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Beta-Adrenergic Blockade: Is It the Prudent Choice against Sympathetic Overdrive in Patients with Hypertension or Heart Failure?

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Abstract

The development of hypertension and heart failure is correlated with the hyperactivation of the sympathetic nervous system. Beta-blockers are often considered a good therapeutic option in such clinical scenarios. However, the choice of β-blocker is a concern because of certain aspects like associated metabolic disturbances with their usage. Metoprolol has been reported to have the potential to alleviate sympathetic overdrive in patients with hypertension and heart failure. S-Metoprolol is the chirally pure β-blocker with favorable pharmacological features, improved safety profile, and allied clinical advantages versus racemic metoprolol; given this, can it be an effective therapeutic option against sympathetic overdrive in patients with hypertension and/or heart failure is not fully recognized yet. In this review, we attempted to discuss the current facts around sympathetic overdrive linked with hypertension as well as heart failure and pertaining pharmacological intervention with a focus on β-blockers in these clinical situations with an emphasis on the likely beneficial role of S-metoprolol.

Keywords
- sympathetic overdrive
- hypertension
- heart failure
- beta-blocker
- metoprolol
- S-metoprolol

Introduction

The sympathetic nervous system (SNS) regulates several physiological conditions like electrolyte balance, maintenance of homeostatic state, and blood pressure (BP).[1] Sympathetic overdrive (SO) is indicative of increased activity of SNS and clinically can be correlated in terms of elevated heart rate (HR) and/or persistent rise in BP.[2–4] Incidence of SO linked with hypertension and/or heart failure (HF) associated with SO is predominantly reported in the young patient population.

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While specific causes of an increase in SNS are mostly unknown, genetic influences and behavioral and lifestyle factors appear to be usually involved. Increased SNS activity is believed to contribute to the pathophysiology of HF through multiple mechanisms, including desensitization of cardiac β-adrenergic receptors and adverse effects on excitation-contraction coupling. Sympathetic inhibition with specific pharmacological intervention in the management of hypertension seems to be the essential approach to tackle SO associated with hypertension. Among various available pharmacological agents, β-blockers shown to have beneficial effects by acting against elevated HR. Therapeutic usage of β-1 selective agents (e.g., bisoprolol and metoprolol) has usually been free of metabolic disturbances versus nonselective types of β-blockers (e.g., propranolol and timolol).[5] S-Metoprolol is a chirally pure form of metoprolol that has reported favorable pharmacokinetics and pharmacodynamics profile including highly specific action on β-1 receptors. In this review, we discuss the current essentials of SO associated with hypertension and pharmacological intervention with the β-blockers in these conditions with a focus on the likely beneficial role of S-metoprolol.

Sympathetic Overdrive and Its Key Clinical Impact

SO is reported to be a key mechanism involved in essential hypertension, and its deleterious cardiovascular consequences are well recognized.[6,7] Given figure portrays SO and its linkage with the key cardiovascular parameters. SO has been also associated with obese younger patients with hypertension.[6] Elevated HR beyond 85 bpm (linked with SO) could lead to the development of hypertension, especially in young individuals. European guidelines on the management of hypertension acknowledged the importance of tachycardia and recommend that resting HR be measured at each visit. Tachycardia and SO are closely linked to the early morning peak in the ischemic event(s).[7,8]

Reported epidemiological data suggest that 25% of rural and 33% of urban Indians suffer from hypertension.[8–10] Around 6 out of 10 newly diagnosed patients with hypertensive in India reported to have SO.[10] There is a huge prevalence of SO (over 62%) in Indian patients with hypertension.[11] By looking at such an epidemiological perspective on hypertension, it is prudent to look for the various notable pathophysiological aspects involved with hypertension. Targeting the right pathophysiological mechanisms with the right drugs can bring out control this situation. As reported in a recent India heart study inclusive of 18,918 newly diagnosed patients with hypertension, over half of the participants were observed with an elevated resting HR of 79.8 ± 9.6 bpm. This evidence supported to look for the use of antihypertensive drugs with HR-lowering effects in Indian patients with hypertension.[12] In case of HF, SO is (i) directly related to the severity of symptoms and thus with the New York Heart Association (NYHA) functional class; (ii) inversely related to measures of left ventricular function, such as left ventricular stroke work, stroke volume, and ejection fraction; and (iii) independent of the ischemic or idiopathic nature of the disease.[13]

Role of Beta-Blockers against Sympathetic Overdrive

Beta-blockers have been associated with long-term beneficial effects on mortality and cardiovascular disease when used in people with HF or acute myocardial infarction. They are expected to have similar beneficial effects when used as first-line therapy for hypertension. Modulation of sympathetic activation is considered an important goal of antihypertensive therapy, particularly in young or middle-aged patients. The maximum efficacy in terms of the marked reduction in the peripheral and cardiac SNS activity with an effective BP control and the control over the HR has been shown by β-blockers versus available antihypertensive agents.[10,14] Beta-blockers vary in their specificity toward different receptors, and accordingly, the effects produced depend on the type of receptor(s) blocked as well as the organ system involved. Beta-1 blockade seems to be suitable for various clinical settings like a patient(s) with sympathetically driven hypertension or patients with labile hypertension. Clinical scenarios like central obesity in younger subjects have been linked to increased sympathetic nerve activity and BP; this hemodynamic scenario is ideal for β-1 blockade.[15] As per several hypertension guidelines and the evidence, β-blockers can be the initial therapy in young patients with hypertension,[16] especially those who are intolerant to or contraindicated from the usage of angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists.[17]

Beta-blockers remain the mainstay of treatment for patients with congestive heart failure (CHF) because of their inherent property to counteract the sympathetic overactivity associated with left ventricular dysfunction, in addition to lowering the HR, contractility, and BP, thus lowering the mortality in HF. The beneficial effects of β-blockers are further supported by a meta-analysis of randomized control trials showing a total reduction of mortality and HF-related sudden death in patients with CHF. The choice of the β-blocker in a given situation could be based upon various pharmacodynamic criteria like selectivity of action depending on β-adrenoceptor subtype and pharmacokinetic profile. Associated adverse effect profile can be the notable criteria as well; for example, β-blocker like atenolol is known to cause certain metabolic disturbances. Nebivolol has the highest β1-selectivity seen so far, together with additional vasodilating and antioxidative properties. It is currently applied in the treatment of hypertension and CHF.[17] Metoprolol is a selective β1-blocker approved to treat conditions like angina, HF, myocardial infarction, atrial fibrillation/flutter, and hypertension.[18] In younger patients with hypertension, the β-1 blockade would be a judicious choice for the prevention of major adverse cardiac events like myocardial infarction. Such receptor selectivity of β-blockade would result in several patient benefits like no to minimal cigarette smoking interaction and the risk of type-2 diabetes development.[19]

Metoprolol either alone or in combination with other antihypertensive drugs has been reported as the most commonly prescribed antihypertensive drug against SO in patients with hypertension as per the study by Padmanabhan et al exhibiting its good efficacy and tolerability profile. In said study, metoprolol usage versus other available antihypertensive drugs was shown to offer a significant reduction in both systolic and diastolic BPs around 24.61 and 13.99 mm Hg, respectively, on follow-up visits, accompanied by a HR reduction in 14.53bpm approximately.[10] This suggests the clinical utility and beneficial role of metoprolol against SO in patients with hypertension.

S-Metoprolol against Sympathetic Overdrive: Role and Clinical Benefits

Chirality is an emerging concept in pharmaceutical medicine that suggests the existence of different forms of the given drug molecule. Metoprolol does exhibit chirality with its two available forms as R-metoprolol and S-metoprolol. S-metoprolol (chirally pure drug) bears favorable pharmacological actions that ultimately offer certain clinical benefits and makes it a smarter choice versus R-metoprolol in cardiovascular conditions including hypertension associated with sympathetic hypertension as shown in the given table. Several clinical studies have demonstrated that chirally pure molecules like S-metoprolol versus racemate metoprolol exhibit certain clinical advantages such as better safety profile and comparable or equivalent therapeutic action even at lower drug dose versus standard dose and this is attributed to its greater affinity toward β1-receptor.[20–22] S-metoprolol is a highly β-1 selective agent and is usually not associated with metabolic disturbances like a disturbance in blood lipid or blood glucose levels versus other nonselective β-blockers.[15]

The role of S-metoprolol in the management of hypertension and comorbidities has been studied earlier and has specifically been shown to have lesser side effects. It is considered safer in specific patient populations like patients with hypertension and chronic obstructive pulmonary disease (COPD) and/or diabetes mellitus with comparable responder rates at even at a half dosage versus racemate metoprolol.[20] S-metoprolol has been reported as a good therapeutic choice in patients with hypertension and coexisting COPD.[21] Efficacy, safety, and overall tolerability of S-metoprolol 50 mg extended release (ER) versus racemic metoprolol 100mg ER in the treatment of hypertension have been reported with a good clinical outcome.[22]

Another clinical trial with 2,000 participants had shown that S-metoprolol 25/50 mg ER tablet can be a good choice for patients with hypertension.[23] This implies the possible clinical utility of S-metoprolol in routine clinical practice in specific populations like young patients with hypertension where the prevalence of SO is high.

S-Metoprolol administered at half the dose of the racemate was shown to exhibit comparable safety and better response rate in patients with angina and coexisting hypertension.[24] S-Metoprolol alone and in combination with other antihypertensive agents have been also assessed in patients with hypertension and associated angina and/or diabetes mellitus with a good safety profile.[25]

In a recent Indian survey, approximately 89% of healthcare provider (HCP) reported β-blockers as the drug of choice in patients with augmented SO, and S-metoprolol was reported to be the most preferred β-blocker agent that was recommended by 76% of HCP in patients with hypertension and coexisting SO.[26] In the reported clinical trial, S-metoprolol succinate ER reduced BP and HR in hypertensive patients of CHF. Furthermore, there was a marked improvement in NYHA class and symptoms of CHF in all patients.[27]

Conclusion

SO plays a part in hypertension and HF development that may progress and aggravate further cardiovascular risk. Modulation of SO represents an important goal of treatment in such clinical scenarios allowing to achieve of greater cardiovascular protection. Beta-blockers seem to have a promising role in counteracting the SO by reducing the SO in patients with hypertension and/or HF and metoprolol seems to be the preferred β-blocker in patients. S-Metoprolol is a chirally pure β-blocker with definitive clinical advantages and seems to have a beneficial role in hypertension and HF associated with SO.

Disclosure

The views expressed in this publication represent those of the author(s).

Conflicts of Interest

None declared.

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