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Review article

Medical treatment of hypertrophic cardiomyopathy – What do we know about it today?

Pavel Gregor *, *Karol Čurila*

Cardiocenter, 3rd Department of Internal Medicine – Cardiology, University Hospital Kralovske Vinohrady and Third Medical Faculty of Charles University, Czech Republic

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ABSTRACT

Beta-blockers represent a cornerstone of the treatment of symptomatic hypertrophic cardiomyopathy – they are the first-line therapy for obstructive and non-obstructive forms. Sympathetic modulation leads to the deceleration of heart rate at rest and after exertion, and unconvincingly to the improvement of left ventricular diastolic function and obstruction. Medications include also nondihydropyridine *calcium channel blockers* without significant vasodilatory properties, i.e. verapamil and diltiazem. Other medications used are class IA antiarrhythmic drugs – *disopyramide* or *cibenzoline*, which can be administered to patients with obstructive forms when first-line agents have not been effective. *Amiodarone* and *diuretics* can be used in special indications. Some other agents including statins are in the stage of clinical investigation.

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* *Corresponding author at*: 3rd Department of Internal Medicine – Cardiology, University Hospital Kralovske Vinohrady and Third Medical Faculty of Charles University, Srobarova 50, 100 34 Prague 10, Czech Republic. Tel.: +420 267162700.
E-mail address: pavel.gregor@fnkv.cz (P. Gregor).

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Introduction

Many publications have been written about medical treatment of hypertrophic cardiomyopathy (HCM) in past. The first one of them, describing the effect of beta-blockers in HCM [1], was published shortly after the antihypertensive effect of beta-blockers had been described for the first time. HCM is one of the few heart disorders, in which the same medications have been used constantly for several decades. The first-line agents include two main drug groups: beta-blockers and calcium channel blockers.

Despite the above mentioned facts, pharmacologic treatment of HCM is associated with several ambiguities and surprising gaps in knowledge, mainly regarding novel agents. Some drugs tested several decades ago are not already used – particularly some older beta-blockers [2]. Perhaps, the most important issue is the fact that vast majority of studies performed in past had designs incompatible with the present requirements for drug studies; results of double blinded, placebo-controlled trials are almost not available in HCM.

If we dealt with pharmacologic treatment of HCM in the extent the last European classification described it [3], this article would have been quite extensive and complicated. According to this classification, cardiomyopathies are defined as diseases of the heart, when myocardium is structurally and functionally abnormal, and other disorders that could cause the impairment of myocardium as coronary artery disease, hypertension, heart valve disease, and congenital heart defects have been excluded. Currently HCM comprises, apart from idiopathic hypertrophic cardiomyopathy, also other disorders that are capable of producing myocardial hypertrophy as lysosomal storage diseases (Fabry disease), glycogen storage diseases (Pompe and Danon-type), myocardial hypertrophy in Friedreich's ataxia, Noonan syndrome, mitochondrial myopathies, and even initial stages of heart amyloidosis and other disorders. In further text, we will concentrate only on ''classical'' idiopathic HCM, which will simplify the topic.

Following review should describe medications used in the treatment of HCM and summarize our knowledge on the individual agents and drug groups.

Beta-blockers

Beta-blockers create a cornerstone of the treatment of symptomatic hypertrophic cardiomyopathy – they are the first-line therapy for obstructive and non-obstructive forms [2,4]. Beta-blockers were invented by James Black in 1960 as drugs for treatment of angina pectoris (he was awarded the Nobel Prize in 1988). Their antihypertensive effect was described already in 1964, and two years later, a paper demonstrating good effect of beta-blockers in HCM was published [1]. The important findings supporting administration of beta-blockers in HCM were higher concentrations of epinephrine in the samples of interventricular septum acquired during surgery [5] and also increase in left ventricular gradient associated with exertion and catecholamines [6].

Eight different beta-blockers (propranolol, praktolol, acebutol, nethalidol, nadolol, bisoprolol, sotalol, metipranolol) have been used in patients with HCM in 12 studies comprising 450 individuals [2].

Sympathetic modulation causes the deceleration of heart rate at rest and after exertion, which could have led to the improvement of *left ventricular diastolic function*, but the evidence supporting this assumption has been found only in few studies [7,8]. Other studies have not confirmed improvement of diastolic function with beta-blockers in patients with HCM [9]. Moreover, positive effect of beta-adrenergic stimulation on diastolic function was demonstrated [10], which further questioned the effect of beta-blockers. In any case, prolongation of diastole improves the coronary perfusion.

Beta-blockers cause a reduction in maximal contraction velocity, which can lead to the change in the extent of systolic anterior movement and so in the magnitude of left ventricular outflow tract *obstruction* in patients with HCM. However, the impact on resting gradient is questionable. Intravenous administration of beta-blockers has more pronounced effect and can rarely even lead to complete resolution of pressure gradient [11]. Long-term oral administration of beta-blockers can influence the magnitude of obstruction very little, and some works have not actually showed any change in the gradient [12].

Beta-blockers can also decrease the rate of supraventricular and ventricular *arrhythmias* in patients with HCM [4,8] although the effect is not convincing [13].

Undoubtedly, beta-blockers can influence a wide range of *symptoms* in HCM patients. Chest pain was diminished or completely disappeared in 50–70% of patients with HCM [13,14]. Dyspnea improved only in patients with the most severe functional limitations – NYHA class III–IV [13].

In HCM, beta-blockers have no impact on prognosis of the disease or sudden death rate, unlike in coronary artery disease, although some studies showed some favorable effect on mortality [14].

Calcium channel blockers

Calcium channel blockers used in HCM include primarily nondihydropyridine agents without significant vasodilatory properties, i.e. verapamil and diltiazem. The idea to use calcium channel blockers in HCM was first elaborated by