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Original article

Phosphodiesterase inhibitor for heart failure with preserved ejection fraction: A systematic review and meta-analysis

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ABSTRACT

Background: Although heart failure with preserved ejection fraction (HFpEF) is a serious disease, only limited options are available for its treatment. Recent studies have analyzed the effects of phosphodiesterase (PDE) inhibitors, especially PDE5 and PDE3 inhibitors, in patients with HFpEF, with mixed outcomes.

Methods: We searched PUBMED and EMBASE databases up to August 2021. Randomized controlled trials (RCTs) and clinical trials that tested the effects of PDE inhibitors on patients with HFpEF were included as eligible studies. Indicators of left ventricular (LV) function, pulmonary arterial pressure (PAP), right ventricular (RV) function, exercise capacity, and quality of life (QOL) were used to evaluate the efficacy of PDE inhibitors in HFpEF.

Results: Six RCTs that reported in 7 studies were included to evaluate the efficiency of PDE inhibitors on HFpEF patients. In the pooled analysis, PDE inhibitors showed insignificant changes in the ratio of early diastolic mitral inflow to annular velocities, left atrial volume index, pulmonary artery systolic pressure (PASP), pulmonary vascular resistance (PVR), peak oxygen uptake, 6-minute walking test distance, as well as Kansas City Cardiomyopathy Questionnaire score. However, substantial improvement was observed in the tricuspid annular plane systolic excursion (TAPSE). Additionally, the regression analysis showed that PDE inhibitor administration time is a critical factor for the decrease in PASP.

Conclusions: PDE inhibitors did not effectively improve LV function, PAP, exercise capacity, and QOL in patients with HFpEF. However, they improved RV function with significant difference, suggesting that PDE inhibitors might be a promising option for HFpEF patients with RV dysfunction.

Abbreviations: BD, baseline data; cAMP, cyclic adenosine monophosphate; CD, change data; cGMP, cyclic guanosine monophosphate; E/e′, early diastolic mitral inflow to annular velocities; FD, final data; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City cardiomyopathy questionnaire; LAVI, left atrial volume index; LV, left ventricular; MeSH, Medical Subject Heading; NT-proBNP, N-terminal fragment of the precursor to brain-type natriuretic peptide; PAP, pulmonary arterial pressure; PASP, pulmonary artery systolic pressure; PDE, phosphodiesterase; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QOL, quality of life; RCTs, randomized controlled trials; RV, right ventricular; RR, risk ratio; SMD, standardized mean difference; TAPSE, tricuspid annular plane systolic excursion; VO_2, oxygen uptake; 95% CIs, 95% confidence intervals; 6MWT, 6-minute walking test.

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1. Introduction

Heart failure with preserved ejection fraction (HFpEF) has emerged as a grave health and epidemiological issue with high rates of morbidity and mortality; however, there are no known evidence-based treatment strategies available to date (Dunlay et al., 2017). The treatment dilemma of HFpEF is largely derived from its heterogeneous nature that is usually accompanied by a series of associated diseases, including hypertension, diabetes mellitus, obesity, and atrial fibrillation (Dunlay et al., 2017; Cuijpers et al., 2020; Guo et al., 2022). Additionally, right ventricular (RV) dysfunction has been frequently observed in HFpEF; sustained increase in pulmonary pressures can directly result in increased RV afterload, leading to RV failure, which is associated with an even worse outcome (Gorter et al., 2016; Gorter et al., 2018; Gomes-Neto et al., 2019; Berglund et al., 2020; Obokata et al., 2020). Thus, increasing knowledge of RV dysfunction and listing it as a therapeutic target might aid the treatment efficacy of HFpEF (Obokata et al., 2019; Berglund et al., 2020).

Numerous pharmacotherapy trials have been conducted on patients with HFpEF, including the ones that target RV dysfunction (Hoendermis et al., 2015; Nadur et al., 2021). The most widely studied agents include phosphodiesterase (PDE) inhibitors, guanylate-cyclase stimulators, and inhaled sodium nitrite (Bonderman et al., 2014; Hoendermis et al., 2015; Simon et al., 2016; Zhang et al., 2018). PDE inhibitors comprise a superfamily with 11 subfamilies, among which PDE3 inhibitors are mainly used as inotrope for acute heart failure and PDE5 inhibitors for pulmonary hypertension (PH) treatment (Derici et al., 2019). PDE inhibitors act as a super-enzyme family that is mainly involved in the repression of hydrolysis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). This feature of PDE inhibitors indicates its role as a promoting agent for HFpEF therapy (Kramer et al., 2019).

PDE inhibitors are known to exert differential effects on patients with HFpEF (Redfield et al., 2013; Wang et al., 2017; Nanayakkara et al., 2020). Sildenafil is one of the most extensively investigated PDE5 inhibitors in patients with HFpEF (Ovchinnikov et al., 2018; Emdin et al., 2020). Although previous studies have shown beneficial effects of sildenafil on cardiovascular function in patients with HFpEF; the RELAX trial and its ancillary analysis observed no improvement in exercise capacity and cardiac function (Guazzi et al., 2011; Redfield et al., 2013; Hussain et al., 2016). Moreover, recent studies have demonstrated the effects of milrinone, a PDE3 inhibitor, on patients with HFpEF; extended-release oral milrinone with a dosage of 14 mg has been confirmed to significantly improve the quality of life (QOL) of patients after 28 days of administration (Nanayakkara et al., 2020). These observations indicated the need for large-scale clinical trials to further evaluate pharmacological interventions or to explore novel subtype agents.

Given that the PDE5 inhibitors predominantly exert biological effects in PH, it was hypothesized that they could effectively improve RV dysfunction in patients with HFpEF with PH (Ovchinnikov et al., 2018). On the contrary, PDE3 inhibitors act as a therapeutic option for patients with HFpEF by directly increasing cardiac function, which might explain the differential effects of PDE inhibitors on patients with HFpEF. However, whether PDE inhibitors provide benefit to patients with HFpEF or it could only be a treatment for specific subgroup of these patients need further investigation. Thus, this systematic review and meta-analysis systematically evaluated the current literature to investigate the efficacy of PDE inhibitors in patients with HFpEF to reveal the potential clinical role of PDE inhibitors across the spectrum of HFpEF phenotypes and offer more evidence for HFpEF treatment.

2. Methods

2.1. Data sources and search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to conduct this meta-analyses and systematic reviews (Moher et al., 2015). PubMed and Embase databases were searched from inception of the database to 31 August 2021. Searches were limited to RCTs and clinical trials in all languages. We searched PubMed using free search text terms combined with Medical Subject Heading (MeSH) with the terms of "diastolic heart failure" and "phosphodiesterase inhibitor". The detailed search terms have been shown in Supplementary material. Additionally, potentially eligible studies were also checked and reviewed from other electronic databases without language restriction.

2.2. Selection strategy

Two reviewers (K.Z. and C.X.) independently screened titles and abstracts and removed duplicate retrieved records. Full text that considered as eligible should satisfy the following inclusion criteria: (1) the RCT or clinical trial performed in patients with HFpEF, (2) PDE inhibitors were used in these patients, (3) assessed at least one of the following outcome parameters: left ventricular (LV) function, pulmonary arterial pressure (PAP) and right ventricular (RV) function, exercise capacity and QOL, (4) individuals in control group and PDE inhibitor treatment group were satisfied with the same HFpEF diagnosis criteria and all parameters at baseline had no significance. Any disagreement in terms of the inclusion of an article was resolved by consensus with a third investigator.

2.3. Data extraction

Data extraction was conducted by the two authors, and they independently used a predefined, standardized protocol and data conversion formulas. One investigator extracted the following data from included studies and a second investigator checked the extracted data. The disagreement was resolved by consensus. Information was extracted including study design, characteristics, and outcomes. Basic characteristics involved in years of publication, study design, sample number, gender, cardiac function, comorbidities, drug delivery protocol and time. Outcomes of LV function, PAP and RV function, exercise capacity and QOL were respectively extracted for analysis. The primary and secondary outcomes were summarized as Table S1.

2.4. Quality assessment

Risk of bias was independently assessed by two investigators (Z. H. and S.L.) using the Cochrane Collaboration's risk of bias tool (RevMan5.3 software). Seven domains were evaluated, including random sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, selective reporting, intention-to-treat analysis, and other sources of bias, which has been shown in Table S2. Each of the items will be evaluated by the two reviewers as having low, high, or unclear risk of bias.

2.5. Statistical analysis

The change data (CD) calculated by the baseline data (BD) and final data (FD) using the formulas 1 and 2 were extracted from individual studies, and the pooled risk ratio (RR) and corresponding 95% confidence intervals (CIs) were calculated for each out-

come by CD. The results were presented as standardized mean difference (SMD) with 95% CIs. The heterogeneity of the data was quantified using the Q statistic and the I^2 statistic. High heterogeneity was considered significant when $P < 0.05$ for the Q statistic or when the $I^2 > 50\%$. Effect sizes of PDE inhibitors with the difference between the placebo and medication groups were pooled using the random-effects model. Meta-regression analysis of drug delivery time was performed to determine whether it was related to the outcome, and the correlation was considered significant when the value of $P > |t|$ was < 0.05. These analyses were performed using STATA, v12.

$$SD_1(C) = \sqrt{SD_1(B)^2 + SD_1(F)^2 - (2 \times R_1 \times SD_1(B) \times SD_1(F))} \quad (1)$$

$$mean_1(C) = mean_1(F) - mean_1(B) \quad (2)$$

where $SD_1(C)$, $SD_1(B)$, and $SD_1(F)$ were separately the standard deviation of the CD, BD, and FD. $Mean_1(C)$, $Mean_1(B)$, and $Mean_1(F)$ were separately the mean of the CD, BD, and FD. R_1 was an imputed correlation coefficient of 0.5.

3. Results

3.1. Eligible studies and characteristics

The search strategy included 43 publications. After screening for titles and abstracts, there were 18 studies remaining for full-text review. Eleven studies were excluded mainly because they did not report the identified results. Six RCTs that reported in seven studies were finally included for the qualitative analysis (Guazzi et al., 2011; Redfield et al., 2013; Borlaug et al., 2015; Hoendermis et al., 2015; Liu et al., 2017; Belyavskiy et al., 2020; Nanayakkara et al., 2020) (Fig. 1).

Table 1 shows the characteristics of these studies. In the pooled data, 433 individuals diagnosed as HFpEF were divided into placebo and PDE inhibitors treated groups. Among them, the mean percentage of females was 51%, mean age ranged from 69 to 77 years, and most of BMI was >30 kg/m^2. Also, the main concomitant diseases included hypertension, diabetes, and atrial fibrillation. PDE inhibitors used in the analyzed trials mainly included sildenafil and milrinone with a delivery time of 1–12 months (Table 1).

3.2. Quality assessment

The Cochrane risk of bias assessment tool was used to perform a quality assessment. Summary assessments of the risk of bias for an outcome within each trial was summarized in Fig. S1 and Table S2. Among these evaluated studies, six were identified as good (including a duplicated RCT), and one was considered as moderate mainly because of without random design.

3.3. Outcomes

3.3.1. LV function

Among these analyzed studies, LV diastolic function was mainly presented as the ratio of early diastolic mitral inflow to annular velocities (E/e′) and left atrial volume index (LAVI, mL/m^2)

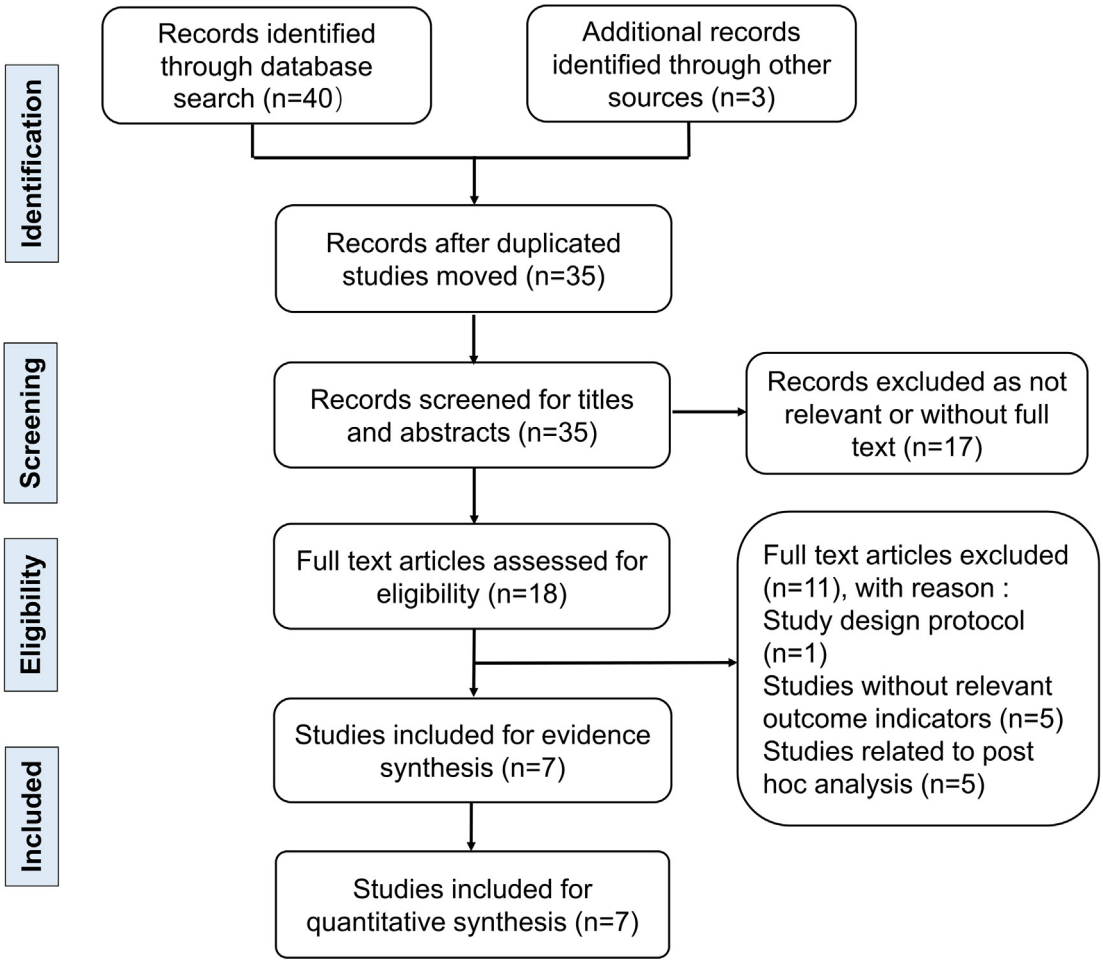

Fig. 1. Flow diagram of the systematic review.

Table 1
Characteristics of studies included in the meta-analysis.

Source	Design	Sample No.	Mean age (years) mean (SD)	Sex (% female)	NYHA class, LVEF (%), mean (SD)	Body mass index (kg/m^2) mean (SD)	Comorbidities, (%)	Medication
Nanayakkara et al. 2020	Double- blind, placeboRCT	23	77 (6)	74	III61 (6)	32 (1)	Hypertension (87);Diabetes (34.5) ;IHD (26.1) ;AF (39.1)	Extended- release milrinone minitabs (14 mg total dose), twice daily for 28 day
Belyavskiy et al., 2020	Open-label RCT	50	71 (7)	52	II–III61 (5)	30 (5)	Hypertension (100);AF (30) ;IHD (44) ;Diabetes (28) ;CKD (80)	Sildenafil 25 mg TID for 3 months, followed by 50 mg TID for 3 months (6 months)
Hoendermis et al. 2015	Double-blind, placebo-RCT	52	74 (10)	71	II–III58 (4)	29 (6)	CAD (33);Cerebrovascular disease (15) ;AF (62) ;Diabetes (35) ; Hypertension (90);Hypercholesterolaemia (52)	Sildenafil 20 mg TID for 2 weeks, titrated to 60 mg three times daily to 12 weeks
Borlaug et al. 2015	RCT	48	70 (3)	58	II–III60 (1.3)	30.6 (2.2)	Hypertension (79);Diabetes (35) ;Obese (56) ;CAD (33) ;AF (27)	Sildenafil 20 mg TID for 12 weeks, titrated to 60 mg TID to 24 weeks
Redfield et al. 2013	Double blind RCT	216	69 (4)	48	II–III60 (5.5)	32.9 (2.7)	Hypertension (85);IHD (39) ;AF (51) ; Diabetes (43)COPD (19)Anemia (35)	Sildenafil 20 mg, 3 times daily for 12 weeks, followed by 60 mg, 3 times daily for 12 weeks
Guazzi et al. 2011	Double blind RCT	44	73 (6)	20	60 (5)	31 (10)	Hypertension (100)Diabetes (16)	Sildenafil 50 mg thrice daily for 12 months

AF: atrial fibrillation, CAD: coronary artery disease, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, IHD: ischemic heart disease, LVEF: left ventricular ejection fraction, RCT: randomized clinical trial.

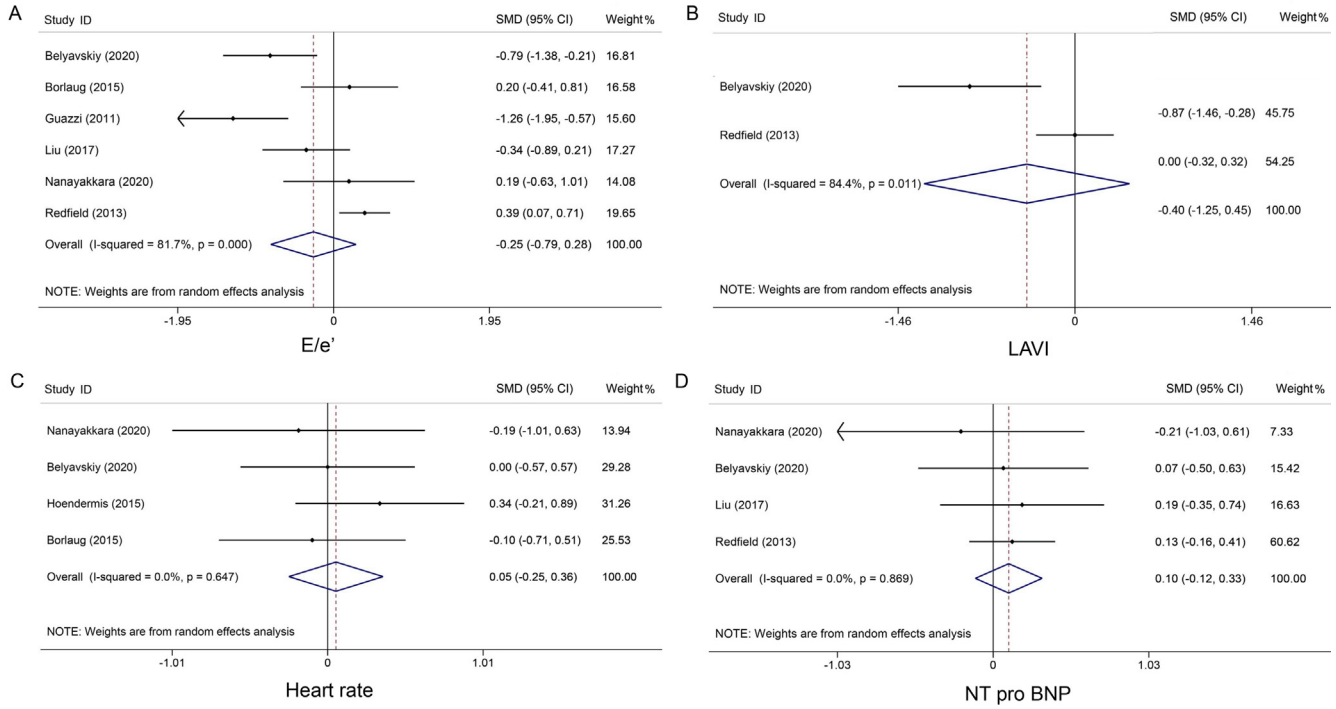

Fig. 2. Forest plot showing effects of PDE inhibitors on LV function. All results are reported as a SMD (Placebo-PDE inhibitor) with a 95% CI. A. E/e′. B. LAVI. C. Heart rate. D. NT-proBNP. E/e′, the ratio of early diastolic mitral inflow to annular velocities; NT-proBNP, N-terminal fragment of the precursor to brain-type natriuretic peptide; PDE, phosphodiesterase; SMD, standardized mean difference; LAVI, left atrial volume index; 95% CI, 95% confidence interval.

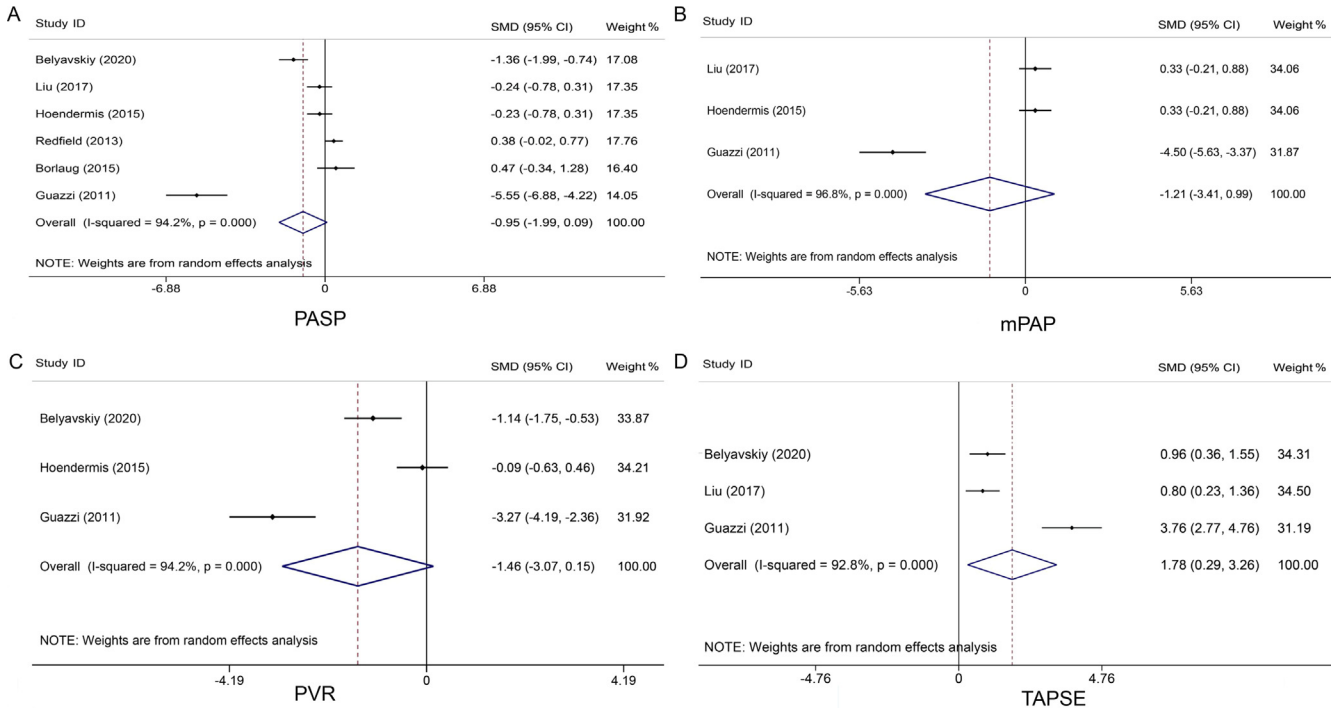

Fig. 3. Forest plot for the effect of PDE inhibitors on PAP and RV function. All results are reported as a SMD (Placebo-PDE inhibitor) with a 95% CI. A. PASP. B. Mean PAP. C. PVR. D. TAPSE. PASP, pulmonary artery systolic pressure; PAP, pulmonary arterial pressure; PDE, phosphodiesterase; PVR, pulmonary vascular resistance; SMD, standardized mean difference; TAPSE, tricuspid annular plane systolic excursion; 95% CI, 95% confidence interval.

(Redfield et al., 2013; Belyavskiy et al., 2020). Six studies reported the impact of PDE inhibitors on E/e′ value, and pooling across analysis showed no significant change in 182 patients with HFpEF who were treated with PDE inhibitors as compared with the placebo group (SMD [95% CI], −0.25 [−0.79, 0.28], $P = 0.353$) (Fig. 2A). Additionally, LAVI had been tested in two studies with 105 patients treated with PDE inhibitors, which also showed an absence of significance after drug delivery compared with the placebo group (SMD [95% CI], −0.4 [−1.25, 0.45], $P = 0.358$) (Fig. 2B). Thus, this result indicated that PDE inhibitors could not improve LV diastolic

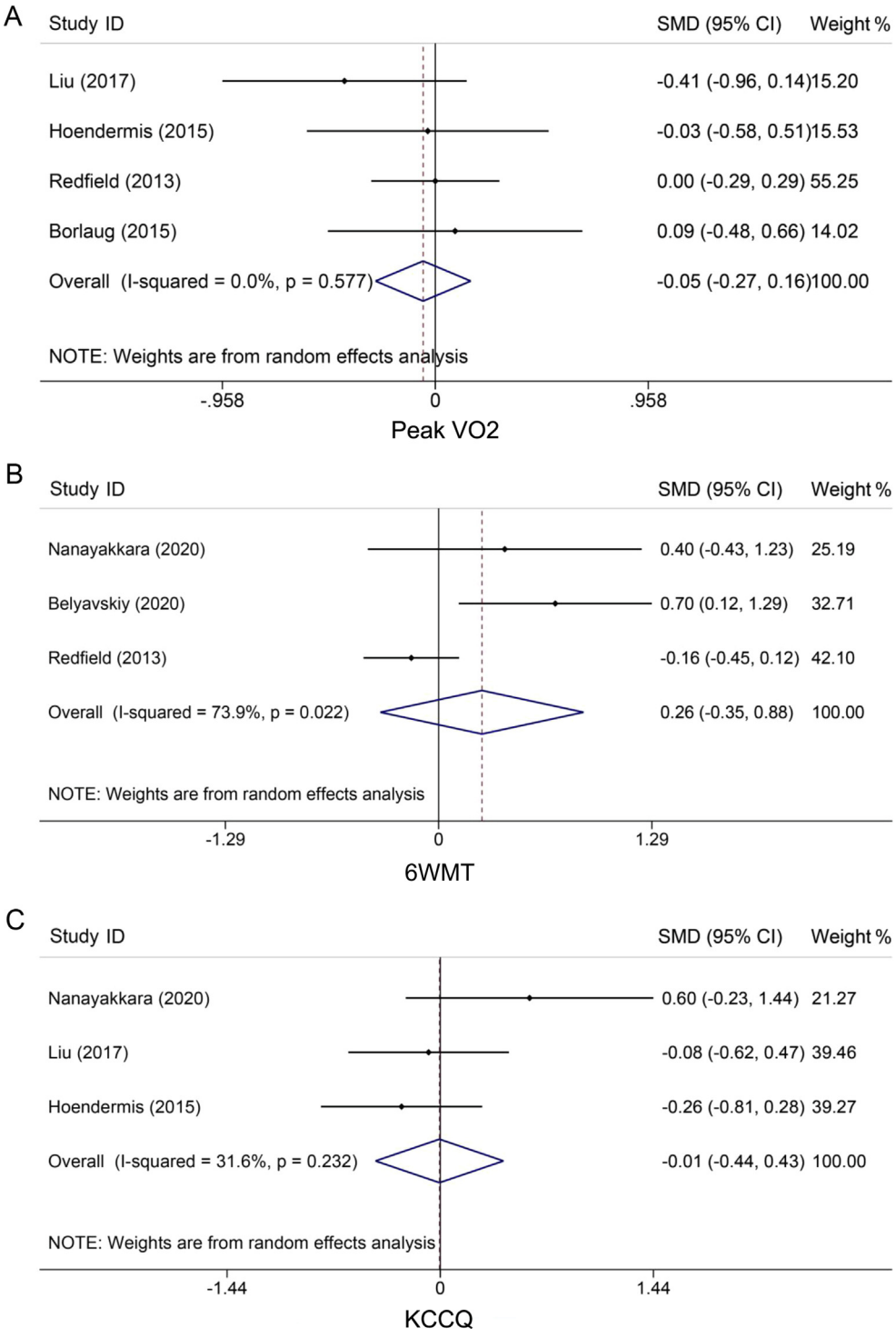

Fig. 4. Forest plot showing effects of PDE inhibitors on exercise capacity and QOL. All results are reported as a SMD (Placebo-PDE inhibitor) with a 95% CI. A. Peak VO_2. B. 6WMT. C. KCCQ. KCCQ, Kansas City cardiomyopathy questionnaire; PDE, phosphodiesterase; SMD, standardized mean difference; VO_2, oxygen uptake; 6MWT, 6-minute walking test; 95% CI, 95% confidence interval.

function in patients with HFpEF, yet the heterogeneity of both E/e′ and LAVI was statistically different.

Furthermore, a heart rate that is considered as an indicator to reflect cardiac function was also assayed in four RCTs. The pooled analysis revealed no significant changes in patients with HFpEF after treatment with PDE inhibitors compared with the placebo group (SMD [95% CI], 0.05 [−0.25, 0.36], P = 0.73) (Fig. 2C). The heterogeneity of heart rate was identified as without significance. Besides, four studies with 314 patients were tested NT-proBNP level and did not show any significance after treatment with PDE inhibitors compared with the placebo group (SMD [95% CI], 0.1 [−0.12, 0.33], P = 0.361), without evident heterogeneity (Fig. 2D). This indicated that PDE inhibitors had not exactly improved LV function, especially the diastolic function, in patients with HFpEF.

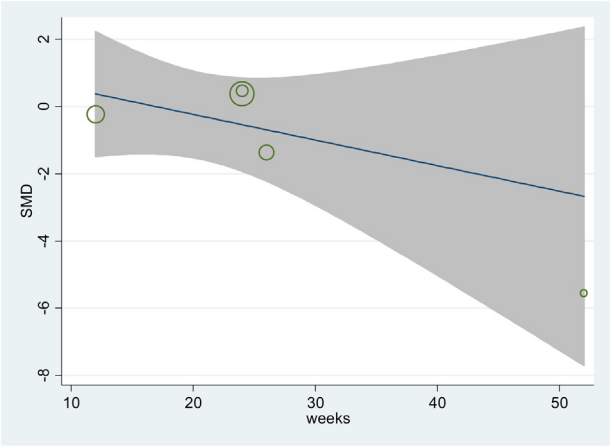

Fig. 5. Meta-regression of drug delivery time and PASP of HFpEF patients. Bubble plot revealing the association (P = 0.031) between PDE inhibitor treatment and PASP. PASP, pulmonary artery systolic pressure; PDE, phosphodiesterase; SMD, standardized mean difference; TAPSE, tricuspid annular plane systolic excursion.

3.3.2. PAP and RV function

Six trials with 159 patients with HFpEF tested pulmonary artery systolic pressure (PASP, mmHg) after treatment with PDE inhibitors. The pooled data showed that PASP decreased but without statistical significance after treatment with PDE inhibitors compared with the placebo group (SMD [95% CI], −0.95 [−1.99, 0.09], P = 0.073) (Fig. 3A). Also, mean PAP (mmHg) reduced without significance in the PDE inhibitors treated group compared with placebo group (SMD [95% CI], −1.21 [−3.41, 0.99], P = 0.281) (Fig. 3B). The heterogeneity of PASP and mean PAP among the studies were identified to be significant.

A pooled analysis using data from three RCTs showed a distinctive decrease in pulmonary vascular resistance (PVR, Wood units) but without significance after treatment with PDE inhibitors compared with the placebo group (SMD [95% CI], −1.46 [−3.07, 0.15], P = 0.075) (Fig. 3C). However, three studies with 146 patients tested the tricuspid annular plane systolic excursion (TAPSE) to evaluate RV function, and revealed a statistical increase after treatment with PDE inhibitors (SMD [95% CI], 1.78 [0.29, 3.26], P = 0.019) (Fig. 3D). Similarly, the heterogeneity of PVR and TAPSE was also found to be substantially significant, but its cause could not be further analyzed for the limited studies. Therefore, these results suggested that PDE inhibitors could not effectively reduce PAP but significantly increase RV systolic function.

3.3.3. Exercise capacity and QOL

One of the most widely used indicators to evaluate exercise capacity is peak oxygen uptake (VO_2) (Gomes-Neto et al., 2019). After pooled analysis, three studies involving 336 patients with HFpEF showed the absence of significant change in peak VO_2 after treatment with PDE inhibitors without statical heterogeneity (SMD [95% CI], −0.05 [−0.27, 0.16], P = 0.616) (Fig. 4A). Additionally, three studies also tested 6-minute walking test (6MWT) in HFpEF patients and exhibited an absence of significance in the PDE inhibitors treatment group compared with the placebo group (SMD [95% CI], 0.26 [−0.35, 0.88], P = 0.403) (Fig. 4B). This result demonstrated that PDE inhibitors did not markedly improve exercise capacity in HFpEF patients.

Kansas City Cardiomyopathy Questionnaire (KCCQ) score is a widely used heart failure-specific QOL scale, with a higher score indicating better QOL. A pooled analysis using data from three RCTs involving 127 patients with HFpEF did not show obvious changes in the KCCQ score after treatment with PDE inhibitors (SMD [95% CI], −0.01 [−0.44, 0.43], P = 0.982) (Fig. 4C). The heterogeneity was not statistically significant, suggesting PDE inhibitors exerting insignificant effects on QOL for patients with HFpEF.

3.4. Regression analysis differential effects of drug delivery time

Regression analysis was performed to verify whether drug delivery time in these trials could cause differential effects in patients with HFpEF. Among these analyzed outcomes, PASP change showed an obvious decrease but with high heterogeneity after treatment with PDE inhibitors in patients with HFpEF. After data pooling from the six trials, PASP was positively correlated to drug delivery time, and a longer treatment duration with PDE inhibitor was more beneficial for patients (Fig. 5). Thus, differential effects of PDE inhibitors on patients with HFpEF based on drug delivery time may suggest its efficiency in the pathological courses.

4. Discussion

The principal finding of this meta-analysis was that PDE inhibitors could not significantly improve LV function, PAP, exercise capacity and QOL, but substantially improved RV dysfunction in patients with HFpEF. Although PAP had no statical difference, there was a marked decrease tendency in PASP and PVR after treatment with PDE inhibitors. Long-term administration of PDE inhibitors was more likely to reduce PASP for patients with HFpEF.

A decrease in the TAPSE acts as a surrogate of RV systolic dysfunction (Obokata et al., 2019). In this meta-analysis, we have found that PDE inhibitors might significantly improve RV function via increasing TAPSE, though its heterogeneity has been found to be substantially significant. RV dysfunction was an extremely common pathophysiological consequence in patients with HFpEF, and its presence predicted a worse prognosis (Obokata et al., 2020). However, there are currently no established strategies to treat RV dysfunction in patients with HFpEF. Recent trials have demonstrated differential effects of therapeutic strategies in patients with HFpEF, including clinical PDE inhibitors (Gorter et al., 2018). The PDE5 inhibitor sildenafil is an established drug for patients with PH, but it presents mixed results in HFpEF (Guazzi et al., 2011; Redfield et al., 2013; Petit et al., 2021). Although Guazzi et al. (Guazzi et al., 2011) has reported PDE5 sildenafil could significantly reduce RV function after 6–12 months administration in 44 patients with HFpEF, later study showed without significant change in RV function and clinical status after sildenafil treatment for 12 weeks (Liu et al., 2017). This difference may be resulted by the baseline of included patients and sildenafil delivery time, which should be a reason of high heterogeneity in this study. Intriguingly, a PDE3 inhibitor milrinone was also studied for the reduction of RV afterload in patients with HFpEF and reported exerting an improvement in RV function (Kaye et al., 2016; Nanayakkara et al., 2020). This was consistent with our analysis that PDE inhibitors could effectively correct RV dysfunction. However, the different subtypes of PDE inhibitors may be another reason for the heterogeneity of TAPSE in this study. Unfortunately, the main reason of this heterogeneity in this meta-analysis had not been further analyzed for the limited studies. This result still needs more trails to confirm.

The most important indicators to evaluate PAP in these analyzed studies include PASP, mean PAP, and PVR, which generally reflect the afterload of the heart. Although the pooled data did not manifest a significant change in PAP, it showed an apparent decrease in PASP and PVR after treatment with PDE inhibitors. After regressive analysis, it was revealed that the decrease in PASP was positively correlated with the drug delivery time. In sildenafil-treated studies, Guazzi et al. (2011) reported an improvement in

pulmonary and RV hemodynamics, as well as QOL after 6-month treatment in patients with HFpEF, which further improved after 12-month drug delivery. However, a single sildenafil administration in patients with HFpEF failed to increase circulating cGMP levels and did not improve RV performance (Petit et al., 2021). Liu et al. (2017) further demonstrated that treatment with sildenafil for 12 weeks in patients with HFpEF did not markedly improve cardiac and pulmonary parameters. Thus, drug delivery time needed to be considered in further studies.

Besides, patients with HFpEF who were treated with sildenafil for 12 weeks or 24 weeks showed conflicting results in improved exercise capacity and clinical status when compared with the placebo group (Redfield et al., 2013; Liu et al., 2017). In this meta-analysis, we also did not observe a significant improvement in LV function and exercise capacity. Sildenafil might display opposing effects on ventricular and vascular function in patients with HFpEF, indicating that the beneficial effects of sildenafil in systemic vasculature and endothelium were insufficient to improve clinical status or its deleterious effects of cardiac function result in the inconspicuous benefits for HFpEF (Borlaug et al., 2015).

KCCQ is a main tool to reflect QOL, which has been used in three analyzed RCTs. In this meta-analysis, it has been found that PDE inhibitors could not significantly improve QOL in patients with HFpEF. However, studies also evaluated QOL in patients with HFpEF with other scales, which showed conflicting results (Guazzi et al., 2011; Redfield et al., 2013; Liu et al., 2017). Given the limited analyzed trails and inconsistent evaluation for QOL, further studies are required to determine its effect after treated with PDE inhibitors in patients with HFpEF.

Additionally, it has also been identified that a subset of precisely characterized patients with HFpEF with pre-and postcapillary PH could benefit from PDE5 inhibitor, including improvement in exercise capacity, pulmonary hemodynamic parameters, and RV function (Kramer et al., 2019; Belyavskiy et al., 2020). This result also needs further trials of precision treatment with PDE inhibitors in patients with HFpEF. Most pharmacological agents used in clinical trials, including those targeting the nitric oxide and cGMP pathways, have largely been neutral in HFpEF (Gorter et al., 2018). Thus, identifying effective treatments for patients with HFpEF remains a major therapeutic challenge.

5. Limitations

This meta-analysis exists following limitations. Firstly, the sample size of this systematic review is relatively small, which may lead to deviation. Secondly, most outcome indicators involve in this meta-analysis with a high heterogeneity, but the source of these heterogeneities has not been analyzed since the limited trails. Besides, the subtype of PDE inhibitors possess different functions in PH and cardiac function, which might also be an explanation of these variables in results.

6. Conclusions

This meta-analysis is the first to highlight the beneficial effects of PDE inhibitors in patients with HFpEF. The current meta-analysis illustrated that PDE inhibitors did not significantly change LV function, PAP, exercise capacity, and QOL in patients with HFpEF, while the RV function was substantially improved after administration of PDE inhibitor. The PASP decrease was positively correlated with drug delivery time, though its change was not statically significant. Thus, it could be speculated that PDE inhibitors might be a promising therapeutic option to correct RV dysfunction in patients with HFpEF, which probably gain more benefits in reducing PAP via extending medication time. Nevertheless, these results need further investigation with more clinical trials due to the limited trails analyzed in this study.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2022.05.012.

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