Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction-
A Review of Literature

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ABSTRACT
The objective of this review is to do a literature search on the effectiveness of isosorbide mononitrate in heart failure patients with preserved ejection fraction. Heart failure with preserved ejection fraction (HF-PEF) also known as diastolic heart failure is the clinical syndrome of heart failure associated with near-normal systolic function. It is a manifestation of signs and symptoms of heart failure with an ejection fraction greater than 45% and is characterised by reduced ventricular filling and elevated left ventricular filling pressure. There is an increased risk for the occurrence of congested cardiac failure or atrial fibrillation in such patients. Many drugs like diuretics, beta blockers, ACE inhibitors can be used to treat the above condition although nitrates being the most common choice of drugs to enhance activity tolerance in patients with heart failure and a preserved ejection fraction. This review aims at studying the effect of isosorbide mononitrate in heart failure patients with a preserved ejection fraction. Heart failure is a serious problem and can be fatal. Hence it is ideal to know the correct choice of medical treatment of such conditions.

INTRODUCTION
Heart failure (HF) occurs in two major subtypes (1-3). Heart failure has been attributed to systolic dysfunction, as evidenced by a LV ejection fraction of ≤ 45%. This HF phenotype is referred to as HF with reduced ejection fraction (HFrEF) and is characterised by a progressive ventricular dilation. Heart failure characterised by dyspnea, fluid retention, and exercise intolerance, also occurs in cases of normal ejection fraction (>50%). This form of HF is referred to as HF with preserved ejection fraction (HFpEF) and is generally characterised by hypertrophy of the left ventricle (LV) along with increased interstitial fibrosis.(1) Individuals with HFpEF are the elderly people, more likely to be female, and have a lower incidence of coronary artery disease but greater occurrence of atrial fibrillation(3). A leading cause of HFpEF is hypertension, and the hallmark of HFpEF is diastolic dysfunction or impaired relaxation of the LV. Individuals with HFpEF exhibit a higher number of non-cardiac conditions like diabetes, obesity, peptic ulcer disease, cancer, chronic obstructive pulmonary disease, psychiatric
disorders, and anaemia\(^{(3)}\). The pattern of hypertrophy seen in HFrEF, coupled with prolonged relaxation times, is commonly observed in the elderly irrespective of the presence of HF. HFrEF can be described as a very complex clinical syndrome rather than a disease, which may make the diagnosis of HFrEF challenging.

**DIAGNOSIS**

Detecting the syndrome is done by clinical assessment, echocardiography and evidence from biomarkers (BNP and proBNP)\(^{(4,5)}\). HFrEF diagnosis requires documentation of a cardiac dysfunction, both systolic and diastolic\(^{(6)}\). Echocardiography is the main tool used in HF diagnosis. It is used to define aetiology and to assess the extent of remodelling. It has also been widely used to assess the therapeutic impact of various pharmacological interventions upon remodelling\(^{(7)}\).

**TREATMENT AND IMPLICATIONS IN THE ELDERLY POPULATION**

No proper and completely successful treatment has been demonstrated to reduce morbidity and mortality in patients with HF-PEF. Diuretics are used to control sodium and water retention and relieve breathlessness and edema. Adequate treatment of hypertension and myocardial ischemia is important, as is the control of the ventricular rate in patients with atrial fibrillation. The use of pharmacological and non-pharmacological therapies is recommended by the HF guidelines in both non-elderly and elderly patients, with specific cautions. Sub-optimal therapy is due to secondary complications and difficulty in management, reduced compliance, increased susceptibility to renal dysfunction, impairment of sodium and water excretion, and therapy aggravated postural hypotension and bradyarrhythmias. However nitrates have proved to be a good choice of treatment for heart failure patients with preserved ejection fraction.

**ROLE OF NITRATE THERAPY IN HEART FAILURE**

Long acting nitrates are considered as the best choice of treatment for anti-anginal therapy and have demonstrated useful effects for treatment of patients with heart failure and preserved ejection fraction (HFrEF). Attenuation of pathological left ventricular (LV) remodelling and improved LV systolic function has been reported\(^{(8)}\). Although no study has directly examined the effects of nitrate monotherapy on survival in HF, symptom relief is a key management goal in patients with HFrEF, whose primary chronic symptom is often exercise limitation\(^{(9)}\).

**RATIONALE FOR NITRATE THERAPY IN HFrEF**

**HEMEODYNAMIC EFFECTS**

A fundamental hemodynamic derangement in HFrEF is the pathologic elevation in LV filling pressure, at rest or on exertion\(^{(9,10)}\). Commonly used organic nitrates, isosorbidedinitrate (ISDN), isosorboide-5-mononitrate (ISMN), and nitroglycerin, reduce ventricular preload by increasing peripheral venous capacitance and reducing LV filling pressure\(^{(11,12)}\). At higher doses, dilatation of pulmonary and systemic resistance vessels occurs\(^{(13)}\), particularly in patients with high arterial pressures\(^{(14)}\). Coronary artery disease is prevalent in HFrEF, and symptoms of angina may occur in patients without angiographically apparent coronary disease\(^{(15)}\). Nitrate-induced coronary vasodilatation may improve subendocardial perfusion, which could benefit HFrEF patients for whom ischaemia is a beneficiary factor. Nitrate induced pre-load reduction may also be beneficial in HFrEF\(^{(16,17)}\). HFrEF patients are frequently elderly and may have autonomic dysfunction, chronotropic incompetence and altered baroreflex sensitivity, all of which may exaggerate hypotension with load changes and thus heighten nitrate intolerance\(^{(18)}\).
**ENDOTHELIAL EFFECTS OF NITRATES**
Nitrate vasorelaxant responses are mediated by the formation of nitric oxide (NO) or a closely related entity\(^{19}\). NO activates soluble guanylyl cyclase (sGC) in vascular smooth muscle, prompting synthesis of the second messenger cyclic guanosine monophosphate (cGMP). Downstream activation of cGMP effector proteins, including cGMP-dependent protein kinase (PKG), leads to a reduction in intracellular calcium, and thus to vasodilation. Endothelial-dependent vasodilation is impaired in patients with HFpEF, compared with healthy age-matched controls, and correlates with greater symptoms and poorer exercise capacity\(^{20}\). Exogenous NO delivery or enhancement of endogenous NO biosynthesis may therefore improve endothelial function\(^{21}\).

**MYOCARDIAL EFFECTS OF NITRATES**
Increased NO bioavailability with nitrates, and thus cGMP/PKG signalling, may improve LV diastolic function and ameliorate myocardial hypertrophic remodelling. Low PKG activity has been implicated in the development of myocardial hypertrophy, delayed relaxation and increased passive stiffness\(^{22}\). While direct augmentation of PKG improves myocardial diastolic properties in vivo, whether chronic nitrate therapy will enhance cGMP, PKG activity and myocardial diastolic function in HFpEF is unclear.

**NITRATE RESISTANCE**
Prolonged exposure is widely recognized to induce true nitrate tolerance\(^{23,24}\). This is thought to involve vascular processes such as impaired nitrate biotransformation, increased ROS production with impaired clearance, sGC desensitisation to NO, enhanced sensitivity to endogenous vasoconstrictors, and increased cGMP phosphodiesterase activity, all of which inactivate nitrate vasodilator effects\(^{25}\). The extent of tolerance is dose-related and low-doses or intermittent dosing regimens with low-nitrate or nitrate-free intervals may be sufficient to prevent its occurrence\(^{24,26}\). Although, a combination of hydralazine and nitrates is suggested to reduce nitrate tolerance and is utilized in HFrEF, the additional vasodilation and afterload reduction imparted by hydralazine may prove excessive in HFpEF due to the differences in pressure-volume relationships, and may mask a beneficial effect of lone nitrate therapy in HFpEF. Furthermore, tolerance differs between nitrate preparations, as once daily Isosorbide mononitrate was shown to be devoid of tolerance in patients with coronary artery disease\(^{27,28}\). Therefore, once daily lone Isosorbide mononitrate therapy has been selected for NEAT-HFpEF.

**RATIONALE AND DESIGN OF NEAT-HFpEF**
NEAT-HFpEF is a multicenter, randomized (1:1), double-blind, placebo-controlled, crossover study designed to test the hypothesis that once daily extended-release Isosorbide mononitrate, at a maximally tolerated dose (30–120mg), improves daily physical activity in patients with HFpEF. Daily activity will be assessed and the primary endpoint will be a within-patient comparison of 14-day average achieved during the Isosorbide mononitrate treatment phase, compared with placebo.

**CONCLUSION**
HFpEF is multifactorial and involves several interconnected physiological systems. Detecting the syndrome is still difficult because of its non-specific nature of symptoms and signs, especially in the elderly population. While HF-PEF patients are at higher risk of death and hospitalizations than similar age and co-morbidity profile patients, treatment is still empirical. Drugs that enhance ventricular-vascular coupling by targeting both ventricular and vascular stiffness can be of added benefit in treating HFpEF, especially when combined with actions or other drugs that target cardiomyocyte stiffness at the level of the myofilaments or energetics. Since HFpEF is a
disease characterized by comorbidities, many of which impact negatively on cardiovascular-renal function, a multi-drug approach will likely prove essential, but the exact combination will need to be defined. To date, there is no empiricalevidence for the effectiveness of particular drugs in treating HFpEF, emphasisingthe need for additional large clinical trials. New drugs that target underlying inflammation, oxidative stress, and ageing-related dysfunctions may prove to be particularly effective for HFpEF. This is why there is urgent need of increased awareness and clinical research in the field.

REFERENCES
1. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J. 2011; 32:670–679. [PubMed: 21138935]
2. Phan TT, Shivu GN, Abozguia K, et al. The pathophysiology of heart failure with preserved ejection fraction: from molecular mechanisms to exercise haemodynamics. Int J Cardiol. 2012; 158:337–343. [PubMed: 21794933]
3. Liu Y, Haddad T, Dwivedi G. Heart failure with preserved ejection fraction: current understanding and emerging concepts. CurrOpinCardiol. 2013; 28:187–196. [PubMed: 23274284]
4. Paulus WJ, van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth. J Am Coll Cardiol 2010; 55: 526 –537.
5. Maeder MT, Kaye DM. Heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol 2009; 53: 905–918.
6. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007; 28: 2539–2550.
7. Doughty RN, Whalley GA, Walsh HA, et al. CAPRICORN Echo Substudy Investigators. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. Circulation 2004; 109: 201–206.
8. Elkayam U, Johnson JV, Shotan A, Bokhari S, Solodky A, Canetti M, Wani OR, Karaalp IS. Double-blind, placebo-controlled study to evaluate the effect of organic nitrates in patients with chronic heart failure treated with angiotensin-converting enzyme inhibition. Circulation. 1999; 99:2652–2657. [PubMed: 10338458]
9. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail. 2010; 3:588–595. [PubMed: 20543134]
10. Penicka M, Bartunek J, Trakalova H, Hrabakova H, Maruskova M, Karasek J, Kocka V. Heart failure with preserved ejection fraction in outpatients with unexplained dyspnea: A pressurevolume loop analysis. J Am Coll Cardiol. 2010; 55:1701–1710. [PubMed: 20394874]
11. Battock DJ, Levitt PW, Steele PP. Effects of isosorbidedinitrate and nitroglycerin on central circulatory dynamics in coronary artery disease. Am Heart J. 1976; 92:455–458. [PubMed: 822703]
12. Elkayam U. Nitrates in the treatment of congestive heart failure. Am J Cardiol. 1996; 77:41C–51C. [PubMed: 8540455]
13. Packer M, Medina N, Yushak M, Lee WH. Comparative effects of captopril and isosorbidedinitrate on pulmonary arteriolar resistance and right ventricular function in
patients with severe left ventricular failure: Results of a randomized crossover study. Am Heart J. 1985; 109:1293–1299. [PubMed: 3890506]

14. Haber HL, Simek CL, Bergin JD, Sadun A, Gimple LW, Powers ER, Feldman MD. Bolus intravenous nitroglycerin predominantly reduces afterload in patients with excessive arterial elastance. J Am Coll Cardiol. 1993; 22:251–257. [PubMed: 8509548]

15. Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2014; 63:2817–2827. [PubMed: 24768876]

16. Yaginuma T, Avolio A, O’Rourke M, Nichols W, Morgan JJ, Roy P, Baron D, Branson J, Feneley M. Effect of glyceryl trinitrate on peripheral arteries alters left ventricular hydraulic load in man. Cardiovasc Res. 1986; 20:153–160. [PubMed: 3085950]

17. Stokes GS, Barin ES, Gilfillan KL. Effects of isosorbide mononitrate and aii inhibition on pulse wave reflection in hypertension. Hypertension. 2003; 41:297–301. [PubMed: 12574098]

18. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation. 2011; 123:2006–2013.; discussion 2014. [PubMed: 21555723]

19. Ignarro LJ, Lippton H, Edwards JC, Baricos WH, Hyman AL, Kadowitz PJ, Gruetter CA. Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrites, nitroprusside and nitric oxide: Evidence for the involvement of s-nitrosothiols as active intermediates. The Journal of pharmacology and experimental therapeutics. 1981; 218:739–749. [PubMed: 6115052]

20. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, Redfield MM. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2010; 56:845–854. [PubMed: 20813282]

21. Schwarz M, Katz SD, Demopoulos L, Hirsch H, Yuen JL, Jondeau G, LeJemtel TH. Enhancement of endothelium-dependent vasodilation by low-dose nitroglycerin in patients with congestive heart failure. Circulation. 1994; 89:1609–1614. [PubMed: 8149528]

22. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013; 62:263–271. [PubMed: 23684677]

23. Munzel T, Daiber A, Gori T. Nitrate therapy: New aspects concerning molecular action and tolerance. Circulation. 2011; 123:2132–2144. [PubMed: 21576678]

24. Gupta D, Georgiopoulou VV, Kalogeropoulos AP, Marti CN, Yancy CW, Gheorghiade M, Fonarow GC, Konstam MA, Butler J. Nitrate therapy for heart failure: Benefits and strategies to overcome tolerance. JACC Heart failure. 2013; 1:183–191. [PubMed: 24621868]

25. Munzel T, Daiber A, Gori T. Nitrate therapy: New aspects concerning molecular action and tolerance. Circulation. 2011; 123:2132–2144. [PubMed: 21576678]

26. Elkayam U, Roth A, Mehra A, Ostrzega E, Shotan A, Kulick D, Jamison M, Johnston JV, RahimtooLA SH. Randomized study to evaluate the relation between oral isosorbidedinitrate dosing interval and the development of early tolerance to its effect on left ventricular filling pressure in
patients with chronic heart failure. Circulation. 1991; 84:2040–2048. [PubMed: 1934379]

27. Chrysant SG, Glasser SP, Bittar N, Shahidi FE, Danisa K, Ibrahim R, Watts LE, Garutti RJ, Ferraresi R, Casareto R. Efficacy and safety of extended-release isosorbide mononitrate for stable effort angina pectoris. Am J Cardiol. 1993; 72:1249–1256. [PubMed: 8256699]

28. Gunasekara NS, Noble S. Isosorbide 5-mononitrate: A review of a sustained-release formulation (imdur) in stable angina pectoris. Drugs. 1999; 57:261–277. [PubMed: 10188765]