

Determinants of submaximal exercise capacity in patients at risk for heart failure with preserved ejection fraction—results from the DIAST-CHF study

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Abstract

Objectives and Background The aim of this study was to identify determinants of submaximal exercise capacity as measured by 6 min walking distance in patients at risk for heart failure with preserved ejection fraction (HFpEF).

Methods A cross-sectional analysis from the prospective cohort programme Prevalence and Clinical Course of Diastolic Dysfunction and Heart Failure (DIAST-CHF) that included a total of 1937 patients (age, 50–85 years) with >1 risk factor (hypertension, atherosclerotic disease, diabetes mellitus, and obstructive sleep apnoea) was carried out. Besides comprehensive clinical phenotyping, standardized 6 min walk test and state-of-the-art echocardiography were performed, and blood samples for biomarker assessment were obtained. Patients with an ejection fraction <50% or without evaluable exercise test were excluded from this analysis.

Results One thousand three hundred eighty-seven patients fulfilled all criteria for this analysis. In the univariate analysis, 6 min walk distance was inversely related to E/e' values ($P < 0.001$). In the multivariate analysis, 6 min walk distance decreased significantly with age, female sex, increasing body mass index, diabetes, chronic obstructive lung disease, and peripheral artery disease. However, the association of 6 min walk distance with resting parameters of diastolic function was significantly attenuated with multivariate regression. In contrast, mid-regional pro-adrenomedullin, mid-regional pro-atrial natriuretic peptide, and N-terminal pro-B-type natriuretic peptide were independently associated with submaximal exercise capacity when added to the base model (all $P < 0.001$).

Conclusions Classical risk factors for heart failure and neuroendocrine activation are independently associated with submaximal exercise capacity, while diastolic function parameters obtained at rest were not. This observation substantiates the role of co-morbidities as relevant contributors to the clinical picture of HFpEF and the limitation of resting indices of diastolic function for diagnosing HFpEF.

Keywords Exercise capacity; Diastolic dysfunction; Biomarkers

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Introduction

Elderly patients with classical cardiovascular risk factors may demonstrate reduced exercise capacity, even before a formal diagnosis of heart failure is made. These patients may eventually evolve into overt heart failure with preserved ejection fraction, and a better understanding of factors contributing to this progression is mandatory.

In fact, heart failure with preserved ejection fraction (HFpEF) has been found to be as prevalent as heart failure with reduced ejection fraction (HFrEF), and diastolic dysfunction (DD) is considered the pivotal pathophysiological mechanism in these patients.^[1–3] This abnormality can be readily diagnosed by echocardiography and left ventricular filling pressures can be approximated.^[4] Its prevalence increases with age and certain cardiovascular risk factors like diabetes or hypertension.^[5,6] It is therefore tempting to speculate that DD is responsible for reductions in physical functioning in a significant number of elderly patients at high cardiovascular risk, but without reduced left ventricular ejection fraction (LV-EF). However, we have recently observed that biomarkers of neurohumoral activation were more strongly associated with self-perceived physical quality of life than echocardiographic indicators of DD.^[7] Self-perceived physical functioning on the other hand is not completely concordant with objective measures of exercise capacity as determined by cardiopulmonary exercise testing or simpler methods like the 6 min walk test (6-MWT), which is readily applicable in large epidemiological cohort studies.^[8]

Therefore, the aim of the present analysis was to investigate the association between submaximal exercise capacity as measured by a 6-MWT, clinical parameters, echocardiographically determined DD at rest, and differential neuroendocrine activation. We used the large-scale DIAST-CHF cohort after exclusion of patients with reduced EF (<50%) or without valid 6-MWT for this analysis.

Methods

Participants

The ongoing DIAST-CHF study is a prospective, multicenter, observational study, which is part of the nationwide German Competence Network Heart Failure.^[9] In 2004 and 2005, 1937 patients aged 50–85 years with at least one risk factor for heart failure or with established heart failure were enrolled. Risk factors were hypertension, atherosclerotic disease (e.g. coronary artery disease), diabetes mellitus, or sleep apnoea syndrome. An apparently healthy group served as controls. Patients were referred by a network of primary care physicians. The only exclusion criterion in this all-comers trial was unwillingness to participate or inability for logistic reasons. DIAST-CHF complies

with the Declaration of Helsinki, the protocol was approved by all responsible ethics committees and all patients gave written informed consent prior to inclusion.

All patients underwent a detailed medical history, a comprehensive physical examination, and a 12 lead electrocardiogram. As a simple estimate of submaximal exercise capacity, a 6-MWT was performed according to a pre-specified standard operations procedure.^[8]

For the present analysis, we excluded patients with systolic dysfunction or systolic heart failure (left ventricular ejection fraction <50%), patients without adequate echocardiographic assessment of diastolic function, and patients without a validated 6-MWT.

Echocardiography and diastolic function

Echocardiography at rest was performed on a Hewlett-Packard Sonos 5500 (Hewlett-Packard, Andover, MA, USA) by experienced investigators trained on the protocol. The protocol followed the recommendations of the American Society of Echocardiography and included comprehensive evaluation of diastolic function including tissue Doppler measurement of peak velocities of early (E) and late (A) diastolic mitral inflow and early (e') and late (a') myocardial relaxation velocities, E wave deceleration time and peak systolic and diastolic pulmonary vein flow velocity. Echocardiographic parameters of cardiac remodelling included left ventricular wall thickness mass index (LVMI) as calculated by the Devereux formula and left atrial and ventricular dimensions and volumes.^[10,11] Randomly chosen echo examinations were reviewed by the DIAST-CHF echo core lab at the University of Essen (Germany) for quality assurance.

Diastolic function was classified by an algorithm defined in the study protocol of DIAST-CHF and described in detail in the work of Edelmann *et al.*^[7] For the present analysis, all patients with any grade of DD were retrospectively classified to have normal (DD–) or elevated (DD+) filling pressures according to the current American Society of Echocardiography criteria.^[12] As a continuous lead parameter for DD, the filling index E/e' was calculated. Patients without diastolic dysfunction were classified as normal (N).

Biomarkers of neurohumoral activation

Blood samples were drawn after 15 min rest in the prone position, centrifuged and immediately stored at –80 °C. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured with a commercially available electrochemiluminescence immunoassay on an Elecsys® analyser (Roche Diagnostics GmbH, Mannheim, Germany);^[13] Midregional pro-adrenomedullin (MR-proADM) with a fully automated assay BRAHMS MR-proADM KRYPTOR (BRAHMS GmbH, Hennigsdorf, Germany);^[14]

Midregional pro-atrial natriuretic peptide (MR-proANP) with the fully automated sandwich immunoassay BRAHMS SERISTRA® (BRAHMS GmbH, Hennigsdorf, Germany);^[15] C-terminal Endothelin-1 precursor fragment (CT-proET1) with the sandwich assay BRAHMS SEVACON LIA® (BRAHMS GmbH, Hennigsdorf, Germany);^[16] and the C-terminal portion of proavopressin (CT-proAVP) with a sandwich immunoluminometric assay by BRAHMS.^[17]

Statistical analysis

To investigate determinants of 6 min walk distance, patients with values above the median were compared with those below. For continuous variables, means \pm standard deviations are given. Neurohormones with skewed distribution are expressed as median (interquartile range). Absolute numbers (percentage) are given for categorical variables. Means were compared by Student's *t*-test for independent samples, medians by Mann–Whitney *U* test, and proportions by chi-square test. Independent associations of clinical characteristics, echocardiographic variables, and neurohormones with 6 min walk distance were elucidated by several multivariate linear regression analyses. Firstly, a basic model was built based on those demographic variables and clinical parameters that significantly differed between groups. Continuous echocardiographic parameters indicative of diastolic function as well as DD classification were then added separately. Five biomarkers of neurohumoral activation were entered into a separate multivariate regression model to select those most strongly associated with 6 min walk distance before adding these markers to the clinic or echocardiographic models. For biomarkers that were independently associated, scatterplots were produced, and Pearson's bivariate correlation coefficients were calculated. Decadic logarithms were used for the neurohormones because of their skewed distributions for statistical analyses. All tests were performed two sided at 5% significance level.

All analyses were performed with spss 19.0 software (SPSS, Chicago, IL, USA).

Results

Of 1937 patients included in DIAST-CHF, two were retrospectively excluded because of age <50 years. From the remaining 1935 subjects, 393 were excluded for the present analysis (27 with missing LV-EF, 201 with LV-EF \leq 50%, 165 with non-gradable diastolic function because of atrial fibrillation or missing parameters), and 155 due to missing data for the 6-MWT.

The median 6 min walking distance in the remaining 1387 patients was 532 m. Clinical characteristics, co-morbidities, and current medication stratified by 6 min walk distance

above versus below the median of 532 m are shown in *Table 1*: *E/e'* was higher and DD was more frequent in those with lower 6 min walk distance. Also, biomarkers of neuroendocrine activation were higher in these patients. As expected, there were considerable imbalances in co-morbidities and demographic variables between both groups. There was a significant trend towards lower 6 min walk distances with increasing DD class obtained at rest: 570 \pm 78 m for normal diastolic function (N) versus 511 \pm 114 m for DD without elevated filling pressures and 492 \pm 111 m for DD with elevated filling pressures (*Figure 1*). Overall, resting *E/e'* correlated weakly with 6 min walk distance (R^2 0.025, $P < 0.001$).

In multivariate regression analyses, the following clinical characteristics were found to be independently associated with a lower 6 min walk distance and therefore formed the 'base model': higher age, female sex, higher body mass index, diabetes, COPD, and peripheral artery occlusive disease (PAOD). When we individually added echocardiographic functional and structural parameters to the base model, none was independently associated with 6 min walk distance (*E/e'*: $P = 0.644$, LAVI: $P = 0.151$, LVMI: $P = 0.695$). There was a non-significant trend ($P = 0.088$) for the independent association with DD classification. Among the five biomarkers evaluated, MR-proADM, MR-proANP, and NT-proBNP were independently associated with 6 min walk distance. When added to the base model or a model including DD classification, all three markers remained independently associated with submaximal exercise capacity (models 1–3 in *Table 2*). In bivariate correlation, the markers correlated moderately, albeit more strongly than *E/e'*, with 6 min walk distance (*Figures 2–4*).

In the final multivariate model (model 3 in *Table 2*), higher age was associated with a decrease in 6 min walk distance by -36.8 m (per 10 years increase), female sex with -35.9 m, body mass index with -40.2 m (per 10 kg/m²), diabetes with -30.8 m, COPD with -29.6 m, and PAD with -31.4 . DD classification missed the significance ($P = 0.100$) for a reduction of -7.5 m per class increase. High MR-proADM was associated with a reduction of -42.7 m (per 10-fold concentration increase) and NT-proBNP of -66.1 m (per 10-fold concentration increase), while MR-proANP was directly associated ($+60.8$ m per tenfold higher MR-proANP concentration). The latter, however, was only observed in combination with NT-proBNP, but not when MR-proANP was individually added to the base model or in bivariate correlation with 6 min walk distance (*Figure 4*). The ratio of MR-proANP/NT-proBNP was by itself independently predictive of 6 min walk distance in multivariate analysis (*Figure 5* and model 4 in *Table 2*).

Discussion

In stable outpatients at risk for developing overt heart failure with preserved left ventricular ejection fraction, median 6 min

Table 1. Patient characteristics according to group allocation

	6 min walk distance ≤532 m (n = 695)	6 min walk distance >532 m (n = 692)	P-value for difference
Demography and clinical characteristics			
Age (a)	68 ± 8	63 ± 7	<0.001
Female sex	423 (60.9%)	335 (48.4%)	<0.001
BMI (kg/m ²)	29.9 ± 5.1	27.5 ± 4.1	<0.001
SBP (mmHg)	148 ± 22	146 ± 21	0.272
DBP (mmHg)	83 ± 12	84 ± 12	0.032
Heart rate (1/min)	71 ± 12	70 ± 11	0.808
eGFR (mL/min)	72 ± 19	77 ± 16	<0.001
History and co-morbidities			
CAD	144 (20.7%)	68 (9.8%)	<0.001
COPD	65 (9.4%)	29 (4.2%)	<0.001
PAOD	47 (6.8%)	12 (1.7%)	<0.001
Diabetes mellitus	205 (29.5%)	114 (16.5%)	<0.001
Hyperlipidemia	321 (46.2%)	228 (32.9%)	<0.001
Hypertension	609 (87.6%)	486 (70.2%)	<0.001
Smoker	77 (11.1%)	75 (10.8%)	0.472
Echocardiography			
LV-EF (%)	61.8 ± 6.3	61.6 ± 6.0	0.379
LVEDD (mm)	48.1 ± 5.8	49.1 ± 5.5	<0.001
LVESD (mm)	30.2 ± 5.6	30.2 ± 5.1	0.992
LVMI (g/m ²)	114.8 ± 26.4	113.5 ± 25.9	0.391
LAVI (ml/m ²)	24.5 ± 6.8	23.1 ± 6.6	<0.001
e' lat. (cm/s)	7.7 ± 2.3	8.7 ± 2.8	<0.001
a' lat. (cm/s)	11.5 ± 3.0	11.5 ± 2.7	0.666
A-wave (cm/s)	84.4 ± 18.8	75.6 ± 18.3	<0.001
E-wave (cm/s)	71.6 ± 18.9	71.5 ± 17.0	0.890
E/A	0.9 ± 0.3	1.0 ± 0.3	<0.001
E/e' lat. ratio	10.1 ± 4.1	8.9 ± 3.4	<0.001
Diastolic dysfunction: None (N)	68 (9.8%)	171 (24.7%)	<0.001
Normal filling pressures (DD)	444 (63.9%)	412 (59.5%)	
Elevated filling pressures (DD+)	183 (26.3%)	109 (15.8%)	
Neurohormones			
NT-proBNP (pg/mL)	105.1 (56.1; 203.3)	75.9 (42.8; 137.6)	<0.001
MR-proANP (pmol/L)	91.7 (63.1; 135.1)	79.4 (59.0; 109.3)	<0.001
MR-proADM (nmol/L)	0.609 (0.521; 0.742)	0.519 (0.454; 0.604)	<0.001
CT-proAVP (pmol/L)	4.0 (2.5; 7.7)	3.6 (2.2; 5.7)	<0.001
CT-proET1 (pmol/L)	57.2 (49.3; 67.1)	51.8 (45.3; 59.8)	<0.001
MR-proANP/NT-proBNP	0.86 (0.58; 1.31)	1.04 (0.68; 1.59)	<0.001

Values are presented as mean ± standard deviation, number (proportion) or median (interquartile range).

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate (according to MDRD); CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease; LV-EF, left ventricular ejection fraction; LVEDD and LVESD, left ventricular end-diastolic and end-systolic diameter; LVMI, left ventricular mass index; E/e', ratio of early diastolic mitral inflow to early diastolic tissue Doppler velocity of the lateral mitral annulus; LAVI, left atrial volume index; NT-proBNP, N-terminal pro-brain natriuretic peptide; MR-proANP, midregional pro-atrial natriuretic peptide; MR-proADM, midregional pro-adrenomedullin; CT-proAVP, C-terminal portion of pro-vasopressin; CT-proET1, C-terminal endothelin-1 precursor fragment.

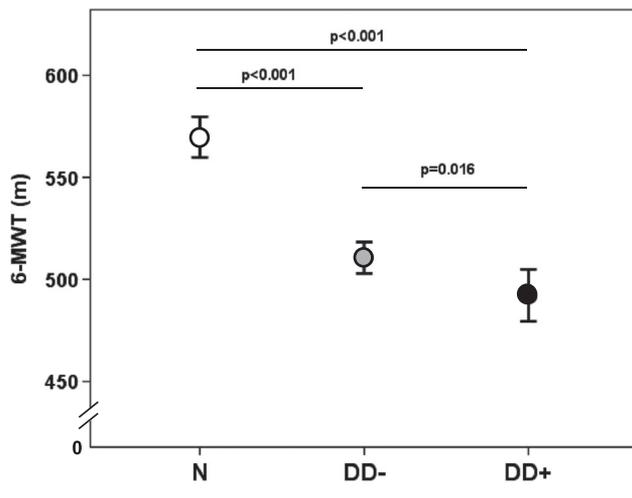
walk distance was reduced as compared with age-matched controls. This points to reduced submaximal exercise capacity in patients at risk for developing heart failure with preserved ejection fraction already in the preclinical stage. In other words, there is reduced objective exercise capacity already detectable while patients subjectively still feel well.

This is an important aspect, because heart failure with preserved ejection fraction is a syndrome difficult to treat. One potential reason for treatment failures in phase II and phase III trials was a too advanced stage of the disease, where pharmacological interventions just came too late to reverse the underlying pathophysiology.^[18] Therefore, objective detection reduced exercise capacity in a Stage B HFpEF patient

may represent a valuable therapeutic target in order to prevent progression into overt symptomatic heart failure.

However, to this end, the underlying mechanisms leading to reduced exercise capacity need to be determined. DIAST-CHF is the largest cohort of patients with full clinical phenotyping and standardized 6-MWT. In fact, 1387 patients fulfilled all criteria for this analysis including an ejection fraction >50% and a validated 6-MWT. This allowed statistical analysis of the impact of a number of clinical and echocardiographic parameters on submaximal exercise capacity. Our main findings were that demographic (age, sex, and obesity) parameters and co-morbidities (COPD, diabetes, and PAD) impacted more on exercise capacity than parameters of diastolic

Figure 1 Six minute walk test (6-MWT) according to diastolic function (N = normal, DD- = diastolic dysfunction with normal filling pressures, DD+ = diastolic dysfunction with elevated filling pressures).

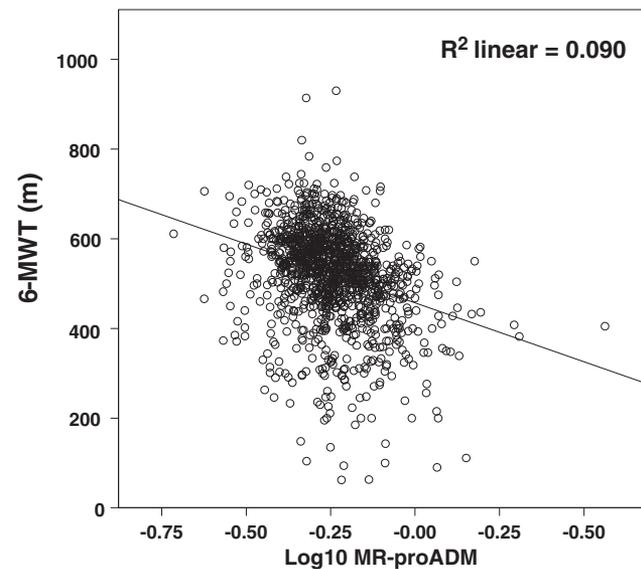


dysfunction obtained at rest. In contrast, parameters of neuroendocrine activation (NT-proBNP, MR-proADM, and MR-proANP) were independently associated with 6 min walk distance.

Diastolic dysfunction, co-morbidities, and exercise capacity

The impact of demographic variables and co-morbidities on submaximal exercise capacity in mostly asymptomatic risk patients beyond age is of potential clinical relevance. Two hypotheses can be derived from this observation: (a) the

Figure 2 Scatter plot for the bivariate association of 6 min walk test (6-MWT) and mid-regional pro-adrenomedullin (MR-proADM).



development of HFpEF is a progressive process that may (in contrast to many forms of systolic heart failure) evolve over decades and (b) this process makes HFpEF and its clinical precursor stages (Stages A and B) particularly prone to preventive but less to curative therapeutic approaches.

The absence of an independent association of echocardiographic diastolic function parameters is more surprising at first sight. Diastolic dysfunction is believed to be the most relevant pathophysiological mechanism in patients with HFpEF. In our analysis, there was only a weak statistical trend for a

Table 2. Multivariate linear models with 6 min walk distance as dependent variable

Variable	Base model		Model 1		Model 2		Model 3		Model 4		Model 5	
	B	P-value	B	P-value	B	P-value	B	P-value	B	P-value	B	P-value
Age (years)	-4.66	<0.001	-4.48	<0.001	-3.84	<0.001	-3.68	<0.001	-4.04	<0.001	-4.45	<0.001
Sex	-42.37	<0.001	-42.05	<0.001	-36.17	<0.001	-35.90	<0.001	-37.45	<0.001	-40.82	<0.001
BMI (kg/m ²)	-4.74	<0.001	-4.59	<0.001	-4.17	<0.001	-4.02	<0.001	-4.73	<0.001	-4.61	<0.001
Diabetes	-29.78	<0.001	-29.42	<0.001	-31.25	<0.001	-30.81	<0.001	-32.57	<0.001	-32.92	<0.001
COPD	-33.99	0.001	-32.95	0.002	-30.44	0.005	-29.56	0.007	-32.49	0.003		
PAOD	-45.19	0.001	-43.62	0.002	-32.78	0.017	-31.35	0.022	-35.24	0.010		
DD-classification			-7.81	0.088			-7.45	0.100			-9.78	0.033
log10 NT-proBNP					-43.39	<0.001	-42.70	<0.001				
log10 MR-proANP					59.73	0.003	60.78	0.003				
log10 MR-proADM					-65.55	0.023	-66.12	0.022				
log10 (MR-proANP/NT-proBNP)									43.47	<0.001		
Adjusted R ² for model	0.236		0.234		0.253		0.255		0.246		0.223	

BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; MR-proANP, midregional pro-atrial natriuretic peptide; MR-proADM, midregional pro-adrenomedullin.

Model 1 = age, sex, BMI, diabetes, COPD, PAOD + DD-classification.

Model 2 = age, sex, BMI, diabetes, COPD, PAOD + log10 NT-proBNP, log10 MR-proANP, log10 MR-proADM.

Model 3 = age, sex, BMI, diabetes, COPD, PAOD + DD-classification, + log10 NT-proBNP, log10 MR-proANP, log10 MR-proADM.

Model 4 = age, sex, BMI, diabetes, COPD, PAOD + log10 (MR-proANP/NT-proBNP).

Model 5 = age, sex, BMI, diabetes + DD-classification.

Figure 3 Scatter plot for the bivariate association of 6 min walk test (6-MWT) and N-terminal pro-brain type natriuretic peptide (NT-proBNP).

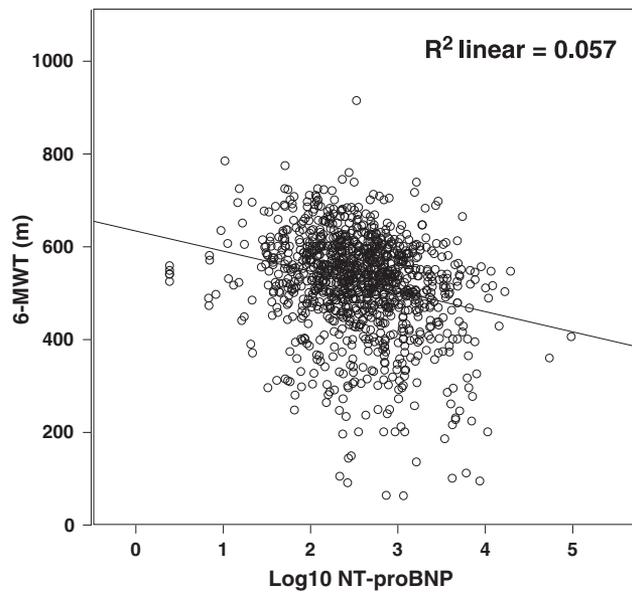
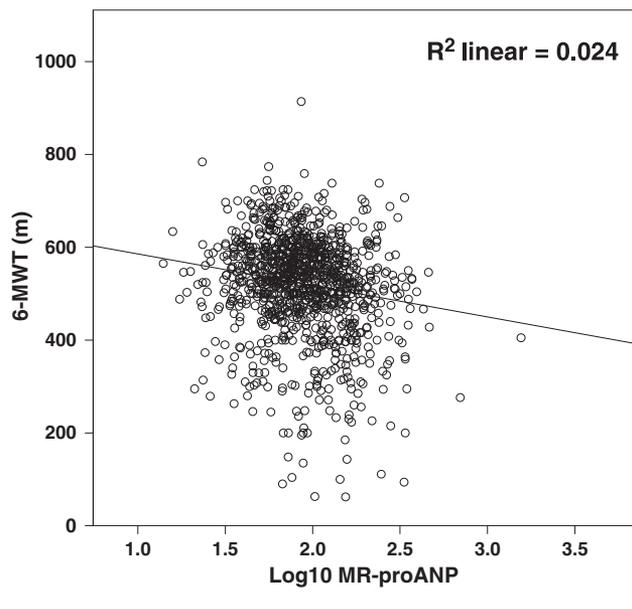
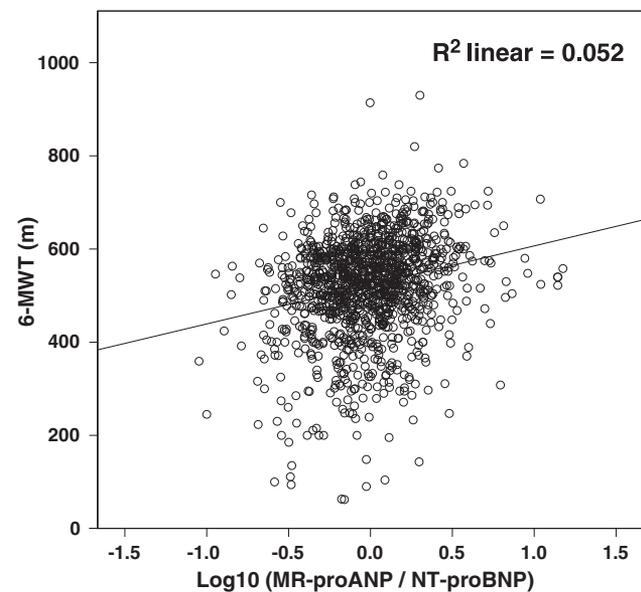


Figure 4 Scatter plot for the bivariate association of 6 min walk test (6-MWT) and mid-regional pro-atrial type natriuretic peptide (MR-proANP).



lower 6 min walk distance in patients with echocardiographic signs of elevated filling pressures (a group mostly comprised of those with $E/e' > 15$) and no association with E/e' as a continuous variable. However, previous publications on diastolic dysfunction and exercise capacity are somewhat conflicting.

Figure 5 Scatter plot for the bivariate association of 6 min walk test (6-MWT) and ratio of mid-regional pro-atrial type natriuretic peptide (MR-proANP) and N-terminal pro-brain type natriuretic peptide (NT-proBNP).



For example, exercise capacity was not related to invasively measured pulmonary capillary wedge pressures in other series, questioning the immediate relevance of filling pressures for exercise intolerance in patients with preserved ejection fraction.^[19–21] Also, E/e' ; assessed immediately after submaximal exercise was not independently associated with reduced exercise capacity in another study after multivariate adjustment for only two clinical variables, even without consideration of co-morbidities.^[22] Nevertheless, an independent association of E/e' with exercise capacity has been described in patients at cardiovascular risk undergoing stress echocardiography.^[23] From our data, we therefore suggest that in pre-clinical stages of HFpEF, echocardiographic parameters of diastolic dysfunction obtained at rest do not predict submaximal exercise capacity beyond clinical parameters and co-morbidities. This may be overcome in the future by introducing exercise echocardiography into the diagnostic armamentarium of HFpEF diagnosis, similar to the current standard of a stress test for diagnosing stable coronary artery disease. More surprisingly, parameters of structural remodelling of the heart, such as left atrial volume index and left ventricular mass index, with 6 min walk distance did not independently predict reduced exercise capacity in our large cohort, which may be related to the relative mild remodelling in our mostly Stage A and B cohort.

In summary, submaximal exercise capacity in preclinical HFpEF is less determined by left ventricular remodelling and diastolic dysfunction at rest but more by demographic variables and co-morbidities. This finding is in line with data from

the Aldo-DHF trial, one of the largest randomized Phase IIb trial in HFpEF patients to date: The change of exercise capacity did not correlate with the change of E/e' obtained at rest in the treatment arm.^[24] It has become clear over the past years that patients with HFpEF are quite a heterogeneous group both with regard to the mechanism of cardiovascular dysfunction as well as epidemiological characteristics. Patients with HFpEF appear to often have abnormalities of left ventricular contraction that are only revealed by more advanced imaging techniques like left ventricular strain or torsion analysis.^[25] Although reduced LV-twisting is directly associated with impaired untwisting and therefore diastolic dysfunction, other mechanisms might actually be more relevant for reduced exercise capacity than resting diastolic dysfunction per se. Also, patients with HFpEF tend to be older and to have more co-morbidities than those with HFrEF.^[25] These co-morbidities have a stronger impact on mortality as well as heart failure symptoms and self-reported physical quality of life.^[26,27] Therefore co-morbidities may play a relatively larger role in the aetiology of reduced exercise capacity in elderly patients at high cardiovascular risk with normal LV-EF than abnormalities in diastolic function. Interestingly, in the study by Grewal *et al.*, adjustment in multivariate analyses could only be made for risk factors, but not for major co-morbidities.^[23] Both PAOD and COPD (which were strongly associated with submaximal exercise capacity in our analyses) are associated with arterial stiffening, which has elegantly been shown to be directly linked to an elevation in E/e' .^[28–30] In fact, when we eliminate these co-morbidities from our base model, DD classification, mostly expressing increased filling pressures, is significantly associated with 6 min walk distance (model 6 in *Table 2*). Therefore, one reason for the discrepancy between the study by Grewal *et al.* and ours may be the disregard of co-morbidities as confounding variables in the former leading to an overestimation of the association between E/e' and exercise capacity.

Biomarkers of impaired exercise capacity

Interestingly, we found a highly significant association between submaximal exercise capacity and biomarkers of neurohumoral activation. This is in concordance with and support of a previous report from our cohort in which MR-proADM and NT-proBNP were independently associated with self-reported physical quality of life.^[7] We have argued before that these markers of stress to the heart or peripheral circulation may be more simple and sensitive 'downstream' integrators of diverse cardiovascular defects and therefore be more informative with regard to the share that cardiovascular pathologies have in reduced exercise capacity in broader populations. At the same time, these markers are not specific for individual pathologies, although they may hint at important mechanisms. For

example, in a seminal paper by Borlaug, exercise capacity in HFpEF was mostly limited by a blunted increase in heart rate and vasodilator response rather than by impaired left ventricular filling.^[20] Limited vasodilator response may be more closely represented by MR-proADM, which is produced in the vasculature than by NT-proBNP (which is representative of central hemodynamics), explaining the added information about submaximal exercise capacity in multivariate analyses.^[31,32] Similarly, we found an—at first glance paradoxical—positive correlation of MR-proANP with submaximal exercise capacity in multivariate analyses. While high levels of MR-proANP as an isolated marker, expressing increased left atrial wall stress, would be expected to correspond to low exercise capacity, the opposite is true when NT-proBNP levels are taken into consideration. We speculate that in the presence of cardiac pathology with elevated NT-proBNP, low levels of MR-proANP indicate a dysfunctional left atrium rather than low left atrial wall stress. In fact, persistent left atrial standstill has been shown to be associated with low levels of ANP, probably because of the loss of endocrinologically active atrial cardiomyocytes.^[33,34] Further support for this speculation is given by the fact that a high ratio of MR-proANP to NT-proBNP was by itself independently predictive for a low 6 min walk distance. Recent analyses shed light on the crucial role of left atrial function in relation to left ventricular structure for exercise capacity in patients with HFpEF and strengthen its role as a target for future research.^[35,36] Finally, our speculations regarding MR-proANP are currently not supported by experimental research and should be therefore taken only cautiously in consideration.

Strengths and limitations

Our sample is one of the largest prospectively cohorts of well-characterized patients at risk for heart failure. We applied detailed echocardiographic techniques for diastolic function assessment and performed standardized 6-MWT. As a primary care based population of largely unselected patients with co-morbid conditions, it may be more representative for a broad range of patients than highly selected populations from clinical trials. A 6-MWT is designed for submaximal exercise capacity and representative of everyday tasks and physical functioning (and impairment) under standard conditions but does not adequately reflect, e. g. peak oxygen consumption with maximal exercise capacity.^[21]

However, diastolic function parameters were only obtained at rest and were only moderately altered in a significant portion of participants. Exercise echocardiography is currently tested as a better approach to define diastolic (and systolic) dysfunction despite a normal EF. We cannot exclude (and even assume) that exercise-derived diastolic

function parameters may largely impact on exercise capacity in a preclinical HFpEF cohort. Due to the setting of our cohort, we did not measure exercise E/e' , which may hold more information about exercise capacity because of impaired left ventricular filling than E/e' under resting conditions.^[22] Similarly, an invasive method to evaluate diastolic dysfunction was not feasible in a cohort of this magnitude.

Conclusions

We conclude that diastolic dysfunction determined at rest is, after adjustment, not associated with reduced submaximal exercise capacity in patients at risk for heart failure. Demographic parameters and co-morbidities are strong modifiers

of the association between resting diastolic dysfunction and exercise capacity in this population.

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Conflicts of Interest

None declared.

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