Haemodynamic changes of interatrial shunting devices for heart failure: a systematic review and meta-analysis

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Abstract

Aims To assess the efficacy and safety, primarily in relation to the haemodynamic effects, of interatrial shunting devices (ISD) for the treatment of heart failure (HF), we conducted a systematic review and a meta-analysis.

Methods and results We used the MEDLINE, Cochrane Library, Embase, and PubMed databases to identify clinical studies (published to 4 August 2021) that evaluated the effect of ISD on HF. The primary endpoint was defined as changes in pulmonary capillary wedge pressure (PCWP). Secondary endpoints included (i) other haemodynamic indexes, including cardiac output (CO), right atrial pressure (RAP), and mean pulmonary artery pressure (mPAP) by right heart catheterization, and (ii) change from baseline in 6 min walk distance (6MWD). After a literature search and detailed evaluation, six trials enrolling a total of 203 individuals were included in the quantitative analysis. Pooled analyses showed that after ISD implantation, PCWP decreased by a mean 3.10 mmHg [95% confidence interval (CI) -4.56 to -1.64; \( I^2 = 0\% \); \( P < 0.0001 \)]. Overall, CO increased by 0.77 L/min (95% CI 0.02 to 1.52; \( P = 0.04 \); \( I^2 = 82\% \)), but there were no significant changes in RAP or mPAP. The mean 6MWD increased by 32.33 m (95% CI 10.74 to 53.92; \( P = 0.003 \); \( I^2 = 0 \)) after ISD implantation.

Conclusions Interatrial shunting device can effectively reduce PCWP, increase CO and 6MWD, and has no obvious adverse effects on the right heart and pulmonary pressure. Studies with larger sample size and longer follow-up time are needed for further verification.

Keywords Interatrial shunting devices; Heart failure; Haemodynamic changes; Pulmonary capillary wedge pressure; Meta-analysis

Introduction

Heart failure (HF) is a heterogeneous condition with wide variations in presentation, aetiology, and pathophysiology.1 Currently, the incidence of HF in Europe is reported as 0.3% person-years for all age groups and about 0.5% person-years in adults,2 although its true prevalence is likely higher.1 Although notable progress has been made in the treatment of systolic left ventricular HF (LVHF) in recent years, it remains a formidable challenge, and HF-related morbidity and mortality remain high.3

The core mechanism of LVHF is that decreased left ventricular function leads to increased left ventricular end-diastolic pressure, which in turn leads to elevated left atrial (LA) pressure and pulmonary capillary wedge pressure (PCWP), finally resulting in pulmonary oedema and decreased oxygen exchange capacity. Increased LA pressure and PCWP in HF patients are associated with worsening symptoms, lower functional capacity, and worse quality of life and prognosis.5,6 The observation that patients with the combination of mitral stenosis and a congenital atrial septal defect (Lutembacher syndrome) are less symptomatic...
patients with isolated mitral stenosis of similar severity due to LA pressure offloading supports the idea that reducing LA pressure by left-to-right shunt may be effective in reducing PCWP and relieving the symptoms of pulmonary oedema. This indicates that opening a shunt channel between the left and right atria could be effective in reducing LA pressure and relieving the symptoms of HF. In recent years, a number of devices have been developed for LA decompression, most of which use the interatrial septum as the site of shunt placement.

In this study, we conducted a meta-analysis to comprehensively evaluate the effectiveness of interatrial shunting devices (ISDs) for the management of HF.

Methods

Literature search and study selection

A systematic review (registered on PROSPERO as CRD 42021277080) of the published literature was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. To identify all published clinical studies that evaluated the effects of interatrial shunting for treating HF, we performed a comprehensive online search of the published literature (until 4 August 2021) using the MEDLINE, Cochrane Library, Embase, and PubMed databases. The search strategy used relevant keywords and medical subject heading terms, including HF, ISD, and atrial septostomy. To avoid missing relevant data, additional trials were identified by hand-searching bibliographies from included studies and reviews.

Eligibility criteria

Studies qualified for inclusion if the reports included sufficient information on key points. These criteria were as follows: (i) a detailed study protocol with rigorous inclusion and exclusion criteria; (ii) the subjects were patients with HF; (iii) individuals enrolled received haemodynamic assessment at baseline and during follow-up; and (iv) if a primary study had more than one follow-up, only those with results of haemodynamic assessment and the longest follow-up time were included. Abstracts, case reports, conference presentations, editorials, and expert opinions were excluded.

Data extraction and critical appraisal

Data abstraction was conducted by two authors who independently used a predefined, standardized protocol and data collection instrument. Information was recorded on study design, demographic characteristics, haemodynamic assessment, functional changes, and major adverse events. Any discrepancies were resolved by consensus among the authors. To assess the study quality and risk of bias, the Cochrane Collaboration’s risk of bias and ROBINS-I tools were used.

Primary and secondary endpoints

The primary endpoint was defined as changes in PCWP. Secondary endpoints were changes in other haemodynamic parameters, including cardiac output (CO), right atrial pressure (RAP), and mean pulmonary artery pressure (mPAP). In addition, functional capacity, primarily defined by 6 min walk distance (6MWD) and New York Heart Association (NYHA) classification, was also evaluated. Major adverse events were defined as death, HF rehospitalization, and device-related adverse events.

Statistical analyses

Continuous variables were reported as means ± standard deviations (SDs), whereas numerical data were expressed as numbers and percentages (%). Pooled analyses were calculated using fixed-effect models (I² < 50%), whereas random-effect models were applied in case of any heterogeneity across studies (I² ≥ 50%). To detect any publication bias, we visually examined funnel plots for PCWP and further assessed asymmetry using the Egger regression asymmetry test. To test the stability of our meta-analysis further, we performed multiple subgroup analyses according to type of device, type of HF, sample size, and follow-up time. All P values were two-tailed, and significance was set at P < 0.05. Statistical analyses were performed using the RevMan software package (Review Manager, Version 5.1; The Cochrane Collaboration, Oxford, UK) and Stata software 12.0 (StataCorp, College Station, TX, USA). As with other studies using similar analysis methods, the patient cohort pre-procedure was defined as the comparison group.

Results

A total of 269 records were identified in the searches. Of these, 242 were excluded after the screening of the title and abstract. Of the remainder, 19 papers were excluded after full-text review, and two articles were excluded because of incomplete data. Six studies were included with a total of 203 enrolled patients, of whom 181 underwent implantation of an ISD (Figure 1 and Table 1).

Tables 1 and 2 summarize the characteristics of the included studies. No studies were randomized controlled studies except for REDUCE LAP-HF I. One trial only enrolled individuals with HF with reduced ejection fraction (HFrEF),
Table 1 Characteristics of included studies

| Study and reference citation | Year | Device | Design | LVEF | NYHA class | Included number | Follow-up | Device occlusion/stenosis (n) | Adverse events |
|------------------------------|------|--------|--------|------|------------|----------------|----------|-------------------------------|---------------|
| Søndergaard *et al.*          | 2014 | IASD   | Pilot trial | ≥45% | III/IV     | 11             | 1 month | 0                            | 1             |
| REDUCE LAP-HF                 | 2016 | IASD   | Single-arm study | ≥40% | II–IV     | 64             | 12 months | 0                            | 20           |
| Proof-of-principle cohort study | 2016 | V-Wave | Cohort study | ≤40% | III/IV     | 10             | 3 months | 0                            | 1             |
| REDUCE LAP-HF I              | 2018 | IASD   | Randomized control trial | ≥40% | III/IV     | 44             | 1 month | 0                            | 2             |
| First-in-human experience    | 2018 | V-Wave | Non-randomized | >15% | III/IV     | 38             | 12 months | 19                           | 3             |
| AFR-PRELIEVE TRIAL           | 2019 | AFR device | Pilot study | ≥15% | III/IV     | 36             | 3 months | 0                            | 11            |

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 2 Demographic characteristics of participants from the included studies

|                        | Søndergaard *et al.* | REDUCE LAP-HF | Proof-of-principle cohort study | REDUCE LAP-HF I treatment/control | First-in-human experience | AFR-PRELIEVE TRIAL |
|------------------------|----------------------|---------------|---------------------------------|-----------------------------------|--------------------------|-------------------|
| Age (years)            | 70 ± 11.9            | 69 ± 8        | 62 ± 8/ | 69.6 ± 8.3/70.0 ± 9.2 | 66 ± 9 | 67.3 ± 8.6 |
| Male sex (%)           | 45%                  | 35%           | 90%    | 63.6/36.4 | 92% | 21% |
| HFrEF/HFrEF (%)        | 11/0                 | 64/0          | 44/0   | 83/38.3  | 68% | 55.6%
| CAD (%)                | 36%                  | 36%           | 90%    | 93/88.3  | 68% | 55.6% |
| HT (%)                 | 91%                  | 81%           | 70%    | 81.8/90.9 | 84% | 66.7% |
| DM (%)                 | 45%                  | 33%           | 70%    | 54.5/54.5 | 68% | 52.8% |
| Atrial fibrillation/flutter (%) | 36%       | 36%           | 70%    | 59/91    | 53% | NA   |
| IV/IV (%)              | 9/2                  | 46/0          | 10/0   | 22/0; 21/1 | 37/1 | 33/3 |
| LVEF (%)               | 57 ± 9               | 47 ± 7        | 25 ± 8 | 59.9 ± 9.0/ | 50 ± 9 (HFrEF), 51.5 ± 6 (HFrEF), | |

BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HFrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HT, hypertension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation.

Data are mean ± SD or n (%).
and three trials\textsuperscript{13,14,16} only enrolled individuals with HF with preserved ejection fraction (HFrEF), while two trials\textsuperscript{17,18} enrolled both HFrEF and HfPEF patients. Three studies\textsuperscript{13,14,16} used the InterAtrial Shunt Device (IADS, DC Devices Inc, Tewksbury, MA, USA), two studies\textsuperscript{15,17} used the V-Wave interatrial shunt device (V-Wave, V-Wave Ltd, Or Akiva, Israel), and one trial used Atrial Flow Regulator (AFR, Occlutech, Istanbul, Turkey).\textsuperscript{18} Follow-up time ranged from 30 days to 12 months.

Primary endpoint data were available in all trials. Pooled analyses showed that there was a significant reduction of PCWP [mean difference (MD), \(-3.10\) mmHg; 95% confidence interval (CI), \(-4.56\) to \(-1.64\); \(P < 0.0001\)] after ISD implantation. There was no heterogeneity between these studies (\(I^2 = 0\); \(P = 0.64\); Figure 2).

The secondary endpoints showed a significant effect of ISD in increasing CO, with MD of 0.77 L/min (95% CI 0.02 to 1.52; \(P = 0.04\); \(I^2 = 82\%\)). There were no significant changes in RAP (MD 0.76 mmHg, 95% CI \(-0.20\) to \(1.72\); \(P = 0.12\); \(I^2 = 0\)) or mPAP (MD \(-0.95\) mmHg, 95% CI \(-3.12\) to \(1.22\); \(P = 0.39\); \(I^2 = 0\)). The results of the meta-analysis showed a significant increase in 6MWD (MD 32.33 m, 95% CI 10.74 to 53.92; \(P = 0.003\); \(I^2 = 0\)) (Figure 3).

By the end of follow-up, the proportion of patients with NYHA Class III–IV had decreased from 88.6% to 32.8%, and the proportion of patients with NYHA Class I–II had increased from 11.4% to 67.2% (Supporting Information, Table S1).

The median follow-up of the six included studies was 3 months. Analysis of major adverse events showed that among the 203 patients included, the incidence of death was 3.0%, HF hospitalization rate was 11.3%, and 3.9% of patients had device-related adverse events (Supporting Information, Table S1).

Subgroup analysis also showed no significant differences among the different devices and types of HF in the change in 6MWD. Again, the data from follow-up within 6 months showed more significant changes in CO, while the data of follow-up beyond 6 months showed less significant changes. However, the improvement of 6MWD was significant both within and after 6 months (Supporting Information, Figures S1 and S2).

According to the Cochrane Collaboration’s risk of bias and ROBINS-I tools, one paper\textsuperscript{14} was assessed as being at serious risk of bias due to missing data. The patients included in this study were each on a stable drug treatment; however, the selected medical therapy after device treatment was not reported, making it impossible to determine whether the drug may have affected patient outcomes. Therefore, a moderate degree of confounding bias may have been present. All studies were deemed to be at low risk of bias in the other domains, and no study was deemed to be at a critical risk of bias. For the primary endpoint of changes in PCWP, visual inspection of funnel plots of all studies showed partial symmetry. Egger’s linear regression showed that no potentially significant publication bias existed for the endpoint (95% CI: \(-5.06\) to \(0.24\); \(P = 0.065\); Supporting Information, Figure S3).

**Discussion**

This meta-analysis aimed to evaluate the effect of ISD on HF, especially in terms of haemodynamic changes. Incorporating the available published evidence, we found that ISD implantation was significantly associated with a reduction in PCWP. There was also an incremental effect on CO and 6MWD, with no significant changes in RAP or mPAP.

Increased PCWP and LA pressure leading to pulmonary congestion is the core mechanism of chronic HF.\textsuperscript{5} Elevated PCWP at rest and during exercise is associated with impaired functional capacity, negatively affecting quality of life and prognosis.\textsuperscript{6} In patients with HFrEF, PCWP has been reported to be the only haemodynamic variable independently associated with 6MWD at rest or during peak exercise.\textsuperscript{19} A computer simulation study in HfPEF showed that through a shunt
diameter of 8–9 mm, PCWP can be reduced by 3 mmHg at rest and by 11 mmHg during exercise. A smaller shunt diameter will reduce the decline in PCWP, especially during exercise, while the improvement brought by a larger shunt diameter is limited. In this study, all types of ISD included provide shunt channels within this diameter range. As expected, our study showed that ISD can significantly reduce PCWP, by an average of 3.1 mmHg, and subgroup analysis showed that there was no significant difference among the included devices.

Although most studies included in our analysis were based on preoperative and postoperative comparison of the same group of patients, the effectiveness of ISD in reducing PCWP has also been verified by randomized controlled studies. A randomized, blinded, sham-controlled clinical trial showed that 1 month after IASD implantation, peak PCWP decreased by 3.5 ± 6.4 mmHg in the treatment group, while no significant improvement could be seen in the control group. However, the overall size of this trial was small, and therefore, it does not provide adequate power to evaluate clinical effects.
benefit or safety. Although not included in this analysis, the study using the LA-to-CS shunt also showed a significant decrease in PCWP (Δ − 9 mmHg; inter-quartile range: −9.5 to −8 mmHg). In addition to resting PCWP, PCWP during exercise has also been shown to be an independent predictor of long-term mortality. Several studies have observed the changes in PCWP both at rest and during exercise, showing that ISD can effectively reduce PCWP in both conditions. The REDUCE LAP-HF study showed that in patients with HFrEF, 6 months after successful placement of IASD, 52% of patients had a reduction in PCWP at rest and 58% had a lower PCWP during exertion. This improvement in PCWP provides a haemodynamic basis for the improvement of symptoms, activity tolerance, and quality of life for HF patients.

While interatrial shunting was initially mainly used in HfPEF and achieved good results, our analysis showed that ISD may be equally effective for patients with HFrEF. Among all the included studies, only one study specifically focused on HFrEF and showed that ISD can significantly reduce PCWP and improve heart function, 6MWD, and quality of life as well. Several trials that included both HfPEF and HFrEF patients produced similar results, further indicating that ISD is a potential treatment for patients with either HfPEF or HFrEF.

Cardiac output is a direct indicator of cardiac function and strongly predictive of prognosis in chronic HF. Abudiab et al. showed that the reduction in oxygen consumption during exercise in patients with HfPEF is mainly due to insufficient CO relative to metabolic demand, implying that treatments designed to enhance CO response with stress may prove beneficial in improving exercise capacity and outcomes in these patients. Our study found that CO increased after ISD implantation, which may provide a mechanistic explanation for the observed improvements in exercise ability and quality of life. However, there is obvious heterogeneity among studies, notably in the methods of measuring CO. Oximetry, the Fick method, the thermodilution method, and echocardiography measurement were used in different studies. The conclusions reached via different methods are similar: CO increased or at least remained the same after ISD implantation. Another issue is that some studies did not clearly identify whether the CO measured is left-sided or right-sided; theoretically, the left-to-right shunt created by ISD may increase the CO of the right heart (Qp) but have a negative effect on the left heart (Qs). However, one study showed a 27% increase in Qp with no reduction in Qs following IASD both at rest and during exercise. This may be related to the redistribution of volume and improvement in cardiac function after ISD. Further research is needed to clarify the changes in CO, especially left-side CO, after ISD.

Our meta-analysis showed that 6MWD increased by a mean 32.33 m, which is consistent with improvement in symptoms, exercise tolerance, and left ventricular ejection fraction, and is an independent predictor of all-cause mortality in patients with HF. A meta-analysis found that improvement in 6MWD was also associated with improved health-related quality of life and decreased mortality and hospitalization. In general, a 30–50 m increase in 6MWD is considered a clinically significant improvement, associated with significant improvement in NYHA functional class and health-related quality of life. Consistent with the improvement in 6MWD, there were sustained improvements in NYHA class and quality of life as shown in some studies. The 1 year results of a randomized controlled trial that included 44 individuals showed that the IASD group had a trend towards reduced need for HF-related admissions or visits requiring intravenous diuretics (0.22, 95% CI 0.08–0.58 vs. 0.63, 95% CI 0.33–1.21, per patient-year, P = 0.06), and the incidence of major adverse cardiac, cerebrovascular, and renal events was also lower, although this finding did not reach statistical significance (possibly due to the small sample size). In another study comparing survival predicted from baseline data using the Meta-analysis Global Group in Chronic Heart Failure risk survival score, IASD implantation was associated with a significant reduction in mortality in HfPEF (10.2/100 vs. 15.2/100, P = 0.04).

### Table: Subgroup analysis of pulmonary capillary wedge pressure

| Subgroup | No. of studies (n) | MD (95%CI)       | P-value | P-value for subgroup difference |
|----------|-------------------|------------------|---------|---------------------------------|
| Device   |                   |                  |         |                                 |
| IASD     | 3                 | −3.10 (−5.18, −1.03) | 0.003   |                                 |
| v-Wave   | 2                 | −2.68 (−5.22, −0.14) | 0.04    |                                 |
| AFR      | 1                 | −3.90 (−7.39, −0.41) | 0.03    |                                 |
| Type of HF |                   |                  |         |                                 |
| HfPEF    | 3                 | −3.10 (−5.18, −1.03) | 0.003   | 0.62                            |
| HFrEF    | 1                 | −6.00 (−12.16, 0.16) | 0.06    |                                 |
| Both     | 2                 | −2.74 (−4.92, −0.56) | 0.01    |                                 |
| Follow up period (m) | |                  |         |                                 |
| ≥ 6      | 2                 | −2.00 (−4.08, 0.08)  | 0.06    | 0.15                            |
| < 6      | 4                 | −4.17 (−6.21, −2.12) | 0.001   |                                 |
| Participants number | |                  |         |                                 |
| ≥ 20     | 4                 | −2.46 (−4.12, −0.79) | 0.004   | 0.12                            |
| < 20     | 2                 | −5.24 (−8.28, −2.21) | 0.0007  |                                 |

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3.4/100 patient-years, \( P = 0.02 \)). These results suggest that by significantly reducing PCWP, ISD can significantly reduce symptoms, improve exercise capacity, and improve quality of life and may even reduce mortality in HF patients.

In terms of the durability of the effect of ISD treatment, our subgroup analysis showed that ISD can significantly reduce PCWP in the early period (<6 months) after the procedure, but its effect may be weakened afterwards (≥6 months). Over time after the implantation of ISD, redistribution of blood and adaptation and adjustment of the body may occur, and the changes in PCWP caused by the left-to-right shunt may change. Although the trend was observed, the difference between the two periods was not statistically significant \( (P = 0.15) \). In the REDUCE LAP-HF study, 64 patients with HFrEF followed up at the 6th and 12th months showed a sustained and meaningful clinical benefit as reflected by continued positive changes in left ventricular end-diastolic volume index and right ventricular end-diastolic volume index, NYHA class, and 6MWD. Considering that the number of patients receiving ISD treatment remains limited and the available follow-up time is still short, the long-term effect of its use requires further observation.

Another concern with ISD is the potential for right heart overloading and pulmonary artery pressure increase because of the left-to-right shunt. Our meta-analysis found that ISD did not significantly increase RAP or mPAP. At follow-up, echocardiographic measurements of right ventricular function remained stable and right ventricular ejection fraction remained significantly elevated. A randomized controlled study also showed that 1 month after IASD, RAP and mPAP did not change significantly, and there was no significant difference in the IASD patients compared with the control group. Although there was an increase in right ventricular size in the IASD group \( (\text{mean} \pm \text{SD}, 7.9 \pm 8.0 \text{ mL/m}^2) \) compared with the control group \( (–1.8 \pm 9.6 \text{ mL/m}^2; \ P = 0.002) \) at 6 months, no further increase occurred at 12 months. A previous study based on atrial septal defects suggests that small shunts (usually <10 mm) are not associated with any deleterious haemodynamic effect. In the REDUCE LAP-HF I trial, pulmonary vascular resistance (PVR) during exercise tended to be lower in the IASD group after the procedure. A pooled analysis of two trials with a total of 79 patients receiving IASD showed that Qp and pulmonary artery oxygen content increased by 27% and 7% following IASD and were associated with a 17% reduction in PVR, a 12% reduction in PA elastance, and a 24% increase in PA compliance. These results suggest that ISD does increase the volume load of the right heart but, with an appropriate shunt diameter (usually 8–9 mm) and a relatively small shunt (Qp/Qs < 1.5), can effectively reduce the LA pressure without significant adverse effects on right heart function. Long-term clinical data are needed to provide definitive data on the potential impact of interatrial shunts on right ventricular function.

Following device implantation, most studies have recommended aspirin in combination with clopidogrel for 6 months in patients who are not under anticoagulation therapy, and in patients receiving anticoagulation (warfarin or direct oral anticoagulant), aspirin is added to the antithrombotic regime. Most studies were free of thrombotic or embolic events, although one study reported a gastrointestinal bleeding event likely related to warfarin. Further studies are needed to determine the optimum antithrombotic and anticoagulation regimen after shunt implantation. Another potential adverse event in such settings is the occurrence of atrial fibrillation due to right atrial dilatation; however, one randomized study showed that none of the study participants in normal sinus rhythm at baseline developed new-onset atrial fibrillation or flutter during the 1 month follow-up period. Studies with longer follow-up are still needed to observe this phenomenon.

As a new and invasive therapy, ISD showed a good safety profile: device-related adverse event rate was 3.9% in our analysis. The most difficult and risky part of the operation is the atrial septal puncture. Operators experienced in transseptal puncture seem to have a relatively short learning curve.

### Study limitations

First, our meta-analysis only included one randomized study; five of the included studies were non-randomized controlled studies, which creates inherent potential for bias from confounding factors. However, results from existing randomized trials are consistent with our conclusions. Second, medical therapy management was not reported in detail in most studies. It was not possible to determine whether the drug was an intervening factor in the outcomes, so a moderate degree of confounding bias may be present. Third, the longest follow-up period of studies included in this article was 12 months. Current published studies lack long-term longitudinal follow-up data. For instance, whether prolonged increased pulmonary artery flow might induce increased vascular resistance is difficult to prove with such limited follow-up. Although ISD proved to be effective and safe in the short term, longer follow-up is required to determine the long-term benefits or complications of the procedure.

### Conclusions

A key insight from our analyses is that ISD was associated with significant and clinically relevant reductions in PCWP and improved 6MWD, without changes in RAP or mPAP. ISD appears to be both a safe and effective treatment for HF. Randomized controlled trials with larger sample sizes and longer follow-up periods are needed for further verification.
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Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. NYHA functional class at baseline and at follow-up.

Table S2. Details of adverse events.

Figure S1. Outcomes of subgroup analysis of CO. CI = confidence interval; CO = cardiac output; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MD = mean difference.

Figure S2. Outcomes of subgroup analysis of 6MWD. 6MWD = 6-min walk distance; CI = confidence interval; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MD = mean difference.

Figure S3. Funnel plot displaying SMD and SE for pulmonary capillary wedge pressure. SE = standard error; SMD = standard mean difference.

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