62)	0.53
Sleep apnoea	−1.22 (−2.25 to −0.19)	0.02	−1.10 (−1.99 to −0.21)	0.02
BMI (per +5 kg/m^2)	−1.60 (−2.04 to −1.15)	<0.001	−1.58 (−2.01 to −1.16)	<0.001
Mean arterial pressure (per +10 mm Hg)	+0.15 (−0.13 to +0.44)	0.30	−0.10 (−0.38 to +0.18)	0.49
Pulse pressure (per +10 mm Hg)	−0.24 (−0.45 to −0.02)	0.03	−0.10 (−0.32 to +0.12)	0.38
Heart rate on ECG (per +10 bpm)	−0.25 (−0.51 to +0.01)	0.06	−0.25 (−0.49 to 0.00)	0.05
Chronotropic incompetence	−1.42 (−2.83 to −0.01)	0.05	−1.92 (−3.14 to −0.70)	0.002
Ventricular-vascular coupling index (per +0.05)	+0.13 (+0.03 to +0.23)	0.009	+0.04 (−0.04 to +0.13)	0.29
Haemoglobin (per +1 g/dL)	+0.59 (+0.33 to +0.86)	<0.001	+0.19 (−0.08 to +0.46)	0.16
eGFR (per +10 mL/min/1.73m^2)	+0.18 (0.00 to +0.36)	0.05	−0.09 (−0.25 to +0.07)	0.29
ACE inhibitor/angiotensin receptor blocker	−0.80 (−1.59 to −0.01)	0.05	+0.50 (−0.30 to +1.30)	0.22
Betablocker	−1.19 (−1.92 to −0.46)	0.001	−0.60 (−1.30 to +0.10)	0.10
Diuretic	−1.41 (−2.06 to −0.75)	<0.001	−0.17 (−0.80 to +0.46)	0.59

hypertension or diabetes mellitus (Table 3). Also higher pulse pressure values, lower resting heart rates, chronotropic incompetence, lower haemoglobin levels, impaired renal function and the intake of ACE inhibitors, beta-blockers or diuretics were significantly related to higher E/e′ values. Higher BMI was only by trend ($p = 0.09$) associated with higher E/e′. In multiple adjusted regression analyses only higher age, female gender, higher pulse pressure values as well as a lower resting heart rate, chronotropic incompetence, and beta-blocker intake remained significantly related to higher E/e′ values.

3.3. Association of NT-proBNP with demographic and clinical characteristics

As shown in Table 4, in simple regression analyses higher NT-proBNP values were significantly related to higher age, coronary artery disease, and to a presence of atrial fibrillation. Lower BMI, lower haemoglobin levels and impaired renal function, higher pulse pressure values, the intake of beta-blockers and also of diuretics were significantly related to higher NT-proBNP levels. A trend was seen for the association to sleep apnoea ($p = 0.05$), hypertension ($p = 0.08$) and cerebrovascular

Table 3
Cross-sectional relationships of E/e′ with general characteristics.

Variable	Associated difference in E/e′ (echocardiography)			
	Unadjusted (simple regression)		Adjusted (multiple regression)	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Age (per +10 years)	+1.05 (+0.55 to +1.55)	<0.001	+0.73 (+0.18 to +1.28)	0.009
Female sex	+1.23 (+0.47 to +2.00)	0.002	+1.18 (+0.30 to +2.05)	0.008
Coronary heart disease	+0.45 (−0.33 to +1.24)	0.26	−0.11 (−1.02 to +0.80)	0.81
Hypertension	+1.83 (+0.44 to +3.21)	0.01	+0.37 (−1.15 to +1.88)	0.64
Hyperlipidaemia	+0.66 (−0.15 to +1.46)	0.11	+0.18 (−0.70 to +1.07)	0.69
Diabetes mellitus	+1.18 (+0.15 to +2.21)	0.03	+0.81 (−0.23 to +1.84)	0.13
Cerebrovascular disease	+0.83 (−0.42 to +2.08)	0.19	+0.82 (−0.38 to +2.01)	0.18
Peripheral arterial disease	+0.21 (−1.75 to +2.17)	0.84	+0.59 (−1.27 to +2.46)	0.53
COPD	+0.43 (−1.73 to +2.58)	0.70	+0.03 (−2.09 to +2.14)	0.98
Atrial fibrillation	+0.31 (−1.43 to +2.04)	0.73	+0.68 (−1.12 to +2.49)	0.46
History of depression	+0.26 (−0.96 to +1.49)	0.67	+0.44 (−0.74 to +1.63)	0.47
Sleep apnoea	−0.56 (−1.75 to +0.63)	0.36	−0.32 (−1.48 to +0.84)	0.59
BMI (per +5 kg/m^2)	+0.47 (−0.07 to +1.01)	0.09	+0.45 (−0.10 to +1.00)	0.11
Mean arterial pressure (per +10 mm Hg)	−0.15 (−0.48 to +0.18)	0.38	−0.01 (−0.38 to +0.36)	0.97
Pulse pressure (per +10 mm Hg)	+0.47 (+0.22 to +0.72)	<0.001	+0.30 (+0.01 to +0.59)	0.04
Heart rate on ECG (per +10 bpm)	−0.47 (−0.77 to −0.17)	0.002	−0.36 (−0.68 to −0.04)	0.03
Chronotropic incompetence	+1.93 (+0.31 to +3.56)	0.02	+1.74 (+0.15 to +3.33)	0.03
Ventricular-arterial coupling index (per +0.05)	−0.03 (−0.14 to +0.09)	0.65	0.00 (−0.11 to +0.11)	1.00
Haemoglobin (per +1 g/dL)	−0.45 (−0.76 to −0.14)	0.005	−0.09 (−0.45 to +0.26)	0.60
eGFR (per +10 mL/min/1.73m^2)	−0.24 (−0.44 to −0.03)	0.02	−0.02 (−0.23 to +0.20)	0.89
ACE inhibitor/angiotensin receptor blocker	+1.05 (+0.14 to +1.96)	0.02	+0.14 (−0.90 to +1.18)	0.79
Betablocker	+2.28 (+1.45 to +3.10)	<0.001	+1.59 (+0.67 to +2.50)	0.001
Diuretic	+1.50 (+0.74 to +2.26)	<0.001	+0.44 (−0.38 to +1.27)	0.29

Table 4
Cross-sectional relationships of NT-proBNP with general characteristics.

Variable	Associated ratio in NT-proBNP			
	Unadjusted (simple regression)		Adjusted (multiple regression)	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Age (per +10 years)	×1.63 (1.45 to 1.85)	<0.001	×1.31 (1.16 to 1.49)	<0.001
Female sex	×1.10 (0.90 to 1.34)	0.36	×0.89 (0.73 to 1.08)	0.24
Coronary heart disease	×1.29 (1.05 to 1.58)	0.02	×1.18 (0.96 to 1.45)	0.12
Hypertension	×1.37 (0.96 to 1.97)	0.08	×1.01 (0.73 to 1.42)	0.93
Hyperlipidaemia	×1.02 (0.82 to 1.26)	0.87	×0.94 (0.77 to 1.14)	0.53
Diabetes mellitus	×0.80 (0.62 to 1.05)	0.11	×0.81 (0.65 to 1.02)	0.07
Cerebrovascular disease	×1.34 (0.97 to 1.85)	0.08	×1.15 (0.88 to 1.49)	0.31
Peripheral arterial disease	×1.03 (0.61 to 1.85)	0.91	×1.03 (0.67 to 1.58)	0.89
COPD	×0.78 (0.44 to 1.37)	0.38	×0.74 (0.46 to 1.19)	0.21
Atrial fibrillation	×6.04 (3.90 to 9.37)	<0.001	×5.87 (3.89 to 8.90)	<0.001
History of depression	×0.79 (0.58 to 1.08)	0.14	×0.90 (0.70 to 1.17)	0.43
Sleep apnoea	×0.74 (0.54 to 1.00)	0.05	×0.78 (0.60 to 1.01)	0.06
BMI (per +5 kg/m^2)	×0.83 (0.72 to 0.96)	0.01	×0.87 (0.77 to 0.98)	0.03
Mean arterial pressure (per +10 mm Hg)	×0.96 (0.88 to 1.04)	0.30	×1.03 (0.95 to 1.12)	0.42
Pulse pressure (per +10 mm Hg)	×1.07 (1.00 to 1.14)	0.04	×1.02 (0.96 to 1.09)	0.53
Heart rate on ECG (per +10 bpm)	×0.94 (0.87 to 1.02)	0.16	×0.93 (0.87 to 1.00)	0.05
Chronotropic incompetence	×1.43 (0.94 to 2.18)	0.10	×1.51 (1.06 to 2.14)	0.02
Ventricular-arterial coupling index (per +0.05)	×1.00 (0.97 to 1.03)	0.93	×1.01 (0.99 to 1.03)	0.43
Haemoglobin (per +1 g/dL)	×0.83 (0.77 to 0.90)	<0.001	×0.85 (0.79 to 0.92)	<0.001
eGFR (per +10 mL/min/1.73m^2)	×0.89 (0.85 to 0.94)	<0.001	×0.95 (0.91 to 1.00)	0.05
ACE inhibitor/angiotensin receptor blocker	×1.11 (0.88 to 1.41)	0.39	×0.92 (0.73 to 1.15)	0.46
Betablocker	×2.03 (1.64 to 2.50)	<0.001	×1.65 (1.35 to 2.02)	<0.001
Diuretic	×1.34 (1.10 to 1.64)	0.004	×1.20 (1.00 to 1.44)	0.05

diseases ($p = 0.08$). In multiple regression analyses higher age, the presence of atrial fibrillation, lower resting heart rate ($p = 0.05$), chronotropic incompetence, lower BMI, lower haemoglobin levels and, by trend, an impaired renal function ($p = 0.05$) as well as beta-blocker and diuretics intake ($p = 0.05$) remained significantly related to higher NT-proBNP levels.

3.4. Association of LAVI with demographic and clinical characteristics

As shown in Table 5, in simple regression analyses higher values of LAVI were significantly related to higher age, female gender, hypertension, atrial fibrillation, pulse pressure, and to the intake of ACE inhibitors/angiotensin receptor blockers, beta-blockers as well as of diuretics. A trend was seen for the association to the mean arterial pressure ($p = 0.06$), and peripheral arterial disease ($p = 0.08$). In multiple regression analyses higher age, female gender, the presence of atrial fibrillation, lower resting heart rate, higher mean arterial pressure, lower haemoglobin levels as well as the intake of ACE inhibitors/angiotensin receptor blockers, and beta-blockers were related to higher LAVI values.

3.5. Association of LVMI with demographic and clinical characteristics

As shown in Table 6, in simple regression analyses higher values of LVMI were significantly related to higher age, female gender, cerebrovascular disease, higher pulse pressure, lower resting heart rate,

Table 5
Cross-sectional relationships of left atrial volume index with general characteristics.

Variable	Associated difference in left atrial volume index			
	Unadjusted (simple regression)		Adjusted (multiple regression)	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Age (per +10 years)	+2.40 (+1.37 to +3.44)	<0.001	+1.58 (+0.53 to +2.63)	0.003
Female sex	−2.88 (−4.47 to −1.29)	<0.001	−3.49 (−5.18 to −1.80)	<0.001
Coronary heart disease	+1.25 (−0.39 to +2.89)	0.14	−0.17 (−1.94 to +1.59)	0.85
Hypertension	+3.05 (+0.14 to +5.95)	0.04	−0.53 (−3.45 to +2.39)	0.72
Hyperlipidaemia	−0.20 (−1.89 to +1.49)	0.82	−0.76 (−2.47 to +0.94)	0.38
Diabetes mellitus	−0.34 (−2.50 to +1.83)	0.76	−0.83 (−2.82 to +1.16)	0.41
Cerebrovascular disease	+0.91 (−1.69 to +3.52)	0.49	−0.06 (−2.36 to +2.24)	0.96
Peripheral arterial disease	+3.65 (−0.43 to +7.73)	0.08	+3.07 (−0.51 to +6.65)	0.09
COPD	+1.45 (−3.04 to +5.95)	0.53	+2.58 (−1.50 to +6.65)	0.22
Atrial fibrillation	+13.48 (+10.10 to +16.86)	<0.001	+15.02 (+11.56 to +18.49)	<0.001
History of depression	+0.37 (−2.21 to +2.96)	0.78	+0.77 (−1.53 to +3.07)	0.51
Sleep apnoea	+1.71 (−0.77 to +4.20)	0.18	+1.24 (−0.99 to +3.46)	0.28
BMI (per +5 kg/m^2)	−0.06 (−1.19 to +1.07)	0.92	−0.63 (−1.69 to +0.43)	0.25
Mean arterial pressure (per +10 mm Hg)	+0.66 (−0.03 to +1.34)	0.06	+0.83 (+0.12 to +1.54)	0.02
Pulse pressure (per +10 mm Hg)	+0.76 (+0.24 to +1.28)	0.004	+0.42 (−0.14 to +0.97)	0.14
Heart rate on ECG (per +10 bpm)	−0.50 (−1.12 to +0.13)	0.12	−1.05 (−1.66 to −0.44)	0.001
Chronotropic incompetence	+2.33 (−1.08 to +5.73)	0.18	+2.13 (−0.92 to +5.19)	0.17
Ventricular-arterial coupling index (per +0.05)	+0.16 (−0.07 to +0.40)	0.18	+0.11 (−0.09 to + 0.32)	0.28
Haemoglobin (per +1 g/dL)	−0.33 (−0.99 to +0.32)	0.32	−0.96 (−1.63 to −0.28)	0.006
eGFR (per +10 mL/min/1.73m^2)	+0.02 (−0.41 to +0.46)	0.91	+0.32 (−0.09 to +0.73)	0.12
ACE inhibitor/angiotensin receptor blocker	+2.58 (+0.68 to +4.49)	0.008	+2.14 (+0.12 to +4.16)	0.04
Betablocker	+3.38 (+1.62 to +5.14)	<0.001	+2.20 (+0.44 to +3.97)	0.01
Diuretic	+2.11 (+0.50 to +3.71)	0.01	+1.35 (−0.24 to +2.94)	0.10

Table 6
Cross-sectional relationships of left ventricular mass index with general characteristics.

Variable	Associated difference in left ventricular mass index			
	Unadjusted (simple regression)		Adjusted (multiple regression)	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Age (per +10 years)	+3.93 (+0.42 to +7.44)	0.03	+4.48 (+0.69 to +8.28)	0.02
Female sex	−16.20 (−21.34 to −11.06)	<0.001	−16.44 (−22.47 to −10.41)	<0.001
Coronary heart disease	+2.41 (−3.06 to +7.87)	0.79	−7.04 (−13.37 to −0.71)	0.03
Hypertension	+5.37 (−4.34 to +15.07)	0.28	−1.74 (−12.18 to +8.71)	0.75
Hyperlipidaemia	+3.44 (−2.16 to +9.04)	0.23	+4.08 (−2.04 to +10.20)	0.19
Diabetes mellitus	+1.96 (−5.24 to +9.16)	0.59	−0.12 (−7.26 to +7.02)	0.97
Cerebrovascular disease	−9.56 (−18.19 to −0.93)	0.03	−10.83 (−19.09 to −2.58)	0.01
Peripheral arterial disease	+7.89 (−6.11 to +21.90)	0.27	+7.76 (−5.41 to +20.94)	0.25
COPD	−8.89 (−23.82 to +6.05)	0.24	−9.99 (−24.57 to +4.60)	0.18
Atrial fibrillation	−0.25 (−12.57 to +12.07)	0.97	+6.79 (−5.80 to +19.39)	0.29
History of depression	+2.58 (−5.93 to +11.10)	0.55	+4.86 (−3.32 to +13.03)	0.24
Sleep apnoea	−0.11 (−8.40 to +8.18)	0.98	−1.67 (−9.70 to +6.35)	0.68
BMI (per +5 kg/m^2)	+1.26 (−2.48 to +5.01)	0.51	+0.14 (−3.66 to +3.93)	0.94
Mean arterial pressure (per +10 mm Hg)	+1.83 (−0.45 to +4.11)	0.12	−0.06 (−2.61 to +2.49)	0.96
Pulse pressure (per +10 mm Hg)	+3.67 (+1.95 to +5.39)	<0.001	+2.83 (+0.85 to +4.81)	0.005
Heart rate on ECG (per +10 bpm)	−4.13 (−6.25 to −2.00)	<0.001	−3.19 (−5.43 to −0.95)	0.005
Chronotropic incompetence	+9.51 (−1.81 to +20.82)	0.10	+5.82 (−5.13 to +16.77)	0.30
Ventricular-arterial coupling index (per +0.05)	+0.54 (−0.24 to +1.32)	0.18	+0.22 (−0.52 to + 0.97)	0.56
Haemoglobin (per +1 g/dL)	+2.85 (+0.67 to +5.02)	0.01	+0.16 (−2.27 to +2.59)	0.90
eGFR (per +10 mL/min/1.73m^2)	+1.30 (−0.13 to +2.73)	0.08	+1.31 (−0.15 to +2.76)	0.08
ACE inhibitor/angiotensin receptor blocker	+4.79 (−1.57 to +11.14)	0.14	+1.73 (−5.45 to +8.91)	0.64
Betablocker	+4.63 (−1.31 to +10.57)	0.13	+2.07 (−4.25 to +8.38)	0.52
Diuretic	+4.14 (−1.23 to +9.50)	0.13	+4.72 (−0.96 to +10.39)	0.10

and lower haemoglobin levels. In multiple regression analyses higher age, female gender, cerebrovascular disease, higher pulse pressure, and lower resting heart rate, remained to be related to higher LVMI values.

3.6. Interrelation of peakVO2, E/e′, NT-proBNP, LAVI, and LVMI

Table 7 is shown the unadjusted (bivariate) as well as the adjusted (partial) correlations of peakVO2, E/e′, NT-proBNP, LAVI, and LVMI among each other. In bivariate correlation analyses peakVO2 was significantly associated with E/e′ and $\log_{10}$ NT-proBNP, but not with LAVI and LVMI. Unadjusted, E/e′ was significantly related to all other parameters. After multiple adjustment also the association of peakVO2 with E/e′ and $\log_{10}$ NT-proBNP lost their significance. After multiple adjustment the association of E/e′ with $\log_{10}$ NT-proBNP, LAVI, and LVMI (by trend) and also the association of LAVI and LVMI remained to be significant.

4. Discussion

Aldo-DHF is the first large randomised, controlled HFpEF trial with rigorous inclusion criteria for cardiac remodelling/diastolic dysfunction, and comprehensive phenotyping of all patients. Here, we report baseline data from the $n = 422$ patients recruited into the trial and analyzed the association of demographic and clinical variables with parameters of exercise capacity (peakVO2), parameters of diastolic dysfunction (E/e′), neurohumoral activation (NT-proBNP) as well as left atrial and left ventricular remodelling (LAVI/LVMI). Our study has the following main findings:

1) Age is the only factor that negatively impacted on all parameters: peakVO2, E/e′, NT-proBNP, LAVI, and LVMI.
2) Besides older age and female gender, isolated co-morbidities and chronotropic incompetence negatively impacted on peakVO2 whereas higher pulse pressure values, lower resting heart rates, chronotropic incompetence and beta-blocker treatment were associated with an impaired resting diastolic function.
3) Higher BMI was associated with lower levels of NT-proBNP. Besides higher age, presence of atrial fibrillation, chronotropic incompetence, lower haemoglobin levels, diuretic, and beta-blocker treatment were also independently related to higher NT-proBNP levels.
4) Albeit significant, unadjusted correlations between peakVO2, E/e′ and NT-proBNP were at best moderate and LAVI and LVMI were not related to exercise capacity. After multiple adjustment also the associations of peakVO2 with E/e′ and NT-proBNP lost their significance.

4.1. Population studied

We included 422 patients with symptoms of heart failure, preserved ejection fraction and echocardiographically proven diastolic dysfunction.

Table 7
Bivariate (above diagonal) and partial (below diagonal) correlations of the endpoints.

	PeakVO2	E/e′	Log_{10} NT-proBNP	LAVI	LVMI
	Pearson's correlation coefficient (*P*-value)				
PeakVO2	–	−0.16 (0.001)	−0.16 (0.001)	−0.02 (0.66)	+0.08 (0.09)
E/e′	+0.01 (0.87)	–	+0.31 (<0.001)	+0.31 (<0.001)	+0.12 (0.02)
Log_{10} NTproBNP	−0.09 (0.08)	+0.21 (<0.001)	–	+0.43 (<0.001)	+0.11 (0.03)
LAVI	+0.03 (0.55)	+0.29 (<0.001)	+0.24 (<0.001)	–	+0.29 (<0.001)
LVMI	+0.05 (0.37)	+0.09 (0.06)	+0.07 (0.18)	+0.20 (<0.001)	–
	Partial correlation coefficient (*P*-value)				

Partial correlations were controlled for age, sex, coronary heart disease, hypertension, hyperlipidaemia, diabetes mellitus, cerebrovascular diasease, peripheral arterial disease, COPD, atrial fibrillation, history of depression, sleep apnoea, BMI, mean arterial pressure, pulse pressure, heart rate, chronotropic incompetence, ventricular-arterial coupling index, haemoglobin, eGFR, ACE inhibitor/angiotensin receptor blocker, betablocker, diuretic.

Our study population resembles patients with HFpEF in epidemiological studies, which are predominantly female, of older age and with numerous co-morbidities [6–8,10,15,21,22]. As a consequence of the complex study design also addressing safety aspects some co-morbidities (e.g. diabetes mellitus, atrial fibrillation) were underrepresented in the Aldo-DHF trial. However, when compared to prior large interventional trials, patients were of similar age (CHARM-Preserved) or younger (I-PRESERVE) and, as shown by the distribution of NYHA functional class and NT-pro BNP levels in our cohort, rather representative of an out-patient, clinically stable HFpEF cohort [15,23]. The vigorous in- and exclusion criteria (e.g. anaemia, severe renal dysfunction and pulmonary disorders) also for safety aspects and the need for repeated spiroergometric measurements may have refrained older, more co-morbid and sicker patients from participating in Aldo-DHF. However, advanced HFpEF in elderly patients is associated with a high rate of non-cardiac death [24]. Therefore, interventions targeted to the cardiovascular system in symptomatic HFpEF may be more effective in earlier stages of the disease and at a younger age range [15,25].

4.2. Role of diastolic dysfunction

In Aldo-DHF all patients underwent detailed echocardiography including comprehensive evaluation of diastolic function according to current diagnostic guidelines [11]. This is a major step forward in comparison to previous and ongoing interventional studies, where a significant number of patients do not have diastolic dysfunction which is believed to be causative in HFpEF [26,27]. Nevertheless, it has not been examined up to now, whether a more specific definition of patients beyond their clinical presentation and confirming a normal or preserved left ventricular ejection fraction is really superior and improves the "correct" identification of patients with HFpEF [11,28].

4.3. Impacting factors on exercise capacity

In our study, older age, female gender, presence of CAD, higher BMI, sleep apnoea and chronotropic incompetence remained significant predictors of impaired exercise capacity after multivariate adjustment. These results underline the crucial role of ageing with the incremental impact of co-morbidities as a major determinant in HFpEF patients [29]. Hypertension and diabetes mellitus only tended to be independently related to peakVO2 in our cohort. This is complementary to reports investigating exercise performance in patients with diastolic dysfunction and suggests that there are similarities in exercise limiting factors between diastolic dysfunction and HFpEF [30]. It has recently been shown that in HFpEF comorbidities relevantly impact symptoms and prognosis [24,31]. The lack of an independent effect of hypertension and diabetes in our study may be explained by the high prevalence of hypertension and the relatively small number of patients with diabetes [30]. Chronotropic incompetence was, albeit less frequent in our cohort, also strongly related to exercise capacity. Because there is evidence that chronotropic incompetence negatively interfere also with prognosis, this important subgroup of patients need to be identified and treated in a more specialized manner [23].

4.4. Impacting factors on resting left ventricular filling index

E/e′ is an accepted continuous marker of progressive diastolic dysfunction, an indicator of left-ventricular end-diastolic pressure and hence recommended for diagnosing HFpEF, either alone or in conjunction with other parameters [11,32,33]. Moreover, E/e′ provides prognostic information in patients at risk for and with HFpEF [9,34]. However, there is only limited evidence regarding the independent interference of demographic and clinical factors with E/e′ in HFpEF. In our study, higher age, female gender, pulse pressure, lower resting heart rates, chronotropic incompetence and beta-blocker therapy were independent of other factors associated with higher E/e′ values. These results further substantiate recent data showing that the presence of chronotropic incompetence further increases morbidity in patients with HFpEF [35]. In addition, in the ELANDD trial, heart rate reduction due to nebivolol resulted in a decrease of exercise capacity in patients with HFpEF [36]. However, our patients did not suffer from increased heart rates, therefore the negative association also between resting heart rates, beta-blocker treatment and resting left ventricular filling index might be of limited generalizability. Furthermore, data from SENIORS suggest a prognostic benefit due to beta-blockers also in HFpEF [37]. Therefore, the role of heart rate and the effects of changes of heart rate also on diastolic function need to be more comprehensively addressed in future studies.

4.5. Impacting factors on neurohumoral activation

NT-proBNP values of patients included into the Aldo-DHF trial were lower than reported in I-PRESERVE [38]. However, compared to I-PRESERVE our patients were younger, had to a large extent a preserved renal function and were found to be in lower NYHA classes. Furthermore, in Aldo-DHF only 5% of patients presented with atrial fibrillation (26% in I-PRESERVE) and no one with pulmonary congestion (39% in I-PRESERVE). In line with data from I-PRESERVE, we found a large number of bivariate associations of demographic and clinical variables with NT-proBNP. In addition, we found that atrial fibrillation, lower eGFR, lower BMI and lower haemoglobin levels were associated with higher NT-proBNP values and were able to confirm that lower heart rate and beta-blocker intake were also independently related to higher NT-proBNP values in our sample of predominantly NYHA II HFpEF patients. This, again, strengthens the hypothesis that lower heart rates are not automatically beneficial and consequently heart rate reduction in HFpEF, at least in patients with adequately controlled heart rates as in our cohort, will not necessarily result in a clinical improvement [36,38]. The role of NT-proBNP in HFpEF is probably less prominent than in HFrEF and newer cardiac markers (e. g., MR-proADM, GDF-15) may play a more important role [39,40].

4.6. Association of maximal exercise capacity, resting left ventricular filling index, neurohumoral activation and left atrial and left ventricular remodeling

Whether peakVO2, E/e′, NT-proBNP, LAVI, and LVMI are correlated among each other in patients with HFpEF has not been investigated so far. We found that, albeit significant, bivariate associations among parameters were moderate. Key parameters of LA and LV remodelling were related to E/e′ and NT-proBNP. Of particular interest, the unadjusted association of maximal exercise capacity with resting E/e′ and NT-proBNP was explained by variables included into multivariate model, the significance was lost after controlling for co-variates. The finding that resting diastolic function as well as neurohumoral activation was not independently linked to exercise capacity strongly supports the concept of symptomatic HFpEF as a multicausative disease. It is known that independent of age and gender, peakVO2 is reduced in HFpEF [10,15,41-43]. However, there is only little evidence regarding the association of maximal exercise capacity with diastolic function and no evidence regarding the impact of neurohumoral activation on maximal exercise capacity in HFpEF. Guazzi et al. demonstrated that severity of diastolic dysfunction reflects the decrease in exercise capacity in HFpEF [44]. In an interventional study in HFpEF we were able to show that an improvement in exercise capacity was associated with an improvement in diastolic function whereas NT-proBNP levels remained unchanged [15]. In contrast, our data suggest that physical limitation in HFpEF cannot easily be explained by resting diastolic function or measurable neurohumoral activation. Exercise intolerance in HFpEF is multi-factorial and therapeutic approaches addressing exercise capacity should therefore not only aim to improve single pathological mechanisms. Our data further suggest that besides parameters recommended in current diagnostic guidelines, demographic and other clinical variables must be carefully considered for correct diagnosing of HFpEF patients [11,45].

4.7. Strengths and limitations

Thus far, Aldo-DHF is the largest prospective randomised multicentre trial with HFpEF patients and echocardiographically proven diastolic dysfunction. The standardized evaluation of exercise capacity by a core-lab-certified study centres in all patients is another advantage. The geographic distribution of study sites (only Germany and Austria) with only Caucasians included might limit the possibility to transfer study results to other ethnicities and countries.

We predominantly included NYHA II patients and due to design aspects some co-morbidities such as diabetes mellitus and atrial fibrillation were underrepresented wherefore our results cannot easily extrapolated to older, more co-morbid and clinically more affected patients with HFpEF. Additionally, the need for bicycle exercise testing may have refrained a relevant number of patients with a general inability for maximal exercise testing (e.g. for orthopedic reasons) from participation in the Aldo-DHF trial which reduces the generalizability of our findings. Diastolic function was investigated only using the surrogate measure left ventricular filling index and only under resting conditions. Exercise measurements of diastolic function might have had more explanatory power in this ambulatory and clinically stable patient cohort since diastolic LV stiffness and the rise in LV filling pressures during exercise are known to contribute to the reduction in tolerance in patients with HFpEF [46]. Furthermore, E/e′ as a single surrogate measure of diastolic function does not adequately reflect left ventricular end diastolic volume. Furthermore, other factors with known potential to influence exercise capacity or diastolic function such as endothelial function were not investigated in the present study.

4.8. Clinical implications

Multiple factors affect exercise capacity in HFpEF and the reduced exercise capacity can only be partly explained by changes e. g. in resting diastolic function or measures of LV remodelling and neurohormonal activation. Co-morbidities, which have been shown to affect functional status in HFpEF to a larger degree than in HFrEF, need to be more thoroughly and systematically investigated when considering the diagnosis HFpEF [31]. Our group and others recently showed that exercise training not only improves central hemodynamics or diastolic function, but also peak exercise capacity which probably is explained by co-affecting of non-cardiac alterations like peripheral muscle function [15,47]. Treatment options for HFpEF should therefore not only aim to improve diastolic dysfunction and to reverse left ventricular remodelling, but also address the complex non-cardiac pathophysiology of the disease.

5. Conclusion

In this so far largest comprehensively characterized cohort of HFpEF patients demographic and clinical characteristics differentially interact with exercise capacity, resting left ventricular filling index, neurohumoral activation, left atrial and left ventricular remodelling. Exercise capacity correlated with left ventricular filling index and neurohumoral activation, but these correlations were significantly attenuated after multiple adjustments. Exercise intolerance in HFpEF is multi-factorial and therapeutic approaches addressing exercise capacity should therefore not only aim to improve single pathological mechanisms.

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