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# Therapeutic potential of phosphodiesterase type 5 inhibitors in heart failure with preserved ejection fraction and combined post- and pre-capillary pulmonary hypertension

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## ARTICLE INFO

## ABSTRACT

*Objective:* Heart failure with preserved ejection fraction (HFpEF) is frequently associated with pulmonary hypertension (PH), which substantially impacts survival. Based on pulmonary vascular resistance (PVR) and the diastolic pressure gradient (DPG), current guidelines distinguish between isolated post-capillary PH (IpcPH) and combined post- and pre-capillary PH (CpcPH). However, the therapeutic consequences of this sub-classification remain entirely unclear. We specifically investigated the efficacy and safety of PDE5i in patients with HFpEF and CpcPH.

*Methods:* In 40 hemodynamically precisely characterized patients with HFpEF and Cpc-PH who were treated with a PDE5i for at least 12 months, the therapeutic effect on 6-minute walk distance (6MWD), WHO functional class (FC), NTproBNP levels, right ventricular function, and hospitalization rates was evaluated.

*Results:* Patients' mean age was $73 \pm 9$ years, and comorbidities were frequent (78% hypertension, 58% atrial fibrillation, 35% diabetes). Initially, 38 patients (95%) were in WHO-FC III and 2 patients (5%) in WHO-FC II. Prior to PDE5i initiation, mean PAPm was $46.2 \pm 10.3$ mmHg, PAWP $21.2 \pm 4.7$ mmHg, DPG $5.5 \pm 7.2$ mmHg, and PVR $6.2 \pm 3.0$ WU. After 12 months of PDE5i therapy, the 6MWD increased from initially $277 \pm 17$ to $340 \pm 18$ m ($p < 0.001$), and the proportion of patients in WHO-FC I/II increased from 5% to 37.5%. NTproBNP levels decreased by 33% ($p = 0.004$), and TAPSE improved from $16.8 \pm 0.7$ mm at baseline to $18.2 \pm 0.6$ mm ($p = 0.01$). The rate of HF-associated hospitalizations was substantially lower in the 12 months post PDE5i initiation compared to the prior 12 months. The DPG had no impact on the response to therapy. No deaths occurred, and typical side effects of PDE5i were observed.

*Conclusion:* These data indicate that at least a subset of precisely characterized patients with HFpEF and CpcPH who tolerate PDE5i may benefit from targeted therapy. A randomized study in this particular sub-population is warranted.

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## 1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complex syndrome with high morbidity and mortality, for which therapeutic options remain limited [1–3]. HFpEF is frequently complicated by pulmonary hypertension (PH), which is associated with aggravated symptoms and substantially impacts survival. Depending on the method of pulmonary artery pressure (PAP) measurement, definition of PH, and populations studied, the prevalence of PH in patients with HFpEF is in the range of 80–90% [4–6]. Several studies have shown that PA systolic pressure (PASP) estimated by echocardiography strongly predicted all-cause and cardiovascular mortality in HFpEF independently of known predictors of outcome [4,7]. Moreover, HFpEF patients commonly display right ventricular (RV) dysfunction at rest, which is associated with elevated PAP, occurs at more advanced stages, and represents a strong predictor of death [8,9]. The combination of diminished RV-function and elevated PAP [6,10], and impaired RV-PA coupling [11,12], are particularly associated with poor outcome.

In patients with left heart disease (LHD), PH is primarily caused by backward transmission of elevated left-sided filling pressure, causing post-capillary PH [13–15]. Therefore, the primary strategy to improve pulmonary hemodynamics is optimization of volume status and filling pressures. Indeed, remote monitoring of PAP by implantable devices and PAP-based control of volume load substantially reduced the rate

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of HF-associated hospitalizations in HF patients including those with HFpEF [16], and reductions in diastolic PAP were associated with improved survival [17]. This highlights the importance of optimized volume control as the primary strategy to resolve PH in patients with HF.

Nevertheless, in a subset of patients a pre-capillary component may persist despite optimized volume control [13]. Based on pulmonary vascular resistance (PVR) and the diastolic pressure gradient (DPG), current guidelines therefore distinguish between isolated post-capillary PH (IpcPH) and combined post- and pre-capillary PH (CpcPH) [18]. Elevations of PVR (>3 WU) and/or DPG (≥7 mmHg) are thought to indicate pulmonary vascular disease (PVD) in addition to LHD. However, the therapeutic consequences of this sub-classification remain entirely unclear.

While preliminary studies suggested potential benefit of targeted PH therapies, particularly phosphodiesterase type-5 inhibitors (PDE5i), in PH-LHD (reviewed in: [13–15]), data from controlled clinical studies in HFpEF are scarce, and small randomized controlled trials (RCT) have yielded seemingly conflicting results: In two studies that enrolled HFpEF patients without documented PH or with IpcPH, the PDE5i sildenafil showed no benefit [19,20]. Conversely, in a third trial that was conducted before the current classification (IpcPH vs. CpcPH) was introduced, but included patients fulfilling the hemodynamic criteria of CpcPH, sildenafil was reported to improve hemodynamics and RV function [21]. The latter is consistent with a recent analysis from the COMPERA registry, indicating that patients with HFpEF and severe PH may benefit from targeted PH therapy [22].

When viewed together, the above trial results should not be considered conflicting, but likely reflects the distinct hemodynamic profiles and phenotypes of the studied cohorts. This highlights the need for proper hemodynamic characterization and phenotyping, and further research [23]. Here, we specifically focus on the subgroup of patients with HFpEF and CpcPH, and report the treatment response to PDE5i therapy, and its association with hemodynamic variables.

## 2. Patients and methods

### 2.1. Patients, treatment and follow-up

We retrospectively analysed a series of 40 hemodynamically precisely characterized patients with HFpEF and CpcPH, who were treated with a PDE5i for at least 12 months. HFpEF was confirmed according to the definition in the ESC-guidelines [24]: History and/or clinical signs of HF, LVEF ≥50%, elevated NT-proBNP levels, and ≥1 of the following criteria: (i) relevant structural heart disease (LV-hypertrophy and/or left atrial enlargement), (ii) echocardiographic signs of diastolic dysfunction. In addition, the $H_2FPEF$ score was utilized to further verify HFpEF in our cohort [25]. Hemodynamically, CpcPH was defined by a meanPAP ≥25 mmHg, PAWP >15 mmHg, and PVR >3 WU and/or DPG ≥7 mmHg, as diagnosed by right heart catheterization (RHC) and specified by current guidelines [18]. All patients were compensated ("euvolemic"), on optimized HFpEF therapy (blood pressure control, diuretics) at the time of RHC, were in WHO-FC II or III, and had a 6MWD >50 m. At baseline, invasive and non-invasive tests were performed within 48 h. During follow-up, all tests were routinely performed on the same day. PDE5i were applied at the dosages approved for PAH (Sildenafil 20 mg three times/day; Tadalafil 20 mg once daily, uptitrated within 4 weeks to 40 mg once daily). Follow-up was conducted for 12 months and included 6MWD, NTproBNP-levels, echocardiographic parameters of RV-function, WHO-FC, and hospitalization rates (Fig. S1). Patients with pre-capillary PH or IpcPH were not included. Only patients not undergoing interventional/device therapy who remained on PDE5i monotherapy for ≥12 months were eligible for the analysis (patient selection, see Fig. S2). The analysis was approved by the local Ethics Committee of the University of Cologne.

### 2.2. Right heart catheterization

CpcPH was confirmed by RHC in all patients. For the analysis, the pressure tracings of all patients were analysed in a standardized and blinded manner, according to current guidelines [13,14,18]. All pressure values were measured at end-expiration (means from three cardiac cycles [five cycles in atrial fibrillation]). Per standardized RHC protocol, the pressure transducer was routinely placed at the mid-thoracic level. Post-capillary PH was defined by a meanPAP of ≥25 mmHg and a PAWP >15 mmHg (mean value integrating the v-wave) at end-expiration under resting conditions [13,14,18,26]. RHC also included the measurement of cardiac output (CO), mixed venous oxygen saturation (SvO$_2$), and calculation of TPG (=PAPm-PAWP), DPG (=PAPd-PAWP), PA compliance (=stroke volume/PAPs-PAPd), PVR (=[PAPm-PAWP]/CO), stroke volume index (SVI) and RV stroke work index (RVSWI). All pressure gradients were calculated using end-expiratory values.

### 2.3. Exclusion of significant lung disease and pulmonary embolism

Significant chronic lung disease was routinely ruled out by spirometry (FVC >60% predicted; FEV1 >60% predicted) and CT lung-scan (absence of significant parenchymal abnormalities), and chronic thromboembolic PH was excluded by ventilation/perfusion scan in all patients [18].

### 2.4. Echocardiography

Transthoracic echocardiography was performed using the Philips iE 33 system (Philips GmbH, Hamburg, Germany), equipped with a 2,5 MHz transducer. Assessments of right heart morphology and function included right atrial area, RV end-diastolic diameter (RVEDD), tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (FAC), and tricuspid regurgitation velocity (TRV). The systolic tricuspid pressure gradient ($\Delta P_{max}TV$) was calculated from TRV by the modified Bernoulli equation, and PA systolic pressure (PASP) was estimated as the sum of $\Delta P_{max}TV$ and estimated right atrial pressure. Additionally, the TAPSE/PASP ratio was calculated as an index of RV-PA coupling [6,10]. Significant left-sided valvular disease (≥moderate) was ruled out by Doppler-echocardiography. All measurements were performed according to current guidelines [27].

### 2.5. Six-minute walking test

Exercise capacity was evaluated by the six-minute walk test, which was standardized according to the guidelines of the ATS [28]. All subjects were made familiar with the test prior to the first measurement, and were then used to perform it at their routine follow-up visits.

### 2.6. NTproBNP serum levels

NTproBNP was measured by the Elecsys proBNP II Test (Roche Diagnostics GmbH, Mannheim, Germany); normal values are age-adjusted, but the overall cut-off value is <125 ng/l.

### 2.7. Hospitalizations

HF-associated hospitalizations were defined as hospitalizations due to signs of decompensated HF associated with dyspnea and pulmonary congestion/pleural effusion and/or peripheral edema and/or ascites and/or requiring i.v. diuretic therapy.

### 2.8. Statistical analysis

Qualitative variables were summarized using count and percentage, quantitative variables using means ± standard deviation (SD). In case of missing values, last observation carried forward (LOCF) was used. Changes in values of quantitative variables (i.e. before and after treatment) were described by means ± standard error (SEM) and tested using the paired *t*-test at two-sided significance level 5%. Time-to-event distributions were summarized by the Kaplan-Meier method and compared using the log-rank test. *p*-Values <0.05 were considered statistically significant, though no adjustment for multiple testing was done. Calculations were done in Excel (Microsoft Corp., Redmond, WA) and SPSS Statistics (IBM Corp., Armonk, NY).

## 3. Results

### 3.1. Patient characteristics

Demographics, patient characteristics at baseline, co-morbidities and concomitant medications are listed in Table 1. All patients were on stable doses of diuretics for at least 2 weeks prior to the initial RHC and initiation of PDE5i. In addition to guideline-based HFpEF diagnosis [4], the $H_2HFPF$ score [25] was 5.95 ± 0.29, further validating HFpEF in our cohort. Echocardiographic evaluation revealed an RV phenotype (enlarged right heart chambers, RV > LV), significant PH, and/or diminished RV-function in all patients (Table S1).

### 3.2. Pulmonary hemodynamics at baseline

Pulmonary hemodynamics at baseline is summarized in Table 2. All patients had severe PH, which was CpcPH by definition in all cases. In addition to impaired standard hemodynamics, PA compliance (PA$_C$) was substantially reduced at 1.5 ± 0.7 ml/mmHg. Hence, the hemodynamic profile was highly indicative of the presence of significant PVD in these patients.

Since according to current guidelines, CpcPH may be reflected by an increase of PVR and/or DPG [18], we also analysed the distribution of

these two variables in our cohort. As depicted in Fig. S3A, 42.5% of patients had elevations of both PVR and DPG, and another 55% had an elevated PVR with normal DPG. In contrast, isolated elevation of DPG with normal PVR was rare, and patients with IpcPH (normal PVR and DPG) were excluded. Consequently, almost all of our patients displayed an elevated PVR and reduced $PA_C$, whereas subgroups with normal or elevated DPG were equally distributed (Fig. S3B).

### 3.3. Changes in prognostically relevant clinical parameters

This highly selected and precisely characterized cohort of patients with HFpEF and CpcPH underwent treatment with a PDE5i (sildenafil n = 24, tadalafil n = 16) for at least 12 months, and the therapeutic effect on clinically important parameters carrying prognostic information was closely monitored during follow-up visits up to 12 months. In most patients, PDE5i therapy was associated with a rapid and sustained improvement of symptoms and clinical parameters. After 12 months of PDE5i therapy, the 6MWD substantially increased from initially 277 ± 17 to 340 ± 18 m, resulting in a net increase of 63 m ($p < 0.001$), and NTproBNP levels decreased from 3.191 ± 559 ng/l at baseline to 2.130 ± 472 ng/l ($-33\%$, $p = 0.004$) (Fig. 1A/B). In addition, RV function moderately improved at 12 months (TAPSE 18.2 ± 0.6 vs. 16.8 ± 0.7 mm at baseline, RV-FAC 42.5 ± 1.3 vs. 37.2 ± 1.1% at baseline, both $p = 0.01$), and the proportion of patients in WHO-FC I/II increased from 5% at baseline to 37.5% at 12 months (Fig. 1C/D). No differences were observed between the treatment responses to sildenafil versus tadalafil (Fig. S4). A detailed analysis of other echocardiographic variables indicated improvements in right heart parameters, but unchanged HFpEF parameters (Table S1). In particular, the TAPSE/PASP ratio as an index of RV-PA coupling improved significantly from 0.27 ± 0.02 to 0.35 ± 0.02. Importantly, diuretics were only moderately changed, and body weight remained constant throughout the observation period (71.7 ± 3 kg initially vs. 71.5 ± 2 kg at 12 months) (Fig. S5), so that the changes in measured parameters may not be attributable to optimized volume status and reduced left ventricular filling pressure. No deaths occurred in the investigated group, and the typical side effects of PDE5i (headache, flushing, nasal congestion) were observed.

**Table 1**
Demographics, patient characteristics, comorbidities, cardiovascular risk factors and concomitant medication in the 40 patients with HFpEF and Cpc-PH.

| | All (n = 40) | DPG ≥ 7 mmHg (n = 18) | DPG < 7 mmHg (n = 22) |
|---|---|---|---|
| *Patient characteristics* | | | |
| Age, years | 73 ± 9 | 72 ± 9 | 74 ± 9 |
| Gender, m/f (%) | 47/53 | 47/53 | 45/55 |
| 6MWD, m | 277 ± 17 | 280 ± 16 | 275 ± 17 |
| NTproBNP, ng/l | 3191 ± 559 | 3404 ± 568 | 3012 ± 549 |
| WHO-FC II/III, n (%) | 2(5)/38(95) | 0 (0)/18 (100) | 2 (9)/20 (91) |
| BMI, kg/m² | 27.5 ± 4.6 | 28.9 ± 5.8 | 26.3 ± 2.7 |
| SBP, mmHg | 135 ± 24.3 | 126 ± 17.1 | 144 ± 26.9 |
| DBP, mmHg | 72 ± 13.5 | 73 ± 14.7 | 71 ± 12.3 |
| Heart rate, bpm | 71 ± 19 | 73 ± 18.0 | 69 ± 19.7 |
| GFR, ml/min | 49.9 ± 21.9 | 49.1 ± 24.5 | 50.8 ± 18.7 |
| *Comorbidities/CV risk factors* | | | |
| Hypertension, n (%) | 31 (77.5) | 13 (72.2) | 18 (81.8) |
| Diabetes, n (%) | 14 (35) | 6 (33.3) | 8 (36.4) |
| Atrial fibrillation, n (%) | 23 (57.5) | 10 (55.6) | 13 (59.1) |
| CAD, n (%) | 26 (65) | 13 (72.2) | 13 (59.1) |
| BMI > 30 kg/m² | 8 (20) | 7 (38.9) | 1 (4.5) |
| *Concomitant medication* | | | |
| Loop diuretics, n (%) | 33 (83) | 15 (83.3) | 18 (81.2) |
| Thiazides, n (%) | 19 (48) | 10 (55.5) | 9 (40.9) |
| MR antagonists, n (%) | 12 (30) | 6 (33.3) | 6 (27.3) |
| ACEI/ARB, n (%) | 27 (67.5) | 13 (72.2) | 14 (63.6) |
| Beta blockers, n (%) | 31 (77.5) | 15 (83.3) | 16 (72.8) |
| CCB, n (%) | 11 (27.5) | 4 (22.2) | 7 (31.8) |

**Table 2**
Pulmonary hemodynamics as assessed by right heart catheterization.

| | All (n = 40) | DPG ≥ 7 mmHg (n = 18) | DPG < 7 mmHg (n = 22) |
|---|---|---|---|
| Systolic PAP, mmHg | 74.7 ± 16.9 | 75.6 ± 16.6 | 74.0 ± 17.2 |
| Diastolic PAP, mmHg | 26.6 ± 8.7 | 31.4 ± 7.1 | 22.7 ± 6.6 |
| Mean PAP, mmHg | 46.2 ± 10.3 | 48.1 ± 11.4 | 44.6 ± 9.0 |
| PAWP[a], mmHg | 21.2 ± 4.7 | 20.4 ± 3.7 | 21.8 ± 5.4 |
| RAP, mmHg | 12.8 ± 6.3 | 12.8 ± 5.5 | 12.8 ± 7.1 |
| CO, l/min | 4.5 ± 1.4 | 4.1 ± 1.4 | 4.7 ± 1.3 |
| CI, l/min/m² | 2.4 ± 0.7 | 2.3 ± 0.6 | 2.5 ± 0.7 |
| TPG, mmHg | 25.4 ± 8.1 | 28.2 ± 8.5 | 23.0 ± 6.7 |
| DPG, mmHg | 5.5 ± 7.2 | 11.0 ± 5.2 | 0.9 ± 5.3 |
| Heart rate, bpm | 74.3 ± 17.7 | 76.7 ± 19.5 | 72.3 ± 13.5 |
| Stroke volume, ml | 60.8 ± 19.2 | 54.4 ± 18.5 | 66.4 ± 16.1 |
| Stroke volume index, ml/m² | 32.4 ± 9.5 | 29.8 ± 9.8 | 34.6 ± 8.3 |
| PVR, WU | 6.2 ± 3.0 | 7.5 ± 3.8 | 5.1 ± 1.4 |
| $PA_C$, ml/mmHg | 1.5 ± 0.7 | 1.5 ± 0.9 | 1.5 ± 0.4 |
| RV stroke work index | 14.8 ± 4.6 | 14.0 ± 4.7 | 15.4 ± 4.2 |
| $SvO_2$, % | 60.5 ± 7.3 | 59.0 ± 8.3 | 61.9 ± 6.0 |

[a] In patients in whom PAWP could not be reliably measured, LVEDP was recorded and used for calculations of TPG, DPG, and PVR. Data represent means ± SD.

### 3.4. Impact of the DPG on the treatment response

Aside from prognostication and survival analyses, the relevance of the CpcPH definition and its components for the prediction of response to targeted PH therapies is entirely unclear at present. In our cohort, almost all patients displayed an elevated PVR >3 WU, as well as a reduced $PA_C$, whereas patients with elevated or normal DPG were equally distributed (Fig. S3B). These latter subgroups were not significantly different with respect to other variables (Table 1). Fig. S6 illustrates the improvements of the 6MWD and NTproBNP levels in the subgroups with DPG ≥7 mmHg or DPG <7 mmHg, respectively. These data suggest that the DPG may not have significant impact on the treatment response to PDE5i in patients with HFpEF, elevated PVR and reduced $PA_C$.

### 3.5. HF-associated hospitalizations in the pre-treatment phase and during PDE5i therapy

In order to evaluate whether improvements of the above clinical parameters would translate into a reduction of morbidity events, we analysed the frequency of HF-associated hospitalizations during the 12 months prior to treatment initiation with a PDE5i versus the 12-month period during PDE5i therapy. This analysis revealed that both the cumulative and total number of HF-associated hospitalizations were significantly lower during PDE5i therapy as compared to the time period before PDE5i initiation (Fig. 2).

### 4. Discussion

LHD, and HFpEF in particular, by far comprises the most common cause of PH globally, with a high prevalence in the elderly population [4,13,29]. The data presented herein indicate that at least a subset of patients with HFpEF who display PH (meanPAP ≥25 mmHg) and an elevated PVR (>3 WU) despite optimized volume control, may benefit from targeted PH-therapy with a PDE5i. The therapeutic potential is indicated by significant improvements in a number of clinically meaningful parameters including exercise capacity, WHO-FC, NTproBNP levels, and measures of RV-function. In addition, the rate of HF-associated hospitalizations was substantially lower during the 12 months of PDE5i therapy as compared to the 12 months prior to treatment initiation. The DPG, currently among the parameters defining CpcPH (in addition to PVR), had no significant impact on the treatment response in our patients. Finally, diuretic use and body weight remained stable throughout the observation period, suggesting that the observed therapeutic effect is not attributable to optimization of volume load.
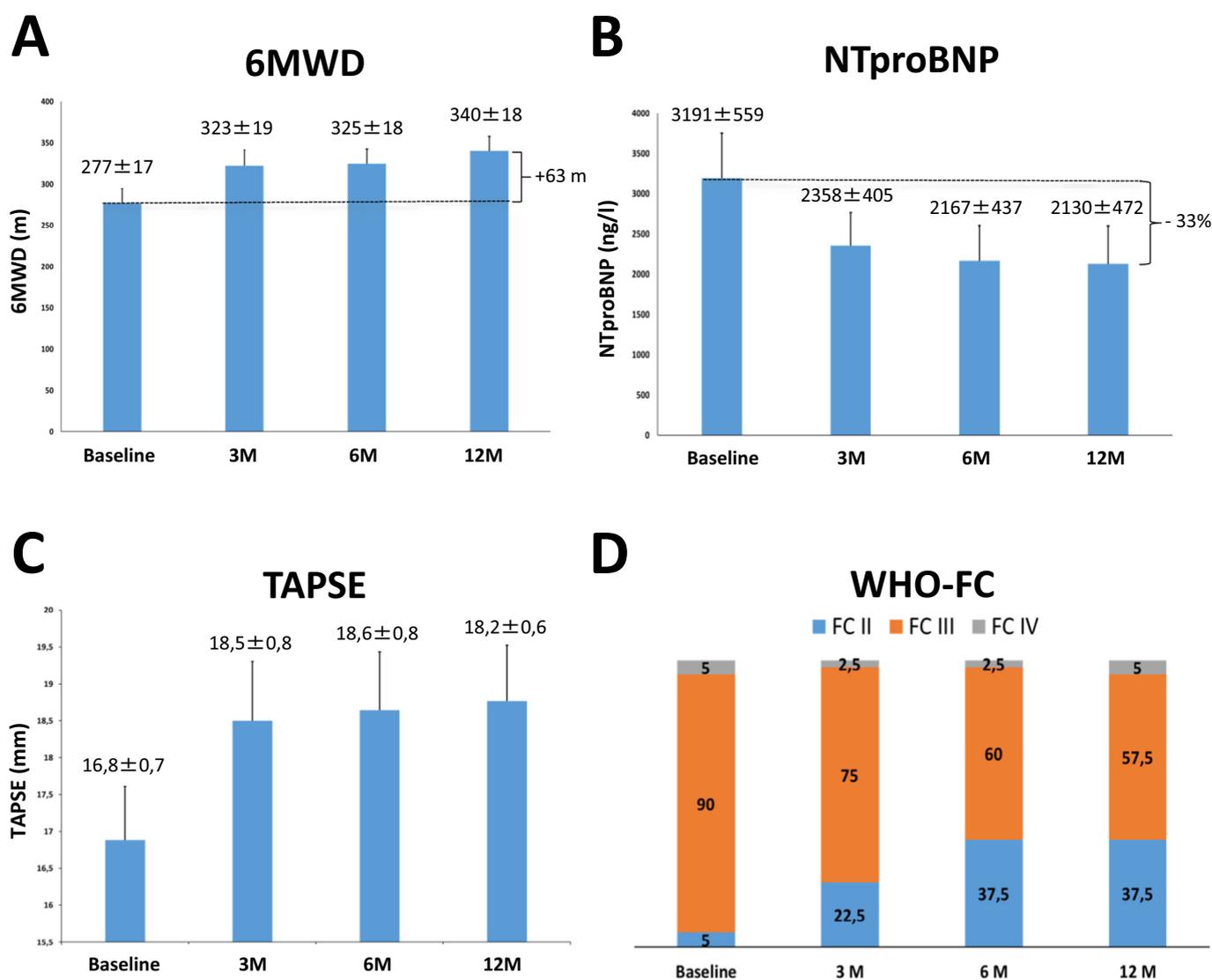
**Fig. 1.** Response to phosphodiesterase type 5 inhibitor (PDE5i) therapy at 3, 6, and 12 months compared to baseline values. (A) 6-minute walking distance (6MWD); (B) NTproBNP serum levels; (C) tricuspid annular plane systolic excursion (TAPSE); (D) WHO functional class (WHO-FC). Numbers represent mean values ± SD; *$p < 0.05$ vs. baseline. For 6MWD and NTproBNP levels, the mean change from baseline at 12 months is given.

It is important to note that our data were obtained in highly selected and hemo-dynamically precisely characterized patients with HFpEF and CpcPH in whom PVR and/or DPG remained elevated despite optimized volume control, indicating that PH was not only due to backward transmission of elevated filling pressures in HFpEF, but also to additional PVD. Hence, the results are not generalizable to patients with HFpEF, or to patients with HFpEF and PH.

The current sub-classification of post-capillary PH (IpcPH vs. CpcPH) is based on elevations of PVR and/or DPG [18]. In our series, almost all patients had an elevated PVR, whereas an increased DPG was present in approximately half of the patients, and an isolated increase of the DPG with normal PVR was found in only one patient. This distribution is consistent with other cohorts of patients with LHD who underwent RHC [30–32], indicating that an isolated elevation of DPG is a rather rare condition whereas an elevation of PVR with or without increased DPG is much more common.

The fact that the DPG was not associated with the treatment response to PDE5i in our series may be consistent with recent studies that evaluated the role of hemodynamic variables for prognostication in PH-LHD. Whereas a DPG ≥7 mmHg was predictive of poor survival in one cohort [5,31], a number of recent studies did not find an association between the DPG and survival in patients with PH-LHD [32–38].

Instead, other hemodynamic variables were predictive, particularly PVR and PA$_C$ [32,35,36,39]. Both of these were substantially impaired in our cohort of patients, indicating the presence of PVD. Interestingly, Palazzini and co-workers compared survival in IpcPH and CpcPH to an "intermediate group" with either elevated DPG or PVR (which was almost exclusively driven by PVR >3 WU and DPG <7 mmHg) and found that survival was worse in patients with CpcPH and the "intermediate group" when compared to IpcPH, whereas no survival difference was detected between patients with CpcPH and the "intermediate group", further supporting the role of PVR over DPG [32]. Furthermore, PVR and PA$_C$, but not TPG or DPG, were associated with survival, which is consistent with another recent analysis in a large number of patients undergoing RHC, which demonstrated that PVR was the strongest hemodynamic predictor of death in patients with PH-HFpEF [40].

Recent work highlighted important differences in the pathophysiology of CpcPH versus IpcPH. Whereas IpcPH is mainly characterized by an increased hydrostatic pressure and "alveolar-capillary stress failure", which is associated with impaired endothelial permeability, protein loss and interstitial edema, a specific feature of CpcPH is capillary remodeling, including both arteriolar muscularization and pulmonary vein arterialization [14,41]. When assessing clinical and biological insights into CpcPH, Assad et al. performed a genetic analysis and identified
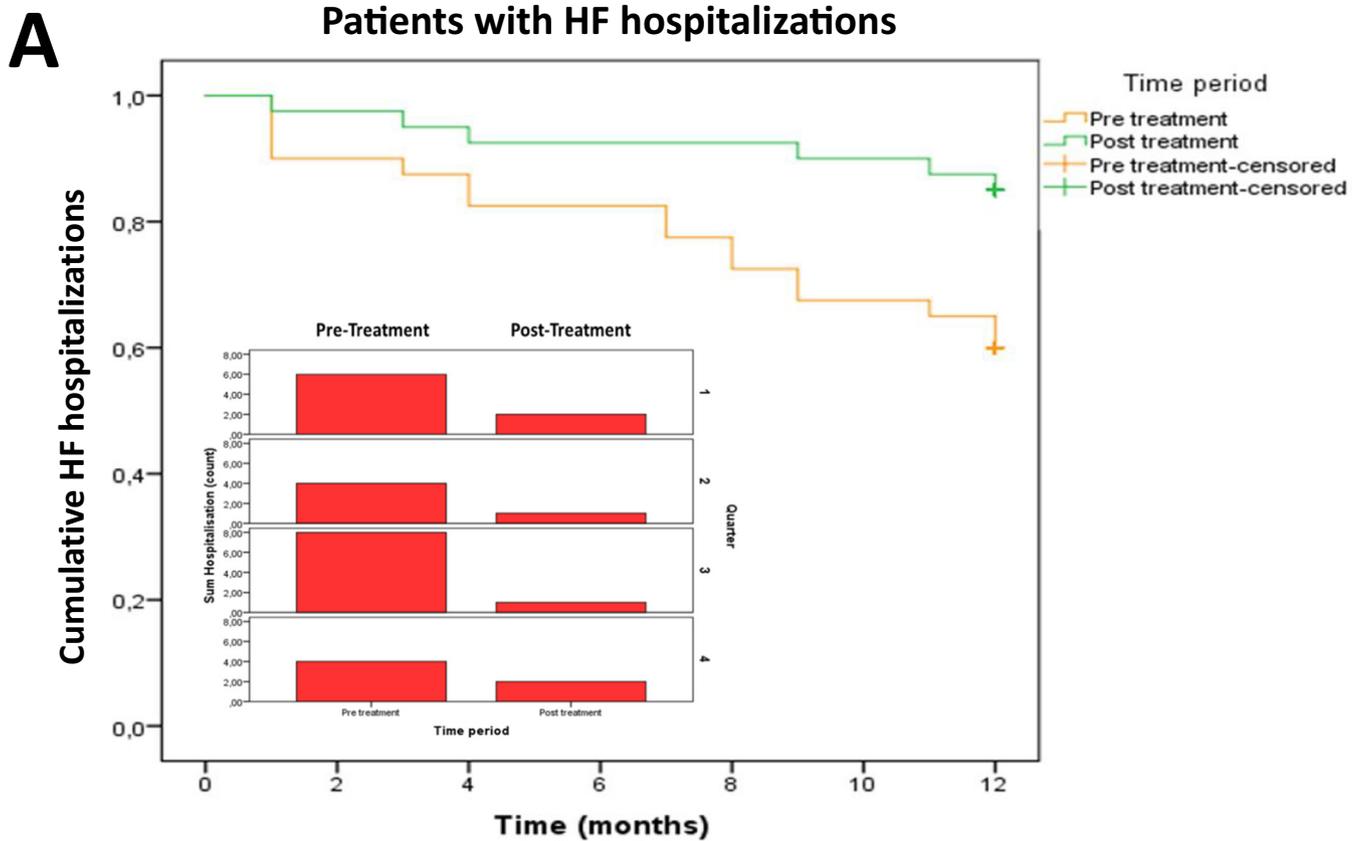
## A                    Patients with HF hospitalizations



**Fig. 2.** Frequency of heart failure (HF)-associated hospitalizations during the 12-month period prior to phosphodiesterase type 5 inhibitor (PDE5i) initiation versus the 12-month period during PDE5i therapy. Shown are the cumulative numbers of patients with HF-associated hospitalizations (only first event considered); *inset*: Total number of HF-associated hospitalizations (multiple hospitalizations per patient counted), divided by quartiles.

genes and biological pathways involving cell structure, extracellular matrix, and immune function in the lung known to contribute to pulmonary arterial hypertension (PAH) pathophysiology. Hence, CpcPH shares molecular, genetic and pathological similarities to PAH, suggesting that it may resemble a distinct and highly morbid PH sub-phenotype [38]. This likely explains the different results obtained in RCTs investigating the effects of PDE5i therapy in distinct subpopulations of patients with HFpEF-PH [19–21], and also provides the rationale for patient selection and treatment response in the present analysis.

Our results must therefore be put into perspective to other studies in the context of HFpEF-PH. In the RELAX trial, conducted in 216 patients with HFpEF without documented PH, the PDE5i sildenafil did not improve exercise capacity or clinical status [19]. In another RCT performed in 52 patients with HFpEF and IpcPH, sildenafil also failed to improve hemodynamics, clinical status or exercise capacity [20], which may be expected in the absence of a detectable treatment target in the pulmonary circulation. A third RCT was conducted before the current classification (IpcPH vs. CpcPH) was introduced, and included 44 patients with HFpEF and PH who predominantly fulfilled the hemodynamic criteria of CpcPH [21]. In this case, sildenafil led to significant improvements in hemodynamics and RV function. This is consistent with our observation reported herein, and also with recent data from the COMPERA registry, indicating that patients with HFpEF and severe PH may benefit from targeted PH therapy [22]. In addition to the hemodynamic phenotype, the type of intervention is obviously crucial. In this context, our findings are diverse from the recent MELODY-1 study in which the ERA macitentan failed to show benefit in patients with HF and CpcPH [42]. This may reflect differences in the tolerability and efficacy of ERA versus PDE5i in PH-HFpEF, as recently reported in registries [22].

The treatment effect in our patients was mainly characterized by improvements in exercise capacity, NTproBNP levels, and WHO-FC. The clinical meaningfulness of these changes and the relevance of the measured parameters during follow-up warrant discussion. To this end, data from 3 independent cohorts just became available that validated the risk stratification strategy in PAH as suggested in the ESC/ERS guidelines [18]. In all cohorts, the above 3 non-invasive parameters (6MWD, BNP/NTproBNP, WHO-FC) and particularly their changes during follow-up were among the strongest predictors of outcome in patients with PAH [43–46]. Given the overlap in clinical and pathophysiological features between PAH and CpcPH, the observed changes are most likely also clinically meaningful in the present cohort. Our findings of improved 6MWD, WHO-FC, and NTproBNP levels are consistent with those of patients with hemodynamically severe PH and HFpEF in the COMPERA registry [22].

In addition to the above parameters, several echocardiographic variables estimating RV function including TAPSE, RV-FAC, RA area and the TAPSE/PASP ratio were improved by PDE5i therapy. Given the prognostic relevance of RV dysfunction in HFpEF [8,9], these improvements may also be considered clinically meaningful. Improvement of RV/PA coupling as indicated by the TAPSE/PASP ratio may be of particular relevance [6,10]. In this sense, when compared to other studies [6,10,35,36,47,48], our patients demonstrating a mean $PA_C$ of $1{,}5 \pm 0{,}7$ ml/mmHg, an SVI of $32{,}4 \pm 9{,}5$ ml/m$^2$, and a TAPSE/PASP ratio of $0{,}27 \pm 0{,}02$ must be considered a "high risk" group. Finally, we observed a substantially lower hospitalization rate due to HF during PDE5i therapy in comparison to the 12 months prior to PDE5i initiation, which is also known to correlate with morbidity and mortality in both HFpEF and PAH patients [49,50].

## 4.1. Limitations

While our study is the first to report on the treatment response to PDE5i in the specific subset of patients with HFpEF and CpcPH, several strengths and limitations need to be highlighted. Strengths may include the precise hemodynamic characterization and specific focus on CpcPH, the optimization of volume status before initiation of therapy, and the complete data sets with very few missing variables, thus reflecting high quality data. Important limitations include the limited number of patients, the retrospective nature of the analysis, the single center approach, the lack of a control group, and open-label therapy, which may result in a bias towards overestimation of the treatment response. However, given the magnitude of the observed changes, particularly with regards to NTproBNP levels (which are less prone to investigator bias), our data are highly indicative of a true treatment effect.

Furthermore, we focused on patients who tolerated a PDE5i for at least 12 months, which may be viewed as a "responder analysis". However, given the design of recent HF trials such as PARADIGM-HF[51], which utilized a "run-in" period before randomization to ascertain drug tolerability before enrolment, capturing the treatment effect in patients who tolerate a targeted therapy may be of particular relevance for individual treatment decisions. A similar approach is currently being utilized in the context of CpcPH in the ongoing SERENADE study [ClinicalTrials.gov-Identifier: NCT03153111].

## 5. Conclusions

In accordance with the ESC/ERS PH guidelines [18], we discourage the uncritical use of PH therapies in patients with HFpEF-PH. However, our data obtained in hemodynamically precisely characterized patients indicate that patients with HFpEF and evidence of PVD, i.e. CpcPH, may benefit from targeted therapy with PDE5i. These data support the importance of proper phenotyping of patients with HFpEF-PH. Given the limitations of this retrospective analysis, our data may be considered hypothesis-generating and may inform larger randomized studies. An RCT evaluating the efficacy and safety of a PDE5i in the subset of patients with HFpEF-CpcPH is warranted, and is currently under way (PASSION).

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