Screening for Hypertrophic Cardiomyopathy in Asymptomatic Children and Adolescents

Psychosocial consequences and impact on quality of life and physical activity

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ABSTRACT

The aim of this thesis was to describe the consequences of being diagnosed with hypertrophic cardiomyopathy (HCM) while being asymptomatic, taking into consideration psychosocial effects and medical aspects of diagnosis and treatment.

Methods: Quality of life (QoL) was measured according to Lindström before the diagnosis, and after two years, comparing with healthy controls. Psychosocial consequences of the diagnosis were explored in interviews with children and their parents and analysed using content analysis. Exercise performance was measured at baseline and after one year in patients randomized to no pharmacological treatment or selective or non-selective high-dose beta-blocker therapy.

Results: The total QoL score was similar in both groups at baseline and at follow-up. Parents described an immediate reaction of shock, grief and feelings of injustice but were also grateful that their child had been diagnosed and was still asymptomatic. The diagnosis resulted in a change in life-style for most families due mainly to restrictions of sports activities. Parents had difficulties to adapt to the new life but after re-adjustment they regained hope and confidence. The children described an involuntary change of their daily life with limitations and restrictions because of life-style recommendations and this also affected their social context. However, after a reorientation process they felt hope and had faith in the future. There was no significant difference in exercise capacity between the groups at baseline, or after one year of observation versus beta-blocker treatment.

Conclusions: Family screening for HCM did not appear to negatively influence QoL. Children diagnosed with HCM through family screening went through an involuntary change of daily life, mainly ascribed to life-style-modifications. They strived to create a life where they could feel secure and have faith in the future, and with the support of parents and health care professionals they achieved a new state of normality. Neither selective nor non-selective beta-blockade caused significant reductions in exercise capacity in patients with HCM above that induced by life-style changes.

Keywords: adolescents, beta-blocker therapy, children, exercise performance, family screening, hypertrophic cardiomyopathy, inherited cardiac disease, lifestyle recommendations, parents experiences, psychosocial consequences, quality of life, transition.

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SAMMANFATTNING PÅ SVENSKA

Syftet med avhandlingen var att beskriva de psykosociala konsekvenserna för symptomfria barn och ungdomar av att genom familjescreening diagnostiseras med hypertrofisk kardiomyopati (HCM) samt att studera effekten av behandling med betablockerare på deras arbetsförmåga.

Metoder: Livskvalitet värderades enligt Lindström före diagnosbeskedet samt i en uppföljning efter två år och jämfördes med livskvalitet hos friska kontroller. Den känslomässiga upplevelsen av diagnosbeskedet utforskades i intervjuer med barn och föräldrar. Intervjutexterna analyserades med innehållsanalys. Effekten av beta-blockad på den fysiska arbetsförmågan värderades hos patienter randomiserade till behandling med högdos selektiv eller icke selektiv betablockad eller till ingen medicinsk behandling.

Resultat: Det förelåg ingen skillnad i den totala livskvaliteten mellan grupperna i utgångsläget eller i uppföljningen. De första reaktionerna beskrevs av föräldrarna i intervjuerna som präglade av chock, sorg, och känsla av orättvisa men även av tacksamhet att deras barn diagnostiserats och fortfarande var symptomfria. Diagnosen resulterade i en förändrad livsstil för de flesta familjerna framför allt genom restriktioner i fysisk ansträngning och deltagande i sport. Efter en ibland svår omställnings- och förändringsprocess anpassade föräldrarna sig och kände hopp och trygghet. Barnen beskrev att de genomgick en ofrivillig förändring som påverkade deras dagliga liv i hög grad till följd av livstilsförändringarna med restriktioner av fysisk aktivitet. Detta hade också en negativ effekt på den sociala gemenskapen. Efter en nyorienteringsperiod kände de dock hopp inför framtiden. Inga signifikanta effekter på fysisk prestationsförmåga av behandling med högdos beta-blockerare kunde påvisas.

Konklusion: Familjescreening för HCM påverkade inte livskvaliteten negativt. De barn som diagnostiserades med HCM genomgick en ofrivillig och påtvingad förändring av det dagliga livet huvudsakligen till följd av livsstilsråd med restriktioner i fysisk aktivitet. Med stöd från föräldrarna och sjukvårdspersonal kunde de uppnå en ny känsla av normalitet. Vare sig selektiva eller icke selektiva beta-blockare i högdos tycktes negativt påverka arbetsförmågan, utöver effekten av livsstilsförändringarna.

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Bratt E-L, Östman-Smith I, Sparud-Lundin C, Axelsson Å B. Parents' experiences of having an asymptomatic child diagnosed with hypertrophic cardiomyopathy through family screening. Cardiol Young 2011 Feb; 21(1):8-14.

II. Bratt E-L, Östman-Smith I. Selective or non-selective high-dose beta-blockade – evaluation of exercise capacity in children and adolescents with hypertrophic cardiomyopathy. Submitted for publication

III. Bratt E-L, Östman-Smith I, Axelsson Å B, Berntsson L. Quality of life in asymptomatic children and adolescents before and after diagnosis of hypertrophic cardiomyopathy through family screening. Submitted for publication.

IV. Bratt E-L, Sparud-Lundin C, Östman-Smith I, Axelsson Å B. Children's and adolescents experience of being diagnosed with hypertrophic cardiomyopathy through family screening. Submitted for publication.

CONTENT

ABBREVIATIONS

HCM	Hypertrophic Cardiomyopathy
QoL	Quality of Life
ECG	Electrocardiography
SBP	Systolic Blood Pressure
SCD	Sudden Cardiac Death
HDBB	High Dose Beta-Blocker therapy
WHO	World Health Organization
LQTS	Long QT Syndrome
AHA	American Heart Association
ACC	American College of Cardiology
ESC	European Society of Cardiology
LV	Left Ventricle

DEFINITIONS IN SHORT

HCM	HCM is defined as primary and inappropriate hypertrophy in a non-dilated heart, with normal or exaggerated systolic function, in the absence of valvar outflow obstruction or underlying systemic disease [1-5].
Children and adolescents	This thesis focuses on children and adolescents but paper II also includes young adults over 25 years of age and in paper I focus were on parents. A child is according to the United Nation´s convention on the right of the child, a human being between 0-18 years of age [6]. In this thesis the definition "children" also includes adolescents.
Quality of life	Quality of life (QoL) was measured according to the model of Lindström [7] which defines QoL as the essence of existence of the individual, which presupposes necessary internal and external resources for a good life.
Family screening	Screening in first-degree relatives.
HDBB	A minimum dose of 5 mg/kg per day of propranolol or equivalent doses of other beta-blockers [8].

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the commonest cause of sudden cardiac death (SCD) during childhood and adolescence [9, 10]. Therefore family screening is recommended to detect individuals at risk [3]. Such a screening policy will result in a number of asymptomatic children and adolescents receiving a diagnosis of a chronic and potentially life-threatening disease. An early diagnosis may decrease the risk of SCD through life-style advice, and medical therapy if indicated, but the diagnosis may also have negative consequences. Quality of life (QoL) could be negatively affected and life-style changes necessitated by the diagnosis might be associated with negative psychosocial consequences, especially during adolescence. Beta-blockers are in the front-line in the treatment of symptomatic individuals with HCM, and studies of the effect of high-dose beta-blocker therapy (HDBB) in such patients have shown promising results. However, fear of side effects, such as impaired physical performance, could possibly discourage the initiation of a beta-blocker regime in asymptomatic patients.

Before embarking on a screening program for early diagnosis in asymptomatic individuals it is therefore important to evaluate the psychosocial consequences and effects on QoL of such screening. It is also important to evaluate possible side effects of HDBB. This is the focus of this thesis.

HYPERTROPHIC CARDIOMYOPATHY

HCM is a genetically transmitted heart muscle disease defined by the presence of left ventricular hypertrophy. It carries a risk of malignant arrhythmias, SCD and heart failure. Symptoms range from none at all to severe with profound exercise limitations and recurrent arrhythmias. It is the most common medical cause of SCD during exercise in childhood and adolescence [9-11].

History

The first description of hypertrophy of the heart muscle was given by Liouville and Hallopeau in the late 19th century [5, 12, 13]. The morphological and haemodynamic features of the disease were further described in the mid 20th century [14, 15]. In the 1980s the clinical pathophysiology of the disease was defined, and the growing recognition that most cases were familial led to a determined effort to identify the underlying genetic defect [5, 11].

Epidemiology

The prevalence of HCM in the adult population is estimated to be 1:500 [16-18] and the annual incidence of HCM in children 0-20 years is between 0.2-0.5/100000 [19-22]. There is a skewed gender distribution with a male preponderance. Annual incidence rates of 0.59/100000 for males and 0.35/100000 for females have been reported. This is the same for childhood and adult populations [10, 19, 20, 22, 23]. However, according to the consensus document on HCM by American College of Cardiology (ACC) and European Society of Cardiology (ESC) the disease affects men and women equally and occurs in many races and countries, although it appears to be under-diagnosed in women, minorities, and under-served populations [2]. The incidence has been found to be higher in Hispanic and black, than among white children [20].

Pathophysiology

HCM is defined as a primary and inappropriate hypertrophy in a non-dilated heart, with normal or exaggerated systolic function, in the absence of valvar outflow obstruction or underlying systemic disease [1-5]. Most patients with HCM have an asymmetric pattern of LV hypertrophy [3]. The usual clinical diagnostic criterion for HCM in adults is a maximal left ventricular (LV) wall thickness greater than or equal to 15 mm. For children the criterion has been a wall thickness greater than the predicted 95th centile for age and body surface area [24]. Since this results in some false positives, it has been proposed to also use a wall-to-cavity ratio greater than the 99th centile [25] to increase the specificity of the diagnosis. It is now recognised, as the result of molecular genetic-clinical correlations, that milder degrees of hypertrophy may also indicate HCM [2, 26]. Genotype-phenotype correlations have shown that virtually any wall thickness is compatible with the presence of a HCM mutant gene [2]. Younger children may even carry a HCM gene without having LV hypertrophy at all [24]. If hypertrophy is present LV wall thickness range from mild (depending on age from 9-11 mm) to massive (22 – exceptionally rarely $\geq$ 30mm) [3, 24]. Substantial LV remodelling with appearance of hypertrophy occurs characteristically with accelerated body growth during adolescence [27].

Distinguishing obstructive and non-obstructive forms of HCM is based on the presence or absence of an LV outflow gradient. Presence of obstruction is a strong predictor of disease progression and more severe symptoms and complications [2]. Mildly increased LV wall thickness potentially due to HCM should be distinguished from the athlete's heart since regular training by itself is associated with cardiac remodelling and cardiac hypertrophy. In endurance athletes there is a proportional increase in wall thickness and cavity size, so that the wall to cavity ratio remains normal [25, 28 2, 29-33]. Another feature of HCM is small vessel disease, in which intramural coronary vessels are narrowed by medial hypertrophy and fibrosis. Myocardial scarring is also found [3, 5].

Histologically, HCM is characterized by myocyte disarray, in which individual cardiomyocytes vary in size and shape and form abnormal intercellular connections, usually with expansion of the interstitial compartment and areas of replacement fibrosis [3, 5]. This is associated with diastolic dysfunction which often precedes the onset of overt hypertrophy [33-35]. This is also the mechanism behind some of the complications in patients with HCM. The myocyte disarray and myocardial scarring probably serves as an arrythmogenic substrate predisposing to life threatening electrical instability, which appears to be the main mechanism of sudden death [3].

Genetics

HCM is an autosomal dominant disorder predominantly affecting genes encoding cardiac sarcomere proteins [2, 3]. Several hundreds of mutations scattered among at least 27 recognized HCM sensitive genes have been identified. The most common genetically mediated form of HCM is associated with mutations in more than ten genes encoding proteins critical to cardiac sarcomere [36-38]. This includes the most common mutations such as beta-myosin heavy chain (MYH7) and myosin binding protein C (MYBPC3) which account for approximately 80 % of all genotyped individuals [2, 3, 36, 37, 39]. Because of the autosomal dominant type of this mutation, persons who have a parent with a positive mutation in one of these genes run a 50 % risk of inheriting the mutation. However not all individuals harbouring a genetic defect will express the clinical features of HCM [24, 33].

Clinical presentation and symptoms

Most individuals with HCM have few symptoms, if any, and the diagnosis is often made incidentally or during family screening. Dyspnoea and fatigue or chest pain during exertion are the most common presenting symptoms. Palpitations and rapid heart action sometimes also occur [5, 26, 40]. The severity of symptoms might vary from day to day. The main cause of syncope in patients with HCM are arrhythmias and blood pressure fall on exercise, sometimes aggravated by dynamic outflow tract obstruction [41].

Clinical Course

HCM has the potential to present clinically during any phase of life, from infancy (fetal) to old age. The clinical course is variable and patients may stay stable over long periods. An adverse clinical course can proceed in different pathways that dictate the variation in treatment strategies. A wide range is represented and includes patients suffering from SCD, progressive symptoms with exertional dyspnoea, chest pain, syncope or presyncope and progression to advanced congestive heart failure. HCM is a complex disease with premature death in some patients whilst others reach normal life expectancy with mild or no symptoms and with or without major treatment interventions [2].

Mortality and risk for sudden death

In one study [8], including untreated children with a clinical presentation (including murmur), the overall annual mortality rate was as high as 6.6%, with an annual mortality of 3.5% in totally asymptomatic subjects. Annual sudden death mortality was 2.5% [8]. The mortality rate in patients treated with high-dose beta-blockers is significantly lower, around 0.2% [1, 8]. However, sudden death mortality is not the same at different ages, being very low below 8 years of age, and at it's highest between 8-16 years of age [10]. According to the Swedish national death registry HCM related death certificates are 0.112 per 100 000 age specific population in the 8-16 years age range, and the annual mortality in girls tend to peak at the age of 10-11 years whereas in boys this occurs at 15-16 years of age [10].

Diagnosis

A clinical diagnosis of HCM is established by echocardiography and electrocardiography (ECG) but additional investigations, as described below, are needed to identify patients at high risk of sudden cardiac events [3].

Family history of unexpected non-traumatic death below 50 years of age and/or any knowledge of premature death due to heart muscle disease or arrhythmia within the family [40].

History, penetrating the existence of symptoms such as unexplained syncope or presyncope especially exercise-related syncope, episodes of palpitations and breathlessness on exertion [40].

Physical examination should include auscultation of characteristic cardiac murmurs and measurement of systolic blood pressure (SBP) to exclude hypertension as the primary cause of hypertrophy [5, 26, 29].

Echocardiography including also short-axis cross-sectional views is the most important examination. It can determine the location and degree of hypertrophy, as well as systolic and diastolic function. In childhood a maximal wall thickness > 95th centile for age and body surface area should ideally be combined with some supporting feature such as increased wall-to-cavity ratios, elevated systolic wall-to-cavity ratio, abnormalities of diastolic function or a pathological ECG for a clear phenotype diagnosis [8, 24, 25].

12-lead ECG demonstrates a wide variety of patterns [3]. ECG can be normal with mild degrees of hypertrophy or show T-wave changes with or without the presence of extensive hypertrophy [5, 26, 31].

Holter registration for detection of atrial and/or ventricular arrhythmias or conduction disturbances is of extreme importance in HCM once the diagnosis has been established [4, 5, 26].

Exercise test is an important part of risk stratification. It evaluates the physiological response to exercise including blood pressure and arrhythmias. A poor blood pressure response during exercise is associated with an adverse long-term prognosis [5, 42-45].

Magnetic resonance imaging (MRI) is of particular value in HCM when two-dimensional echocardiography is unable to document the site and extent of hypertrophy [4, 5, 26].

Genetic screening for high-risk mutant genes is possible in some clinics. Genetic analysis has the potential to provide a definitive diagnosis of carrier status. Once the diagnosis is established in an individual and if a disease-causing mutant gene is identified, genetic testing of asymptomatic relatives at risk might be advisable [31].

Risk stratification

It is a challenge to identify the small cohort of individuals who are at risk for severe complications. In order to detect these individuals, every person who is diagnosed with HCM, need to be evaluated according to risk factors.

Major risk factors for sudden cardiac death

1. Family history of sudden death in a first-degree relative younger than 30 years with HCM [4].
2. Previous cardiac arrest or ventricular tachycardia [4, 5].
3. Syncope related to exertion or loss of consciousness without a known causal factor [4].
4. Pathological SBP response during or after an exercise test [4, 5].
5. Non-sustained or sustained ventricular tachycardia noted on Holter registration [4, 5].
6. Maximum LV wall thickness of $\geq$30mm in adults [5]. Maximal wall thickness greater than 190% of the 95th centile prediction limits for age in children and adolescents [1].

Additional suggested risk factors for sudden cardiac death

1. Atrial fibrillation [46].
2. Myocardial ischemia [46].
3. LV outflow obstruction [46].
4. High risk mutation [46].
5. Intense competitive physical exertion [46].
6. ECG amplitude QRS-sum in limb leads more than 10mV [1]. High precordial ECG voltages as expressed by a large Sokolow-Lyon index [8].

Treatment strategies

Treatment of asymptomatic patients with no risk factors is controversial. However symptomatic patients and/or patients at high risk, should be treated. The treatment strategies described below are the most common used within the paediatric age range.

Life-style recommendations. Previous studies suggest that refraining from competitive sports result in lower mortality rates [47-49]. Therefore it is important that patients with HCM receive information regarding restriction of such physical activity that is thought to increase the risk of sudden death [2, 3, 50-53]. Health care professionals face the paradox of advising HCM patients to avoid regular exercise and sport, which are regarded as therapeutic for several other cardiovascular diseases [31]. The advice should be based on the recommendations published by ACC and/or ESC and individualised through interaction with the patient [31, 51, 54]. Restriction from participating in competitive sports, especially those with high cardiac demand, are necessary and one should recommend instead amateur and leisure time sports activities [31, 54].

Recommendations for amateur and leisure-time sports activities. Guidelines for patients with HCM according to AHA and ESC*

Sports not recommended	
Baseball	Sprinting
Basketball	Soccer
Bodybuilding	Windsurfing*
Rock climbing*	Scuba Diving*
Road cycling	Squash
Ice hockey	Tennis (single)
Rowing/canoeing	Track events
High intensity weights	
Sports allowed on an individual basis	
Moderate intensity weights	Motorcycling*
Cross country skiing/downhills	Sailing*
Horseback riding*	Stationary rowing
Jogging	Swimming
Running	
Sports permitted	
Stationary bicycle	Skating
Bowling	Tennis (double)
Brisk walking, moderate hiking	Treadmill
Golfing	Low-intensity weights

* These activities involve either a risk for traumatic injury or are water related which should be taken under consideration regarding patients with an increased risk for impaired consciousness [31, 54].

Beta-blocker therapy continues to be at the frontline of medical therapy for children and adults with HCM [8, 40, 55-57]. Pharmacological treatment of heart failure includes the administration of beta-blockers, which prolong diastole by reducing the heart rate and improve ventricular filling. Beta-blockers may also decrease the outflow gradient [4, 58]. Beta-blockers can be effective in relieving symptoms in patients with severe chest pain, dyspnoea, and syncope during exertion caused by LV outflow tract obstruction [5]. Therapy with HDBB have been shown to reduce mortality in childhood HCM, both sudden death mortality and heart-failure related mortality [1, 8]. Propanolol (non-selective) has in addition a membrane stabilizing action and increases the threshold for ventricular fibrillation [40]. Side effects of beta-blocker therapy (more common in non-selective beta-blockers) include restless sleep with intense dreams, hypoglycaemia after prolonged fasting (rare) and impotence (rare).

Disopyramide has beneficial effects both on diastolic function and on the dynamic outflow obstruction, and the effect is additive to the effect of beta-blockers. It is also antiarrhythmogenic [40].

Treatment regimes described below are also used in the paediatric age range although more rarely:

Implantable Cardioverter Defibrillator (ICD) offers a good, but not absolute, protection against death caused by ventricular fibrillation, although complications are frequent [59]. Implantation during childhood can be technically complicated and the rate of inappropriate shocks is high. It should be combined with pharmacological therapy [40, 59, 60]. Surgical myectomi can relieve the outflow gradient. The outflow tract is then enlarged by a resection of muscle from the hypertrophied septum [60].

Endocarditis prophylaxis should be advocated in patients with outflow obstruction as well as in patients with a markedly dilated left atrium [2, 61].

SCREENING

Screening is often discussed in the light of the classic Wilson and Jungner criteria [62] which are still considered as the golden standard.

Wilson and Jungner screening critera

1.	The condition should be an important health problem.
2.	There should be an accepted treatment for patients with recognized disease.
3.	Facilities for diagnosis and treatment should be available.
4.	There should be a recognizable latent or early symptomatic stage.
5.	There should be a suitable test or examination
6.	The test should be acceptable to the population
7.	The natural history of the condition, including the development from latent to declared disease, should be adequately understood
8.	There should be a policy on whom to treat as patient.
9.	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10.	Case-finding should be a continuing process, and not a "once and for all" project.

Several new criteria have also emerged and are described by Andermann *et al* [63].

In the Swedish guidelines from the National Board of Health and Welfare six groups in the population are defined:

1.	Asymptomatic – no population screening
2.	Symptomatic - physical examination, family history, ECG and echocardiography
3.	**History of SCD, cardiomyopathy or arrhythmia in close family - physical examination, family history, ECG and echocardiography**
4.	Abnormal findings on physical examination – medical follow up with adequate examinations
5.	Accidentally found abnormal resting-ECG - physical examination, family history, ECG and echocardiography
6.	Asymptomatic competitive elite athletes – resting ECG, physical examination and family history

Bold text - groups of individuals focused on in this thesis [64].

Family screening

Family screening is motivated in populations with increased risk, such as children with a parent with HCM who have a 50% risk to inherit the mutation [2]. Family screening for HCM is usually performed without access to DNA analysis, using history, physical examination, echocardiography and ECG. Screening should start at no later than six years of age with annual evaluations until 20 years of age [40]. Adult first-degree relatives should undergo examinations every 2nd-5th year [2, 40, 65]. Family screening might result in a cascade screening if/when adult siblings are diagnosed and their children should be screened. Published official guidelines recommend family screening in inherited cardiac disease, and this has become a policy recommended by the Swedish National Board of Health and Welfare [64].

Pre-participating screening in athletes

There is an international ongoing discussion regarding pre-participating screening of athletes. Different screening regimes and protocols are used in Europe and USA. Pre-participating screening in athletes has been practised in Italy for the last 30 years and several studies have shown a concomitant decrease in sudden cardiac death fatality rate [31, 47-49, 51]. In Sweden, athletes at elite level should be screened according to published and current guidelines [64, 66].

Ethical considerations and screening

Screening for HCM in children needs to be discussed in the light of the ethical concerns it might raise. From an ethical perspective it is complex to receive an adequate informed consent from a child to participate in screening procedures. Children´s capacity to consider risks and assess consequences depends on age and developmental level and is therefore sometimes limited. However, an adolescent ought, together with his/her guardians, be able to discuss and decide

together. The UN Convention on Rights of the Child (article 3) describes that in all actions concerning children, whether undertaken by public or private social welfare institutions, the best interests of the child shall be a primary consideration [6]. It is also stated (in article 12) that institutions, services and facilities responsible for the care of children shall conform with the standards established by competent authorities, particularly in the areas of safety and health [6]. It is essential to develop age-adapted information in order to improve the pre-conditions that screening has to be preceded by.

TRANSITION

This thesis uses the concept of transition as a framework as it covers different simultaneous transitions in the same person. Changes in health and onset of illness in individuals initiate a process of transition which by itself may in turn affect health negatively [67]. The framework of transition consists according to Meleis et al [67] of:

Types and pattern of transition. Examples of transitions that make individuals vulnerable are **illness experiences** such as diagnosis and treatment procedures; **developmental and life span transitions** such as adolescence, aging and death; **social** and **cultural transitions** such as migration, retirement and family caregiving [67].

Properties of transition experiences. Transitions are complex and multidimensional. Properties of transition experience has been identified as; awareness, engagement, change and difference, time span, critical points and events. **Awareness** is connected to perception, knowledge and recognition of a transition experience. A person must have some awareness of the change that is occurring. **Engagement** can include seeking for information, using role models, actively preparing and proactively modifying activities. **Change and difference**, all transitions are related to change but transition is described as a long-term process. Change can be related to critical events, disruption in relationships, perception or identities. Transitions are both the result of change and result in change. Examples of different conflicting expectations are feeling different or being perceived as different. **Time span,** transitions are characterised by flow and movement over time through a period of instability, confusion and distress to an end with a new beginning or a period of stability. In some transitions **critical points and events** are evident. Example of critical points can be the diagnosis of illness [67].

Transition conditions: facilitators and inhibitors. It is important to understand the individual experience during transition and to explore

the personal and environmental conditions that facilitate or hinder a healthy transition progress. **Personal conditions** are meanings attributed to events that precipitate the transition process. They may facilitate or hinder a healthy transition process. Cultural beliefs and attitudes are other personal conditions that may inhibit or promote the transition process. Socioeconomic status might also affect the process. Preparation and knowledge supports the transition process. Knowledge of what to expect during the transition process and what strategies that might be helpful in managing transition. **Community conditions** also facilitate or inhibit transitions as does **societal conditions.**

Process indicators are characterised by feeling connected (the need to feel and stay connected), interacting (with caregivers and social surroundings), location and being situated, developing confidence and coping. **Outcome indicators** emerged from mastery of new skills (to manage their new situation) and the development identity reformulation.

Transition is described as a middle-range theory, which is characterised by limited range and less abstract than grand theories. It also addresses a specific phenomenon [67]. This thesis mainly addresses the transition from being healthy to being diagnosed with HCM, being a parent of a healthy child to being a parent of a child diagnosed with HCM and the transition during adolescence. However other important aspects within the framework of transition are also considerable and applicable.

PREVIOUS RESEARCH

QoL and psychosocial consequences

There is a lack of studies on the psychosocial consequences of family screening for HCM. However, Meulenkamp et al [68] performed an interview study on children diagnosed through family screening as having LQTS, HCM or familial hypercholesterolemia. Some of their patients were given advice on restrictions in future careers and physical activities and most received prophylactic medication. Most children in that study coped quite effectively with their condition and their parents confirmed the impression of a successful adaptation. This study also concluded that feelings of control appeared to be of paramount importance for the coping process. Children who doubted the effectiveness of preventive measures appeared to have more problems with compliance. In another study, Smets et al [69] studied health-related QoL in a group of children diagnosed with LQTS, HCM or familial hypercholesterolemia and found no significant differences from a reference group. Some previous studies focused on the consequences of predictive genetic testing and positive carrier status for inherited cardiovascular disease in children, adolescents and adults. However these studies did not include a homogenous group of patients with HCM. The study groups in these reports consist of patients with LQTS and familial hypercholesterolemia [68-71]. Adults diagnosed with LQTS coped quite well with their situation even though they experienced worries and limitations in daily life [70]. For the parents in this study [70], the main concern were about their children and grandchildren. They also expressed that it would be an advantage for the children to grow up with the knowledge of the disease rather than suddenly obtaining such information later during childhood or adolescence [70]. Children who grow up with the knowledge of the disease (LQTS) have time to adjust according to parental perceptions [72]. Parents of carrier children tested positive for LQTS remained preoccupied with the disease for at least 18 months after and showed difficulties to adjust to the new status of their

children [73, 74]. In addition, other data claim that fear and uncertainty fade over time even if it is overwhelming at the time of the diagnosis of LQTS [72].

QoL has been studied in adult patients with symptomatic HCM and it was concluded that these patients have substantial restrictions in health related QoL [75]. In contrast, asymptomatic adult patients with a positive HCM-mutation carrier status do not show an impaired QoL [76]. This is also consistent with studies of health related QoL in children with a positive carrier status of inherited cardiovascular diseases (HCM, LQTS and familial hypercholesterolemia) [69, 77].

Effect of beta-blocker therapy on QoL. Some investigators speculate that beta-blocker therapy may affect growth in young children or impaire school performance but without substantiating such claims [2, 5]. The effect of beta-blockers on QoL has been studied but with conflicting results, depending on whether healthy individuals or patients with cardiac disease were studied. In a meta-analysis of patients treated for chronic heart failure with beta-blockers Dobre et al [78] did not find any deleterious effects on QoL. No similar studies have been published in children.

Other studies of QoL within paediatric cardiology using the same questionnaire have shown that children born with hypoplastic left heart syndrome did not have a decreased overall QoL compared to healthy controls. However these children showed a lower self-esteem, basic mood and peer acceptance than healthy controls [79]. QoL in children with pulmonary atresia rated well regarding the external and internal spheres but tended to rate lower regarding the personal sphere. Overall QoL did not differ compared to healthy controls [80]. A study from Norway [81], including children with different congenital heart defects, could not detect a lower total QoL although rates regarding psychosomatic symptoms were higher and peer acceptance was lower compared to controls. In a thesis published by Ternestedt [82] assessing QoL in children born with an atrial septal defect or Fallot´s tetralogy, using a similar questionnaire, indicated no negative

psychosocial effects or negative consequences on QoL in the long term perspective. These studies are highlighted due to the fact that they used the same QoL model based on the same theories and concerned the field of paediatric cardiology.

However, the focus in this thesis is not on children with congenital heart defects.

HDBB treatment and exercise performance in HCM

The use of HDBB is controversial, particularly in asymptomatic patients, because of the concerns about presumed side effects such as impairment of exercise tolerance. Healthy individuals treated with standard doses of beta-blockers show impaired maximal exercise capacity [83]. There are a few small studies on the effect of short-term beta-blocker therapy on exercise performance in patients with HCM with conflicting results. A reduction (but with less symptoms) for nadolol [84] or unchanged or even improved exercise tolerance with propranolol [85, 86].

Studies on exercise performance in healthy individuals on beta-blocker therapy have shown a discrepancy between selective and non-selective beta-blockers. Non-selective beta-blocker therapy has been reported to result in a decrease of maximum physical exercise performance whereas selective beta-blockers had no effect as compared to placebo [85, 87]. However, non-selective beta-blockers are more effective than selective beta-blockers in preventing pathological blood pressure response to exercise [40, 88].

RATIONALE

The medical, technical and genetic developments within medicine and caring science create new skills and knowledge. New diagnostic methods and treatment strategies focusing on different groups of individuals at certain risk necessitate knowledge of how to meet and support these individuals in the situations they and their families are confronted to. Ethical issues also need to be illuminated and discussed. These complex issues require a high level of professionalism among health care professionals involved in the care of these patients [89].

There are potential side effects and consequences due to medical therapy (beta-blockers), non-pharmacologic therapy (lifestyle recommendations) and screening of asymptomatic children and adolescents. Side effects not only include physical sensations such as possible impaired physical performance it also include possible psychosocial consequences and impact on QoL.

Before starting a program for early diagnosis in asymptomatic individuals it is therefore important to evaluate the psychosocial consequences and effects on QoL of such screening.

There are promising results of HDBB in children and adolescents with HCM. However, it is necessary to create an improved evidence base for therapy with HDBB to establish whether it has important negative consequences.

AIM

The overall aim of this thesis was to describe the consequences of being diagnosed with HCM while being asymptomatic taking into consideration both psychosocial and physical aspects of the diagnosis and the treatment regime from different perspectives and within the child's and family's context.

Aim Paper I

To describe the experiences of the parents of screening-positive children with regard to how the diagnosis affected daily family life.

Aim Paper II

To evaluate exercise capacity in patients with HCM before and one year after start of HDBB and to compare them with contemporary controls with mild HCM without beta-blocker treatment, but who are recommended the same life-style changes.

Aim Paper III

To measure the impact of screening on QoL in asymptomatic children with HCM before and after diagnosis. An additional aim was to compare QoL in those children with QoL in children who also had a first-degree relative with HCM, but who were negative on screening.

Aim Paper IV

To describe children´s and adolescents´ experiences of being screened positive for HCM and how this impacts on daily life.

MATERIAL AND METHODS

Methodological viewpoints

This thesis contains both qualitative and quantitative approaches in order to deepen the insight into the study population from a holistic perspective. A holistic approach assumes that the whole is understood as a complex system that is greater than the sum of its parts [90].

Quantitative methods dominate the medical research area and are influenced by the positivistic paradigm that postulate that a "real" reality exists out there and that one should approach this reality through assessing the "truth". Quantitative researchers often ask "how much" or "how many". Qualitative research and methods aim to find meaning behind the numbers. Qualitative research is often based on interviews or observations and the intention is to answer the question "how", "what" and "why". The qualitative approach is useful to describe human experiences and give them a deeper understanding [90]. Thus, there is a value in integrating qualitative and quantitative methods in order to further develop knowledge in medical and nursing research. Only one of the approaches was used within the same study in this thesis. In paper I and IV we chose a qualitative approach to explore and describe the experiences of parents and children. In paper II and III a quantitative approach was used to evaluate and measure exercise performance and QoL. Parents and children's experiences of the diagnosis are subjective whilst measurement and evaluation of exercise performance and QoL is objective.

Design

Paper	I	II	III	IV
Design	Descriptive Explorative	Randomized controlled	Prospective case control	Descriptive Explorative
Data collection	Interview	Exercise test	Questionnaire	Interview
Analysis	Content analysis	Statistical analysis	Statistical analysis	Content analysis
Sampling	Parents	Children, adolescents and emerging adults	Children and adolescents	Children and adolescents
Included (n)	12	24	54[1]	13
Male/female	5/7	16/8	33/21[2]	11/2
Median age	42.5 (38-47)	15 (7-25)	11 (2-19) [3]	14 (7-18)

[1] HCM n=13 (at baseline and follow up), Controls n=41 (baseline), Controls n=15 (follow up).
[2] HCM 11/2, Controls 22/19. [3] HCM 11 years (5-18), Controls 11 years (2-19).

Setting

There is a lack of prospective randomized studies on the effect of any therapy on disease progress, morbidity and mortality in HCM in the literature. This thesis and the studies included are part of an ongoing randomised controlled intervention study with the aim to establish whether beta-blocker therapy modifies progression of disease in symptom-free patients with HCM.

Adult patients with the diagnosis of HCM were contacted after an extensive review of several hundreds of hospital records with appropriate diagnostic code from three hospitals in Gothenburg. A letter was sent with information about the research project and an invitation to contact the research group if they were interested. They were asked whether they had children or not. If they had adult children these were also invited to contact the research group. Those who contacted us were informed according to current guidelines of research ethics.

During the commencement of the intervention study the idea of evaluating QoL and psychosocial consequences of diagnosing asymptomatic children through family screening arose. It was decided to study both the psychosocial and the physical aspects of receiving the diagnosis of HCM, and also to study the impact on the parents (which resulted in paper I, III, IV). These issues were mentioned in the ethical application.

This thesis will only present findings from paper I-IV. Findings from the intervention study that aims to establish whether beta-blocker therapy modifies progression of disease in symptom-free patients with HCM will be published separately.

Sampling, participants and data collection

The whole investigation period extended from January 2005 to December 2009. In paper II participants where recruited from January 2005 to December 2008, in paper III from January 2005 to December 2007. These dates represent baseline. Both these studies are follow-up studies with follow-up after 13 months (paper II) and 22 months (paper III).

In paper I and IV the recruitment was performed from January 2007 to December 2009. All participants were consecutively recruited from one specialist outpatient clinic in Sweden and from the main intervention study described before.

All participants were recruited from the intervention study to paper I, III, IV. Participants in paper II were already included in the intervention study.

Paper I and IV

The same person (E-L B) conducted all interviews. The interviewer had previously met the participants in her role as health-care professional at the outpatient clinic. To emphasize the fact that the interviewer was in the role of a researcher, the interviewer had private clothes instead of the hospital uniform. The interviews were conducted at the hospital, in a private room, which was familiar to the participants since they had been there many times before during outpatient visits. Three interviews were performed in the homes of the participants on their own request. All interviews were audiotaped and transcribed verbatim by the first author (E-L B). All participants had to understand and speak the Swedish language.

In paper I the interviews were guided by two open-ended main questions and a set of sub-questions. The two main questions were asked to all parents participating in the study. ‘‘Can you describe your reactions, experiences, and thoughts regarding how the

diagnosis affected your child's and the family's daily life during the immediate time period after the diagnosis?''. The second main question asked was ''How do you experience your family's daily life at present? Twelve families were invited to participate in the study. Seven mothers and five fathers from ten different families accepted the invitation. Two families declined and both had girls diagnosed with HCM.

In paper IV the participants were invited to talk freely about their experiences and thoughts after they received the information about the diagnosis. The interviews were guided by open-ended main questions and a set of sub-questions using an interview guide. The two main questions asked to all children participating in the study were "Can you describe your reactions, experiences, and thoughts regarding how the diagnosis affected you and your daily life during the immediate time period after the diagnosis?'' and "How do you experience your daily life at present?".

The median timing of the interviews was 18 months after diagnosis. Fifteen children and adolescents were invited and 13 agreed to participate. Two children declined, they were both girls.

Paper II

Twenty-four patients completed the exercise test at baseline and at follow-up at a median of 13 months after inclusion in the study. All 24 individuals had a complete risk-assessment. Patients who were risk factor positive were recommended treatment with propranolol, a non-selective beta-blocker, or if there were contraindications to this, a selective beta-blocker (metoprolol). Patients with no risk factors were randomized either to follow-up, without pharmacological treatment or to selective beta-blocker therapy with metoprolol. For the exercise study the two subgroups receiving metoprolol (or because of side effects atenolol) were added together to form the "selective" group (Figure 1).

Figure 1. Flowchart describing how the study groups were arrived at.

The target dose of beta-blocker was 6.0 mg/kg/day of metoprolol or propanolol, or a minimum of 4.0 mg/kg/day with sufficient beta-blockade on 24 hour Holter monitoring [8].

Before study entry, and after one year, all patients underwent incremental bicycle (Monark ergomedic 839E) exercise tests with a ramp protocol starting at 1 watt/kg, with 10 watts increments each minute to maximum exercise capacity. The exercise test was performed with the patient in a sitting position. We monitored 12-lead ECG (Welch Allyn Cardio Perfect 1.5.0.434), SBP (manual measurements) and respiratory rate every minute before, during and a minimum of 15 minutes after exercise.

Paper III

Seventy-seven asymptomatic children and adolescents underwent ECG and echocardiographic examinations between 2005 and 2007 because of a family history with a first-degree relative diagnosed with HCM (Figure 2). Inclusion criterion was age 2-19 years at baseline. Not being able to speak the Swedish language was an exclusion criterion. Fifty-four children and adolescents were asked to participate in the study before the cardiac investigations were performed. All accepted and filled out the questionnaire at baseline. This constituted the baseline dataset. Follow-up was performed at a median of 22 months after diagnosis, and 28 patients had a complete follow-up. The healthy control group was recruited among children coming for evaluation because they had a first-degree relative with HCM, but had a normal ECG and ultrasound examination. All individuals who were asked to participate filled out the questionnaire at baseline and those children who were planned for a cardiac follow-up after two years were asked to fill out the questionnaire at follow-up (Figure 2).

Twenty-six of the 41 children in the control group filled out the questionnaire at baseline at the time of family-screening but were found to be healthy with no follow-up, follow-up later than two years or with follow-up in another hospital. They all belonged to the 54

who accepted participation. In these 26 children only baseline data are available (Figure 2).

Twenty-three patients with a first-degree relative were not included due to practical reasons at the time of diagnosis (n=18) or due to language problems (n=5). Two out of these 23 were diagnosed with HCM but didn't receive a questionnaire or didn't fill out the questionnaire before they received information about the diagnosis (Figure 2).

DATA ANALYSIS

QoL measurements

QoL was measured according to the model of Lindström [7] defined as the "essence of existence" of the individuals. We used this model since it was validated in large general population studies in children and used in studies of children with congenital heart disease [79-81].

The model examines the necessary internal and external resources for a good life, taking into consideration the three spheres of external, interpersonal and personal aspects. "The essence of existence" means that the persons set priorities in their context to describe what is most important to their existence as observed in objective terms and subjective perception.

Furthermore, the model is based on a theoretical frame with a consistent conceptual basis defined as satisfaction with areas of life that are important to the individual such as health and functioning, psychological/spiritual, social, economic and family domains [7]. The model also has a dynamic dimension, changing the QoL response to developmental aspects, i.e. physical and social demands associated with age.

The questionnaire explored the socioeconomic status of the family, structure and function of networks and psychological wellbeing of the child and its family. Both objective and subjective aspects were covered in all dimensions. The overall QoL included the external and interpersonal spheres.

The external living conditions, i.e. the socioeconomic status of the family, were described in terms of working, economic and housing conditions. In paper III the external sphere variables are presented together with socioeconomic variables. A comparison in this sphere between HCM-patients and children screened as normal was irrelevant to perform since there were 10 siblings of HCM-patients in

the control group at baseline, and the family selection criteria were the same for all individuals included, thus socioeconomic circumstances would be expected to be very similar.

The interpersonal conditions (the structure and function of networks) were explored with questions covering family networks, intimate relationships and extended networks.

The personal conditions were analysed with questions asking about activities, self-esteem (measured as the parent's perception of the child's capabilities).

Content analysis

Content analysis is a technique to analyse a text in various steps. It has its roots in mass media and propaganda analysis for calculation of words, concepts or other content appearing in the text [91]. Today two principal ways of using content analysis are evident, a quantitative approach which is often used in media research and a qualitative approach often used in nursing research [91, 92]. When performing content analysis focus can be either on latent or manifest content and levels. Manifest content is similar to the surface message present in the text and describes the visible and obvious components. Latent content is the deep structural meaning of the text and deals with relationship aspects and involves an interpretation of the underlying meaning of the text [92]. In paper I and IV analysis focused on the latent content of the text but during the analysis the manifest content was also evident.

The unit of analysis in paper I and IV consists of verbatim written interview text. The analysis process has been influenced by how Graneheim and Lundman [92] describe content analysis. The interviews were read several times to obtain the sense of the whole. The text was divided into meaning units which are words, sentences or paragraphs containing aspects related to each other through their content or context. The meaning units were condensed which means shortening the text without losing the core. The condensed meanings were

abstracted and labelled with a code. The code allows the data to be thought of in new and different ways and should be understood in relation to the context [92]. At this level the analysis process continued with the creation of categories. When creating categories from the codes no data should fall between two categories. A category answers the question "what" and can be identified as a thread throughout the codes. The concept of themes is considered to be a thread of underlying meanings through condensed meaning units, codes or categories, on an interpretative level. A condensed meaning unit, code or a category can fit into more than one theme and a theme can be constructed by sub-themes or divided into sub-themes [92]. In paper I and IV themes emerged from the text, we used themes as the data could not be excluded from each other as rigorous as in categories.

Statistics

Paper II

Statistical analysis was carried out using SPSS software (PASW statistics 18.0). The non-parametric Kruskal-Wallis test was used for intergroup comparisons and the Wilcoxon signed test was used for paired comparisons within groups, with each patient serving as his own control. Fisher's two-tailed exact test was used to compare proportions. Spearman's rank correlation was used to analyse correlations between dose of beta-blocker and change in exercise capacity from baseline to follow-up. The statistical significance level used was 5 %.

Paper III

The statistical analysis was performed using SPSS software (PASW statistics 18.0). In the analysis, all QoL indicators were represented by dichotomous variables taking the value as one if above average, and zero if below average. The QoL-scores are the sums of simple variables over specified subsets of QoL-indicators. Thus, there are the total, subjective and objective QoL-scores as well as separate scores

for each of the spheres. In calculation of scores and in the multivariate analyses all internally missing values (unanswered questions) were substituted with the mean value for that variable in its age group. This was done to obtain the same number of entered measures for all individuals, since the entire record is often discarded in multivariate analysis if one variable has a missing value. Proportions based on simple variables exceeding base level and means of such proportions within a sphere were used in the analysis. A two-related-sample test, Wilcoxon signed-rank –test was used for within-groups comparisons between baseline and 2-years follow-up, and the Mann-Whitney U-test test was used when comparing the different groups. Categorical data were compared with two-tailed Fischer´s exact test. The statistical significance level used was 5 %.

ETHICAL CONSIDERATIONS

The studies included in this thesis were performed according to the Declaration of Helsinki [93]. At the time of commencement of study I, III and IV local ethics committee approval was not required for studies involving questionnaires or interviews, today it is mandatory. Both written and verbal information about the study were given, stressing that participation was entirely voluntary, and informed consent was obtained. Confidentiality was guaranteed. Families were recruited among participants in the main intervention study approved by the local research ethics committee (Study Code ÖS 257-02).

Children, adolescents and guardians had to give their consent to participation. Adapted written information was developed and enclosed to older children and adolescents. According to the Declaration of Helsinki [93] some research populations are particularly vulnerable and need special protection, including those who can not give or refuse consent for themselves such as children. The Swedish law of research ethics 2003:460 18 § states that children older than 15 years who are able to comprehend the consequences of participating in research can give informed consent themselves. In all other situations when the person is younger than 18 years both parents (guardians) have to be informed and give their consent. It is necessary to provide age-adapted information in order to give the child the best possible chance to participate in the decision, even if younger than 15 years. Participation is not allowed if the guardians agree and the child disagrees. Similarly article 3 in the UN Convention on the Rights of the Child states that in all actions concerning children, the best interests of the child shall be a primary consideration. It also states (article 12) that parties shall assure the child who is capable of forming his or her own views the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance to the age and maturity of the child [6].

The primary purpose of descriptive research is to collect and analyse data, not to change people [90]. However, interviews can be considered as interventions, they affect people. An awareness of this is necessary to minimize the effects of the interview on the participant.

Another ethical issue is the possible effect that the researcher as a person might have on the participants. The participants were not unfamiliar to the researcher which might have affected some of them to agree to participation. It is a challenge to perform research in one´s own setting, sometimes being a researcher and sometimes a health care professional [94]. It was important to emphasize the role as a researcher particularly during the interviews. This was the reason why the interviewer wore private clothes instead of the hospital uniform. On the other hand it might have been a benefit that the researcher was known to the participants, this might have affected them to talk more freely.

RESULTS

Summary of findings

- Overall QoL was not significantly affected by the diagnosis.
- Parents and children had immediate experiences of grief and fear but were at the same time grateful for early diagnosis.
- Life-style recommendations had the most obvious impact on daily life.
- Both parents and children went through similar processes and finally reoriented towards hope and faith in the future.
- No significant decrease in physical exercise performance could be detected comparing patients on selective or non-selective HDBB with controls without medical therapy.

Effects on QoL

There was a larger proportion of boys in the group that screened positive for HCM in childhood whilst it was an equal gender distribution in the group that was normal on screening, however the difference did not reach statistical significance (p=0.06). Parents' occupation, educational level and housing conditions were similar between HCM group and controls with no statistically significant differences in proportions.

Children with HCM were more often the only child compared to controls at baseline (p=0.002), and at follow-up (p=0.005). There were no indications of any differences in available time or in satisfaction with family network from baseline to follow-up and no differences between groups could be detected. However, a significant difference was detected in the intra-group comparison in the control group (p=0.03) regarding satisfaction with social support, which increased (Table 1).

There was a significant difference in household size with a higher proportion of families with less than four members in families with children with HCM, at both baseline (p=0.004) and follow-up (p=0.01) compared to families where the children screened negative (controls) (Table 1).

Major negative life events such as separation, divorce, or death, were no more frequent in the group of children with HCM than in controls (Table 1). The total outcome regarding the interpersonal QoL was very similar within and between groups (Table 3).

There was no indication of a worsening QoL from before diagnosis to follow-up. No significant differences were noted in self-esteem, peer acceptance or satisfaction with school. Psychosomatic symptoms were significantly more common in the group of children diagnosed with HCM already before the diagnosis as compared to children who screened negative for HCM (p=0.015) (Table 2). The total outcome in the personal sphere was similar in both groups (Table 3).

The only significant difference at follow-up concerns the average for objective variables (Table 3), which might be influenced by the exercise-restrictions necessitated by the diagnosis reducing the scores for average weekly time spent in intensive physical activity/week ($p=0.04$), whereas there was no difference in physical activity before the diagnosis ($p=0.48$). In contrast, the physical activity score in the controls did not decrease between baseline and follow-up ($p=0.33$). There were no significant differences in child activity levels or in the child-parent activity levels in the intra-group comparisons from baseline to follow-up in HCM-children or in controls, neither were there any differences noted between the groups (Table 2).

Parents and children's experiences of the diagnosis

Themes and subthemes in paper I and IV emerged within a similar course, although parents and children had different experiences from their different perspectives. The diagnosis was perceived as having more or less implications on daily life and on the future. Parents and children went trough the initial process with various emotional responses, reactions and strategies. However, gratitude for being diagnosed was expressed by both parents and children and a gradual normalization of life and a reorientation towards the new future was evident.

Initial period

The *immediate reactions* in parents were characterized by grief and shock, feelings of injustice but also by gratefulness. Both parents and children described *grief* during the initial period (I, IV). Parents felt *grief* because they mourned their child's changed life situation (I). Children experienced an *involuntary change* with feelings of disappointment, loss of freedom of choice and feelings of injustice. Grief was a thread and seen as the expressed latent content of the theme (IV**)**. Children described loss in terms of losing the freedom of choosing leisure time activities, education and future professions, which they grieved. Feelings of injustice and disappointment were described and thoughts and questions about why the disease hit them were expressed. Parents also described the diagnosis as unfair and expressed feelings of injustice.

Children had to deal with the fact (IV) that they were diagnosed with a chronic condition that was life threatening and they had to face a painful reality. Some children described that they accepted the diagnosis as a matter of fact, whilst others, especially older children, described that they preferred to repress the information, they wanted life to continue unchanged.

Gratitude of having been diagnosed before any serious or even life threatening complication had occurred were described by both parents and children **(**I, IV**)**.

Daily life

Daily life was affected both in the individual and social context. Parents' experienced *a drastic change of everyday life* (I). They also felt that death became a close, realistic, and existential threat that could strike the family in a very realistic way. This led to feelings of vulnerability and weakness. Loss of the freedom of choice was also highlighted by parents (I) emerging from the knowledge that their child had lost his/her freedom of choice. Fear due to the life-threatening character of the disease was described by both parents and children (I, IV). Parents feared death and they strongly connected it with physical exercise (I). Fear and anxiety became obvious every time the child participated in any kind of physical activity. Some parents also stated that sudden death could have been a possible scenario if the child had not been diagnosed (I). Children feared the unknown and what the diagnosis would lead to and the risk of dying suddenly (IV).

Children described experiences of *an involuntary change* (IV) in life and a large impact on daily life (IV). This was based mainly on the experiences from the life-style recommendations, which were experienced as limitations and restrictions. A neglecting and negative attitude towards the life-style recommendations was obvious in some children. Some didn´t want to accept or follow the advice given (IV). Descriptions of experienced fatigue and even exhaustion during or after physical activity were described, sometimes expressed as a possible side effect of the beta-blocker therapy (IV).

The tangibility of the disease (IV) appeared in different situations in daily life. The disease became close and real at bedtime or in situations that were quiet and peaceful and allowed thoughts to roam. In these situations thoughts and anxiety became entwined and

sometimes frightening. The disease became especially present when they had to decide about participation in physical activities.

Adaptation to a life with new reference frames and a change in daily life-style was an essential task. They had to adapt to new options in life and sometimes reconsider future plans (IV). Some families had to change life completely, they had to adapt to a new life (I). Especially families involved in sports activities. It affected the whole family life with friends, physical activities and plans for the future (I, IV).

Social changes (IV) in the child's community also became a central issue. Suddenly their natural environment for leisure-time activities and school was affected as a consequence of the life-style recommendations. In some cases the whole social context was lost which affected them deeply. Social support was important and in younger ages often came from the closest family while for adolescent's friends, teachers and girlfriend/boyfriend also contributed.

To inform others of the disease gave a sense of relief and made them feel more secure. Friends and relatives had a protective function. For example they often reminded them of activities that were not appropriate (IV). Parents wanted to protect without circumscribing, trying to find a balance between protection and restriction. They wanted to give positive support, to give the child freedom to act responsibly. Parents sometimes experienced that they became a part of circumscribing the child's life (I).

Future outlooks

The theme *striving for* a *normalisation of life* (I) appeared from parents' experience that their usual frame of reference to life was no longer valid. They felt that it was important to return to a normal life, striving for control to reduce the feelings of chaos. In achieving this they strived to adapt to the new life, to find a balance, and to feel secure.

Having the child diagnosed and under frequent medical check-ups made parents feel secure. To have close contact and easy access to a liaison nurse helped them to regain control in everyday life. To learn about the disease and its risks also contributed to a feeling of safety (I). Children described a sense of control (IV) which was described as an understanding of the importance of compliance to the medications and life-style recommendations. Thoughts about what might happen if they did not take their medication or participated in inappropriate physical activities were also described (IV). Children described responsibility as an important part in taking control over life. To be responsible was described as complying with medication and life-style recommendations. Worries of serious complications made them adapt and develop an understanding of the importance of their own responsibility (IV).

An optimistic aspect in the reorientation process in both parents and children were that they *had hope and faith in future* (I, IV). Some parents described the frequent medical check-ups and pharmacological treatment as a reason for their optimistic view of the future while other parents described it as due to the fact that the child was diagnosed before any symptoms had come up. Parents also expressed an optimistic attitude to beta-blocker therapy as a part of effective treatment (I).

Some children described that initially they lost faith in the future and that their life felt ruined at the time of diagnosis but at the time of the interview some 18 months later they had reconsidered and no one expressed those feelings or thoughts anymore. They had gone through a process that changed their reference-frames in life and they seemed to have had adapted and *reoriented* (IV).

Themes and subthemes paper I

Theme	Sub-theme
Immediate reactions	Grief and shock
	Feelings of injustice
	Gratefulness
A drastic change in life	Death as a reality
	Loss of freedom of choice
	Feelings of fear and anxiety
A striving for a normalisation of life	To feel secure
	To protect without circumscribing
	To adapt to the new life
	To have faith in the future

Themes and subthemes paper IV

Navigating from being healthy to having a chronic life threatening heart disease

Theme	Sub-theme
Involuntary change	Grief
	Fear
	Gratitude
	Dealing with fact
Impact on daily life	Limitations
	Tangibility
	Adaption
	Social changes
Reorientation	Sense of control
	Responsibility
	Hope and faith in the future

Exercise performance and beta-blocker therapy

We could not detect any significant differences in exercise capacity either in watt/kg (p=0.7) or in watt/m^2 (p=0.2) between the groups at baseline. Boys had a higher work capacity than girls when expressed as watt/kg, median 2.7 (range 2.1-3.8) versus 2.4 (2.1-2.7; p =0.007), but the difference was not significant when expressed as watt/m^2 (height squared), boys median 63.3 (30.7-80.6) versus 57.9 (44.1-59.8;p = 0.32). Neither were there any significant differences between the study groups in exercise capacity at follow up in watt/kg (p=0.77) or in watt/m^2 (p=0.71) (Table 4). SBP rise on exercise was not significantly different at follow-up compared to baseline in any group (Table 4) and no individual developed a pathological blood pressure response due to beta-blocker therapy (Fig. 3 A-C).

Table 4. **Exercise results**

Values given as median (interquartile range)

Figure 3 A. Exercise capacities (in watt/m^2) at baseline and at follow up in the control group.

Figure 3 B. Exercise capacities (watt/m^2) at baseline and at follow up in the group treated with selective beta-blocker therapy.

* Oval dots at the end of the lines indicates those patients who had a pathological blood pressure response during or after exercise test at baseline or at follow up.

Figure 3C. Exercise capacities (watt/m^2) at baseline and at follow up in the group treated with non-selective beta-blocker therapy.

* Oval dots at the end of the lines indicates those patients who had a pathological blood pressure response during or after exercise test at baseline or at follow up.

DISCUSSION

Family screening for HCM is recommended to detect individuals at risk to develop symptoms and fatal complications [2]. This thesis addresses possible complex psychosocial consequences and side effects of screening for HCM and treatment with HDBB in asymptomatic children diagnosed through family screening. Such studies are important in order to be able to decide about and to design screening policies for HCM.

Transition and the HCM diagnosis

This thesis focuses on how the diagnosis and awareness of the disease resulted in a transition in both parents and children. The transition from being a parent of a healthy child to being a parent of a child with a chronic disease is described using middle range theory transition as a framework. The child´s transition from being asymptomatic and considering themselves healthy to having a chronic heart disease necessitating medical therapy and life style changes is also described. In concordance with Meleis et al [67] transitions are both a result of change and a cause of change in life, relationships, and environment and transition experiences are not identical. Each transition is characterized by its own individuality and complexity. It is crucial to reflect over the complexities of the transition experiences and to try to identify and clarify the needs [67].

Impact of diagnosis and lifestyle recommendations

In line with other studies, the diagnosis of an inherited heart condition was followed by a dramatic change in the life situation of the family, inducing severe distress in most parents [72-74]. Although parents were grateful that their child was diagnosed before any serious complications had occurred they were concerned about how the child would handle the recommendation to give up favourite activities with friends and other interests that in many cases engaged the whole family.

Team sports such as soccer, handball and ice-hockey are popular sports among children and adolescents in Sweden but not advisable for patients with HCM. Involvement in sports is good for physical and psychological well-being in children and adolescents and the AHA [54] states that an abrupt removal from such activities can be devastating. The necessity of life-style modifications according to current guidelines [31, 54, 64, 66] was associated with fear and anxiety both in the parent and the affected child (paper I and IV) and similar reactions are reported in studies of patients with LQTS [70, 72]. In this thesis, as in other studies [68, 70, 72, 73] this anxiety was most pronounced in direct time relation to physical activities. This seemed to be a particular trauma for families with a prominent interest in the participation in team sports. Nevertheless there were parents who did not experience much anxiety. Those were usually parents with children who were considered as calm and preferred peaceful play-activities, having no interest in sports. These parents didn't experience that the diagnosis and the following life-style modifications caused any dramatic changes in life.

Parenthood

Parents described how they tried to minimize their fears by eliminating situations that could cause serious complications focusing on safeguarding during everyday life and activities. They strived to protect without circumscribing, and this has also been described in parents with children diagnosed with LQTS [72]. Support to parents with advice on daily activities seems to be crucial.

Peers and the illusiveness of normality

Adolescents with a chronic condition may become marginalized by peers, rejected for being different at a time when body image and identity largely depend on conformity [95]. However, marginalisation from peers did not seem to be a problem according to present study, neither did a deviation from the illusiveness of normality. Children seemed to adapt quite well in the medium-term perspective. Luyckx et al [96] found that adolescents with congenital heart disease tackled

their identity formation process similarly to how their healthy peers did. In our study (paper III) self-esteem, peer acceptance and satisfaction with school did not decrease in children diagnosed with HCM compared with baseline data or compared to controls.

To our knowledge there are few previous studies on how asymptomatic adolescents who are informed having a life-threatening chronic disease, handle normative developmental tasks, such as identity formation.

Some children had no daily awareness of the disease while others were forced to make active decisions whether they should participate in certain activities. Children interested in sports often had their social network in the sports community. Thus the diagnosis didn't only ruin their possibility to pursue their greatest interest, it also affected and changed their social context. Even if we didn't find any significant changes in paper III measuring QoL the subjective experiences described in paper IV is somewhat contradictory.

QoL after diagnosis

The concept of assessing QoL has gained increasing importance as part of follow-up programs in parallel with the implementation of family screening. We have shown in paper I and IV that the immediate emotional impact of the diagnosis was considerable both in parents and in children, but that the families soon adapted to the situation and appreciated the regular contact with a specialist clinic. The screening had no significant detrimental effects on QoL. This has also has been shown in earlier studies of QoL in children with HCM and other inherited cardiovascular diseases [69, 77, 97].

An interesting finding was that psychosomatic symptoms were more common in children with HCM at pre-diagnosis compared to controls, but not at follow-up. This rests on a small excess in frequency of headaches and stomach symptoms, which could be a finding by chance in a small sample.

Our results are in line with previous studies using the same QoL-model, studying children with congenital heart defects, focusing on the overall QoL [79-81]. However significant differences were detected in specific areas of Qol such as the personal sphere [79-81].

At what age should screening be considered?

We observed that the impact of the initial diagnosis seemed to be more severe, and the process of adaptation more turbulent, in the adolescents than in younger children. There are medical reasons why screening ought to be carried out before the risk of sudden death becomes significant around eight years of age [10], and the findings in paper I and IV indicate that there also might be psycho-social reasons why the first screening should be carried out in early childhood, rather than at the beginning of adolescence. Suppression of awareness of the disease was more common in older ages whilst the younger children often accepted the diagnosis and life-style changes quite quickly. This is also supported by previous studies of adults diagnosed with LQTS and parents to children diagnosed with LQTS [70, 72]. Children who grow up with activity restrictions have time to adjust [72]. Another argument for performing the first screening in early childhood is that an early diagnosis reduces the risk of later having to reconsider choice of profession, as a positive diagnosis does rule out a few professions [72].

The effect of beta-blocker therapy on exercise capacity

The results in paper II indicate that HDBB therapy by itself does not impair physical exercise capacity to any significant degree in this specific group of patients, in spite of the fact that the maximum heart rate was significantly decreased. One possible mechanism to explain the maintained exercise capacity could be an improvement in diastolic function leading to an increased stroke volume to compensate for the lower heart rate. Improvement by beta-blocker therapy of diastolic function in adult HCM-patients has been reported [98, 99]. An improved diastolic function has also been reported in children and young adults

on a regime identical to that in our study [100]. In the present study comparable reductions in maximal exercise heart rate occurred with both selective- and non-selective beta-blocker therapy indicating equivalent beta-blockade. Nevertheless, there was no significant impairment of exercise performance in any of the groups. Even if it is not possible in this rather small study to reliably separate the effects on exercise capacity of life-style modifications from the effects of beta-blocker treatment, the differential effect depending on gender suggests that life-style modifications, consisting of restricting energetic exercise such as soccer and ice-hockey, by themselves inevitably have some effect on aerobic capacity and therefore exercise capacity, and are the main cause of the changes observed.

Follow-up programs and need for support

Health care professionals should organise the screening programme according to published recommendations [2, 18, 31, 64]. Follow-up of screening-positive individuals should be based on their needs, psychosocial as well as medical. A screening program ought to offer support and disease specific education including information about risk of complications, self-management, medical therapy and life-style recommendations. This kind of support might help to achieve compliance with medical treatment and life-style advice. Sufficient support for affected families is a cornerstone in creating a basis for these individuals to live a good life even after the diagnosis.

The healthcare team should include a liaison nurse specialised in inherited cardiac disease and a cardiologist, with access to a physiotherapist and a psychologist. The importance for patients in meeting healthcare professionals who are familiar with the specific issues of inherited cardiac diseases and the specific needs of those individuals and their families, has also been described in studies on patients with LQTS [70].

METHODOLOGICAL LIMITATIONS AND CONSIDERATIONS

A limiting factor in paper II and III is the modest number of patients included and the skewed gender distribution. It is a challenge within paediatric cardiology to perform studies with high power based on large numbers of participants, especially in a small country like Sweden.

In paper II it cannot be excluded that HDBB had a negative effect on exercise capacity that was too small to be detected in a study of this size. Because it would be unethical to withhold internationally accepted advice on life-style changes to some patients, it was not possible to reliably separate the effects on exercise capacity of life-style modifications from the effects of beta-blocker treatment. What one could have done was to use a questionnaire to evaluate changes in physical exercise habits, to measure intensity, time spent on training and what kind of physical activities they attended to in order to assess change over time and the impact of life-style changes on physical exercise.

Even though there were a limited number of participants also in paper I and IV it is essential to remember that in qualitative research intention is not to generalize [90, 92, 101, 102]. Data were collected from the participants' memories of their experiences of the diagnosis within a two year time period. However, we were interested in how the experiences of the diagnosis changed over time. It could be that some individuals may not have recalled their experiences accurately, which could affect the findings of the study. However, children six years of age and older have cognitive and language capabilities to be interviewed, and their autobiographical memory has been shown to be very accurate and stable over time [103]. In paper IV interview duration was short but this is a well-known feature when interviewing children, and long interviews should be avoided because of children's limited ability to concentrate [104, 105].

Patterns of experiences of the participants are likely transferable to other individuals within the same situation. In quantitative traditions the quality criterions; validity, reliability and generalizability are used to describe trustworthiness of a study. In qualitative research the concepts credibility, dependability and transferability are used for the same purpose [90, 92]. To increase trustworthiness in paper I and IV the interview analysis was constantly checked and discussed until agreement about possible interpretation was reached.

All participants in paper I, III, IV were born in Sweden. Had there been a more diverse ethnic group other findings may have emerged. Furthermore a majority of the participants were males or were parents of boys, which also might affect the results. This reflects however the gender balance in childhood HCM [10, 23]. All participants were recruited from only one specialist clinic which might also have affected the findings.

In paper III the advantage of the method used is that it captures most relevant aspects of life, including physical, social, and mental components. The instrument used here is a generic one, which refers to a general approach available to anyone regardless of condition or situation. A more rigorous and detailed analysis might have been possible if the answers to the questionnaire were not dichotomised and that is the reason for our subscore-analysis of certain interesting variables. Regarding the statistical analysis imputing values is not a solution to bias caused by non-response. If there is a bias due to selective non-responses for individual variable, it will most likely remain. There was zero non-respondent rate. However due to organizational reasons 23 patients were not sent questionnaires, and two of these were diagnosed with HCM. In order to allow the individuals time to adapt to their new life situation, and time for the adaptation to develop fully, we delayed the formal QoL follow-up assessment for about two years after the screening diagnosis.

When studying small groups of patients the lack of statistically significant differences does not necessarily mean there are no differences. It can also be due to a lack of statistical power. In such

situations the use of a combination of quantitative and qualitative methods increase the chance of reaching a deeper insight in the subjective experiences of the participants.

CONCLUSIONS

- We found no evidence of negative effects on QoL from screening asymptomatic children for HCM.

- The diagnosis of HCM and the accompanying life-style advice affected daily life, especially for those with a high interest in sports.

- Despite a stressful initial period after the diagnosis, both parents and children usually reoriented successfully.

- The diagnosis appeared to affect adolescents and parents more than younger children.

- Both parents and children felt grateful that the disease was detected before any fatal events occurred.

- An early diagnosis gives parents better possibilities to advice their child to pursue physical activities which are within the lifestyle recommendations for HCM patients and thus gain a social network of peers among suitable leisure activities.

- HDBB does not seem to negatively influence the physical performance as measured using exercise test. Some children stated however that they experienced increased fatigue even if their exercise capacity was unchanged objectively.

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Knowledge about how asymptomatic patients react when they receive the information about a chronic life-threatening disease is necessary to offer good patient- and family-support when planning a program for family screening. Health professionals have to consider the specific needs in these families.

- Educational programs should be age-adapted and should take into consideration the whole family in order to achieve a high compliance and adaptation and to give patients an instrument for taking responsibility for their own health.

- Modern web-based communication channels could be used to meet the needs of frequent support and education that this thesis has highlighted.

- Follow-up should also include well-structured, clearly expressed written information addressing schoolteachers and leisure-time activity leaders who can play an important role in the adaptation.

- Health-care professional teams specialized in inherited cardiac diseases need to be established. The relationship of anxiety to physical activities highlights the possible benefit of involving physiotherapists and/or psychologist in the follow-up.

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