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The progress and controversial of the use of beta blockers in patients with heart failure with a preserved ejection fraction

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ABSTRACT

Beta blockers are a recommended therapy in patients with heart failure with reduced ejection fraction (HFrEF). Beta blockers markedly and unequivocally reduce mortality in patients with heart failure with reduced ejection fraction. However, the beneficial effects of beta blockers in patients with heart failure with preserved ejection fraction(HFpEF) are not well established. In this review, we will assess the evidence basis of the recommendations for beta blockers and discuss emerging concerns about the use of beta blockers in patients with HFpEF. The available evidence for beta blockers is limited and it remains uncertain whether beta blockers have a beneficial role in the treatment of HFpEF in the absence of an alternative indication for their use.

Contents

1. Introduction

Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, peripheral edema and pulmonary crackles) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.

The main terminology used to describe HF is historical and is based on measurement of the left ventricular ejection fraction (LVEF). HF comprises a wide range of patients, from those with normal LVEF (typically considered as ≥50%); HF with preserved EF (HFpEF)] to those with reduced LVEF (HFrEF) (typically considered as ≤50%). Patients with an LVEF in the range of 40–49% represent a 'grey area', which we now define as heart failure with mid-range ejection fraction (HFmEF). Differentiation of patients with HF based on LVEF is important due to different underlying etiologies, demographics, co-morbidities and response to therapies [1,2].

HFpEF is a rather homogeneous entity. The diagnosis of HFpEF is more challenging than the diagnosis of HFrEF. Patients with HFpEF generally do not have a dilated left ventricle (LV), but instead often have an increase in LV wall thickness and/or increased left atrial (LA) size as a sign of increased filling pressures.

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LVEF is normal and signs and symptoms for HF are often non-specific and do not discriminate well between HF and other clinical conditions. Patients with HFpEF are a heterogeneous group with various underlying etiologies and pathophysiological abnormalities. Most have additional 'evidence' of impaired LV filling or suction capacity, also classified as diastolic dysfunction, which is generally accepted as the likely cause of HF in these patients [1].

Beta blockers reduce mortality and morbidity in symptomatic patients with HFrEF, despite treatment with an ACEi and, in most cases, a diuretic [3–7]. However, no medications have consistently improved outcomes in HFpEF [8]. Despite lack of data supporting their benefits, medications commonly used for HFrEF, such as beta blockers, are frequently prescribed for HFpEF [9,10]. Indeed, in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist study, almost 80% of participants with HFpEF took beta blockers. BetaBlockers remain essential in patients with HFrEF, but whether the beta blocker is effective or not in those with HFpEF is controversial. In this study, we will review the progress of beta blockers in the management of patients with HFpEF.

2. Pathophysiological mechanisms

During the progression and exacerbation of heart failure, the sympathetic nervous system becomes hyperactive. The resultant increase in β-adrenergic receptor (β-AR) stimulation to cardiomyocytes initially produces a positive inotropic effect, primarily via the activation of the β1AR-stimulating G (Gs) protein–adenylate cyclase–cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA) signaling pathway [11]. However, persistent β1AR stimulation triggers apoptosis of cardiomyocytes and leads to hypertrophy, fibrosis and maladaptive remodeling of the diseased hearts, via mechanisms that depend on calcium/calmodulin-dependent kinase type II (CaMKII), but not on PKA [12,13].

The mechanisms by which beta blockers exert benefit are uncertain [14]. Blocking adrenergic receptors has direct effects on cardiomyocytes, reduces heart rate, alters vascular function, and modifies the neuro-endocrine response to heart failure [15]. β1AR and β2AR are coexpressed in the heart, but exhibit distinct functions under certain pathological circumstances, such as chronic HF. Previous studies shown that the deficiency of β2AR enhanced isoproterenol or doxorubicin-induced myocardial injuries and mortality in mice [16,17], and the loss-of-function β2 adrenergic receptor (ADRB2) Thr164Ile mutation is associated with increased mortality in patients with HF [18]. In addition, β2AR-Gi signaling pathway abrogates β1AR-induced loss of cardiomyocytes and negates both β1AR-mediated and β2AR-mediated positive inotropic effects by negating the activation of L-type calcium channel and CaMKII [19]. Our recent data indicated that patients with heart failure harboring the Gly16 allele in the gene for β2 adrenergic receptor (β2AR) had an increased risk of the composite end point events relative to patients who were homozygous for Arg16. Notably, these patients showed a beneficial response to beta blocker treatment in a G allele-dose-dependent manner, whereas Arg16 homozygotes had no response to beta blocker therapy [19]. Interestingly, the reduced inhibition of the β1AR-Gs signaling pathway by the β2AR-Gi in ADRB2-Gly16-expressing myocardial cells may explain why the G allele carriers are hypersensitive to beta blockers therapy [20]. In addition, bisoprolol provided anti-inflammatory and anti-oxidative effects in association with the improvement in survival rate in the HFpEF model rats [21]. Importantly, the importance of these mechanisms may vary by etiology, left ventricular phenotype, heart rhythm and clinical indication.

3. Hypertension, cardiac hypertrophy and HFpEF

Longstanding hypertension ultimately leads to HF, and, as a consequence most patients with HF have a history of hypertension. Conversely, absence of hypertension in middle age is associated with lower risks for incident HF across the remaining life course. Cardiac remodeling to a predominant pressure overload consists of diastolic dysfunction and concentric left ventricular hypertrophy [22]. When pressure overload is sustained, diastolic dysfunction progresses, filling of the concentric remodeled left ventricle decreases, and HF with preserved ejection fraction ensues. Diastolic dysfunction and HF with preserved ejection fraction are the most common cardiac complications of hypertension [22]. At least in part, hypertension is the most frequent and potent risk factor for the development of HFpEF. The pathophysiological association of hypertension and HFpEF is complicated and extends beyond left ventricular hypertrophy and diastolic dysfunction. Treatment of hypertension is crucial for preventing new onset of HFpEF. Identification of hypertensive patients with increased risk of developing HFpEF and subsequent aggressive antihypertensive treatment could be an effective preventing measure. No specific antihypertensive treatment has yet been shown to reduce morbidity or mortality in patients with HFpEF and large randomized clinical trials have reported neutral results [23]. However, some classes of antihypertensive agents are of some benefit. Diuretics have been shown to relieve symptoms while angiotensin-converting enzyme inhibitor (ACEi), Angiotension receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs), and specifically perindopril, candesartan and spironolactone reduce HF hospitalization rate and symptoms [23]. There is weak evidence that nebivolol may be associated with small reduction in mortality and hospitalization [23].

4. The potential effects of beta blockers in patients with HFpEF

Metoprolol prevented not only the development of left ventricular hypertrophy but also the progression of diastolic dysfunction, and improved survival in rats with diastolic heart failure. The preventive effect of metoprolol on myocardial fibrosis is considered as one of the mechanisms contributing to halt the progression of diastolic dysfunction [24]. Moreover, bisoprolol administration, particularly at high dose, improved the survival rate of the diastolic heart failure model, at least in part through the attenuation of inflammatory changes and oxidative stress [21]. These data indicated that beta blockers exerted beneficial effects on diastolic heart failure in experimental studies.

The SWEDIC study demonstrated that treatment with carvedilol resulted in a significant improvement in E/A ratio in patients with heart failure due to a left ventricular relaxation abnormality [25]. However, these doppler echocardiographic indices have many limitations for the assessment of left ventricular diastolic function in subjects with preserved EF, and thus, it is difficult to make conclusive remarks based on results of the SWEDIC study [25]. The J-DHF study was a prospective, randomized, open, blinded-endpoint design, and the results of the J-DHF study suggest that the standard dose prescription of carvedilol is effective in HFpEF [26]. However, another study indicated that use of beta blockers in patients with HFpEF was associated with lower all-cause mortality but not with combined all-cause mortality or heart failure hospitalization [27]. Recent data indicated that among hospitalized patients with HFpEF and a discharge heart rate $\geq$70 beats/minute, high-dose beta blockers use was associated with a significantly lower risk of all-cause mortality, but not with heart failure hospitalization [28]. These

data indicated that beta blockers use had beneficial effects on patients in HFpEF.

However, some other studies demonstrated that beta blockers use was negative on the management of patients with HFpEF. Although the OPTIMIZE-HF study [29] demonstrated that incident beta blockers use was clinically effective and independently associated with lower risks of death and re-hospitalization in elderly patients admitted with heart failure, patients with preserved systolic function had poor outcomes, and beta blockers did not significantly influence the mortality and re-hospitalization risks for these patients. It is plausible to speculate that the HFpEF patients of the OPTIMIZE-HF study were also treated with low doses of beta blockers, and that the absence of beneficial effects of beta blocker on HFpEF in the OPTIMIZE-HF study was at least partly explained by the underdose of beta blockers [29]. Recently, further analysis of OPTIMIZE-HF concluded that the dose of beta blocker does not affect the clinical outcome in HFpEF patients; however, the median follow-up was only 2.2 years [30]. Interestingly, another study demonstrated that benefits of beta blockers emerged at follow-up for 3 years but not for 1 year in patients with heart failure [31]. Thus, dose and duration of follow up of beta blocker therapy may be key determinants of the effects of beta blockers on clinical events in HFpEF patients [32].

Beta blockers reduced all-cause and cardiovascular mortality compared to placebo in sinus rhythm, an effect that was consistent across LVEF strata, except for those in the small subgroup with LVEF $\geq$50% [33]. The Korea Acute Heart Failure (KorAHF) is a prospective observational multicentre cohort study. The 5,625 patients hospitalized for acute HF syndrome in 10 tertiary university hospitals across the country have been consecutively enrolled between March 2011 and February 2014. The final data indicated that use of beta blockers is associated with reduced all-cause death but not with reduced rehospitalization [34]. However, some other studies indicated that beta blockers use in HFpEF patients exerted no beneficial effects on the risk of composite cardiovascular events. Beta blockers use in HFpEF patients was associated with an increased risk of composite cardiovascular events. In particular, beta blockers use in HFpEF patients without previous myocardial infarction was associated with higher risks of all-cause death, major cardiovascular events, and heart failure hospitalization [35]. It is well established that HFpEF is a generic term of heterogeneous pathophysiology and is not a sole disease. All of the clinical trials and observational studies present facts to us, and it is speculated that "one size fits all approach" may be a cause for inconsistent results of previous studies and for a lack of evidence about the therapeutic strategy of HFpEF until now.

In addition, HFpEF is often accompanied by atrial fibrillation. According to current guidelines, beta-blockers or non-dihydropyridine calcium channel blockers alone are the first choice drugs for rate control in atrial fibrillation [36,37]. Previous studies have shown that treatment with betablockers tends to reduce exercise capacity, whereas treatment with calcium blockers may preserve or even improve exercise tolerance [38,39]. However, few studies have compared betablockers and calcium channel blockers with once daily dosage without simultaneous treatment with digitalis. Recent study compared exercise capacity with four different rate-reducing drug treatments. The exercise capacity (peak VO2) was significantly lower during treatment with metoprolol and carvedilol compared with baseline (no treatment) or treatment with diltiazem and verapamil. Compared with baseline, treatment with diltiazem and verapamil significantly reduced the NT-proBNP levels both at rest and at peak exercise, whereas treatment with metoprolol and carvedilol increased the levels [40]. These data indicated that rate-reducing treatment with diltiazem or verapamil preserved exercise capacity and reduced levels of NT-proBNP compared with baseline, whereas treatment with metoprolol or carvedilol reduced the exercise capacity in patients with permanent atrial fibrillation [40].

5. Conclusions

Currently, there is no established therapeutic intervention to improve the prognosis of HFpEF. The previous observational and randomized controlled trials studies provided inconsistent conclusions about the effects of beta blockers on HFpEF. Future studies are awaited to make a conclusive remark about the effects of beta blockers in HFpEF. However, a "one size fits all approach" as in previous clinical trials is likely inappropriate to figure out the potential effects on HFpEF, because the pathophysiology of HFpEF is heterogeneous. Future clinical studies may be required to target a part of HFpEF with some specific characteristics.

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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