CONGENITAL HEART DISEASE AND GENERAL PRACTICE

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"Oh for a lodge in some vast wilderness,
Some boundless contiguity of shade…"

from William Cowper: the Task

CONTENTS

Chapter 1

General introduction

The treatment of patients with congenital heart disease (CHD) has progressed vastly over the last five decennia. In the Netherlands, around 200,000 children are born each year, around 1,800 of whom have a CHD. This incidence – 6 – 8 per thousand live births – is reported to be similar round the world [1], making CHD the world's commonest congenital anomaly [2].

In the Netherlands, this high incidence and the improved treatment options both mean that the number of people surviving CHD is increasing by approximately 5% per year [3]. No longer are most patients with a CHD children: the paediatric population is now outnumbered by the adult population [4, 5]. Although accurate statistics on prevalence are lacking, as many as 70,000 children and adults with different types of CHD are estimated to be alive in the Netherlands today. Representing a prevalence of approximately 4 per 1000 patients [3, 6], this approaches the prevalence of insulin-dependent diabetes mellitus (11 per 1000 patients) and rheumatoid arthritis (9 per 1000 patients), which are considered to be common diseases in general practice.

CHD consists of a wide variety of anomalies that arise before birth. The sensitivity of the heart to perturbations may lie in the complexity of its development in utero. The defects underlying CHD are thought to be mutations in the known regulators of the heart development during embryogenesis; more complex forms of CHD might be explained by altered haemodynamics secondary to the primary defect that can lead to changes in blood-flow, thereby causing structural defects. But although genetic errors and environmental influences are also known to contribute to the origin of CHD, most CHDs seem to be of multifactorial origin [7-12].

While the true incidence of CHD is unknown, estimates range from 6 to 8 per 1000 live births [13, 14], the differences depending on which types of defects are included. Some of the anomalies, such as transposition of the great arteries, are life-threatening and need immediate treatment; others, such as small ventricular septal defects, are without any symptoms and tend to be self-limiting.

Fifty percent of patients with CHD need specific medical or surgical treatment. In the 1950s, about 50% of children with CHD died within the first year of life, and less than 15% of them reached adulthood. While the introduction of more accurate diagnostic tools, together with improvements in surgical techniques, anaesthesia and peri-operative intensive care all led to a decline in peri-operative mortality, the development of open heart surgery with cardiopulmonary bypass then increased the probability of survival into adulthood [15]. Currently, at least 85% of patients reach adulthood [6]. The long-

term consequences of a CHD range from normal to mild or moderate restriction of cardiopulmonary capacity; the disease may also progress to heart failure [13, 16].

Without exception, primary medical treatment in the Netherlands is provided by paediatric cardiologists and cardiothoracic surgeons in specialised medical centres. As a result, many of the patients with serious sequelae (any abnormality following or resulting from a disease or injury or treatment), remain under the surveillance of paediatric or congenital cardiologists. Many others, generally those with no problems or only minimal residual ones, are referred back to their general practitioners (GP), certainly with regard to aspects of general health care. This means that GPs will eventually see an increasing number of CHD patients, and will need to be able to differentiate between cardiac-related complaints and non-cardiac problems. GPs therefore have to be equipped to recognize and differentiate between these problems.

The history of treatment options and treatment outcomes for transposition of the great arteries (TGA) – one of the commonest CHDs – illustrates the spectacular progress that has been made in this field. In the days before this lesion was treated surgically, few new-borns with TGA survived; approximately 90% died in the first months of life. The introduction of balloon atrioseptostomy (a catheter intervention technique according to Rashkind) and of the aortopulmonary shunt (Blalock and Taussig), both in the 1940s, meant that palliative treatment became available and systemic oxygenation could be improved. But the effects of these techniques persisted for only a limited number of years, and did not lead to normal life-expectancy. The outlook for these patients improved dramatically in the 1950s, when the atrial switch procedure (Senning or Mustard operation) was introduced. However, due partly to the extensive atrial surgery and the fact that the right ventricle remained the ventricle supporting the systemic circulation, there were severe long-term complications, such as ventricular failure, sinus-node dysfunction and baffle-related problems.

A new development in the mid 1970s was the arterial switch operation. Initially, its introduction was beset by technical issues and ethical controversies, and its discontinuation was considered. However, as the long-term outlook after an arterial switch operation was thought to be so much better, the atrial switch procedure was gradually abandoned as treatment of first choice. Although an arterial switch does not bring entirely normal life expectancy, the long-term prognosis for transposition of the great arteries is far better than after atrial switch, and most patients are now in an excellent clinical state [17-19].

Although, in most cases, the long-term prognosis of CHD is very favourable, total correction is often not achieved; most patients have at least minimal life-long residual lesions or sequelae, or develop sequelae over time. These have to be recognised during medical consultation. New technical tools such as echocardiography, bicycle-ergometry

and cardio-MRI are all helpful in follow-up of patients with CHD: by facilitating the assessment of secondary effects of CHD, they provide vital insight into patients' future prospects. But as many of these facilities are available only in specialised medical centres, they cannot be used by doctors in general practice, like GPs.

The favourable prognosis means that paediatric cardiologists and congenital cardiologists will no longer be the only doctors involved in the long-term medical care of patients with CHD. Increasingly, doctors in general practice will deal with all sorts of medical issues involving these patients [2]. In the Netherlands, however, the general practice system has not yet been properly prepared for the growing number of patients with CHD. GPs are not used to dealing with the signs, symptoms and issues concerning this group of patients. There are two reasons for this: the past absence of such patients in their practices, and thus their lack of experience with them; and a shortage of information combined with an absence of guidelines. Many GPs thus feel insecure about managing the care of this group of patients.

In an attempt to produce a formal review on the question, we conducted a literature-search on PubMed using the MESH headlines "family practice", "general practice" and "heart disease, congenital". This gave only six results that were applicable [20-25]. Three papers involved cardiac murmurs in the diagnostic phase, and one involved the cost-effectiveness of GPs' referrals to a cardiologist to diagnose cardiac murmurs [24]. Only two papers addressed the management of CHD in general practice; the most applicable paper was written fifty years ago, by Harrington in 1962! [20].

Thus, although GPs have very little information and no specific guidelines on the management of CHD, they are nonetheless expected to recognise symptoms that may or may not be caused by residual cardiac lesions. This is an important judgement: some patients require additional specialist medical or surgical treatment, such as that for arrhythmias, ventricular dysfunction or valvular regurgitations. While GPs are supposed to distinguish between one subgroup of patients who require additional specialist treatment and one who can be treated by GPs themselves, they entirely lack the specific tools that would enable them to make a proper medical judgement. Bensky et al concluded that proper financial judgement of primary care physicians may restrict the number of expensive and unnecessary referrals of cardiac murmurs to cardiologists [24] . Apart from this financial judgement, no literature is available on medical judgement and the need for referral.

Against this background, this thesis is intended to take the first step towards providing specific information that is required by doctors working in general practice and towards developing diagnostic tools that can be used in general practice.

As mortality is improving, the focus is now shifting to morbidity and quality of life (QOL). These two are closely related, as psychosocial functioning and QOL can both be impaired by morbidity: children and adolescents with CHD have more behavioural and emotional problems than subjects in the general population [26].

It was in recognition of the importance of health to QOL that the concept of health-related QOL was introduced, its function being to assess aspects of an individual's subjective experience that relate directly and indirectly to health, disease, disability and impairment and the effectiveness of treatment [27]. Effectively, it combines the interests of medical doctors and psychologists with regard to psychosocial functioning – a combination that, in the Netherlands, is very much the competence of a GP.

Assessment of health-related QOL in children involves specific problems. Children differ from parents in their understanding of health and of the causes and implication of illness [28]. Children may interpret questions differently and adopt a different time perspective regarding the course of a disease [29]. The literature has found low concordance between QOL ratings made by children themselves and those by proxies such as parents [30, 31]. As parent-reports are not a substitute for child-reports or vice versa, the child's own perspective is important in measurements of psychosocial functioning, and thus of QOL. It is therefore important to know the opinion of children themselves, not only in questionnaires but also when conducting interviews during history-taking.

It is also important to know to what extent factors associated with the medical course in early childhood are predictive for that psychosocial functioning and possibly behavioural and emotional problems. It will then be possible to identify aspects of the treatment and support of children with CHD requiring special attention. Although several predictors have already been identified, ranging from maternal perceptions [32] to medical variables such as age at surgical repair, deep hypothermic circulatory arrest and number of heart operations [33, 34], few recent studies have assessed medical predictors of long-term behavioural and emotional problems.

The present study

Elements of cardiac and psychological status of a population of patients invasively treated for CHD were examined in a cross-sectional study of a consecutive cohort of patients in five diagnostic CHD groups who had undergone their first invasive treatment between January 1990 and January 1996 at Erasmus University Medical Centre Rotterdam, all at an age younger than 15 years. The sample of diagnostic CHD groups in this study encompasses the following: atrial septal defect (ASD), ventricular septal defect (VSD),

transposition of the great arteries (TGA), tetralogy of Fallot (TOF), and pulmonary stenosis (PS).

The aim of this thesis is to inform doctors in general practices about cardiac and psychological outcomes after invasive treatment for CHD at young age. The thesis is also intended to describe the first steps towards the development of diagnostic tools that might help those in general practice to recognise residual problems of CHD.

The specific objectives of this study are:
1. To develop a practical tool for general medical practice by describing the association between information derived from face-to-face interviews and objectively assessed parameters.
2. To present the long-term clinical outcome (including mortality, incidence of sequelae and functional status) of patients who had undergone operations for selected cardiac anomalies.
3. To investigate the predictive value of medical variables on psychopathology in selected children and adolescents with CHD.

These objectives are intended to initiate a process whereby GPs provide better-focused surveillance, better counselling and better-integrated healthcare for patients with CHD. A secondary objective is to achieve better-informed communication between medical specialists and GPs.

Outline

Chapter 2 presents a study in which a simple tool is introduced that can be used in general practice and also seems to be predictive for exercise performance by bicycle ergometry.

In the *Chapters 3, 4, 5 and 6* the follow-up status (including mortality, incidence of sequelae and functional status) was determined, and a comparison was made between two cohorts of patients treated in different periods of time. The objective was to improve insight into the prospective of patients treated invasively for CHD.

Chapter 7 studies factors associated with the medical course in early childhood and their predictive value for psychosocial dysfunction, and possibly for secondary behavioural and emotional problems.

Chapter 8 provides summary and general discussion with specific attention for aspects and consequences of the growth of the number of patients with CHD in general practice.

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Chapter 2

Self-appraisal of exercise capability predicts exercise performance in children invasively treated for congenital heart disease

Introduction of the EASY score, a functional classification

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Chapter 3

Follow-up outcomes ten years after arterial switch operation for transposition of the great arteries: comparison of cardiological health status and health-related quality of life to those of normal reference population

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ABSTRACT

To investigate cardiological health status and health-related quality of life after the arterial switch operation (ASO) for transposition of the great arteries (TGA) in comparison with a normative reference group. Chart review and cross-sectional systematic follow-up, including echocardiography, exercise testing, electrocardiography, were performed on all survivors of ASO for TGA between 1990 and 1995. Health-related quality of life (HRQOL) was assessed using a standardized questionnaire. A normative reference group was included. Forty-nine survivors (median age at operation 13 days, mean age at follow-up 11 ± 2 years (37/49 with intact ventricular septum (TGA/IVS) were identified, 33/49 patients (67%) (22/33 TGA/IVS) participated in cross-sectional follow-up. Cumulative 10-years event-free survival was 88%, re-intervention rate 6%. Aortic root dilatation occurred in 70% of patients, none had severe aortic regurgitation. Left ventricular function was normal. Exercise performance (85% of reference-capacity, $p=0.02$), maximal oxygen uptake (85%, $p<0.01$) and peak heart rate (95%, $p<0.01$) were decreased. Exercise electrocardiogram was normal as was rhythm status. Unfavourable outcomes on HRQOL were found for motor functioning and positive emotional functioning. Overall there were no significant differences between TGA/IVS and TGA/VSD.

Conclusion

At mid- to long-term follow up after ASO, major events and re-interventions (6%) occur infrequently. Exercise capacity and maximal oxygen uptake are lower than those in a reference population, which could not be related to diminished ventricular function. Aortic root-dilatation is frequent, irrespective of anatomical subgroup. Severe aortic regurgitation or left ventricular dilatation was not found. The unfavourable health-related quality of life deserves further attention.

INTRODUCTION

Transposition of the great arteries (TGA) is found in approximately 5% of all newborns with congenital heart disease [62]. Since the late 1950s, a succession of strategies for surgical repair of TGA resulted in the introduction of the present-day technique: the arterial switch operation (ASO). Underlying this introduction was the assumption that the benefit of normalisation of circulatory pathways, a systemic left- instead of systemic right ventricle, would considerably improve patients' prospects. And indeed, quite a number of studies showed excellent results concerning general health status [63-65]. ASO is still regarded as one of the highlights in cardio-thoracic surgery.

Recent studies have proved that sequelae after the ASO are not as imaginary as initially thought. Problems related to dilatation of the pulmonary valve and root in the systemic circulation, resulting in aortic root-dilatation (ARD), aortic valve regurgitation (AR), stenosis of re-implanted coronaries and impaired ventricular function, as well as distortion of the pulmonary arteries, have all been reported [66-68].

Information about the combined cardiological and psychological health status after ASO is scarce and should ultimately be tested against a normal reference population.

To establish incidence and clinical importance of the reported sequelae, systematic follow-up studies are necessary in well-defined patient-populations.

Therefore we investigated mortality, morbidity and health-related quality of life in patients ten years after ASO for TGA and compared them with a matched healthy control group (cardiological health status) or normative reference group (health related quality of life).

MATERIALS AND METHODS

Patient selection

Fifty-five patients could be identified from the medical records of the Departments of Cardio-thoracic Surgery and Paediatric Cardiology, who had undergone an ASO for TGA (TGA with intact ventricular septum (TGA/IVS) and TGA with ventricular septal defect (TGA/VSD)) at the Erasmus Medical centre between 1990 and 1995. Five patients (all TGA/IVS) were completely lost to follow-up; one patient (TGA/IVS) died from tracheomalacia. From the remaining 49 survivors a retrospective chart review was performed. The chart review included detailed assessment of pre-, per- and postoperative parameters to identify baseline characteristics (table 1) and events during follow-up (table 2).

Table 1. Baseline characteristics and follow-up of survivors versus patients

	Survivors	Patients	P
Number of patients	49	33	
Male (%)	78	72	0.6
Prostin preoperative (%)	67	48	0.1
Rashkind septostomy (%)	52	61	0.4
VSD closure (%)	24	33	0.6
Age at follow-up (years)	11 ± 2 (5-14)	11 ± 1 (7-13)	0.2
Reintervention rate (%)	8	6	0.5
Follow-up duration (years)	11 ± 2 (5-14)	11 ± 1 (7-13)	0.2

* median age

Table 2. List of events and incidence during follow-up

Event	Follow-up time	Treatment	Incidence * survivors	patients
Pulmonary hypertension	directly PO	Medication	1	
Myocardial infarction	directly PO	Medication	1	
Superior caval vein thrombosis	directly PO	VPD	1	
Severe supravalvular PS	2 years	TAP implantation		1
Subvalvular ridge in LVOT	4 years	Surgical resection		1
Severe valvular PS	10 years	Balloon valvuloplasty	1	

Abbreviations:
PO=postoperatively, PS=pulmonary stenosis, LVOT=left ventricular outflow tract,
VPD=ventriculo peritoneal drainage, TAP=trans-annular patch,
TGA=transposition of great arteries, IVS=intact ventricular septum.
* Survivors and patients mentioned are all TGA/IVS.

All 49 survivors included in this chart review were eligible for cross-sectional (prospective) analysis if they met the following inclusion criteria: 1) residence in the Netherlands, 2) Dutch speaking, 3) no underlying chronic disease or syndrome with mental retardation. Evaluation consisted of a full medical history, physical examination, echocardiography, exercise testing, standard-12-lead ECG, 24-hour ambulatory electrocardiography and psychological examination by a psychologist. Ultimately, 33 patients agreed to participate in this follow-up. Twenty-two of these patients had an intact ventricular septum (TGA/IVS) and eleven patients had also a VSD besides the TGA (TGA/VSD).

Selection of the medical reference group

A reference group of 33 healthy schoolchildren was selected, matched for gender and age. Children involved in organised sport activities for more than six hours a week were excluded. The study was approved by the national Central Committee on Research in-

volving Human Subjects. Written informed consent was obtained from all patients and healthy controls (medical reference group) as well as their parents.

Electrocardiography

Standard twelve-lead electrocardiograms were performed on a Cardio Perfect 4.0 machine.

The electrocardiograms were interpreted by a single observer (WBdK).

Twenty-four hours ambulatory ECG

A three-channel recorder was used. Arrhythmias were judged according to Garson's criteria [69].

Echocardiography

Conventional echocardiography (was carried out in patients and controls), consisting of trans-thoracic M-mode and two-dimensional echocardiography, as well as echo-Doppler measurements, using a Philips Sonos 5500 ultrasound system (Philips Medical Systems, Best, the Netherlands), was carried out in patients and controls. Severity of stenosis was classified as follows: mild (peak flow: 2-3 m/s), moderate (3-4 m/s) or severe (> 4 m/s). Valvular regurgitation was graded on a four-point scale as absent or trivial, mild, moderate (or) and severe. All echocardiography data of patients was compared with that of the reference group. Aortic root dimensions were also judged according to the reference values of Roman [70].

A chart review of all available echocardiography reports from our own patient population was carried out, in order to gain an insight into moment of onset and to detect a possible trend in time, concerning AR.

Maximal exercise capacity

Patients and references performed a symptom limited, maximal exercise bicycle-test using a stepwise incremental protocol on a Jaëger Oxycom Champion System (Viasys Healthcare GmbH, Hoechberg, Germany) that allowed breath-by-breath ergometry. Workload was increased every minute by 10, 15 or 20 Watts according to the Godfrey protocol [71]. Before and during the test, ECG monitoring was performed in a sitting position. Patients and references were encouraged to perform until exhaustion. The respiratory quotient (RQ) was used to objectify maximal performance. Exercise performance was regarded as maximal, when subjective exhaustion combined with a RQ ≥ 1.05 at peak exercise was reached. The following parameters were obtained: maximal achieved workload (Watt), maximal oxygen uptake (VO2-max) (ml/kg/min), peak heart rate (beats/min) and RQ. Parameters of patients were compared with those of references.

Major events during follow-up

Major events were defined as 1) death, 2) interventions and re-interventions required for cardiac disease, and 3) use of cardiac medication.

Health related quality of life (HRQOL)

HRQOL is defined as health status weighted by the subjective, emotional impact of problems in health status. The TNO-AZL Child Quality of Life Questionnaire (TACQOL) is a generic instrument, designed to assess general aspects of HRQOL of children [72]. It consists of seven scales (see Table 6) and assesses the occurrence of functional problems. If such problems do occur, negative emotional reactions are assessed too. On all scales a higher score indicates a better HRQOL (range of sum-scores: 0-32). The satisfactory reliability and validity of the TACQOL child form have been described in detail [73]. Data of patients were compared with those from Dutch normative samples with comparable age-ranges, derived from the manual [72].

Statistical methods

Continuous variables were presented as mean and standard deviation. Cumulative event-free survival curve was calculated according to Kaplan-Meier analysis. To compare the patients groups with the reference group Fisher's exact test was used and student's t-tests were used to compare continuous variables. One-sample t-tests were used to test differences in groups' means between the patients sample and reference group on TACQOL scales. In all analyses the level of significance was set at $p < 0.05$ (2-tailed).

RESULTS

Patient characteristics

Forty-nine consecutive survivors after ASO for TGA (n=37 TGA/ IVS; n=12 TGA/VSD) were eligible for cross-sectional (prospective) analysis. Thirty-three survivors (n=22 TGA/IVS; n=11 TGA/VSD) agreed to participate in the cross-sectional (prospective) part of the study.

Baseline characteristics did not differ between the overall group of 49 survivors and the subgroup of 33 patients included in prospective analysis. Mean age at follow up, i.e. at last clinical or outpatients' visit in survivors and at prospective evaluation in participants was 11 ± 1 years and 72% were male (Table 1).

Reference population

The reference population consisted of 33 healthy schoolchildren (72% male) with a mean age of 11 ± 1 years. The mean body weight of the reference population was 38 ± 8 kg

(patients: 38 ± 11 kg) and the mean height of the references was 149 ± 9 cm (patients: 147 ± 12 cm).

Operation

All ASOs with or without VSD-closure, were performed with cardiopulmonary bypass and hypothermia. Cold cardioplegia was used in all patients. Lecompte's manoeuvre was applied in all cases. Transfer of the coronary arteries was performed by trap-door techniques. Mean age at operation did not differ statistically significantly for TGA/IVS (0.07 ± 0.09 (0.01-0.41) years) and TGA/VSD(0.02 ± 0.90 (0.02-0.89) years(p= 0.10). Mean perfusion time was 147 ± 44 (97-266) minutes (TGA/IVS: 135 ± 37 (97-250); TGA/VSD: 170 ± 50 (127-266); p=0.03) mean aortic cross-clamp time was 93 ± 32 (68-151) minutes (TGA/IVS: 86 ± 18 (68-145); TGA/VSD: 109 ± 20 (81-151); p=0.02). Mean lowest nasal temperature was 23 ± 3 (17-27) degrees Celsius (TGA/IVS: 23 ± 3 (17-27); TGA/VSD: 22 ± 3 (17-27); p=0.19).

Major events during follow-up

Percentage of major events during follow-up did not differ significantly between the overall group of 49 survivors (10%) and the group of 33 patients (6%) included in prospective analysis (p=0.5) (Table 2). For the overall group of 49, cumulative major event-free survival was 88% at 10 years follow-up (Figure 1). One patient (TGA/IVS) developed iliac and femoral vein thrombosis 2.5 years after surgery. This event was regarded as a non-cardiac and a non-ASO-related event.

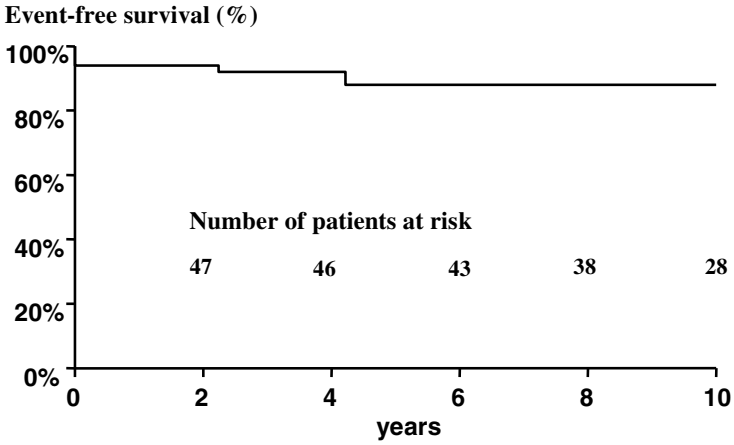

Figure 1. Cumulative event-free survival
Kaplan-Meier curve for survival in the absence of major events (defined as death, interventions and re-interventions required for cardiac disease, and use of cardiac medication) in all survivors of arterial switch operation for transposition of the great arteries

Echocardiography

In the 33 patients, assessment of cardiac dimensions showed that aortic annulus and aortic root were significantly wider in patients than in references (Table 3). An aortic root-dilatation (ARD > 95th percentile) was found in 23 patients (70%) (Table 4). Based on the graphs of Roman, mean Z-scores of the aortic root were 3.2 ± 2.4 (-2.2 to 9.4) (Figure 2) and eighteen patients (55%) had a Z-score exceeding 3. Aortic root sizes did not differ statistically significant between patients with TGA/IVS and TGA/VSD. Mild or moderate AR was shown in 48% of the patients (TGA/IVS: 55%; TGA/VSD: 45%; p=0.6) (Table 4). No severe AR was seen. Left ventricular dimensions and fractional shortening (FS) were within normal limits. One patient (TGA/VSD) showed a slightly subnormal FS of 25%. Inflow patterns of both atrioventricular valves were within normal limits, with the exception of tricuspid valve deceleration time (Table 3). There were no differences between both subgroups. Mild or moderate supravalvular pulmonary stenosis (PS) was found in 56% of patients (TGA/IVS: 53%; TGA/VSD: 60%; p=0.1). Valvular- or supravalvular aortic stenosis (AS) and valvular PS was not detected (Table 4).

Table 3. Echocardiographic results of patients compared with references

		References	TGA all	p *	TGA+VSD	TGA+IVS	p **
M-mode recordings							
LVED	mm	43.4 ± 3.7	43.0 ± 5.3	0.7	43.6 ± 6.0	42.7 ± 5.1	0.6
LVES	mm	27.1 ± 2.6	27.4 ± 4.3	0.8	27.3 ± 5.6	27.4 ± 3.7	0.9
FS LV	%	37.3 ± 4.3	36.3 ± 5.0	0.4	37.6 ±5.9	35.7 ± 4.5	0.3
IVSED	mm	6.3 ± 1.2	6.9 ± 1.7	0.08	7.6 ± 1.8	6.5 ± 1.5	0.07
LVPWED	mm	5.4 ± 1.2	6.2 ± 2.1	0.07	6.7± 2.6	6.0 ± 1.9	0.4
2-D							
Aortic annulus	mm	16.7 ± 1.9	19.7 ± 2.4	<0.001	20.7 ± 3.0	19.2 ± 1.9	0.08
Asc. Aorta	mm	18.0 ± 2.4	19.7 ± 4.3	0.07	22.0 ± 8.0	18.6 ± 2.7	0.04
Aortic root	mm	21.4 ± 2.2	27.8 ± 4.9	<0.001	29.5 ± 6.5	27.0 ± 3.8	0.3
Pulm.annulus	mm	20.4 ± 2.8	19.4 ± 3.6	0.4	18.0 ± 2.4	20.2 ± 4.0	0.3
Atrioventricular flows							
Mitral E	m/s	1.04 ± 0.17	1.10 ± 0.23	0.7	1.13 ± 0.25	1.03 ± 0.22	0.3
Mitral A	m/s	0.46 ± 0.11	0.45 ± 0.10	0.7	0.49 ± 0.12	0.44 ± 0.09	0.2
Mitral E/A		2.28 ± 0.54	2.47 ± 0.83	0.5	2.48 ± 0.93	2.46 ± 0.80	0.9
Mitral DT	sec	0.16 ± 0.03	0.18 ± 0.08	0.6	0.17± 0.03	0.16 ± 0.05	0.8
Tricus E	m/s	0.75 ± 0.17	0.75 ± 0.17	1.0	0.78 ± 0.19	0.74 ± 0.17	0.6
Tricus A	m/s	0.39 ± 0.11	0.44 ± 0.12	0.2	0.42 ± 0.17	0.45 ± 0.09	0.6
Tricus E/A		1.98 ± 0.57	1.85 ± 0.70	0.2	1.89 ± 1.08	1.74 ± 0.55	0.2
Tricus DT	sec	0.17 ± 0.04	0.20 ± 0.05	0.05	0.19 ± 0.03	0.19 ± 0.06	0.8

Abbreviations:
LVED=left ventricular end-diastolic diameter., LVPW=left ventricular posterior wall end-diastolic dimension, FS=fractional shortening, Asc=ascending, LVES=left ventricular end-systolic diameter, Pulm=pulmonary, LV=left ventricle, IVSED=inter ventricular septum end diastolic diameter, RV=right ventricle, VSD=ventricular septal defect, IVS=intact ventricular septum.
* Differences between all TGA patients and references
** Differences between TGA/VSD and TGA/IVS

Table 4. Cardiac lesions in 33 patients

Residual lesions	TGA all (%) n=33	TGA/IVS (%) n=22	TGA/VSD (%) n=11	P*
LVOT obstruction	3 (a)	5 (a)	0	0.2
RVOT obstruction	56 (b)	53 (c)	60 (d)	0.5
AR	48 (e)	55 (f)	45 (g)	0.6
PR	33 (h)	25 (i)	50 (j)	0.1
MR	12 (k)	9 (l)	18 (m)	0.5
Residual VSD (1)	3	0	9	
ARD (2)	70	68	73	0.8
LVH (3)	3	0	9	0.2

Additional information:

a Subvalvular aortic stenosis; max.flow: 3.6 m/s. Residual stenosis after surgical resection.
b 37% mild and 15% moderate obstruction.
c 33% mild and 20% moderate obstruction.
d 50% mild and 10% moderate obstruction.
e 45% mild and 3% moderate AR.
f 55% mild AR.
g 27% mild and 18% moderate AR.
h 33% mild PR.
i 25% mild PR.
j 50% mild PR.
k 12% mild MR.
l 9% mild MR.
m 18% mild MR.
1 No hemodynamic relevance.
2 Defined as aortic root > 95th percentile.
3 Septal thickness at 98th percentile.
* TGA/IVS vs. TGA/VSD

Aortic regurgitation was reported for the first time at a mean postoperative duration of 47 months (range: 1 week to 10.5 years) (TGA/IVS: 46 months (range 1 wk to 10.5 years); TGA/VSD: 34 months (1 wk to 6.5 years)). No patients showed progression of severity of AR.

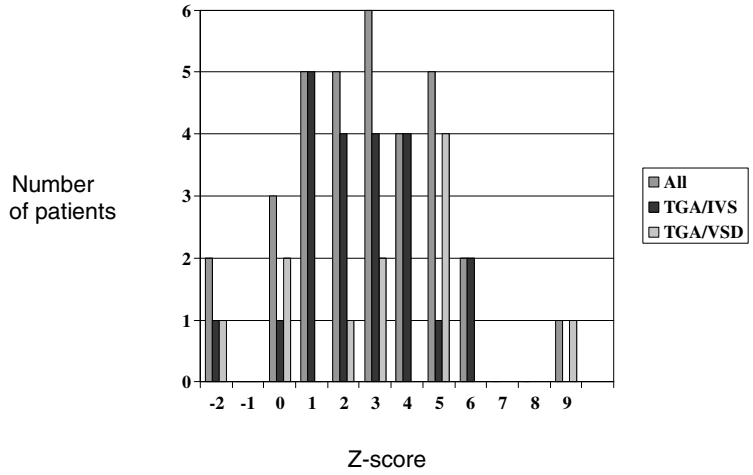

Figure 2. Aortic root dimensions, expressed as Z-score according to Roman-criteria [9] vs. number of patients

ECG

A QTc-duration exceeding 440 msec (418 ± 22; (381-465)) was observed in 6 patients (18%), 8 (24%) had a first-degree atrio-ventricular block and four of them (12%) had a right bundle branch block. No patients showed evidence of myocardial infarction or ischemia and no ventricular hypertrophy was seen.

All, but one patient (TGA/VSD) in atrial rhythm, were in sinus rhythm of which 33% had short periods of atrial rhythm. One patient (TGA/IVS) revealed 1600 atrial ectopic beats within 24 hours. Two patients (Both TGA/IVS) demonstrated 4000-5000 single ventricular ectopic beats within 24 hours, one of them showed 500 doublets. According to Garson's criteria all recorded numbers are within normal limits. No significant differences between TGA/IVS and TGA/VSD were found.

Exercise capacity

Maximal exercise capacity, maximal oxygen uptake and peak heart rate of patients were significantly lower than those of controls. No significant differences between TGA/IVS and TGA/VSD were found (Table 5).

Thirty-two (97%) patients exercised to maximal effort with a RQ exceeding 1.05. During the test no ischemic changes on ECG were detected. No patient developed arrhythmias or presented cardiac complaints.

Table 5. Exercise capacity of patients compared with references

	References	TGA all	P*	TGA/IVS	TGA/VSD	P**
Max. exercise capacity (watts)	120 ± 30 (70-180)	102 ± 33 (60-160)	0.02	97 ± 32 (60-160)	113 ± 35 (75-160)	0.2
Max. oxygen uptake (ml/min/kg)	48 ± 8 (29-60)	41 ± 8.3 (25-57)	< 0.01	42 ± 7.8 (28-57)	39 ± 9.6 (25-53)	0.3
Respiratory quotient	1.18 ± 0.08 (1.02-1.36)	1.20 ± 0.08 (1.05-1.43)	0.5	1.20 ± 0.09 (1.05-1.43)	1.18 ± 0.08 (1.05-1.32)	0.5
Peak heart rate (bpm)	186 ± 9 (165-209)	177 ± 12 (153-200)	<0.01	177 ± 11 (153-197)	176 ± 14 (153-200)	0.9

* TGA all vs. References
** TGA/IVS vs. TGA/VSD

TACQOL

31 Patients completed the TACQOL-child form (Table 6). Compared with same-aged peers from the general population, patients aged 8-15 years reported poorer HRQOL as to motor functioning and positive emotional functioning. Effects sizes on these domains were medium [74]. No further differences were found on other TACQOL scales. Overall, there are no significant differences between the mean scale scores of the TGA/IVS versus the TGA/VSD group.

Table 6. Mean scores, SD's and Cohen's D on the TACQOL child form for TGA patients and reference group for ages 8-15 years

	TACQOL child form				
	All				
	TGA		Reference		
Scales	M (n=31)	SD	M (n)	SD	Cohen's D
Pain and physical symptoms	24.6	5.3	24.3 (2327)	5.3	0.1
Motor functioning	27.6*	4.3	29.8 (2330)	3.2	0.7
Autonomy	30.0	3.5	NA	NA	NA
Cognitive functioning	27.4	4.6	28.0 (2330)	4.1	0.1
Social functioning	28.6	3.5	NA	NA	NA
Positive emotional functioning	11.9*	3.3	13.3 (2324)	2.7	0.5
Negative emotional functioning	11.7	4.5	11.6 (2324)	2.6	0.04

* Significant ($p < 0.05$) difference.
NA=Not available

DISCUSSION

Results of the present study

The results of this study on the mid-to long-term after an ASO for TGA, show that the occurrence of major events is relatively low. The overall re-intervention rate in our population was 6% and 88% of the patients was free of major events after 10 years. Compared to other studies these rates tend to the lower limits of those reported in literature [17, 64, 75].

Remarkably, in the cross-sectional prospective part of the study, exercise capacity was significantly reduced compared with a healthy reference population. This finding could not be explained by differences in left ventricular size, systolic performance or diastolic function, as assessed from LV inflow parameters. Right ventricular systolic performance was judged normal. The prolonged right ventricular deceleration time of the e-wave suggests some impairment of RV relaxation, but this seems an unlikely explanation for the diminished exercise capacity. Myocardial ischemia during exercise could not be demonstrated. Our results confirm earlier observations of dilatation of the aortic root, which was accompanied by mild aortic regurgitation in 45% of the patients, but the dilatation did not result in either severe regurgitation or LV dilatation. The occurrence or amount of AR could not be related to the presence of a VSD [76]. Limited obstruction of the RVOT or pulmonary artery was present in 56% of the patients during follow-up, requiring re-intervention in only 2 of 49 survivors (4%). Rhythm status was excellent.

Comparison to other studies

Although the ASO is generally considered the operation of choice for TGA and a highlight of congenital cardiac surgery, concerns have included long-term effects of coronary transfer, fate of pulmonary valve and root in the systemic circulation, effects of potential distortion of the distal pulmonary arteries, long-term function of both ventricles and exercise capacity [67, 77-79].

Although initial reports on ventricular function after ASO have been encouraging, relatively few studies have been done on longer term function [18, 65, 80, 81] and comparison with healthy controls has hardly been performed [18, 65]. Recently, Hui and co-workers compared LV function of 31 patients at a mean of 9.4 years after ASO and 20 healthy controls [18]. The patients had a significantly lower LV fractional shortening and ventricular circumferential fibre shortening. Factors associated with reduced LV performance were older age at operation, longer cardiopulmonary bypass time and longer circulatory arrest [18]. In our study no association with these factors could be demonstrated. Hui and co-workers used dobutamine stress-testing and detected wall motion abnormalities in 22 of 32 patients. All patients in who wall motion abnormalities were detected, had impaired ventricular performance at rest. All had normal coronaries

on angiography [18]. Taylor and co-workers, using MRI, reported myocardial viability defects in 2 of 16 asymptomatic patients at a mean of 10 years after ASO [82]. These defects could be related with known coronary artery problems in these patients. In both studies, global LV and RV function were normal with normal regional wall motion and suggest that ventricular function after ASO could be depressed, both by factors related to myocardial protection during ASO, as well as to the effects of coronary artery transfer [18, 82]. The same studies demonstrated that in the absence of wall motion abnormalities, depressed ventricular function is uncommon, as confirmed in our study [18, 81, 82]. A remarkable finding of our study is the signs of mild diastolic dysfunction of the right ventricle. A recent study on RV function in a smaller but otherwise similar patient group after ASO using MRI also found RV diastolic function dysfunction, which was related to RV hypertrophy [83]. The functional consequences of these findings are probably limited at mid-term follow-up. However, diastolic function decreases with age, diastolic dysfunction may precede systolic dysfunction and RV diastolic dysfunction has been related to functional impairment in other types of congenital heart disease [84].

Exercise function

Exercise testing after ASO has been reported by a few groups in recent years [18, 79]. Reybrouck and co-workers studied 15 children at 8.5 years after ASO. Chronotropic impairment was established in 14 of 15 patients. Ventilatory respiratory threshold and slope of maximal oxygen uptake (VO2-max) versus exercise intensity were significantly lower than normal [79]. This was attributed to residual hemodynamic lesions as present in the large majority of patients [85], despite normal echocardiographic assessment of LV function [79]. Mahle and co-workers studied 31 children at a mean of 11 years after ASO [85]. Maximal work and VO2-max were within normal range, although direct comparison with a reference population was not made. Chronotropic impairment was established. Normal exercise capacity was also established in a study of 56 patients at 11 years after ASO [85]. Considering the results of our study and recent literature, there is reason for concern about the exercise performance in patients after ASO for TGA, since normal exercise performance is not a universal finding. Exercise performance might be limited by the presence of residual lesions. However, in several studies, including our own, severe lesions had been treated accordingly. Minimal to moderate residual lesions do not seem to affect ventricular function measurements. Impaired coronary perfusion during exercise might be another explanation, but we did not observe ECG-changes during exercise, compatible with impaired perfusion. Mahle and co-workers observed ST-segment depression in 2 of 22 patients, but without impaired exercise performance or diminished VO2-max [85]. Myocardial perfusion defects had been documented by Norozi and Ohuchi [86, 87]. All patients with coronary perfusion defects had abnormal LV echocardiograms at rest [86, 87]. Clearly, chronotropic impairment due to impaired

cardiac parasympathetic innervation, as demonstrated in earlier studies, may contribute to reduced exercise performance [85, 86]. Recent observations of diminished activity levels in ASO patients may also point towards a reduced training state as an alternative explanation [19].

Aortic root and aortic regurgitation

Aortic root dilatation has been a consistent finding in ASO patients [77, 82, 88]. At a mean follow-up duration of 5 years, 21-50% of patients showed at least moderate root dilatation (Z score > 3) [88]. At least in the first 10 years after ASO, aortic root dilatation does not progress with time in most series [88]. From a clinical point of view, aortic root dilatation has been related to previous pulmonary artery banding [77, 88]. On a structural basis a vascular difference in transposition of the great arteries has been demonstrated [89]. The relationship between root dilatation and AR is less clear. At a relatively long period of follow-up, severe AR was absent in our study and LV dimensions were normal. Incidences of 19-60%, either mild or moderate AR, have been reported [66, 77, 88]. Relatively high percentages of severe AR (up to 7%) have only been reported in 2 of the larger studies [65, 77]. Risk factors for AR may be multi-factorial and include pre-operative and operative factors such as pulmonary artery banding before ASO, the presence of a VSD, tissue characteristics of the pulmonary valve, coronary reimplantation techniques and sub-aortic outflow surgery [66, 77]. In a recent study in a large patient sample, the presence of a VSD or AR at discharge after ASO were the only risk factors for late AR after ASO [76]. In our study, no differences were noted between the groups with TGA/IVS and TGA/VSD for aortic root size and amount of AR.

Health related Quality of Life

A recent meta-analysis [90] showed that patients with TGA have significantly poorer cognitive functioning compared to normative data. In agreement with our results, this could not be related to anatomic complexity in a recent study in a larger cohort [91]. Hövels-Gürich et al.[92] found that parents reported more behavioural impairment for patients long-term after ASO operation compared to controls, but that HRQOL, as reported by patients themselves, was generally not reduced and mainly dependent on somatic state and endurance capacity. Impairments in cognitive and motor functioning, and reduced exercise capacity were significantly related to the occurrence of psychiatric disorders [92] and may negatively influence health related quality of live.

In the present study patients showed poorer HRQOL compared to reference peers in the domains of motor functioning and positive emotional functioning. Our unfavourable results with regard to motor functioning may be associated with our findings indicating poorer exercise capacity [44]. This fits the recent observation of Moons et al. [93], who demonstrated in children with congenital heart disease that physical activities during a

sports camp positively influenced self-perceived health status, including physical functioning, and role-emotional functioning at three months follow-up [93].

Limitations of the study

This was an observational study on the mid- to long-term effects of ASO for TGA. As such it described a single-centre experience in a relatively limited number of patients. Causal relationships for observed abnormalities could not be assessed, as is common in clinical studies of this kind. Although 16 survivors of the eligible group did not participate in the prospective part of the study, analysis showed no statistically significant differences between the group of 49 potential eligible survivors and the subgroup of 33 patients.

Ventricular function was assessed with conventional echocardiographic techniques. Recently, tissue-Doppler imaging, particularly strain and strain rate imaging, has emerged as a potentially more sensitive technique to detect functional abnormalities. Technical limitations of available ultrasound systems prevented the assessment of tissue-Doppler data in this study. Time limitations prevented the use of MRI, the current 'gold-standard' for assessment of ventricular function, particularly of the right ventricle. Ideally, coronary artery stenosis could have been assessed with angiographic techniques. In our institution coronary angiography is only used in case of clear clinical signs of myocardial ischemia. These signs were absent in all patients.

Conclusion

At mid-to long-term follow-up after ASO, the occurrence of major events and re-intervention rate (6%) is low. Exercise capacity and maximal oxygen-uptake are lower than that in a reference population and could not be related to a diminished ventricular function. Aortic root dilatation is frequent, but does not result in either severe aortic regurgitation, or LV dilatation, irrespective of anatomical subgroup.

Outcomes on health-related quality of life were unfavourable as to motor functioning and positive emotional functioning.

ABBREVIATIONS

AR	aortic regurgitation
ARD	aortic root dilatation
AS	aortic stenosis
ASO	arterial switch operation
ECG	electrocardiogram
FS	fractional shortening
HRQOL	health related quality of life
IVS	intact ventricular septum
LV	left ventricle
LVOT	left ventricular outflow tract
MRI	magnetic resonance imaging
PS	pulmonary stenosis
RQ	respiratory quotient
RV	right ventricle
RVOT	right ventricular outflow tract
TACQOL	TNO-AZL child quality of life
TGA	transposition of the great arteries
VSD	ventricular septal defect

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Chapter 4

Enlarged right ventricular size at 11 years follow-up after closure of secundum type atrial septal defect in children

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ABSTRACT

Background

The fate of right ventricular dimensions after surgical closure of secundum type atrial septal defects remains unclear. Objectives of this study were to assess ventricular dimensions, exercise capability and arrhythmias of patients operated for secundum type atrial septal defect and compare the results with those in healthy references.

Methods

Seventy-eight consecutive patients underwent surgical closure for a secundum type atrial septal defect between 1990 and 1995. Forty-two patients were included and underwent a cross-sectional evaluation including echocardiography, magnetic resonance imaging, exercise testing, and 24-hours ambulatory electrocardiography. Patients were matched with healthy controls for gender, body surface area and age.

Results

Mean age at surgery was 4.6 ± 2.8 years, mean age at follow-up 16 ± 3 years. There were no residual intracardiac lesions. Mean right ventricular end-systolic volume was significantly larger in patients (142 ± 26 ml) than in references (137 ± 28ml) ($p = 0.04$). In 25% of the patients right ventricular end-systolic volume was larger than the 95th percentile for references. No relevant arrhythmias were detected. Exercise testing did not reveal differences with healthy references: maximal power (169 ± 43 Watt patients vs. 172 ± 53 controls)($p=0.8$), maximal oxygen uptake (38 ± 8 ml/min/kg vs. 41 ± 13)($p=0.1$).

Comment

After surgical closure of secundum type atrial septal defect, right ventricular end-systolic volume is increased. These findings have no impact on rhythm status or exercise capacity at this stage of follow-up, but may have implications for the timing of surgery or the technique of closure if confirmed in longer follow-up.

INTRODUCTION

The long-term prognosis of children who underwent surgery for a secundum type atrial septal defect, does not differ from the normal population with regard to mortality, morbidity and exercise tolerance.[1-5]

In some echocardiographic studies, however, right ventricular enlargement was found to persist long-term after closure.[1, 2, 5] In contrast, recent observations using optimal imaging techniques such as magnetic resonance imaging, point towards normalization of right-ventricular size.[6] These observations need further confirmation in direct comparison with references, as they may have implications for (timing of) treatment strategies.

Studies in the 1980's and 1990's have reported arrhythmias as a major concern for the long term.[1, 7-11] Relatively scarce information is available on the rhythm status of patients with secundum type atrial septal defect, operated on more recently.[6]

Information on the mid-term to long-term follow-up of patients operated on for secundum type atrial septal defect remains important for comparison with non-surgical closure results, and to evaluate the results of current surgical management.

The aim of our study was to assess mid-term prognosis of right ventricular dimensions, rhythm-status and exercise capacity in patients operated for a secundum type atrial septal defect.

We therefore performed a cross-sectional study in a homogenous group of patients with secundum type atrial septal defect. Results of magnetic resonance imaging and exercise-testing were compared with those of matched healthy reference groups.

MATERIALS AND METHODS

The study population consisted of all 30-day survivors after surgical closure of a secundum type atrial septal defect performed at Erasmus Medical Centre between 1990 and 1995. Patients were identified from the medical records of the Departments of Cardio-thoracic Surgery and Paediatric Cardiology. Patients were eligible for prospective analysis if they met the following inclusion criteria: secundum type of atrial septal defect without other cardiac malformations, residence in the Netherlands, Dutch speaking and no underlying syndrome with mental retardation. From the medical records pre-, per- and postoperative parameters were collected.

Seventy-eight consecutive patients, who had been operated upon for a secundum type atrial septal defect, were identified. Seven of them were completely lost to follow-up, as they had moved abroad postoperatively and 13 patients suffered from Down's syndrome. Sixteen of the 58 remaining survivors refused to participate in the cohort evaluation

because of practical reasons. Ultimately, 42 patients agreed to participate in the prospective cross-sectional part of the study. Between 2005 and 2006 all patients visited the outpatients' clinic for medical history, physical examination, echocardiography, exercise testing, standard 12-lead electrocardiography, 24-hours ambulatory electrocardiography and magnetic resonance imaging. The study was approved by the national Medical Ethical Review Board in the Netherlands. Written informed consent was obtained from all patients, references as well as their parents.

Reference group

A reference group of healthy schoolchildren and adolescents matched with the patients for gender and body surface area was selected to undergo magnetic resonance imaging. Another reference group of healthy schoolchildren and adolescents matched for gender, age and height, was selected to undergo a bicycle exercise test. Different groups were used after consultation with the institutional review board, in order to minimize the burden of participation for healthy subjects. Children or adolescents involved in organised extracurricular sports activities for more than six hours a week were excluded. This was done since the normal physical activity level in the relevant population is mainly determined by travel related physical activity (a high percentage of children or adolescents in the relevant age group cycle to school or work), school related physical education and organised sports activity. Hours spent during extracurricular organised sports activity hardly ever exceed 6 hours. [12]

Clinical evaluation

Standard Electrocardiogram

Standard twelve-lead electrocardiograms were performed on a Cardio Perfect 4.0 machine (CardioControl, Northampton, England). Electrocardiograms were interpreted by a single observer (WBdK). We compared results according to criteria described by Rijnbeek et al.[13]

Twenty-four hours ambulatory electrocardiogram

A three-channel recorder (Philips, Andover, USA) was used on a day with usual activities. Arrhythmias were judged according to Garson's criteria.[14]

Echocardiography

Conventional echocardiography was carried out, consisting of transthoracic M-mode and two-dimensional echocardiography, as well as pulsed-wave and continuous-wave Doppler measurements, using an ultrasound Philips Sonos 5500 (Philips Medical Systems, Best, the Netherlands). A fractional shortening of > 28% was regarded as normal.

Pulmonary arterial hypertension was diagnosed if a tricuspid regurgitation with a maximal flow of 2.8 m/s was detected. Measurements by Schnittger were used for reference values.[15]

Magnetic Resonance Imaging

MRI-imaging was performed on a GE 1.5-T Signa CV/I scanner (GE healthcare, Milwaukee, Wisconsin, USA) using dedicated phased-array coils. All images were acquired during breath-holds at end-expiration. A multi-phase, multi-slice volumetric data-set was acquired using a fast two dimensional cine scan employing steady-state free precession. Imaging parameters were as previously reported.[16]

Flow measurements were performed perpendicular to flow using a standard two dimensional flow-sensitized scan. Scans were retrospectively gated starting the acquisitions on the R-wave. Temporal resolution was approximately 40 ms per cardiac phase and 24 phases were reconstructed retrospectively. Imaging parameters were as previously reported.[16, 17] Ventricular size was normalized to body surface area as previously reported [18]

Maximal exercise capacity

A maximal exercise bicycle-test was performed using a stepwise incremental protocol on a Jaëger Oxycom Champion System (Viasys Healthcare GmbH, Hoechberg, Germany) that allowed breath-by-breath-ergometry. Workload was increased every minute by 10, 15 or 20 Watts according to the Godfrey protocol.[19] The respiratory quotient was used to objectify maximal performance. Exercise performance was regarded as maximal when subjective exhaustion combined with a respiratory quotient ≥ 1.10 at peak exercise was reached. The following parameters were obtained: maximal achieved workload (Watt), maximal oxygen uptake (VO2-max) (ml/kg/min), peak heart rate (beats/min) and respiratory quotient. Results were compared with values from the references.

Statistical methods

Continuous data was presented as mean with standard deviation and ranges. Student's t-tests were used to compare the two groups. Chi-square test and, if appropriate, Fisher's exact test was used for the comparison of categorical variables. In all analyses the 2-sided level of significance was set at $p < 0.05$.

Associations between clinically relevant parameters and MRI (ventricular dimensions and function) or exercise test results were assessed by paired samples T-test.

Shapiro-Wilk test was used to test for normality.

SPSS V17 was used as statistical package.

RESULTS

Baseline characteristics from the chart-review showed differences between the group of 58 survivors and the group of 42 patients on duration of follow-up (10.9 ± 3.6 vs. 16.5 ± 3.3, p=0.02 and age at last follow-up (6.1 ± 2.3 vs. 11.8 ± 1.8, p=0.02). This can be explained by the fact that some of the survivors were dismissed from continued surveillance at short term after surgery. Data of the 42 patients that were included in the prospective cross-sectional study are given in table 1.

Data were sufficiently distributed for parametric testing.

Table 1. Baseline characteristics*

	ASD-II patients
Number	42
Gender, Male (%)	36
Female (%)	64
Age at surgery (years)	4.6 ± 2.8
Weigth at surgery (kg)	17 ± 7
Age at follow-up (years)	16 ± 3
Follow-up duration (years)	12 ± 2
Weight at follow-up (kg)	60 ± 17
Height at follow-up (cm)	169 ± 10
Rhythm, sinus rhythm (%)	95
nodal (%)	5
Cardiac medication (%)	0

* Data are given as mean ± standard deviation

Operation

The operative procedure included median sternotomy and complete cardiopulmonary bypass. The defects were closed by direct suturing in 40 and in 2 by a pericardial patch. In one patient lateral thoracotomy was performed on cosmetic grounds. Mean perfusion time was 39 ± 20 (21-188) min; aortic cross-clamp time 15 ± 8 (6-35) min. and lowest nasal temperature 31 ± 3 (17-33)°C. Between 1990 and 1995, 78 patients have been operated on for secundum type atrial septal defect. No peri operative deaths were recorded. One patient required mediastinal re-exploration because of post-operative haemorrhage. During follow-up no late re-interventions were needed and none of the patients died.

Standard 12-lead electrocardiogram

Forty patients (95%) were in sinus rhythm. Two patients (5%) showed junctional rhythm. Another patient had a complete right bundle branch block and one other patient had a

first degree atrio-ventricular block, blocks that have not been recorded pre-operatively. No ventricular hypertrophy was detected electrocardiographically.

Ambulatory 24-hour electrocardiogram

Thirty-eight patients (90%) were examined. In four of them assessment did not succeed because of technical problems with the recorder. No cardiac symptoms were reported during the registration. Twenty patients (48%) were in continuous sinus rhythm and one patient in a continuous junctional rhythm. The others (50%) showed sinus rhythm with short periods of non-sinus, atrial rhythm. No signs of atrial arrhythmias (fibrillation, flutter, ectopic, tachycardia) were noted. In four patients (10%) a first degree atrio-ventricular block was seen continuously on the recordings, in spite of the absence of this block at 12-lead electrocardiogram in three of them.

Echocardiography

None of the 42 patients had a residual atrial septal defect. Echocardiographically, dimensions of both ventricles were within normal limits (Table 2).[15] Fractional shortening of the left ventricle in all but one patient was normal. Semi-quantitative assessment of the right heart did not reveal dilatation of the right ventricle. Trivial tricuspid regurgitation was observed in 6 patients, mean peak flow was 2.2 ± 0.3 (1.8-2.5) m/s. One patient showed trivial mitral regurgitation. Nine patients displayed trivial pulmonary regurgitation; mean peak flow was 1.5 ± 0.4 (0.8-2.2) m/s. Thirty-two patients showed normal ventricular septal motion, in 10 patients decreased motion of the septum was detected and no patients displayed a paradoxical pattern of the septum. No hemodynamically significant abnormalities were identified. Mean mitral and tricuspid E/A ratios, parameters for diastolic ventricular function, were 2.32 and 1.85 respectively (Table 2) and similar to the reference group.

Table 2. Echocardiographic results *

			ASD-II patients
Number			42
M-mode	Left ventricular diameter ED	cm	4.6 ± 0.5
	Left ventricular diameter ES	cm	3.0 ± 4
	Fractional shortening	%	36 ± 4
	Interventricular septal diameter ED	mm	7.5 ± 1.9
	Left ventricular posterior wall diameter ED	mm	6.6 ± 1.4
	Left ventricular mass	g/m^2	54 ± 17
2D echo	Left ventricular area	cm^2	26 ± 6
	Right ventricular area	cm^2	19 ± 6
	Length left ventricle ED	cm	6.9 ± 0.8
	Length left ventricle ES	cm	5.9 ± 0.9
	Length right ventricle ED	cm	6.4 ± 0.9
	Length right ventricle ES	cm	5.4 ± 0.8
Doppler	Flow aorta	m/sec	1.27 ± 0.19
	Flow pulmonary artery	m/sec	1.15 ± 0.26
	Flow right pulmonary artery	m/sec	1.03 ± 0.32
	Flow left pulmonary artery	m/sec	0.95 ± 0.23
	Mitral valve early filling peak velocity	m/sec	1.10 ± 0.24
	Mitral valve atrial filling peak velocity	m/sec	0.49 ± 0.16
	Mitral valve early / atrial filling velocity ratio		2.32 ± 0.77
	Mitral valve deceleration time	sec	0.17 ± 0.04
	Tricuspid valve early filling peak velocity	m/sec	0.77 ± 0.17
	Tricuspid valve atrial filling peak velocity	m/sec	0.45 ± 0.13
	Tricuspid valve early / atrial filling velocity ratio		1.85 ± 0.68
	Tricuspid valve inflow deceleration time	sec	0.16 ± 0.05

* Data are given as mean ± standard deviation

Abbreviations :

ED= end diastolic

ES= end systolic

MRI

In 32 of the 42 patients magnetic resonance imaging performed. Of ten patients, four of them refused to undergo the examination and six of them did not complete the examination because of claustrophobia. Results of magnetic resonance imaging are given in table 3. Mean right ventricular end-systolic volume was significantly larger in patients. In 25% of patients the right ventricular end-systolic volume was larger than the 95^{th} percentile. Left ventricular dimensions in patients did not differ from those in references.

Table 3. Magnetic resonance imaging dimensions and flows
Mean ± S.D.

		ASD-II patients	references*	p-value
Number		**32**	**32**	
Age	years	16.7 ± 2.9	16.3 ± 3.7	0.6
Body surface area	m^2	1.69 ± 0.26	1.68 ± 0.25	0.8
Right ventricular ED volume	ml	142 ± 26	137 ± 28	
Right ventricular ED volume **	ml/m^2	84 ± 15	82 ± 17	0.5
Right ventricular ES volume	ml	62 ± 19	53 ± 14	
Right ventricular ES volume **	ml/m^2	37 ± 11	32 ± 8	0.04
Right ventricular stroke volume	ml	79 ± 15	84 ± 19	
Right ventricular stroke volume**	ml/m^2	47 ± 9	50 ± 11	0.3
Right ventricular ejection fraction	%	56 ± 8	61 ± 6	0.08
Left ventricular ED volume	ml	131 ± 25	131 ± 25	
Left ventricular ED volume **	ml/m^2	78 ± 14	78 ± 15	0.9
Left ventricular ES volume	ml	48 ± 12	46 ± 13	
Left ventricular ES volume **	ml/m^2	28 ± 6	27 ± 8	0.5
Left ventricular stroke volume	ml	84 ± 16	86 ± 19	
Left ventricular stroke volume**	ml/m^2	50 ± 9	51 ± 11	0.7
Left ventricular ejection fraction	%	63 ± 6	65 ± 7	0.1

* Gender and BSA matched
** Indexed to BSA
Abbreviations:
ED= end diastolic
ES= end systolic

The stroke volumes of the left and right ventricle (83 ± 16 ml. versus 80 ± 15 ml.; p=0.5) were similar in patients and references; stroke volumes across the pulmonary and aortic valves (86 ± 19 ml. versus 89 ± 21 ml. ; p=0.2) were similar as well.

No association between ventricular dimensions and function were found (all p-values > 0.4). Also no association with age or weight at surgery could be established (p= 0.7 respectively p=0.8)

Exercise testing

Maximal exercise capacity was assessed in 38 patients. Four patients failed to perform to exhaustion. Mean exercise capacity was 169 ± 43 (80-300) Watt, mean maximal oxygen uptake was 38 ± 8.2 (20-55) ml/min/kg and mean maximal heart rate was 162 ± 17 (155-209) beats per minute. All three scores were slightly less than those in references (Table 4), but there were no significant differences (p-values respectively 0.8, 0.1 and 0.4). No correlation between exercise capacity and age at surgery or follow-up duration could be demonstrated.

Table 4. Exercise testing*

	ASD-II patients	references **	p
Number			
Exercise capacity (Watts)	169 ± 44 (80-300)	172 ± 53 (105-300)	0.8
Peak oxygen uptake (ml/min/kg)	38 ± 7.7 (20-55)	41 ± 13 (23-60)	0.1
Peak heart rate (bpm)	183 ± 14 (128-209)	184 ± 13 (151-208)	0.4

* Data are given as mean ± standard deviation (range)
** Gender and age matched

COMMENT

This study is the first to provide direct comparison of cardiac dimensions between young patients with secundum type atrial septal defect and a matched reference group, using the current technique of choice for assessment for right ventricular dimensions, cardiac magnetic resonance imaging. We found that, compared with a healthy reference population, right ventricular end-systolic volume was significantly increased after a mean follow-up duration of 12 years. Other cardiac dimensions and biventricular ejection fraction were similar to those in the reference group. Exercise tolerance was normal, as expected. None of the patients demonstrated symptomatic arrhythmias. No residual atrial septal defects or other relevant sequelae were detected and none of the patients used cardiac medication. No major cardiac events during follow-up could be demonstrated. Quality of life, reported on earlier in this population, was good.[20] These data provide further evidence of excellent mid-term to long-term outcome of surgical closure of secundum type atrial septal defect. This provides a basis for comparison with non-surgical closure follow-up data.[21]

A remarkable observation from our study is the enlargement of the right ventricle in a young population with secundum type atrial septal defect. Compared to the healthy reference population the right ventricle was enlarged in 25% of the patients.[18] In patients operated on at older age, right ventricular dilatation has been a relatively consistent finding at echocardiography. Few data exists on the myocardial basis of right ventricular remodelling after prolonged right ventricular volume overload. Factors influencing persisting right ventricular dilatation after closure of a secundum type atrial septal defect may be related to duration of volume overload (age at operation) and closure technique. We did not establish a relation between age at operation and right ventricular dilatation. Earlier studies reporting on surgical closure of secundum type atrial septal defects in children, showed residual right ventricular dilatation 5 years after closure.[5] More recent studies in children suggest normalization of right ventricular size, as assessed with magnetic resonance imaging at 20 years follow-up.[6] However, in that study by Bolz and co-workers, in children operated at a mean age of 7 years, magnetic resonance imaging

volumes were compared to reported normal values, that may have included data acquired with different magnetic resonance imaging sequences.[22] After device closure, rapid normalization of right ventricular size has been reported using echocardiographic assessment of right ventricular size.[23] In children, too few data are available to demonstrate a relationship between age and right ventricular dimensional changes after device closure.[24, 25] In adults results of studies on this relationship have been equivocal. The rate of remodelling may be influenced by the technique of closure, which points towards the potential effects of myocardial protection and interventional technique during closure.[26]

The observed dilatation of the right ventricle in our study raises several questions: First, what is the functional significance of this observation and second, should this observation lead to a reconsideration of the age of elective closure of secundum type atrial septal defect?

The functional significance of the dilated right ventricle seems limited. Global systolic performance of the right ventricle and left ventricle was maintained, as was the biventricular diastolic function. Exercise capacity of the patients was normal, none of the patients used cardiac medication and arrhythmias were all asymptomatic. This is in accordance with studies in patients operated on at older ages and with longer follow-up, in whom the effects of dilatation of the right ventricle, as assessed echocardiographically, seemed limited. The clinical relevance of the observed increase in the number of patients with right ventricular dilatation over time in some studies, remains to be established.[2] On the other hand, significant right ventricular dilatation resulting from prolonged volume overload has been suggested to have a negative effect not only on right ventricular function but also on left ventricular function.[27] This may be a reason for measures in order to prevent right ventricular dilatation. Currently, elective surgical closure of moderate to large size secundum type atrial septal defect, is usually performed between 4 and 6 years of age and it can be speculated that earlier closure of secundum type atrial septal defect might prevent long-term right ventricular dilatation.[28] Although the results of cardiac surgery at young age in general are excellent, the main argument to delay surgery is spontaneous closure or reduction of size below levels with hemodynamic relevance. In defects smaller than 6 mm, closure rates up to two-third of the patients have been reported.[28] The natural history of larger defects has been less well assessed. McMahon and co-workers studied the change in maximal diameter retrospectively, in the group with moderate size secundum type atrial septal defect. They found that 10% of this group showed a significant reduction in size (to below 6 mm) during a 3 year follow-up. In the group with a secundum type atrial septal defect larger than 12 mm, no spontaneous reduction in size occurred.[28] Based on these data, it could be argued that for a secundum type atrial septal defect with important shunt size, judged not to be candidates for device closure, delaying surgery to 3 – 6 years of age does not have any advantages, and may

contribute to long-term right ventricular dilatation. However, based on the reports of rapid reduction of right ventricular size after device closure and the potential avoidance of cardiopulmonary bypass, candidates for device closure should be carefully selected.

Arrhythmias, particularly of supraventricular origin, have been a major concern in the late follow-up after surgical closure of atrial septal defects.[1, 7, 9, 22, 29] With the improvements of surgical techniques, these problems have been reduced considerably.[9] In a recent series of patients operated on at older age Roos-Hesselink and co-workers reported 6% of symptomatic supraventricular tachyarrhythmias at a mean follow-up of 26 years.[2] Few reports of arrhythmias after operation in young children have been published recently.[6] Our results confirm the general impression that arrhythmias have become rare after early surgical closure of secundum type atrial septal defect. We did not note any signs of clinically relevant arrhythmias. The same is true for pulmonary hypertension, of which we found no evidence in this study. This was in contrast to earlier studies that found percentages of 13% and 28% pulmonary arterial hypertension.[3, 30]

Limitations

Major limitation of this study is the relatively small number of patients, limiting statistical power. However, this is one of the largest homogeneous groups of ASD-II patients. The lack of detached evaluation of regional ventricular function e.g. using tissue Doppler techniques may be considered a limitation.

In the reference population, children or adolescents involved in organised extracurricular sports activities for more than six hours a week were excluded. This was done to exclude a very small number of extremely physically active children. If these children would not have been excluded, the exercise performance data provided as reference might have been skewed towards somewhat higher values than currently reported.

The use of separate reference groups for MRI and exercise testing for ethical reasons could be considered a limitation. However, since these groups were randomly selected from the same larger general normal population, we consider this to be a minor limitation.

Conclusion

This study confirms the generally excellent condition of young patients at mid-term after surgical closure of a secundum type atrial septal defect. However, with magnetic resonance imaging, the current 'gold standard' technique for assessment of right ventricular size, an enlargement of right ventricular end-systolic volume was noted. These findings have no clinically relevant influence on rhythm status or exercise capacity at this stage of follow-up, but may have implications for the timing of surgery or the technique of closure. Longer follow-up is required to reveal the functional consequences of the findings.

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Chapter 5

Exercise capacity and ventricular function in patients treated for isolated pulmonary valve stenosis or tetralogy of Fallot

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ABSTRACT

Background

We hypothesized 1.) that long-term ventricular outcome and exercise capacity would be better in patients with isolated pulmonary valve stenosis (PS) treated with balloon pulmonary valvuloplasty (BPV) than in patients operated for tetralogy of Fallot (TOF), and 2.) that ventricular outcome and exercise capacity would not be different in PS patients and healthy controls.

Methods

We included 21 PS patients after BPV (16.2 ± 5.2 yrs) and 21 patients operated for TOF (16.6 ± 5.6 yrs), matching them for gender, age at treatment, and age at study. Patients underwent cardiovascular magnetic resonance (CMR) imaging, exercise testing, 12-lead ECG and 24-hour Holter monitoring for assessment of right ventricular (RV) size and function, pulmonary regurgitation (PR), exercise capacity and electrocardiographic status. Healthy controls for CMR imaging and exercise testing were matched for gender and age at study.

Results

RV volumes and PR percentage were significantly larger in TOF patients than in PS patients; biventricular ejection fraction (EF) was not different. PR was mild in most PS patients. RV end-systolic volume was significantly larger in PS patients than in healthy controls; RVEF was significantly lower. Both patient groups had similar exercise test results. Peak workload and VO_2 max. were significantly lower in PS patients than in healthy controls.

Conclusions

Longstanding mild PR in PS patients can lead to an enlarged RV, reduced RV function and reduced exercise capacity. Despite more PR and larger RV volumes in TOF patients, exercise capacity and biventricular function are similar in both patient groups.

INTRODUCTION

Residual pulmonary regurgitation (PR) often occurs after treatment for congenital heart disease (CHD), particularly after repair of tetralogy of Fallot (TOF)[1-4] and isolated pulmonary valve stenosis (PS)[5-8]. The effects of severe PR on right ventricular (RV) function and clinical outcome include RV dilatation, decreased right and left ventricular (LV) function, reduction of exercise capacity, arrhythmias, and increased risk of sudden cardiac death[1-3,9-10]. A pulmonary valve replacement (PVR) is often considered in patients treated for TOF, but the best time for performing a PVR is still uncertain, especially in patients with asymptomatic PR [11-15].

Before corrective treatment, the RV is subjected to pressure overload in both types of CHD. In TOF patients, this is combined with hypoxemia caused by a right-to-left shunt at the ventricular level (ventricular septal defect (VSD)). Treatment options also differ significantly: TOF patients undergo a surgical repair in early childhood, whereas patients with isolated PS are now treated with percutaneous balloon pulmonary valvuloplasty (BPV)[16]. These factors may add to differences in long-term outcome with respect to RV function and clinical status.

Long-term outcome in patients after treatment for isolated PS has been studied less extensively than in patients after repair of TOF and most reports in PS patients focus primarily on results of residual pulmonary valve (PV) peak gradients. Results at long-term follow-up are excellent in the majority of the patients, although mild PR is often reported. While most studies have used echocardiography in their evaluation of long-term outcome in patients treated for isolated PS [5-8], very few have used the current gold standard technique for assessing RV size and function, i.e. cardiovascular magnetic resonance (CMR) imaging [17].

This study was therefore based on two hypotheses: 1) We hypothesized that long-term ventricular function, exercise capacity and clinical status would be better in patients treated for isolated PS than in patients treated for TOF. 2) We hypothesized that ventricular function, exercise capacity and clinical status in PS patients would not differ from those in healthy controls.

To test these hypotheses, we compared the long-term outcome in PS patients after BPV with those in a matched group of TOF patients and in a matched group of healthy controls.

METHODS

Patients

The study population of the PS patients consisted of patients who underwent balloon pulmonary valvuloplasty for isolated pulmonary valve stenosis at the Erasmus Medical Center between 1990 and 1995. Thirty patients could be identified from the medical records of the Departments of Pediatric Cardiology and Cardiothoracic Surgery; 21 agreed to participate in the current study. They underwent CMR imaging, exercise testing, echocardiography, 12-lead electrocardiography (ECG), and 24-hour Holter monitoring. These PS patients were compared to patients after repair of tetralogy of Fallot. Patients with TOF undergo the aforementioned tests as part of routine clinical care in our centre. TOF patients were randomly selected from the clinical database and were matched to the PS patients for gender, age at treatment, and age at study. Medical records were reviewed for patient characteristics.

Healthy controls, which were matched for gender and age at study, were randomly selected from our databases of healthy volunteers, who had participated in a study to obtain normal values of biventricular function with CMR imaging or in a study to obtain normal values of exercise capacity. Since not all healthy controls had undergone both tests, 2 separate control groups were composed: one for results of CMR imaging and the other for results of exercise testing.

The research study was approved by the local Ethical Committee; all patients, and if required, their parents, gave informed consent.

Echocardiography

Conventional echocardiography was carried out, consisting of transthoracic M-mode and two-dimensional echocardiography, as well as pulsed-wave and continuous-wave Doppler measurements, using an ultrasound Philips Sonos 5500 (Philips Medical Systems, Best, the Netherlands). The maximum peak gradient across the PV was determined using Doppler measurements and calculated using the modified Bernoulli equation ($\Delta P = 4*(Vmax.^2)$). PR was semi quantitatively classified as none, mild, moderate or severe, according to the length, the width and the localization of the regurgitant flow[18].

CMR image acquisition

CMR imaging was performed using a 1.5 Tesla system (General Electric, Milwaukee, WI, USA) and an 8-channel phased-array cardiac surface coil. Standard localizer imaging planes were acquired to plan a short axis set and flow measurements of the pulmonary valve. The short axis set, using steady-state free precession cine imaging, was acquired from base to apex. Typical imaging parameters were: repetition time 3.5 msec., echo time 1.5 msec., flip angle 45°, slice thickness 8 – 9 mm., inter-slice gap 0 – 1 mm., field

of view 320 × 240 mm., and matrix 160 × 128 mm. Flow measurements were performed perpendicular to flow. Typical imaging parameters were: repetition time 4.8 msec., echo time 2.6 msec., flip angle 18°, slice thickness 7 mm., inter-slice gap 0 mm., field of view 290 × 220 mm, and matrix 256 × 128 mm. Velocity encoding was set at 150 cm/sec. and was increased whenever phase aliasing occurred. All images were obtained during breath-hold in end-expiration.

CMR analysis

Analysis was performed on a commercially available Advanced Windows workstation (General Electric Medical Systems), equipped with the software packages QMASS (version 5.2) and QFLOW (version 3.2) (Medis Medical Imaging Systems, Leiden, the Netherlands).

The ventricular volumetric data set was quantitatively analyzed using manual outlining of endocardial and epicardial borders in end-systole and end-diastole. Papillary muscles and trabeculations were included in the ventricular cavity. The interventricular septum was included in the left ventricular mass. Ventricular mass was calculated as the difference between the epicardial and endocardial contours multiplied by the slice thickness and a specific gravity of the myocardium of 1.05 g/ml [19].

The following parameters were calculated: biventricular end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF) and mass. Pulmonary regurgitation (in milliliters) was normalized for systolic SV in the main pulmonary artery and was expressed as a percentage. Additionally, RV effective stroke volume (eff. SV) was calculated to correct for PR: RVeff.SV = RVSV − PR volume. Results were indexed for body surface area (BSA). To minimize observer variability, all data sets were analyzed by the same observer (SEL).

Exercise test

Patients performed a maximal bicycle exercise test on a Jaëger Oxycom Champion System (Viasys Healthcare, Hoechberg, Germany). Workload was increased by 15 – 20 Watts per minute. Patients were encouraged to perform until exhaustion. Tests were regarded as maximal when the respiratory quotient (RQ) at peak exercise was ≥ 1.05. The following parameters were recorded: peak heart rate, peak workload, peak oxygen uptake (VO_2 max.), anaerobic threshold (AT), and the ventilatory response to carbon dioxide production (VE/VCO_2). The AT was determined using the V-slope method[20]. The VE/VCO_2 slope was obtained by linear regression analysis of the data acquired throughout the entire period of exercise.

Electrocardiography

A standardised 12-lead ECG was obtained to determine rhythm status, QRS duration and QT interval corrected for heart rate. A 24-hour Holter monitoring was performed in patients on a day with usual activities.

Statistical analysis

Data are expressed as mean (± standard deviation), as median (range) or as counts (percentages). Differences in continuous data between groups of patients were evaluated using the Student t-test, paired t-test or with nonparametric tests. Differences in categorical data between groups of patients were evaluated with the chi-square or Fisher exact test.

Analysis was performed using the SPSS statistical software package version 15.0 (SPSS, Inc., Chicago, Ill, USA). A p-value < 0.05 was considered to indicate statistical significance.

RESULTS

The patient characteristics are displayed in table 1. There were no significant differences in height, weight, and BSA between the 2 patient groups, who were matched for gender, age at treatment and age at study. NYHA class was not significantly different between the PS and TOF patients.

In 7 TOF patients, a palliative shunt had been placed before corrective surgery (33%); 14 TOF patients had corrective surgery with the use of a transannular patch (70%). In 4 patients with TOF, additional surgery had been performed after the initial surgery and before participation in the study. This included closure of a residual VSD in 3 patients and additional relief of pulmonary stenosis in all 4. Three patients with isolated PS had undergone a re-intervention after BPV and before participation in the study. One PS patient first underwent a repeat BPV, but eventually a surgical relief of the repeat pulmonary stenosis was needed twice. One other PS patient underwent closure of a persistent ductus arteriosus; another had surgical repair of moderate tricuspid regurgitation.

The pulmonary valve peak gradient before treatment was significantly higher in PS patients than in TOF patients (83 ± 21 mmHg (PS patients) vs. 63 ± 20 mmHg (TOF patients), $p = 0.004$) (table 1). The PV peak gradient significantly decreased immediately after treatment in both patient groups, and decreased even further at long-term follow-up in PS patients. The PV peak gradient immediately after treatment was not significantly different between PS patients and TOF patients. Even so, the PV peak gradient at long-term follow-up was not significantly different between the patient groups.

Table 1. Characteristics of the study population and results of echocardiography

Characteristic	PS patients (N = 21)	TOF patients (N = 21)
Male	9 (43%)	9 (43%)
Height (cm)	165 (± 13)	159 (± 13)
Weight (kg)	58 (± 20)	53 (± 14)
BSA (mm^2)	1.62 (± 0.33)	1.53 (0.25)
NYHA Class		
- Class I	20 (95%)	16 (76%)
- Class II	1 (5%)	5 (24%)
Age at treatment (yrs)	3.6 (± 4.2)	3.0 (± 3.2)
Age at study (yrs)	16.2 (± 5.2)	16.6 (± 5.6)
Interval between treatment and study (yrs)	12.6 (± 2.1)	13.7 (± 3.1)
Echocardiography		
PV peak gradient before treatment (mmHg)	83 (± 21)*	63 (± 20)
PV peak gradient immediately after treatment (mmHg)	26 (± 10)†	26 (± 15)†
PV peak gradient at long-term follow-up (mmHg)	15 (± 11)‡	20 (± 9)

Reported data are expressed as mean (SD) or as counts (percentages).
* Significant difference between PS patients and TOF patients.
† Significant difference between results before treatment and immediately after treatment.
‡ Significant difference between results immediately after treatment and at long-term follow-up.
Abbreviations: PS = pulmonary stenosis; TOF = tetralogy of Fallot;
BSA = body surface area; NYHA = New York Heart Association;
PV = pulmonary valve.

At long-term follow-up, 20 PS patients (95%) and all TOF patients had pulmonary regurgitation; this was predominantly classified as mild or moderate in PS patients, and as moderate or severe in TOF patients.

CMR imaging

PR percentage was significantly higher in TOF patients than in PS patients (PR: 30 ± 13% (TOF patients) vs. 10 ± 10% (PS patients), $p < 0.001$) (table 2). Right ventricular volumes (EDV, ESV, SV) and mass were also significantly larger in TOF patients than in PS patients (RVEDV: 131 ± 29 ml/m^2 (TOF patients) vs. 101 ± 20 ml/m^2 (PS patients), $p = 0.001$; RVESV: 66 ± 20 ml/m^2 (TOF patients) vs. 51 ± 15 ml/m^2 (PS patients), $p = 0.009$). RV effective SV, biventricular EF and LV volumes and mass were not significantly different between the 2 patient groups.

Table 2. Results of CMR imaging

Parameter	PS patients (N = 19)	TOF patients (N = 21)	Healthy controls (N = 21)
Age (yrs)	16.2 (± 5.2)	16.6 (± 5.6)	16.5 (± 5.0)
BSA (m^2)	1.62 (± 0.33)	1.53 (0.25)	1.62 (± 0.23)
PR (%)	10 (± 10)*	30 (± 13)	N/A
Right Ventricle			
EDV (ml/m^2)	101 (± 20)*	131 (± 29)	90 (± 18)
ESV (ml/m^2)	51 (± 15)*†	66 (± 20)	41 (± 9)
SV (ml/m^2)	50 (± 7)*	65 (± 12)	49 (± 11)
eff.SV (ml/m^2)	45 (± 6)	45 (± 6)	49 (± 10)
EF (%)	50 (± 6)†	50 (± 6)	54 (± 3)
Mass (gr/m^2)	17 (± 4)*	22 (± 5)	17 (± 3)
Left ventricle			
EDV (ml/m^2)	81 (± 11)	85 (± 14)	85 (± 14)
ESV (ml/m^2)	36 (± 7)	38 (± 10)	36 (± 6)
SV (ml/m^2)	45 (± 6)	47 (± 7)	49 (± 11)
EF (%)	55 (± 4)	55 (± 5)	57 (± 5)
Mass (gr/m^2)	53 (± 11)	52 (± 10)	50 (± 11)

Reported data are expressed as mean (SD).
* Significant difference between PS patients and TOF patients.
† Significant difference between PS patients and healthy controls.
Abbreviations:
CMR = cardiovascular magnetic resonance; PR = pulmonary regurgitation;
EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; eff.SV = effective stroke volume; EF = ejection fraction; N/A = not applicable. Other abbreviations as in table 1.

RVESV was significantly larger in PS patients than in healthy controls, and RVEF was significantly lower (RVESV: 51 ± 15 ml/m^2 (PS patients) vs. 41 ± 9 ml/m^2 (healthy controls), p = 0.02; RVEF: 50 ± 6% (PS patients) vs. 54 ± 3% (healthy controls), p = 0.02). RVEDV was larger in PS patients than in healthy controls, but this was not statistically significant (RVEDV: 101 ± 20 ml/m^2 (PS patients) vs. 90 ± 18 ml/m^2 (healthy controls), p = 0.09). All other parameters were not significantly different between PS patients and healthy controls.

Exercise test

The exercise test results are given in table 3. None of the parameters was significantly different between PS patients and TOF patients. Peak heart rate, peak workload, VO_2 max., and the AT were significantly lower in PS patients than in healthy controls (VO_2 max.: 36 ± 10 ml/kg/min. (PS patients) vs. 44 ± 7 ml/kg/min. (healthy controls), p = 0.004). The VE/VCO_2 slope was not significantly different between PS patients and healthy controls.

Table 3. Results of exercise testing

Parameter	PS patients (N = 19)	TOF patients (N = 19)	Healthy controls (N = 21)
Age (yrs)	16.2 (± 5.2)	16.6 (± 5.6)	16.2 (± 4.1)
Height (cm)	165 (± 13)	159 (± 13)	166 (± 15)
Peak heart rate (/min)	176 (± 15)*	181 (± 12)	185 (± 8)
Peak workload (Watt)	142 (± 40)*	138 (± 34)	186 (± 44)
	(N = 19)	**(N = 15)**	**(N = 21)**
RQ at peak exercise	1.17 (± 0.07)	1.15 (± 0.06)	1.17 (± 0.07)
VO_2 max. (ml/kg/min)	36 (± 10)*	38 (± 7)	44 (± 7)
AT (ml/kg/min)	26 (± 8)*	27 (± 6)	32 (± 6)
VE/VCO_2 slope	29 (± 5)	30 (± 5)	28 (± 5)

Reported data are expressed as mean (SD)
* Significant difference between PS patients and healthy controls.
Abbreviations:
RQ = respiratory quotient; VO_2 max. = peak oxygen uptake; AT = anaerobic threshold; VE/VCO_2 slope = ventilatory response to carbon dioxide production. Other abbreviations as in table 1.

Electrocardiography

12-lead ECG data were available for all patients. All patients were in sinus rhythm. The QRS duration was significantly longer in TOF patients than in PS patients (127 ± 23 msec. (TOF patients) vs. 95 ± 20 msec. (PS patients), $p < 0.001$). A complete right-bundle branch block (RBBB) was significantly more present in TOF patients than in PS patients (a complete RBBB in 15 TOF patients (71%) vs. 1 PS patient (5%), $p < 0{,}001$). The heart rate, PQ time, and QT time corrected for heart rate were not significantly different.

Results of 24-hour Holter recordings were available for all PS patients and 11 TOF patients. There were no significant differences in mean, minimal or maximal heart rate, and total supraventricular premature beats. The median number of total ventricular premature beats (VPB) was higher in TOF patients than in PS patients, although this was not statistically significant (number of VPBs: 2 (0 – 7341) (TOF patients) vs. 1 (0 – 890) (PS patients), $p = 0.07$). One PS patient had 1 run of ventricular tachycardia (VT), consisting of 5 heart beats. Another PS patient had 2 runs of supraventricular tachycardia (SVT), consisting of 13 heart beats in total. None of the TOF patients showed runs of VT or SVT.

DISCUSSION

Our results show that adolescent patients with isolated pulmonary valve stenosis and tetralogy of Fallot, whose age at treatment, duration of follow-up, and residual RV outflow gradient were similar, have similar clinical outcomes (NYHA class, and exercise

performance). Although clinical condition, as assessed using the NYHA class, was good in the majority of the patients, exercise performance was significantly reduced in both patient groups. Residual PR in the PS group was mild, with a mean PR percentage of 10 ± 10% versus 30 ± 13% in the TOF group. Considering the differences in techniques used to relieve the RV outflow stenosis, it was not unexpected to find more PR after treatment for TOF than for isolated PS. Although RV volumes were significantly larger in TOF patients than in PS patients, LV size, RV effective SV, and biventricular function were not significantly different. Despite the minimal residual RV outflow stenosis and mild PR in the PS group, CMR imaging revealed a larger RVESV and a lower RVEF in the PS group compared with the results in healthy controls.

Relatively few studies have reported on the long-term clinical outcome after BPV for isolated PS. Our study confirms that PR is generally mild in PS patients at follow-up after BPV[5-8]: only 3 PS patients in our study had a PR percentage > 20%. RV enlargement has been considered uncommon in PS patients after BPV. Assessment of RV dimensions in most previous studies, however, has been done using echocardiography [5,7,21]. Recently, Harrild et al. studied PS patients after BPV using CMR imaging and reported that mild PR and mild RV dilatation were often present at long-term follow-up, but that severe PR and severe RV dilatation were very uncommon [17]. Our own results demonstrated that longstanding mild PR in PS patients is associated with an increase in RVESV and a decrease in global RV function. Furthermore, our PS patients had a reduced exercise capacity. These results confirm those of the study by Harrild et al., who also found a reduced VO_2 max. in PS patients.

Although results of exercise testing in patients after repair of TOF are available in the literature, their results differ considerably [10-11,22]. In adults operated on for TOF, VO_2 max. has varied between 58% and 80% of predicted values[10,22]. Age at operation and duration of follow-up are important factors to consider. The good results in our TOF group might be explained by our patients' relatively young age at surgery and young age at study relative to those of the TOF patients described in earlier studies. A younger age at surgery has been recognised to be related to a more favourable clinical outcome[3].

In contrast with our second hypothesis, exercise performance in PS patients was significantly lower than in healthy controls. This might in part be explained by impaired chronotrophy, since the maximal heart rate was significantly lower than in healthy controls. It is striking that the TOF patients in our study had similar results on exercise testing as PS patients, despite significantly higher amounts of PR. A similar result was also found in a study by Yetman et al., who compared a group of pediatric PS patients after surgical valvulotomy with a matched group of TOF patients[23]. Remarkably, exercise capacity was more severely impaired in the PS patients in Yetman's study than it was in the TOF patients. The authors argued that this might result from diastolic RV restriction in TOF patients, which was suggested to improve exercise capacity, as reported by Gatzoulis et

al.[24]. This has however, not been confirmed either in pediatric and adolescent TOF patients who were operated on at a younger age or in a recent study in adult TOF patients [22,25].

In recent years, an abnormal ventilatory response to exercise, as assessed by an elevated VE/VCO_2 slope, has been shown to be a powerful predictor of cardiac-related mortality in patients with CHD [10,26]. Our results were comparable to the results reported by Giardini et al., who found a VE/VCO_2 slope of 31 ± 5 in their total group of TOF patients[10]. In our study however, the VE/VCO_2 slope was not significantly different between PS patients and healthy controls and was also not different between the 2 patient groups.

Our study confirms the adverse effects of longstanding PR. At the same time, exercise performance and ventricular function were comparable between the PS and TOF group, despite important differences in RV dimensions. Based on the fact that exercise capacity was similar in both patient groups, the relatively short hypoxemic period before corrective surgery doesn't seem to have a negative influence on exercise capacity in these TOF patients at the current follow-up duration. It seems therefore that other factors have more impact on exercise capacity, like for example the amount of PR or global RV function. PR percentage was not correlated with peak oxygen uptake or the VE/VCO_2 slope however, although the limited number of patients in the study is a factor to consider. The similar biventricular function in our PS and TOF patients might be an explanation for their similar exercise test results.

A recent functional analysis of 3 components of the RV in adolescent TOF patients by Bodhey et al., demonstrated that the ejection fraction of the apical trabecular component, which provides the major ejectile momentum, is maintained in patients with slight to moderate ventricular dysfunction[27]. In TOF patients operated on at a young age, RV contractile reserve is also well preserved[28]. These findings suggest that RV myocardial performance may be well maintained in TOF patients operated on at a young age, despite enlarged RV size. The RV may therefore be well suited to perform its role of maintaining LV preload in this situation.

It might be speculated that long-term prognosis in TOF patients eventually will be worse than in PS patients, since TOF patients already have a more severe RV dilatation at this follow-up duration. Previous studies have suggested that there is a threshold for the dimension of the RVEDV, above which the RV does not recover completely, even if a PVR is performed[11-12,14-15].

Arrhythmias are an important problem in patients with residual PR, particularly in patients with TOF [9,29]. Significant ventricular arrhythmias in PS patients are uncommon[30], which is in agreement with our results. A QRS duration of > 180 msec. and an older age at repair are associated with a higher risk of ventricular tachycardia and sudden death [9]. Dietl et al. reported a significant reduction in ventricular arrhythmias in TOF

patients who had had a transatrial repair than in those who had had a transventricular repair[29]. Significant ventricular arrhythmias in our TOF patients were uncommon. This relates to the mild QRS prolongation, young age at repair and transatrial surgical repair in most of the patients. None of our patients had a QRS duration > 180 msec.

Limitations

No echocardiographic data was available for 10 TOF patients before treatment and for 2 TOF patients immediately after treatment, in all of whom the assessment of RV outflow gradients had been based on results from cardiac catheterizations. Particularly, the significant difference in PV peak gradient before treatment between PS patients and TOF patients should therefore be interpreted with caution.

In some of the older TOF patients, data from exercise testing and 24-hour Holter monitoring were missing. Since exercise capacity might be better preserved at a younger age, this may have resulted in an overestimation of the exercise capacity in the TOF patients.

We studied children, adolescents and young adults treated at a young age. Our results are therefore representative for patients with a similar age and follow-up-duration.

Since we only had small patient groups, a limited statistical power is a factor to consider.

Future perspectives

Assessment of RV volumes and function with CMR imaging in patients treated with BPV for isolated PS has hardly been done before. We found that PS patients had a larger RV, a lower RV function, and a lower exercise capacity than healthy controls, although their clinical condition was excellent. Since we only had a small PS patient group, results should be confirmed in larger studies. Serial follow-up studies in PS patients are necessary to evaluate the degree of progression of their PR and RV dilatation and to see how this influences their clinical condition and exercise capacity later in life.

Serial follow-up data might also be useful to evaluate whether certain parameters, like PR percentage and RV dilatation, might be more progressive in the TOF group and to see how this would then influence biventricular function and exercise capacity at longer term follow-up.

Conclusion

In contrast to our hypothesis, pediatric and adolescent patients with isolated pulmonary valve stenosis have a lower exercise capacity, a larger right ventricle and a lower RV function than healthy controls, although their clinical condition is excellent. However, exercise performance and biventricular function are similar to those in patients with tetralogy of Fallot, despite more severe pulmonary regurgitation and larger RV volumes in Fallot patients.

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Chapter 6

Outcomes in survivors after surgical closure of ventricular septal defects: ready for referral back to general practice?

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Chapter 7

Medical predictors for long-term behavioural and emotional outcomes in children and adolescents after invasive treatment for congenital heart disease

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ABSTRACT

Background

To test: 1) the predictive value of medical variables for long-term parent-reported behavioural and emotional problems in children and adolescents who underwent invasive treatment for congenital heart disease in infancy; 2) the relationship between parental psychological distress and parental reports on problems in children.

Methods

The Child Behavior Checklist was used to investigate to what extent behavioural and emotional problems in 7-17-year-old children with congenital heart disease can be predicted by: (1) medical history, (2) therapeutic intervention and direct post-interventional course, (3) long-term medical course, (4) present contact with physicians, and (5) present medical status. The General Health Questionnaire was used to assess parental distress (especially anxiety).

Results

Higher Child Behavior Checklist Total Problems scores were predicted by cardiac medication prior to therapeutic intervention. Palliative intervention (Rashkind procedure) prior to therapeutic intervention was associated with more favourable scores on Total Problems and Externalising. Long-term maternal distress was significantly related to parent-reported problems in children.

Conclusion

Long-term behavioural and emotional outcomes are only marginally predicted by medical variables. In counselling of children with congenital heart disease ad their parents attention should be paid to the fact that long-term maternal distress has an influence on parent-reported problems in children.

INTRODUCTION

Since mortality and morbidity in patients with congenital heart disease have improved significantly over the past decades, increasing attention is now being given to long-term behavioural and emotional outcome and quality of life of these patients [1-3]. It is important to know to what extent factors associated with the medical course in early childhood are predictive for long-term behavioural and emotional outcomes.
In the previous decades, several predictors for behavioural and emotional problems in children with congenital heart disease have been identified, varying from maternal perceptions [4] to medical variables such as age at surgical repair, deep hypothermic circulatory arrest, and number of heart operations [5,6]. Studies in which medical predictors of long-term behavioural and emotional problems are assessed in a recent sample of children treated for congenital heart disease in the era after 1990, however, are lacking.

In literature it has also been described that the behavioural and emotional functioning of children with congenital heart disease is more a function of maternal anxiety than severity of the cardiac defect [4, 7-9]. Studies linking directly long-term parental anxiety or distress to long-term behavioural and emotional problems in children, however, are scarce. Moreover, the influence of long-term parental distress and anxiety on the behavioural and emotional development of children with congenital heart disease has been neglected.

The present study is part of a follow-up study on long-term medical and psychosocial outcomes in children, adolescents and young adults who underwent invasive treatment for congenital heart disease recently, that is between 1990-1995. In this follow-up we found that parents of children and adolescents with congenital heart disease evaluated the patients' behavioural and emotional problems, on average, as significantly more unfavourable as parents from a normative reference group [10].

The aim of the present study was to determine which medical variables predicted long-term behavioural and emotional problems, in order to identify children and adolescents who are at risk for later maladjustment. We investigated: 1) to what extent long-term behavioural and emotional problems can be predicted by: medical history, therapeutic intervention and direct post-interventional course, long-term medical course, present contact with physicians, and present medical status; 2) the relationship between long-term parent-reported behavioural and emotional problems in children with congenital heart disease and long-term psychological distress (i.e. anxiety) of both mothers and fathers.

METHODS

Long-term outcome variables

The Child Behavior Checklist was used to obtain standardized parents' reports of behavioural and emotional problems in children aged 7-17 years [11]. The problem section consists of 120 problem items. Parents rate their child's behaviour during the preceding six months on a 3-point scale (0 = not true; 1 = somewhat or sometimes true; 2 = very true or often true). Good validity and reliability have been established [11,12] and was confirmed for the Dutch version [13]. The Child Behaviour Checklist consists of eight specific syndrome scales, and two broad band syndromes designated as Internalising and Externalising. A Total Problems score can be obtained by summing the scores on all individual problem items. A higher score indicates a higher level of problems. For this particular study, the scales Internalising, Externalising and Total Problems were used.

The 28-item version of the General Health Questionnaire, a reliable and valid standardised self-report, was used to assess the level of psychological distress [14]. The General Health Questionnaire contains four scales, which are concerned with: somatic symptoms, anxiety and sleeplessness, social dysfunctioning and serious depression. The total scale score can be calculated by summing the scale scores. Cronbachs alpha for the total score is .94 [14]. For this particular study, the scale anxiety and sleeplessness and the total scale score (assessing psychological distress) were used.

Predictor variables

Table 1 shows five clusters of predictor variables which were chosen on theoretical and/or medical grounds. Data were derived from medical examination during the follow-up and through retrospective medical file search. The variable hypothermia was dichotomised: 0 = moderate hypothermia (22 degrees Celsius and higher), 1 = deep hypothermia (below 22 degrees Celsius). The variable scar judged by physician was dichotomised: 0 = well healed, 1 = moderately or poorly healed. The variable sinus rhythm was dichotomised: 0 = sinus rhythm present, 1 = sinus rhythm absent. Most dichotomous prediction variables were coded as: 0 = no, favourable or risk absent and 1 = yes, unfavourable or risk present. The variable cardiovascular drug in the cluster present medical status was excluded since it occurred in only one patient. The variable "restrictions imposed by physician" was operationalized by one question for patients: Do you feel restricted by the physician? Patients treated with cardiac medication prior to therapeutic intervention received diuretics or prostaglandin E_1. Patients with a palliative intervention prior to therapeutic intervention underwent a Rashkind procedure.

Table 1. Descriptive characteristics of the four diagnostic groups and the total patient sample on the predictor variables.

Predictor variables	Cardiac diagnosis														
	ASD n=27			VSD n=43			TGA n=31			PS n=13			Total n=114		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Medical history															
Duration of pregnancy, in weeks		38.3	3.4		39.3	2.5		39.7	1.8		40.0	0.9		39.3	2.4
Weight at birth, in grams		2985.3	857.8		3056.5	721.7		3312.3	686.0		3444.5	411.5		3168.8	717.3
Cardiac medication prior to therapeutic intervention (Diuretics, Prostaglandin E_1)															
Yes	0			33			29			0			62		
No	27			10			2			13			52		
Diuretics	0			33			15			0			48		
Prostaglandin E_1	0			0			14			0			14		
Palliative intervention prior to therapeutic intervention (Rashkind procedure)															
Yes	0			0			18			0			18		
No	27			43			13			13			96		
Rashkind and Prostaglandin E_1	0			0			8			0			8		

	ASD			VSD			TGA			PS			Total		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Therapeutic intervention and direct postinterventional course															
Age at first therapeutic intervention (years)		3.2	1.2		0.7	1.1		0.16	0.5		1.4	1.3		1.3	1.5
Hypothermia															
Below 22 degrees Celsius	1			1			7						9		
22 degrees Celsius or more	26			42			24						92		
Direct postinterventional course (up to 2 weeks postinterventional course)															
With complications	2			1			4			0			7		
Without complications	25			42			27			13			107		
Time on Intensive Care Unit (days)		1.0	0.4		1.9	1.6		4.8	5.1		0.1	0.3		2.4	3.4
Long-term medical course															
Number of hospitalisations as a result of heart problems since first therapeutic intervention															
1 or more	0			3			1			1			5		
0	27			40			30			12			109		

	ASD			VSD			TGA			PS			Total		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Number of hospitalisations as a result of other problems															
1 or more	13			18			15			4			50		
0	14			25			16			9			64		
Present contact with physicians															
Medical check-ups for the heart															
Once a year or more	0			3			1			1			5		
Less than once a year	27			40			30			12			109		
Restrictions imposed by physician															
Yes	1			3			2			1			7		
No	26			40			29			12			107		
Present medical status															
Scar judged by physician															
Moderately or poorly healed	3			2			5						10		
Well healed	24			41			26						91		
Maximum oxygen uptake (ml/min/kg)		39.5	7.0		42.2	8.9		41.0	9.3		36.7	11.0		40.6	9.0
Sinus rhythm															
Absent	1			1			3			1			6		
Present	26			42			28			12			108		

Abbreviations:
ASD=atrial septal defect; VSD=ventricular septal defect; TGA=transposition of the great arteries; PS=pulmonary stenosis

Inclusion and exclusion criteria

During the follow-up, which took place in 2003-2004, consecutive surviving patients of 4 diagnostic groups, who underwent their first invasive treatment for congenital heart disease between 1 January 1990 and 1 January 1996 in the Erasmus University Medical Centre Rotterdam, and who were younger than 15 years at the time of the treatment, were eligible. The sample in this study encompassed the following cardiac diagnostic groups: surgical closure of atrial septal defect, surgical closure of ventricular septal defect, arterial switch operation of transposition of the great arteries and balloon dilatation for pulmonary stenosis. Patients with proven syndromes of mental retardation, including Down syndrome, were excluded.

Patient sample and parent sample

The target population consisted of 246 consecutive surviving patients. At follow-up 40 patients were lost (23 moved abroad, 17 were untraceable). Of the remaining 206 patients, 35 patients aged 18-28 years were not included since the Child Behavior Checklist did not cover this age-range. 171 patients were aged 7-17 years (age-range of the Child Behavior Checklist) at follow-up. From the Child Behavior Checklist sample parents of 46 patients refused to participate for practical or emotional grounds. Of these 46, 24 patients were aged 7-12 and 22 patients 13-17 years. Parents of 125 children aged 7-17 years completed the Child Behavior Checklist. One questionnaire was not usable because of incomplete information. The final Child Behavior Checklist sample consisted of parents of 66 male and 58 female patients (total Child Behavior Checklist sample=124). The response rate was 73%. Ten patients of this final Child Behavior Checklist sample did not participate in the medical part of the study. For a total of 64 boys and 50 girls (mean age 11.8 years, SD=2.4) both a Child Behavior Checklist parent-report and complete medical data were available. Of this sample of 114 patients, 68 mothers and 23 fathers completed the General Health Questionnaire.

Overall, there were no differences between the non-responders and those participating in the study as to the distribution of patients over diagnostic groups, the age and gender distributions of patients.

Socio-economic status was scored on a 9-point scale of parental occupation, with scores 1 to 3 corresponding with elementary and so called 'lower' occupations (level 1), 4 and 5 corresponding with so called 'middle' occupations (level 2), and 6 to 9 corresponding with so called 'higher' and scientific occupations (level 3) [16].

The number of patients in each diagnostic group was: 27 patients with surgical closure of atrial septal defect (mean age 13.9 years, SD=1.9), 43 patients with surgical closure of ventricular septal defect (mean age 11.3 years, SD=2.2), 30 patients with an arterial switch operation of transposition of the great arteries (mean age 10.4 years, SD=1.8) and 13 patients with a balloon dilatation for pulmonary stenosis (mean age 12.5 years, SD=2.7).

Assessment procedure

The research protocol was approved by the central committee on research involving human subjects before the start of the study. All patients were traced and approached uniformly. After an information letter was received, patients were called for an appointment by the research assistant. Before participating in the study, parents and/or patients signed an informed consent and returned it by mail. The definite cardiac diagnosis was checked by a paediatric cardiologist (W.H.). During the psychological investigation in the Erasmus University Medical Centre, parents of 7-17-year-old patients completed the Child Behavior Checklist and the General Health Questionnaire in the waiting room whilst their child underwent a follow-up examination.

Statistical analysis

A three-phase strategy was followed, for each of the three outcome measures. The method of multiple linear regression analysis was applied. Since socio-economic status did not have a main effect on any of the outcome variables, it was not included in the models. In phase 1, each of the separate predictor variables was tested on the Child Behavior Checklist outcomes (single analysis). This was done to explore the predictive quality of each predictor separately. In phase 2, each cluster (i.e. combination) of predictors was related to the Child Behavior Checklist outcomes (multiple analyses). The following clusters were used: medical history, therapeutic intervention and direct post-interventional course, long-term medical course, present contact with physicians, and present medical status. Since this phase served as a first, broad selection of predictors, the p-values were set to levels of 0.20 (for entry) and 0.25 (for removal). The procedure used was backward elimination procedure. Variables remaining in the regression model, applying to the clusters of predictor variables, were candidate-predictors for the final model. The final model in phase 3, p-values were set at 0.05 (for entry) and 0.051 (for removal), contained all significant variables from phase 2. Variables which showed significant results in this final model were considered the final predictors of Child Behavior Checklist outcomes. In order to correct for sex and age effects, sex and age were entered into each analysis in phases 1, 2 and 3. In order to prevent multicollinearity, the tolerance level (i.c. Variance Inflation Factor) was checked. The Variance Inflation Factor was not allowed to exceed the value of 4. The linearity assumption was assessed by examining the scatter plots, with the continuous predictors on the x-axis and the dependent variables on the y-axis. The scatter plots showed that no other than linear relationships were to be expected. In the tables, the betas presented are standardized regression coefficients which express the relative importance of strength of the relationship between each predictor variable and the outcome variable. Plus versus minus sign indicates respectively the positive versus negative direction of the relation between the predictor variable and the outcome variable.

To investigate the relationship between long-term parent-reported behavioural and emotional outcomes regarding the patients and long-term psychological distress of parents, Pearson correlations were performed on the Child Behavior Checklist outcomes and the scale score on anxiety and sleeplessness and the total scale score of the General Health Questionnaire, for both mothers and fathers separately.

RESULTS

Table 2 shows the results of phase 1 analyses. Cardiac medication prior to therapeutic intervention was significantly associated with a higher (that is an unfavourable) Externalising score, whereas the diagnostic categories of atrial septal defect and pulmonary stenosis significantly predicted lower scores on Externalising. Palliative intervention (Rashkind procedure) prior to therapeutic intervention was associated with more favourable scores on Child Behavior Checklist Total Problems The variable scar judged by the physician as moderately or poorly healed was significantly associated with a higher Internalising score. Since phase 2 analyses served as a first selection of predictors and as an in-between model, the results are not presented here.

The results of the final model are presented in Table 3. Higher Child Behavior Checklist Total Problems scores were predicted by cardiac medication prior to therapeutic intervention. Palliative intervention prior to therapeutic intervention was associated with lower (that is favourable) scores on Child Behavior Checklist Total Problems and Externalising. The diagnostic categories of atrial septal defect and pulmonary stenosis were associated with lower scores on Child Behavior Checklist Externalising.

Table 2. Prediction of outcomes on Child Behavior Checklist by separate predictor variables adjusted for sex and age

Predictor variables	Total Problems β	Internalising β	Externalising β
Medical history			
Duration of pregnancy, in weeks	-0.01	-0.01	0.04
Weight at birth, in grams	-0.08	-0.06	-0.09
Cardiac medication prior to therapeutic intervention	0.23	0.05	0.29*
Palliative intervention prior to therapeutic intervention	-0.22*	-0.18	-0.13
Cardiac diagnosis (reference: ventricular septal defect)			
Atrial septal defect	-0.19	<-0.01	-0.29*
Transposition of the great arteries	-0.18	-0.00	-0.20
Pulmonary stenosis	-0.16	0.02	-0.23*
Therapeutic intervention and direct postinterventional course			
Age at first therapeutic intervention, in years	-0.19	-0.15	-1.32
Hypothermia	0.09	0.12	0.11
Direct postinterventional course	0.04	0.08	0.02
Time on Itensive Care Unit	0.07	0.02	0.09
Long-term medical course			
Number of hospitalisations as a result of heart Problems since first therapeutic intervention	0.11	<0.01	0.17
Number of hospitalisations as a result of other problems	0.08	0.10	0.03
Present contact with physicians			
Medical check-ups for the heart	-0.12	-0.09	-0.08
Restrictions imposed by physician	-0.08	-0.13	-0.01
Present medical status			
Scar judged by physician	0.11	0.20*	-0.01
Maximum oxygen uptake	-0.08	-0.23	-0.11
Sinus rhythm	-0.04	-0.06	0.02

* $P < 0.05$

Table 3. Final results of significant predictors of Child Behavior Checklist Total Problems and Externalising by main terms entered in the regression model

	Constant	Unstandardized coefficients β	95% CI	Standard error	Standardized coefficients β	*P*	Multiple R
Total Problems							
[a]Cardiac medication prior to therapeutic intervention	25.90	13.34	3.50 to 23.17	4.96	0.31	0.008	0.34
[a]Palliative intervention prior to therapeutic intervention		-16.94	-27.70 to -5.29	5.65	-0.28	0.004	
Externalising							
[a]Palliative intervention prior to therapeutic intervention	9.06	-3.80	-7.21 to -0.39	1.72	-0.22	0.029	0.32
[a]Cardiac diagnosis (reference category: ventricular septal defect)							
Atrial septal defect		-4.25	-7.65 to -0.84	1.72	-0.28	0.015	
Pulmonary stenosis		-4.46	-8.46 to -0.46	2.02	-0.22	0.029	

[a] Dichotomous predictor variables were coded as: 0 = no, favourable or risk absent, 1 = yes, unfavourable or risk present.

Pearson correlations were calculated between the Child Behavior Checklist scores and the scores of the General Health Questionnaire (total scale score, score on anxiety and sleeplessness). For mothers, the Pearson correlation coefficients ranged from 0.42 to 0.54 (Table 4). All correlations were significant at a significance level of $p<0.01$. This means that mothers of children with congenital heart disease who reported more long-term behavioural and emotional problems for their children showed more psychological distress and anxiety themselves. According to Cohen [16], correlations of 0.10 to 0.29 are considered small, correlations of 0.30 to 0.49 are considered medium and correlations above 0.50 are considered large. Medium correlations were found for mothers between the score on Externalising and the scores of the General Health Questionnaire (anxiety and sleeplessnes and the total score), and also on Internalising and the score on anxiety and sleeplessnes. Large correlations were found for mothers between Child Behavior Checklist Total Problems and the scores of the General Health Questionnaire and between Child Behavior Checklist Internalising and the total score of the General Health Questionnaire. For fathers the directionality of the associations showed a similar pattern: a positive trend was found although the correlations between the Child Behavior Checklist scores and the scores of the General Health Questionnaire were not significant.

Table 4. Correlation of Child Behavior Checklist outcomes and General Health Questionnaire outcomes

	General Health Questionnaire Anxiety and sleeplessness		General Health Questionnaire Total score	
Child Behavior Checklist	**Mothers n=68**	**Fathers n=23**	**Mothers n=68**	**Fathers n=23**
Internalising	0.49**	0.25	0.52**	0.32
Externalising	0.47**	0.38	0.42**	0.34
Total Problems	0.54**	0.35	0.51**	0.30

** $P < 0.01$

Furthermore, no differences were found on psychological distress between parents of the four diagnostic groups, and no differences were found between parents of children undergoing cardiac surgery versus catheter intervention.

DISCUSSION

The final prediction model of this study showed that cardiac medication prior to therapeutic intervention was a significant predictor of long-term behavioural and emotional problems in 7-17-year-old children who underwent invasive treatment for congenital heart disease, as reported by their parents on the Child Behavior Checklist Total Problems score. Remarkably, palliative intervention prior to therapeutic intervention (Rashkind procedure for transposition of the great arteries patients) was a significant predictor for less long-term behavioural and emotional problems, as reported by parents on the Total Problems score and the Externalising scale.

Furthermore, the present study's results showed that patients who underwent a surgical closure of an atrial septal defect, a balloon dilatation for pulmonary stenosis or a palliative Rashkind procedure for transposition of the great arteries have a lower risk of developing externalising problems compared to patients who have been treated for a ventricular septal defect. Apart for the externalising problems, the type of definitive intervention (atrial septal defect, ventricular septal defect and transposition of the great arteries treated by surgical intervention and pulmonary stenosis treated by catheter intervention) is not significantly related to behavioural and emotional problems as reported by parents of the patients.

Several investigators have evaluated the effects of diagnosis on long-term behavioural and emotional problems. They did not find a relationship between the type and severity of the cardiac defect and the emotional (mal)adjustment of children with congenital heart disease [4,5,17,18]. In a prediction study involving adults, Van Rijen et al. [19] also found that patients operated for a ventricular septal defect have a higher risk of developing particularly externalising problems. We do not have direct a causal explanation for

the higher risk of developing externalising problems in children with a ventricular septal defect, found in the present study.

The only significant predictors found in this study all appeared to originate from the cluster medical history. Of the patients in our sample 54% (n=62) was treated with cardiac medication (diuretics or prostaglandin E_1) prior to therapeutic intervention. Table 1 showed that patients treated with cardiac medication were diagnosed with a ventricular septal defect or transposition of the great arteries. We consider cardiac medication prior to therapeutic intervention as a marker for more serious cardiac illness.

From the design of this study it is not possible to provide an explanation as to why cardiac medication prior to therapeutic intervention would lead to higher total problem or externalising scores. However, use of cardiac medication prior to therapeutic intervention (diuretics or prostaglandin E_1) is related to the severity of infants' clinical state. From our data it can be assumed that children with more serious conditions received cardiac medication until surgical intervention could be performed. We suggest that the time period that a child receives cardiac medication, in order to get well enough to undergo cardiac surgery, may be a period of fierce uncertainties and stress. This may influence parental perceptions regarding severity of the cardiac defect and coping of parents with the situation. Furthermore, it might negatively influence parent-child interactions. The time between diagnosis and therapeutic intervention did not predict long-term behavioural and emotional outcomes. Why patients who were both treated initially with cardiac medication and a palliative intervention prior to the therapeutic intervention did not show more unfavourable long-term behavioural and emotional outcomes remains unclear. It is not known whether and to which extent side effects of cardiac medication can negatively influence later behavioural and emotional adjustment. As far as we know, this has not been reported. This topic should be investigated in future research.

In a prediction study executed about 15 years ago at our centre, Utens et al. [5] found that the significant predictors for long-term behavioural and emotional problems, identified at that time (i.e. a greater number of heart operations, deep hypothermic arrest, a short gestational age, and older age at surgical repair), also originated from the clusters of medical history and heart surgery. These previous predictors were not the same as those found in the present study. In the study population of Utens et al. [5], however, all patients received surgical treatment. The transposition of the great arteries group was operated using the Mustard technique and patients with pulmonary stenosis were operated upon using inflow occlusion and valvotomy or with the use of cardiopulmonary bypass. Furthermore, patients with Tetralogy of Fallot and a miscellaneous diagnostic group were included. Predictors associated with higher Total Problems scores at that time, such as a greater number of heart operations and deep hypothermic arrest can be considered as relevant for this previous population. Most of the patients of our current

sample, however, were treated once (except of the group who had a palliative intervention prior to therapeutic intervention) and did not have reoperations.

A remarkable finding of our study is that variables concerning the present medical status and the present contact with physicians were not significantly associated with the occurrence of behavioural and emotional problems. Furthermore, we showed that behavioural and emotional problems are only marginally predicted by variables reflecting the medical history; these variables explain a maximum of 12% of the variance.

Previously, we found that according to parent-reports' of behavioural and emotional problems, a significant proportion of children with congenital heart disease scored in the deviant range (16.9%) compared to the normative reference group (10.2%) [10]. According to patients themselves (Youth Self-Report) the proportion of children and adolescents scoring in the deviant range, was comparable to that in the reference group [10]. Since the percentage of patients scoring in the deviant range, according to patients self-report, was not different compared to that in the reference group (-or simply stated: the number of deviant cases was relatively low), it was statistically not warranted nor logic to perform regression analyses on these self-report outcomes, using medical predictor variables. Because of this finding and moreover, considering the fact, that for the Child Behavior Checklist (7-17 years) and the Youth Self-Report (11-17 years) not only different age-ranges but also different normative reference groups were used, we decided for the present study to use only the parent-reports.

In addition, previous results of this same sample [10] also showed that 11-17-year-old children with congenital heart disease reported more behavioural and emotional problems (e.g. for Child Behavior Checklist Total Problems) than did their parents about them. These previous results showed that the differences between child- and parent-reports in the congenital heart disease sample, however, were smaller than in the reference group.

The consequences of our results are that in counselling children with congenital heart disease and their parents, attention should be paid to patients who have received more intense medical care and cardiac medication prior to therapeutic intervention, since cardiac medication can be considered a marker for severe illness. Assessment of behavioural and emotional outcomes in children with congenital heart disease may reveal problems that are not readily apparent in the routine clinical practice. It consequently may offer guidelines for counselling children with congenital heart disease.

In clinical practice attention should also be paid to the level of parental psychological distress. Our data indicate that long-term maternal and paternal distress was positively related to parent-reported behavioural and emotional problems in children with congenital heart disease. Among fathers, however, no significant correlations were found between the Child Behavior Checklist scores and the scores of the General Health Questionnaire. An explanation for this would be that the sample size is rather small (only 25%

fathers). During the psychological investigation in our hospital most of the patients were accompanied by their mother.

Lawoko and Soares [7] examined differences in distress and hopelessness among parents of children with congenital heart disease, parents of children with other diseases, and parents of healthy children. Mothers within all parent groups had higher levels of distress and hopelessness than fathers, with the highest levels among mothers of children with congenital heart disease compared to mothers in the other groups.

Van Horn et al. [20] examined concerns expressed by mothers of children with congenital heart disease during hospitalization and 2 to 4 weeks after discharge. Distress about mothers' prominent concerns during hospitalization (prognosis, psychological adjustment, and impact on the family) decreased postdischarge, as did mother's anxiety and depressed mood. Mothers' perceptions of medical severity were associated with distress about psychosocial issues postdischarge. Mother's level of anxiety was not associated with the number of their concerns or with distress about those concerns during or after hospitalization. The researchers concluded that illness-related concerns are not necessarily a function of disease severity or mother's emotional state [20].

Our findings showed that parental psychological distress was unrelated to cardiac diagnosis or the type of intervention. This is in line with data showing that the severity of the congenital heart disease does not predict parental distress [4, 7, 9]. Wray and Sensky [21], for example, found no differences in distress between parents of children with cyanotic and acyanotic lesions both before and after surgery.

In conclusion our results indicate that, overall, the use of cardiac medication before surgical or interventional treatment was associated with unfavourable long-term behavioural and emotional outcomes. A palliative intervention prior to therapeutic intervention was associated with favourable long-term outcomes. Causal relationships need to be established. Future research should include assessment of parental mental health, also of fathers. This is important and valuable since parental mental health can affect parent-reports as to behavioural and emotional problems in their children (i.e. risk of overreporting), and even more important, it will influence the emotional development of their children.

Limitations of the present study

The present sample of children with congenital heart disease contains four diagnostic groups, with specific age ranges, and is therefore not completely representative for all congenital heart disease anomalies. Though our response rate was satisfactory, medical outcomes and parent-reported behavioural and emotional problems and psychological distress could not be assessed in all eligible patients/parents. The findings regarding paternal data are based on a small sample of a few fathers with a child with congenital heart disease. To what extent this may have influenced our data is unknown.

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Chapter 8

Summary

SUMMARY

Chapter 1

This chapter is an introduction to the subject of congenital heart disease (CHD) and general practice. As the treatment of patients with CHD has improved enormously, more and more patients now survive their cardiac anomaly into adulthood. As a result, general practitioners will increasingly have to deal with these patients in their practices.

The primary aim of this thesis was to add to the information on CHD that is available to GPs, to enable them to target care better, to have better informed communication with medical specialists in the field, to improve their counselling of patients with CHD. The thesis also takes a first step towards the development of tools that can be used in the care of these patients in general medical practice.

This cross-sectional study comprised five of the most common diagnostic categories of CHD: atrial septal defect (ASD), ventricular septal defect (VSD), transposition of the great arteries (TGA), tetralogy of Fallot (TOF) and pulmonary stenosis (PS). The patients were selected from a consecutive cohort of patients who had undergone their first invasive treatment between January 1990 and January 1996, and who were younger than 15 years at the time of treatment.

Although severe sequelae may appear in these categories, some are symptomatic of relatively mild residual problems of the sort that makes it likely that this group of patients will present in general practice. These studies have thus presented data on prognosis, mortality, functional status, prediction and resemblance between subjective and objective findings. But because they contain a selection of five diagnostic groups within specific age ranges, their results are not completely representative of all diagnostic categories of CHD.

Chapter 2

It would be very convenient for general practice if a simple tool could predict the results of one of the technical facilities used in medical centres. Because such facilities are largely lacking in general practice, most GPs depend on the information they gather in face-to-face interview and from findings during physical examination. This explains our attempt to start the development of a simple tool in the form of a practical set of questions predictive for bicycle ergometry.

We tested the association between self-appraisal of exercise performance (as expressed in a simple 4-item score; EASY score) and measures of exercise performance in a group of children aged 8-15 years who had been invasively treated for CHD with minimal or no sequelae. This EASY score was assessed on the basis of the answers to uniform questions in face-to-face interviews with the children themselves.

There was a clear association between EASY score and performance during exercise testing (maximal workload and peak oxygen uptake). The higher the maximal workload and the rise in peak oxygen uptake, the higher the EASY score.

In Chapters 3, 4, 5 and 6, follow-up status (including mortality), incidence of sequelae, and functional status were all determined, and two cohorts of patients treated in different periods of time were compared. The objective was to obtain greater insight into and understanding of the prospects for patients invasively treated for CHD.

Chapter 3

We examined patients who survived an arterial switch operation for transposition of the great arteries, and compared the results with those from a healthy reference group.

Cumulative event-free survival was 88%, and re-interventions were necessary in only 6% of the patients. Echocardiography showed that up to 70% had an aortic root dilatation – a considerable percentage -, even though this is a known sequel to arterial switch operations. Nonetheless, neither root dilatation, severe aortic regurgitation, nor left ventricular dilatation has been found yet. And, while comparison of parameters of exercise performance in patients with those in the healthy reference group displayed a decreased performance in patients, no association with aortic root dilatation could be demonstrated.

Chapter 4

Although long-term prognosis in some studies of children who underwent surgery for a secundum type atrial septal defect (ASD-II) seems not to differ from that in the normal population, studies in the 1980s and 1990s reported that arrhythmias were a major long-term concern. The objectives of the study in this chapter were to assess ventricular dimensions, exercise capability and arrhythmias in patients who had an operation for ASD-II, and to compare the results with those in the healthy reference group.

None of the 42 patients in our study had a residual ASD; the mean follow-up duration was 12 years. There were no major cardiac events during follow-up, and quality of life was good (as reported earlier in this population).

The use of cardiac magnetic resonance imaging as an optimal imaging technique for assessing right-ventricular dimensions showed that the right-ventricular end-systolic volume (RVESV) in 25% of our patients was larger than the 95th percentile; at the same time the other dimensions were within regular limits.

With respect to the functional consequence and clinical relevance of the increased RVESV, these findings seemed to have no impact on rhythm status or exercise capacity at this stage of follow-up. We found no association between ventricular dimensions and

age or weight at surgery, although the number of patients might have been a limitation in this regard.

Chapter 5

Effects and clinical outcome were investigated in a population consisting of two groups of patients: firstly, patients with isolated pulmonary valve stenosis (PS) treated with balloon pulmonary valvuloplasty (BPV) and secondly, patients who had been operated on for tetralogy of Fallot (TOF). Results were compared among the two groups and with results from a healthy reference group. The effects of PS and TOF may include right-ventricular dilatation, decreased ventricular function, reduced exercise capacity, arrythmias, and increased risk of sudden cardiac death.

We found that right-ventricular volumes and mass were significantly larger in TOF patients than in PS patients. Right-ventricular end-systolic volume (RVESV) was significantly larger in PS patients than in healthy controls. Although the parameters of exercise testing did not differ between PS and TOF patients, they were significantly lower than in healthy references. While QRS duration was longer in TOF patients than in PS patients, 24-hour Holter recordings did not reveal significant differences.

Chapter 6

Although very few papers have been published in the past 20 years on the specific outcome of surgical treatment of ventricular septal defects (VSD), mortality and morbidity have improved considerably during two decades. Previously, mortality was considerable and severe sequelae such as pulmonary hypertension often occurred during follow-up.

Nowadays, late mortality and number of residual VSDs are virtually non existing. Despite this favourable prognosis, a small number of the patients in our study had mild aortic or mitral regurgitation, and some had fractional shortening below the lower limit. While many patients who had surgery in the 1970s had pulmonary hypertension on a regular basis, this no longer seems to be an issue for patients who had an operation for VSD.

Chapter 7

Children and adolescents with CHD who underwent invasive treatment have more behavioural and emotional problems than those in the general population. These problems often reduce the quality of life (QOL), which in patients with CHD is not determined solely by the absence of disease. These problems also tend to be more persistent when patients grow up.

We wished to establish the extent to which factors associated with the medical course of CHD in early childhood are predictive for psychosocial dysfunction, and possibly for

secondary behavioural and emotional problems. To isolate these factors, we studied the complete medical history from birth until the time of the study.

The study showed that cardiac medication before therapeutic intervention was a significant predictor of long-term behavioural and emotional problems. Remarkably, palliative intervention prior to therapeutic intervention was a significant predictor for fewer behavioural and emotional problems.

The study also showed that patients who had had surgical closure of an ASD-II, a balloon dilatation for PS, or a palliative Rashkind procedure for TGA had a lower risk of developing behavioural and emotional problems than patients who had been treated for a ventricular septal defect. Apart for externalising problems, the type of definitive intervention was not significantly related to behavioural and emotional problems as reported by parents. We have no causal explanation for the higher risk of developing behavioural and emotional problems.

Chapter 8

This summary and general discussion addresses various aspects of the growth in the number of patients with CHD, and the consequences of these to doctors involved in the care of patients with CHD.

We conclude that if patients with CHD are to be received properly by doctors in general practice, it is essential that GPs undergo post-doctoral training and other training from paediatric and congenital cardiologists. Guidelines and standards should also be established.

GENERAL DISCUSSION

Advances in medical treatment have increased the prevalence of patients with congenital heart disease (CHD), further increasing the number of patients with CHD who are later referred back to general practices, at least for aspects of general health care. Although this makes it inevitable that a role should be reserved for general practitioners (GPs) in the care of patients with CHD, the exact nature of this role is still a matter of discussion.

The aim of this thesis was to develop a practical diagnostic tool for use in general practice and to present information relevant to general practice on clinical outcomes in patients who have been operated on for CHD.

This chapter discusses the outcome of the studies in this thesis and their potential relevance for general practice. The format for this discussion follows that of the brochure *Informatie voor de huisarts over aangeboren hartafwijkingen* (i.e. "Information for GPs on congenital heart defects") produced in the Netherlands recently by VSOP, PAH and NHG [1], which elucidates general focus points for the surveillance of patients with CHD by general practitioners in the Netherlands. These points are subdivided into three approximate categories: before, during and after treatment.

Focus points before treatment

This thesis does not cover the situation directly after diagnosis and before treatment of patients with a CHD. Recommendations for the stage directly after definite diagnosis include advice to the GP to contact the patient personally, and, in the case of children, also their parents. Under these recommendations the GP inquires about the patients' experiences in the period preceding the definite diagnosis, and is open on the question of whether the patient-doctor relationship was influenced by the approach he or she had chosen. The GP also inquires about the extent to which acceptance of having a CHD and psychological adjustment is developing. Similarly, the GP asks about the arrangements that have been made with the relevant paediatric or congenital cardiologists about the coordination of medical care and follow-up. Finally, the GP also establishes the patients' expectations concerning general health care [1].

Personal experience suggests that even at this early stage it may also be necessary to ensure proper communication between GP and the medical specialists responsible for the CHD-related problems.

Focus points during treatment

During treatment in a specialised centre, health care between GP and the relevant specialists should be fully harmonised. It is important to clarify who should be applied to firstly in the event of medical complaints. As most GPs are not fully informed about the range of possible sequelae in CHD, swift correspondence or communication is a major issue.

Correspondence will also keep the GP well informed about the status of the individual patient, and about the risks, complications and sequelae of the specific treatment. In the event of complications, the GP refers to paediatric or congenital cardiologists. Common, non-cardiac problems can be treated by the GP.

Focus points after treatment

After surgical or transcatheter treatment, specific cardiac problems can still occur or develop. In general, these include arrhythmias, valvular dysfunction, aortic-root dilatation, pulmonary hypertension, ventricular dysfunction and related symptoms such as fatigue. Other important items to be addressed are prophylaxis of endocarditis, psychosocial adjustment and counselling with regard to employability, insurance and procreation

Arrhythmias

Arrhythmias are a risk in all types of CHD, sometimes as a result of the anomaly itself, and sometimes as a result of surgical treatment or its sequelae. Most of the arrhythmias seen in our studies occurred across all five diagnostic groups. At the time of the study, however, none of them was severe or of clinical interest, though close attention to possible arrhythmias is nonetheless necessary at all times. Severe ventricular arrhythmias can result in acute cardiac arrest, and can occur after treatment of several types of CHD. The GP's role is to pay close attention to patients who have palpitations or irregular heartbeats. In this situation, an ECG could be made in general practice. Using the means of communication now available, this could then be sent to a specialists' centre for further evaluation and consultation.

Valvular dysfunctions

Valvular dysfunctions can be secondary to treatment of CHD. For example, as Chapter 5 confirms, pulmonary regurgitation is a very frequent sequel to corrective surgery for TOF or balloon dilatation for valvular PS. Possibly as a result, in certain patients in both these patient groups, exercise performance was significantly reduced, despite the fact that nearly all patients were in good clinical condition.

Because valvular dysfunction tends to deteriorate during follow-up, it should be checked at regular intervals. As the two patient groups discussed in Chapter 5 will not be discharged from regular specialist surveillance, attention to deteriorating pulmonary regurgitation remains guaranteed; simultaneously, the GP will evaluate aspects of general health in relation to a potential deterioration in valvular function. As valvular dysfunction may have an adverse effect on ventricular function, the GP should actively assess signs of heart failure in these patients. The severity of pulmonary regurgitation can be assessed by proper auscultation.

Patients who are operated on for VSD regularly have valvular dysfunction (Chapter 6). For this reason, regular check-ups are appropriate, also in view of the current lack of information on progression over time. All in all, check-ups should recommence in

patients who had an operation for VSD in the past but were later dismissed from regular specialists' check-ups. If necessary, the GP might be involved in tracing these lost patients.

Aortic root dilatation

Aortic root dilatation is a complication of the arterial switch operation for TGA. During prolonged follow-up, root dilatation might progress and aortic regurgitation be imminent. In our group of patients, who were considered without exception to be physically healthy, we detected no aortic regurgitation (Chapter 3). It is nonetheless essential that GPs are informed about this imminent deterioration and are thus alert. Again, proper auscultation should put the GP on the right track.

Pulmonary hypertension

Pulmonary hypertension might be a sequel of prolonged left-to-right shunting, which can occur when a large septal defect was closed at a later stage. Fortunately, our study found no signs of pulmonary hypertension in either of the patient groups with ventricular or atrial septal defects (VSD or ASD) (Chapters 4 and 5); this was almost certainly due to timely detection and treatment. The role of the GP is to know the signs and symptoms of these lesions and to refer these patients without delay.

Fatigue

Fatigue is a very indistinct complaint with which many patients present in general practice. Besides all other causes, chronic fatigue can also be related to cardiac problems or to the use of cardiac medication, e.g. β-blockers. Our study shows that the mean exercise capacity of the patients with CHD was below that of normal references (Chapters 3, 4, 5 and 6). This might be a sequel to the CHD itself, but might also be psychological in nature – an effect of excessive parental apprehension or restraint regarding their children's pursuit of sports.

A remarkable finding in this thesis was right-ventricular systolic dilatation in a number of patients in our ASD-II population (Chapter 4). The clinical relevance and possible negative effect of the right-ventricular dilatation assessed on right or left ventricular function remains to be established. These findings indicate that right-ventricular systolic dilatation may have long-term adverse effects on ventricular function, even in patients who are considered to have been cured by closure of a simple septal defect. Many of these patients are seen infrequently in specialist centres, or are lost to follow-up altogether. If a patient presents with fatigue, GPs thus need to be aware of the increased risk of heart failure in patients treated for CHD.

Endocarditis-prophylaxis

Endocarditis-prophylaxis is obligatory in patients with dysfunctional cardiac valves or artificial valves, even if there is a risk of mild bacterial infections. In this regard, close attention to newly introduced guidelines is obligatory. Blood-cultures should be taken before antibiotic treatment of any serious infections.

Psychosocial adjustment

Psychosocial adjustment in the event of a CHD is important to avoid future behavioural and emotional problems. Previous studies have identified several predictors of psychosocial maladjustment, ranging from maternal perceptions to medical variables such as age at surgical repair, deep hypothermic circulatory arrest, and the number of heart operations.

In our study we tried to determine medical variables that may predict these behavioural and emotional problems (Chapter 7). Long-term behavioural and emotional outcomes in our study were predicted only marginally by medical variables: less favourable scores were predicted by cardiac medication prior to therapeutic intervention. Remarkably, palliative intervention (through the Rashkind procedure) before therapeutic intervention was associated with more favourable scores. Long-term maternal distress was significantly related to parent-reported problems in children.

Causal relationships need to be established. In the counselling of children with CHD and their parents, attention should be paid to the fact that these factors influence problems reported in children (Chapter 7).

Counselling and consultation

Counselling and consultation on issues such as life expectancy, genetic background, heredity risks and pregnancy risks generally takes place during consultation at paediatric or congenital cardiologists' outpatient clinics. For further explanation or additional questions, however, patients might turn to their GP – who should therefore be sufficiently equipped to stand by.

Study design

The design of the study described in these thesis followed that of earlier studies by Meijboom et al. [2] in 1995 and by Roos-Hesselink et al. [3] in 2004. Like our own study, these were part of more extensive quality-of-life studies examining medical and psychosocial functioning and behavioural outcomes. The psychosocial and behavioural aspects of our study population were published by Spijkerboer [4] in 2006.

Limitations of the study

Our study described a single-centre experience in a relatively limited number of patients.

A well-known disadvantage of research studies on patients with CHD is the availability of relatively small diagnostic groups, which thus restrict statistical power. In view of the small group sizes, we asked a number of patients with CHD to participate in different studies in our institution. A certain indifference on the part of the patients was therefore noticeable, which was reflected in a lower percentage of participation.

Future prospects

In our study we achieved our aims of developing a practical diagnostic tool and presenting clinical outcomes of patients who had been operated on for CHD. Our search for the predictive value of medical variables on psychopathology showed that long-term maternal distress was related to parent-reported problems in children.

In her thesis, Roos-Hesselink [3] recommended that the need for follow-up care for each patient with CHD should be established in at least one initial consultation at a specialised cardiac centre. Plainly, we support this recommendation. Despite the absence of major subjective physical shortcomings and disorders in a general physical examination, the results of additional examinations showed the presence of underlying structural malformations in all five diagnostic categories. The sequelae established in patients with CHD in our study show that regular surveillance should be recommended or restarted. It is essential that GPs are informed about these sequelae in patients with CHD, and are aware of them and their potential effects.

We would also like to stress that consultation by or referral to a specialist centre is obligatory for any patient who develops medical complaints related to an established CHD. However, the cause of the medical signs and symptoms seen in general practice is often unclear, and sometimes it may be impossible to determine whether or not they are cardiac in origin. With the EASY-score (Chapter 2), we tried to develop a tool that would be easily useable in general practice and that made it easier to establish whether or not cardiac origins were likely to underlie a particular sign or symptom. Although it remains unclear whether this score is applicable in patients with severe sequelae, and although its validity and inter-observer and intra-observer variations still have to be studied, this EASY score might be of use in general practice in the future.

At all times, a multidisciplinary centre must be easily accessible for consultation and referral by GPs. This may require a network of various different doctors: paediatric and congenital cardiologists, congenital cardiac surgeons, general paediatricians, GPs, and doctors in well-child clinics. In the Netherlands these networks may also provide a solution to potential reductions in the regional availability of specialised care expected to result from the long-awaited reduction in the number of CHD centres, a move that is intended to lead to the concentration of specialised medical expertise.

We realise that post-doctoral education and training of doctors in general practice by paediatric and congenital cardiologists will play an inevitable role in bringing CHD and general practice together. But we are confident that it will eventually lead to better health care for the growing population of patients with CHD.

This thesis represents a first attempt to bring general practice and CHD a little bit closer – on idea that CHD is no longer as unusual as it once seemed. Guidelines and standards should be established in the near future.

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SAMENVATTING

De belangrijkste doelstelling van het in dit proefschrift beschreven onderzoek was de onderbouwing en uitbreiding van informatie over aangeboren hartafwijkingen (AHA) ten behoeve van huisartsen en dokters werkzaam in de algemene praktijk.

Daartoe is een cohort patiënten onderzocht die tussen 1990 en 1995 invasief zijn behandeld vanwege AHA, waarbij na een follow-up periode van ca. 10 jaar gekeken is naar de gevolgen en restafwijkingen van aandoening en behandeling.

Hoofdstuk 1

In dit hoofdstuk werden de achtergrond en doelen van het onderzoek geschetst. In de afgelopen decennia zijn diagnostische technieken, alsmede chirurgische en katheter behandelingen geleidelijk steeds verder ontwikkeld. Dit heeft ertoe geleid dat de lange termijn overleving van patiënten met een AHA enorm is verbeterd met als gevolg een steeds groeiende populatie van patiënten met een AHA. Als gevolg daarvan zal de huisarts in toenemende mate worden geconfronteerd met deze patiëntengroep in de dagelijkse praktijk.

Het primaire doel van dit proefschrift is uitbreiding van de informatie over AHA voor dokters werkzaam in de algemene praktijk en voor huisartsen in het bijzonder. Deze informatie zou moeten leiden tot een beter gefocuste blik van de huisarts met betrekking tot de gevolgen van de aandoening, een betere communicatie tussen huisartsen en specialisten in het veld en als gevolg daarvan een verbetering van de begeleiding en algemene gezondheidszorg voor patiënten met een AHA.

Ook werd getracht een eerste stap te zetten in de ontwikkeling van handvatten voor de huisarts die praktisch toepasbaar zijn in de algemene praktijk.

In onze studie werden vijf van de meest voorkomende diagnostische categorieën van AHA geïncludeerd: atrium septum defect type II (ASD-II), ventriculair septum defect (VSD), transpositie van de grote arteriën (TGA), tetralogie van Fallot (TvF) en valvulaire pulmonaal stenose (PS). De betrokken patiënten werden geselecteerd uit een opeenvolgend cohort van patiënten die hun primaire invasieve behandeling kregen tussen januari 1990 en januari 1996 en die jonger waren dan 15 jaar ten tijde van deze behandeling. Alhoewel er ernstige sequelae kunnen optreden in de geselecteerde categorieën, kan er ook soms sprake zijn van milde of slechts minimale resterende gevolgen. In deze studie betreft het een groep patiënten die zich, zo nodig, zal vervoegen in de huisartsenpraktijk voor medische zorg.

De verschillende studies die zijn uitgevoerd in onze studie hebben betrekking op prognose, mortaliteit, functionele status, voorspellende factoren en overeenkomst tussen subjectieve en objectieve bevindingen.

Omdat deze studie bestaat uit een selectie van vijf diagnostische categorieën binnen specifieke leeftijdsgrenzen, zijn de resultaten niet zonder meer representatief voor alle diagnostische categorieën van AHA.

Hoofdstuk 2

De dagelijkse algemene praktijk zou erg geholpen zijn met praktisch toepasbare middelen die bevindingen zouden voorspellen van aanvullend onderzoek zoals beschikbaar in de gespecialiseerde zorg. Omdat de technische faciliteiten die nodig zijn voor dit aanvullend onderzoek ontbreken in de huisartsenpraktijken, zijn huisartsen grotendeels afhankelijk van informatie uit anamnese en bevindingen uit algemeen lichamelijk onderzoek. Deze studie probeert een eerste aanzet te geven in de ontwikkeling van een eenvoudig toepasbaar handvat, namelijk een praktisch vragenlijstje, dat voorspellend is voor de resultaten van fietsergometrie.

We onderzochten de associatie tussen de inschatting van de inspanningscapaciteit door de patiënt zelf, zoals uitgedrukt in een 4-item score (EASY score), met metingen van de inspanningscapaciteit in een groep kinderen tussen de 8 en 15 jaar oud, die invasief zijn behandeld voor een AHA. De EASY score werd berekend op basis van vier uniforme vragen, die werden gesteld tijdens de anamnese aan de kinderen zelf.

Onze onderzoeksgroep toonde milde of minimale sequelae.

Er werd een onmiskenbare associatie vastgesteld tussen EASY score en inspanningscapaciteit tijdens fietsergometrie (maximaal vermogen en zuurstofopname-capaciteit). Hoe hoger het maximaal vermogen en de zuurstofopname-capaciteit, hoe hoger de EASY score.

In de hoofdstukken 3, 4 en 5 werden follow-up status, inclusief mortaliteit, incidentie van sequelae en functionele status bepaald. Ook werden twee cohorts van patiënten die in verschillende tijdvakken werden behandeld, met elkaar vergeleken.

Het doel hiervan was het verkrijgen van een beter inzicht in de perspectieven van patiënten die invasief zijn behandeld voor AHA.

Hoofdstuk 3

We onderzochten patiënten die een arteriële switch operatie ondergingen vanwege een TGA en vergeleken de resultaten met die van een gezonde referentie groep.

De cumulatieve “event”-vrije overleving van de patiënten was 88%. Heringrepen vonden plaats in 6% van de patiënten. Echocardiografisch onderzoek liet zien dat ongeveer 70% van de patiënten een aortawortel-dilatatie had. Niettegenstaande het feit dat deze dilatatie een bekende complicatie is na arteriële switch operaties, is het percentage van 70% substantieel te noemen. Ondanks de worteldilatatie werd er (nog) geen aortaklepinsufficiëntie of ventriculaire dilatatie waargenomen.

De gemiddelde inspanningscapaciteit van TGA patiënten bedroeg 85% van die van de referentiegroep. Er was geen relatie tussen verminderde inspanningscapaciteit en aortawortel-dilatatie.

Hoofdstuk 4

Alhoewel de lange-termijn prognose van kinderen die een operatie ondergingen vanwege een ASD-II in sommige studies niet leek te verschillen van de normale populatie, rapporteerden andere studies ritmestoornissen als een grote bron van zorg op de lange termijn. De onderzoeksobjectieven in deze studie omvatten ventriculaire dimensies, inspanningscapaciteit en ritmestatus en vergelijking van de bevindingen met die van een gezonde referentiegroep.

Geen enkele patiënt in onze studie had een rest-ASD. De gemiddelde follow-up duur was circa 12 jaar. Er waren tijdens de follow-up duur geen relevante cardiale complicaties opgetreden en de kwaliteit-van-leven, waarover reeds eerder werd gepubliceerd door Spijkerboer et al., was goed. CardioMRI ("magnetic resonance imaging" van het hart) werd gebruikt als optimale afbeeldingtechniek voor de beoordeling van de dimensies van de rechter ventrikel. In 25% van onze patiënten werd een eind-systolisch volume van de rechter ventrikel (RVESV) vastgesteld dat groter is dan de 95ste percentiel, terwijl de andere cardiale dimensies binnen de regulaire grenzen bleven. De functionele consequenties en klinische relevantie van het vergrote RVESV beschouwend, lijkt deze bevinding geen invloed te hebben op de ritmestatus of de inspanningscapaciteit van het hart, althans in dit stadium van follow-up. In deze studie kon geen associatie worden aangetoond tussen ventriculaire dimensies en leeftijd of gewicht ten tijde van de operatie. Hierbij moet een gelimiteerde "power" van de studie door het beperkte aantal patiënten in ogenschouw worden genomen.

Hoofdstuk 5

In een groep bestaande uit patiënten met een geïsoleerde PS die behandeld werden middels ballon-valvuloplastiek en patiënten die geopereerd werden vanwege TvF, werd de klinische uitkomst onderling en met die van een gezonde referentiegroep vergeleken.

Mogelijke restverschijnselen van PS en TvF zijn: dilatatie van de rechter ventrikel, verminderde ventriculaire functie, afname van inspanningscapaciteit, ritmestoornissen en verhoogd risico op acute hartdood. In onze studie waren de volumina en massa van de rechter ventrikel significant groter in TvF patiënten dan in PS patiënten. Het eind-systolisch volume van de rechter ventrikel (RVESV) was significant groter in PS patiënten dan in de gezonde referentiegroep. Inspanningstesten lieten geen verschil zien tussen PS en TvF patiënten, maar het inspanningsvermogen was significant lager in PS en TvF patiënten dan in de gezonde referentiegroep. Bij ECG registratie was de gemiddelde QRS-

duur langer in TvF patiënten dan in PS patiënten; 24-uurs Holter- registratie liet geen significante verschillen in ritmestatus zien.

Hoofdstuk 6

Ondanks het feit dat er de laatste 20 jaar slechts weinig wetenschappelijke aandacht was voor het specifieke beloop na chirurgische behandeling van VSD's, verbeterde de mortaliteit en morbiditeit gedurende de laatste decennia toch aanzienlijk. In vroeger tijden was de mortaliteit een factor om rekening mee te houden en ernstige sequelae als pulmonale hypertensie werden geregeld gediagnosticeerd tijdens poliklinische controles. Momenteel is de late mortaliteit, het aantal rest VSD's en het percentage pulmonale hypertensie enorm afgenomen en komt eigenlijk nauwelijks meer voor.

Niettegenstaande de gunstige prognose werd in onze studie in een klein aantal patienten een milde aorta- of mitralis insufficiëntie waargenomen en vertoonden sommige patiënten een fractionele verkortingsfractie beneden de gehanteerde ondergrens van 30%. In onze studie vertoonden patiënten die geopereerd werden in de jaren 70, regelmatig pulmonale hypertensie; bij onze patiënten die in de jaren 90 werden geopereerd waren geen tekenen van pulmonale hypertensie meer aanwijsbaar.

Hoofdstuk 7

Kinderen en adolescenten met een AHA die daarvoor invasief zijn behandeld, hebben meer last van emotionele- en gedragsproblemen dan patiënten uit de gemiddelde populatie. Deze problemen hebben vaak een negatieve invloed op de kwaliteit-van-leven van patiënten, die niet alleen wordt bepaald door de afwezigheid van ziekte, en hebben tevens de neiging in sterkere mate te persisteren bij het toenemen van de leeftijd. Wij bestudeerden in welke mate de factoren die geassocieerd zijn met de medische behandeling op vroege leeftijd, voorspellend zijn voor psychologisch disfunctioneren en mogelijk ook voor secundaire emotionele- en gedragsproblemen. Om deze factoren te isoleren werd de complete medische levensloop van geboorte tot aan het moment van de studie bestudeerd.

Onze studie toonde aan dat hartmedicatie die gegeven werd voordat de invasieve behandeling plaatsvond, een significante voorspeller was voor emotionele- en gedragsproblemen op lange-termijn. Opmerkelijk was de bevinding dat palliatieve interventie voordat de invasieve behandeling plaatsvond, een significante voorspeller was voor minder emotionele- en gedragsproblemen. Verder volgde uit het onderzoek dat patiënten die een operatie ondergingen vanwege een ASD-II, een ballondilatatie vanwege PS of een palliatieve Rashkind-procedure voor TGA een lager risico hadden emotionele- en gedragsproblemen te ontwikkelen dan patiënten die een operatie ondergingen vanwege een VSD.

Behalve voor externaliserende problemen is het type van invasieve behandeling niet significant geassocieerd met emotionele- en gedragsproblemen, zoals gerapporteerd door de ouders van de patiënten.

Helaas, hebben we geen oorzakelijke verklaring kunnen vinden voor het verhoogde risico op het optreden van emotionele- en gedragsproblemen.

Hoofdstuk 8

Dit hoofdstuk bevat een algemene discussie met een speciale focus op de gevolgen van het steeds toenemende aantal patiënten met AHA voor de dagelijkse praktijk van de huisarts.

Geconcludeerd werd dat nascholing en training van huisartsen door kindercardiologen en congenitaal cardiologen onontkoombaar is om de follow-up van patiënten met AHA en huisartsenpraktijk nader tot elkaar te brengen. Protocollen en standaarden zijn daarbij tevens noodzakelijk.

DANKWOORD

Het schrijven van dit proefschrift is, zachtjes gezegd, geen korte termijn project geweest.

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Pa, het is verschrikkelijk jammer dat je de verdediging van het proefschrift niet meer mee hebt kunnen maken.

Marlies, ik houd van je.

CURRICULUM VITAE

Wilfred de Koning werd op 14 mei 1956 geboren in Delft. Na het behalen van zijn VWO diploma aan het Christelijk Lyceum Delft, rondde hij een studie biochemie af aan het Van Leeuwenhoek Instituut te Delft.

In 1984 startte hij met de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam, welke in 1990 werd afgerond met het behalen van de artsenbul. Vervolgens werkte hij gedurende 3 jaar als arts-assistent klinische genetica en gynaecologie achtereenvolgens in het Dijkzigt-ziekenhuis te Rotterdam en het Reinier de Graaf Ziekenhuis te Delft.

Hierna werkte hij enkele jaren als korpsarts bij het Korps Landelijke Politiediensten te Driebergen.

In 1997 werd gestart met de huisartsopleiding te Rotterdam (opleider: Prof.dr. S. Thomas).

Nadat in 2000 de registratie als huisarts een feit was, begon hij naast zijn werk als huisarts met het geven van klinisch vaardigheden onderwijs op de afdeling PKV(praktische klinische vaardigheden) van het ErasmusMC te Rotterdam, waarvan hij ook enkele jaren afdelingshoofd was. Tegelijkertijd verzorgde hij samen met Prof.dr. W.A. Helbing de huisartsennascholing "kindercardiologie voor de huisarts".

Medio 2002 startte hij met een promotieonderzoek op de afdeling kindercardiologie (promotor: Prof.dr. W.A. Helbing) van het ErasmusMC/Sophia te Rotterdam. Dit onderzoek vond plaats in samenwerking met de afdeling cardiothoracale chirurgie (afdelingshoofd: Prof.dr. A.J.J.C. Bogers) en de afdeling cardiologie (epidemioloog: Dr. R.T. van Domburg).

Wilfred de Koning is getrouwd met Marlies de Groot en woont in Gorinchem.