Outcomes following general anaesthesia in children with hypertrophic cardiomyopathy

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Abstract

Background
Children with hypertrophic cardiomyopathy (HCM) have historically been considered to be high risk candidates for general anaesthesia (GA), but there is currently a paucity of evidence regarding the safety of anaesthesia and peri-operative outcomes in this population.
Methods
Clinical features and outcomes of all paediatric patients (<18 years) with HCM undergoing GA between 2000-2016 were reviewed.
Results
86 patients (median 12.4 years (IQR 6.5, 14.9)) underwent 164 separate GA procedures. Aetiology included non-syndromic disease (n=44, 56%), malformation syndromes (n= 22, 26%), inborn error of metabolism (n=10, 12%) and neuromuscular disease (n=4,5%). At the time of GA, mean maximal wall thickness (MWT) on echocardiography was 19mm (SD+/-8mm), 23 patients (14%) had severe left ventricular hypertrophy (MWT >30mm) and 35 patients (21%) had a hemodynamically significant left ventricular outflow tract (LVOT) gradient (>50mmHg). The majority (n=143, 87%) had no peri-operative complications. 20 patients (12%) had minor peri-operative complications: bradycardia (n=4), hypotension (n=15) or transient ST segment changes (n=1). One patient (0.6% of GA procedures) experienced a cardiac arrest during anaesthetic induction with death occurring 3 days later. Clinical parameters (including age, MWT, LVOT gradient, systolic and diastolic dysfunction) were not associated with an increased risk of complications
Conclusions
This is the largest published series to date of paediatric HCM patients undergoing GA, which demonstrates that, in an expert centre, patients can be anaesthetized with a relatively low peri-anaesthetic mortality (0.6%) and prevalence of minor complications (12%). Future studies are required to systematically identify clinical features that may predict anaesthetic risk.

Background

Hypertrophic cardiomyopathy (HCM) is the second most common cause of cardiomyopathy during childhood, with an estimated annual incidence of 0.24-0.47 per 100,000 [1-3]. The majority of disease is caused by mutations in the cardiac sarcomere protein genes[4], however aetiology is heterogeneous and also includes malformation syndromes, inborn errors of metabolism and neuromuscular diseases. Phenotypic expression is highly variable, but can include severe left ventricular hypertrophy (LVH), dynamic left ventricular outflow tract obstruction (LVOTO), impaired diastolic function and a predisposition to ventricular arrhythmias. The dynamic nature of LVOTO in HCM, caused by systolic anterior motion of the mitral valve (SAM), means that gradients can be exacerbated by changes in heart rate, heart rhythm, preload and/or afterload, with resulting hemodynamic instability. Although global systolic function is typically preserved, patients with HCM commonly have reduced LV compliance and diastolic dysfunction and are reliant on pre-load to maintain cardiac output. Finally, the hypertrophied left ventricle has an increased myocardial oxygen demand, resulting in a higher risk of coronary blood flow insufficiency and myocardial ischemia. Given these characteristics, children with HCM have historically been viewed as high risk general anaesthesia (GA) candidates. Peri-operative outcomes of adult HCM patients have been reported in the literature, although often with conflicting findings. However, there is currently a lack of evidence regarding the optimal peri-operative management and safety of GA in the paediatric HCM population. The aim of this study was to determine the safety and outcomes of paediatric patients with HCM undergoing GA in a specialised centre.

Patients and Methods

Patients:

Clinical cardiac and anaesthetic data from children with HCM undergoing GA under the age of 18 years at Great Ormond Street Hospital between 2000 and 2016 were reviewed retrospectively. Patients were identified from anaesthetic records and a clinical database. All patients fulfilled conventional diagnostic criteria for HCM (maximal left ventricle wall thickness greater than two standard deviations (SD) above the predicted body surface area (BSA)-corrected mean in the absence of abnormal loading conditions)[5,6] . Patients were not included in this series if they underwent anaesthesia for cardiac surgery requiring cardiopulmonary bypass; had a ventricular assist device in situ (VAD); or were post heart transplantation. When patients had more than one anaesthetic, data were collected from all episodes, with descriptive demographic data obtained from the first anaesthetic, and clinical and peri-operative data obtained relevant to each episode of anaesthesia.

Data collection:

Anonymized, non-invasive clinical information from the time of anaesthetic was collected including: demographics; aetiology; pedigree; symptoms; and two-dimensional (2D) transthoracic echocardiography (TTE) data. Aetiology was classified as non-syndromic in the absence of a diagnosis of a RASopathy syndrome (Noonan or other malformation syndrome), neuromuscular disease (including Friedreich's ataxia) or inborn error of metabolism. Echocardiographic measurements were made according to current guidelines[7,8]. Specifically, maximum LV wall thickness (MLVWT) was defined as the greatest thickness in any single segment at end diastole as measured by 2D echocardiography. Peri-operative information collected included: details of procedure performed; anaesthetic management; intraoperative pharmacological and physiological data; post-operative care; and complications occurring intra-operatively or within 24 hours of anaesthesia. Hypotension, tachycardia and bradycardia were

defined as values more than 30% above or below patient's own baseline or those outside age-specific normal values.

Major complications were defined *a priori* as peri-operative mortality, myocardial infarction (MI), stroke or congestive cardiac failure (CCF). Minor complications were defined *a priori* as a transient disturbance in blood pressure, heart rate or arrhythmias requiring treatment, or the need for an unplanned intensive care admission.

Definitions:

Severe LVH was defined as MLVWT ≥ 30mm in any myocardial segment[6]. Impaired left ventricular systolic function was defined as LV fractional shortening < 25%, as measured in parasternal long or short axis (2D or M Mode) or ejection fraction <50% using Simpson's biplane volumetric method[7]. LV diastolic dysfunction was assessed to be present if two out of the four variables used to assess diastolic function were out of normal range for age and body surface area (annular E' velocity, average E/E' ratio, LA volume and peak TR velocity)[8]. LVOT obstruction was defined as an instantaneous peak Doppler LVOT pressure gradient ≥ 30mmHg at rest. A hemodynamically significant gradient was considered to be an instantaneous peak Doppler gradient ≥ 50mmHg[9]. Non-sustained ventricular tachycardia (NSVT) was defined as three or more consecutive ventricular beats at a rate of greater than 120 beats/min with a duration of less than 30 seconds on ambulatory electrocardiograph (ECG) recordings[5].

Ethical approval:

This study was approved by Great Ormond Street Hospital/ University College London Institute of Child Health Research and Development Office.

Statistical analysis:

All statistical analyses were performed using STATA (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). BSA was calculated from height and weight[10]. Normally distributed continuous variables are described as mean +/- standard deviation with two group comparisons conducted using Student *t* test. Skewed data are described as median (interquartile range, IQR) with two group comparisons performed using Wilcoxon rank sum. To determine the association between relevant predictors and a composite outcome of primary or secondary outcomes, univariate analysis was performed using Chi Squared test or Fishers exact test. To account for multiple comparisons, the Bonferroni correction was applied, accepting a p value <0.05 as significant for all analyses.

Results

Demographics:

Eighty-six eligible patients with HCM under the age of 18 underwent 164 separate general anaesthetics between 2000 and 2016. 78 patients (90%) underwent more than one anaesthetic. 48 patients (56%) had non-syndromic HCM, of whom 22 (46%) had undergone genetic testing. Pathogenic mutations in sarcomeric protein genes were identified in 15 patients (68% of those tested). 22 patients (26%) had a RASopathy syndrome, 10 (12%) an inborn error of metabolism and 4 (5%) a neuromuscular disorder. Data on baseline clinical characteristics and co-morbidities are shown in *table 1*. 4 patients had a previous history of an out of hospital arrest. 13 patients (15%) had a history of NSVT on ambulatory ECG monitoring

Clinical phenotype at time of anaesthesia:

Mean MLVWT at the time of anaesthesia was 19mm (SD 8.3mm, range 4-49mm). The distribution of hypertrophy was asymmetric in 106 patients (68%), concentric in 47 (30%), and biventricular in 3 (2%). 23 patients (14%) had severe LVH. Of 47 patients (31%) with LVOTO

at rest, 35 patients (21%) had a hemodynamically significant gradient (>50mmHg) and one patient had severe outflow tract obstruction (>90mmHg). 87 patients (53%) had echocardiographic evidence of impaired LV diastolic performance and 10 patients (6%) had impaired LV systolic function. 24 patients (15%) had an ICD in situ at the time of anaesthesia. 105 patients (64%) were on medical therapy for symptom control. 46 patients (28%) were on more than one medication (*table 1).*

Indication for general anaesthetic:

150 (91%) general anaesthetics were for elective procedures. The indication for anaesthetic is shown in *table 2.*

Peri-operative anaesthetic management:

Details on peri-operative anaesthetic management are summarized in *table 3.* The lead anaesthetic provider was a consultant cardiac anaesthetist in 75 (46%), consultant non-cardiac anaesthetist in 76 (46%) and a senior anaesthetic trainee doctor in 13 (8%). 100 patients (61%) had an intravenous induction; phenylephrine was used empirically at induction in 8 patients (5%) with no subsequent recorded hypotension. In 153 patients (93%), anaesthesia was maintained with volatile agents. All patients had intra-operative non-invasive cardio-respiratory monitoring, 47 patients (29%) had invasive arterial blood pressure monitoring and 14 (9%) central venous pressure monitoring.

Peri-operative complications :

Of a total of 164 anaesthetics in children with HCM, 143 (87%) had no peri-operative complications. 20 patients (12%) had minor peri-operative complications: 15 patients had intra-operative hypotension requiring treatment; 4 had intra-operative bradycardia requiring treatment; and 1 patient had transient ST segment changes not requiring treatment. 1 patient (0.6%) had a

major complication, with cardiac arrest occurring after induction of general anaesthesia requiring extracorporeal-cardiopulmonary resuscitation (ECPR) and death occurring three days later. This patient had familial HCM with a severe phenotype: asymmetric hypertrophy (MWT 20mm); LVOTO at rest (55 mmHg) managed with medical therapy (atenolol and disopyramide) and short AV delay dual chamber pacing; and evidence of left ventricular diastolic impairment with left atrial dilatation. A primary prevention ICD had previously been implanted following syncopal events and the detection of NSVT on ambulatory ECG monitoring. No clinical parameters were associated with an increased risk of reaching the composite outcome of any post-operative complication (Table 4).

Post-operative course:

Post-operative recovery took place on a cardiology ward for 91 patients (55%), including 10 (6%) who had undergone non-cardiac procedures. 17 patients (10%) were managed post-operatively on intensive care, including 2 patients who had an unplanned admission: one following a failed extubation, and one post cardiac arrest requiring extracorporeal membrane oxygenator (ECMO) support (as described above). Length of stay ranged from 0 to 21 days (median 1 day); 104 procedures (63%) were completed as day-case admissions and did not require an overnight stay.

Discussion

To our knowledge, this is the largest study of peri-anaesthetic outcomes in children with HCM to date. The results demonstrate that, in a heterogeneous cohort of HCM patients having a GA at an experienced centre, the majority of patients (n=143, 87%) had no peri-operative complications and two thirds of procedures were performed as day-cases requiring no overnight stay. Minor

peri-operative complications were seen in 12% of patients but there was one peri-operative mortality (0.6%) in an adolescent with severe HCM.

Comparison with previous literature

To date, no large cohort studies describing the safety of general anaesthesia in paediatric HCM have been published and most of the literature consists of single case reports. The largest published paediatric series reported the outcome of 129 patients with different cardiomyopathies undergoing anaesthesia in a single centre, of whom 50 had HCM[11]. No deaths were reported among the HCM patients, but the study was limited by a lack of detailed clinical description of patients. The scarcity of paediatric data mean that expected outcomes for these patients are often extrapolated from adult studies, the findings of which have been conflicting. Early reports described a high frequency of peri-anaesthetic adverse events of up to 40% in adult HCM patients[12]. However, more recent studies describing larger populations of patients have reported a lower risk of cardiovascular adverse events, although the risk is nonetheless increased compared to controls[13]. In the study by Dhillon and colleagues, 20% of HCM patients reached a composite end point of death, myocardial infarction (MI), stroke or congestive cardiac failure (CCF); this was mostly driven by decompensated CCF and the absolute number of deaths, MI, or stroke was low and not significantly different to what was seen in an age-matched control group[14]. The reported proportion of adult HCM patients dying in the peri-operative period in the literature ranges from 4 to 6.7%[13,14], which is higher than that seen in our cohort. This difference in mortality is unlikely to be explained by a milder disease phenotype. Whilst the adult studies had a higher proportion of patients with LVOTO (53% vs 30.5%) and diastolic dysfunction (93% vs 55%), the absolute maximal wall thickness and proportion of patients with a previous ventricular arrhythmia were not significantly different. The difference in mortality could be explained by the

higher proportion of patients in the adult cohorts with additional co-morbidities such as hypertension, diabetes, and atrial fibrillation which are known to independently increase the risk of a GA.

Identifying patients at high risk of adverse events

Although the prevalence of adverse events is lower than historically reported, the ability to identify patients at higher risk would help guide clinical management. However, no data currently exist to guide peri-anaesthetic risk stratification in paediatric HCM. In an adult cohort, the presence of LVOT obstruction at rest (gradient >30mmHg), a high American Society of Anesthesiologists (ASA) risk score [15]or intra-operative hypotension were associated with a higher risk of having an adverse event[14]. Our ability to systematically investigate individual risk factors for an adverse peri-operative outcome in this study was limited by low numbers of adverse events in this cohort. No single parameter, including MLVWT, LVOTO and diastolic impairment, was found to be associated with a peri-anaesthetic complication. However, it is likely that the combination of certain phenotypic features may confer a higher risk. Certainly, the single patient who experienced a major complication had severe disease with significant left ventricular hypertrophy, LVOT obstruction, diastolic impairment and a history of ventricular arrhythmias. While larger studies are required to identify clinical features' that may confer a higher anaesthetic risk, in clinical practice, it is essential that each individual patient is systematically assessed prior to a GA.

Importance of expert centres

Childhood HCM is a rare disease and compared to adult HCM populations, the disease in childhood is more heterogeneous in terms of aetiology, symptoms and outcomes.[3,16,17] The cohort of childhood HCM patients reported here is representative of other cohorts described in population-based or registry studies[1,2,18]. It includes patients with phenotypically severe disease as defined by severe left ventricular hypertrophy, left ventricular outflow tract obstruction, diastolic impairment and previous ventricular arrhythmias. The results are therefore likely to be generalizable to the wider paediatric HCM population. However, this cohort is derived from a single centre with medical, surgical and anaesthetic expertise in managing patients with this heterogeneous disease. To allow for individualised peri-operative planning, a multi-disciplinary team meeting (including the paediatric HCM specialists and anaesthetic consultants) is held in advance of any procedure requiring a general anaesthetic. The low prevalence of adverse outcomes may not be replicable in non-specialist centres. It is important to note that early reports from adult cohorts, which reported a higher prevalence of adverse events, were indeed derived from non-specialist centres. This includes the largest cohort of HCM patients undergoing GA to date (n=227), which identified patients from the US National Hospital Discharge Survey[13], a fifth of whom underwent GA procedures in community based hospitals which may lack the expertise to manage these patients. This study reported an increased risk of death (odds ratio 1.61) or MI in adults with HCM compared to age matched controls, a finding that has not been replicated in subsequent cohort studies from specialist centres. The low prevalence of adverse outcomes reported here highlights the importance of developing expertise at a specialist centre.

Limitations

This study is limited by problems inherent to retrospective studies, including missing or incomplete data. Additionally, although this is the largest cohort of paediatric HCM patients undergoing a GA reported in the literature, the interpretation of the prevalence of complications

is limited by the absence of age matched controls. Previous studies have reported 30-day mortality of 1.1/10,000 (95% CI 0.4-2.6) in a non-selective cohort of children undergoing GA at a tertiary paediatric hospital[19]. In contrast, in the largest study to date assessing outcomes following non-cardiac surgery in children with congenital heart disease (CHD), higher post-operative mortality 3.9-8.2% rates were described in patients with moderate (defined as repaired CHD with residual hemodynamic abnormality) and severe (including patients with ventricular dysfunction requiring medication or uncorrected cyanotic heart disease) CHD compared to controls (1.7-1.2%)[20]. This suggests that, although children with HCM have a higher incidence of major complications following anaesthesia compared to the general population, the risk may be lower than in children with other cardiac disease. This series did not include patients undergoing cardiac surgery requiring CPB as the interpretation of the *a priori* defined complications (in particular disturbances in blood pressure, heart rate or arrhythmias) would not be possible once CPB was established. Future studies investigating the outcome of children with HCM undergoing GA for procedures requiring CPB would be useful.

Conclusion:

This study reports the largest published series of patients with paediatric HCM undergoing general anaesthesia and demonstrates a relatively low peri-anaesthetic mortality (0.6%) and prevalence of minor complications (12%). The findings suggest that, in an expert centre, children with HCM can be anesthetised with a low risk of adverse events. Future studies are required to systematically identify clinical features that may predict anaesthetic risk.

What is already known on this topic

- Children with Hypertrophic cardiomyopathy (HCM) have historically been considered to be high risk candidates for general anaesthesia (GA), but there is currently a paucity of evidence regarding the safety of anaesthesia and peri-operative outcomes in this population.

What this study adds

- In an expert centre, paediatric patients with HCM can be anaesthetized with a low peri-anaesthetic mortality (0.6%) and low prevalence of minor complications (12%). Future studies are required to systematically identify clinical features that may predict increased anaesthetic risk.

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Table 1: Baseline clinical characteristics:

		Number (%)
Male gender		50 (58)
Age, yrs (median (range))		12.4 (0-18.4)
Weight, Kg (median (range))		38.6 (2-101)
Cardiac medications		
	Beta-blockers	91 (55)
	Disopyramide	38 (23)
	Calcium channel blockers	16 (10)
	Amiodarone	10 (6)
Comorbidities (n)		
ENT	OSA	3
Orthopaedic	Scoliosis	4
	Polyarthralgia	1
Respiratory	Asthma	4
Congenital cardiac disease	VSD	1
	Aortic stenosis	1
Neurology	Epilepsy	1
	Autistic spectrum disorder	3
	Developmental delay (acquired/congenital)	3
	hydrocephalus	1
Metabolic	Diabetes mellitus	2
Renal	Polycystic kidney	1

Data expressed as number (%). Total number of patients is 86 unless otherwise stated**.** ENT = Ears, nose and throat, OSA = Obstructive sleep apnea, VSD = ventricular septal defect

Table 2: Indication for general anaesthetic

		Number (%)
Cardiac		87 (53)
	Implantation/threshold testing of ICD	56
	Diagnostic cardiac catheterisation	7
	Interventional cardiac catheterisation	1
	EPS	9
	Pacemaker implantation	8
	Loop recorder insertion	4
	Trans-oesophageal echocardiogram	2
General surgical		11 (7)
	Gastrointestinal	7
	Biopsy/excision	4
Radiology		26 (16)
	Diagnostic	9
	Interventional	17
Orthopaedic		12 (8)
Ears, nose and throat		8 (5)
Dental		8 (5)
Plastics		2 (1)
Neurosurgery		2 (1)
Urology		7 (4)
Respiratory		1 (<1)

Data expressed as number (%). Total number of GA procedures is 164. ICD = Implantable cardioverter defibrillator, EPS = electrophysiology study,

Table 3: Peri-anaesthetic management

Anaesthetic detail			Number (%)
Lead anaesthetic provider	**Consultant - Cardiac**		75 (46)
	Consultant - Non-Cardiac		76 (46)
	Senior trainee doctor		13 (8)
Anxiolytic premedication used			34 (21)
Mode of induction	**Gaseous**		60 (37)
		Sevofluarane	60
	Intravenous (IV)		100 (61)
		Propofol & opioid	40
		Etomidate & opioid	33
		Ketamine & opioid	5
		Propofol only	15
		Other	7
	Mixed (IV + gas)		4 (2)
Airway Management	**Endotracheal intubation**		142 (87)
	Laryngeal Mask Airway		19 (12)
	Other		3 (2)
Maintenance	**Volatile**		153 (93)
	TIVA		9 (5)
	Not specified		2 (1)
Vasopressor agent (n=17, 10%)	**Phenylephrine**		14 (9)
	Noradrenaline		3 (1)

Data expressed as number (%)

Table 4: Comparison of patients by the presence of complications.

	Complication	No Complication	P value
Age, yrs (median (IQR))	10.74 (0.23 - 16.6)	10.4 (0.01 - 18.43)	>0.999
Weight, Kg (median (range))	39.6 (5.6 - 77)	39.6 (2-101.4)	>0.999
Emergency procedure, n%	10% (n=2/21)	8% (n=11/140)	>0.999+
ASH distribution, n%	65% (n=13/20)	67% (n=91/136)	>0.999
Systolic dysfunction, n%	20% (n=4/20)	4% (n=6/136)	0.064
Diastolic dysfunction, n%	89% (n=16/18)	74% (n=71/96)	>0.999
LVOT gradient, n% >50mmHG	24% (n=5/21)	17% (n=23/136)	>0.999+
MLVWT > 30mm, n%	15% (n=3/20)	16% (n=20/129)	>0.999+

Data expressed as % (n=proportion of patients with available data). Comparisons performed using Chi-Squared test unless otherwise stated. + Fishers Exact test. LVOT = left ventricular outflow tract, MLVWT = maximal left ventricular wall thickness, ASH = Asymmetric septal hypertrophy