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Can the Use of β-Adrenergic Blockers for Treatment of HFpEF Worsen Diastolic Dysfunction? - A Review Based on Concept of MyBP-C

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Abstract

Heart failure can be classified based on ejection fraction as reduced Heart Failure Reduced Ejection Fraction (HFrEF), moderate Heart Failure Moderate Ejection Fraction (HFmEF) and preserved Heart Failure Preserved Ejection Fraction (HFpEF). Indeed, use of beta-blockers in Heart Failure (HF) reduces mortality and morbidity. However, the controversial effect of the use of beta-blockers in HFpEF is of great concern. HFpEF is associated with a high mortality and hospitalization rate probably due to lack of evidence-based treatment. Hence a proper understanding behind the pathophysiologic mechanism of HFpEF is important. Recently Myosin Binding Protein C (MyBP-C), a cardiac-specific protein, has been shown to be involved in various cardiac pathologic conditions. Phosphorylation of MyBP-C is crucial for normal systolic and diastolic heart function. A failing heart is associated with hypophosphorylation of MyBP-C. Use of beta-blockers in HFpEF would prevent β-Adrenergic stimulation of MyBP-C by Protein Kinase A (PKA) and can worsen diastolic dysfunction in HFpEF.

Keywords: HFpEF; heart failure; beta-blocker; MyBP-C.

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1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is becoming a serious emerging epidemic concern associated with high morbidity and mortality [1]. It has a prevalence rate of about 50% of HF cases and is expected to be the most common type of HF in the future [2]. With a significant increasing life expectancy during the past years [3] and a rapidly aging population, the prevalence of HFpEF is also expected to increase. A well-established relationship between age and prevalence of HFpEF has been reported according to the PREVEND study [4]. Moreover, the latter showed that increasing age is associated with increasing prevalence of comorbidities such as hypertension, diabetes, and atrial fibrillation among others, which is thought to play an important role in the increasing prevalence of HFpEF. These observations are backed up by other studies reporting that most affected individuals turn out to be the elderly and female [5, 6]. In the past, there was a major challenge in term of diagnosis and treatment of HFpEF. Nowadays, with the emergence of new technologies and medical advancements such as echocardiography and use of biomarkers, make it easier to recognize and diagnose HFpEF. Moreover, several guidelines about the diagnosis of HFpEF have been published [7, 8]. Patients with HFpEF has a poor survival rate with greater than 8 times mortality rate for 5 years [9]. The main reasons behind such high mortality rate in HFpEF could be a lack of evidence-based treatment [2] most probably due to a lack of understanding behind the underlying mechanism and pathophysiology.

2. Classification of Heart Failure & diagnosis of HFpEF

Heart failure can be classified as heart failure with reduced ejection fraction (HFrEF), heart failure with moderate ejection fraction (HFmEF) and heart failure with preserved ejection fraction (HFpEF). Guidelines set up by the European Society of Cardiology and the American College of Cardiology defines the diagnosis of HFpEF as; (1) presence of signs and symptoms of heart failure; (2) left ventricular ejection fraction of ≥50%; and (3) evidence of left ventricular dysfunction (elevated natriuretic peptides and structural modifications such as **Left Ventricular Hypertrophy** (LVH) and/or **Left Atrial Enlargement** (LAE); or diastolic dysfunction) [10, 11]. Diastolic dysfunction is a major contributor of HFpEF and most patients exhibit hypertrophy [12]. The Framingham Classification of heart failure is the most commonly accepted criteria for evaluation of heart failure. However, there is no specific algorithm to validate the diagnosis of HFpEF thus making the diagnosis of HFpEF a major challenge. The use of echocardiography with normal **Left Ventricular Ejection Fraction** (LVEF) and clinical signs and symptoms of HF according to Framingham criteria seem important for the diagnosis of HFpEF. Moreover, new emerging biomarkers closely associated with an onset of HFpEF have been identified including cystatin C, resistin, galactin-3 and growth differentiation factor-15 [13]. These biomarkers meet the criteria set by Morrow and de Lemos [14] to be used as novel biomarkers of HFpEF.

3. Use of β-Adrenergic blockers in Heart Failure

β-blockers are mainstay drugs used as part of the treatment regime of HFrEF [11] and they reduce the cardiovascular mortality and morbidity [15]. Their role in HFpEF is yet to be studied. Increased sympathetic activity in HFpEF can lead to a reduction in diastolic time filling, onset of hypertension and arrhythmias. Hence

theoretically, use of β-blockers could be beneficial in HFpEF patients by decreasing the sympathetic activity. A meta-analysis conducted by Liu and his colleagues [16] reported that beta-blockers decreased mortality. Another improved meta-analysis carried by Chirag and his colleagues [17] showed that based on observational studies, a 19% decrease in all-cause mortality is associated with the use of beta-blockers in HFpEF patients and based on RCTs, no benefits were observed with use of beta-blockers. However, based on the two meta-analyses conducted, there was no significant improvement of hospitalization with use of beta-blockers.

4. MyBP-C and Heart Failure

β-Adrenergic–stimulated phosphorylation of MyBP-C is important for regulation of crossbridge formation thus enhancing cardiac contractility [18]. A high level of phosphorylation is critical for normal cardiac function, whereas dephosphorylation has been associated with heart failure.[19] Following β-Adrenergic stimulation phosphorylation is increased [20] and phosphorylated MyBP-C has crucial role in modulating ventricular contraction and relaxation in order to meet the circulatory demand. Dephosphorylation of MyBP-C has been reported to cause both systolic and diastolic function dysfunction. The pressure developed within the ventricle as well as the force developed within the myocardium during systole is dependent on the crossbridge formation, which is, in turn depends on phosphorylation of MyBP-C [21, 22].

A study conducted in mice showed that following β-adrenergic stimulation of phospho-ablated MyBP-C, there is a marked decrease in the peak pressure developed [23]. This demonstrates the importance of phosphorylated MyBP-C for normal systolic function. Ventricular relaxation is not only calcium-dependent but also relies on the rate of crossbridges detachment [24], which in turn also depends on phosphorylation of MyBP-C and TnI [25]. The inability of MyBP-C to phosphorylate efficiently prolong the time to reach maximum relaxation during diastole [21] leading to diastolic dysfunction as seen in hypertrophic cardiomyopathy [26]. Pathologic examination of myocardium samples from **Hypertrophic Cardiomyopathy** (HCM) patients showed reduced MyBP-C phosphorylation[27] implying that proper relaxation is greatly dependent on MyBP-C phosphorylation [28].

5. Understanding the differences between diastolic dysfunction, diastolic heart failure and HFpEF

It important to understand the differences between diastolic dysfunction, diastolic heart failure, and HFpEF. Diastolic dysfunction is not a clinical syndrome but just a condition whereby myocardial relaxation is impaired leading to increased filling pressures [8]. Diastolic dysfunction does not mean the presence of heart failure. For instance, unlike diastolic dysfunction, heart failure is a clinical syndrome associated with a series well defined of signs and symptoms caused by the inability of the heart to either pump blood and/or fill the ventricles properly in order to meet the circulatory demand [29].

HFpEF previously known as diastolic HF, consist of several pathophysiologic mechanisms [30-34]. It now understood that HFpEF is not the same as diastolic HF as the latter consists merely of a single mechanism and hence is not present in all HFpEF patients [35]. Hence it can be said that diastolic HF can be present in HFpEF but not always. The observation made by a study conducted by Prasad and his colleagues [36] among patients

with HFpEF showed that diastolic dysfunction only accounted for 2% of all the HFpEF patients, suggesting that diastolic dysfunction is a subset of HFpEF and is not always present.

6. How β-Adrenergic blockers can worsen diastolic dysfunction in HFpEF based on the concept of MyBP-C

It has been clearly discussed above that there exists a strong relationship between hypophosphorylation of MyBP-C and diastolic dysfunction, which is a major component of HFpEF. Moreover, it is known than β-adrenergic–stimulated phosphorylation of MyBP-C by PKA is essential for proper systolic as well as diastolic function.

The differences between diastolic dysfunction, diastolic HF and HFpEF have been well discussed above as well. And from our knowledge of β-Adrenergic–stimulated phosphorylation of MyBP-C, we now know that failing heart is associated to hypophosphorylation of MyBP-C. In clinics, it is a common practice for physicians to prescribe beta-blockers for HF patients [15], including that of HFpEF. Since a failing heart is already associated with hypophosphorylation of MyBP-C, the use of beta-blockers will further exacerbate hypophosphorylation, thus worsening diastolic dysfunction. In spite of a decrease in mortality associated with the use of beta-blockers as observed from meta-analyses by Chirag and his colleagues there is no significant decrease in hospitalization [17]. Further worsening diastolic dysfunction with the use of beta-blockers could explain the high hospitalization rate for HFpEF.

7. Conclusion

HFpEF is becoming an epidemic of concern with a high prevalence rate of 50% of all HF cases. Due to lack of evidence-based treatment, HFpEF is associated with a high mortality rate. It is of high importance to understand the mechanism associated with HFpEF, which will give a better insight about the correct treatment principle of HFpEF. As far as the use of beta-blockers in HFpEF is concerned, it has both beneficial as well as controversial effects.

Beta-blockers decrease the sympathetic activity thus preventing increase diastolic time filling or an onset of arrhythmias and hypertension. Hence, use of beta-blockers in HFpEF reduces mortality and morbidity. On the other hand, efficient ventricular relaxation is dependent on proper β-Adrenergic–stimulated phosphorylation of MyBP-C. Use of beta-blockers may exacerbate hypophosphorylation of already poorly phosphorylated MyBP-C that is associated with failing heart. This suggests that use of beta-blockers in HFpEF can worsen diastolic dysfunction. More studies need to be conducted to establish the exact role of beta-blockers in HFpEF.

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