

Beta-Blockers in Pediatric Hypertrophic Cardiomyopathies

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Abstract: Congestive cardiac failure accounts for 36% of childhood deaths in hypertrophic cardiomyopathy, and in infants with heart failure symptoms before two years of age, the mortality is extremely high unless treatment with beta-receptor antagonists is instituted. The mechanism of heart failure is not systolic dysfunction, but rather extreme diastolic dysfunction leading to high filling pressures.

Risk factors for development of heart failure are a generalized pattern of hypertrophy with a left ventricular posterior wall-to-cavity ratio >0.30 , the presence of left ventricular outflow tract obstruction at rest, and the co-existence of syndromes in the Noonan/Leopard/Costello spectrum. The 5-year survival of high-risk patients is improved from 54% to 93% by high-dose beta-blocker therapy (>4.5 mg/kg/day propranolol). The mechanism of the beneficial effect of beta-blockers is to improve diastolic function by lengthening of diastole, reducing outflow-obstruction, and inducing a beneficial remodelling resulting in a larger left ventricular cavity, and improved stroke volume. Hypertrophic cardiomyopathy is associated with increased activity of cardiac sympathetic nerves, and infants in heart failure with hypertrophic cardiomyopathy show signs of extreme sympathetic over-activity, and require exceptionally high doses of beta-blockers to achieve effective beta-blockade as judged by 24 h Holter recordings, often 8-24 mg/kg/day of propranolol or equivalent.

Conclusion: Beta-blocker therapy is without doubt the treatment of choice for patients with heart failure caused by hypertrophic cardiomyopathy, but the dose needs to be carefully titrated on an individual basis for maximum benefit, and the dose required is surprisingly large in infants with heart failure due to hypertrophic cardiomyopathy.

Keywords: Beta-blocker, congestive heart failure, diastolic function, hypertrophic cardiomyopathy, Noonan's syndrome, outflow obstruction, propranolol.

INTRODUCTION

Congestive cardiac failure (CCF) accounts for 36% of childhood deaths in hypertrophic cardiomyopathy (HCM) [1], and 56% of deaths in adults with HCM [2]. Yet risk factors for CCF-related death in HCM have attracted far less scientific attention than risk factors for sudden death, and many studies do not even report modes of death. However, risk factors for sudden death and risk factors for CCF-related death are clearly different, at least in HCM with clinical presentation in childhood [1].

IDENTIFICATION OF HYPERTROPHIC CARDIOMYOPATHY PATIENTS AT HIGH RISK OF HEART FAILURE

In childhood HCM the independent risk factors for CCF-death are heart failure symptoms below 2 years of age, and a generalized pattern of left ventricular hypertrophy, expressed as a posterior left ventricular wall-to-cavity ratio of greater than 0.30 at diagnosis [1, 3, 4]. A concentric pattern of hypertrophy also confers a greater risk than an asymmetrical hypertrophy [3], as does left atrial enlargement and/or restrictive physiology, and a maximal wall thickness $>Z$ -score of 6 [3-6]. Left ventricular outflow tract obstruction also has

a strong association with unfavourable outcome both in childhood [7] and in adult HCM [8]. Noonan-Leopard-Costello spectrum syndrome-associated HCM, is often characterised by the presence of left ventricular outflow tract obstruction and a presentation with heart failure [1, 3, 7, 9, 10], and is associated with a significantly worse survival than idiopathic or familial HCM in childhood [7, 11]. In childhood most CCF-related deaths in HCM occur in the first two years of life [3, 7, 11]. CCF in the infant is not associated with impaired systolic contractility but is instead seen in a setting of a very small cavity with marked systolic hyper-contractility, often with dynamic outflow obstruction and mitral incompetence caused by the systolic anterior movement of the mitral valve apparatus. Sometimes this is misinterpreted as a structural mitral valve problem, but the mitral valve reflux is a purely secondary phenomenon, and if the outflow obstruction is controlled by pharmacotherapy the mitral valve incompetence disappears with it. Thus the heart failure is caused by grave impairment of diastolic filling, not by a low ejection fraction.

TREATMENT OF HEART FAILURE IN HCM

The prognosis with a presentation of HCM with heart failure in infancy is very grave unless treated correctly. Early reports described 100% mortality among infants with HCM and heart failure below one year of age treated with conventional therapy such as digoxin and diuretics [12], and the first survivor of a symptomatic presentation in infancy was reported by Shand *et al.*, who had treated the associated outflow obstruction with propranolol [13]. A subsequent study

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in adult HCM patients established that the dose of propranolol required to produce a high degree of pharmacological blockade of circulating catecholamines averaged 6 mg/kg body weight, larger than the dosage conventionally used [14]. This approach was adopted by Östman-Smith and co-workers, and was found to significantly improve survival of children with hypertrophic cardiomyopathy, both idiopathic/familial HCM, and Noonan/Leopard/Costello associated HCM [15]. The scientific rationale for this therapy was that HCM was known to be associated with increased sympathetic nervous activity, and that compensatory cardiac hypertrophy in animal models can be blocked or reduced by beta-receptor blocking therapy (see [15] for references). The improved survival was due to a reduction both in heart-failure and sudden deaths. This study also showed a non-significant trend for calcium channel blocker therapy to potentially increase the risk for heart failure-related death. A further analysis looking only at the HCM patients that were at high risk for developing heart failure indeed showed a much improved survival with high-dose beta blocker therapy, but that calcium channel-blocker therapy had a significantly worse survival not only compared with high-dose beta-blockers but also with therapy with conventional doses of beta-blockers (see Fig. 1) [16]. Respective 5-year survival rates were 54% for no therapy or conventional diuretic therapy, 85% for conventional doses of beta-blockers (1-4 mg/kg/day of propranolol), 93% for high-dose beta-blockers (>4.5 mg/kg/day of propranolol) and 44% for the calcium-channel blocker group. Thus calcium channel blocker therapy appears contra-indicated in patients at high risk of developing heart failure, in this analysis defined as heart failure symptoms below two years of age, or a posterior wall-to-cavity ratio >0.30 at diagnosis [16]. Independent confirmation of benefit of beta-blocker therapy in infants with HCM

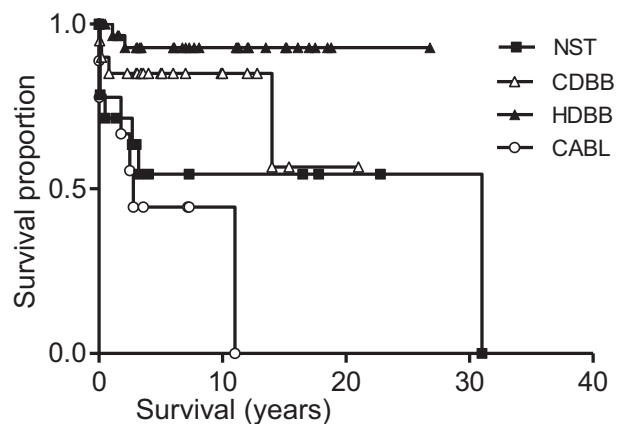


Fig. (1). Kaplan-Meier survival curve illustrating patients that were high risk for heart-failure related death by either having a presentation with heart failure symptoms below 2 years of age, or having a left-ventricular wall-to-cavity ratio of >0.30. Median age at presentation was 1.2 years (inter-quartile range 0.4-16.7 years). Symbols: NST: no therapy or diuretics (n=14); CDBB: Conventional-dose beta-blockers (1-4 mg/kg propranolol or equivalent in other beta-blockers), n=20; HDBB: high-dose betablocker (<4.5 mg/kg of propranolol or equivalent, n=31); CCBL: calcium-channel blockers (verapamil 2.0-12.0 mg/kg, n=9). HDBB is the only treatment regime with significantly better survival than NST (p=0.003), but CCBL had significantly worse survival than both CDBB (p=0.006) and HDBB (p=0.0001).

was provided by Skinner *et al.*, who reported that in a consecutive series of patients with evidence of persisting idiopathic HCM, 3 died, neither of whom received beta-blocker therapy, while all the 10 survivors had received beta-blocker therapy [17]. In childhood HCM some units have adopted a policy of treating virtually all patients with beta-blockers at diagnosis, an example is Texan Children's Hospital where 87% of patients received beta-blocker therapy, and 15 year survival was 82% [6], which represents a remarkably good survival, as compared to only 60% 5-year survival in childhood HCM patients with no specific therapy [15]. The mechanisms of beta-blocker benefit are probably multiple: it reduces outflow tract obstruction, it improves diastolic function, and it probably also has a beneficial effect on disease progression, and may even cause some reduction of hypertrophy when high doses are employed [1, 18-20].

An important practical point is that mitral incompetence in the setting of dynamic outflow tract obstruction should not be treated with angiotensin-converting enzyme inhibitors or other types of after-load reduction, since it aggravates the outflow gradient and makes mitral incompetence even worse. In the setting of heart failure and dynamic outflow tract obstruction which is not controlled by beta-blocker therapy alone, there is no contra-indication for adding a negative inotrope such as disopyramide to help with the reduction in the outflow gradient [18], it can be done safely as long as the patient is well beta-blocked, I have even introduced disopyramide with obvious benefit in infants with such severe heart failure that they required ventilator support. This is due to the fact that not only does disopyramide help to reduce the outflow gradient, but it also improves diastolic function in HCM [18, 21, 22]. Disopyramide should however not be used in patients who have congestive failure in the setting of late-stage dilation with reduced systolic contractility. For end-stage heart failure there is no contra-indication to use of beta-blocker therapy in moderate doses, but otherwise supportive therapy with diuretics, always including spironolactone, is recommended, as well as early consideration of referral for cardiac transplantation. Once the ventricle starts to dilate the downhill course is often rapid even when systolic contractility still remains in low normal range, because it is still predominantly a problem of high diastolic filling pressures. There is a substantial risk for early development of secondary pulmonary hypertension, so very close monitoring of the right heart pressures by means of tricuspid valve regurgitation velocities is recommended.

PRACTICALITIES OF BETA-BLOCKER THERAPY

It is generally agreed that beta-blocker therapy is the first-line choice for symptomatic pediatric patients [18, 23, 24], but the dose range employed is important. If mortality is analysed in dose bands (propranolol dose equivalents) the annual all cause cardiac mortality with 1-2.9 mg/kg/day is 4%, with 2-5.9 mg/kg/day 1.8%, and with 6 mg/kg/day and above 0.6% [18]. These doses may appear large compared with those used in adults, in spite of the results of Frank *et al.*, suggesting 6 mg/kg is required for effective beta-blockade [14] usually around 2 mg/kg/day is recommended in adults, but this is all explicable on the basis of the pharmacokinetics of beta-blockers in childhood. For carvedilol, which is metabolized by the same enzyme system as propra-

nolol, the weight adjusted drug clearance is 3.9 times faster in 1-year olds compared with a 19-year old, and to maintain the same plasma levels as adults infants require a dose 4.3 times higher, 2- to 11-year olds 2.9 times higher, and 12-15-year olds 1.4 times higher [25]. This is the reason why infants in heart failure sometimes require very high doses, 20 mg/kg/day and more, to achieve effective beta-blockade [15], but you need to achieve good beta-blockade to obtain maximum benefit. It is also often necessary to employ larger doses than is required in children of the same age but other indications for beta-blocker therapy, since the activity of cardiac sympathetic nerves is pathologically increased in HCM, with resulting elevated norepinephrine levels in the cardiac circulations [26], thus one needs a higher beta-blocker concentration to achieve competitive blockade. It is not really sensible to try to target a specific dose in mg/kg, because not only is speed of metabolism very age dependent, but there are also large individual differences in drug elimination due to polymorphisms in the metabolizing enzyme systems. The only rational approach is therefore to judge beta-blocker dose on the physiological effect in the individual patient, and you are looking for a very profound beta-blockade with a substantial reduction in heart rate variability, and maximal heart rates. In both infants and older children in heart failure this is best judged by a 24 h Holter ECG recording, and illustrations of which types of heart rate patterns that are desirable at different ages can be found in Östman-Smith and co-workers original study [15]. The important thing to remember is that the faster the heart rate the greater the impairment of cardiac filling, thus slowing the heart rate improves stroke volume to such an extent that resting cardiac output is maintained or improved, and that older children can maintain an unchanged physical exercise capacity on ergometer bicycle testing in spite of 25-30% reductions in maximal exercise heart rate [27, 28]. It is clearly not a good idea from the point of view of precipitating side effects to dive in straight away with an enormous dose, but in the presence of heart failure time to control the situation is short, and the rate of dose increase needs to be rapid. With an infant in heart failure I would tend to start with an oral dose of 2mg/kg of propranolol four times daily (*i.e.* 8 mg/kg/day), but expect to have to increase the dose if the effect is insufficient, perhaps every other day if the situation is not critical. However I know colleagues who have successfully started off with 8 mg/kg three times daily (*i.e.* 24 mg/kg/day) in a child on ventilator support with excellent effect. One further thing to keep in mind is that children with Noonan/Leopard/Costello spectrum disorders all have hyperfunction mutations in various kinases, and I have observed in some such children extra-ordinarily fast drug metabolism with very short half-life of the effect of a given dose. One such infant actually required 80 mg/kg/day of propranolol to maintain good beta-blockade (!), but in that instance we actually verified plasma levels with drug assays to make sure we were not overdosing, and if one needs doses >24 mg/kg in an infant it would be wise to try to get drug assays done. The serum concentrations of propranolol required in childhood HCM is usually 200-900 µg/l [15], but particularly in young children with CCF concentrations up to 1 100 µg/l are sometimes required. Once you have achieved optimal beta-blockade and a good therapeutic effect on symptoms, it is very important to maintain the benefit by remembering to

increase beta-blocker dose in parallel to growth. Not uncommonly have I observed that when follow-up is transferred from the regional specialist centre to the local hospital one forgets to increase the beta-blocker dose with growth, which often eventually results in progression of hypertrophy and recurrence of outflow tract obstruction quite unnecessarily.

SIDE EFFECTS OF BETA-BLOCKERS

In patients with heart failure due to HCM side effects of beta-blockers are surprisingly rare even with the very high doses I have employed. Only about one tenth of patients on high-dose beta-blocker therapy need to change type of beta-blocker because of side-effects [15]. Physical growth improves, and there have been no instances of impaired development reported, but one potentially serious side effect to be on the lookout for is hypoglycaemia after long fasting (or in relation to severe gastro-intestinal upset). This is clearly a risk specifically for non-selective beta-blockers such as propranolol, but nowadays with manufacturers cutting down on tablet sizes available for metoprolol, 10 mg propranolol tablets (which can be dissolved in water or juice just before administration) is the only viable option for titrating and maintaining treatment in infants unless one gets special suspensions (which have a much shorter shelf-life) made up. Carvedilol is not suitable for HCM treatment, since the alpha-blocking action causes too much reduction in after-load, and you cannot achieve sufficient beta-blockade without making the child hypotensive. Bisoprolol is an option for older children but tablet sizes make accurate tailoring of dose in infants with heart failure difficult, and I have no experience of using it in children below 4 years of age. Parents always need to be warned about this potential risk of hypoglycaemia. They should be advised to avoid prolonged fasting and to encourage intake of milk, or other suitable snack with slow-release carbohydrates, close to bedtime, and to make sure that breakfast is not skipped. In the case of stomach-upset glucose containing electrolyte replacements drinks should be given, if the patient cannot hold them down he/she needs admitting to hospital for intravenous fluid and glucose replacement. A sudden drop in beta-blocker serum concentration causes a rebound activation of sympathetic activity with a risk of arrhythmia and should be avoided, if needed beta-blocker therapy should be administered intravenously. One must then remember that the intravenous dose of propranolol is only one tenth of the oral, since portal hepatic metabolism is by-passed. This is obviously also an important point to remember if treatment is initiated intravenously.

The most commonly experienced side effect of propranolol and metoprolol treatment in large doses is seen more in older children and adolescents, not in infants, and that is excessive dreaming or even nightmares, that sometimes can be experienced as almost hallucinations on awakening. These symptoms can be got rid of by changing to equivalent doses of bisoprolol as first choice, or atenolol, but atenolol is suitable only for those patients who are not perceived to be at risk for arrhythmia problems, as lipophilic beta-blockers are better than hydrophilic ones such as atenolol for arrhythmia prophylaxis [18]. A more detailed discussion about the pharmacokinetics and rare side effects can be found in

Östman-Smith 2010 [18]. An important point in minimising side effects, and maximising benefit, is to use slow-release preparations and long-acting beta-blockers, and giving even these in twice daily doses to achieve as even 24 hour blood levels as possible. Slow-release propranolol capsules are actually quite practical even in infants as soon as they can take soft solids on a spoon, because the capsule can be opened and the contents mixed into yoghurt or porridge etc, and simply spooned in. If dreaming is beginning to become a problem last dose should be taken around 18-19 in the evening instead of just before bedtime. The only drawback to slow-release tablets is that drug absorption becomes poor if the child develops severe diarrhoea, so under such circumstances one should temporarily revert back to ordinary propranolol in four times daily dosage.

CONCLUSION

Beta-blocker therapy is without any doubt the treatment of choice for patients with heart failure caused by hypertrophic cardiomyopathy, but the dose needs to be carefully titrated on an individual basis for maximum benefit, and the dose required is surprisingly large in infants with heart failure due to HCM.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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I am the sole author of the review text. (Fig. 1) is based on data published by myself, B. Keeton and G. Wettrell.

PATIENT CONSENT

The data were collected in a de-identified manner from existing clinical records, therefore individual consent from patients was not sought in accordance with the ethical approval for the study.

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