Pharmacological therapy for hypertrophic cardiomyopathy: what is the evidence for success?

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The available experience from studies of pharmacological treatment of patients with hypertrophic cardiomyopathy was mainly gained in selected patient samples, with severe symptoms or a complicated clinical setting. Moreover, most reports on drug efficacy are based on either acute mechanistic studies or non-controlled patient cohorts, which are usually rather restricted in numbers and followed for limited periods of time. Bearing in mind the symptomatic presentation of hypertrophic cardiomyopathy, which is sometimes highly variable and influenced to a degree by sympathetic arousal, it is understandable that a considerable placebo effect may occur when initiating any type of treatment. Considering the pathophysiology that underlies symptoms of hypertrophic cardiomyopathy, it is not surprising that the pharmacological agents that are most advocated are beta-blockers and calcium channel blockers – drugs that impact on several of the factors that are responsible for the symptoms. Other compounds that may be used include antiarrhythmic drugs, of which disopyramide – combining antiarrhythmic with negative inotropic properties – has attracted particular interest.

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Introduction

Teare[1] presented the first comprehensive overview of hypertrophic cardiomyopathy in 1958. This description of myocardial hypertrophy out of proportion to the haemodynamic workload, mainly involving the interventricular septum and with myocyte disarray and fibrotic changes, is still valid. The risk for sudden death and the accumulation of cases in certain families indicated hereditary components of the disease. Details regarding aetiology, genetics, structure and pathophysiology are given elsewhere in this supplement, as are details regarding diagnostic procedures and prognostication. The present review focuses on pharmacological therapy in patients with hypertrophic cardiomyopathy. In this context some pathophysiological and symptomatic characteristics of the disease should be highlighted.

Treatment objectives

Pharmacological treatment is but one aspect of the general management of patients with hypertrophic cardiomyopathy, which includes activities that range from genetic counselling to interventions such as pacing, implantable cardioverter-defibrillators and open-heart surgery, as recently reviewed by Spirito et al.[2]. Treatment goals are to decrease progression of disease, to bring symptomatic relief and to protect against complications, in particular sudden death.

When considering the institution of treatment, including with drugs, it should be recognized that many patients with hypertrophic cardiomyopathy are fairly asymptomatic. In such persons the disease is often detected during screening of families with cardiomyopathy or as a result of other coincidental circumstances. Progression of disease is usually rather slow in a general population of such patients, with a low annual mortality[3,4].

Available experience from pharmacological treatment in patients with hypertrophic cardiomyopathy has primarily been gained in selected patient groups, usually referred to specialist hospitals because of occasional severe symptoms or because of a complicated clinical picture. Moreover, most reports on drug efficacy are based either on acute mechanistic studies or on non-controlled patient cohorts that are usually rather restricted in numbers and followed for limited periods of time. This is perhaps not surprising when it is considered that most studies on the fundamental aspects of drug therapy in hypertrophic cardiomyopathy were conducted well before the present era of evidence-based medicine. In addition, some were conducted before the introduction of echocardiography as the ‘gold standard’...
diagnostic procedure, resulting in a more population-based view of the disease.

Bearing in mind the sometimes highly variable symptomatic presentation of hypertrophic cardiomyopathy, which is influenced to a degree by sympathetic arousal, it is understandable that a considerable placebo effect may occur when initiating any type of treatment. This was highlighted by Linde et al.[5], in a study of the placebo effect of pacemaker implantation. It is reasonable to assume that similar effects underlie part of the efficacy that has been ascribed to, for example, beta-blockers and calcium channel blockers.

Another important factor regarding pharmacological treatment is that none of the suggested drug treatments has been subjected to clinical trials that were designed and powered to permit firm conclusions as to whether the agents impact on the prognosis or the natural history of the disease, or the capacity to reduce the risk for sudden death. In combination with the known side effects of recommended drugs, this should incite some caution when considering the need for treatment in individual patients. Nevertheless, clinical experience from the use of drugs in symptomatic patients indicates that a properly tailored pharmacological approach may help.

**Therapeutic targets**

The most common symptoms in hypertrophic cardiomyopathy include the following: dyspnoea; anginal chest pain; fatigue, including decreased exercise tolerance; and presyncope/syncope, which is often induced by exertion or postural changes. These symptoms relate to a number of pathophysiological conditions that, alone or in combination, may be the primary causative factors. Pharmacological treatment of hypertrophic cardiomyopathy interferes with these pathophysiological conditions; the following text briefly addresses those conditions.

The diastolic dysfunction that occurs in hypertrophic cardiomyopathy – diastolic filling of the ventricles – is partly related to decreased myocardial compliance caused by the hypertrophy, but it is also influenced by impairment of early diastolic filling caused by decreased or prolonged myocardial relaxation. The latter may relate to subendocardial ischaemia and disturbed calcium homeostasis[6].

Another important factor that underlies symptoms in hypertrophic cardiomyopathy is myocardial ischaemia. This may be induced by several factors, including small-vessel disease with thickened intramural coronary arteries; compression of septal perforators and impaired subendocardial blood flow due to elevated filling pressure; and impaired myocardial relaxation. Mismatch between the coronary vasculature and hypertrophic myocardial mass may also contribute.

Obstruction of the left ventricular outflow tract is one of the classic components of hypertrophic cardiomyopathy. It is not a constant component, however, manifesting in perhaps 25–30% of patients. This obstruction relates to narrowing of the left ventricular outflow tract as a result of septal hypertrophy combined with deficiencies in the mitral valve. The latter include a systolic anterior movement of the leaflets toward the septal wall, which has been ascribed to a Venturi effect or drag forces, and abnormal insertion of the papillary muscles.

Apart from diastolic dysfunction, myocardial ischaemia and obstruction to the ejection of blood, systolic failure of the left ventricle may occur; however, this usually does not occur until late in the course of the disease. Thus, 10–15% of patients with hypertrophic cardiomyopathy progress toward left ventricular dilatation and chronic heart failure caused by progressive wall thinning and scar formation. A causative factor is believed to be repeated episodes of myocardial ischaemia. Treatment in the more advanced stages of hypertrophic cardiomyopathy is changed to conventional treatment for congestive heart failure, which is beyond the scope of the present review. However, it may be stated that drugs that are commonly considered contraindicated in the pure form of hypertrophic cardiomyopathy (i.e. digitalis and angiotensin-converting enzyme inhibitors) may become treatments of choice in the final stages of disease.

Hypertrophic cardiomyopathy also provides a substrate for arrhythmias, among which ventricular tachycardia and fibrillation are considered the cause of at least some of the syncopal attacks and sudden deaths that may occur. Supraventricular tachycardia – in particular atrial fibrillation – is of concern in these patients, often causing a rapid and substantial haemodynamic deterioration superimposed on the already compromised filling capacity of the ventricles. Further information on arrhythmias related to hypertrophic cardiomyopathy is presented elsewhere in this supplement.

Arrhythmia is not the only possible mechanism behind syncopal attacks and sudden death. They may also relate to an inadequate ability to increase cardiac output during exertion, which may also be the reason for postural presyncope and dizzy spells.

Considering the pathophysiology that underlies symptoms of hypertrophic cardiomyopathy, it is not surprising that the pharmacological agents that are most advocated are beta-blockers and calcium channel blockers – drugs that impact on several of the factors that are responsible for the symptoms. Other compounds that are used include antiarrhythmic drugs (see elsewhere in this supplement), of which disopyramide – combining antiarrhythmic with negative inotropic properties – has attracted particular interest.

Sherrid et al.[7] recently summarized medications taken by 50 patients followed in the hypertrophic cardiomyopathy programme at St Lukes-Roosevelt Hospital Centre in New York. Of the patients studied, 10 did not receive any medication because they were asymptomatic. Twelve patients were on calcium channel blockers only; 10 were on beta-blockers; and 43% of the 40 treated patients received more than one medication.

**Beta-blockers**

Soon after the initial description of hypertrophic cardiomyopathy, beta-blockade in the form of propranolol...
was tested and shown to reduce symptoms in patients with this disease. Beta-blockade decreases the impact of various factors that limit myocardial oxygen consumption; in particular, the negative chronotropic response to exercise following the institution of such drugs may benefit diastolic filling of the ventricles. It has been claimed that anginal chest pain is easier to handle with beta-blockers than is breathlessness[8]. It has also been speculated, but never proven, that beta-blockers may prevent arrhythmias, thereby potentially preventing sudden death. This has perhaps been the rationale behind the prophylactic use of beta-blockers, even in those patients without symptoms, but this indication does not yet have scientific support.

In one randomized, double-blind, crossover trial, that included only 18 patients, the beta-blocker nadolol was compared with the calcium channel blocker verapamil and placebo during periods of 4 weeks each[9]. Neither drug improved the maximal oxygen uptake. The peak exercise workload was reduced by more than 10 W in 81% of patients during nadolol treatment and in 25% during verapamil treatment, a difference that reached statistical significance. Nevertheless, 81% of patients (eight patients expressed a preference for verapamil and five for nadolol) preferred drug treatment to placebo. Verapamil improved self-reported physical performance during the period of treatment as compared with nadolol, and tended to improve some other measures of health-related quality of life and symptoms as compared with nadolol and placebo. One reported side effect was sinus bradycardia during the nadolol treatment period.

Regarding the choice of beta-blocker, most of the original studies were done with propranolol, which was the only available beta-blocker at the time when interest in treatment of hypertrophic cardiomyopathy began. It has been claimed that a lack of peripheral beta-2-andrenergic receptor blocking capacity may render beta-1-blockers less efficient[10]. This has not been verified in clinical trials, however. In our practice metoprolol is the initial drug of choice in many patients.

The simplest way to ensure that a reasonable degree of beta-blockade has been achieved is to assess its effect on heart rate. The dosages of beta-blockers do not differ from those usually prescribed, and they should be sufficient to exert a reasonable effect on resting and exercise heart rate.

**Calcium channel blockers**

Of the various calcium channel blockers, verapamil in particular has been the focus of interest for treatment of hypertrophic cardiomyopathy. Calcium channel blockers with a more selective vascular effect should be avoided, bearing in mind the sensitivity of patients with hypertrophic cardiomyopathy (the obstructive form in particular) to afterload reduction.

The first report on the beneficial use of verapamil came from Kaltenbach et al.[11] in 1979. That report was soon followed by many others, as reviewed by Hess et al.[12], Mechanisms that underlie the efficacy of calcium channel blockers may include interaction with abnormalities of diastolic filling that are induced by disturbed calcium kinetics. Verapamil is believed to improve diastolic filling by reducing asynchronous regional diastolic abnormalities and by improving relaxation, rather than by improving the decreased ventricular compliance. Anti-ischaemic effects of verapamil have also been suggested, but not consistently verified[13]. The response to intravenous verapamil has been considered predictive of continued efficacy, including increased exercise tolerance, during chronic treatment[14].

Although verapamil is the most extensively studied calcium channel blocker and is the only one for which there are at least some reports from long-term follow-up studies comparing this drug with other therapeutic modalities[15], there are still no valid comparisons between different calcium channel blockers. In a double-blind, crossover comparison between diltiazem and verapamil, there were no significant differences between these two drugs[16]. In that study, which recruited 32 patients, the treatment periods were limited to 1 week each.

With regard to the optimal dose, the available guidance suggests that it is reasonable to titrate the dose upwards in an attempt to find a reasonable balance between symptomatic benefit and avoidance of side effects. These are mainly reported as hypotension, sinus node depression, atrioventricular block and occasionally deterioration of left ventricular failure, including increased pulmonary congestion.

In a long-term, retrospective, follow-up study that compared medical and surgical therapies for treatment of hypertrophic cardiomyopathy, Seiler et al.[15] followed 139 patients for an average of 8-9 years. A total of 60 patients were assigned to the medical group; 20 of these patients were on propranolol (166 mg . day\(^{-1}\)) and 18 were on verapamil (360 mg . day\(^{-1}\), whereas 22 received no therapy. A total of 79 patients underwent septal myectomy. The cumulative survival was significantly better among surgically than among medically treated patients. Among the medically treated patients, those on verapamil had an improved survival as compared with those on propranolol or those without treatment. Comparing the 10-year survival rate in patients on verapamil (80%) and in those treated surgically (84%), there was no significant difference. That study is limited by being a retrospective analysis that compared groups that were not necessarily comparable because of patient selection bias. For example, the likelihood that patients would be treated surgically must have been higher for those with greater left ventricular outflow tract gradient. Moreover, the number of patients in each subgroup was rather limited. Nevertheless, it appears that verapamil is favourable to propranolol for pharmacological therapy, which perhaps can serve as a guide in the lack of formal comparisons.

**Disopyramide**

Disopyramide, in dosages of 400–600 mg . day\(^{-1}\), is considered a most effective treatment for relief of left ventricular outflow tract obstruction. This drug has also
been claimed to be more effective than propranolol in improving exercise tolerance\textsuperscript{17}. In a comparison with propranolol, disopyramide in particular decreased left ventricular outflow tract resistance as a result of its negative inotropic effect and by enhancing systemic vascular resistance\textsuperscript{18}. Propranolol had a more pronounced effect on left ventricular diastolic parameters. Disopyramide has also been suggested to improve the balance between oxygen demand and supply in patients with hypertrophic obstructive cardiomyopathy\textsuperscript{19}.

Vagolytic side effects, concerns regarding proarrhythmic potential, and in particular lack of reported long-term sustained beneficial effects of disopyramide are the major limitations of this drug for treatment of hypertrophic cardiomyopathy.

**Beta-blockers, calcium channel blockers, or both**

Very few trials have compared the two main pharmacological groups of agents used for treatment of hypertrophic cardiomyopathy. In the randomized trial by Gilligan \textit{et al.}\textsuperscript{19} it appeared that verapamil had some advantages over the beta-blocker nadolol. Kober \textit{et al.}\textsuperscript{20} conducted a retrospective case–control study, recruiting patients from several centres. That study indicated similar benefits with verapamil and propranolol with regard to symptomatic relief. This conclusion was not corroborated by the findings of a short-term, placebo-controlled, crossover trial of these two drugs, which favoured verapamil\textsuperscript{21}. Thus, there is only vague information obtainable from comparisons of these two major pharmacological treatment modalities.

Combinations of beta-blockers and calcium channel blockers have been used, but these are not supported by trial data. The risk for side effects, some of which are shared by these two classes of drugs, should incite caution when introducing such a therapy. Rather than experimenting with perhaps less efficient combinations of drugs, it is better to advocate some of the more invasive options, but which are less dramatic than open heart surgery. These include dual chamber pacing and septal alcohol ablation (reviewed elsewhere in this supplement).

**Conclusion**

Pharmacological treatment of hypertrophic cardiomyopathy will continue to be a option for many patients. It is clear, however, that many patients are asymptomatic and that there is no proof that drugs such as calcium channel blockers and beta-blockers may prevent progression of disease or sudden cardiac death. In symptomatic patients beta-blockers as well as calcium channel blockers have been used. Justification for such treatment is based on rather poorly designed, often mechanistic and short-term observations, without any control groups, which is in striking contrast to current exacting standards of evidence. Formal comparisons of the efficacies of different drugs are lacking.

It seems mandatory to test new treatment modalities, such as cardiac pacing and septal alcohol ablation, against pharmacological treatment in appropriate, reasonably sized patient populations, in studies that employ randomized designs. Perhaps one way to conduct such a comparison would be stop pharmacological treatment in patients who remain on drugs, despite being treated with cardiac pacing or septal alcohol ablation.

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