



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 $\leq 45\%$. 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 HFpEF, coupled with prolonged relaxation times, is commonly observed in the elderly irrespective of the presence of HF. HFpEF can be described as a very complex clinical syndrome rather than a disease, which may make the diagnose of HFpEF challenging.

DIAGNOSIS

Detecting the syndrome is done by clinical assessment, echocardiography and evidence from biomarkers (BNP and proBNP)^(4,5). HF-PEF 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 (HFpEF). 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 HFpEF, whose primary chronic symptom is often exercise limitation⁽⁹⁾.

RATIONALE FOR NITRATE THERAPY IN HFPEF

HEMODYNAMIC EFFECTS

A fundamental hemodynamic derangement in HFpEF is the pathologic elevation in LV filling pressure, at rest or on exertion^(9,10). Commonly used organic nitrates, isosorbidedinitrate (ISDN), isosorbide-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 HFpEF, 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 HFpEF patients for whom ischaemia is a beneficiary factor. Nitrate induced pre-load reduction may also be beneficial in HFpEF^(16,17). HFpEF 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 HFpEF, 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 characterised 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 empirical evidence for the effectiveness of particular drugs in treating HFpEF, emphasising the 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.

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