The Efficacy of Nitrite Therapy for the Treatment of Heart Failure: A Meta-Analysis of Randomized Controlled Trials

Quan Zhou,1 Qin Zhang,2 Huaqiang Xu1

1Department of Critical Care Medicine, Suizhou Central Hospital, Hubei University of Medicine, Suizhou, China; 2Department of Thyroid & Breast Surgery, Xiangya Hospital Central South University, Hunan Province, China

ABSTRACT

Introduction: The efficacy of nitrite therapy for the treatment of heart failure remains controversial. We conducted a systematic review and meta-analysis to explore the impact of nitrite therapy on heart failure.

Methods: We searched the PubMed, EMbase, Web of Science, EBSCO, and Cochrane Library databases through November 2019 for randomized controlled trials (RCTs) assessing the effect of nitrite therapy on heart failure. This meta-analysis was performed using the random-effect model.

Results: Three RCTs are included in the meta-analysis. Overall, compared with the control group for heart failure, nitrite therapy is associated with significantly reduced PCWP (Std. MD=-1.22; 95% CI=-1.81 to -0.63; P < 0.0001) and improved PAC (Std. MD=0.71; 95% CI=0.16 to 1.27; P = 0.01), but reveals no substantial influence on peak VO2 (Std. MD=-0.19; 95% CI=-0.49 to 0.11; P = 0.21), systolic BP (Std. MD=-3.98; 95% CI=-8.24 to 0.28; P = 0.07), mean BP (Std. MD=-1.53; 95% CI=-3.37 to 0.31; P = 0.10), or heart rate (Std. MD=0.40; 95% CI=-0.14 to 0.94; P = 0.15).

Conclusions: Nitrite therapy may show some benefits to heart failure.

INTRODUCTION

Heart failure widely occurs in clinical work, and the etiology of heart failure mainly includes ischemic and non-ischemic causes [Francis 2019; McMurray 2019; Solomon 2019]. Ischemic or non-ischemic cardiomyopathy classification has important prognostic implications [Felker 2002; Lipinski 2017]. Only 50% patients with heart failure have a preserved ejection fraction. Accumulating evidence suggest that impairments in nitric oxide availability plays important roles in the pathophysiology of heart failure [Paulus 2013; Shah 2008]. Therapies targeting the nitric oxide pathway have been explored to treat heart failure, but a clear benefit is not observed [Redfield 2013; Redfield 2015; Pieske 2017].

The inorganic nitrate/nitrite pathway represents a different means of restoring nitric oxide signaling [Reddy 2017]. Unlike the organic nitrates such as isosorbide mononitrate and dinitrate, inorganic nitrite is converted to nitric oxide in a 1-step reaction in the presence of hypoxia and acidosis, which can be facilitated by exercise. Several acute and short-term, single-center studies have documented improved cardiac hemodynamics and exercise capacity with inorganic nitrate/nitrite in patients with heart failure [Borlaug 2015; Zamani 2015; Eggebeen 2016; Simon 2016; Zamani 2017].

The efficacy of nitrite therapy for heart failure has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting [Borlaug 2015; Borlaug 2018; Borlaug 2016]. With accumulating evidence, we therefore performed a systematic review and meta-analysis of RCTs to investigate the efficacy of nitrite therapy in patients with heart failure.

MATERIALS AND METHODS

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis were conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [Moher 2009].

Search strategy and study selection: Two investigators independently searched the following databases (inception to December 2019): PubMed, EMbase, Web of Science, EBSCO, and Cochrane Library databases. The electronic search strategy was conducted using the following keywords: nitrite, and heart failure. We also checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) population: patients with heart failure; (ii) intervention: nitrite therapy; (iii) comparison: placebo; (iv) study design: RCT.

Data extraction and outcome measures: We extracted the following information: author, number of patients, age, female, body mass index, NT-proBNP and detail methods in each group, etc. Data independently was extracted by two
investigators, and discrepancies were resolved by consensus. We also contacted the corresponding author to obtain data, when necessary.

The primary outcomes are pulmonary capillary wedge pressure (PCWP) and pulmonary artery compliance (PAC). Secondary outcomes include peak oxygen consumption (VO2), systolic blood pressure (BP), mean BP, and heart rate.

**Quality assessment in individual studies**: Methodological quality of the included studies is independently evaluated using the modified Jadad scale [Jadad 1996]. There are three items for Jadad scale: randomization (0-2 points), blinding (0-2 points), and dropouts and withdrawals (0-1 points). The score of Jadad scale varies from 0 to 5 points. An article with Jadad score £ 2 is considered to be of low quality. If the Jadad score ≥ 3, the study is thought to be of high quality [Kjaergard 2001].

**Statistical analysis**: We estimate the standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (PCWP, PAC, peak VO2, systolic BP, mean BP, heart rate). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I2 statistic, and I2 > 50% indicates significant heterogeneity [Higgins 2002]. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

### RESULTS

**Literature search, study characteristics and quality assessment**: A detailed flowchart of the search and selection results was shown in Figure 1. (Figure 1) After the initial search of databases, 275 publications were searched. Eighty-six duplicates and 184 papers after checking the titles/abstracts were excluded. Two studies were removed because of the study design and three RCTs ultimately were included in the meta-analysis [Borlaug 2015; Borlaug 2018; Borlaug 2016].

![Flow diagram of study searching and selection process](image)

**Table 1. Characteristics of included studies**

| NO. | Author | Nitrite group | Control group | Jada scores |
|-----|--------|---------------|---------------|-------------|
|     |        | Number | Age (years) | Female (n) | Body mass index (kg/m²) | NT-proBNP (pg/mL) | Methods | Number | Age (years) | Female (n) | Body mass index (kg/m²) | NT-proBNP (pg/mL) | Methods |
| 1   | Borlaug 2018 | 53 | 68 (9) | 36 | 35.6 (6.4) | 471 (624) | Inhaled nitrite at 46 mg 3 times a day for 1 week followed by 80 mg 3 times a day for 3 weeks | 52 | 68 (12) | 23 | 35.0 (7.0) | 528 (669) | Matched placebo | 5 |
| 2   | Borlaug 2016 | 13 | 67 (9) | 6 | 33.2 (30.3, 38.2) | 551 (66, 1227) | Inhaled sodium nitrite (90 mg) | 13 | 72 (10) | 8 | 30.8 (24.3, 36.0) | 977 (196, 3683) | Matched placebo | 4 |
| 3   | Borlaug 2015 | 14 | 69 (6) | 9 | 32.0 (7.0) | 249 (118-890) | Infusion of sodium nitrite (50 mg/kg/min) | 14 | 70 (8) | 8 | 33.4 (6.6) | 585 (107-1575) | Matched placebo | 3 |

Values are mean (SD) or median (interquartile range)
The baseline characteristics of three eligible RCTs in the meta-analysis are summarized in Table 1. The three studies were published between 2015 and 2018, and sample sizes ranged from 28 to 105, with a total of 159. Two included RCTs reported inhaled nitrite [Borlaug 2018; Borlaug 2016], while the remaining RCT reported infusion of sodium nitrite [Borlaug 2015].

Among the three studies included here, two studies reported PCWP and PAC [Borlaug 2015; Borlaug 2016], three studies reported peak VO2, systolic BP and mean BP [Borlaug 2015; Borlaug 2018; Borlaug 2016], and two studies reported heart rate [Borlaug 2015; Borlaug 2016]. Jadad scores of the three included studies varied from 3 to 5, and all three studies were considered to be high-quality ones, according to quality assessment.

Primary outcomes – PCWP and PAC: PCWP were measured at end-expiration (mean of ≥3 beats) using 2-F, high-fidelity micromanometer-tipped catheters advanced through the lumen of a 7-F, fluid-filled catheter. PAC represented the stroke volume/pulmonary artery pulse pressure. These two outcomes were important to measure the cardiac function and analyzed with the random-effects model.

Compared with the control group for heart failure, nitrite therapy resulted in significantly reduced PCWP (Std. MD=-1.22; 95% CI=-1.81 to -0.63; \( P < 0.0001 \)) with no heterogeneity among the studies (I²=0%; heterogeneity \( P = 0.79 \)) (Figure 2) and increased PAC (Std. MD=0.71; 95% CI=0.16 to 1.27; \( P = 0.01 \)) with no heterogeneity among the studies (I²=0%; heterogeneity \( P = 0.61 \)) (Figure 3) (Figure 2) (Figure 3)

Sensitivity analysis: No heterogeneity was observed among the included studies for the primary outcome, and thus we did not perform sensitivity analysis via omitting one study in turn to detect the heterogeneity.

Secondary outcomes: Cardio-pulmonary function and hemodynamic stability were commonly used to assess the treatment efficacy of heart failure. Peak VO2 was thought to be the gold-standard indicator of functional capacity in patients with heart failure and great impairment may result in adverse outcomes [Guazzi 2005; Reddy 2018]. We performed the meta-analysis of peak VO2, systolic BP, mean BP, and heart rate to assess the efficacy of nitrite therapy.

In comparison with the control group for heart failure, nitrite therapy showed no obvious impact on peak VO2 (Std. MD=-0.19; 95% CI=-0.49 to 0.11; \( P = 0.21 \)) (Figure 4), systolic BP (Std. MD=-3.98; 95% CI=-8.24 to 0.28; \( P = 0.07 \)) (Figure 5), mean BP (Std. MD=-1.53; 95% CI=-3.37 to 0.31; \( P = 0.10 \)) (Figure 6), or heart rate (Std. MD=0.40; 95% CI=0.14 to 0.94; \( P = 0.15 \)) (Figure 7) (Figure 4) (Figure 5) (Figure 6) (Figure 7)
DISCUSSION

The pathophysiology of heart failure is complex and involves left and right ventricular dysfunction, vascular limitations, and impairments in the periphery [Sharma 2014; Borlaug 2011; Borlaug 2014]. These patients commonly have the elevation in cardiac filling pressures at rest and with exercise [Maeder 2010; Anderson 2015]. Elevated left ventricular filling pressures results in symptoms of dyspnea, followed by pulmonary hypertension and development of right ventricular dysfunction, which may be associated with increased risk of death [Melenovsky 2014; Dorfs 2014]. Many patients with heart failure encounter the cardiac, vascular, and skeletal muscle abnormalities, which limit physical capacity [Borlaug 2010; Pryzbek 2019; van der Meer 2019]. These patients commonly have high prevalence of hypertension, coronary disease, diabetes, and sleep apnea [Ergatoudes 2019].

Treatments targeting to reduce filling pressures may be effective in these patients. Limitations in NO availability plays a key role in driving the elevations in filling pressures and pulmonary hypertension in heart failure, and agents targeting the NO/cGMP pathway represents important potential in alleviating filling pressures [Sharma 2014; Greene 2013]. In contrast to the organic nitrates, inorganic nitrate leads to no development of endothelial dysfunction [Vanderpool 2015; Lundberg 2008]. Nitrite provides a hypoxia-sensitive NO source that is preferentially active at the time of greatest need, and induces more targeted NO delivery [Borlaug 2016].

Inorganic nitrate/nitrite is believed to alleviate heart failure via targeting nitric oxide delivery during exercise [Reddy 2017]. Several studies demonstrated improvements in hemodynamics, submaximal exercise endurance, and peak VO2 using therapies targeting the inorganic nitrate/nitrite pathway [Borlaug 2015; Zamani 2015; Eggebeen 2016; Zamani 2017; Reddy 2017]. Preclinical and clinical studies revealed the benefits from inorganic nitrite and nitrate in heart failure [Borlaug 2015; Vanderpool 2015; Zamani 2015; Bhushan 2014]. Oral nitrate (delivered as beetroot juice) was found to improve exercise capacity, vasodilation, and CO reserve when given either as a single dose or as repeated doses over 1 week [Zamani 2015; Eggebeen 2016]. Intravenous nitrite was associated with reduced PCWP at rest and during exercise in heart failure [Borlaug 2015; Ormerod 2015]. Our meta-analysis confirms that nitrite therapy can remarkably reduce PCWP and improve PAC in patients with heart failure.

Measures of both maximal functional capacity (peak VO2) and volume of daily activity (accelerometry) are used to assess the efficacy of inorganic nitrite for heart failure. Reduction in
peak VO2 indicates high cardiac filling pressures that alleviate the symptoms of dyspnea and abnormalities peripheral to the heart in the vasculature and skeletal muscle [Reddy 2018; Obokata 2018; Houstis 2018; Eisman 2018; Weiss 2017]. In this meta-analysis, there is no statistical difference of peak VO2, systolic BP, mean BP or heart rate between nitrite therapy and placebo in patients with heart failure.

In addition, inhaled nitrite at 46 mg 3 times a day for 1 week followed by 80 mg 3 times a day for 3 weeks in patients with heart failure with preserved ejection fraction reveals no obvious favorable influence on daily activity levels, quality of life, functional class, cardiac filling pressures, or N-terminal fragment of the prohormone brain natriuretic peptide levels as compared to placebo [Borlaug 2018]. Several reasons may account for the discrepant findings and bias. Firstly, nitrite therapy is administered by intranasal or intravenous infusion, which may produce different levels of efficacy. Secondly, heart failure with or without preserved ejection fraction results in different cardiac function, and preserved ejection fraction may comprise the efficacy of nitrite therapy for heart failure. Thirdly, the doses and methods of nitrite therapy is various in each RCT and may produce some bias for the pooling results.

This meta-analysis has several potential limitations. Firstly, our analysis is based on three RCTs, and more RCTs with large sample size should be conducted to explore this issue. Next, there are some discrepant findings, which may be caused by different doses and methods of nitrite therapy and various cardiac function among included RCTs. Finally, some important outcomes such as ejection fraction, mortality, and hospitalization cannot be analyzed based on current studies.

**CONCLUSIONS**

Nitrite therapy may provide some efficacy for the treatment of heart failure.

**REFERENCES**

Andersen MJ, Olson TP, Melenovsky V, Kane GC, Borlaug BA. 2015. Differential hemodynamic effects of exercise and volume expansion in people with and without heart failure, Circ Heart Fail. 8(1) 41-8.

Bhushan S, Kondo K, Polhemus DJ, Otsuka H, Nicholson CK, Tao YX, Huang H, Georgopoulou VV, Murohara T, Calvert JW, Butler J, Lefer DJ. 2014. Nitrite therapy improves left ventricular function during heart failure via restoration of nitric oxide-mediated cytoprotective signaling, Circ Res. 114(8) 1281-91.

Borlaug BA. 2014. The pathophysiology of heart failure with preserved ejection fraction, Nature reviews. Cardiology. 11(9) 507-15.

Borlaug BA, Anstrom KJ, Lewis GD, Shah SJ, Levine JA, Koepp GA, Givertz MM, Felker GM, LeWinter MM, Mann DL. 2018. Effect of inorganic nitrite vs placebo on exercise capacity among patients with heart failure with preserved ejection fraction: the INDIE-HFpEF randomized clinical trial, Jama. 320(17) 1764-1773.

Borlaug BA, Koepp KE, Melenovsky V. 2015. Sodium nitrite improves exercise hemodynamics and ventricular performance in heart failure with preserved ejection fraction, Journal of the American College of Cardiology. 66(15) 1672-1682.

Borlaug BA, Melenovsky V, Koepp KE. 2016. Inhaled sodium nitrite improves rest and exercise hemodynamics in heart failure with preserved ejection fraction, Circulation research. 119(7) 880-886.

Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. 2010. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction, Circulation: Heart Failure. 3(5) 588-595.

Borlaug BA, Paulus WJ. 2011. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment, Eur Heart J. 32(6) 670-9.

Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzl RP, Pieske B, Neumann FJ. 2014. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction, Eur Heart J. 35(44) 3101-12.

Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzl RP, Pieske B, Neumann FJ. 2014. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction, Eur Heart J. 35(44) 3101-12.

Eggebeen J, Kim-Shapiro DB, Haykowski M, Morgan TM, Basu S, Brubaker P, Rejeski J, Kitzman DW. 2016. One Week of Daily Dosing With Beetroot Juice Improves Submaximal Endurance and Blood Pressure in Older Patients With Heart Failure and Preserved Ejection Fraction, JACC: Heart Failure. 4(6) 428-437.

Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, Cunningham TF, Hardin KM, Baggish AL, Ho JE. 2018. Pulmonary capillary wedge pressure patterns during exercise predict exercise capacity and incident heart failure, Circulation: Heart Failure. 11(5) e004750.

Ergouades C, Schaufelberger M, Andersson B, Pivodic A, Dahlström U, Fu M. 2019. Non-cardiac comorbidities and mortality in patients with heart failure with reduced vs. preserved ejection fraction: a study using the Swedish Heart Failure Registry, Clinical Research in Cardiology. 1-9.

Felder GM, Shaw LK, O’Connor CM. 2002. A standardized definition of ischemic cardiomyopathy for use in clinical research, Journal of the American College of Cardiology 39(2). 210-8.

Francis GS, Tang WW. 2019. Pathophysiology of congestive heart failure, Reviews in cardiovascular medicine. 4(S2) 14-20.

Greene SJ, Gheorghiade M, Borlaug BA, Pieske B, Vaduganathan M, Burnett Jr. JC, Roessig L, Stasch JP, Solomon SD, Paulus WJ, Butler J. 2013. The cGMP signaling pathway as a therapeutic target in heart failure with preserved ejection fraction, Journal of the American Heart Association. 2(6) e005356.

Guazzi M, Myers J, Arena R. 2005. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure, Journal of the American College of Cardiology. 46(10) 1883-1890.

Higgins JP, Thompson SG. 2002. Quantifying heterogeneity in a meta-analysis, Statistics in medicine. 21(11) 1539-58.

Houstis NE, Eisman AS, Pappagianopoulos PP, Wooster L, Bailey CS, Wagner PD, Lewis GD. 2018. Exercise intolerance in heart failure with preserved ejection fraction: a prospective study using the American Heart Association, Circulation. 137(2) 148-161.

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. 1996. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Controlled Clinical Trials. 17(1) 1-12.

Kjaergard LL, Villumsen J, Gluud C. 2001. Reported Methodologic Quality and Discrepancies between Large and Small Randomized Trials in Meta-Analyses, Annals of Internal Medicine. 135(11) 982-989.

Lipinski MJ, Luger D, Epstein SE. 2017. Mesenchymal Stem Cell Therapy for the Treatment of Heart Failure Caused by Ischemic or
Non-ischemic Cardiomyopathy: Immunosuppression and Its Implications, Handbook of experimental pharmacology, 243, 329-333.

Lundberg JO, Weitzberg E, Gladwin MT. 2008. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics, Nature reviews. Drug discovery. (2) 156-77.

Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. 2010. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction, J Am Coll Cardiol. 56(11) 857-67.

McMurray JJ, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, B lohlávek J. 2019. Dagagliflozin in patients with heart failure and reduced ejection fraction, New England Journal of Medicine. 381(21) 1995-2008.

Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. 2014. Right heart dysfunction in heart failure with preserved ejection fraction, Eur Heart J. 35(48) 3452-62.

Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Journal of clinical epidemiology. 62(10) 1006-12.

Obokata M, Olson TP, Reddy YN, Melenovsky V, Kane GC, Borlaug BA. 2018. Haemodynamics, dyspnoea, and pulmonary reserve in heart failure with preserved ejection fraction, European heart journal. 39(30). 2810-2821.

Ormerod JO, Arif S, Mukadam M, Evans JD, Beadle R, Fernandez BO, Bonser RS, Feelsch M, Madhani M, Frenneaux MP. 2015. Short-term intravenous sodium nitrite infusion improves cardiac and pulmonary hemodynamics in heart failure patients, Circ Heart Fail 8(3). 567-71.

Paulus WJ, Tchöpe C. 2013. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation, Journal of the American College of Cardiology. 62(4) 263-271.

Pieske B, Maggioni AP, Lam CS, Pieske-Kraigher E, Filippatos G, Butler J, Ponikowski P, Shah SJ, Solomon SD, Scalise AV. 2017. Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOLuble guanylate Cyclase stimulatorR in heArT failureP patients with PRESERVED EF (SOCRATES-PRESERVED) study, European heart journal 38(15). 1119-1127.

Pryzby M, MacDonald M, Stratford P, McQuarrie A, Richardson J, McKelvie R, Tang A. 2019. Long-term enrollment in cardiac rehabilitation benefits cardiorespiratory fitness and skeletal muscle strength in men with cardiovascular disease, Canadian Journal of Cardiology.

Reddy YN, Andersen MJ, Obokata M, Koepp KE, Kane GC, Melenovsky V, Olson TP, Borlaug BA. 2017. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction, Journal of the American College of Cardiology. 70(2) 136-148.

Reddy YN, Lewis GD, Shah SJ, LeWinter M, Semigran M, Davila-Roman VG, Anstrom K, Hernandez A, Braunwald E, Redfield MM. 2017. Inorganic Nitrite Delivery to Improve Exercise Capacity in Heart Failure with Preserved Ejection Fraction (INDIE-HFpEF): Rationale and Design, Circulation. Heart failure. 10(5).

Reddy YN, Olson TP, Obokata M, Melenovsky V, Borlaug BA. 2018. Hemodynamic correlates and diagnostic role of cardiopulmonary exercise testing in heart failure with preserved ejection fraction, JACC: Heart Failure. 854.

Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, LeWinter MM, Joseph SM, Shah SJ, Semigran MJ. 2015. Isosorbide mononitrate in heart failure with preserved ejection fraction, New England Journal of Medicine. 373(24) 2314-2324.

Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL. 2013. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial, Jama. 309(12) 1268-1277.

Shah SJ, Gheorghiade M. 2008. Heart failure with preserved ejection fraction: treat now by treating comorbidities, Jama. 300(4) 431-433.

Sharma K, Kass DA. 2014. Heart failure with preserved ejection fraction: mechanisms, clinical features, and therapies, Circ Res. 115(1) 79-96.

Simon MA, Vanderpool RR, Nouraie M, Bachman TN, White PM, Sugahara M, Gorcsan J III, Parsley L, Gladwin MT. 2016. Acute hemodynamic effects of inhaled sodium nitrite in pulmonary hypertension associated with heart failure with preserved ejection fraction, JCI insight. 1(18).

Solomon SD, McMurray JJ, Anand IS, Ge J, Lam CS, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B. 2019. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction, New England Journal of Medicine. 381(17) 1609-1620.

Van der Meer P, van der Wal HH, Melenovsky V. 2019. Mitochondrial Function, Skeletal Muscle Metabolism, and Iron Deficiency in Heart Failure, Am Heart Assoc.

Vanderpool R, Gladwin MT. 2015. Harnessing the nitrate-nitrite-nitric oxide pathway for therapy of heart failure with preserved ejection fraction, Circulation. 131(4) 334-6.

Weiss K, Schär M, Panjratn GS, Zhang Y, Sharma K, Bottomley PA, Golozar A, Steinberg A, Gerstenblith G, Russell SD. 2017. Fatigability, exercise intolerance, and abnormal skeletal muscle energetics in heart failure, Circulation: Heart Failure. 10(7) e004129.

Zamani P, Rawat D, Shiva-Kumar P, Geraci S, Bhuta R, Konda P, Doulias PT, Ischiropoulos H, Townsend RR, Margulies KB, Cappola TP, Poole DC, Chirinos JA. 2015. Effect of inorganic nitrate on exercise capacity in heart failure with preserved ejection fraction, Circulation. 131(1) 371-80; discussion 380.

Zamani P, Tan V, Soto-Calderon H, Beraun M, Brandimarto JA, Trieu L, Varakamant S, Doulias PT, Townsend RR, Chittams J. 2017. Pharmocokinetest and pharmacodynamics of inorganic nitrate in heart failure with preserved ejection fraction, Circulation research. 120(7) 1151-1161.