Congenital heart disease at adult age

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Two roads diverged in a wood, and I-
I took the one less traveled by.

Robert Frost from: “The road not taken”

Aan Frank
Aan Leontien, Michiel, Evianne en Sietske

Contents

Chapter 1

Introduction

Congenital cardiac defects are by far the most common congenital anomalies. Of all live births around the world, approximately 1% is born with congenital heart disease.[1] This number is even higher if patients with a bicuspid aortic valve are included.[2] Accordingly, in the Netherlands every year around 1800 children are born with a congenital heart defect. Of these, about 50% cure spontaneously or do well without medical or surgical treatment. In the 1960's, before the development of cardiac surgery with cardiopulmonary bypass, about 50% of the children with congenital heart disease requiring therapy died within the first year of live and less than 15% reached adulthood.[3] Especially patients with transposition of the great arteries had a very poor survival: 90% of the patients died in the first month of life and less than 1% reached adult age. Of tetralogy of Fallot patients 10% survived until adult age.

Rapid progress has been made over the past 30 years in the diagnosis and surgical treatment of congenital heart disease. Survival into adulthood became possible since the introduction of open-heart surgery with the use of cardiopulmonary bypass. Currently, instead of 85% *mortality* in the first 20 years of life, in the group of patients that require therapy, the 20-years *survival* became 85% or more. More accurate diagnosis, improved surgical skills and dedicated postoperative care have lead to a decline in peri-operative mortality and provided treatment options for complex congenital cardiac defects that had been considered as inoperable until recently. As a consequence, the number of patients requiring follow-up has increased, as well as the complexity of their residual defects.[4,5] Total correction is rare and most patients have residual lesions and sequelae, requiring life-long follow-up.

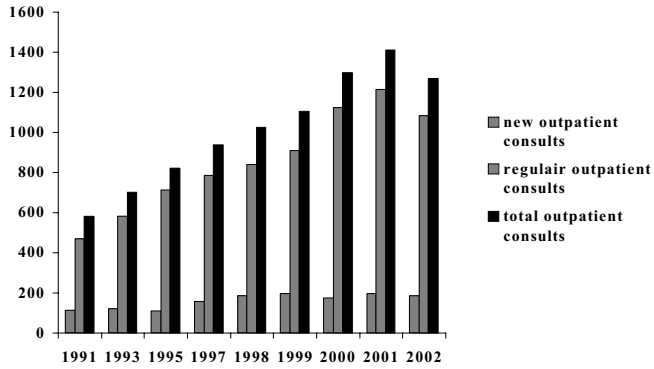
Because many patients now reach adult life and adult cardiologists – not trained for the diagnosis and treatment of congenital heart defects - are inheriting these patients from their pediatric colleagues, a new subspecialty in cardiology has been created: adult congenital heart disease. Pioneers in this field like Joe Perloff and Jane Somerville have made a plea for dedicated care in specialised centres to establish optimal care and to collect follow-up data to provide rational advice about lifestyle and future outlooks.[6,7] In the 1990's, the Canadians were the first to put together guidelines for adult congenital heart disease and based on these, guidelines were composed and published by the working group for congenital heart disease of the Netherlands Society of Cardiology in 2000.[8]

In the Netherlands, it is estimated that at least 25.000 adults, but maybe as much as 70.000 adults with different types of congenital heart disease are alive; accurate statistics on prevalence rates are lacking. This is one of the reasons why in the Netherlands a nation-wide database is being created for adults with congenital heart disease: the Concor database. Estimates from the United Kingdom suggest that in the year 2000 there were close to 150.000 adults with congenital heart disease in Great Brittain.[9] This number is growing with 5% per year. Whereas in the past 30 years the majority of patients with a congenital heart defect were children, nowadays the adult population has outnumbered the paediatric population and the distribution of healthcare resources will need to be modified. The health care systems in most developed countries have not yet properly addressed the needs of these

adult patients.[10] There is a serious shortage of professionals trained to take responsibility for these adult patients. New resources should be allocated to this growing population. Expert skills are required for cardiologists and cardiac surgeons working in this field, but also additional services in magnetic resonance imaging, interventional catheterisation, electrophysiology, high risk pregnancy and reproductive counselling are required.

In Rotterdam there has been a large increase in adults visiting the cardiology department, requiring and seeking specialised care over the past 15 years. The adolescents and adults are being referred from the Sophia Children's hospital, but also about 50% of the patients are referred from other hospitals. A stable growth occurred in the number of patients seen annually (Figure 1). With a total number of 2400 adult congenital patients, the Thoraxcentre is one of the larger centres for adult congenital heart disease.

Figure 1 Adults with a congenital heart disease, outpatient clinic



The prevalence of the various congenital hearts defects in adults is continuously monitored in the Netherlands. All large centres for adult congenital heart disease in the Netherlands participate and include their patients, with permission, in this nation-wide database. Figure 2 shows the prevalence of the different diagnosis in the Concor database. Also DNA material was gathered in these patients.

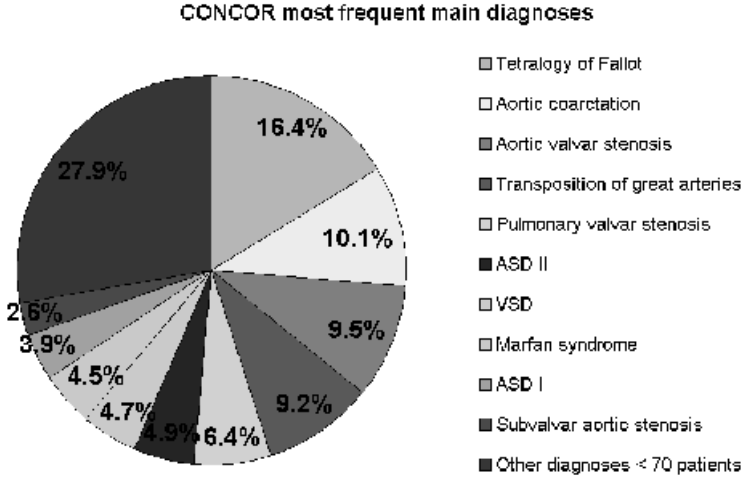
Although we are grateful for the progress that has been made, residual defects and late complications are not uncommon and it remains unclear whether life expectancy in these patients is normal. Besides long-term survival, also morbidity is of great interest. Many patients have residual lesions requiring additional medical or surgical treatment during follow-up, in particular for arrhythmias, ventricular dysfunction, and valve regurgitation. A clear need exists to understand better the late pathophysiology after surgery and define the mode and optimal timing of further interventions including drug therapy, catheter interventions and surgical procedures.

The collection and analysis of long-term follow up data is an important method of gaining more knowledge in this field and will help paediatric cardiologists and surgeons to modify early management to optimise later outcome.

Furthermore, as patients with congenital heart disease reach their 20s, insurability increasingly becomes an issue. Prospects for insurance for young adults with complex congenital heart lesions are poor. Current practise is not based closely on

the limited available knowledge of natural history of congenital heart disease. As additional long-term survival data become available on the natural and post operative survival of these congenital defects, it is hoped that insurance requirements will be modified to afford this group the insurance coverage needed to obtain adequate medical and financial security.

Figure 2 Concor database



Besides mortality and morbidity, psychosocial problems play an important role in this particular patient population. Chronic illness, scars, and limitation of activities may interfere with a normal social life. Our efforts should also focus on the quality of life. Advice is often sought on sports participation, driver license, sexual intercourse, employment, and insurance. Many affected women want to have children of their on. Pregnancy however, is associated with profound physiological cardiovascular changes. Maternal cardiac defects and cardiovascular function have a mutual impact on the course and outcome of pregnancy.[11]

The aim of the present thesis is to present the long-term outcome after surgery for congenital heart disease of patients operated at young age, who are now adults and to give an overview of the problems seen in adult patients with congenital heart defects.

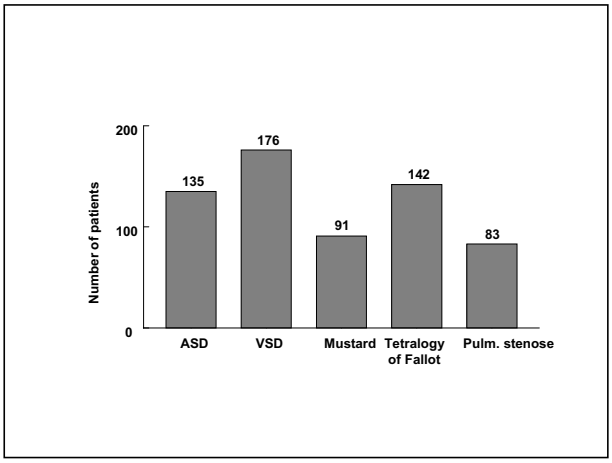
Specifically the aim of the present study is:

1. To present the long-term outcome of patients with congenital heart disease, including mortality, incidence of arrhythmias, need for reintervention and functional status.
2. To determine the changes over time in adults with congenital heart disease in an unselected cohort of operated patients.
3. To assess the importance of the different determinants (for example age at operation and cardiac diagnosis) on long-term survival and morbidity.
4. To describe the psychosocial functioning in adults with congenital heart disease.
5. To give information on pregnancy in adults with congenital heart disease.

We studied the long-term outcome of all patients operated in Rotterdam at young age (<15 years) between 1968, the year that open-heart surgery started in Rotterdam, and 1980. In this “Quality of life” study, the total cohort of consecutively operated patients with the 5 most common heart defects was systematically studied, to avoid selection bias of worse cases. The long period of follow-up (22-34 years) allows good insight in problems occurring during childhood and (young) adulthood. At follow-up in 1990 [12,13] and again in 2001 the patients underwent an extensive clinical evaluation and were studied with electrocardiography, echocardiography, exercise testing, and 24-hour Holter monitoring. What further distinguishes this study from other studies is the psychological evaluation of patient’s “quality of life”. Susan van Rijen, psychologist, has presented the psychological part of this study as a thesis in 2003.[14]

The 5 most common anomalies operated in childhood forming the basis of the “Rotterdam Quality of life study” are atrial septal defect (ASD), ventricular septal defect (VSD), transposition of the great arteries operated with a Mustard procedure (Mustard), tetralogy of Fallot (TOF) and pulmonary stenosis (PS). The number of patients in the different diagnosis groups is shown in Figure 3.

Figure 3 Number of patients operated upon in the period 1968-1980; the larger diagnosis groups



We studied late survival, but also the incidence of problems such as reoperations, major arrhythmias, and heart failure and we analysed the functional status. Apart from the “Rotterdam quality of life study” other groups of adult patients with congenital heart disease deserve attention. Coarctation of the aorta used to be thought of as a correctable lesion, but also these patients have residual lesions.[15] Particular attention is necessary for associated bicuspid aortic valve pathology and aortic arch problems. Furthermore, the first results of adult patients with complex heart disease treated with a Fontan circulation are presented. An overview of the psychological results of the “Quality of life study” is given and the aspects of congenital heart disease concerning the management of pregnancy and inheritance risks are discussed.

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Chapter 2

Excellent survival and low incidence of arrhythmias, stroke and heart failure long-term after surgical ASD closure at young age (a prospective follow-up study of 21-33 years)

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Abstract

Aims
Although studies have suggested good long-term results, arrhythmias, pulmonary hypertension and left ventricular dysfunction are mentioned as sequelae long-term after surgical atrial septal defect closure at young age. Most studies were performed only by questionnaire and in a retrospective manner. The long-term outcome is very important with regard to employability and insurability.

Methods and Results
One hundred thirty five consecutive ASD-patients, operated in childhood, were studied longitudinally with ECG, echocardiography, exercise testing and Holter-recording 15 (10-22) and 26 (21-33) years after surgery. During follow-up no cardiovascular mortality, stroke, heart failure and no pulmonary hypertension occurred. Symptomatic supraventricular tachyarrhythmias were present in 6% after 15 years, and an additional 2% occurred in the last decade; 5% needed pacemaker implantation. No relation was found between arrhythmias and the type of ASD, baseline data, right ventricular dimensions, or age at operation. Left and right ventricular function and dimension remained unchanged. Slightly more patients had right atrial dilatation at last follow-up. Exercise capacity was comparable with the normal Dutch population.

Conclusions
The long-term outcome after ASD closure at young age shows excellent survival and low morbidity. The incidences of supraventricular arrhythmias is lower then in natural history studies of ASD patients and also lower then after surgical correction at adult age.

Introduction

Secundum type atrial septal defect can cause volume overload of the right heart with late development of right heart failure, elevated pulmonary vascular resistance, atrial arrhythmias, or systemic embolism.[1 - 4] Closure is recommended to avoid these sequelae. More recently atrial septal defect closure with a device using cardiac catheterization has gained acceptance.[5] Small residual shunts are often found with

this technique.[6] For comparison of surgical and device closure it is important to have good insight in the long-term outcome of surgical correction. Results of medium-term follow-up study after surgical correction are good, but prospective studies of long-term follow-up focussing on arrhythmias, cardiac failure, exercise capacity, residual shunts and stroke are rare. It has been postulated, that after early repair of atrial septal defect, the survival is good, but sinus node dysfunction, atrial fibrillation and flutter, right ventricular dilatation, pulmonary hypertension and left ventricular dysfunction are mentioned as sequelae,[7 - 13] although the incidence of these sequelae in consecutive series of patients who were operated at young age is not known. Murphy et al studied the 27-32 years outcome after surgical repair of ASD in all age groups and the incidence of postoperative atrial arrhythmias appeared related to the age of the patient at the time of repair.[8] However, this study included only 33 patients operated at young age (operated <11 years) and was performed retrospectively and by written questionnaires and telephone interviews. Meijboom et al reported a good outcome 9-20 years after ASD closure at young age, with a low incidence of symptomatic arrhythmias, however signs of sinus node disease and ventricular ectopy were found on 24-hour Holter recordings in up to 45% of the patients.[14]

The aim of this study is to provide data on mortality and morbidity, which is critically important with regard to the employability and insurability of the long-term survivors of repair of atrial septal defects, and also can be used for comparison with the recently developed device closure techniques.

We present the longitudinal follow-up of 21-33 years (mean 27 years) after surgical closure of an atrial septal defect in all 135 patients who underwent this operation at the Thoraxcentre between 1968 and 1980 and were < 15 years of age at the time of surgery. Stroke, heartfailure, incidence of arrhythmias, changes in ECG, exercise capacity and echocardiographic parameters were studied. Furthermore, the predictive value of the asymptomatic arrhythmias seen on the Holter recordings ten years ago is determined. [14]

Methods

Patients

All patients who underwent surgical repair for secundum type ASD or sinus venosus type ASD at our institution between 1968 and 1980 and who were < 15 years of age at the time of the operation were included in the study. The first follow-up study was performed in 1990,[14] the second follow-up study from September 2000 to December 2001. The cardiac examination included medical history, physical examination, standard 12-lead electrocardiography (Holter), 24-hour ambulatory electrocardiography, echocardiography, and bicycle ergometry. If the patient refused to visit the clinic, a written questionnaire was sent to the patients to obtain information on morbidity. The institutional Medical Ethical Committee approved the study. All patients gave their consent.

Electrocardiography

Standard 12-lead surface electrocardiograms were analysed for the height of the P wave (measured in lead II), duration of the P wave and the PR interval (measured from the initial deflection of the P wave to the initial deflection of the QRS complex). A first-degree atrioventricular block was defined by a PR interval > 200 milliseconds.

Furthermore, the widest QRS duration was determined (from the initial deflection of the QRS complex to where the terminal deflection crosses the baseline, taken in any chest lead with the widest complex and where the deflections were acute enough to permit accurate assessment). A QRS duration > 120 msec was defined to be a complete bundle branch block. A single observer made all ECG measurements (JR-H).

Holter monitoring
A three-channel recorder was used. Sinus node dysfunction was assessed during 24 hour Holter monitoring using the modified Kugler criteria: nodal escape rhythm, sinusarrest > 3 sec or severe sinusbradycardia (<40 beats/min at night or <50 beats/min during daytime).[13]

Echocardiography
Two-dimensional echocardiography and echo-Doppler studies were performed using a Hewlett-Packard Sonos 5500 echocardiograph. All echocardiographic studies were performed on the same machine. Left atrial dimension and left ventricular end-diastolic and end-systolic dimensions were assessed using M-mode echocardiography in the parasternal view. A left atrium dimension > 45 mm and a left ventricular end-diastolic dimension of > 58 mm were considered enlarged. A fractional shortening less then 0.30 was defined as decreased. Parasternal, apical four-chamber and subcostal views were used to assess right atrium and right ventricular dimensions. This was done by means of visual estimate by two experienced cardiologists (FM and SS). Multiple echocardiographic views were examined using colour flow to identify residual shunts. Doppler-echocardiography was used for the assessment of blood flow velocities. Right ventricular systolic pressure was estimated from tricuspid regurgitation jet velocity; diastolic pulmonary pressure from the pulmonary regurgitation flow velocity. Pulmonary hypertension was defined as a tricuspid regurgitation flow velocity > 3.0 or a pulmonary regurgitation flow velocity > 2.5 m/sec.

Bicycle ergometry
Maximal exercise capacity was assessed by bicycle ergometry with stepwise increments of workload by 20 Watts per minute. Exercise capacity was compared to that in normal individuals corrected for age, sex, and body height. Exercise capacity < 85% of the predicted value was considered to be decreased.

Arrhythmias were defined to be symptomatic if antiarrhythmic medication was prescribed, cardioversion was necessary, catheter ablation or surgical arrhythmia treatment had been applied, or pacemaker implantation had been necessary. Major Events were defined as cardiac surgery, stroke, symptomatic arrhythmia, or an episode of heart failure.

Data analysis
Data are presented as mean values and standard deviation, unless indicated otherwise. The Chi-square and Fisher's exact test were used for the comparison of discrete variables. The Student t-test was used to compare continuous variables. The level of significance was chosen at $p < 0.05$.

Tests were performed for the total group of patients, as well as separately for the secundum type ASD and the sinus venosus type group. Results of the total group

will be presented, unless significant differences were observed between these 2 sub-groups.

Results

Patients

All 135 patients who had undergone primary surgical ASD (secundum and sinus venosus type) repair in the Thoraxcentre between 1968 and 1980 at age < 15 years, were included. A secundum type ASD was present in 105, and a sinus venosus type ASD in 30 patients. Age at operation was 7.5 ± 3.5 years (range 0 to 14). There was no in-hospital or early mortality. The baseline characteristics off all 135 patients are described in Table 1.

Table 1 Demographic data, data of pre-operative cardiac catheterisation and surgical data showing the group in total, the group investigated in 1990 and in 2001 and finally the group who did not participate in the second follow-up study (no second study)

	Total	1990	2001	No second study
Number of patients	135	104	94	41
Male	59 (44%)	44 (42%)	39 (41%)	20 (49%)
Female	76 (56%)	60 (58%)	55 (59%)	21 (51%)
Cardiac catheterisation				
QP-QS ratio	2.3:1	2.3:1	2.3:1	2.3:1
Peak syst. Press PA	26	26	26	26
PAPVD	27%	26%	26%	27%
Surgical data				
Age at operation (yr)	7.5 ± 3.5	7.3	7.5	7.5
Complete CPB (% of pts)	96	96	96	96
Direct closure (% of pts)	76	75	75	76
Closure with patch (% of pts)	24	25	25	24
Sinus venosus type ASD (% of pts)	22	22	23	21
Follow-up since surgery		15	26	-
Age at the time of study		22	33	-

QP-QS ratio = ratio pulmonary flow -systemic flow; PA = pulmonary artery; PAPVD = partially abnormal pulmonary venous drainage; CPB = cardiopulmonary bypass

The details of preoperative clinical findings, including cardiac catheterisation, data on surgical technique and postoperative course have been described earlier.[14] Information on survival was obtained in all 135 patients. During follow-up, no cardiovascular mortality occurred, 1 patient died, due to suicide, 15 years after his operation, 134 survived. Survival and survival free of major events are given in Figure 1.

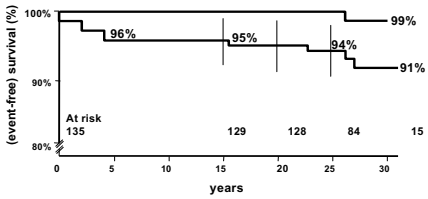

Figure 1 (event-free) Survival after ASD closure
Survival and survival free of major events (death, n=1; cardiac surgery, n=1; stroke, n=0; symptomatic arrhythmia, n=10; episode of heart failure, n=0)

After a mean follow-up of 15 years (range 10-22), 104 patients (77%) participated in the first follow-up study.[14] Of these, 94 patients (70% of the original 135 patients and 90% of the 104 patients studied in 1990) fully participated in the second follow-up study after a mean follow-up of 26 years (range 21-33) after surgery with a mean age at the time of study of 33 years.

No significant differences were found between the baseline characteristics of the patients who participated and the patients who did not participate in the follow-up studies (Table 1).

The four patients who received the written questionnaire returned this, and they are in good clinical health, have not been admitted to the hospital and have not experienced tachyarrhythmias.

Major cardiac events

Before 1990 one additional cardiac operation was performed for closure of a patent arterial duct. No cardiac operations were necessary between 1990 and 2001. No stroke and no episodes of heart failure occurred during follow-up. No patient was using diuretics. In 1990 symptomatic supraventricular arrhythmias were present in 7 patients (6%): 3 were treated medically for periods of atrial flutter or fibrillation, and 4 others needed pacemaker implantation. Of these 7 patients, 3 were readmitted between 1990 and 2001: one patient suffered from pacemaker endocarditis, he was treated with antibiotics for six weeks and the pacing system was replaced, while 2 other patients needed pacemaker battery replacement. Between 1990 and 2001, three additional patients had new symptomatic arrhythmias: one needed pacemaker implantation for sinus node disease, one patient had recurrent atrial flutter treated with several electrical cardioversions and radiofrequency catheter ablation, and one patient received medical therapy for supraventricular arrhythmias.

Analyses were performed, investigating the role of localisation of the ASD (secundum type or sinus venosus type), baseline data (such as pre-operative shunt size, age at operation, year of operation, and surgical techniques), right ventricular and atrial dimensions at follow-up, age at follow-up and duration of follow-up in relation to the presence or absence of symptomatic arrhythmias. No relation was found.

Medical history and physical examination

When questioned about their current general health, 88.3% considered their health as very good or good, and 11.7% as moderate. Nobody judged it as bad. This is not

different from the health assessment of the normal Dutch population.[16] Patient's own appreciation of the physical condition was in 13% better, 51% the same, 33% slightly worse and 3% much worse compared with that of eleven years ago.[14] On the question whether the patients suffered from palpitations 20% answered yes in 1990 and 28% in 2001. Physical examination revealed that the mean length of the patients remained unchanged (172.4 mm in 1990 and 172.5 mm in 2000), whereas the mean weight rose from 64.1 kg in 1990 to 73.7 kg in 2000 ($p<0.0001$). The mean pulse rate lowered from 72 to 67 beats per minute ($p=0.0004$). Signs of heart failure were not found.

Electrocardiography

Twelve-lead electrocardiograms and 24-hour ambulatory electrocardiograms data are presented in Table 2.

Table 2 Standard 12-lead electrocardiogram and 24 hour Holter electrocardiogram

	1990	2001	*P* value
ECG			
Rhythm			
Sinus	90%	89%	ns
Atrial	6	5	
Nodal	1	2	
Atrial flutter	-	1	
Pacemaker	3	3	
PR interval	153.7	153.2	ns
PR > 200 ms		5%	ns
QRS duration	88.3	96.1	<0.0001
QTc segment	350	388	ns
P-wave duration	84	85	ns
P-wave height in II	0.30	0.29	ns
P-wave morph. normal	87%	81%	ns
P-wave axis	46'	40'	ns
QRS axis	63'	54'	0.0006
No LVH or RVH	95.9%	95.4%	ns
24-hour Holter			
Supraventricular arrhythmias	45	36	0.02
Sinusnode disease	39	27	0.03
SVT	6	18	0.3
Paroxysmal A fibrillation	0	0	ns
Paroxysmal A flutter	0	2	ns
Ventricular arrhythmias	43	25	0.02
Multi PVC/doublets	39	23	0.01
VT 3-10 complex	3	4	ns
VT > 10 complex	-	-	
Conduction disturbances	17	8	0.01
First degree AV block	14	8	ns
Second AV block	2	-	ns
Third AV block	-	-	

SVT=supraventricular tachycardia; PVC=premature ventricular complexes; AV=atrioventricular

Sinus rhythm was seen in 1990 in 90% of the patients and 89% in 2001. The PR-interval did not change during this 10-year period. P-wave duration and p wave height did not change significantly in 10 years time. The QRS-duration increased, but no new bundle branch block occurred.

Holtermonitoring
On 24-hour Holter 2 patients showed paroxysmal atrial flutter in 2001, which was not present in 1990. These 2 patients did not differ from other patients with regard to right atrial enlargement, right ventricular dilatation or left atrial enlargement. Signs of sinus node dysfunction were found in 39% in 1990, and 27% in 2001. One of the patients needed pacemaker implantation in the period 1990-2001. Ventricular arrhythmias including multiform premature ventricular complexes, doublets and short ventricular tachycardias (3-10 complexes) were seen on Holter in 1990 in 43% of the patients. During the following ten years, none of these patients experienced symptomatic ventricular arrhythmias or sudden death and the incidence of ventricular arrhythmias on 24-hour holter diminished to 25% in 2001.

Echocardiography
Echocardiographic findings are summarised in Table 3 and 4. Residual shunts were not found. Dimension of right ventricle, left atrium and left ventricle remained unchanged over time. The percentage of patients with right atrium dilatation increased from 5.8% in 1990 to 18.7% in 2001 (p=0.5).

Table 3 Echocardiograpic parameters comparing 1990 and 2001

	1990	2001	P value
RA dilatation	5.8%	18.7%	0.5
RV dilatation	26.0%	23.5%	0.7
LA dilatation	10.0%	5.9%	0.5
LV dilatation	9.5%	5.7%	0.5
LV systolic function normal	97.1%	95.5%	ns
RV systolic function normal	100%	100%	ns
Valve insufficiency (more then trace)			
AoI	0%	1.1%	ns
MI	11.5%	13.5%	ns
PI	44.2%	45.0%	ns
TI	42.3%	48.3%	ns
Vmax TI	2.1 m/s	2.2 m/s	ns
Vmax PI	1.6 m/s	1.5 m/s	ns

RA=right atrium, RV=right ventricle, LA=left atrium, LV=left ventricle, AoI=aortainsufficiency, MI=mitral insufficiency, PI=pulmonic insufficiency, TI=tricuspid insufficiency, Vmax=maximal velocity found with doppler echocardiography

Mitral valve regurgitation did not progress in ten years and none of the patients developed substantial pulmonary regurgitation. Hemodynamically insignificant pulmonary and tricuspid regurgitation did not progress, but one patient developed severe aortic regurgitation. No pulmonary hypertension was found and estimated pulmonary artery pressure was stable over time. Left and right ventricular function remained unchanged over the last ten years, and none of the patients was having a left ventricular shortening fraction less then 20% at last follow-up. Although 20% of

the patients had a left ventricular shortening fraction between 20 and 30%, most of these patients had post-operative abnormal septal motions, but were judged to have a further normal systolic function, only 4.5% of the total group was judged as having diminished systolic left ventricular function. Only one patient showed paradoxical septal motion.

Table 4 Echocardiographic parameters 2001 in detail

		enlarged			
Chamber size	normal		mild		moderate
RA	67%		14.3%		18.7%
RV	76.9%		11.0%		12.1%
LA	85.5%		5.5%		7.7%
LV	93.3%		4.4%		2.2%
Hypertrophy					
LVH	94.8%		2.6%		2.6%
RVH	94.5%		5.5%		-
Function					
LV function	95.5%		4.5%		-
RV function	100%		-		-
	>30%		20-30%		>20%
Left ventricular fractional shortening	80%		20		-
Valve regurgitation	no	trace	1+	2+	3/4+
AoI	98.8	1.1	-	-	1.1
MI	52.8	33.7	9.0	3.4	1.1
PI	29.2	25.8	36.0	9.0	-
TI	13.5	38.2	28.1	14.6	5.6
	<2.5 m/s		2.5-3.0 m/s		>3.0 m/s
Vmax TI	88.5%		11.5%		-
	<1.5 m/s		1.5-2.0 m/s		>2.0 m/s
Vmax PI	46.5%		49.3%		4.2%

See legend Table 3. LVH=left ventricular hypertrophy, RVH=right ventricular hypertrophy

Bicycle ergometry

The results of exercise testing in 1990 and 2001 are given in Table 5. The exercise capacity, corrected for age, sex and body height, diminished by 9% in ten years, but remained comparable with the total Dutch population. During exercise testing, no new arrhythmias were revealed. Pre-operative findings, surgical procedures, echocardiographic parameters, age at the time of operation or duration of follow-up were not predictive for diminished exercise capacity.

Table 5 Bicycle ergometry

	1990	2001
number of patients	101	91
max heart rate	92%	92%
max exercise capacity	104%	95%
significant arrhythmia	-	-

Type ASD

Sinus venosus type ASD and secundum type ASD differed with regard to sex: the sinus venosus type ASD-patients were predominantly males (66%), whereas in the secundum type ASD group we found predominantly females (63%), (p-value=0.004). Furthermore the patients with sinus venosus type ASD had greater shunts (shuntratio 2.6:1 versus 2.2:1 in the secundum type ASD patients, p=0.04), had more often partially abnormal pulmonary veins, and more often a patch was used during surgery (100% in the sinus venosus group versus 3% in the secundum ASD group). The sinus venosus type and secundum type ASD did not differ significantly with regard to the incidence of arrhythmias, the exercise performance or the outcome on echo-Doppler parameters (dimensions, ventricular function, valve insufficiency, or pulmonary artery pressure).

Discussion

The long-term outcome (21-33 years) of children who had undergone surgical closure of hemodynamically significant ASD was investigated in this study. Although the general opinion is that the long-term results will be good, no hard data are available. We present a unique longitudinal study of consecutive patients with long-term (21-33 years) follow-up, studied, not only with written questionnaire or telephone interview, but also with a thorough clinical investigation. We found an excellent survival with no cardiovascular mortality. Complications such as right heart failure, stroke or elevated pulmonary vascular resistance did not occur. Only one additional cardiac operation was performed (for closure of a patent arterial duct). No residual ASD was found. Pacemaker implantation was performed in 4 patients before 1990 and in 1 patient between 1990 and 2001. One pacemaker patient developed endocarditis.

The development of atrial arrhythmias is described after ASD closure, and has been studied thoroughly in adults.[8,17,18] Studies of long term follow-up in adults demonstrate that the incidence of new atrial arrhythmias is unchanged following surgical closure of ASD compared to those treated conservatively. Some studies suggest that older age at operation is a risk factor for persistent atrial arrhythmias and development of new atrial arrhythmias after surgery,[17-19] while the incidence of atrial arrhythmias appears lower in patients operated at younger age. Nevertheless, Meijboom et al reports up to 45 % of the patients having some form of asymptomatic atrial arrhythmias on Holter recording, 15 years after surgery.[8,14] In this same cohort of patients we observed a low incidence (2%) of symptomatic arrhythmias in the subsequent decade and 36% asymptomatic atrial arrhythmias. No patient had chronic atrial fibrillation, one patient developed persistent atrial flutter, one needed pacemaker implantation, and one patient received antiarrhythmic medication for supraventricular tachycardias. Thus, the predictive value of the asymptomatic arrhythmias seen on Holter recording seems limited. The prevalence of atrial fibrillation in the general population is studied mainly in older age groups and is estimated to be 3/1000 in those aged 45-49 years.[20] The reported incidence of atrial fibrillation and flutter in natural history studies of ASD patients is 15-40 percent in 30-35 year-olds and comparable with the incidence of arrhythmias after surgical ASD closure at adult age, and this is substantially higher then the 3% found in our study, suggesting that early closure is beneficial indeed.[1,17,18,20]

The aetiology of late atrial arrhythmias following surgical closure of ASD is not well explained. Long standing volume overload, varying degrees of pulmonary hypertension, ventricular dysfunction, congenital defects in the atrial conduction tissue, and surgical scars have all been implicated.[22,23] Our data imply that it is unlikely that the congenital defect in the conduction tissue is an important factor in the aetiology of the arrhythmias, since few symptomatic arrhythmias occurred. It is possible that the atria of young patients have greater remodelling potential and that this patient population may therefore be at lower risk for the development of late atrial arrhythmia's.[6] Transcatheter device closure may have an extra advantage over surgical closure on the incidence of arrhythmias, but improvement of right heart morphology after device closure and the effect of avoidance of an atriotomy scar remain to be determined.[24] Electrocardiographic parameters such as P wave height and PR interval, which may predict the occurrence of atrial arrhythmias, remained stable for ten years. This, together with the low incidence of new symptomatic arrhythmias in the last ten years, leads to the prediction that only few additional arrhythmias will develop in these patients. Continuing follow-up is warranted to verify this assumption.

The clinical condition of the patients appeared excellent at follow-up: the exercise capacity was comparable with normal individuals corrected for age, sex and body height. Furthermore, the incidence of right ventricular dilatation and valve regurgitation on echocardiographic images was low, and not different from ten years ago. The percentage of patients with a dilated right atrium increased from 5.8 in 1990 to 18.7% in 2001. This was not a significant increase ($p=0.5$), but also others reported a remaining dilatation of the right atrium after ASD closure compared to controls.[24]

Whether transcatheter device closure will have the same excellent results remains to be determined, especially while up to 50% of the patients have residual shunts after device closure after one year of follow-up.[6]

In our study we found no differences in outcome between the patients with sinus venosus type ASD and secundum type ASD with regard to the incidence of arrhythmias, exercise capacity and hemodynamic status.

Study limitations

In this study the follow-up is incomplete. After 15 years 104 (77%) and after 26 years, 94 (70%) from the originally 135 operated patients participated in the study. Since 1990 1 patient died, 5 were lost and 4 were unwilling to come to the hospital. Nevertheless, the latter 4 patients did return the questionnaire, and reported to be in good clinical health. Furthermore, we found no difference in characteristics between the patients who did and who did not participate in the follow-up study, so we expect that the incomplete follow-up will have no impact on the outcome of the study.

Conclusion

The long-term outcome after ASD closure at young age shows an excellent survival with no cardiovascular mortality and low morbidity. The development of supraventricular arrhythmias is lower then in natural history studies of ASD patients and also lower then after surgical correction at adult age. The clinical condition of the patients is very good and stable.

These excellent long-term results are critically important for the employability and insurability, and ASD patients should encounter no obstacles in finding jobs and have life insurance policies consistent with standard rates.

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Chapter 3

Outcome of patients after surgical closure of ventricular septal defect at young age: longitudinal follow-up of 22-34 years

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Abstract

Background
Long-term survival and clinical outcome after surgical closure of a ventricular septal defect is poorly documented. Such data are important for the future perspectives, medical care, employability, and insurability of these patients.

Methods
One-hundred-seventy-six consecutive patients underwent surgical closure of an isolated VSD between 1968 and 1980 in our hospital. A systematic follow-up study was performed in 1990 and again in 2001.

Findings
Late survival was poorer than in the general population. Pulmonary hypertension and right ventricular hypertrophy were present in the 4 patients who died suddenly, late after operation. During follow-up no new pulmonary hypertension became manifest. Re-operations were necessary in 6%. Some patients (4%) developed sinus node disease late after repair, requiring pacemaker implantation. At last follow-up (91 survivors) 92% of the patients were in NYHA class I. Pulmonary hypertension was found in 4%, and aortainsufficiency in 16%. Patients experience difficulties in application for insurance.

Conclusion
Among patients with surgically repaired ventricular septal defects, late results were good, although some late sudden deaths occurred in the patients with pulmonary hypertension. Furthermore, some patients developed sinus node disease late after repair, requiring pacemaker implantation. Employability is good, but pregnancy and insurance matters need further attention.

Introduction

Isolated ventricular septal defect (VSD) is by far the most common congenital heart defect, and surgical closure of a VSD is the most common open-heart procedure performed in pediatric cardiac surgery.[1] Apart from a high perioperative mortality, patients operated in the 1950's and 1960's showed a higher-than-normal prevalence

of sudden death and serious arrhythmia during follow-up.[2] Since then, significant changes have taken place such as early correction of a large VSD to avoid pulmonary vascular disease and broader indications for closure in patients with moderate shunts. Furthermore, many improvements in operative and perioperative care were achieved. It has been postulated that patients with surgically closed VSDs in the1970's do well, with a normal life expectancy. Most adult patients have been discharged from routine cardiological follow-up.[3,4] Partly as a result of this policy, data on late survival, sequelae such as arrhythmias, pulmonary hypertension and aortic insufficiency and employability and insurability is sparse.[5 - 10] This report describes the long-term survival and clinical course in a single center cohort of 176 consecutive patients operated upon in our institution between 1968 and 1980 at young age, with 22-34 years follow-up. Changes in ECG, exercise capacity and echocardiographic parameters were examined. Employability and insurability issues were addressed.

Methods

Patients

All 176 patients with surgical repair of an isolated ventricular septal defect at our institution between 1968 and 1980 at young age (<15 years) were included in this study. The year 1968 was chosen as starting point because in this year cardiac surgery was started in our center and 1980 was chosen to have more than 20 years follow-up. The details of preoperative clinical findings, including cardiac catheterisation, localization and type of ventricular septal defect, data on surgical technique and postoperative course have been described earlier and are summarized in Table 1.[4] After a median follow-up of 15 years (range 11-23 years), 109 patients (79% of those eligible for follow-up) participated in the first follow-up study performed in 1991.[4]

The target population of the second follow-up (2001) consisted of the 109 patients of the first follow-up.

The follow-up status was determined by examination at our institution and the cardiac examination included medical history, physical examination, standard 12-lead electrocardiography, 24-hour ambulatory electrocardiography (Holter), echocardiography and bicycle ergometry. Furthermore, a psychological interview was performed.

The Medical Ethical Committee approved the study. All patients gave their written consent.

Electrocardiography

Standard 12-lead electrocardiograms were analyzed for cardiac rhythm, the height of the P wave (measured in lead II), duration of the P wave and the PR interval. A first-degree atrioventricular block was defined by a PR interval > 200 milliseconds.

Furthermore the Median frontal plane P wave axis and QRS axis were determined, as was the widest QRS duration. A QRS duration > 120 msec was defined to be a complete bundle branch block: a positive QRS complex in lead V1 was categorized as right bundle branch block and a negative QRS complex as left bundle branch block. A single observer made all ECG measurements.

Holter monitoring
Sinus node dysfunction was assessed during 24 hour Holter monitoring using the modified Kugler criteria: nodal escape rhythm, sinusarrest > 3 sec or severe sinusbradycardia (<30 beats/min at night or <40 beats/min during daytime).[11] Ventricular tachycardia was defined as 3 or more consecutive ventricular beats with a heartrate of > 100 beats/minute.

Two-dimensional echocardiography
Echocardiography was performed using a Hewlett-Packard Sonos 5500 echocardiograph. M-Mode measurements of left atrial and left ventricular end-diastolic and end-systolic dimensions were made in the parasternal view. A left atrium > 45 mm and left ventricle end-diastolic dimension > 58 mm were considered enlarged. A fractional shortening of the left ventricle of < 30% was considered abnormal. Right ventricular dimensions and function were judged by visual estimate by two experienced cardiologists. Dimensions were scored as normal, mildly, moderately or severely dilated. Right ventricular function was graded as normal, mildly, moderately or severely impaired. Of each patient the study of 1990 was compared with that of 2001. The degree of tricuspid regurgitation (minimal, moderate, or severe) was estimated with color-Doppler by the width and length of the regurgitant jet. Pulmonary hypertension was defined by an early diastolic pulmonary regurgitation flow velocity of > 2.5 m/s or, in the absence of right ventricular outflow obstruction, a tricuspid regurgitation flow velocity > 3.0 m/sec. Multiple echocardiographic views were examined using color flow to identify residual shunts.

Bicycle ergometry
Maximal exercise capacity was assessed by bicycle ergometry with stepwise increments of the workload of 20 Watts per minute. Exercise capacity was compared to that in normal individuals corrected for age, sex and body height.

Cardiovascular events
Cardiovascular events are defined as any of the following: re-operation, pacemakerimplantation, tachyarrhythmia requiring treatment (medication, electrical cardioversion or ablation), endocarditis or congestive heart failure.

Data analysis
Data are presented as median and range, unless indicated otherwise. The Chi-square and Fisher's exact test were used for the comparison of discrete variables. The Student t-test was used to compare continuous variables. All tests used were two-tailed. The Mc Nemar test of symmetry was used to compare the 15- and 26 years outcome. Cumulative survival curves were constructed using the Kaplan-Meier method. Among patient subgroups the logrank test was used to compare survival curves. The level of significance was chosen at $p < 0.05$. Multivariable Cox-regression analysis was performed for survival.

The variables tested were birth weight, type of palliation, main pulmonary artery systolic pressure, pulmonary artery/aorta ratio, age at operation, year of operation, use of deep hypothermia, use of cold cardioplegia, aortic crossclamp time, right ventricular incision, peri-operative complications, residual lesions. Continuous variables were not categorised in the model.

The proportional hazards assumptions were tested by constructing interaction terms between the variables and time to each end-point. Cox regression analyses

showed no statistically significant interactions with time (each p>0.05). The model selection is based on the stepwise principle, where the limit to enter and to remove a variable was both 0.05.

Results

Patients

Median age at operation was 4 years (range 0 to 13). The baseline characteristics of all 176 patients are described in Table 1.

Table 1 Baseline characteristics of 176 consecutive patients who underwent VSD closure between 1968 and 1980

	Total group	1990	2001	p-value
Number of patients	176	109	95	
Age at operation in years	4 (0-13)	4 (0-13)	4 (0-13)	0.9
Age < 1 year in %	34	32	32	0.9
Age at the time of follow-up in yrs	-	19 (10-33)	30 (21-44)	
Time from OK to follow-up in yrs	-	15 (11-23)	26 (22-34)	
Preop RV syst pressure in mmHg	67 (40-112)	66 (40-110)	66 (40-110)	0.8
Pre op QP/QS	2.2 (0.7-6.0)	2.2(0.7-6.0)	2.2(0.8-6.0)	1.0
Pulm resistance in dyne/sec cm $^{-5}$	233(50-980)	246(62-825)	249(62-825)	0.9
Aortic cross clamp time in min	39 (10-85)	35 (14-80)	35 (14-80)	0.9
Type of VSD: perimemb in %	77	85	82	0.5
Previous PA banding in %	9	6	5	0.8
RV-incision in %	45	51	47	0.3

Numbers between brackets give the range

Information on survival is complete for the total cohort of 176 patients. Twenty-three (12%) patients died before 1991. Of the 109 patients who participated in the first follow-up study, 2 patients died, 7 were lost to follow-up and 5 participated only by written questionnaire. The remaining 95 patients (95% of those eligible for follow up) fully participated in the second follow-up study with a median follow-up of 26 years (range 22-34 years) after surgery, and with a median age at the time of study of 30 years (range 21-44). No significant differences were found between the baseline characteristics of the patients who participated in the follow-up studies and the patients who did not (Table 1). There were 57 males (60%) and 38 females (40%).

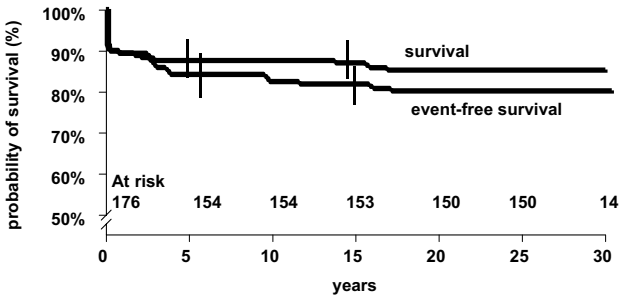
Mortality

Nineteen patients died within 30 days after operation (Figure 1). Late death occurred in 6 patients (4%). Of these 6 patients who died late postoperatively 4 had documented residual pulmonary hypertension and they all died suddenly respectively 3, 4, 16 and 18 years postoperatively. These 4 patients all showed right ventricular hypertrophy on their ECG. One patient died during re-operation for aortic valve surgery and 1 patient died of a non-cardiac cause (fire accident).

Cardiovascular events

The 25 years event-free survival for the hospital survivors was 80% (Figure 1). *Reoperations* were performed in 6 patients: 2 residual VSD (10 and 21 years after the initial operation), 1 discrete subaortic stenosis and 3 RV-outflow tract obstruction (at a median interval of 6 years after the initial operation). Additional cardiac surgery

Figure 1 (Event-free) survival after VSD closure



was performed in 4 patients: 1 persisting arterial duct, 1 aortic valve replacement after endocarditis, and 2 aortic coarctation. *Pacemaker implantation* was performed in 6 patients; 2 for surgical atrioventricular block shortly after operation and 4 because of sick sinus syndrome more than 15 years after surgery. One patient underwent *radiofrequency catheterablation* for intra-atrial reentry tachycardia. Two patients with co-morbidity, suffered from *endocarditis* late after VSD closure leading to aortic valve replacement in one, and pacemaker replacement in the other patient.

Clinical evaluation

Of the patients, 92% was in NYHA class 1, and 8% in class 2. Five patients (5%) were taking medication: oral anticoagulation in 1 (artificial aortic valve), betablockers in 2, and ace-inhibitors in 2 patients. Oxygen saturation (measured with Nellcor) was 98% (range 94-100%). No patient showed signs of heart failure.

Electrocardiography

The ECG findings are described in Table 2. We found no difference between transatrial and transventricular approach (with right ventricular incision) regarding the incidence of a right bundle branch block on the ECG during follow-up. A prolongation of the QRS-complex and P-wave duration occurred between 1990 and 2001.

Twenty-four hour ambulatory monitoring

None of the patients had atrial flutter or fibrillation on the 24-hour ambulatory monitoring in 1990 or 2001. Junctional escape rhythm was found in 2001 in 23% of the patients, signs of sinus node disease were found in 9% of the patients, but no ventricular pauses longer than 3 seconds occurred.

Ventricular tachycardia of more than 10 complexes were not found, and 8% showed ventricular tachycardia of 3-10 complexes.

Table 2 Standard 12-lead ECG long term after surgical VSD repair

	1990	2001	p-value
Number of patients	109	95	
Rhythm (%)			
Sinus	106 (97)	88 (93)	0.3
Nodal	1 (1)	2 (2)	
Atrial	1 (1)	1 (1)	
Pacemaker	1 (1)	4 (4)	
Aflutter	-	-	
PR interval ±SD (msec)	147 ±30	152 ±28	0.05
PR > 200 msec (%)	2	5	0.2
QRS duration ±SD(msec)	101 ±20	113 ±26	0.01
RBBB (%)	23	29	0.06
QTc segment ±SD(msec)	398 ±40	398 ±27	0.9
QRS axis ±SD (degree)	52 ±30	43 ±33	0.01
P duration ±SD (msec)	84 ±15	91 ±17	0.01
P-wave height ±SD (cm)	0.17 ±0.07	0.17 ±0.07	0.3
P-wave axis ±SD(degree)	39 ±26	35 ±27	0.09
LVH (%)	7	11	0.05
RVH (%)	8	7	0.5

Echocardiography

Echocardiography was performed in 95 patients (Table 3). Left ventricular dimensions were normal in 96% of the patients. Pulmonary hypertension was found in 4%. These 4% were not different from the total group concerning the age at operation. We found no change in median pulmonary artery pressure between 1990 and 2001. Aortic regurgitation was present at last follow-up in 15 patients (16%): mild in 13 and moderate in 2 patients. Over the last ten years 2 patients showed progression from mild to moderate aortic regurgitation. No severe aortic valve regurgitation was encountered and no significant change in mitral-, tricuspid- or pulmonary regurgitation was noted (Table 3). Using Cox multivariable regression we found no relation between the presence of moderate aortic or mitral insufficiency and the duration of follow-up, age at surgery, right ventricular incision during surgery, type of VSD or left ventricular function (fractional shortening on echo).

Exercise capacity

Ninety-three patients exercised to maximal effort. The median exercise capacity in these patients was 91% (range 43 -226) of the predicted values in 2001, while it was 100% in 1990. During the test 5 patients had an increase of ventricular extrasystoles and 1 patient developed supraventricular tachycardia. No ventricular tachycardia occurred. We found no relation between exercise capacity in 2001 and median pulmonary artery pressure before surgery, duration of aortic cross clamp time, presence or absence of a right bundle branch block on the ECG, young age (<1 year) at operation or left ventricular function (fractional shortening on echo).

Risk factors for late death

Multivariable Cox-regression revealed 2 predictors for late mortality (Table 4). A ‘median pulmonary artery pressure of more than 70 mmHg before operation’ and ‘perioperative complications’ (reoperation, arrhythmia, infection) were predictors for late mortality.

Table 3 Echocardiographic results in 95 patients after surgical VSD repair

	1990	2001	p value
Number of patients	109	95	
LA dimension ±SD (mm)	32 ±5	37 ±6	0.2
LVED dimension ±SD (mm)	50 ±4	52 ±5	0.1
LA dilatation (%)	4 (4)	9 (9)	0.02
LV dilatation (%)	11(10)	4 (4)	0.01
RA dilatation (%)	19 (20)	19 (20)	0.9
RV dilatation (%)	13(14)	13(14)	0.7
LVH (%)	5 (5)	9 (10)	0.1
RVH (%)	4 (4)	7 (7)	0.3
Mean FractShort.LV (%)	34	34	0.8
Good RV syst function (%)	109 (100)	94 (99)	0.8
Valve insuff (%)			
AoI	16 (15)	15 (16)	0.6
mild	16 (15)	13 (14)	
moderate	0	2 (2)	
MI	13 (12)	11 (12)	0.9
mild	13 (12)	11 (12)	
moderate	0	0	
PI	26 (24)	27 (28)	0.3
mild	26 (24)	25 (26)	
moderate	0	2 (2)	
TI	45 (41)	40 (42)	0.7
mild	43 (39)	36 (38)	
moderate	2 (2)	4 (4)	
Vmax TI ±SD	2.4 ±0.4	2.4 ±0.4	0.8
Vmax PI ±SD	1.5 ±0.3	1.6 ±0.3	0.6
Pulmonary hypertension (%)	7 (6)	4 (4)	0.4
Small residual VSD (%)	9 (8)	8 (8)	0.8

Table 4 Multivariable Cox regression
End point: late death (>1 year after surgery)

Independent predictors	HR	95%CI
- Median pulmonary artery pressure before surgery per 10 mmHg increase	1.29	[1.05-1.58]
- Post-operative complications	7.8	[2.6-24.1]

Social life

Of the 95 patients seen at last follow-up, 70% had some sort of relationship (stable relation 16%, living together 19%, married 35%). A total of 72% had no children, 12% had 1 child and 16% had 2 or more children. Regarding the daily activities, 82% of the patients had a paid job. On the question if the patient had ever encountered difficulties with respect to insurance policies, 75% of the patients answered yes. With

respect to which insurance policy, 33% had problems with health insurance, 42% with mortgage, and 55% with life insurance.

Discussion

This series is unique in that it comprises a cohort of consecutive patients operated at young age at a single institution with longitudinal follow-up of 22-34 years. Apart from a considerable historical early mortality (13%), we experienced 4% (6 patients) late mortality. This study also provides new data documenting sinus node disease developing late after surgery and insurability of the patients.

Mortality

The operative mortality of 13% found in this study represents the patients with large VSDs operated upon in the time period of 1968-1980. At present these figures have improved dramatically. The focus of this study was on late events in hospital survivors, and statistical analyses were confined to this patient population.

There was a 4% (6 patients) late mortality among the 153 patients who survived operation, and 5 of the 6 deaths were attributed to cardiovascular causes. This is higher than in the general population. For comparison, in patients undergoing surgical closure of atrial septal defect who were studied in the same manner, no cardiac deaths occurred during 26 years follow-up.[12] The most likely explanation for this late mortality is right ventricular hypertrophy due to long-standing right ventricular pressure overload, causing ventricular arrhythmias. In all 4 patients who died suddenly late after operation, right ventricular hypertrophy was found. Cardiac hypertrophy is the common denominator in all cases reported in detail of VSD-associated sudden death.[13] It is known that the incidence of ventricular arrhythmias and sudden death in *non-operated* VSD-patients is high (20-90%), suggesting that, damage to the ventricle is due especially to pressure overload.[2,13] Ventricular arrhythmias were found in 42% of our patients on ambulatory ECG monitoring in 1990, none of these patients experienced clinical significant arrhythmias or sudden death in the following 11 years. Therefore, we conclude that there is no clear predictive value of ventricular ectopic activity found on 24-hour Holter monitoring. Others reported ventricular arrhythmias varying from 18 to 39%.[8,10]

We did not find patients developing pulmonary hypertension late after surgery. Pulmonary pressure neither diminished, nor progressed during follow-up. Our study reports the late outcome of patients operated in the late 60s and 70s. Since then, changes have occurred and for some time, VSDs with large left to right shunts are treated in infancy and therefore in the present time pulmonary hypertension late after surgery will largely be prevented. The 4% of patients in our study with pulmonary hypertension at present are at risk for sudden death in the future and for these high-risk patients intensified surveillance is justified and maybe prophylactic implantation of an internal defibrillator should be considered.

Since no follow-up data are available for patients who died prior to the follow-up, we only included the follow-up data of the surviving patients. This may lead to biased results.

Clinical condition

The functional outcome in late survivors was good with the vast majority of patients being in NYHA class I, a median exercise capacity of 91% and only five patients (5%)

using medication. Although a second cardiac operation was necessary in 10% of the patients, in only 2% it concerned a residual VSD. A small, hemodynamically insignificant residual VSD was found in 8% of the patients, which is in line with, or slightly better than in other reports.[2,14]

Bacterial endocarditis occurred rarely (only 2 patients), and was not even directly related to the VSD: in 1 patient the aortic valve was involved and the other patient suffered from pacemaker-endocarditis. Also others report a very low incidence of endocarditis after VSD closure, so endocarditis prophylaxis should be given only in patients who have concomitant pathology such as pacemaker leads or valve disease or have a residual VSD. Routine-use of prophylaxis seems not indicated after successful closure of an isolated VSD. The occurrence of *aortic insufficiency* is one of the issues after VSD-surgery. The incidence in this cohort of patients was 16%, which is higher than in other reports.[2] In most studies, however, no extensive cardiovascular examination was performed. The degree of aortic insufficiency was mild and did not change significantly in 10 years time. Aortic valve surgery was necessary in 1 patient only, and that was because of endocarditis. Left ventricular dilatation was found in a minority of patients only. No significant heart failure was found and no signs of left ventricular dysfunction, which is very important for the future perspectives of these patients.

Conduction disturbances

Pacemaker implantation was necessary in 6 patients (4%). The 2 patients with surgical block had a pacemaker implanted shortly after surgery. Striking is the fact that 4 patients developed sinus node disease with need for pacemaker implantation more than 15 years after surgery. A possible cause of this late sinus node dysfunction is cannulation of the right atrium for cardiopulmonary bypass, but it is after a surprisingly long period of time that this sinus node disease becomes manifest.[15] In 1990 20% of the patients already had minor indicators of sinus node dysfunction, under which the 4 who needed the pacemaker implantation later on, confirming the progressive nature of the disease.[4] Furthermore, the PR-interval increased and even so the incidence of a first degree AV block. The prolongation of the QRS-complex may indicate late myocardial reaction to the earlier ventricular overload. The late occurrence of clinically significant sinus node disease necessitating pacemaker implantation has not been reported before in this patient group, perhaps because most of these patients do not have regular cardiological follow-up.

Social life

Employability is excellent in our patient's sample. It seems that finding a paid job is not a major issue in our group. However, starting a family seems more problematic. Only 28% of the patients had children, although the fast majority had a stable relationship. This is low compared with the general population.[16] The explanation may be fear that pregnancy may cause damage to the female patient or fear for congenital heart disease in the offspring. Another explanation may be that fertility is negatively influenced by heart surgery at young age. The numbers are relatively small in our study and more research is necessary in this field. Probably, more attention should be paid to give proper information to these patients about the different aspects of pregnancy. Finally, because the long-term prognosis is excellent in the absence of pulmonary hypertension, application for insurance should be able without problems in the large majority of patients.[17] However, 75% of the patients in

our study experienced obstacles to obtain insurance policies, especially with life insurance. Since the prognosis after surgical correction of VSD has further improved over the last 30 years, it is time that also insurability will improve in these patients.

Conclusion

Adults who underwent surgical VSD closure in childhood generally do well, but survival is lower than that of the general population. Late mortality was found in 4%, especially in the patients with pulmonary hypertension and right ventricular hypertrophy. In our study no new pulmonary hypertension late after surgery developed.
The overall clinical condition of the survivors at last follow-up was satisfying and complications such as endocarditis, arrhythmias and clinical significant aortainsufficiency occurred rarely. Sinus node disease requiring pacemaker implantation was found in 4% of the patients, more than 15 years after surgery. This underscores the need to follow these patients, who have been subjected to open heart surgery before 1980, indefinitely with special attention for the development of sinus node disease. Employability is good, but pregnancy needs further attention. The results of this study can be used as a guideline for insurance policies.

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Chapter 4

Long-term outcome after surgery for pulmonary stenosis (a longitudinal study of 22-33 years)

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Submitted

Abstract

Background
Long-term (>20 years) survival and clinical outcome are only partly documented in patients who underwent surgical repair for isolated pulmonary stenosis. Yet, such data are of critical importance for the future perspectives, medical care, employability, and insurability of these patients.

Methods
Ninety consecutive patients underwent surgery for pulmonary stenosis between 1968 and 1980 at the Thoraxcenter. A systematic follow-up study was performed in 1990 and again in 2001.

Findings
Survival was 96% after 25 years. Reintervention was necessary in 15% of the patients, mainly for pulmonary regurgitation. Right atrial and ventricular dilatation and paradoxical septal motion were associated with the need for reoperation. No major ventricular arrhythmias occurred. Supraventricular arrhythmias occurred, only in patients with severe pulmonary insufficiency and disappeared after reoperation. At last follow-up 67% of the patients was in NYHA class 1 and maximal exercise capacity was 90% of normal. Pulmonary insufficiency was present in almost all patients (94%).

Conclusion
Although long-term survival and quality of life are good, pulmonary regurgitation is found in almost all patients 22-33 years after surgical repair for isolated pulmonary stenosis. Reoperation for pulmonary insufficiency was necessary in 9%, especially after the transannular patch technique.

Introduction

Surgical valvotomy or valvectomy was the treatment of choice for valvular pulmonary stenosis before the use of balloon angioplasty.[1] The surgical approach evolved from closed valvulotomy, first performed in 1948, to open valvulotomy using inflow occlusion, and finally, open valvulotomy with the use of cardiopulmonary bypass.[2] With the latter technique the extent of surgery can be adapted to the needs of the individual patient and can vary from a simple commissurotomy, to a complete right

ventricular outflow tract reconstruction with a transannular patch or homograft. Current surgery is associated with low early mortality and good short to intermediate term results.[3,4] However, there are few reports of late outcome of patients, operated upon with more modern surgical techniques.[5,6] In fact, biased information has been gathered, because many adult patients have been discharged from routine cardiological follow-up and the adult cardiologist in particular sees patients who developed symptoms. Reliable information about the "natural history" after surgical valvotomy for isolated pulmonary valve stenosis can only be obtained if an unselected surgical cohort is investigated. Such information is important with regard to the future perspectives, employability and insurability of these patients. Our study presents the long-term survival (22-33 years) and clinical outcome of a single center cohort of consecutive patients operated for isolated pulmonary stenosis between 1968 and 1980.

Methods

Patients

Ninety patients had surgical repair of an isolated pulmonary stenosis at our institution between 1968 and 1980 at young age (<15 years). Preoperative clinical findings, including cardiac catheterisation, and details of the surgical procedure were collected from patients hospital records. Information on survival was obtained.

A first follow-up study was performed in 1990: 51 patients were invited to participate in the study. By an administrative mistake, the other 39 patients were not invited! From the 51 invited patients, 45 (88%) participated in the first follow-up study in 1990. The patients of the 1990-study were invited for a detailed second follow-up study, in 2001 of whom 38 participated. The cardiac examination included medical history, physical examination, standard 12-lead electrocardiography (Holter), 24-hour ambulatory electrocardiography, echocardiography, and bicycle ergometry.

The Medical Ethical Committee approved the study. All patients gave their written consent.

An attempt was made to locate and contact all 90 patients. Five had died, 17 were lost and the remaining 68 patients were alive. In addition to the 38 patients who participated in the detailed follow-up study, 21 patients returned a written questionnaire with information on morbidity.

Electrocardiography

Standard 12-lead electrocardiograms were analyzed for cardiac rhythm, the height and duration of the P wave (measured in lead II) and the PR interval. A first-degree atrioventricular block was defined by a PR interval > 200 milliseconds. Furthermore the median frontal plane P wave axis and QRS axis were determined, as was the longest QRS duration. A QRS duration > 120 msec was classified as a complete bundle branch block: a positive QRS complex in lead V1 was categorized as right bundle branch block and a negative QRS complex as left bundle branch block. A single observer made all ECG measurements (JR-H).

Holter monitoring

Sinus node dysfunction was assessed during 24 hour Holter monitoring using the modified Kugler criteria: nodal escape rhythm, sinusarrest > 3 sec or severe

sinusbradycardia (<30 beats/min at night or <40 beats/min during daytime).[7] Ventricular tachycardia was defined as 3 or more consecutive ventricular beats with a heart rate of > 100 beats/minute.

Two-dimensional echocardiography

Echocardiography was performed using a Hewlett-Packard Sonos 5500 echocardiograph. M-mode measurements of left atrial and left ventricular end-diastolic and end-systolic dimensions were obtained in the parasternal long axis view. A left atrium > 45 mm and left ventricle end-diastolic dimension > 58 mm were considered enlarged. A fractional shortening of the left ventricle of < 30% was considered decreased. Right ventricular dimensions and function were assessed by visual estimate by two experienced cardiologists (FM and SS). Of each patient the study of 1990 was compared with that of 2001. The degree of valve regurgitation (minimal, moderate, or severe) was estimated with color-Doppler by the width and length of the regurgitant jet. A blood flow velocity across the pulmonary valve <1 m/sec was considered normal.

Bicycle ergometry

Maximal exercise capacity was assessed by bicycle ergometry with stepwise increments of the workload of 20 Watts per minute. Exercise capacity was compared to that in normal individuals corrected for age, sex and body height.

Data analysis

Data are presented as median values and standard deviation, unless indicated otherwise. Chi-square and Fisher's exact tests were used for the comparison of discrete variables. Student t-tests were used to compare continuous variables. The level of significance was chosen at $p < 0.05$. The Mc Neman test of symmetry was used to compare the 14- and 25 years outcome. Cumulative survival curves were constructed using the Kaplan-Meier method with the corresponding 95% confidence intervals.

Results

Patients

Median age at operation was 5.0 ± 3.8 years (range 0 to 14). The pressure difference between right ventricle and pulmonary artery before surgery was 95 ± 39 mmHg (range 36-200). The surgical technique is summarized in Table 1.

Table 1 Surgical technique and age at operation

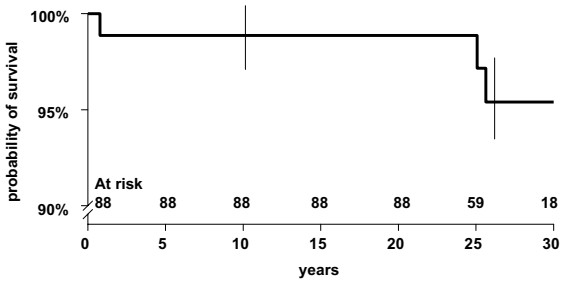
Surgical technique	1968-1974	1975-1980	total period	median age at operation (years)
Inflow occlusion				
- transpulmonary approach	33	14	47	7
Cardiopulmonary bypass				
- transpulmonary approach	4	9	13	6
- transventricular approach	10	7	17	5
- transannular patch	1	11	12	1
- homograft RV-PA	1	0	1	10
All patients	49	41	90	5

The transpulmonary approach was used in most of the patients and a transannular patch was inserted in 13% of the patients.

Survival

Peri-operative mortality occurred in 2 patients. Late survival after PS repair was 96% at 25 years (Figure 1).

Figure 1 post discharge survival after PS surgery



Follow-up

After a median follow-up of 16 ± 3 years, 45 patients participated in the first follow-up study. Of these, 2 patients died and 38 patients participated in the second follow-up study in 2001 with a median follow-up of 27 years (range 22-33 years) after surgery, and with a median age at the time of study of 32 years (range 22-44). Twenty patients were male (52%) and 18 female (48%). The twenty-one who returned the written questionnaire are in good clinical health, have not been admitted to the hospital for reintervention or pacemaker implantation and only one patient have experienced a tachyarrhythmia treated with medication. The baseline characteristics of the patients who did and who did not fully participate in the follow-up study are described in Table 2.

Table 2 Baseline characteristics of patients with and without follow-up

	with follow-up	without follow-up
Number of patients	45	45
Age at operation	5.0	5.1
Surgical technique		
Inflow occlusion		
Transpulm	12	35
Cardiopulm bypass		
Transpulm.	8	5
Transventric.	14	3
Transann patch	10	2
Homograft RV-PA	1	0
Cardioplegia	4	2
RV-pressure pre-operative	125	103
RV-pressure end procedure	54	55

Reinterventions

Reinterventions were performed in 10 patients (15%). Two patients underwent balloon valvuloplasty because of a substantial residual pulmonary stenosis, respectively 16 and 18 years after surgery. Eight patients needed a reoperation: 2 early, respectively 2 and 3 years after surgery because of residual right ventricular outflow tract obstruction and in 6 patients a pulmonary homograft was implanted because of severe pulmonary insufficiency late (median 20 years, range 16-24) after the initial operation. In 5 of these 6 patients the surgical technique of the primary operation included a transannular patch, while in 1 patient a simple valvotomy was performed. In 2 of the 6 patients in addition a tricuspid valve plasty was performed and in 1 an atrial septal defect was closed. The pre-operative transpulmonary gradient in the 6 patients who needed reoperation was not different from the patients without reoperation. However, right atrial and right ventricular dilatation and paradoxical septal motion were substantially more frequent in the patients who needed reoperation between 1990 and 2001 (Table 3).

Pacemaker implantation was performed in 2 patients because of sick sinus syndrome with a median interval after surgery of 17 years.

Table 3 Echocardiographic results in 1990 of patients with and without need for reoperation in the next decade (1990-2001)

	without reop	with reop	p-value
number of patients	39	6	
Vmax pulmonary valve	1.6m/s	1.7m/s	0.7
Right atrium dilatation	15%	100%	<0.0001
Right ventricular dilatation	10%	67%	<0.05
Paradox septal motion	5%	83%	<0.0001
Severe tricuspid insufficiency	26%	83%	<0.05
Severe pulmonic insufficiency	38%	83%	<0.05

Clinical evaluation

In 1990, 77% of the patients was in NYHA class 1, and 23% in class 2. In 2001, 67% was in NYHA class 1, 30% in class 2 and 3% in class 3 (p=ns). The outcome of patients own health assessment, compared with that of the normal population, is shown in Table 4. One patient was taking cardiac medication: oral anticoagulation and a betablocker. Half of the patients had regular follow-up at a cardiology outpatient clinic. Three patients with severe pulmonary insufficiency needed (repeated) electrical cardioversion for atrial fibrillation or flutter. None of these 3 had a recurrence of arrhythmia after pulmonary valve replacement. No patient showed clinical signs of heart failure. No endocarditis occurred. Of the 18 female patients, 9 had successful pregnancies. None of the offsprings had cardiac defects.

Table 4 Personal health assessment of patients 22-33 years after surgery for pulmonary stenosis compared with the normal Dutch population < 35 years

	patients	normal Dutch population patients
numbers	38	1510
Excellent	22%	40%
Good	70%	50%
Fair	11%	9%
Not good	-	1%
Bad	-	-

P<0.05

Electrocardiography
(Table 5). The QRS-duration increased from 96 to 108 milliseconds in 11 years time, but still is relatively short. Right bundle branch block was present in 22%. We found no difference between transpulmonary and transventricular approach (with right ventricular incision) regarding the incidence of a right bundle branch block during follow-up. The increase in QRS-width was more for the patients who underwent a reoperation: 25 msec (range 12-56) for the patients with and 11 msec (range –10-38) for the patients without reoperation between 1990 and 2001. No patient showed decrease of the QRS-complex after successful surgery. The QRS complex in 2001 was wider for the patients with right ventricular dilatation on echocardiography: 120 msec (range 92-178) versus patients without dilatation: 97 msec (80-130). And also the increase in QRS-width was more: 16 msec for the patients with dilatation and 7 msec for the patients without dilatation.

Table 5 Standard 12-lead ECG long term after surgery for PS

	16yrs	**27yrs**	**p-value**
Number of patients	45	38	
Rhythm (%)			
Sinus	39 (87)	35 (92)	0.3
Nodal	3 (7)	0	
Atrial	3 (7)	1 (3)	
Pacemaker	0	2 (5)	
Aflutter	-	-	
PR interval (msec)	150 ±21	150 ±24	0.15
QRS duration (msec)	90 ±16	100 ±22	<0.0001
RBBB (%)	9	22	<0.01
QTc segment (msec)	387 ±23	392 ±25	0.6
QRS axis (degree)	80 ±20	63 ±17	0.08
P-wave duration (msec)	85 ±11	90 ±13	0.01
P-wave height (cm)	0.30 ±0.06	0.20 ±0.09	0.9
P-wave axis (degree)	60 ±18	56 ±24	0.1
LVH (%)	0	0	1.0

Twenty-four hour ambulatory monitoring
None of the patients had atrial flutter or fibrillation in 1990 or 2001 on 24-hour ambulatory monitoring. Signs of sinus node disease were found at last follow-up in 1 patient. No ventricular pauses longer than 3 seconds occurred. Ventricular tachycardia of more than 10 complexes were not found, 2% showed ventricular tachycardia of 3-10 complexes.

Echocardiography
(Table 6) The maximal flow velocity over the pulmonary valve did not change significantly in 10 years time (1.6 m/s in 1990 to 1.7 m/s in 2001). Pulmonary regurgitation was present at last follow-up in most patients (89%). Over the last 11 years 2 patients showed progression from moderate to severe pulmonary regurgitation. We found no correlation between the presence of pulmonary insufficiency and the age at surgery, or right ventricular incision during surgery. However, we did find a correlation with the use of a transannular patch. In 5 patients the right ventricular dimension increased between 1990 and 2001, in 2 of these also an increase in pulmonary regurgitation was found, in the other 3 pulmonary regurgitation was moderate to severe and remained unchanged. Only 2 of the 6

patients who underwent pulmonary homograft implantation showed regression of right ventricular dilatation. Paradoxical septal motion was found in 8 patients at last follow-up; 7 of these 8 had severe pulmonary regurgitation. Half of the patients (51%) showed moderate to severe tricuspid insufficiency at last follow-up. One patient showed a mild stenosis on the left pulmonary artery (gradient 19 mmHg).

Table 6 Echocardiographic results in 2001, 22-33 years after surgery for PS

	1990	2001	p-value
Number of patients	45	38	
LA dimension (mm)	32 ±6	37±5	0.4
LVED dimension (mm)	44 ±4	46 ±5	0.7
LA dilatation (%)	2 (4)	2 (5)	0.8
LV dilatation (%)	0	0	1.0
RA dilatation (%)	24 (53)	24 (63)	
RV dilatation (%)	23 (51)	20 (53)	
LVH (%)	0	0	1.0
RVH (%)	5 (11)	7 (18)	
Median FractShort.LV (%)	35	33	0.6
Good RV syst function (%)	43 (96)	36 (95)	0.8
Good LV syst function (%)	44 (98)	36 (95)	0.4
Valve insuff (%)			
PI no	7 (16)	4 (11)	0.1
mild	17 (38)	29 (53)	
moderate	7 (16)	6 (16)	
severe	14 (31)	8 (21)	
TI no	11 (24)	8 (21)	0.2
Mild	14 (31)	10 (26)	
Moderate	17 (38)	19 (50)	
Severe	3 (7)	1 (3)	
Vmax TI	2.4 ± 0.3	2.6 ±0.3	0.4
Vmax PS (m/sec)	1.6 ±0.3	1.7 ±0.3	

Maximal exercise

The median exercise capacity was 101% in 1990 and 90% of the predicted values in 2001. Almost all patients showed some decrease in exercise capacity between 1990 and 2001. The median maximal heart rate was in both studies 91% of expected. No arrhythmias occurred. We found no relation between exercise capacity and velocity over the pulmonary valve before surgery, duration of aortic cross clamp time, presence or absence of a right bundle branch block on the ECG, or young age (<1 year) at operation. However, the patients with right ventricular dilatation and severe pulmonary insufficiency significantly showed lower exercise capacity (p=0.04). In 2 of the 6 patients who underwent reoperation because of severe pulmonary regurgitation the exercise capacity improved, in the other 4 it decreased.

Discussion

This series comprises a cohort of consecutive patients operated at young age at a single institution with longitudinal follow-up of 22-33 years. This study shows that the most important sequel after operation for pulmonary stenosis is residual pulmonary regurgitation.

Mortality

Late mortality is low in our study. Others report similar excellent long-term survival.[3,8] Less favourable outcome is found only in patients operated at older age.[3] An explanation for this may be the longer period of right ventricular pressure overload with subsequent right ventricular failure.

Reintervention

Although mortality was low, 15% of the patients needed a reintervention. Hayes et al found a low (4%) need for reoperation during their study, but their study period was 10 years only.[4] In our study also only 3% of the patients needed a reintervention in the first 10 years after surgery and this was for residual pulmonary stenosis. All the other reinterventions were performed 15 years or longer after the first operation, and mainly because of severe pulmonary insufficiency. The need for reoperation was not correlated with the preoperative severity of pulmonary stenosis, but rather with the amount of pulmonary insufficiency, which occurred after surgery. This is similar to the time clinical course in patients with tetralogy of Fallot in whom pulmonary regurgitation leads to clinical problems only after long time. Only now are we beginning to realise that the long-term consequences of pulmonary regurgitation become manifest 15 to 30 years after surgery. This is probably related to the longstanding volume overload of pulmonary regurgitation, leading to right ventricular dysfunction over time. At first, compensatory mechanisms based on right ventricular dilatation and paradoxical septal movement develop and only after a longer period high end-diastolic pressures, secondary tricuspid insufficiency and right-sided heart failure appear. Also other factors such as aging with cell destruction and apoptosis may be responsible for this right sided heart failure. By analyzing the echocardiograhic results of 1990, we found that the patients with need for reoperations during the following decade, had not only significantly more severe pulmonary regurgitation, but also more often right atrial and right ventricular dilatation, paradoxical septal motion and severe tricupid regurgitation. Pulmonary insufficiency occurred especially in the patients who underwent valvuloplasty with use of a transannular patch. The transannular patch technique is a well known risk factor for the development of pulmonary regurgitation in Fallot patients and now proofs to be a risk factor in isolated pulmonary valve stenosis patients as well.[9] This implies that patients after surgical repair of pulmonary stenosis with a transannular patch should be followed carefully, since they are at substantial risk of severe pulmonary regurgitation needing a second, and maybe third operation. A surgical alternative for the use of a transannular patch is the insertion of a pulmonary allograft, and when a patch is still the best alternative for a patient, a long small patch should be inserted to prevent the development of severe pulmonary regurgitation.

Information on equally long-term outcome after balloon valvuloplasty is not yet available, but studies with shorter follow-up intervals, show at least as good results as after surgical treatment.[10,11] Therefore, at the moment, balloon valvuloplasty is the treatment of choice for patients with isolated pulmonary stenosis. Our surgical data

should provide a standard for comparing the long-term outcome with that of percutaneous balloon valvuloplasty.

Residual lesions
Residual pulmonary stenosis at follow-up was mild in all patients. Obviously, this was achieved at the cost of pulmonary insufficiency, which was observed in almost all patients at follow-up. In the patients who underwent a reoperation with pulmonary valve replacement because of residual pulmonary insufficiency, right ventricular dimensions diminished in only 2, and remained unchanged in 4 of the 6 patients. Maybe, this should be an argument in favor of earlier valve replacement in order to prevent irreversible right ventricular dilatation. Pulmonary valve replacement late after right ventricular outflow tract obstruction can be performed with low risk and provides clinical improvement in symptomatic patients, but pulmonary homografts have a limited life-span.[12,13] This same discussion of when to operate residual pulmonary insufficiency is currently being held for Fallot patients and is still not answered with full satisfaction.

Arrhythmias
Clinical significant arrhythmias occurred only in patients with severe pulmonary insufficiency in need of reoperation and, very important, they all disappeared after surgery. As in Fallot patients, the supraventricular arrhythmia seems to be the result of elevated right ventricular filling pressures with subsequent right atrial overload.[14] The prevalence of supraventricular arrhytmia may be a marker for the timing of reoperation.

Clinical condition
At last follow-up NYHA class, subjective well-being and exercise performance was lower than expected as described by others.[15,16] We suggest that pulmonary insufficiency may account for the impairment of clinical condition.[16] Indeed exercise capacity was related to dilation of the right ventricle with severe pulmonary insufficiency. Serial evaluation with stress testing seems a valuable tool to define the moment of reintervention in patients with pulmonary insufficiency after surgical pulmonary valve repair. In Fallot-patients right ventricular function seems to improve after late pulmonary valve replacement for residual insufficiency.[19,20] In the 6 patients in our study, who underwent late reoperation for pulmonary regurgitation, we observed an increase in QRS-duration, instead of decrease and also exercise capacity increased in only 2 of the 6 patients, suggesting that probably 4 of these 6 patients were reoperated to late. Earlier reintervention may be warranted in patients with severe pulmonary regurgitation and right ventricular dilatation.

Study limitations
For administrative reasons, only 51/90 patients were invited to participate in the study. However, because 45/51 (88%) gave their consent, the population studied is not a select group.

Conclusion

Different surgical management techniques for pulmonary stenosis all lead to a good and long-lasting relief of elevated right ventricular pressure, but this is achieved at

the cost of pulmonary insufficiency in virtually all patients. Patients operated upon with a transannular patch are at increased risk for reoperation. Especially right atrial and ventricular dilatation and paradoxical septal motion are predictive for pulmonary regurgitation with need of reoperation. Supraventricular arrhythmias disappeared after reoperation. Pulmonary insufficiency may account for some impairment of clinical condition in these patients.

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Chapter 5

Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22-29 years)

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Abstract

Background
Great concern exists about the abilities of the anatomic right ventricle to sustain the systemic circulation in patients with transposition of the great arteries who underwent a Mustard procedure. A prospective study was performed to examine long term survival, clinical outcome and right ventricular function 25 years after surgery.

Methods
Ninety-one consecutive patients underwent a Mustard procedure between 1973 and 1980. After 14 and again after 25 years (range 22-29) patients were studied with ECG, echocardiography, exercise testing and Holter-monitoring.

Results
The cumulative survival and event-free survival were 77% and 36% after 25 years. Re-operations were necessary in 46%. No impressive loss of sinus rhythm was found. While all patients had good right ventricular function 14 years after repair, 61% of the patients showed moderate to severe dysfunction after 25 years, when studied by echocardiography. Furthermore, the QRS-complex widened and the exercise capacity decreased.

Conclusion
The anatomic right ventricle appears unable to sustain the systemic circulation at long-term follow up and clinical condition of patients late after Mustard repair is declining. We may expect more deaths or need for heart transplantation in the next decade.

Introduction

The atrial switch procedure dramatically improved the survival of children born with complete transposition of the great arteries. For the long-term outcome major concerns are: the fate of the right ventricle supporting the systemic circulation, arrhythmias and, accordingly, long-term survival of these patients.[1-5] Systemic right ventricular dysfunction and loss of sinus rhythm have been reported at long-term follow-up, but it is unclear whether these problems were found in a selection of

"worse cases" or whether systemic right ventricular failure and loss of sinus rhythm are inevitable in all patients.[3,5-8] We performed a systematic follow-up study of a single centre cohort of 91 consecutive patients, who underwent a Mustard procedure in the seventies. In 1990 this cohort was investigated. The outcome then showed good right ventricular function in most patients, and the majority of patients were in sinus rhythm (69%). In 2001, 11 years after the first study, and 22-29 years after the Mustard operation, this same cohort was studied again to assess survival, clinical course, arrhythmia's and systemic ventricular function and to compare the data with the study of 1990.

Methods

Patients

All 91 consecutive patients, who underwent a Mustard repair for transposition of the great arteries at the Thoraxcenter between 1973 and 1980 and who were younger than 15 years at the time of surgery, form the basis of this report. Before the Mustard operation improved atrial mixing was achieved in 15 of the 91 patients (16%) by a Blalock-Hanlon atrioseptostomy and in 65 of the 91 (71%) by a Rashkind balloon atrioseptostomy. Operations were performed with mild hypothermia and complete cardiopulmonary bypass in 18 patients (all between 1973 and 1976) and with deep hypothermia and circulatory arrest in 64 patients. In 9 patients the cooling technique was not described in detail. Cold cardioplegia was used in 38 patients (42%) after 1976. In 36 patients additional surgery for ventricular septal defect (VSD) closure and/or pulmonary valve stenosis (PS) was performed. These 36 patients are further referred to as "complex Mustard".

Follow-up

Survival status was established in all 91 patients. In order to assess cardiac function, a first systematic follow-up study was performed in 1990. At that time 18 patients had died and 5 had moved abroad. Fifty-eight of the remaining 68 patients (79% of the survivors, 85% of those eligible for follow-up) agreed to participate in the first follow-up study. These 58 patients were invited for a second follow-up in 2001. Between 1990 and 2001 2 additional patients died, 1 patient underwent cardiac transplantation, and one patient refused to participate, so 54 participated in the second follow-up study in 2001. Patients who did not participate in this study were contacted by telephone. The evaluation, both in 1990 and in 2001, consisted of a detailed history, physical examination, a standard electrocardiogram (ECG), 24-hour ambulatory ECG, exercise test, and echocardiogram. The institutional Medical Ethical Review Board approved the study. All patients gave their consent.

Electrocardiography

Standard twelve lead surface electrocardiograms were analysed for rhythm, P wave axis, height and duration of the P wave (measured in lead II), PR interval and QRS duration. A QRS duration > 120 msec was defined to be a complete bundle branch block. A single observer made all ECG measurements.

Twenty-four hour ambulatory ECG
A three-channel recorder was used. Sinus node dysfunction was assessed using the modified Kugler criteria and was judged present in the case of nodal escape rhythm, sinusarrest > 3 sec or severe sinusbradycardia (<30 beats/min at night or <40 beats/min during daytime).[9]

Echocardiography
Transthoracic two-dimensional echocardiography and echo-Doppler studies were performed using a Hewlett-Packard Sonos 5500 echocardiograph. The same echocardiographer performed a systematic echo assessment in 1990 and in 2001. Baffle obstruction was diagnosed if there was evidence of obstruction in both the two-dimensional image and in the Doppler flow pattern: low flow velocity (< 0,5 m/s) in superior or inferior caval vein and acceleration to >1.0 m/s in the baffle with the typical flat non-pulsating curve profile. Obstruction to pulmonary venous drainage was diagnosed if the peak velocity at the junction of the pulmonary venous atrium and right atrium exceeded 1.5 m/sec.

A systematic approach to judge right ventricular dimension and function was performed separately by two experienced cardiologists blinded for the other data. Interobserver variability was analysed, and a kappa value of >0.7 was considered excellent. Dimensions were judged as normal, mildly, moderately or severely dilated.

Right ventricular systolic function was graded as normal, mildly, moderately or severely impaired. Acoustic quantification is an automatic border detection technique that has been used for the quantitative assessment of ventricular volume and performance and was used to assess right ventricular ejection fraction in the patients where it was technically feasible. An ejection fraction of > 50% was defined normal. All echocardiographic studies of 1990 were re-evaluated. The degree of tricuspid regurgitation (minimal, moderate, or severe) was estimated with color-Doppler by the width and length of the regurgitant jet and the Doppler flow pattern in the pulmonary veins. Pulmonary hypertension was defined by an early diastolic pulmonary regurgitation flow velocity of > 2.5 m/s or, in the absence of left ventricular outflow tract obstruction, a mitral regurgitation flow velocity of > 3.0 m/sec.

Maximal exercise capacity
Maximal exercise capacity was assessed by bicycle ergometry with stepwise increments of 20 Watts workload per minute. Exercise capacity was compared to that in normal individuals corrected for age, sex, and body height. Exercise capacity < 85% of the predicted normal value was considered to be abnormal.

Major events
Major events were defined as death, cardiac transplantation, re-operation, pacemaker implantation, or hospital admission for arrhythmia, endocarditis or heart failure.

Data analysis
Data are presented as mean and standard deviation, unless indicated otherwise. The Chi-square and Fisher's exact test were used for the comparison of discrete variables. The Student t-test was used to compare continuous variables. All tests used were two-tailed. The Mc Nemar test of symmetry was used to compare the 14- and 25 years outcome. Cumulative survival curves were constructed using the Kaplan-Meier method. Among patient subgroups the logrank test was used to

compare survival curves. The level of significance was chosen at $p < 0.05$. Multivariable Cox-regression analysis was performed for survival, event-free survival and for right ventricular dysfunction. The variables tested were birth weight, type of palliation, 'complex' Mustard procedure, age at operation, year of operation, use of deep hypothermia, use of cold cardioplegia, aortic crossclamp time, right ventricular incision, peri-operative complications, residual lesions, and rhythm at first outpatient visit after operation. Continuous variables were not categorised in the model. The proportional hazards assumptions were tested by constructing interaction terms between the variables and time to each end-point. Cox regression analyses showed no statistically significant interactions with time (each $p>0.05$). The model selection is based on the stepwise principle, where the limit to enter and to remove a variable was both 0.05.

Results

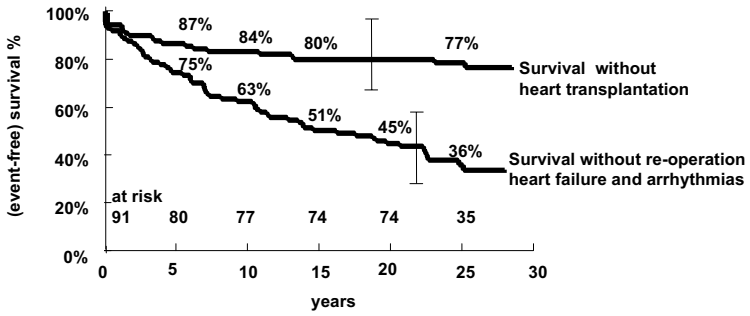
The median age at Mustard operation was 2 years (range 0 – 11 years). Further baseline characteristics and surgical details have been previously reported.[1,6] Information on survival is complete for the total cohort of 91 patients.

Survival

The cumulative survival after the Mustard repair was 80% after 14 and 77% after 25 years (Figure 1). Twenty patients died of whom 5 in the peri-operative period. Of the 15 late deaths (>30 days post-operative), 3 had right ventricular failure and pulmonary edema diagnosed directly after the Mustard procedure, 3 others had atrial flutter/fibrillation, 7 suffered from sudden death 1-15 years after surgery, and 2 patients died 23 and 26 years after surgery due to progressive right ventricular pump failure.

Figure 1

(event-free) Survival after Mustard operation

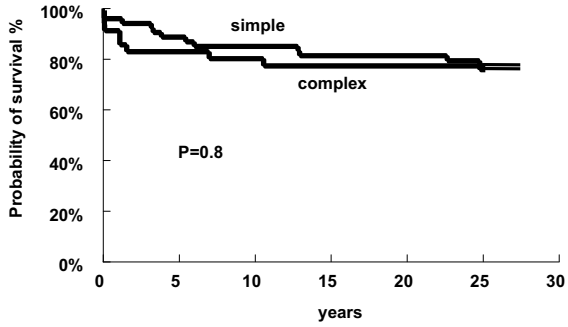


Crossbars present the 95% confidence intervals.

One patient had heart transplantation successfully performed 26 years after her Mustard repair because of failure of the systemic right ventricle. We found no differences in survival between patients with simple versus complex Mustard operation (Figure 2).

Figure 2

Survival after the Mustard operation for transposition of the great arteries



Major events

Cumulative event-free survival after 29 years was 36% (Figure 1). Since the initial Mustard procedure, re-operations were performed in 25 patients (46%) (Table 1). One additional patient had successful balloon angioplasty of a baffle obstruction. The median interval between the Mustard repair and re-operation was 11 years (range 2-29 years). No patients died during re-operation.

Table 1 Reoperations

	number	time since initial repair (+ range) in years
baffle stenosis	17	13 (2-23)
arterial switch	2	9 (8-9)
residual VSD	2	9 (2-16)
aortic coarctation	1	8
patent arterial duct	1	2
subpulmonary stenosis	1	6
tricuspid and mitral valve	1	11

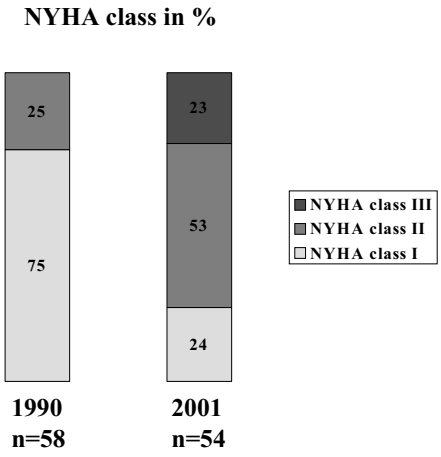
Of the patients seen at last follow-up, five patients (9%) were admitted to the hospital for heart failure. Pacemaker implantation was performed in 16 patients (28%), of whom 4 in the period between 14-25 years follow-up, all 4 because of sinus node disease. Between 14-25 years follow-up 3 patients (5%) were admitted for electrical cardioversion for supraventricular tachycardia and 2 for endocarditis. A total of 42 patients (61%) had at least one hospital admission (for heart failure, endocarditis, arrhythmia, or re-operation) during the total follow-up period.

Clinical evaluation

The median age at evaluation was 16 years in 1990 and 27 years (range 22 - 38 years) in 2001, with a median follow-up of respectively 14 and 25 years (22 - 29 years) after surgery. The clinical condition worsened between 1990 and 2001. After 25 years follow-up 24% of the patients was in NYHA class I (Figure 3). Fifteen patients (29%) were taking one or more drugs: oral anticoagulants in 2, betablockers in 2, digoxin in 3, antiarrhythmics in 4 and ACE-inhibitors in 10 patients. ACE-inhibitors were given because of evident heart failure in 2 patients and for right ventricular dysfunction in 8 patients. Of the 15 female patients, 4 had successful pregnancies.

The mean oxygen saturation was 97% (range 80%-100%). Signs of heart failure (edema, liver enlargement, and elevated central venous pressure) were found at last follow-up in 1 patient.

Figure 3



Electrocardiography

The ECG findings are presented in Table 2. The percentage of patients having sinus rhythm on the 12-lead electrocardiogram diminished from 69% in 1990 to 63% in 2001. The PR-interval and duration of the P-wave increased, but these changes were not statistically significant. The increase in QRS duration from 94 to 110 ms was highly significant ($p<0.0001$) (Figure 4) as was the change in QRS-axis. The QTc duration did not change.

At last follow-up one patient had first degree AV-block and in 9 patients bundle branch block was present.

Twenty-four hour ambulatory monitoring

At last follow-up, none of the patients had atrial flutter or fibrillation (see Table 2). Junctional escape rhythm was seen in 23%. Signs of sinus node disease increased significantly between 14 and 25 years follow-up, but no ventricular pauses longer

than 3 seconds occurred. Ventricular tachycardia of more than 10 complexes were not observed, 8% showed ventricular tachycardia of 3-10 complexes.

Figure 4

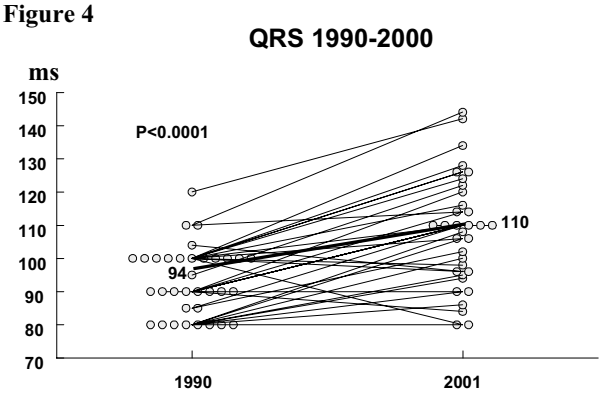


Table 2 Standard 12-lead ECG and 24 hour Holter electrocardiogram

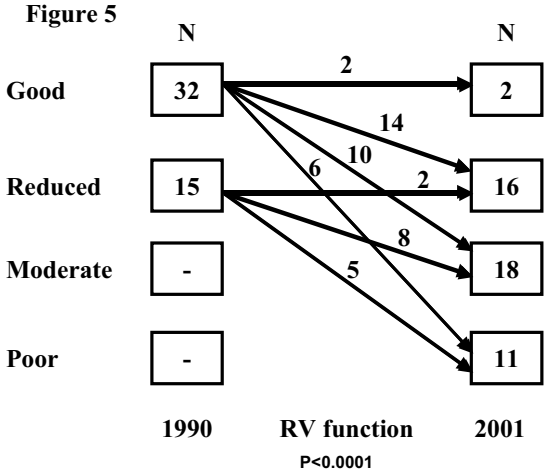
	14 years	**25 years**	**p-value**
	58	54	
12-lead ECG			
Rhythm			0.8
Sinus	40 (69%)	34 (63%)	
Nodal	7 (12%)	7 (13%)	
Atrial	6 (10%)	5 (9%)	
Pacemaker	4 (7%)	8 (15%)	
Aflutter	1 (2%)	-	
PR interval (msec)	157	165	0.09
QRS duration ±SD, (msec	95 ±11	110 ±17	<0.0001
QTc segment ±SD,(msec)	395 ±32	396 ±40	0.7
P-wave duration ±SD	86 ±13	91 ±15	0.06
P-wave height ±SD	0.25 ±0.14	0.25 ±0.14	0.9
P-wave axis ±SD	58 ±23	59 ±26	0.8
24-hour Holter			
Sinus node disease	37%	43%	<0.001
Paroxysmal A fib/flutter	4%	0	0.2
VT >10 beats	0	0	-
VT 3-10 beats	7%	8%	0.7

Echocardiography

Right (systemic) ventricular dimension was dilated in 72% of the patients, which was 58% ten years earlier. The function of this systemic ventricle changed markedly (Figure 5). While right (systemic) ventricular function was normal in 69% after 14 years follow-up, ten years later only 6% of the patients had normal ventricular function (p<0.0001). The ventricular function changed from good to mild in 33%, moderate in 37% and severe dysfunction in 24%. The interobserver variability was

excellent with 90% agreement and a kappa value of 0.86. In 10 patients it was possible to measure the ejection fraction with acoustic quantification, which ranged from 19% to 53% with a mean of 38%. Tricuspid regurgitation was severe in only 2% in 1990, while in 2001 this was the case in 20% of the patients. Tricuspid regurgitation was not more frequent in patients with a “complex-Mustard” procedure. Pulmonary hypertension was found in 3% in 1990 and in 18% in 2001. Twenty-three patients had thirty residual lesions: baffle obstruction in 17, baffle leakage in 2, a residual VSD in 3 and pulmonary valve stenosis in 8 patients.

Figure 5



Exercise tolerance

Fifty patients exercised to maximal effort (1 patient was excluded because of spastic hemiplegia, 1 had psychomotor retardation and 2 patients refused). The maximal exercise capacity in these patients is shown in Figure 6 and was 72% (range 38 - 105) of the predicted normal values in 2001, compared to 84% in 1990 ($p<0.0001$). Thirty-eight patients (76%) had an exercise capacity bellow 85% of the predicted value. The maximal heart rate was 170 beats/minute (82% of expected) in 1990 and 165 beats/minute (84% of expected) in 2001. During the test 5 patients (10%) developed arrhythmias: 3 patients had an increase of ventricular extrasystoles and 2 patients developed paroxysmal supraventricular tachycardia. No ventricular tachycardia occurred.

Risk factors for late death major events and systemic ventricular dysfunction

Multivariable Cox-regression revealed one independent predictor for death, which was the period of surgery: patients operated between 1973 and 1976 showed a worse survival than those operated between 1977 and 1980 (Table 3). For the end point “moderate to severe dysfunction of the right ventricle at last follow-up”, 2 independent predictors were found: atrial flutter at the first outpatient visit after the Mustard repair, and additional repair of VSD and/or PS (‘‘complex-Mustard’’).

Figure 6

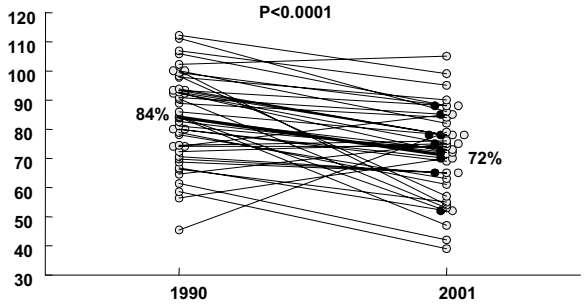


Table 3 Multivariable Cox regression

End point: death		
Independent predictors	HR	95%CI
-Surgery performed before 1977	3.1	1.1-9.5
End point: moderate to severe right ventricular dysfunction		
Independent predictors	HR	95%CI
-Atrial flutter at first follow-up after Mustard repair	3.0	1.1-8.9
-Complex Mustard procedure (VSD and/or PS)	1.9	1.1-4.0

Discussion

This series is unique in that it comprises a cohort of consecutive patients operated at a single institution with longitudinal follow-up of 22-29 years or until death. Our study shows some late attrition and substantial morbidity long-term after the Mustard operation. Most important a clear deterioration in systemic right ventricular function and clinical condition is seen in virtually all patients, between 14 and 25 (22-29) years after Mustard repair for transposition of the great arteries.

Survival

The cumulative survival was 80% after 14 and 77% after 25 years. We found a small continuing attrition rate as the population ages further. In contrast with others, we did not find a difference in survival rate between patients with simple or complex Mustard.[10,11] In the literature, the most frequent cause of late mortality after the Mustard procedure is sudden death, presumed arrhythmic.[2,10-12] In the present study the major cause of death changed from sudden or arrhythmic in the first 14 years after surgery, to progressive heart failure in the period from 14 to 25 years after surgery.

Morbidity
Morbidity was substantial in our Mustard-population with an event-free survival 25 years after surgery of only 36%. Re-interventions were performed in nearly half of the patients. Of the patients seen at last follow-up 28% needed a permanent pacemaker and 29% were using cardiac medication.

Assessment of right ventricular function
Although echocardiographic analysis of systemic right ventricular function has its limitations, we chose to use this technique again in 2001, to allow comparison with the 1990 study. With MRI, 28% of the patients would have been excluded because of a permanent pacemaker and we would not have been able to compare the data with the study of 1990.

We found an excellent interobserver variability on visual estimation of right ventricular function.

Systemic right ventricular function
We observed a striking deterioration of systemic right ventricular function in the decade from 14 to 25 years follow-up. While all patients had good function or only mild dysfunction 14 years after repair, after a median follow-up of 25 years, moderate to server dysfunction developed in 61% of the patients, 33% developed mild dysfunction and in only 6% the function remained good. This time course suggests that, although the right ventricle can sustain the systemic circulation for about 2 decades, development of right ventricular failure will be inevitable in the long run. Another expression of systemic ventricular failure is the increase in the incidence of pulmonary hypertension from 3% to 18% and the increase of severe tricuspid regurgitation from 2 to 20%.

We found a rightward shift of the QRS-axis and marked widening of the QRS-complex. The increase in QRS-duration may be another indicator of deterioration of right ventricular function in these patients.[13] Patients exercise capacity showed a decrease from 84% of the predicted value in 1990 to 72% in 2001 ($p<0.0001$). No significant change in maximal heart rate at exercise was found. The cause of the impaired exercise capacity is still a matter of debate and can be due to impaired systemic ventricular dysfunction or chronotropic incompetence or the fixed atrioventricular filling rate due to the baffle situation. Chronotropic incompetence was not found in our study. Although still 77% of the patients are in clinically fairly good condition (NYHA I or II) after 22-29 years, we saw a deterioration in functional class in 10 years time. Thus, the physical condition of the post-Mustard patients is declining. Echocardiographic data, electrocardiographic measurements, exercise capacity and functional class all show signs of deterioration between 14 and 25 years after surgery. These consistent findings were observed in nearly all patients.

Ventricular dysfunction is recognised as a risk factor for heart failure and death in patients with a systemic right ventricle.[3] If this deterioration progresses at a similar pace, it is likely that many of these patients, now aged 20-38 years, will develop heart failure, will die or need heart transplantation in the next decade. In patients with congenitally corrected transposition, with also the right ventricle supporting the systemic circulation, a survival rate of only 20% at age 60 is found and maybe we will find this same dreadful figure for the Mustard patients as well.[14] Until now the expectation was that the Mustard patients would have a better life expectancy, but the line of developing systemic ventricular dysfunction shows otherwise. The median follow-up in our study (25 years) is the longest reported in the literature and we are

now beginning to see that the outcome of the Mustard patients in fact is comparable with the outcome of patients with congenitally corrected transposition.[2,5,8,15-18] Whether or not medication will improve this outcome, needs to be investigated.

Because abnormal ventricular filling may be due in part to flow limitations by the atrial baffle, the use of ACE inhibitors may be counterproductive and no positive results are found until now.[19] The late arterial switch operation has not shown good results in adults so far and therefore is not an attractive option either.[20,21] Whether resynchronisation therapy with pacing modalities will be of value in these patients, as it seems to be in patients with systemic left ventricular dysfunction and wide QRS-complexes, needs to be investigated.[22]

Cause of systemic right ventricular dysfunction

The cause of right (systemic) ventricular dysfunction remains uncertain. *Impaired atrioventricular transport*, secondary to the rigid baffle-construction may be a contributing factor.[23-25] In our study, however, baffle obstruction occurring in 1990 was not found to be a predictor of right ventricular dysfunction in 2001. We could identify some other risk factors for ventricular dysfunction, such as *atrial flutter* at first follow-up after operation and *complex versus simple* Mustard procedures. The atrial arrhythmias, shortly after the operation are probably an expression of the impaired hemodynamic situation as described by others.[26] Millane found *myocardial perfusion* defects, and Singh found impaired *myocardial flow reserve* in the systemic right ventricle in survivors of the Mustard operation suggesting coronary blood supply to be the main problem.[27,28] Lubiszewska confirmed these findings and found greater perfusion defects more frequently in older patients with longer follow-up, which is in line with our study of deterioration of ventricular function over time.[29] The fact that almost all patients develop right systemic ventricular dysfunction supports the theory that right ventricular dysfunction is inherent to the Mustard situation itself, with the *anatomical right ventricle* functioning as systemic ventricle.

Atrial arrhythmias

Although early atrial arrhythmias were a predictor for late ventricular dysfunction in our study, arrhythmias occurring late after surgery could not be identified as a risk factor for right ventricular dysfunction or death as is described by others.[2,18] We found no significant ongoing loss of sinus rhythm and the incidence of atrial fibrillation and flutter was low in the last ten years, with only 3 patients needing electrical cardioversion. Furthermore, no case of atrial flutter or fibrillation was found on electrocardiograms, 24-hour Holter monitoring or exercise testing. Sinus node disease was the most common arrhythmia but most patients received their pacemaker in the first years after surgery and only 4 patients needed pacemaker implantation in the last 10 years.

Study limitations

The number of patients in this study is limited, as in other studies on grown up congenital heart disease. However, we report follow up on a consecutive cohort of operated patients, without selection bias related to the severity of disease.

It should also be appreciated that assessment of right ventricular function with echocardiography has its limitations. MRI may serve as an additional method for studying right ventricular function. However, in patients who have a pacemaker, magnetic resonance is not a suitable technique and MRI was not available in 1990.

In the present study, serial echocardiography was chosen, to compare data over time, and each patient was used as his own control.

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Chapter 6

Pulmonary regurgitation in adult patients with tetralogy of Fallot.

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Submitted

Abstract

Background
Pulmonary regurgitation is the most common problem in adult patients after surgical correction of tetralogy of Fallot. In order to get a better understanding of how pulmonary regurgitation affects the right ventricle, a longitudinal, long-term follow-up study of patients with varying degrees of pulmonary regurgitation and right ventricular dilatation was conducted.

Methods and Results
Sixty-seven patients, who underwent surgical correction tetralogy of Fallot in childhood, underwent an extensive cardiological examination 15 ± 3 years after surgery. Three subgroups were defined, according to the degree of pulmonary regurgitation and right ventricular size. All events were recorded and the cardiological examination was repeated 26 ± 3 years after surgery.
None of 22 patients with mild to moderate pulmonary regurgitation/ right ventricular dilatation, showed an increase in pulmonary regurgitation or right ventricular dilatation. In the group of patients with severe pulmonary regurgitation and a restrictive right ventricular physiology, the QRS-duration increased significantly. Eighteen out of 30 patients with severe pulmonary regurgitation and severe right ventricular dilatation underwent pulmonary valve replacement. Twelve patients improved, but in 6 patients right ventricular dilatation persisted and further prolongation of the QRS-duration was seen.

Conclusion
Mild pulmonary regurgitation is tolerated well. Patients with a restrictive right ventricular physiology show a significant prolongation of the QRS-duration. Of the patients with severe pulmonary regurgitation and severe right ventricular dilatation, 60% needed valve replacement in the following 11 years. Of these, two-third improved and one-third of these patients had persistent right ventricular dilatation and further prolongation of the QRS-duration.

Introduction

Surgical correction of tetralogy of Fallot consists of closure of the ventricular septal defect and relief of the right ventricular outflow tract obstruction. The latter includes resection of hypertrophic infundibular muscle tissue and, when the pulmonary

annulus and main pulmonary artery are too narrow, a longitudinal incision from the right ventricular outflow tract, across the pulmonary annulus into the main pulmonary artery, which is closed with a transannular patch. There was a liberal use of transannular patches in the 1970's and 1980's, since the most important factor associated with ventricular arrhythmia's and poor survival was identified to be elevated right ventricular pressure persisting after surgery.[1,2,3] The unavoidable consequence of this approach was pulmonary regurgitation, which was usually tolerated remarkably well until adult age. However, once adult, these patients sometimes developed right sided heart failure.[4] Pulmonary valve replacement is the treatment of choice, [5,6,7,8,9] but the optimal timing for this procedure is not clear.[10,11] If valve replacement is postponed too long and the right ventricular ejection fraction has deteriorated too much, right ventricular function will not recover anymore after valve replacement.[12,13] Moreover, a dilated right ventricle, represented by a QRS duration of > 180 msecs, is known to be associated with an elevated risk for ventricular arrhythmia and sudden death.[14,15,16,17,18,19] Accordingly, it has been advocated that a patient with severe pulmonary regurgitation should be operated before the right ventricle is damaged too much. Since artificial valves are no option for pulmonary valve replacement, due to many thrombotic complications[20], a bioprosthesis should be implanted, in spite of its limited longevity. The risks, associated with the unavoidable repetitive valve replacements, are the most important arguments against early pulmonary valve replacement.

In the Thoraxcentre, until recently, a restrictive approach was used: only patients who developed clinical signs that were attributed to right ventricular failure, were referred for pulmonary valve replacement. Whether or not the operated patients benefited from this late pulmonary valve replacement and whether or not patients with pulmonary regurgitation who were not operated upon deteriorated in the subsequent years, was evaluated in this follow-up study.

Methods

Patients

All 142 patients with tetralogy of Fallot (56 female and 86 male), who underwent intra-cardiac surgical repair in our institution between 1968 and 1980 and who were younger than 15 years of age at the time of the operation, were included in this study. Sixty-seven patients, 63 % of all patients eligible for follow-up, had an extensive cardiological evaluation both in 1990[21] and in 2001, respectively 15 ± 3 years and 26 ± 3 years after surgery. The mean age in 2001 was 30 ± 5 years. There were no significant differences between those who participated in the follow-up study and those who did not, in terms of these baseline characteristics[21]. The study was approved by the local Ethical Review Board.

Types of measurements

In 2001 and in 1990 all participants underwent the same set of investigations: interview for the medical history, physical examination, 12-lead ECG, 24-hour ambulatory ECG, echocardiographic examination and bicycle exercise test. All patients underwent an extensive psychological examination, which is reported separately.[22,23.]

Definition of subgroups of the study population
In order to evaluate the effect of long-standing pulmonary regurgitation on the right ventricle, the patients were divided in 3 subgroups, according to the severity of pulmonary regurgitation and size of the right ventricle, on the basis of the echocardiographic assessment in 1990. The groups consisted of patients with mild to moderate pulmonary regurgitation and no, or mild to moderate, right ventricular dilatation (n=22), patients with severe pulmonary regurgitation and mild to moderate right ventricular dilatation (n=15) and patients with severe pulmonary regurgitation and severe right ventricular dilatation (n=30). The latter group is further divided in 2 subgroups: a group that underwent pulmonary valve replacement and a group that did not.

Echocardiographic measurements and definitions
Right ventricular dilatation was assessed by means of M-mode in the parasternal short and long-axis view and by visual estimate in the apical 4-chamber view. Moderate enlargement was defined as a larger than normal right ventricle, but maximally as wide as the left ventricle. The enlargement was judged as severe if the right ventricle was larger than the left ventricle in the 4-chamber view. Pulmonary regurgitation was classified as: 1). absent to light, 2). moderate or 3). severe. The right ventricle was assumed to have a restrictive physiology when end-diastolic antegrade flow was demonstrated with pulsed Doppler in the pulmonary artery, coinciding with the atrial contraction.

ECG measurements
The maximum width of the QRS complex in the 12-lead electrocardiograms was assessed by one cardiologist (J.R-H), who was blinded for the echocardiographic results. The QRS duration was measured as the time from the first deflection from the zero-line to the point where the final part of the QRS-complex again meets the zero-line, in the lead with the maximal QRS duration.

Exercise test
Maximal exercise capacity was assessed by means of bicycle ergometry with stepwise increments of 20 Watts per minute until exhaustion. The outcome was presented as relative to the predicted value for age, sex, and body length.

Statistical analysis
Survival was calculated and presented by means of a Kaplan-Meier survival table. Time-related data are presented as mean values with standard deviation, unless the distribution was very skewed. In that case they are presented as median value and range. A Chi-square test was used for comparison of dichotomized variables, the Student-t test for comparison of two sets of continuous variables with a normal distribution. A p-value < 0.05 was considered to be statistically significant. If a difference is tested and not significant, it is marked as n.s.

Results

Survival and re-operation

Perioperative mortality was 16% (23 patients). Six patients were untraceable. Data on survival and event-free survival was obtained from the remaining 113 patients.
The baseline conditions are presented in Table 1. The overall survival and the event-free survival are presented in Figure 1. The mean interval between surgical correction and re-operation for relief of right ventricular outflow tract obstruction or closure of residual ventricular septal defect was 3.6 ± 6.8 years. The mean interval between surgical correction and pulmonary valve replacement was 18.6 ± 5.4 years. The mean follow-up since pulmonary valve replacement was 6.4 ± 4.4 years.

Figure 1a

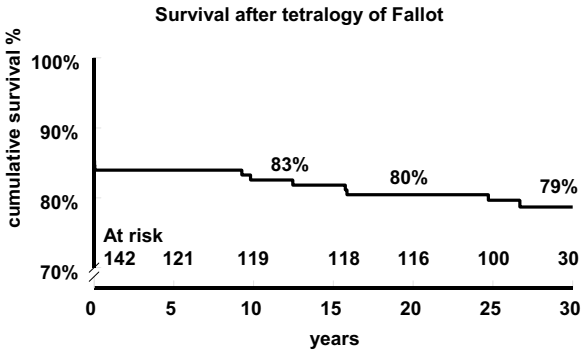


Figure 1b Event-free survival after tetralogy of Fallot (death, reoperation, hosp.admission, rhythm.dist)

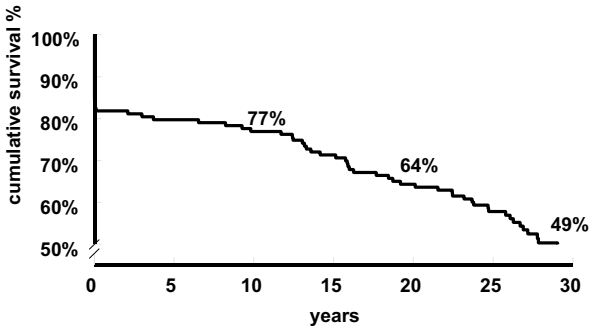


Table 1 Baseline characteristics, prior palliation, type of repair and re-operations

Number of patients	**142**
Male	86 (61%)
Female	56 (39%)
Prior palliative shunt	**50 (35%)**
Age at operation in years (median; range)	**4.6 (range 0.1 – 13.0)**
Use of cold cardioplegia	**47 (33%)**
Type of repair RVOT obstruction:	
Transannular patch	87 (61%)
Infundibulectomy	40 (28%)
RVOT patch	4 (3%)
Aorta monocusp	9 (6%)
Hancock bioprosthesis	2 (1%)
Re-operations < 1990	**19 (13%)**
Type of re-do surgery	
Closure residual VSD	8 (5%)
Relief RVOTO	7 (5%)
RVOT obstruction + VSD closure	1 (1%)
PVR for severe pulmonary regurgitation	3 (2%)
Re-operations > 1990	**15 (10%)**
Type of re-do surgery	
PVR for pulmonary regurgitation	15 (10%)

RVOT = right ventricular outflow tract. VSD =ventricular septal defect. PVR = pulmonary valve replacement.

There were no significant differences in baseline characteristics between the group of patients that participated in the study and the group of patients that did not. The study population was therefore considered as a non-selected, representative part of the total group of operated patients

Subgroup analysis

In Table 2 the most important outcomes and the differences between the subgroups are shown.

1. **Patients with mild/moderate pulmonary regurgitation and mild/moderate right ventricular dilatation at 15 years follow-up**

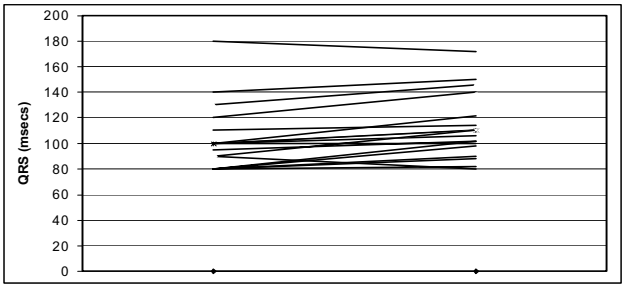
None of the 22 patients had had progressive right ventricular dilatation or progressive pulmonary regurgitation in the additional 11 years of follow-up. The velocity of the tricuspid regurgitation had been 2.6 ± 0.6 m/secs after 15 years and was 2.7 ± 0.6 m/secs after 26 years. The change in QRS-duration is shown in Figure 2a. None of the patients had clinically significant arrhythmia's or were taking anti-arrhythmic drugs.

2. **Patients with severe pulmonary regurgitation and mild/moderate right ventricular enlargement at 15 years of follow-up**

Two out of these 15 patients had progressive right ventricular dilatation and were judged to have a severely dilated right ventricle in 2001. In the 13 other patients, the echocardiographic evaluation of right ventricular size and degree of pulmonary regurgitation did not change over the years. A restrictive physiology of the right ventricle was seen in all these 13 patients, but not in the 2 patients with progressive right ventricular dilatation. The increase of QRS duration of the 15 patients is shown in Figure 2b. None of the patients had clinically significant arrhythmia or was taking anti-arrhythmic drugs.

Figure 2a

QRS prolongation between 1990 and 2001 in patients with mild/moderate pulmonary regurgitation and mild/moderate RV dilatation



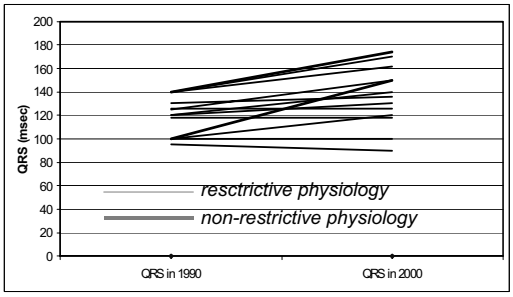
QRS duration in 1990: 107 ± 26 msec

QRS in 2001: 119 ± 25 msec

ΔQRS 10 ± 8 msecs

Figure 2b

QRS prolongation between 1990 and 2001 in patients with severe pulmonary regurgitation and moderate RV dilatation



QRS duration 1990: 120 ± 16 msec

QRS-duur 2001: 139 ± 26 msec

ΔQRS 16 ± 5 msec

3. **Patients with severe pulmonary regurgitation and severe right ventricular dilatation after 15 years of follow-up**

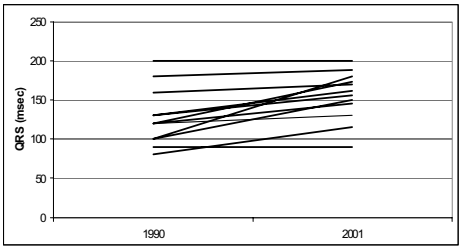
Of the 30 patients with a history of severe pulmonary regurgitation and severe right ventricular dilatation, 18 underwent pulmonary valve replacement and 12 did not. None of the 12 patients without pulmonary valve replacement had developed signs of venous congestion and none reported complaints of deterioration of their clinical condition. The echocardiographic assessment of the right ventricular size and pulmonary regurgitation did not change over the years. Yet, the QRS duration increased significantly; Figure 2c. Two patients developed supraventricular tachycardia and were taking anti-arrhythmic drugs.

None of the patients who underwent pulmonary valve replacement died and the signs of venous congestion disappeared in all patients. Echocardiographic evaluation

revealed a decrease in ventricular size in 12 patients, of whom 5 had an entirely normalized right ventricular size. A severe right ventricular dilatation persisted in 6 patients. In all patients the QRS duration increased until the pulmonary valve replacement. The QRS duration decreased after the operation in 14 patients and increased further in 4 patients (Figure 2d). Seven patients had had symptomatic arrhythmia's: one patient developed ventricular tachycardias, 4 patients had atrial fibrillation and 2 patients had a complete atrioventricular block, for which pacemaker insertion was necessary. Three other patients needed pacemaker implantation for sinus node dysfunction and atrial fibrillation.

Figure 2c

QRS prolongation between 1990 and 2001 in patients with severe pulmonary regurgitation and severe RV dilatation

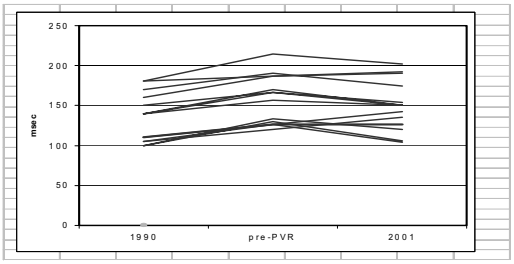


QRS duration 1990: 128 ± 35 msec
QRS duration 2001: 155 ± 30 msec
ΔQRS 28 ± 23 msec

Figure 2d In the patients who had a decrease of right ventricular size after pulmonary valve

Figure 2d

QRS duration in patients with PVR in 1990, just before PVR and in 2001



replacement, the QRS duration increased from 125 ± 22 msec in 1990 to 150 ± 20 msecs before pulmonary valve replacement and returned to 135 ± 21 msec in 2001. In the patients with persistent right ventricular dilatation, the QRS duration was 135 ± 25 msec in 1990, which increased to 190 ± 35 msecs before pulmonary valve replacement and which increased further to 196 ± 30 msec in 2001

Bicycle exercise test

The differences between the subgroups of the results of the exercise tests are shown in Table 2. Only patients who had a persistent right ventricular dilatation after pulmonary valve replacement had a significantly worse result in 2001 than in 1990.

Table 2 Surgical data and a summary of events and follow-up data from 15 to 26 years of follow-up after surgical data

	Mild to moderate PR No/mild / moderate RV dil	Severe PR Moderate RV dil	Severe PR Severe RV dil	
			No PVR	With PVR
No of pts	22	15	12	18
Surgical data				
Age at operation (in yrs)	5.1 ±2.9	3.9 ±2.5	4.3 ±2.7	4.5 ±3.2
Prior palliation (no of pts)	4 (18%)	5 (33%)	3 (25%)	9 (50%)
Transannular patch (no of pts)	2 (9%)	10 (66%)	10 (83%)	14 (78%)
Cold cardioplagia (no of pts)	7 (32%)	6 (40%)	7 (58%)	9 (50%)
Events 15-26 yrs of follow-up				
PVR (no of pts)	0	0	0	15
Arrhythmia's (no. Of pts.)	0	0	2	7
VT	0	0	0	1
SVT	0	0	2	4
ICD	0	0	0	1
PM	0	0	0	5
Echo data after 26 yrs				
Progression RV dil (no of pts) ♦	0	2	0	0
Progression PR♦	0	0	0	0
Diminished RV dil♦	0	0	0	12
ECG data				
QRS-duration after 15 yrs (in msecs)	107 ±26	120 ± 20	127 ± 35	134 ± 29
QRS-duration after 26 yrs (in msecs)	119 ± 25	139 ± 26	155 ± 30	196 ± 30*/ 135 ±21**
Exercise test				
After 15 yrs (% of predicted)	88 ±25%	80 ± 18%	69 ± 27%	71 ± 17%
After 26 yrs (% of predicted)	89 ± 15%	82 ± 14%	80 ± 11%	61 ±12%*/ 80 ±22%**

♦compared with echo data after 15 yrs of follow-up
* persistant RV dilatation after PVR
** normal or slightly dilated RV
PR = pulmonary regurgitation, RV = right ventricle, PVR = pulmonary valve replacement, VT = ventricular tachycardia, SVT supraventricular tachycardia, ICD= intra cardiac defibrillator, PM = pacemaker, TR = tricuspid regurgitation

Discussion

This study shows that mild to moderate pulmonary regurgitation has no tendency to increase in a period from 15 to 26 years of follow-up after surgical correction and that the right ventricle of these patients do not increase in size. This subgroup of patients, has by far the best long-term results of this study.[24,25] Since the patients of this group are operated upon with an approach very similar to modern insights - almost entirely

without the use of a transannular patch and with a very low percentage of previous palliative procedures - this seems to promise good long-term perspectives of the infants operated upon nowadays.[26]

A recognized positive effect of a restrictive right ventricular physiology is that it prevents severe right ventricular dilatation. This is also found in this study: none of these patients had echocardiographic evidence of further dilatation of the right ventricle. Also the exercise capacity remained stable. However, unlike other reports,[27] the exercise capacity was substantially depressed. The decreased exercise capacity is probably explained by the very nature of restriction: the inability to increase end-diastolic volume, which would be necessary for the increase in stroke volume, required during exercise. [28] In contrast to the unchanged echocardiographic data and exercise test, we saw a substantial prolongation of the QRS-duration, suggesting deterioration of right ventricular function.[29,30] Therefore, a regular outpatient control, with special emphasis on right ventricular function, is necessary for patients with a restrictive right ventricular physiology.

As a result of a restrictive policy towards pulmonary valve replacement that was used in Rotterdam, the timing of pulmonary valve replacement was relatively late, when compared to more recent insights. Therrien et al showed that pulmonary valve replacement in patients, in whom the right ventricular ejection fraction was less than 40%, did not result in improvement of right ventricular function afterwards[12]. However, in the patients who underwent pulmonary valve replacement in this study, the right ventricle had deteriorated to such a degree, that there were clinical signs of right ventricular failure and still, 12 out of 18 patients showed a remarkable improvement afterwards. This improvement was seen clinically (the venous congestion disappeared), echocardiographically (reduction of right ventricular size), on the 12-lead ECG (QRS duration decreased substantially) and with the bicycle exercise test. The latter is in line with an earlier report.[31]

On the other hand, in the remaining 6 patients, right ventricular dilatation persisted after pulmonary valve replacement. These patients would probably have benefited from earlier valve replacement. Neither clinical symptoms, nor ECG-data, nor echocardiographic data after 15 years of follow-up could predict whether or not the right ventricle would improve afterwards. Therefore, these data support the concept of earlier pulmonary valve replacement in all patients with severe pulmonary regurgitation and severe right ventricular dilatation, in order to reduce the risk of irreversible right ventricular damage. However, it also shows that pulmonary valve replacement should still be considered in patients who already have a substantially depressed right ventricular function, since there is a good chance for improvement.

The most striking outcome in the group of 12 patients with severe pulmonary regurgitation and severe right ventricular dilatation was the impressive increase in QRS-duration. Analysis of our own data, together with the accumulated evidence in literature, lead to a change in our treatment policy: these patients were referred for pulmonary valve replacement, although they were entirely asymptomatic.

The overall survival up to 30 years of the initial hospital survivors is only slightly lower than that of the normal population. The high early mortality of 16% reflects the surgical risk that was the rule in the 1970's.[32,33] The event-free survival after 26 years is poor: less than 50%. In the early years after the surgical correction the aim of a re-operation was closure of a residual ventricular septal defect or relief of residual right ventricular outflow tract obstruction. In the last 10 years the only type of re-intervention was pulmonary valve replacement, indicating that pulmonary

regurgitation in combination with depressed right ventricular function had become the dominant problem.

The prevalence of supraventricular arrhythmia's in this study is significantly higher than that of ventricular arrhythmia's, [20,34,35,36] both only occurring in patients with severe pulmonary regurgitation and severe right ventricular dilatation; this supports the notion that arrhythmia's are not the result of the congenital heart defect and surgery per sé, but of a poor hemodynamic situation on top of it.[37]

Limitations of the study

The small number of patients and the fact that right ventricular function was not assessed directly, are the two most important limitations of the study. MRI, the tool for assessment of global right ventricular function nowadays and for non-invasive flow-measurements, was not available in 1990 and poorly accessible in our institution in 2001.

Conclusion

Two-third of the patients in this study with severe pulmonary regurgitation and severe right ventricular dilatation, who developed signs of right sided heart failure, benefited from pulmonary valve replacement, with recovery of right ventricular function afterwards. However, in one-third of these patients, severe right ventricular dilatation persisted after valve replacement. These patients might have benefited from earlier pulmonary valve replacement. A more aggressive approach, as advocated in the recent years, seems justified in all patients with severe pulmonary regurgitation and severe right ventricular dilatation, in order to reduce the risk that a patient is operated upon too late. The finding, that the patients with only mild to moderate pulmonary regurgitation had a so much better outcome than the patients with severe pulmonary regurgitation, gives strong support to the current surgical policy to avoid severe pulmonary regurgitation at the initial surgical correction.

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Chapter 7

Atrial Arrhythmias in Adults After Repair of Tetralogy of Fallot Correlations With Clinical, Exercise, and Echocardiographic Findings

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Abstract

Background
The long-term success of intracardiac repair of tetralogy of Fallot is hampered by the occurrence of arrhythmias. Numerous studies have stressed the potential role of ventricular arrhythmias. However, the importance of other arrhythmias in the morbidity of these patients appears to be underestimated. Furthermore, most follow-up studies have been limited to children or adolescents, whereas many patients have reached adulthood after earlier repair of tetralogy of Fallot. The aim of the present study was to determine the incidence of atrial fibrillation, atrial flutter, and other supraventricular arrhythmias in adult patients after intracardiac repair for tetralogy of Fallot and their correlation with surgical and clinical findings.

Methods and Results
The study group consisted of 53 consecutive patients referred to the Thoraxcenter adult congenital heart disease clinic. They underwent repair at a mean age of 9.1 years (range, 0.7 to 55 years). The median age at the time of study was 23.2 years (range, 15 to 57 years; mean age, 26.6 years), with a mean duration of follow-up of 17.5 years (range, 1.4 to 32 years) after surgery. Records were reviewed extensively for evidence of arrhythmias. The follow-up study included routine 12-lead ECG, 24-hour continuous ambulatory monitoring, and echocardiography, and 46 patients underwent exercise testing. Sinus node dysfunction was recorded in 19 patients (36%), of whom 4 required a permanent pacemaker. Atrial fibrillation or flutter was found in 12 patients, and other supraventricular tachycardias were found in 6. The former were more frequently at older age at follow-up. Antiarrhythmic therapy and cardioversion were typically directed at control of atrial (and not ventricular) tachyarrhythmias. Ten patients (19%) showed nonsustained ventricular tachycardia; they were older at initial surgery and older at follow-up and had more intracardiac repairs and longer cardiopulmonary bypass times.

Conclusions
Despite an emphasis on ventricular ectopy in past series, the main sources of morbidity in adult patients after surgical correction of tetralogy of Fallot emanated from atrial arrhythmias, which were present in one third of the patients.

Introduction

The long-term success of primary intracardiac repair for tetralogy of Fallot is hampered by the occurrence of arrhythmias and late sudden death due to arrhythmias.[1 - 4] Numerous studies have stressed the potential role of ventricular arrhythmias in these events.[2, 4 - 17] However, atrial arrhythmias are rarely mentioned, and their role in the morbidity of these patients appears to be underestimated. Only recently has attention been paid to atrial flutter as a culprit arrhythmia.[3,18] Furthermore, most follow-up studies have been limited to children or adolescents, whereas many patients have reached adulthood after earlier repair of tetralogy of Fallot.

In the present report, we present a study of 53 adult patients with repaired tetralogy of Fallot who were seen at the Thoraxcenter Clinic for Adult Congenital Heart Disease to assess the clinical significance of both atrial and ventricular arrhythmias and to establish their relation to surgical and other clinical findings.

Methods

Patients

Fifty-three patients were studied who had surgically repaired tetralogy of Fallot and presented consecutively at the Clinic for Adult Congenital Heart Disease of the Thoraxcenter between July 1990 and April 1993. The evaluation of the patients included a detailed history and clinical examination; review of hospital and clinical records for evidence of arrhythmias on 24-hour ambulatory ECG (Holter) monitoring, monitor strips, and routine ECG; and exercise testing and echocardiography.

Clinical Evaluation

Patients were assessed clinically for functional status according to the New York Heart Association classification. Medication and symptoms were systematically recorded with an emphasis on episodes of palpitations, dizziness, syncope, and cerebral embolism. Special attention was given to signs of right-sided heart failure, pulmonary and tricuspid regurgitation, residual pulmonary stenosis, and residual shunts during physical examination.

Rhythm Registration

All available hospital and clinic records were reviewed for evidence of arrhythmias. The presence of an arrhythmia on any one recording (monitor strip, routine ECG, or Holter recording) was sufficient to code a patient for that rhythm disturbance, excluding arrhythmias related to cardiac catheterization or the perioperative period.

Fifty-three patients had multiple routine 12-lead ECGs, and 52 patients underwent 24-hour continuous ambulatory ECG (Holter) monitoring with a mean of 1.4 tracings (range, 1 to 4 tracings) per patient. One pacemaker-dependent patient in sinus rhythm with complete heart block declined Holter monitoring. Modified chest leads V3 and V5 were recorded with Oxford MR 14 recorders. The tapes were analyzed by trained technicians using Cardiodata PRODIGY or an Oxford MEDILOG MP-14 analyzer. Representative tracings were reviewed by one of the authors with special attention paid to P-wave morphology. The diagnosis of ventricular tachycardia (three or more consecutive ventricular premature beats) was made carefully to avoid misinterpretation of supraventricular as ventricular tachycardia in

view of the high prevalence of complete right bundle-branch block. Sinus bradycardia was diagnosed as a sinus rate of <50 beats per minute during waking hours. Any combination of at least two of sinus bradycardia, abrupt sinus pauses (>1 second in the absence of respiratory variation), and escape beats was coded as sinus node dysfunction. Supraventricular tachycardia consisted of an abrupt salvo of three or more consecutive atrial premature beats at a rate of >100 beats per minute. Atrial fibrillation, atrial flutter, and ectopic atrial rhythm were diagnosed using conventional criteria.

Ventricular arrhythmias were categorized in four groups by using modified Lown criteria[19]: (1) no ventricular arrhythmias or premature ventricular beats of <30 per hour, (2) multiform premature ventricular complexes or couplets of <30 per hour, (3) >30 premature ventricular beats per hour, or (4) ventricular tachycardia (defined as three or more consecutive ventricular beats with a mean rate of >100 beats per minute). Invasive electrophysiological studies were not performed.

Echocardiography

Two-dimensional echocardiography with color Doppler and velocity profiles and M-mode recordings were performed in all patients with a Toshiba SSH 140 A with 3.75- and 2.5-MHz transducers or a Vingmed CFM 750 with a 3.25-MHz transducer. Images were obtained from conventional precordial, subcostal, and suprasternal views. Two-dimensional guided M-mode measurements were made of the left atrial (normal, <45 mm) and left ventricular (normal, <60 mm) end-diastolic dimensions. Right atrial enlargement was identified on four-chamber views if the right atrium was larger than the left. Left ventricular function was assessed qualitatively as normal or abnormal (eg, hypokinesis, akinesis) on two-dimensional images. Color Doppler was used to localize residual shunts (accepted only if confirmed by velocity measurements) and to quantify valvular regurgitation. Regurgitation was determined from multiple views. Tricuspid insufficiency was graded as severe if the insufficiency jet reached the posterior wall of the right atrium. Pulmonic insufficiency was judged as severe if back flow extended from the bifurcation of the pulmonary arteries with a long broad jet beyond the pulmonic valve far into the right ventricular outflow tract. The maximum velocity of regurgitation was determined by continuous-wave Doppler interrogation to assess the maximum instantaneous systolic right ventricular and diastolic pulmonary artery pressure gradient using the modified Bernoulli equation.

Exercise ECG

Symptom-limited exercise on a bicycle ergometer was performed in 46 patients. Exercise tests were not performed in 7 patients. One patient was hemiparetic and 6 others declined, of whom 1 was pacemaker dependent. Workload was increased stepwise by 20 W/min, and the test was terminated when the subject approached exhaustion or a sustained arrhythmia occurred. Performance was compared with standardized data based on age, sex, and height.[20] Rhythm was monitored continuously throughout the test and recovery period. The tracings were reviewed by the authors.

Statistical Analysis

Continuous variables presented as mean ±SD or median (range) were analyzed using two-tailed Student's t test. Univariate analysis for categorical variables was performed using the X^2 test or Fisher's exact test. Differences were considered significant if the null hypothesis could be rejected at the .05 probability level.

Results

The study group of 53 patients underwent complete repair of tetralogy of Fallot at a mean age of 9.1 ± 9.0 years (range, 0.7 to 55 years). The median age at the time of study was 23.3 years (range, 15 to 57 years; mean, 26.6 years). Mean duration of follow-up was 17.5 years (range, 1.4 to 32 years). Twenty-eight patients (53%) were women.

Surgery

Before the definitive surgical correction, 27 patients received an aortopulmonary shunt (Blalock-Taussig in 16, Waterson in 10, and Potts in 1). During the total correction, 47 of the 53 patients had caval cannulation, right atriotomy was performed in 36, and infundibulectomy was done in 51. Pericardial patches for enlargement of the right ventricular outflow tract (transannular) were used in 43 patients, and Dacron patches for closure of the ventricular septal defect were used in all. Five patients received a pulmonary valve bioprosthesis (allograft). A patent foramen ovale was closed in 13. Mean cardiopulmonary bypass time for the first repair was 134 ± 45 minutes. Seventeen patients (30%) required two or more intracardiac operations: 10 closures of a residual ventricular septal defect, 10 implantations of a pulmonary valve bioprosthesis (allograft), and one tricuspid valve replacement.

Clinical Evaluation and Follow-up

At follow-up, 31 of 53 patients (58%) were in New York Heart Association functional class I, 19 (36%) were in class II, and 3 (6%) were in class III (Table 1). Palpitations were felt by 17 patients (32%), and 10 patients (19%) had syncope or near-syncope. Cerebral embolism (not including perioperative events) occurred in 4 patients (7%). On physical examination, a diastolic murmur of pulmonary insufficiency was present in 49 of the 53 patients (92%). None of the 53 patients had edema, and only 4 had elevation of jugular venous pressure.

Eight patients were judged cyanotic, but cyanosis was never severe, and no patient had clubbing. In 4 patients, measured arterial saturations were 96%, 94%, 89%, and 88%. The 2 hypoxemic patients (and 1 without hypoxemia) had residual ventricular septal defects and elevated right ventricular diastolic pressures. The other 5 patients showed no echocardiographic evidence of shunting.

Diuretic use in 9 patients (17%) probably accounted for the low incidence of elevated venous pressure and the absence of edema. Digoxin was administered to 10 patients (19%), and antiarrhythmic agents (propafenone, sotalol, amiodarone) were given to 13 (24%) (9 patients with atrial fibrillation or flutter and 4 with ventricular tachycardia). Three patients received long-term anticoagulation (warfarin).

Cardioversion was used in 6 patients: four times for sustained symptomatic supraventricular tachycardia, once for atrial fibrillation, and once for atrial flutter. It was never required for ventricular arrhythmias.

Two patients died during the study period. The first patient had syncopal episodes and ventricular tachycardias on ambulatory monitoring. Because of severe pulmonary regurgitation and peripheral pulmonary stenosis with high right ventricular pressure (72/7 mm Hg), a pulmonary homograft was implanted together with patch enlargement of the right pulmonary artery. This patient died suddenly at home, 2 weeks after this second operation. The second patient had severe pulmonary regurgitation and a high right ventricular pressure (103/7 mm Hg) after her first repair, but she was considered inoperable because of left pulmonary atresia after a left-side

Blalock-Taussig shunt. She was taking amiodarone and procainamide for frequent attacks of atrial flutter and supraventricular tachycardia and died suddenly. Both patients had demonstrated premature ventricular complexes on their routine ECG.

Six of the 27 women delivered 10 live infants without complications.

Table 1 Surgical and clinical parameters and their correlation with arrhythmias

	All Patients	No AT	SVT	AF/AFl	No VA	Mult/Coup	>30 PVCs	VT
No. of patients	53	35	6	12	6	17	20	10
Age at first repair, y	9	9	5	12	9	7	7	17[3]
Follow-up time, y	17	17	20	18	16	17	18	17
Age at follow-up, y	27	25	25	31[3]	25	24	25	34[3]
Prior shunt, n	27	16	4	8	3	9	8	8
>1 Repair, n	17	9	2	6	1	4	5	7[3]
Mean CPB time, min	134	138	125	128	106	126	126	183[3]
NYHA class I, n	31	23	2	6	5	11	11	4
NYHA class II, n	19	10	4	5	1	6	8	4
NYHA class III, n	3	2	0	1	0	0	1	2
Palpitations, n	17	7	2	8[3]	0	5	6	6[3]
Near-syncope, n	10[1]	4	0	6[4]	0	3	2	5[3]
Cerebral embolism, n	4	2	1	1	0	2	1	1
Cardioversion, n	6	0	4	2	. . .	. . .	. . .	. . .[2]
Digoxin, n	10	2	3	5[3]	1	4	3	2
Diuretics, n	9	3	0	6[4]	1	1	2	5[1]
Antiarrhythmics, n	13	2	2	9[3]	0	2	6	5
Anticoagulants, n	5	2	0	3	1	1	1	2

No AT indicates no atrial tachyarrhythmias; SVT, supraventricular tachycardia; AF/AFl, atrial fibrillation and/or atrial flutter; No VA, no ventricular arrhythmia or <30 PVCs/h; Mult/Coup, multiform ventricular extrasystoles or couplets <30/h; >30 PVCs, >30 premature ventricular compexes per hour; VT, ventricular tachycardia; CPB, cardiopulmonary bypass; and NYHA, New York Heart Association

[1] Three patients had syncope, and seven patients had near-syncope

[2] Although patients who underwent cardioversion often had ventricular arrhythmias, such therapy was in all cases directed to atrial tachyarrhythmias

[3] $P<.05$

[4] $P<.01$ compared with frequency in remaining patients without this arrhythmia

Arrhythmias

Monitor strips during hospitalization showed atrial fibrillation or flutter in 7 patients. Routine 12-lead ECG showed chronic atrial fibrillation or flutter in 3 patients, and 2 patients were in ectopic rhythm. Six patients were pacemaker dependent (2 because of surgically induced complete heart block and 4 because of sinus node dysfunction). Six patients showed premature ventricular complexes on their routine ECG. On Holter monitoring, 6 patients (11%) showed atrial fibrillation or flutter, and 47 (89%) showed ventricular arrhythmias. Exercise testing demonstrated ventricular ectopy in 22 patients (48%), of which four were episodes of nonsustained ventricular tachycardia.

On a review of monitor strips, routine ECGs, and Holter recordings, some degree of sinus node dysfunction was recorded in 19 patients (36%). In 4, it was severe enough to require a permanent pacemaker. Atrial tachyarrhythmia was present in 18 patients (34%), consisting of sustained supraventricular tachycardia in 6 (11%), of whom 4 required DC cardioversion, and atrial fibrillation or flutter was present in 12 patients (23%).

Ventricular arrhythmias were found in 47 (89%). No ventricular arrhythmias or <30 premature ventricular complexes per hour were found in 6 patients (11%); 17

patients (32%) demonstrated multiform ventricular extrasystoles or couplets; 20 patients (38%) had >30 premature ventricular complexes per hour; and 10 patients (19%) had ventricular tachycardia.

The follow-up time was not significantly different between the patients with and those without arrhythmias (Table 1). Compared with patients without arrhythmias, patients with atrial fibrillation or flutter (P=.04) or ventricular tachycardia (P=.017) were older. Age at total repair was higher for patients with ventricular tachycardia (P=.013). There was no association with a previous shunt operation. Longer cardiopulmonary bypass time (P=.0016) and multiple repairs (P=.02) appeared to be associated with ventricular tachycardia.

In most categories of atrial or ventricular arrhythmias, New York Heart Association class I predominated. As expected, palpitations and near-syncope were noted in the patients with atrial fibrillation or flutter and in patients with ventricular tachycardia. The occurrence of cerebral embolism was unrelated to the presence of arrhythmia. All six episodes of cardioversion were required for atrial tachycardia; there was no need for cardioversion to terminate ventricular arrhythmias as sustained ventricular tachycardia was never documented.

Echocardiography

Echocardiographic results are shown in Table 2. There was almost uniform presence of right atrial enlargement (52 of 53; 98%). There were 4 patients with left atrial enlargement, and 3 of these showed atrial fibrillation or flutter as well as ventricular tachycardia. Three patients had a left ventricular abnormality (enlargement or contraction abnormality), and 2 of the 3 had atrial fibrillation or flutter (P=.05). One patient with a segmental contraction abnormality had a transection of a coronary artery branch at the time of initial repair due to an abnormal course of the coronary artery across the right ventricular outflow tract.

Small echocardiographically detectable ventricular septal defects were seen in 25 patients and were significantly associated with atrial fibrillation or flutter (P=.03). Of the 4 patients with left atrial enlargement but without left ventricular abnormality or residual aortopulmonary shunt, all had ventricular septal defects. No correlation could be found between severe tricuspid or pulmonic insufficiency and atrial or ventricular rhythm disturbances. The mean tricuspid insufficiency jet velocity was 2.8 m/s, corresponding to a tricuspid pressure gradient of 31 mm Hg. There was no correlation of the right ventricular pressure with any arrhythmia.

Table 2 Arrhythmias and echocardiographic data

	All Patients	No AT	SVT	AF/AFl	No VA	Mult/Coup	>30 PVCs	VT
No. of patients	53	35	6	12	6	17	20	10
Right atrium enlargement, n	52	34	6	12	5	17	20	20
Right ventricular enlargement, n	50	32	6	12	5	17	19	9
Left atrium enlargement, n	4	1	0	3[1]	0	1	0	3[1]
Left ventricular abnormality, n	3	1	0	2[1]	0	1	0	2
Ventricular septal defect, n	25	16	1	8[1]	4	5	10	6
Pulmonic insufficiency, n	39	27	5	7	3	16	13	7
Tricuspid insufficiency, n	11	7	0	4	3	4	2	2
Tricuspid insufficiency velocity, m/s	2.8	2.7	2.8	2.9	2.7	2.8	2.9	2.7

For abbreviations, Table 1

[1] *P*<.05 compared with frequency in remaining patients without this arrhythmia

Exercise

Peak performance was 29% to 112% of the predicted normal value (mean, 77%). Patients with tricuspid or pulmonic insufficiency reached peak levels of exercise that were similar to those of the other patients. Exercise capacity was significantly lower in the group with atrial fibrillation or flutter (65%; *P*=0.03).

During exercise, 48% of the patients showed ventricular ectopy, of whom 4 demonstrated unsustained ventricular tachycardia. No test was terminated because of sustained arrhythmia. No patients were found to have previously unsuspected ventricular arrhythmias.

Discussion

Despite an emphasis in past series on the importance of ventricular ectopy[2, 4,5–17] and its high prevalence in the present study (89% of the patients), most complaints emanated from patients with atrial arrhythmias.

Incidence of Arrhythmias

The incidence of arrhythmias in adults with surgically repaired tetralogy of Fallot was higher than previously reported (Table 3). Atrial arrhythmias were found in 34% and ventricular arrhythmias were found in 89%, exceeding frequencies found in previous series that exclusively used ambulatory monitoring.[2,4–14] The presence of supraventricular tachycardia in 11% of our patients parallels the experiences of Miyamura et al[10] (19%) and Waien et al[17] (14% to 24%) but is substantially higher than in most other series that used ambulatory monitoring.[15-17] Atrial flutter and fibrillation in particular are remarkable by their absence in other tetralogy of Fallot follow-up studies. In five studies,[8, 21–24] only 13 cases of atrial fibrillation or flutter were reported in 1140 patients. On the other hand, in a collaborative study of 380 patients with atrial flutter (age, 1 to 25 years), only 30 (8%) had tetralogy of Fallot (28 repaired, 2 with shunts only); the denominator (ie, the total number of patients with tetralogy of Fallot from whom these 30 were drawn) was not given.[18]

With respect to supraventricular tachycardia, surface ECGs do not permit separation of atrioventricular nodal reentry from accessory pathways or ectopic atrial foci. However, the clinical importance of this rapid supraventricular rhythm is manifested by the need to cardiovert 4 of 6 of these patients. Similarly, without invasive testing it is not possible to distinguish atrial flutter from atrial reentry around surgical scars. Nevertheless, the need for management of this tachyarrhythmia is equally urgent.

The higher frequency of arrhythmias in the present study may be explained by the methods we used and by patient selection. We carefully sifted through all available material in search of rhythm disturbances as they appeared on monitor strips, routine ECG tracings, and Holter records. The accumulation of multiple Holter tracings in response to complaints increased the chances for detection of arrhythmias in the present study. Furthermore, because we included only adults, the study preferentially selected patients who were older at surgery or who had a longer follow-up interval after surgery and therefore were more likely to represent an earlier era of surgical repair.[23] Only three other studies using ambulatory monitoring have been limited to adults.[15,16,17] Finally, other studies traced patients who had previously undergone surgery at a single institution,[22] who were selected from among volunteers,[13,15,17] or who were chosen to participate.[2]

In contrast, the present study covers all repaired patients who presented at the sole geographic center for adult patients with congenital heart disease in the Rotterdam area. Referral may have been triggered by having reached the upper age for pediatric care, by unfamiliarity of the adult cardiologist or family physician with such patients, or by new symptoms. These indications for referral may account for a higher frequency of arrhythmias. The problems our patients present should not be seen as aberrations from the usual—perhaps more benign—outlook for all patients with successfully repaired tetralogy of Fallot. We stress that they are more likely to be representative of the postrepair tetralogy population referred to well-equipped adult cardiovascular centers.

Table 3 Studies of adults with repaired tetralogy of Fallot

Author	Burns et al[15]	Zahka et al[16]	Waien et al[17]	The present study (Thoraxcenter)
Year	1984	1988	1992	1994
Patient age, mean y	27	26	28	27
Patient age, range, y	18 to 41	19 to 35	18 to 71	15 to 57
Follow-up, y	14	18	14	17
Holter monitoring, n	44	56	36	52
Exercise test, n	+	-	+	+
Atrial arrhythmia, n	-	1 SVT	4 SVT	6 SVT, 12 AF/AFl
Ventricular arrhythmia, %	64	79	56	94

SVT indicates supraventricular tachycardia; AF/AFl, atrial fibrillation and/or atrial flutter; +, yes; and -, not done

Atrial Arrhythmias

The pathological significance of supraventricular tachycardia is hard to interpret. Brief salvos of supraventricular tachycardia have been found on ambulatory monitoring in as many as 22% of healthy individuals.[26] Nevertheless, patients with residual cardiac abnormalities may not tolerate sustained tachycardia, and four of six episodes of cardioversion were required for this arrhythmia. Evidence that transient sinus node dysfunction was noteworthy is provided by the need for pacemakers in 4 such patients and persistent ectopic atrial rhythm in 2 other patients.

Atrial flutter and fibrillation have not been found on routine ambulatory monitoring of healthy persons.[25-28] On the contrary, they are a marker of poor hemodynamics.[22] Atrial flutter and junctional rhythm have been reported in 18% and 46%, respectively, during follow-up of patients with repaired ostium secundum atrial septal defect.[29] After atrial baffle repair of transposition of the great arteries, atrial fibrillation and flutter occur frequently (25%) and continue to increase with duration of follow-up.[30] Atriotomy and atrial sutures may play a role in the development of atrial arrhythmias in these patients and may also be of significance in tetralogy patients.

In the present study, the age at follow-up was significantly higher in the patients with atrial fibrillation or flutter. In addition to age, the presence of left-side pathology in several of our patients appeared to be related to arrhythmias. Three of 4 patients with left atrial enlargement by echocardiography had atrial arrhythmias. None had left ventricular abnormalities or mitral insufficiency. However, all had small residual ventricular septal defects that, in combination with their older age at the time of surgery, may have had some importance. A voluminous shunt (4.3:1) was found only once in a patient demonstrating atrial flutter or fibrillation who had no left-side chamber abnormalities. On the other hand, we found a significant correlation

between left ventricular abnormalities and the incidence of atrial arrhythmias, although this, to our knowledge, was never described in postoperative tetralogy of Fallot patients. The near-universal presence of right-side chamber enlargement prevented any correlation with arrhythmias. Neither pulmonic insufficiency nor tricuspid insufficiency was more frequent among patients with rhythm disturbances.

Much of the morbidity in our patients was due to atrial arrhythmias: 66% of patients with fibrillation or flutter complained of palpitations, and 50% noted dizziness or near-syncope. Antiarrhythmic therapy and cardioversion were typically directed at control of symptomatic atrial—not ventricular—arrhythmias. The relative importance of atrial tachyarrhythmias is also indicated by the fact that even though approximately half of the 10 patients with ventricular tachycardia complained of palpitation or near-syncope, all except 2 symptomatic patients also had atrial flutter or fibrillation. Conversely, among the 10 symptomatic patients with atrial tachyarrhythmias, ventricular tachycardia was present in only 2. Furthermore, patients with atrial arrhythmias demonstrated reduced exercise capacity.

Ventricular Arrhythmias

The correlation between patients with ventricular tachycardia and older age at first repair was described by others[2,7,8,9,21] but is not universally supported.[13,14] The age at follow-up was significantly greater for patients with ventricular tachycardia, whereas the follow-up intervals were similar. Thus, age at first repair and age at follow-up probably should not be considered independent variables. Longer cardiopulmonary bypass time and multiple repairs emerged as significant and have been reported previously.[3,14,23] Damage to the myocardium may have already occurred when older patients were operated on, or the anatomy in these patients may have been more complex. Prior aortopulmonary shunt procedures were not more frequent among patients with ventricular arrhythmias (as noted previously[7,14]) despite reports of such association.[22]

Of the 10 patients with ventricular tachycardia, 60% had palpitations, and 50% had near-syncope. However, when patients with concomitant atrial arrhythmias were removed, the frequency of these same symptoms no longer reached significance. Sustained ventricular tachycardia was never documented, and cardioversion was therefore never required for termination of ventricular arrhythmias.

Although we anticipated a linkage between ventricular ectopy and severe pulmonary regurgitation with secondary marked dilatation of the right side of the heart, no such correlation could be confirmed. This confirms the recent report of Joffe et al.[31] Reberger et al[32] measured right ventricular volumes by nuclear magnetic resonance velocity mapping in patients after surgical correction of tetralogy of Fallot and found a virtually normal range of right ventricular ejection fractions in the majority of their patients with pulmonary regurgitation. However, in the present study, no direct measure of right ventricular function was made, so that, on the basis of the echocardiographic Doppler studies of the amount of pulmonary regurgitation alone, we could not differentiate between patients with and those without myocardial decompensation.

All 3 patients with a left ventricular abnormality had ventricular arrhythmias; 2 of the 3 had ventricular tachycardia, but these numbers were too small to achieve statistical significance.

Prognosis

In contrast to previous reports suggesting the advantage of exercise over resting ECGs to assess clinical risk from arrhythmias,[1,7] this approach yielded no clinically useful new information when compared with Holter testing.

Despite the availability of ambulatory monitoring, the two deaths that occurred during this 3-year period were signaled by the presence of premature ventricular complexes on routine ECG. This finding was limited to only 4 other patients and, when complicated by right ventricular hypertension, should be taken seriously.

Conclusions

Adults with repaired tetralogy of Fallot presenting at centers caring for such patients may differ from those in published series: patients are older and are more likely to have complaints and to have had multiple operations, valvular prostheses, pacemakers, pregnancies, and cardiac medication.

Although it might be assumed that pressure or volume overload of the right atrium and right ventricle would cause dilatation and predispose to arrhythmias, no such relation was demonstrated. Instead, an interesting but not fully understood association with left-side abnormalities and residual ventricular septal defect was found.

Despite an emphasis in past series on the importance of ventricular ectopy and its high prevalence in the present series, the main sources of morbidity in these adult patients emanated from atrial arrhythmias: atrial fibrillation, atrial flutter, supraventricular tachycardia, and sinus node dysfunction. These were present at one time or another in one third of our patients. Antiarrhythmic therapy and cardioversion were typically directed at control of symptomatic or sustained atrial tachyarrhythmias. Pacemakers were needed twice as often for sinus bradycardia as for heart block.

These observations should be useful to physicians who assume the late care of adults with repaired tetralogy. They broaden the focus of attention from ventricular ectopy and atrioventricular block to include atrial and sinoatrial dysrhythmias, paralleling the delayed emergence of these rhythm disturbances in patients with previous Mustard, Fontan, and atrial septal defect repairs.

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Chapter 8

Coronary anomaly imaging by multislice computed tomography in corrected tetralogy of Fallot

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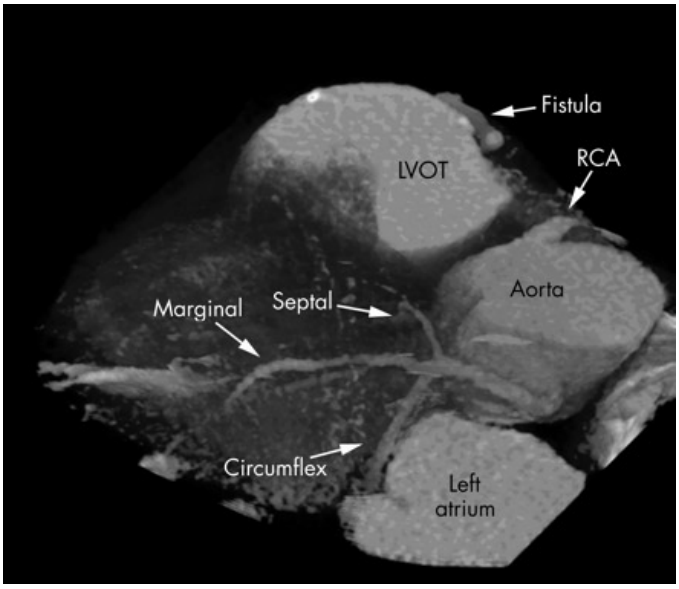
Heart, 2003;89:663-664

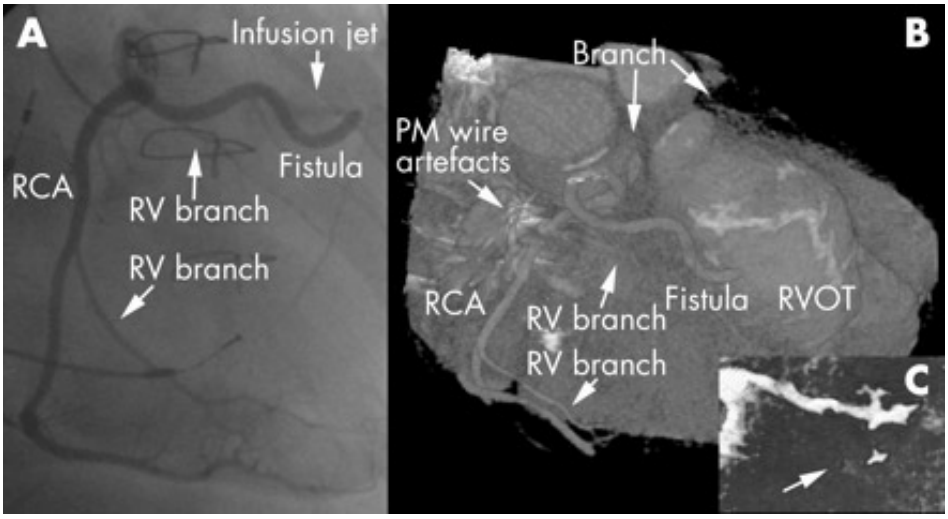
A 47 year old man with corrected tetralogy of Fallot was admitted with clinical heart failure. After prior left sided Blalock anastomosis at the age of 4 years, complete correction was performed at 9 years of age. Before pulmonary homograft insertion at 40, a fistula between the right coronary artery (RCA) and right ventricular outflow tract (RVOT) was detected. The procedure, which involved incision of the RVOT, was complicated by laceration of a small arterial branch, requiring end-to-end anastomosis.

Cardiac catheterisation confirmed the previously described fistula; however, selective intubation of an anomalous left sided coronary artery ostium failed.

At a pacemaker controlled rate of 60 beats/min, ECG gated multislice spiral computed tomography (MSCT) angiography (Somatom VolumeZoom, Siemens, Germany) was performed, during a 42 second breath hold. The volume rendered MSCT angiogram reveals an anomalous coronary artery that originates between the left and non-coronary sinus of Valsalva and trifurcates into a marginal, septal, and circumflex branch (upper panel).

A large calibre vessel, with branches to the right ventricle (RV), originates from an otherwise normal RCA, and terminates at the RVOT (lower panel, A and B), confirmed from inside the RVOT by virtual angioscopy (lower panel, C). A small, previously lacerated arterial branch runs across the RVOT to the anterior interventricular groove (B). The absence of a substantial anterior interventricular branch, and the location of the fistula at the RVOT, suggest that the fistula may have been formed after laceration of an anomalous LAD during surgical correction of tetralogy of Fallot, causing akinesia of the anterior wall.


Fistula
LVOT
RCA
Aorta
Marginal
Septal
Circumflex
Left
atrium


A
Infusion jet
RCA
Fistula
RV branch
RV branch
B
Branch
PM wire
artefacts
RCA
RV branch
Fistula
RVOT
RV branch
C

Chapter 9

Is a bicuspid aortic valve a risk factor for adverse outcome after an autograft procedure?

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Annals of Thoracic Surgery, in press

Abstract

Background
Recently bicuspid aortic valve disease is posed to be a possible risk factor for dilatation of the pulmonary autograft.

Methods
Analysis of all 123 patients in our prospective cohort with their native aortic valve in situ at the autograft procedure.

Results
The bicuspid aortic valve group (n=81) had more males (p=0.05), prior cardiac surgery (p=0.02), prior aortic valve balloondilatation (p=0.01), aortic stenosis (p=0.03) and less deterioration of left ventricular function (p=0.02) than the tricuspid group (n=42).
Hospital mortality occurred in 3 patients (bicuspid 2, tricuspid 1). The follow up was 99% complete (median 5.3 years, sd 3.5, range 0.1-13.4) with a total of 674 patient years. During follow-up 4 patients died (bicuspid 2, tricuspid 2). Overall survival was 95% (95%CI 89-98%) at 5 and 10 years.
Seven patients required reoperation for autograft failure, all structural. Freedom from autograft reintervention was 97% (95%CI 92-100%) at 5 years and 89% (95%CI 79-98%) at 10 years. There were no differences in outcome between the groups.
Four patients required reoperation for allograft failure, all structural. Freedom from allograft reoperation was 99% (95%CI 97-100%) at 5 years and 91% (95%CI 82-100%) at 10 years. There was no difference between the groups.

Conclusions
An autograft procedure in patients with a bicuspid aortic valve is justified. Bicuspid aortic valve disease is not a contraindication for an autograft procedure. Patients with a bicuspid aortic valve will meet the limitations of the autograft procedure in the same frequency as the overall autograft population.

Introduction

Recently the issue was brought up, whether or not a bicuspid aortic valve is a risk factor for adverse outcome after an autograft procedure.[1-5] The presence of a bicuspid aortic valve is associated with aortic dilatation, aneurysm formation and

aortic dissection due to focal abnormalities within the aortic media. Although the aortic and pulmonary arterial wall do differ histologically in the normal situation,[9,10] the pulmonary artery has the same embryological origin as the aorta and undergoes similar degenerative changes. Knowing that the aortic wall is abnormal in patients with a bicuspid aortic valve,[5-8] the causative mechanism for autograft failure was suggested to be an abnormality of the pulmonary arterial as well.[4,5] It is not yet clear, however, whether these differences in patients with a bicuspid aortic valve effectively predispose to clinical autograft failure.[5] This would create a significant problem because in most autograft series, patients with a bicuspid aortic valve mount up to 60-70 % of the patient population.[1,3,11]

From the clinical point of view we would expect such a predisposition to cause problems either at the proximal anastomosis, at the autograft itself or at the distal anastomosis. To assess the outcome after an autograft procedure possible allograft problems should be studied as well. In this regard we analysed in our series of autograft procedures whether or not a bicuspid aortic valve results in a higher rate of autograft failure.

Materials and Methods

The present analysis was conducted in accordance with the regulations of the institutional medical ethical committee, the patients consented to being included in our registry. Between September 1988 and June 2002 134 patients underwent an autograft procedure at our institution. Eleven patients had a previous aortic valve replacement and were excluded from this study, because a history of aortic valve replacement might influence dilatation of the aortic annulus and root.

The remaining 123 patients with their native aortic valve in situ at the autograft procedure were included in the present analysis. Characteristics of patients and operations are presented in Tables 1 and 2. Most of these patients are included in previous reports on different aspects of the autograft procedure.[11-13]

Left ventricular function was assessed by angiography or echocardiography and graded semiquantitatively as good or mildly, moderately or severely impaired.

Aortic valve morphology was determined using the operative reports. A tricuspid aortic valve, defined as having three separate functional leaflets, was found in 42 patients. A bileaflet aortic valve was defined as having two separate functional leaflets. One of these may contain a more or less developed fusion area or raphe. A unicuspid aortic valve was defined as having one commissure and a single functional leaflet. Because of the low numbers of unicuspid valves and because the distinction between unicuspid and bicuspid could not always be made accurately, these two valve types are analysed together and further referred to as the bicuspid group, containing 81 patients.

Preoperatively the aortic annulus was dilated in 2 patients (bicuspid 1, tricuspid 1), the aortic sinuses were dilated in 9 patients (bicuspid 4, tricuspid 5) and the ascending aorta was dilated in 4 patients (bicuspid 3, tricuspid 1).

Concerning the operative technique, the proximal anastomosis of the autograft onto the aortic annulus was done by continuous suturing technique in 98 patients (bicuspid 68, tricuspid 30) and by interrupted sutures in 25 patients (bicuspid 13, tricuspid 12). In all patients the pulmonary valve was replaced by a pulmonary allograft.

Valve-related events were scored as defined by previously published guidelines.[14]

The 11 patients that were excluded because of previous aortic valve replacement, did not differ in outcome from our study cohort (no mortality, 1 autograft

reoperation for structural valve disease at 5.8 years postoperatively, 1 balloondilatation for stenosis of the pulmonary allograft at 0.7 years postoperatively and 1 replacement of the pulmonary allograft at 2.1 years postoperatively)

During follow up patients underwent standardized serial echocardiography at 6 months, 1 year and yearly thereafter to determine autograft and allograft function over time.

All analyses were done using SPSS 10.0 for Windows (SPSS, Chicago, Ill.). Means were compared using the unpaired T-test. The Chi-square test or Fisher's Exact test were used to compare categorical variables. All tests were 2-sided, with an α-level of 0.05. Cumulative survival and freedom from reintervention or valve-related events were analyzed using the Kaplan-Meier method. The survival of a patient started at the time of the autograft procedure and ended at death (event) or last follow up (censoring). The analysis of autograft and allograft survival started at the time of autograft procedure and ended at reintervention (event) or last follow up or patient death (censoring). The log-rank test was used to compare survival between groups.

Results

Patients with a bicuspid aortic valve more often had a history of cardiac surgery (27/81 vs. tricuspid 7/42, p=0.01) as well as prior balloon dilatation of the aortic valve (20/81 vs. tricuspid 3/42, p=0.02)

By definition of our study cohort the etiology of the aortic valve disease is different in the two study groups, Table 1.

The groups differed in the diagnosis posing the indication for surgery. Aortic stenosis, either valvular or subvalvular, and either alone or in combination with aortic regurgitation, was significantly more often the indication for surgery in the bicuspid valve group (65/81 vs. tricuspid 22/42, p=0.002)

At admission for operation, the mean overall weight and length were 58 kg (sd 24, range 4-111) and 156 cm (sd 35, range 48-200) respectively. All patients were in sinus rhythm. In 108 patients, data on left ventricular function from echocardiographic or angiographic studies were available. In this subset of patients the left ventricular function was less often deteriorated in the bicuspid valve group (8/70 vs. tricuspid 12/38, p=0.04), Table 1. In our study group 51 patients were in New York Heart Association class I, 45 in class II, 19 in class III, 5 in class IV and in 3 the class was unknown, there was no difference between the bicuspid and tricuspid valve groups.

The autograft procedure in our center is routinely carried out with the root replacement technique. This yielded 117 root replacement procedures, no subcoronary procedures and only 6 inlay procedures. The inlay procedures were less often carried out in the bicuspid valve group (1/81 vs. tricuspid 5/37, p=0.02). Concomitant procedures were done in 22 patients, without a difference between the groups. No circulatory arrest was applied

Three patients died in hospital. In the bicuspid valve group one patient died of postoperative sepsis and mediastinitis and one due to a myocardial infarction after intraoperative damage to a coronary artery. In the tricuspid valve group a Marfan patient with a root aneurysm in preoperative cardiogenic shock died postoperatively due to cardiac failure.

One patient (bicuspid native aortic valve) needed a permanent pacemaker for postoperative total atrioventricular block. No perioperative transient ischemic attacks

or strokes of any kind were registered. In the early postoperative period, 16 patients (13%) needed mediastinal reexploration for persisting blood loss.

Table 1 Preoperative characteristics

	Total N=123	Bicuspid N= 81	Tricuspid N=42	P
Mean age (years (SD; range))	23 (13;0.3-53)	21 (13;0.3-52)	25 (14;1-53)	0.07#
Male/female ratio	77/46	46/35	31/11	0.08*
Prior cardiac surgery[1]	34	27	7	0.01*
Prior balloon dilatation	23	20	3	0.018*
Diagnosis				0.002*
Aortic valve regurgitation (AR)	36	16	20	
Aortic valve stenosis (AS)	32	28	4	
AR + AS	44	29	15	
Subvalvular AS + AS or ASAR	11	8	3	
Etiology				<0.001*
Bicuspid valve	76	76	0	
Other congenital	23	5	18	
Degenerative	2	0	2	
Rheumatic	9	0	9	
Endocarditis (recently cured)	4	0	4	
Other	9	0	9	
Length (cm, (SD; range))	156(35;48-200)	152(38;48-189	163(27;68-200)	0.08#
Weight (kg; (SD, range))	58(24;4-111)	55(26;4-111)	62(21;15-105)	0.08#
Sinus rhythm	123	81	42	
Creatinin (µmol/L, N=112)(SD, range)	66(23;12-157)	63(23;12-121	72(24;22-157	0.04#
Qualitative LVF (N=108)				0.04*
Good	88	62	26	
Mild/moderate impairment	19	7	12	
Severe impairment	1	1	0	
NYHA class (N=120)				0.75*
I	51	35	16	
II	45	27	18	
III	19	13	6	
IV/V	5	3	2	

SD: standard deviation. NYHA: New York Heart Association. LVF: left ventricular function.
*Fisher's exact test or Chi-square test. # Independent samples test
[1]Prior cardiac surgery concerned in all patients the left ventricular outflow tract: aortic valvotomy in 26 (with closure of ventricular septal defect in 2, enucleation of discrete subaortic stenosis in 1 and aortic root plasty in 1), aortic valve reconstruction in 4 (with closure of ventricular septal defect in 1 and enucleation of discrete subaortic stenosis in 2), enucleation of discrete subaortic stenosis in 3 (with aortic root plasty in 1), myectomy in 1

Follow up was 99% complete. The mean follow-up was 5.5 years (median 5.3, sd 3.5 years, range 0.1-13.4 years) with a total follow-up of 674 patient years. During follow-up another 4 patients died, two patients in each group. Postoperatively one patient, discharged in good health but readmitted after 4 weeks for noncardiac infection, died of sepsis after 7 weeks. One patient died due to recurrent rheumatic fever after 6 months, one after 1.8 years due to cardiac failure and one patient died 4.9 years postoperatively due to cardiac failure after replacement of the autograft with a mechanical prosthesis 4 months earlier.

Table 2 Operative details

	Total N=123	Bicuspid N= 81	Tricuspid N=42	
Type of operation				
Root replacement	117	80	37	0.02*
Subcoronary implantation	0	0	0	
Inlay/miniroot	6	1	5	
Concomitant procedures[1]				0.97*
None	102	67	35	
Yes	22	15	7	
Mean aortic cross-clamp time (SD, range)	139(32;90-238)	136(29;90-225)	146(37;91-238)	0.1#
Mean perfusion time (SD, range)	199(70;114-68)	199(77;114-685)	200(55;125-366)	0.95#
Hospital death	3	2	1	1.0*

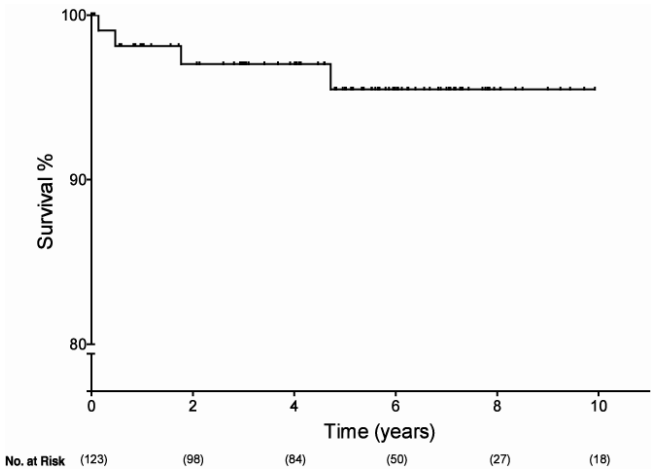
SD: standard deviation

*Fisher's exact test or Chi-square test. # Independent samples test

[1]Concomitant procedures were septal extension in 3, myectomy in 3, enucleation of discrete subaortic stenosis in 5, reduction plasty of the ascending aorta in 4, graft replacement of the ascending aorta in 2, coronary surgery in 4 and mitral reconstruction in 1

Overall survival at 5 and 10 years was 94% (95%CI 89-98%). Figure 1.
Endocarditis was diagnosed in 2 patients, in one patient of the autograft after 3.4 years and in one patient of the allograft after 8.8 years. Both were treated medically.

Figure 1 Cumulative survival after autograft procedure for native aortic valve disease

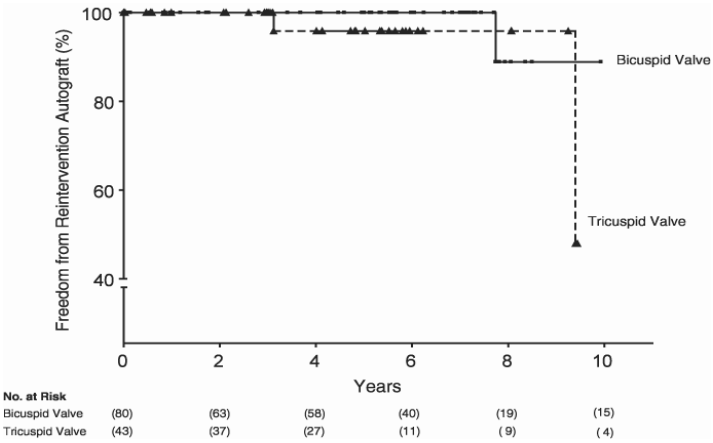


Seven patients required operative reintervention of the autograft, all for structural valve failure. Clinically this consisted in progressive root dilatation with regurgitation of the autograft valve. Macroscopically no signs of degeneration were observed, in particular no stenosis or calcification. Histology of 2 explanted autografts revealed an abrupt focal interruption of the elastin skeleton of the media.[15] In 4 of these patients a mechanical bileaflet aortic valve prosthesis was implanted in the autograft root, 2

patients underwent a prosthetic root replacement and in one patient an allograft root replacement was done. There were no postoperative catheter interventions on the autograft.

Freedom from autograft reintervention was 97% (95%CI 92-100%) at 5 years and 89% (95%CI 80-98%) at 10 years. There were no differences between the 2 groups, Figure 2.

Figure 2 Freedom from autograft reintervention for bicuspid or tricuspid aortic valve disease



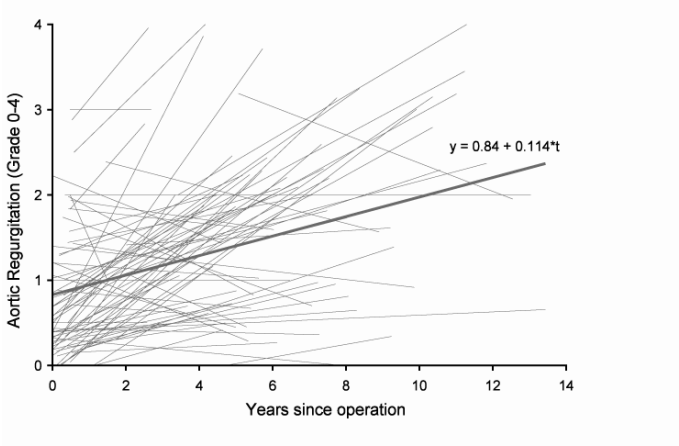
In the 116 surviving patients 493 echocardiographic studies were performed after discharge. Table 3 displays the echocardiographic findings of all 109 patients (excluding death and those patients who were reoperated) at last follow up. Of this last echocardiographic follow up, adequate information was available for 106 autografts and 105 allografts.

In 107 patients (including those who were reoperated or who died during follow up) more than one echocardiographic study with information on autograft regurgitation was available. Figure 3 displays for each patient the linear regression line that reflects the progression of echocardiographic aortic valve regurgitation over time. The bold line represents the overall progression of echocardiographic regurgitation of the whole autograft group over time, which can also be described by the equation: $y=0.84+0.114*t$

Four patients required reoperation for allograft failure, all structural. There were no postoperative catheter interventions on the allograft. Freedom from allograft reintervention was 99% (95%CI 97-100%) at 5 years and 91% (95%CI 82-100%) at 10 years. Figure 4. There was no difference between the bicuspid valve and tricuspid valve group.

Last echocardiographic follow up was available for 100 autografts and 99 pulmonary allografts, Table 3. A right ventricular outflow tract gradient of 30 mmHg or more was found in 15 patients.

Figure 3 Progression of echocardiographic autograft regurgitation over time



For each patient the linear regression line that reflects the progression of echocardiographic aortic valve regurgitation over time is presented. The bold line represents the overall progression of echocardiographic regurgitation of the whole autograft group over time, which can also be described as y_t= 0.84+0.114*t (y_t= regurgitation at time t)

Figure 4 Freedom from allograft reintervention after autograft procedure for native aortic valve disease

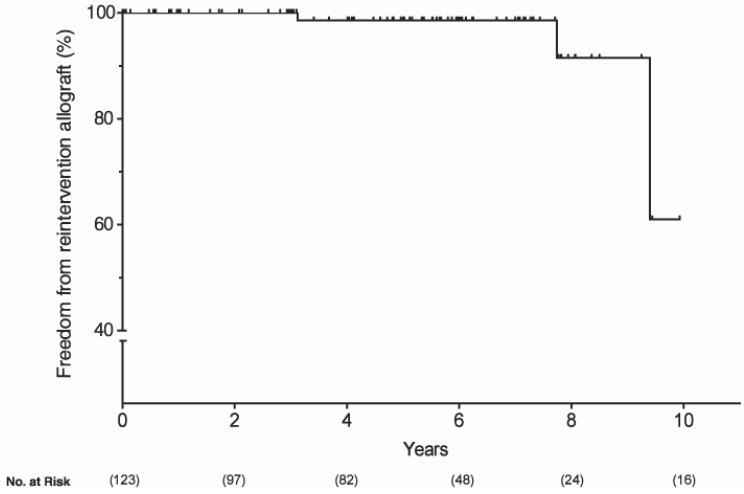


Table 3 Echocardiographic findings at last follow up
(N=109, excluding death and reoperation)

	Aortic regurgitation	Pulmonary regurgitation
Grade 0-1	63	81
Grade 2	32	19
Grade 3	9	3
Grade 4	2	2
Missing	3	4

No gradients were found on the autograft. A right ventricular outflowtract gradient of over 30 mmHg was found in 15 patients, of these 7 were over 50 mmHg

Discussion

It is well known that the aortic and pulmonary arterial wall differ histologically[5,7,9] and that the pulmonary arterial wall changes dynamically during life.[10] In patients with a bicuspid aortic valve the aortic wall is abnormal, with thinner elastic lamellae and a greater distance between the elastic lamellae.[6] The pulmonary arterial wall may show abnormalities in association with bicuspid aortic valve as well.[4,5] However, there is no conclusive evidence so far that the pulmonary arterial wall in patients with a bicuspid aortic valve additionally predisposes to autograft failure.

Clinical analysis has resulted in a limited number of reports on this subject, in part based on selected patients[1,2,4] and in part based on other observations than consecutive cohort series.[3] Nevertheless the advice was put forward to provide additional support for the autograft, in particular at the proximal anastomosis and at the sinotubular junction of the autograft during surgery.[1,2,5]

In our present consecutive series of patients, those with a bicuspid aortic valve showed some baseline differences, compared to the patients with a tricuspid aortic valve. For instance, they had more prior surgery on the aortic valve, they had more prior balloon dilatations on the aortic valve, had a lower male to female ratio, had more often aortic stenosis as preoperative diagnosis and had less often an impaired left ventricular function. Almost exclusively the root replacement technique was applied. However, we found no differences in postoperative events between patients with bicuspid and tricuspid aortic valves. Both survival and reoperation rates were satisfactory. Our series does not confirm that a bicuspid aortic valve is a risk factor for failure after an autograft procedure. Consequently, a bicuspid aortic valve is also not an argument for additional surgical measures providing external support of the autograft in this selection of patients. However, the incidence of autograft regurgitation is certainly a clinical problem, already well known from the series of Ross[16] and is, at least in part, related to autograft root dilatation.[17] Serial echocardiography in our series suggests that autograft regurgitation over time is progressive (0.114 grade per year).

In order to provide additional support for the autograft we pay attention to insert the autograft as close as possible onto the aortic annulus.[13,17] Further follow up studies should provide further information on the results of this technique in comparison with different methods of autograft support.[1,5] The recently described methodology of meta-analysis and microsimulation to assess durability of valve substitutes is very useful in this regard.[12,18]

We conclude that the application of an autograft procedure in patients with a bicuspid aortic valve is justified, that bicuspid aortic valve disease is not a contraindication for an autograft procedure and that patients with a bicuspid aortic valve will meet the limitations of the autograft procedure in the same frequency as the overall autograft population.

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Chapter 10

Aortic valve and aortic arch pathology after coarctation repair

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Abstract

Objective
The association of a bicuspid aortic valve with coarctation of the aorta is well recognized. Yet, not much is known about the incidence of clinical problems related to a bicuspid valve (aortic stenosis and regurgitation), and the incidence of ascending aorta and aortic arch pathology, in combination with coarctation repair.

Patients
Hundred-twenty-four adult patients after surgical correction of aortic coarctation were studied. The incidence of aortic valve, ascending aorta, and aortic arch pathology was determined using echocardiography and magnetic resonance imaging. The median age at coarctation repair was 9 years, and at last follow-up 28 years.

Results
Three patients died due to aorta pathology. Aortic valve disease was found in 63% of the patients, requiring an intervention in 22%, at a median of 13 years after coarctation repair. Ascending aorta dilatation was observed in 28% and aortic arch abnormalities in 23%, among whom kinking of the aortic arch was found in 12%. Antihypertensive medication was used in 24%. In the patients with hypertension the age at operation and age at follow-up were significantly higher ($p=0.0011$ and $p<0.0001$ respectively).

Conclusion
In addition to the well-known problems of hypertension and recoarctation, aortic valve and aortic arch pathology are commonly encountered in patients with previous coarctation repair. Aortic abnormalities may predispose to dilatation and dissection, thus necessitating careful life-long attention in all coarctation patients.

Introduction

Coarctation of the aorta accounts for 8% of congenital heart disease. In the past, coarctation was considered to be a simple “correctable lesion” and surgery, first performed in 1944, was believed to be curative. In keeping with this belief, normotensive patients were often discharged post-operatively without long-term follow-up. However, as increasing numbers of surgically corrected patients reached maturity, it has become clear that almost one third of patients become or remain

hypertensive, despite correction of their lesion, with an increased risk of accelerated atherosclerosis and end organ damage.[1] Furthermore recoarctation occurs in 3-35%.[2, 3, 4]
The association of a bicuspid aortic valve with coarctation of the aorta is well recognized, but estimates of the coarctation patients having a bicuspid valve range from 25 to 85 %.[2,5] The clinical significance of a bicuspid valve in coarctation patients is not well established.

To address these issues, we performed a retrospective study of the patients after coarctation repair seen in our department for adult congenital heart disease with emphasis on both aortic valve and aortic arch pathology.

The specific purpose of this study is a) to assess the prevalence of aortic stenosis or regurgitation in these patients, b) to assess how often dilation of the ascending aorta and pathology of the aortic arch occurs in patients with coarctation and c) to assess a possible correlation of aortic arch pathology with hypertension or recoarctation.

Methods

All patients seen in our department for adult congenital heart disease with surgically corrected coarctation were reviewed. They were included in the study if at least two follow-up echocardiographic studies were available, containing two-dimensional imaging of the aortic root in long-axis parasternal views and complete Doppler evaluation of the aortic valve. Echocardiograms were performed with the use of standard commercially available equipment. A MRI-scan of the thoracic aorta was performed.

Aortic valve morphology was examined by echocardiography in the two dimensional parasternal long-axis and short-axis views. The presence in short-axis views of only two cusps in systole or diastole, or both identified a bicuspid aortic valve. The presence or absence of aortic regurgitation or stenosis was determined with use of Doppler and Color Doppler echocardiography. The severity of aortic regurgitation was graded as minor, moderate or severe. We report aortic stenosis present if the peak velocity over the aortic valve with continuous wave Doppler velocity was > 2 m/sec.

The diameter of the ascending aorta was measured with echocardiography and MRI perpendicular to the long axis of the aorta with use of the leading edge technique at the level of the sinuses of Valsalva. Dilatation was defined as a diameter of 40 mm or more.
Aortic arch morphology was examined with echocardiography and MRI. Abnormalities were categorized as arch hypoplasia, cervical aortic arch or kinking of the aortic arch.
The diagnosis recoarctation was limited to patients who underwent a reintervention for recoarctation.
Hypertension was considered present if medication for hypertension was prescribed.

Data were analyzed by the Wilcoxon Test or the Fischer's exact test as appropriate. Age and duration of follow-up are given as median values with the corresponding 25th and 75th percentiles, or ranges.

A probability value of $p < 0.05$ was considered significant.

Results

Of the 149 adult patients who undergone surgery for coarctation and follow up at our department, 25 had inadequate echocardiograms. The baseline characteristics did not differ between the patients with and without adequate echocardiograms. Hundred-twenty-four patients (71 males and 53 females) had adequate echocardiograms, and are included in this report. They had been operated on by several techniques: resection and end-to-end-anastomosis (91), subclavian flap (14) and graft plasty (10). In nine patients the surgical technique was not described in detail. Associated intracardiac anomalies were recorded at the time of surgery in 67 patients (54%) (Table 1). The median age at coarctation repair was 9 years (range 4-16 years). The time from surgery until last follow-up was 18 years (range 13-25 years). The median age at last follow-up was 28 years (range 20-36 years). During follow-up in the department for adult congenital heart disease 3 cardiac deaths occurred: 1 from acute ascending aorta dissection 14 years after coarctation repair, 1 during aortic arch surgery 20 years after coarctation repair, and the third patient from aortic valve endocarditis, with massive acute aortic regurgitation, 18 years after coarctation repair.

Table 1 Associated heart in defects in 124 patients with aortic coarctation

Associated defects	Number
Ventricular septal defect	18 (15%)
Persistent arterial duct	16 (13%)
Atrial septal defect	4 (3%)
Abnormal mitral valve	4 (3%)
Transposition of the great arteries	3 (2%)
Dextrocardia	1 (1%)

Aortic valve disease

Forty-eight patients had a bicuspid aortic valve, 30 patients had a trileaflet valve and in 46 patients it was difficult to differentiate between a bicuspid and a trileaflet valve, thus a bicuspid valve was found in 62% (48 out of 78 patients). During follow up, aortic valve intervention was performed in 27 patients (22%), 16 for aortic stenosis, 8 for regurgitation and 3 for combined stenosis and regurgitation. Surgery was performed in 25 patients, while two underwent balloon dilatation of a stenotic aortic valve. Figure 1 shows survival free of aortic valve intervention after coarctation repair. In the 97 patients without aortic valve intervention, 23 patients had aortic stenosis, and 28 had aortic regurgitation (mild in 18, moderate in 5 and severe in 5 patients). In total aortic valve disease was observed in 63% of our patients. Of the patients with a bicuspid valve this percentage was as high as 70%. Several factors have been suggested to be related with the development of aortic regurgitation particularly hypertension, recoarctation, dilatation of the ascending aorta and aortic arch pathology.[6, 7] However, none of these factors were significantly correlated with aortic regurgitation in our series.

Aorta pathology

In 60 patients (48%) we found aorta pathology. Dilatation of the ascending aorta was found in 35 patients (28%). This was particularly prominent in patients with a bicuspid valve (Figure 2).

In 28 patients aortic arch pathology was established (23%). Of these, hypoplasia of the arch was found in 10 patients, 4 showed a cervical aortic arch, 8 had severe kinking of the aorta and 8 showed both kinking and a cervical arch.

Figure 1 Survival free of aortic disease

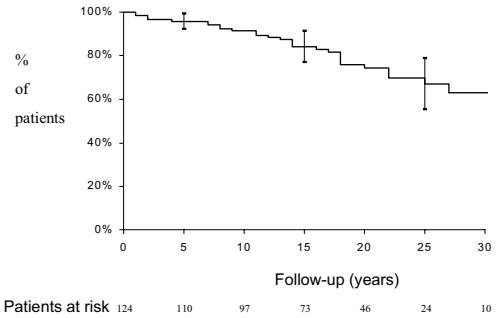
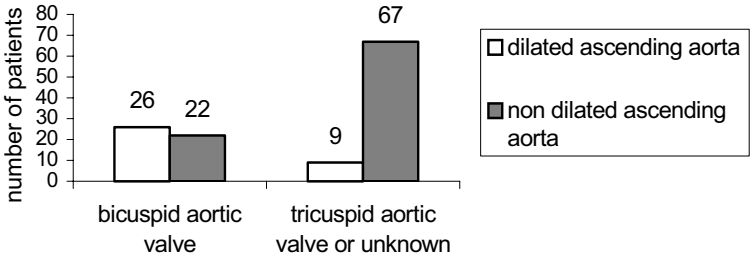


Figure 2 Dilatation of the ascending aorta in relation to the aortic valve morphology

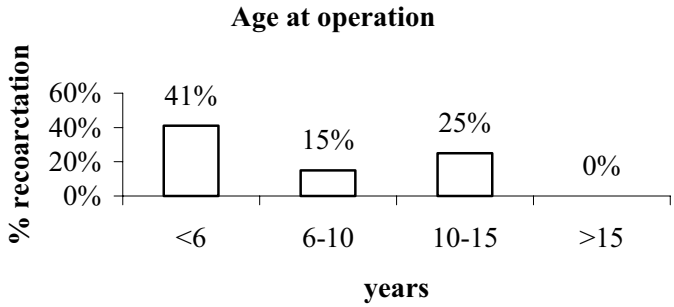


Recoarctation

In 28 patients (23%) recoarctation occurred, treated with surgery in 10 and with balloon dilation in 18 patients after a median interval of 16 years since the initial repair. Figure 3 shows the age at first repair in relation with the need for second intervention. Patients operated at younger age more often needed a re-intervention for coarctation.

To assess the effect of recoarctation repair on the severity of aortic regurgitation we reviewed the 6 patients with moderate to severe aortic regurgitation, who underwent an intervention for recoarctation. Regurgitation remained unchanged in four patients, increased in one, and decreased in one patient.

Figure 3 Age at operation in relation to recoarctation



Hypertension

Of the 124 patients, 30 (24%) used medication for hypertension at the last outpatient visit. Characteristics of patients with and without hypertension are shown in Table 2. In the patients with hypertension the age at operation was significantly higher than in patients without hypertension: 13 versus 6 years (p= 0.0001). Also the age at follow-up was higher in the patients with hypertension: 38 versus 24 years (p< 0.0001)

Table 2 Differences between patients with and without hypertension

	number of patients	patients with hypertension	p Value
Number	124	30 (24%)	
Type of surgery (%)			
-end-to-end	91	19 (20%)	0.2220
-other	33	10 (31%)	
Recoarctation repair (%)			
-yes	28	10 (36%)	0.1350
-no	96	20 (21%)	
Kinking aortic arch (%)			
-yes	16	6 (38%)	0.2163
-no	108	24 (22%)	
Cervical aortic arch (%)			
-yes	12	3 (25%)	1.0000
-no	112	27 (24%)	
Hypoplasia aortic arch (%)			
-yes	10	3 (30%)	0.7047
-no	114	27 (24%)	
Dilatation ascending aorta (%)			
-yes	35	11 (31%)	0.2553
-no	89	19 (21%)	
Aortic regurgitation (%)			
-yes	39	11 (28%)	0.636
-no	85	20 (23%)	

Discussion

In this series of patients after coarctation repair disease of the aortic valve and /or aortic arch were observed frequently.
Aortic valve disease was found in 63% of the patients 19 years after coarctation repair, of whom a third needed aortic valve intervention at a median of 13 years after coarctation repair. Thus, aortic valve problems is a frequent cause of morbidity and mortality of coarctation patients. The association of aortic valve disease and coarctation is mentioned in different reports.[5,7,8] However, the incidence of aortic valve problems after coarctation repair found in our study, is surprisingly high, necessitating careful life-long follow-up of all coarctation patients.

A bicuspid aortic valve was found in 62% of our coarctation patients, which is in line with other reports.[2,5] However, the incidence of aortic valve pathology is higher than in studies of bicuspid aortic valves without coarctation, which emphasizes the additional role of the coarctation in the development of the aortic valve problems.[9,10,11,12] It is likely that hypertension is a cause of the increased incidence of aortic valve problems. Furthermore, the remaining gradient over the coarctation region causing more stress on the aortic valve and aortic wall, resulting in aortic valve disease.
Nevertheless, we could not demonstrate any influence of repairing the recoarctation on the degree of aortic regurgitation.

Dilation of the ascending aorta was found in 28% of the patients. One study has shown a high incidence of ascending aorta dissection in patients with coarctation and bicuspid aortic valve, probably due to dilation of the ascending aorta in combination with persistent hypertension while others suggest that disease of the aortic valve and the aorta itself reflect an intrinsic abnormality of the media, possibly cystic medial necrosis. [6,10,13,14,15] We did not find a significant correlation between dilation of the ascending aorta and hypertension. However, we lost one patient due to dissection, who indeed had a bicuspid aortic valve and a dilated ascending aorta in combination with hypertension. Further study is necessary to determine what features or combination of features are most important risk factors for aortic dissection in these patients. Whether prophylactic surgery of the dilated ascending aorta is indicated in these patients can not be concluded from our data, but a more aggressive approach seems appropriate, especially if we take into account other reports of ascending aorta dissection and substantial late mortality in coarctation patients.[10,12,16]

Aortic arch pathology, other then ascending aorta dilatation, was present in 23 % of our patients. Not only arch hypoplasia, but also a cervical aortic arch and a striking number of patients with kinking of the aortic arch were found. These abnormalities of the arch may play an additional role in the development of hypertension and valve disease in these patients. Patients with kinking of the aortic arch more often were hypertensive than patients without kinking (38% versus 22%), although, due to the small numbers, we could not prove a significant difference (p=0.22). Kinking of the aortic arch has not been reported frequently, possibly because identification of this pathology was difficult, before the era of high quality echocardiography and magnetic resonance imaging. In nearly half of the patients we found some form of pathology of the ascending aorta or aortic arch, apart from the coarctation, suggesting that indeed this is in fact a disease of all parts of the thoracic aorta.

Hypertension

In our study 24 % of the patients used medication for hypertension, comparable with other studies.[17-19] We confirmed the clear relation of hypertension with age at operation and age at follow-up, but did not found a correlation between hypertension and the incidence of aortic regurgitation.[20,21]

Study limitations

The incidence of aortic valve and aortic arch pathology may be slightly overestimated due to patient selection, because a complete cohort of operated patients was not described. However we followed the majority of patients after their operation in our center. In comparison with other coarctation cohorts, our patients had fewer associated heart defects, which is compatible with less selection of more complex coarctation patients.[22] It is more appropriate to assume that the high quality of diagnostic tools give better insight in the real incidence of this pathology.

Conclusion

In addition to the well-known problems of hypertension and recoarctation, aortic valve and aortic arch pathology are commonly encountered in patients with previous coarctation repair. Aortic abnormalities may predispose to dilatation and dissection, thus necessitating careful life-long attention in all coarctation patients.

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Chapter 11

Long-term outcome and quality of life in adult patients after the Fontan operation

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Abstract

The first successful Fontan operation was performed in 1971, and the first cohort of Fontan patients is reaching adulthood with unclear outcome of this palliative procedure. We studied the mortality, morbidity and also the quality of life of our adult Fontan patients.
We examined all patients (n=36), who underwent a Fontan procedure and were seen in our adult outpatient clinic by using electrocardiography, exercise testing and echocardiography. Quality of life was assessed by the Short Form 36 questionnaire.
The mean follow-up period was 15 years (range 0 – 23 years). Of the initial 36 patients, 10 died (28%) at a mean of 10 years (range 0 – 21 years) after Fontan operation and one patient underwent cardiac transplantation. Reoperations were performed in 21 patients (58%) and the most common reason was revision of the Fontan connection. Sustained supraventricular tachycardia was observed in 20 patients (56%) with an increased incidence of arrhythmias with longer follow-up. Thromboembolic events were detected in 9 patients (25%), 5 of whom had adequate anticoagulant levels at the time of event. The tromboembolic event was fatal for 3 patients. A total of 195 hospital admissions (mean 3.8 $\pm$ 2.7 per patient (range 1 – 13)) was recorded. Quality of life assessment showed physical functioning, mental health and general health perception to be significantly lower for Fontan patients than for the normal Dutch population.
Thus, we found high mortality and very high morbidity in adult patients after the Fontan operation. In particular, reoperations, arrhythmias, and thromboembolic events compromise quality of life.

Introduction

Since Fontan and Baudet`s report of the first successful right-side cardiac bypass directing the entire systemic venous blood flow to the pulmonary arteries in a patient with tricuspid atresia, many modifications of this approach have been applied to all forms of functional univentricular heart disease. During the past 2 decades, several modifications of this operation and advances in management after surgery have improved surgical results.[1,2] Unfortunately, late deterioration in functional capacity is described with longer duration of follow-up.[3] As hospital mortality has decreased substantially, late mortality and especially, late morbidity are of great interest.[4-6] The occurrence of late complications such as atrial arrhythmias, ventricular failure,

protein-losing enteropathy and thromboembolic events are increasingly recognised.[7-9] No reports are available concerning quality of life in adult patients with a Fontan circulation.
We evaluated the clinical course of adult Fontan patients, and assessed their quality of life.

Methods

Patients
All adult patients who underwent a Fontan procedure and are regularly attended the outpatient clinic of the Thoraxcenter at the Erasmus Medical Center were included in this study. In 1978, the first Fontan operation was performed in our institute. We studied the long-term follow-up from Fontan operation until last follow-up or death. In 2002, a cross-sectional study of surviving patients was undertaken. All medical and surgical records of the patients were reviewed for reoperations, arrhythmias, hospitalization and thromboembolic events. The cross-sectional evaluation consisted of physical examination, electrocardiography, exercise testing, and echocardiography. Quality of life was assessed with the Short Form 36 (SF-36) questionnaire.

Arrhythmias
The presence of an arrhythmia on any recording device was sufficient to code a patient for that rhythm disturbance, excluding arrhythmias related to cardiac catheterisation or the postoperative period. Supraventricular arrhythmia included any sustained episode of atrial flutter, atrial fibrillation or atrial tachycardia occurring at least 30 days after the Fontan operation.

Exercise capacity
Maximal exercise capacity was assessed by bicycle ergometry with stepwise increments of 10 Watts per minute for workload and compared with standardized data based on age, gender and height.

Echocardiography
Two-dimensional echocardiography with color Doppler, velocity profiles and M-mode recordings were performed. The Fontan connection was evaluated for obstruction in the conduit. Systemic ventricular function was judged by visual estimation of the echocardiographic images and graded as normal, mild, moderate or severe dysfunction.

Quality of life
A detailed health status questionnaire (SF-36) assessed physical functioning, general health, mental health, role limitations caused by physical health problems, energy and vitality, role limitations caused by emotional problems, social functioning, and bodily pain. For each of these health concepts, scores ranged from 0 to 100, with a higher score indicates a better health state.[10,11] The SF-36 has acceptable internal consistency and test-retest reliability.[12]

Statistical analysis

Data are presented as the mean value (SD) unless otherwise stated. The median value and range are presented if data were not normally distributed.

Results

Patients

Thirty-six adult patients with a Fontan procedure, were seen in the outpatient clinic and included in the study. There were 18 men. Mean age at the time of Fontan operation was 12 years (range 2-34 years). Twenty-nine patients were operated in childhood and reached adulthood, and 7 patients underwent the Fontan operation at adult age. The primary cardiac malformation was tricuspid atresia in 21 patients (58%), double-inlet left ventricle in 9 patients (25%) and other complex congenital cardiac anomalies amenable to a modified Fontan operation in 6 patients (17%). Twenty-eight patients (78%) had $\geq$1 palliation procedures before the Fontan operation. The surgical technique used for the Fontan procedure was an anastomosis between right atrium and pulmonary artery in 20 patients (56%), an atrioventricular connection through a conduit to a rudimentary right ventricle in 12 patients (33%), and a lateral tunnel variant of total cavopulmonary connection in 4 patients (11%).

Mortality

Of the initial 36 patients, 10 died (28%) during follow-up and one patient underwent cardiac transplantation. One patient who underwent a Fontan operation in adulthood, died soon after surgery. Four patients died sudden 1, 8, 13 and 14 years after Fontan operation (Figure 1). Three patients died from pulmonary emboli and 2 from severe heart failure. The mean follow-up period of all patients after Fontan operation was 15 years (range 0 – 23 years). Two patients were lost to follow-up 12 and 15 years after Fontan operation.

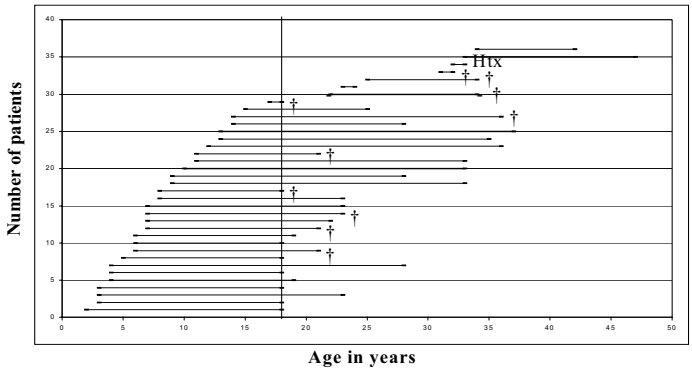
Morbidity

Event-free survival 10 years and 15 years after the Fontan operation was respectively 48% and 16% (Figure 2). Twenty-one patients (58%) needed $\geq$1 reoperations. Thirty-nine cardiac reoperations were performed, consisting of 47 procedures. The most common reoperations were a revision of the atrioventricular connection through a conduit to a rudimentary right ventricle conduit due to obstruction (n = 9), pacemaker insertion (n = 7) and conversion of the modified Fontan circulation to a total cavopulmonary connection (n = 9). Eight patients (22%) needed epicardial pacemaker implantation for sinus node dysfunction (n = 5), surgical related atrioventricular block (n = 2) and atrial flutter with coexisting sinus node dysfunction (n = 1).

In 20 patients (56%) a sustained supraventricular tachycardia was present. All 20 patients received antiarrhythmic therapy. The first episode of atrial tachycardia occurred at ± 5 years (0 -19 years) after Fontan operation. Figure 2 shows the incidence of arrhythmia during follow-up. Amiodarone given in 8 patients (47%), was the most effective drugs for reducing frequency and duration of the supraventricular tachycardia, with an interval of 1.4 years free of arrhythmias. Electrical cardioversion was performed in 14 patients. Two patients underwent catheter ablation of supraventricular arrhythmias, which was successful in 1 patient. All 4 patients with

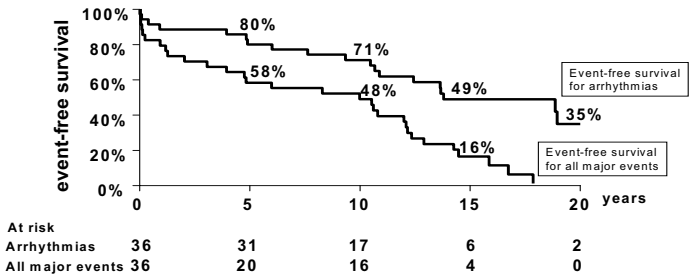
primary total cavopulmonary connection developed severe atrial tachycardia and 2 died due to arrhythmias.

Figure 1 From Fontan operation until last follow-up or death



Time development from age at Fontan operation until last follow-up or death. † is death and HTx is cardiac transplantation

Figure 2 Incidence of arrhythmia during follow-up



This figure shows the event-free survival for all cause mortality and morbidity, including reoperations, hospitalizations, arrhythmias and thromboembolic events. There is a separated curve for the incidence of arrhythmias after Fontan operation

As presented in Table 1, mortality and morbidity due to reoperations (70%) and hospitalization occurred more frequently in patients with sustained atrial arrhythmias. In addition, ventricular dysfunction (60%) and severe atrioventricular regurgitation (25%) was more evident in patients with arrhytmias. After the onset of

the arrhythmia, a new thrombus in the right atrium was found in 2 patients and pulmonary embolism was suspected in 2 additional patients. The 4 late sudden deaths in this series were assumed to be arrhythmogenic. Two patients had documented ventricular tachycardia and 1 of these patients had severe heart failure while waiting for cardiac transplantation. Electrocardiograms at last contact in 23 patients showed 14 (61%) with sinus rhythm, 7 patients with low atrial rhythm and 2 with registered pacemaker activity.

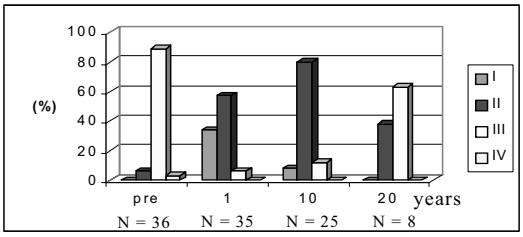
Table 1 Multivariables for patients with and without arrhythmias

	No arrhythmias (n = 16)	Arrhythmias (n = 20)
Morphology		
Tricuspid atresia	10 (62%)	11 (55%)
Double-inlet left ventricle	3 (19%)	6 (30%)
Others	3 (19%)	3 (15%)
Primary Fontan procedure (connection)		
Right atrium–pulmonary artery	10 (62%)	10 (50%)
Right atrium-right ventricle	6 (38%)	6 (30%)
Total cavopulmonary connection	0	4 (20%)
Mean age Fontan operation	10 ± 9,5	14 ± 9,8
Deaths	3 (19%)	7 (35%)
Reoperations	7 (44%)	14 (70%)
Number of hospitalization (mean)	3,4	7,1
Ventricular function		
Good	11 (69%)	8 (40%)
Moderate dysfunction	5 (31%)	9 (45%)
Severe dysfunction	0	3 (15%)
AV regurgitation		
None	8 (50%)	11 (55%)
Grade I/II	7 (44%)	4 (20%)
Grade III/IV	1 (6%)	5 (25%)

Thromboembolic events were detected in 9 patients (25%) 5 of whom had adequate anticoagulants levels at the time of event. Abnormal coagulation factor, in particularly the procoagulation factor protein C was found in 6 patients (17%) and one patient was diagnosed with a deficiency Factor VII. Three (43%) of the 7 patients with abnormal coagulation factor had a thromboembolic event. Two patients had thrombotic obstruction of the Fontan conduit and needed reoperation. Four patients developed pulmonary emboli, 3 of whom died and 1 had a femoral artery thrombosis. Two patients had a cerebral accident with moderate to severe cerebral damage. Protein-losing enteropathy was not reported in our cohort. All patients needed at least 1 hospitalization after Fontan operation. A total of 195 hospital admissions (mean 3.8 ± 2.7 (range 1 to 13)) was recorded. Mean duration of the hospital stay was 9 days ± 11 (range 1 to 101 days). The most common reason for hospitalisation was an arrhythmia.

New York Heart Association classification before the operation showed 32 of the patients (89%) in class III or VI. After the Fontan operation, classification indicated more patients in class II or III; however, with longer duration of follow-up, classification indicated most patients in class III (Figure 3).

Figure 3 NYHA classification pre- and post Fontan operation



With longer duration of follow-up after Fontan operation functional class is declining

In 2002, a cross-sectional study of the 23 surviving patients was undertaken. Exercise capacity was tested in 14 patients (58%). The total work performed was 61% ± 11% of the predicted exercise tolerance. Maximal heart rate during exercise was 145 ± 23 beats per minute. Systemic arterial blood pressures showed minimal increase during exercise, with a mean pressure increase of 26 ± 11 mmHg.

Echocardiographic assessment showed 14 patients (61%) with good systemic ventricular function and 9 patients (38%) with moderate to severe dysfunction of the systemic ventricle. Dilatation of the systemic ventricle was present in 6 patients (25 %). AV valve regurgitation was seen in 13 patients (57%), and was moderate to severe in 4. The right atrium for most patients was markedly dilated, with pronounced echogenicity of low blood flow.

Medication

Twenty-one patients (96%) were receiving anticoagulant therapy. Thirteen of the 23 patients used other cardiac medication, with amiodarone and diuretics being the most common (Table 2).

Table 2 Present medications of the 23 surviving patients after Fontan operation

Medication		Number (%)
Anticoagulants	Coumarin	21 (91%)
	Antiplatelet drugs	1 (4%)
	None, on own request	1 (4%)
Antiarrhythmic drugs		15 (65%)
Diuretics		4 (17%)
ACE inhibitors		2 (9%)

Quality of life:

The questionnaire was completed by 22 patients (96%). Due to language barrier, 1 patient did not complete the questionnaire. The SF-36 dimensions of physical functioning, mental health, and general health perception were significantly lower for

patients with a Fontan circulation than for the normal Dutch population (Table 3). For social functioning, vitality and bodily pain, the patients did not differ from the general population. Fifteen patients (65%) were fully employed. Three unemployed because of their cardiac problems. None of our patients had children.

Table 3 Quality of life based on the SF-36 results compared with population normative data

N = 22	Fontan patients	General population	*P*-value
1. Physical functioning	80.2 (14.5)	93.1 (11.8)	< 0.0001
2.Role – physical	61.9 (40.0)	86.4 (27.6)	< 0.0001
3.Role – emotional	79.4 (34)	85.4 (30.0)	0.4
4. Social functioning	77.6 (26.7)	87.8 (19.1)	0.02
5. Mental health	54.5 (22.6)	78.7 (15.2)	< 0.0001
6. Energy/vitality	68.8 (21.2)	70.7 (16.4)	0.6
7. Pain	79.1 (23.8)	80.9 (19.4)	0.9
8. General health perception	56.7 (21.6)	78.2 (17.3)	< 0.0001

Discussion

This study showed a surprisingly high mortality in rate young adults and a high morbidity rate after the Fontan operation. Arrhythmias, reoperations and thromboembolic events often occurred and all patients had ≥1 hospital admission during follow-up.

Mortality

A possible risk factor for late mortality is surgery at older age.[13,14] In our patients who underwent the Fontan operation at adult age, the mortality was as high as 57%. Three of our patients died suddenly late after Fontan operation, suggesting arrhythmia to play a major role.

Morbidity

Arrhythmias comprised the most common reason for hospital admission.

Our data showed that the prevalence of atrial arrhythmias increased with longer interval after the Fontan operation. A correlation has been found between arrhythmias and reoperations. [15,16] In patients with arrhythmias, moderate to severe ventricular dysfunction was common (60%) and arrhythmias have been associated with right atrial thrombus. The high mortality and morbidity rates associated with arrhythmias make aggressive treatment necessary and it is urgent to convert these patients to sinus rhythm. The hemodynamic situation and the incidence of arrhythmias seem closely correlated, therefore, if new arrhythmias occur, a thorough evaluation of the total Fontan connection is clearly indicated because arrhythmias can be the first sign of hemodynamic deterioration. Amiodarone was found to be the most effective antiarrhythmic drug in our study. Electrophysiologically guided ablation of an arrhythmogenic substrate has become more successful in morphological abnormal hearts and must be considered when pharmacological therapy is insufficient and to avoid lifelong side effects of antiarrhythmic medication.

Thromboembolic events after Fontan operation are a common and serious problem. In this study, the incidence of thromboembolic events during long-term follow-up was 25%, which is higher than in other recent studies reporting an

incidence of 10% to 20%. After a thromboembolic event we found a mortality rate of 38%, which is higher than the 25% reported in the literature.[8,17] Presumable, adult Fontan patients have more severe ventricular dysfunction and therefore cannot cope with the extra hemodynamic burden. Despite the documented frequency and clinical effect of thromboembolic complications, no consensus has been found in the literature regarding anticoagulant therapy, methods (ie, Coumadin vs anti-platelet agents), or duration of therapy. Coumadin is the most effective prophylactic therapy in preventing thromboembolism. Therefore, our regime is to put all patients on lifelong anticoagulant therapy (internation normalized ratio 2,0 to 3,5). Nevertheless, we found a high incidence of thromboembolic events, and more than 50% with adequate levels of anticoagulation. Even higher levels of anticoagulant therapy (internation normalized ratio 3,5 to 4,5) or additional antiplatelet drugs may be necessary in this population.

Despite the abnormal hemodynamic situation, clinicians are frequently impressed by the ability of most patients to lead a nearly normal life. In our study, we found the fast majority to be in New York Heart Assosiation class I or II after 10 years of follow-up, but with time there is a progressive decline in functional status.[3,6,18] Maximal exercise in any patient after Fontan repair is subnormal or, at best, reaches the lower limit of normal. In our adult population, the maximal exercise tolerance was only 61% of the predicted value. In addition, the systemic arterial blood pressure did not increase during exercise. This is a known feature of the Fontan circulation, because it lacks the possibility to significantly accelerate blood flow during exercise.[3] The only mechanism to establish a greater output during exercise, is increasing the heart rate. We found an adequate increase of heart rate during exercise.

Quality of life

There have been several studies on the intellectual, social and emotional development of children and adolescents with congenital heart disease, but no study has been performed in adults after the Fontan operation.[19-21] Our study showed a significantly lower score for physical functioning, mental health and general health perception compared to the normal Dutch population. Hospital mortality has been reduced and many Fontan patients reach adulthood but at the expense of repeated hospital admissions and surgical procedures. The psychological impact of these repeated procedures must be considered, and is very important in adolescence and young adulthood. Social isolation and mental health impairment may be the result of physical incapacity, restricted leisure time activities or parental overprotectiveness.[22] In addition, patients are usually aware of the potential reduction in their life expectancy and physical capabilities. To enhance the patient's long-term quality of life, psychological aspects must be taken into account. An understanding by health professionals of the subjective experiences and dilemmas in these patients is necessary and improvement in care may be gained by offering professional psychological or emotional guidance.

Study limitations

Although long-term follow-up information was available for the large majority of patients, the incidence of transient arrhythmias and thromboembolic complications may not be complete, because we attended to only clinically relevant events. If so, the numbers of complications are underestimated, resulting in even higher morbidity-rates. A profound bias with a retrospective study can occur, firstly when patients are accepted for Fontan operation and secondly by survival from the operation.

Therefore, evaluation of this heterogeneous group for long-term consequences of a Fontan circulation has severe limitations.

Conclusion

We found a high mortality and impressive morbidity in adult patients after Fontan operation with recurrent hospitalizations, arrhythmia, reoperations and thromboembolic events. Adequate anticoagulant therapy is important in all adult patients. Since a longer life does not necessarily mean a better life, knowledge of the emotional response to health status problems is obliged and psychological aspects must be taken into account. The heterogeneity of the patients and their fragile hemodynamic situation demands individualized strategies for management and long-term follow-up in specialized centers for adult congenital heart disease is strongly recommended.

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Chapter 12

Psychosocial functioning of the adult with congenital heart disease: a 20–33 years follow-up

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Abstract

Background
Since knowledge about the psychosocial function of adult patients with congenital heart disease is limited, we compared biographical characteristics, and emotional and social functioning of these patients with that of the reference groups.

Methods and results
Patients with congenital heart disease (N=362, aged 20–46 years), belonging to five diagnostic groups, were subjected to extensive medical and psychological examination, 20–33 years after their first open heart surgery. All the patients were seen by the same psychologist, who examined their psychosocial functioning using a structured interview and questionnaires. The majority (78%)was living independently and showed favourable outcome regarding the marital status. Among married/cohabitant patients, 25–39-year-olds showed normal offspring rates. None of the 20–24-year-old patients had any children. The offspring rate dropped after the age of 40. The proportion of adult patients with a history of special education was high (27%). Accordingly, patients showed lower educational and occupational levels compared to reference groups. As regard to the emotional and social functioning (leisure-time activities), the sample showed favourable results.

Conclusions
Overall, this sample of patients with congenital heart disease seemed capable of leading normal lives and seemed motivated to make good use of their abilities.

Introduction

With the improvement of surgical techniques over the last decades, increasing survival rates of patients with congenital heart disease are resulting in a new and growing patient population: adults with operated congenital heart disease. Medical professionals not only encounter specific medical needs of these patients, but also deal with unique psychosocial characteristics of adults with congenital heart disease. So far, however, little is known about the specific psychosocial problems of these patients when they enter adulthood, or the extent to which they succeed in having a normal life. This might impede medical professionals in tailoring treatment to the specific needs of the adult patients with congenital heart disease, since these patients differ in many aspects from the well-known adult population with acquired

cardiac diseases. The purpose of this study was to provide a clear and solid view on the biographical characteristics and current emotional and social functioning of the adults with congenital heart disease.

Both positive and negative outcomes have been documented regarding the educational and occupational functioning,[1-6] living conditions, marital status and offspring [3,4,5,6] and emotional and social functioning.[1,2,5,6] Deriving a complete picture of the adult patient with congenital heart disease from the existing studies is hampered by several factors, including small sample size, heterogeneous sample composition with regard to the type of congenital heart disease, different age ranges,low-response rate, non-standardised assessment procedures and variation in methods across various studies.

This study is part of a multidisciplinary cohort study of the patients with congenital heart disease, 20–33 years after their first heart surgery. This work concerns the second follow-up of the cohort and offers the unique possibility to study its current psychosocial functioning with a larger sample size and age range in adulthood compared to the previous works. It has been suggested that patients rate the negative impact of the congenital heart disease on their functioning as more serious as they grow older.[6] However, very little information is available about how these patients function later in adulthood.

Therefore, the aims of the present study were: (1) to compare the biographical characteristics and emotional and social functioning of adults with operated congenital heart disease with that of reference groups; (2) to determine the relationship between cardiac diagnosis and the biographical characteristics and emotional and social functioning of the patients; and (3) to determine the effects of sex and age on biographical characteristics and on emotional and social functioning.

Methods

Inclusion criteria

During the first follow-up of this study, which took place between 1989 and 1991, all consecutive patients who underwent their first open heart surgery for congenital heart disease between 1968 and 1980 in the Erasmus MC, and who were younger than 15 years at the time of surgery, were eligible. This population is described in detail elsewhere.[5]

The target population of the second follow-up (2000–2001) consisted of 498 patients of the first follow-up. From the 498 patients, we excluded: 11 deceased patients (one with atrial septal defect, four with ventricular septal defect, two with tetralogy of Fallot, two with transposition of the great arteries and two with pulmonary stenosis), 26 untraceable patients and one patient who had undergone heart transplantation; 61 patients were also excluded because they belonged to a miscellaneous diagnostic group, consisting of a small number of patients with a variety of congenital heart defects.

Patient sample

Of the remaining 399 eligible patients, 37 refused to participate. The present patient sample consisted of the remaining 362 adult patients (mean age: 30.2 years, age range 20–46 years), of which 194 were males and 168 were females. For biographical characteristics, data were available for all the patients, but not on all the

topics. For emotional functioning, data were missing for 11 patients (eight were mentally retarded, one had a linguistic problem, two did not complete the questionnaire). For social functioning, data were missing for two persons (one was mentally retarded, one did not complete the questionnaire). The total number of patients answering each question(naire) are indicated in table 1, table 2, table 3, table 4 and table 5. The overall response rate, corrected for deceased patients and persons lost to follow-up, was 90.7%.

The total number of patients belonging to different diagnostic groups was: atrial septal defect (ASD, *N*=93), ventricular septal defect (VSD, *N*=97), tetralogy of Fallot (ToF, *N*=77), transposition of the great arteries (TGA, *N*=55) and pulmonary stenosis (PS, *N*=40). The mean ages in these diagnostic groups were 32.8, 29.5, 30.2, 26.0 and 31.3 years, respectively. Medical history and physical condition of these patients at the time of the first follow-up are described elsewhere.[7,8,9,10]

For the biographical characteristics and social functioning, recent normative data were derived from the Netherlands Central Bureau of Statistics and, wherever available, were specified by age and sex.[11] These recent reference data were derived from a variety of normative samples. Since these concerned very large samples, the representativeness for the average Dutch situation was warranted. Sample sizes of multiple and very large reference groups were not indicated in table 1, table 2, table 3, table 4 and table 5 to prevent confusion. For emotional functioning, the reference group consisted of 5686 adults (mean age, 34.6 years; age range 15–65 years;2730 males and 2956 females), derived from an extensive Dutch population study.[12]

Instruments

Biographical characteristics

A structured interview was designed to assess biographical variables, such as living conditions, offspring, education and marital and occupational status. Special education included schools for learning-disabled, mentally handicapped and chronically ill children.

Emotional functioning

From the Dutch Personality Questionnaire (DPQ),[12] derived from the California Psychological Inventory,[13] three scales were used, namely hostility (19 items), self-esteem (19 items) and neuroticism (21 items). Hostility measures the extent of criticism, distrust and intolerance towards other people. Self-esteem measures a positive attitude towards work, flexibility and being energetic and self-controlled. Neuroticism measures feelings of stress, depression, instability and insecurity. The response possibilities of the DPQ are: YES = 2, do not KNOW = 1, and NO = 0. A high score of self-esteem indicates a high self-esteem. On the other scales, the higher the scores, the poorer the social adjustment. The internal consistency, stability and validity of the DPQ can be considered favourable.[12, 14] The psychometric qualities of the DPQ are describedelsewhere in more detail.[5]

Social functioning

Leisure-time activities were assessed with standardised items derived from the Netherlands Central Bureau of Statistics.[15,16]

Assessment procedure

During their visit to the Erasmus Medical Centre, patients were interviewed and tested by a psychologist (EvR) and medically examined by a cardiologist. For patients with low intellectual functioning, the question(naire)s were verbally administered, if possible. Of the 362 patients, 28 patients preferred to complete the questionnaires at home. In these cases, the structured interview was done by telephone, except for five patients who refused to have such an interview.

Statistical analyses

For biographical characteristics, proportions of patients are presented in percentages and actual numbers. Levels of significance were calculated only when the patient sample was comparable to reference groups with regard to age and gender. In order to correct for multiple comparisons, only the differences in biographical characteristics with a level of significance lower than 0.01 were considered significant. As to the emotional and social functioning, for the both patient sample and for the reference groups, 95% confidence intervals (CI) were calculated, respectively, around the group means of the DPQ scales and the proportions on leisure-time activities. If the 95% CI of the patient sample did not overlap with those of the reference group, the differences between the group means or the participating proportions were considered significant. Comparisons between diagnostic categories were also performed based on 95% CI. Owing to small cell sizes, statistical differences between diagnostic categories could not always be proven. For the DPQ, Cohen's *Ds* [17] were computed to assess the magnitude of differences in mean scores between the patient sample and the reference groups. According to Cohen's [17]criteria, a standardised difference of 0.20 can be considered as small, 0.50 as medium, and 0.90 as high.

Results

Biographical characteristics

The main biographical characteristics are outlined in Table 1. The majority of the patient sample (78%) was living on their own (defined as living independently), while a total of 18% was not living independently, but with parents or another caretaker. When specified for age and sex categories, the living conditions of the patient sample showed high similarities with those of the reference group. The 25–29 year old females from the patient sample were living on their own, significantly more often compared to the reference group ($p<0.01$). Patients appeared to be living in (or under supervision of) institutions for mentally handicapped significantly more often than the reference group (4 vs. 1%; $p<0.01$), with no significant differences between diagnostic categories.

With respect to the marital status of the patient sample, at least 72% was in some sort of relationship at the time of the interview. For persons living independently ($N=279$), no significant differences in marital status were found between the patient sample and the reference group.

Regarding offspring, a total of 34% of the patient sample had one ore more child(ren). Among married persons or cohabitants ($N=217$), none of the 20–24 year old patients had any children, in contrast to 14% in the reference group. Within the age range of 25–39 years, no significant differences in offspring were found between the patient sample and the reference group. The proportion of patients with

congenital heart disease with offspring drops after the age of 40. Based on median split age groups, no significant differences between the diagnostic categories were found. Table 1 shows that 27% of the patient sample had followed some sort of special education in the past. Of these patients, 85% attended schools for learning-disabled or mentally handicapped children and 15% for chronically ill children. The proportions of patients with a history of special education were significantly higher in the diagnostic categories tetralogy of Fallot (33% (22–44)) and transposition of the great arteries (40% (27–53)) than in the atrial septal defect group (13% (6–20)).

The educational attainments of the patient sample were evaluated excluding those living in institutions for mentally handicapped. For the patient sample, the highest educational level completed was significantly more often a lower level incomparison to the reference group (47 vs. 39%,$p<0.01$). No significant differences in educational attainments were found between the diagnostic categories.

Regarding the daily activities of the patient sample, at least 85% had a paid job (persons on long-term sick leave and working in labour institutions for mentally handicapped included), 7% received some sort of social security benefit and 8% were either attending school or doing full-time household work. Normative data on daily activities were not available. Although no significant differences between diagnostic categories were found, social security benefits were received most often in the diagnostic categories tetralogy of Fallot and transposition of the great arteries (12 and 13%, respectively).

The occupational status of the patient sample is further outlined in Table 2. The patient sample appeared to be significantly overrepresented in the lower level occupations, and underrepresented in the scientific occupations, compared to the reference group. No significant differences in occupational status were found between the diagnostic categories. As to the duration of employment, the patient sample did not differ from the reference group, nor were there any significant differences between diagnostic categories. In the decision to work part-time, the congenital heart disease played a role in 21% of the cases. Although no statistical differences between diagnostic groups were revealed, the congenital heart disease was mentioned as a reason to work part-time most often in the diagnostic categories, transposition of the great arteries, pulmonary stenosis and tetralogy of Fallot (40, 36 and 29%, respectively). Besides specific cardiac problems, weariness was often mentioned as another reason. The estimation of the gross income in the patient sample exceeded that of the reference group to some extent. The congenital heart disease sick-leave percentage was higher than that of the reference group. This was not in accordance with their own perception, since the majority of the patient sample reported to have a lower sick leave than colleagues. Although no statistical differences were revealed, the sick-leave percentage was highest in the diagnostic categories, tetralogy of Fallot and transposition of the great arteries (10.7 and 10.1%, respectively). The congenital heart disease was mentioned as a reason for sick leave in 8% of the cases. Among the diagnostic categories, this was the case most often within the category, transposition of the great arteries (18%). The patients' estimation of career possibilities seemed favourable and equal for all the diagnostic categories. Table 3 provides an overview of the main, more objective, occupational variables for the five different diagnostic categories.

Table 1 Biographical characteristics of the patient sample

	ASD (%) (N=93)	VSD (%) (N=97)	ToF (%) (N=77)	TGA (%) (N=55)	PS (%) (N=40)	Total patient sample (%) (N=362)
Living conditions (N=357)						
With parents	6	18	20	39	10	17 (62)
On one's one	92	77	75	57	82	78 (279)
In institution for mentally handicapped	2	5	5	4	5	4 (15)
Other	0	0	0	0	3	<1 (1)
Marital status (N=357)						
No relationship	21	26	25	38	22	26 (93)
Stable relationship	6	16	12	17	2	11 (39)
Cohabitant	16	19	24	17	28	20 (71)
Married	53	35	37	26	48	40 (143)
Divorced	3	3	1	2	0	2 (8)
Cohabitant or married after divorce	1	1	1	0	0	1 (3)
Offspring (N=357)						
0 children	54	72	63	85	55	66 (234)
1 child	12	12	13	9	18	12 (44)
2 children	24	12	16	4	20	16 (56)
≥3 children	10	4	8	2	7	6 (23)
Former course of education (N=358)						
Special education	13	28	33	40	23	27 (95)
Regular education	87	72	67	60	77	73 (263)
Educational attainment (N=334)						
Lower	47	43	52	48	43	47 (156)
Average	31	36	32	31	43	34 (114)
Higher	22	21	16	21	14	19 (64)
Daily activities (N=362)						
Attending school	2	5	7	9	0	5 (18)
Job	83	82	73	71	77	78 (282)
Unemployed	0	0	3	7	0	2 (6)
Disablement pension[a]	1	0	3	4	0	1 (5)
Volunteer, unpaid work[a]	2	3	1	2	0	2 (7)
Long-term sick leave	2	1	0	2	2	1 (5)
Household	6	1	3	0	10	3 (12)
Labour institution for mentally handicapped	4	6	5	5	8	6 (20)
Activity centre for mentally handicapped[a]	0	2	5	0	3	2 (7)

Abbreviations: ASD, atrial septal defect; VSD, ventricular septal defect; ToF, tetralogy of Fallot; TGA, transposition of the great arteries; PS, pulmonary stenosis. Between the parentheses, the actual numbers of patients for which data were available are indicated

[a]Considered to receive social security benefiets

Table 2 Occupational status of persons with paid work in the patient sample and reference group (persons in labour institutions included)

	Patient sample (*N*=302)			Reference group		*P*-value
	% (N)	M	SD	%	M	
Occupational level (SBC 1992)[a] *(N=236)*[b]						
Elementary	5 (11)			6		NS
Lower	34 (79)			22		<0.0001
Average	39 (93)			41		NS
Higher	18 (43)			22		NS
Scientific	4 (10)			9		<0.001
Duration of employment (*N*=295)						
Full-time (≥36 h a week)						
Total	69 (205)			70		NS
Male	91 (152)			89		NS
Female	41 (53)			40		NS
Part-time						
Total	31 (90)			30		NS
Male	9 (15)			11		NS
Female	59 (75)			60		NS
Reason part-time employment						
Unrelated to heart disease	79 (71)					
Heart disease one of several reasons	11 (10)					
Heart disease the only reason	10 (9)					
Income (gross salary divided by 1000 Euros) (N=220)						
Total		25.9	18.7		21.0	
Sick leave (from previous year) (N=297)[c]						
Mean sick-leave percentages[d]		7.9	31.3		5.5	
Sick leave according to patients						
Less than colleagues	57 (162)					
Equal to colleagues	30 (86)					
More than colleagues	13 (36)					
Reason sick leave						
Unrelated to heart disease	92 (169)					
Heart disease one of several reasons	4 (7)					
Heart disease the only reason	4 (7)					
Perception of career possibilities (N=285)						
Career possibilities according to patients						
Equal to colleagues	92 (262)					
Less than colleagues	8 (23)					

Between parentheses, the actual numbers of patients for which data were available are indicated. [a]Standaard Beroepen Codering 1992 (Standard Occupation Classification), Netherlands Central Bureau of Statistics, [b]Only persons ≥25 years were included, persons living in institutions for mentally handicapped are excluded, [c]Persons on long-term sick leave are also included in this section (total *N*=307), [d]Sick-leave percentage was used instead of number of days on sick leave, since the number of hours a person works a week (full-time/part-time) might vary considerably

Emotional functioning

On the DPQ, the patient sample obtained significantly more favourable results on hostility, self-esteem and neuroticism than the reference group (Table 4). The differences in mean scores could all be considered as medium, according to

Cohen's[17] criteria, except for the effects, for females, on neuroticism, which could be considered as small.

Of the 351 patients who completed the DPQ, 18 patients fulfilled their daily activities in either a labour institution or an activity centre for mentally handicapped and 25 patients completed it at home (one patient belonged to both of these groups). It was assumed that the DPQ reference group did not contain any mentally handicapped. Furthermore, possible bias from home-completed questionnaires should be excluded. Therefore, DPQ scores for the patient sample, after excluding those visiting labour institutions or activity centres for mentally handicapped and patients who completed the DPQ at home (DPQ-Excluded), were calculated. The results of the DPQ-Excluded group were only slightly different from those of the original 351 patient-respondents (Table 3). The DPQ-Excluded group also obtained significantly more favourable results on hostility, self-esteem and neuroticism than the reference group.[7]

Table 3 Summary of main variables concerning occupational status for different cardiac diagnostic groups

	ASD		VSD		ToF		TGA		PS	
	%	M	%	M	%	M	%	M	%	M
Occupational level (SBC 1992)[a] (N=236)[b]										
Elementary	5		6		2		0		7	
Lower	31		35		47		28		19	
Average	42		30		34		48		55	
Higher	18		22		13		19		19	
Scientific	4		7		4		5		0	
Duration of employment (N=295)										
Full-time (≥36 h a week)	68		68		71		75		68	
Part-time	32		32		29		25		32	
Income (gross salary divided by 1000 Euros) (N=220)		27.5		25.0		24.4		21.5		32.9
Sick leave (from previous year) (*N*=297)[c]										
Mean sick-leave Percentage[d]		6.3		8.5		10.7		10.1		2.6

Abbreviations: ASD, atrial septal defect; VSD, ventricular septal defect; ToF, tetralogy of Fallot; TGA, transposition of the great arteries; PS, pulmonary stenosis

[a]Standaard Beroepen Codering 1992 (Standard Occupation Classification), Netherlands Central Bureau of Statistics

[b]Only persons ≥25 years were included, persons living in institutions for mentally handicapped are excluded

[c]Persons on long-term sick leave are also included in this section (total *N*=307)

[d]Sick-leave percentage was used instead of number of days on sick leave, since the number of hours a person works a week (full-time/part-0time) might vary considerably

Effects of diagnostic category, sex and age on emotional functioning of the patients were computed on the DPQ scales. No significant differences were found between the diagnostic categories. As for the sex effects, females scored significantly less favourable on self-esteem compared to males (females: MEAN = 29.9 (29.0–30.8); males: MEAN = 32.0 (31.3–32.7)). Furthermore, in accordance with the reference group, females reported significantly more complaints on neuroticism than males (females: MEAN = 10.3 (9.2–11.5); males: MEAN = 6.5 (5.6–7.4)). To assess age

effects, two categories (20–29 years and 30–46 years), based on the median split of the patient sample, were formed. No significant age effect was found.
Since the number of male vs. female and younger vs. older patients differed across the diagnostic categories on all DPQ scales, sex and age effects were next tested when adjusted to diagnostic category. For each diagnostic category, 95% CI around the mean scores on the DPQ scales of male vs. female, and younger vs. older patients were compared. No significant sex or age effects were found.

Social functioning

Table 5 presents significant differences in participation in leisure-time activities between the patient sample and reference group for different age- and sex-based groups. For all of these differences, participation was higher in the patient sample than in the reference group. Higher participation in leisure-time activities was reported for outgoing activities like going to the movies, visiting clubs and discos and shopping, as well as for domestic activities like playing games and watching TV.
When total sport participation (≥1 h a week) between the diagnostic categories was compared, no significant differences were found. More intensive sport participation (≥5 h a week), however, was found significantly more often in the diagnostic category, ventricular septal defect than in the transposition of the great arteries group (19%(11–27) and 4% (0–9), respectively). Apart from the brain-teasers, which were performed significantly more often by patients with ventricular septal defect and transposition of the great arteries than by the patients with tetralogy of Fallot and pulmonary stenosis, no further significant differences, between the diagnostic categories, in participation in leisure-time activities were found.

Table 4 Mean scores, 95% CI, standard deviations and Cohen's *D* on the DPQ[a] for patient sample and reference group and DPQ-EX.[b] group

DPQ[a]	Patient sample (*N*=351)		Reference (*N*=5686)		Cohen's *D*
	M (CI)	SD	M (CI)	SD	
Hostility	14.9(14.1-15.6)	7.2	18.2(18.0-18.4	6.7	0.5
Self-esteem	31.0(30.5-31.6)	5.3	28.0(27.9-28.1)	5.6	0.5
Neuroticism					
Male[c]	6.5(5.6-7.4)	6.3	10.1(10.0-10.2)	7.5	0.5
Female[c]	10.3(9.2-11.5)	7.6	13.9(13.6-14.2)	8.3	0.4
DPQ-EX (N=307)					
Hostility	15.0(14.2-15.8)	7.2			0.5
Self-esteem	31.2(30.5-31.8)	5.4			0.6
Neuriticism					
Male[d]	6.5(5.5-7.4)	6.4			0.5
Female[d]	10.2(8.9-11.4)	7.5			0.4

[a]Dutch Personality Questionnaire.[12]
[b]DpQ-EX: Dutch Personality Questionnaire – results of patients after exclusion of mailed questionnaire data and patients attending either labour institutions or activity centres for mentally handicapped
[c]Male: patients *N*=190, reference *N*=2730; female: patients *N*=161, reference *N*=2956
[d]Male: patients *N*=167, female: patients *N*=140

Table 5 Significant differences in leisure-time activities (proportions of participation and 95% CI) between patient sample and reference group

Item	18-24 years				25-34 years				35-44 years			
	Males		Females		Males		Females		Males		Females	
	Patient sample (N=50)	Reference group	Patient sample (N=27)	Reference group	Patient sample (N=100)	Reference group	Patient sample (N=98)	Reference group	Patient sample (N=43)	Reference group	Patient sample (N=40)	Reference group
	% (CI)	% (CI)	% (CI)	% (CI)	% (CI)	% (CI)	% (CI)	% (CI)	% CI	% CI	% CI	% CI
Movies							69 (60-79)	53 (48-58)	60 (45-76)	36 (31-41)		
Playing games									88 (78-98)	66 (61-71)	93 (84-100)	73 (68-78)
Walking/ cycling			100	95 (93-97)								
Visiting clubs					49 (39-59)	32 (28-36)			53 (38-69)	24 (19-29)		
Visiting discos							43 (33-53)	25 (21-29)				
Watching TV											100	95 (93-97)
Shopping					79 (71-87)	54 (49-59)	96 (92-100)	83 (79-87)	77 (64-90)	49 (44-54)	95 (88-100)	77 (73-81)

Only significant differences were reported in the table. No significant differences were shown on the following eight items not reported in the table: watching sports, brain-teasers, making music/acting, handicrafts, odd jobs, listening to radio, doing sports, visiting bars

Discussion

Biographical, emotional and social features of the patient sample

Overall, living conditions, marital status and offspring of the patient sample in the present study showed high similarity with the reference groups. Regarding living conditions, Ternestedt et al.[6] also found similarities between patients with congenital heart disease and a normative sample. Kokkonen and Paavilainen[3] and Utens et al,[5] however, did find differences: especially the young patients with congenital heart disease were living with their parents more often than reference groups. The higher mean age and larger age range in adulthood, in the present patient sample, compared to the relative young samples of the previous studies[3,5] provide a possible explanation for these diverging findings. The previously found arrears in living conditions might be equalised later on in adulthood. As to marital status, the results of the present study confirm to those of Ternestedt et al,[6] but are in contrast with the results of Kokkonen and Paavilainen[3] and Gersony et al.[4] The latter found patients with congenital heart disease to be married less often, or get married at a later age compared to the reference groups. It should,however, be mentioned that in the present study, marital status was scrutinised for a selection of the patient sample, namely those already living independently. Offspring was examined only for married persons or cohabitants. Furthermore, in this study, both sexes were included, instead of only females, which might explain the favourable outcome in offspring in contrast to the study of Gersony et al,[4] who found elevated childlessness among congenital heart disease women. It should be noted that decreased rates of offspring for the youngest (20–24 years) and oldest (above 40 years) patients of the sample could not be proven significantly different because of empty and small cells.

In the present study, the proportion of patients with a history of special education can be considered as high. For 15% of those the impact of the congenital heart disease on their school career (hospitalisation, restrictions) seemed to be the main reason for attendance of special education, since they had been in schools for chronically ill children. In the remaining 85%, some sort of learning disability or mental retardation seemed apparent, considering the type of special education they had attended. Additionally, within the patient sample, the highest educational level completed was more often a lower level compared to the reference group. Although it is well known that congenital heart disease patients encounter different barriers in their educational course during childhood, such as absence from school due to illness, treatment or recovery[18,19] and learning-disabilities,[19,20,21] the high number of adult patients with congenital heart disease with a history of special education never appeared so clearly as in this study. This high attendance of special education in the past might have resulted in lower educational attainments in adulthood: a finding, which is highly in contrast with the findings of Brandhagen et al.[2] and Ternestedt et al.,[6] who found an even higher educational level in the adults with congenital heart disease compared to the normative groups.

In accordance with the educational attainments, this patient sample had lower level of occupations significantly more often than the reference group. The duration of employment of the patient sample, however, did not differ from the reference group. The gross income of the patient sample seemed somewhat higher than the reference group. However, it should be mentioned that most patients could only give a rough indication of their income and, owing to social desirability, they might have exaggerated their estimations. The sick-leave percentage of the patient sample was

higher than that of the reference group, although most patients estimated that their sick leave was less than colleagues. This might indicate possible denial. Accordingly, patients with congenital heart disease seemed to have a positive perception of theircareer possibilities. Overall, it can be stated that, despite a somewhat lower occupational level and higher sick leave, the present patient sample showed favourable results regarding the duration of employment, income and perception of career possibilities. Broadly speaking, this confirms the positive findings of previous studies[1,3,4] with respect to employment.

Regarding emotional functioning, Brandhagenet al.[2] found an increased level of psychological stress in adults with congenital heart disease. Shampaine et al.[1] found both positive and negative emotional outcomes. Ternestedt et al.[6] found more favourable emotional outcomes in patients with tetralogy of Fallot compared to patients with atrial septal defect. The present patient sample showed more favourable scores than the reference group on hostility, self-esteem and neuroticism. These findings are similar to those of Utens et al.[5], who studied the same cohort with the same instrument regarding emotional functioning 10 years earlier. In this study,[5] it was suggested that denial mechanisms and high achievement motivation possibly lead congenital heart disease patients to overrate their emotional states. Recently, perseverance has been put forward as a coping mechanism in congenital heart diseasepatients.[6]

Social functioning of the patient sample can be considered favourable. If significant differences were found in participation in leisure-time activities, the congenital heart disease patients obtained more positive scores than the reference group. These overall favourable results on social functioning confirm earlier favourable findings.[4,5]

Effect of cardiac diagnosis

Regarding biographical characteristics, no significant differences between the diagnostic categories were found for living in institutions, having offspring, educational attainments, receiving social security benefits, occupational level and duration of employment. Regarding social functioning, participation in leisure-time activities was highly similar among the different diagnostic categories, except for intensive sport participation.

Overall, it can be stated that individuals within the diagnostic categories transposition of the great arteries and tetralogy of Fallot showed some residual effects from the congenital heart defect as to participation in education, occupation and intensive sport, but further were able to live normal lives. This finding is supported by the fact that no significant differences in emotional functioning were found between the diagnostic categories.

Effects of sex and age

As to living conditions, the 25–29-year-old female patients were living on their own significantly more often than the reference group. Regarding the offspring, the patients seemed to raise families somewhat later, in their 20s, when compared with the reference group. Remarkably, there was a drop of patients with offspring after the age of 40. This is probably due to a cohort effect since for the eldest of the patient sample, the cardiac surgery was not yet available when they were born. Therefore, patients were more likely to be operated at an older age and treated with less advanced techniques compared to the youngest patients in this sample. Also, they were the first congenital heart disease patients to enter adulthood and experience

uncertainties regarding having offspring. The impact of the congenital heart disease on having offspring may, therefore, be greater for the older patients in the sample, compared to the younger ones.

With respect to emotional functioning, female patients scored significantly less favourable on neuroticism (in accordance with the reference group) and self-esteem than male patients. This is consistent with previous findings,[22] which showed that females with congenital heart disease report more somatic complaints than males with congenital heart disease.

Limitations

It should be noted that the present patient sample contains a selection of five frequent diagnostic categories and may, therefore, not be completely representative of all the congenital heart disease anomalies. The present patient sample concerns a generation of congenital heart disease patients who were treated with different techniques than the ones used at present. Since major advances took place in surgical techniques and psychosocial needs could have changed, the results of this study might not fully apply to young patients with congenital heart disease operated upon these days. Biographical characteristics and social functioning of the present study's sample might not be directly applicable to other countries and cultures, since life styles or aspects, for example, availability ofsocial security or educational systems, might differ considerably. Therefore, caution should be taken in generalising the psychosocial functioning of patients with congenital heart disease as described in this study.

For biographical variables, normative data were not always available. Some biographical variables were only looked at under selected conditions (marital status of independently living persons and offspring of cohabitants or married persons). This might be attributed to the favourable results on these variables for the patient sample. Furthermore, some diagnostic categories had relatively small sample sizes, which implied larger 95% CI for these groups. This may have hampered finding differences between the diagnostic groups. Taking into account the large amount of comparisons that were made in this study, the amount of differences in psychosocial functioning between the patient sample and reference group can be considered limited. This strengthens the overall positive outcome for this sample of adult patients with congenital heart disease on biographical characteristics, and emotional and social functioning.

Implications

The present study shows that this sample of adult patients with congenital heart disease has residual problems regarding its educational and occupational status, which seems a reflection of disadvantaged positions in childhood as can beconcluded from the high attendance of special education in the past. However, patients seem to make good use of their abilities as can be concluded from their favourable outcomes on duration of employment and income, and their optimistic outlook on career possibilities. The diagnostic category transposition of the great arteries seems to be hampered by the congenital heart disease most often in their employment, since they mentioned it most often as a reason for part-time working or sick leave.

Taking in consideration further results on biographical characteristics, emotional and social functioning, these adult patients seem capable of leading normal lives. However, some precaution must be taken into account. Some of these positive outcomes, for example regarding sick leave, might be influenced by a tendency in these adult patients to give social desirable answers. Whether this should be explained by denial of restrictions or a coping strategy to keep an optimistic view on their possibilities is unclear. Future research should therefore aim at coping strategies in adult congenital heart disease patients, in order to get a better understanding of how they experience their abilities. Further, the longitudinal development of psychosocial functioning of these patients as well as the influence of medical variables (not yet systematically available) should also be the focus of future research.

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Chapter 13

Congenital heart disease and pregnancy

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Summary

During pregnancy the cardiac output rises with 40-50%. In the first and second trimester mainly stroke volume increases, and in the third trimester especially the heart rate will increase.
More women with congenital heart disease reach adulthood and desire to become pregnant. The hemodynamic changes during pregnancy are an additional burden for them.
Predictors for occurrence of important cardiac problems during pregnancy are: previous cardiac events (heart failure, arrhythmias), lower functional class or cyanosis, obstruction in the left side of the heart or diminished systolic function of the systemic ventricle.
Pregnancy is contraindicated in patients with pulmonary hypertension, in Marfan syndrome with an ascending aorta diameter of >50mm and in severe mitral or aortic stenosis.
Foetal outcome is dependant on the hemodynamic situation of the mother and the medication she is taking. Ace-inhibitors and A-II antagonists are contraindicated during pregnancy. Oral anticoagulation therapy is potential harmful in the first trimester.
The recurrence risk for children varies between 3 and 50%, depending on the nature of the congenital heart disease.

Introduction

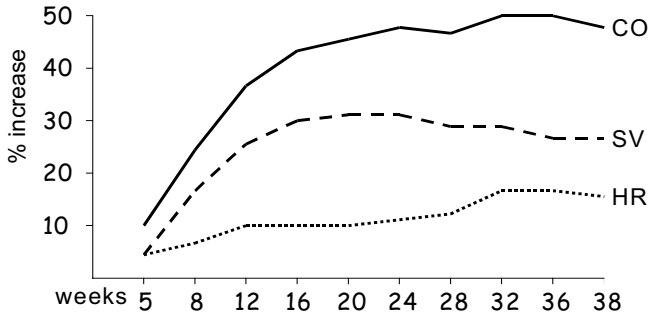
In the Netherlands about 1500 children are born every year with congenital heart disease. During the last decades mortality has decreased substantially in these children and this has resulted in a new patient population: adults with congenital heart disease. In the Netherlands it has been estimated that about 25.000 adults with congenital heart disease are alive at the moment.[1] Pregnancy raises 2 questions: concern if pregnancy might have a negative effect on the health of the female patient and the risk of congenital heart disease for the offspring. A team should guide these patients, consisting of a general practitioner, cardiologist, obstetrician and genetic counsellor.

Physiological changes during pregnancy

Almost every woman with congenital heart disease who would like to become pregnant realises that pregnancy means an extra burden for her heart. To provide proper counselling for these women the hemodynamic burden of pregnancy needs to

be analysed, and consequently this needs to be related to the different types of (corrected) congenital heart disease. The most important factor of this hemodynamic burden is the increase in maternal plasmavolume, which results in an increase in cardiac output of 40 to 50% during pregnancy.[2] At first mainly stroke volume increases and heart rate rises in the second part of pregnancy (Figure1). During the first two trimesters of pregnancy blood pressure and arterial vascular resistance diminish due to the low resistance flow circulation in the uterus and placenta. Towards the end of pregnancy, blood pressure returns to pre-pregnancy-values. Pulmonic vascular resistance diminishes due to the increase in cardiac output with unchanged pulmonary pressure. Adaptation is not limited to the cardiovascular system. Respiratory volume rises to sustain the increase in oxygen that is needed, furthermore there is a higher thrombotic risk during pregnancy. In addition, during normal pregnancy more often supraventricular arrhythmias occur.

Figure 1 Increase of stroke volume and rise of heart rate



Graphical reproduction of increase in cardiac output (CO), stroke volume (SV) and heart rate (HR) during pregnancy. On the X axis the pregnancy duration in weeks, on the Y axis the increase in terms of percentage compared to the baseline before pregnancy

The mother with congenital heart disease

Women with congenital heart disease need timely information about the risks of pregnancy. It is primarily the task of the cardiologist to give this information. In the decision process it is important that the patient can discuss the different options with her general practitioner and/or obstetrician.[3] Recently, the first prospective study was presented describing pregnancy in patients with heart disease.[4] In Canada 599 pregnancies in women with heart disease were described, about 80% of whom had congenital heart disease. In the study four predictors were identified for important cardiac problems during pregnancy (Table 1). Pulmonary oedema and symptomatic

arrhythmia's were the most common. Three women died, all three had more than 1 of the mentioned risk factors. Based on the predictors of this study the individual risk of pregnancy can be estimated. In general, functional class is found to be an important predictor: the risks of women in NYHA functional class I is very low, while women in functional class III or IV have a mortality risk of 7% or higher.[5]

Table 1 Predictors for maternal cardiac events

- Prior cardiac event (heart failure, TIA or CVA) or symptomatic arrhythmia
- Prior cardiac event (heart failure, TIA or CVA) or symptomatic arrhythmia
- NYHA functional class >II or cyanosis
- Left heart obstruction (mitralstenosis; valve area <2cm^2, aorticstenosis; valve area <1.5cm^2 or left ventricular outflowtract obstruction >30mmHg, measured with Doppler)
- Systemic ventricular dysfunction (ejection fraction <40%)

Number of predictors	Estimated risk of cardiac events in pregnancy
0	5%
1	25%
>1	*75%*

(Siu SC et.al., Circulation 2001; 104:515-21)

In the following section different diagnosis groups will be discussed.

Patients with *volume overload of the systemic ventricle*, for example aortic or mitral regurgitation do have a higher risk to develop clinical significant heart failure due to the increased circulating volume during pregnancy. However, because the diminished arterial vascular resistance during pregnancy, most patients do well. From the Canadian study we learned that in patients without symptoms and good systolic function of the systemic ventricle, the risk to develop cardiac problems during pregnancy is in the lowest category (5%) and the mortality risk is even much lower. Echocardiography will be the method of choice (ventricular function), in addition to history and functional class to predict the risks of pregnancy.

Obstructions in the left side of the heart are a much greater risk. In patients with moderate stenosis of the aortic valve, the risk of cardiac problems during pregnancy is clearly increased, although mortality is low.[6] This is due to the relatively fixed cardiac output in these patients while an increase in cardiac output is necessary during pregnancy. Restriction of physical activity is advisable. Patients with mitral stenosis do not bare the physiological increase of heart rate during pregnancy because of the reduced diastolic filling time of the left ventricle. This will lead to increase of dyspnoe. Beta blockade may be prescribed to decrease heart rate, guided by complaints and Doppler inflow pattern over the mitral valve.[7] In patients with a severe aortic stenosis especially the peripartum changes in systemic vascular resistance are risky. Termination of pregnancy has the same risks and is therefore not indicated. If a patient with severe mitral stenosis or aortic stenosis is pregnant, balloon dilatation of the valve or even surgery needs to be considered. Cardiac surgery during pregnancy results in 20% foetal mortality risk. Of course it seems better to discuss with the patient pregnancy and the possibilities of treatment before pregnancy actually occurs.

Impaired systemic ventricular function, is found in patients with left sided valvular disease and in patients who use their anatomic right ventricle as systemic ventricle: congenital correction of the great arteries and transposition of the great arteries treated with a Mustard or Senning procedure. In the case of diminished systemic ventricular function the risk of cardiac problems increases. If the patient

also had previous periods of heart failure or is in functional class III or IV, the risk increases to 75% and as a consequence pregnancy should be discouraged.[2] If patients are in functional class I or II they tend to tolerate pregnancy quite well. Deterioration of right (systemic) ventricular function has been described in 10% of the patients and is sometimes irreversible.[8]

Patients with an uncorrected *atrial septal defect* usually tolerate pregnancy very well, but because of the risk of paradoxical emboly, instructions to prevent thrombosis should be given.

In patients with *uncorrected cyanotic heart disease* the risk of problems increase if the oxygen saturation at rest is below 90%. Deterioration of cyanosis, decline in exercise capacity, heart failure and arrhythmias are seen in a third of these patients.

In patients with *uncorrected tetralogy of Fallot* mortality for the mother is at least 4% and surgical correction is indicated before pregnancy. Surgical correction at adult age is possible with low risks. In *corrected tetralogy of Fallot* pregnancy usually caries low risks. In the case of severe pulmonic regurgitation resulting in clearly reduced exercise capacity or arrhythmia's (supra ventricular tachyarrhythmia's or ventricular tachyarrhythmia's) replacement of the pulmonic valve needs to be considered before pregnancy.

Pulmonary hypertension always caries a great risk and systolic pulmonary pressure greater than 66% of systolic systemic pressure, is an absolute contra indication for pregnancy.[9,10] In particular high risk is found in patients with the so-called *"Eisenmenger syndrome*" (right to left shunt due to high pulmonary vascular resistance for example in the case of a large VSD). In the literature mortality figures as high as 30 to 50% are found. In these patients a fall in peripheral vascular resistance with no change in pulmonary vascular resistance will lead to an increase in the right to left shunt, resulting in severe cyanosis.

In patients with *Marfan syndrome*, pregnancy is a period of elevated risk to suffer from an aortic dissection, in particular during the third trimester and directly postpartum. If the diameter of the ascending aorta exceeds 50 mm, pregnancy should be discouraged. In the case of a aortic diameter of less than 40 mm the risk of dissection and other serious cardiac pathology is 1%, a diameter between 40 and 50 mm increases the risk to 10%.[11,12,13] The risk is even higher in Marfan patients with a family history of aortic dissection. Beta blockade treatment is indicated, also during pregnancy.

Women with congenital heart disease sometimes also carry a higher risk of obstretic complications. For example the risk of hypertension during pregnancy is increased in patients with *coarctation repair* and the risk of peri partum blood loss is increased in patients who need *anticoagulant therapy*.

Foetal risks

Foetal risks can be divided into three categories.
1. the inheritance risk of the congenital heart disease
2. risks as a consequence of maternal hemodynamics
3. risks as a consequence of maternal medication use

1. The inheritance risk varies from 2% to 50% and depends on the type of defect. This is discussed in detail in chapter 14.
2. Risks as a consequence of maternal hemodynamics.
In Table 2 risk factors for foetal problems are given. In the Canadian study the most frequent neonatal problems were premature birth (105 pregnancies) and low birth weight (22 pregnancies).[5] In previous retrospective studies the functional class of the mother and cyanosis proofed to be predictors for foetal and neonatal mortality, which was confirmed by the Canadian study[4,5,14,15]. When the functional class of the mother is class I, foetal and neonatal mortality is almost zero, in the case of maternal functional class IV, mortality rate increases to 30 to 50%. Mild cyanosis with an oxygen saturation above 90% is found to have a percentage of 90% live births, while oxygen rates of lower than 85% have found to give a foetal survival chance of only 12%.[14]

Table 2 Predictors of neonatal events

- NYHA class >II or cyanosis
- Maternal left heart obstruction (mitralstenosis; valve area <2cm^2, aorticstenosis; valve area <1.5cm^2 or left ventricular outflowtract obstruction >30mmHg, measured with Doppler)
- Smoking during pregnancy
- Multiple gestations
- Use of anticoagulants throughout pregnancy

Number of risk factors	Risk of neonatal problems
0	2%
1 or more	4%

(Siu SC et.al., Circulation 2001; 104:515-21)

Risks due to medication use of the mother
The use of cardiac medication during pregnancy is not always preventable, and has a potential negative influence on the foetal development. On the other hand, hemodynamic instability in the mother is also a threat for the foetus. These aspects must be balanced, but often a decision will be made in favour of starting medication for the best well being of both mother and child.

Coumadines may cause chondrodysplacia in a low percentage of children especially when used in the first trimester (especially between the 6th and 9th week). Replacement of coumadines by heparines already before conception has been propagated but is unnecessary and undesirable for the mother. However, if pregnancy has been proven, it is important to instruct the patient to change as soon as possible from coumadines to heparines to minimise foetal risks. It is rational to choose fractionated heparine, which gives a better anticoagulation for the mother, and there is less chance of tromboembolic complications. Although, no clear scientific evidence is available during pregnancy in patients with artificial valves, fractionated heparine (low molecular weight heparine) seems safe.[16,17] In the near future new drugs become available like Ximelagatran and long-acting, subcutaneously administered, factor Xa-antagonists. In the case of manifest heart failure, treatment with *digoxin, furosemide or thiazide* medication is relatively safe.

In the case of treatment with diuretics one should realise the risk of hypoperfusion of the placenta and increased foetal diuresis. Besides medication also bed rest and restricted fluid intake should be advised.

Many complaints and symptoms found in normal pregnant women imitate complaints and symptoms seen in the case of heart failure. Left sided heart failure is diagnosed only when basal crepitations remain present after deep breaths; right sided heart failure is present only when the central venous pressure is increased. *ACE-inhibitors* are absolutely contra indicated during pregnancy: lung hypoplasia and bone hypoplasia have been found when using this medication during the second and third trimester of pregnancy. Furthermore, growth retardation and foetal oliguria, oligohydramnion and persisting arterial duct are found due to the use of these ACE-inhibitors. Also A-II antagonists are contra indicated.

Supraventricular and ventricular arrhythmia's are best treated with *beta-blocking agents*, although a low risk of diminished placenta perfusion with growth retardation of the foetus and bradycardia and hypoglcemia in the infant is described. *Verapamil* carries the risk of foetal AV-block, but may be administered in emergency cases. *Antiarrhythmic agents of class Ic* are not well studied in pregnancy. *Amiodarone* should not be the first choice, because of the negative effect of the foetal thyreoid.[18,19,20]

Non-cardiac medication may also be contraindicated in patients with heart disease. For example, betamimetics, with or without corticosteroids may cause heart failure in patients with diminished ventricular function or left-sided valve disease.

The peri-partum period

In most women who are in functional class I and who experienced no complications during pregnancy, no additional peri-partum actions are necessary. However, stress reduction is desirable. For example this is necessary in patients with heart failure and those at risk for heart failure, women with life-threatening ventricular arrhythmias, severe mitral- or aortic stenosis or with Marfan's syndrome with a dilated aorta. It is advisable to develop a strategy for peri-partum management in which the gynaecologist, anaesthesist and cardiologist are involved. This strategy should be written down and available at any time. In these women a left-lateral position during labour is advisable to reduce hemodynamic changes, (less inferior caval vein compression). Epidural anesthesia may be given to reduce the cardiac burden by pain relief and primary vacuum extraction may be performed to prevent labour during contraction. On the other hand one should realise that epidural anesthesia is contraindicated in patients with severe aortic or mitral stenosis in whom hypotension will form a potential threat.[21] This is also true for women with "Eisenmenger syndrome".

Evidently, rhythm monitoring is indicated during labour in patients with important arrhythmia's and iv drug administration should be possible.

Intra-arterial blood pressure guidance is indicated in patients with severe left sided valve disease or Marfan's syndrome.

Caesarean section is only indicated for obstetric reasons. An exception may be Marfan patients with an ascending aorta dilatation in whom aorta dissection or rupture may occur during the last weeks or during delivery, although this is still under debate. The guidelines advise endocarditis prophylaxis peripartum only when complications occur. However, based on recent literature, routine use of endocarditis prophylaxis is advisable in high-risk patients.[22]

During the first days post partum, a physiologic volume overload occurs, which may lead to heart failure in patients with severe valve disease or systemic ventricular dysfunction. In these women clinical observation for the first 72 hours post partum is mandatory.

Conclusion

Pregnancy is well possible in many, but not all patients with congenital heart disease. Careful counselling is important and should be performed in time. Collaboration between cardiologist, obstetrician, anaesthesist, genetic counsellor and general practitioner is indicated.

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Chapter 14

Inheritance of congenital heart disease

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Submitted

Introduction

Congenital heart defects (CHD) are the most common developmental anomalies and are the leading non-infectious cause of mortality in new-borns. It has been estimated that 4 to 10 live born infants per 1000 have a cardiac malformation (0,4-1,0%), 40% of which are diagnosed in the first year of life. [1,2] The European Registration of Congenital Anomalies (EUROCAT) reported a prevalence of 58.9/10.000 live births in the northern part of the Netherlands (0,6%). Hoffman estimated that the true prevalence of CHD may be as high as 53 per 1000 pregnancies (5,3%), including:
a 20% occurrence of heart defects in spontaneous abortion;
a 10% occurrence in stillbirth; and
a 1% occurrence in live birth.[3]

In spite of tremendous advances in diagnosis and treatment of congenital heart disease, the underlying causes of the majority of CHD are only partly understood. Prior epidemiological studies suggested that Mendelian disorders constituted a very small percentage of CHD and that multiple factors were responsible for the majority of cases.[4] Yet, recent studies have shown that CHD caused by single gene or single locus defects is more common that had been expected.[5] Furthermore, it has become apparent that a higher percentage of heart defects occur in the context of familial disease than previously recognised.[6]

Because many children with corrected congenital heart defect now reach adulthood and childbearing age, the birth prevalence of congenital heart defects, particularly of the more severe defects, may increase in subsequent years.

Classification of causes:

1. Chromosome disorders
At the moment, chromosome disorders are known as the underling cause in eight to ten percent of the new-born babies with congenital heart disease; at adult age this percentage is lower because many children with chromosomal defects die at young age. Examples of patients with a numeric chromosomal defect who reach the adult age are patients with Down's syndrome (complete atrio-ventricular septal defect), Klinefelter syndrome and Turner syndrome (coarctation).

2. Mendelian disorders
Mendelian inheritance (single gene disorders) may be autosomal dominant, autosomal recessive or X-linked. Noonan syndrome, Marfan syndrome and Alagille syndrome are examples of autosomal dominant disorders. Also some isolated cardiac disorders are single gene disorders, such as atrio-ventricular septal defects.

Recent molecular genetic studies suggest that the genetic basis of congenital heart disease has been underestimated.[7,8]

3. Multifactorial inheritance
The majority of congenital heart defects (80-85%) can not be explained by chromosomal or single gene disorders at the moment. In these patients it is assumed that multifactorial causes play a role. Multifactorial inheritance is a model that assumes that a disease is caused by the interaction of several genetic and environmental factors (such as maternal diabetes, maternal infections, alcohol, drugs and smoking).

Genetic mechanisms hampering classification

Several genetic mechanisms contribute to the difficulties in recognising the genetic causes of congenital heart disease:

1. Genetic heterogeneity
Tetralogy of Fallot (ToF) is a common type of congenital heart disease. Although the anatomic features are clear, at least 5 different genetic causes of ToF have been identified: approximately 16% of patients with ToF have a deletion of chromosome 22q11, nearly 7% have trisomy 21 (Down syndrome), and a smaller number of ToF patients has mutations in NKX2.5 or JAG.1 (Alagille syndrome).[9,10] So a genetic cause has been identified in nearly one third of ToF patients; additional genetic causes remain to be identified.

2. Reduced penetrance refers to a situation where an individual who appears normal carries a disease causing gene mutation in a dominant gene. This is observed in familial anomalous pulmonary venous connection, familial atrioventricular septal defect and other familial congenital heart disease.[5]

3. Variable expression refers to the situation that individuals with the same genetic defect show variable phenotypes. The variety of observed malformations caused by mutations in NKX2.5 and the fact that the gene is expressed throughout the heart, suggests that this gene may affect a number of pathways in cardiac development.
A well known example of variable expression is in microdeletion 22q11.2. The features of this microdeletion syndrome may vary from subtle abnormalities like mild velopharyngeal insufficiency being the only feature, to the serious DiGeorge syndrome, with congenital heart defect, mental retardation, hypocalcemia and severe immunodeficiency. Cardiovascular abnormalities seen in patients with 22q11.2 deletion are often abnormalities in the outflow tract, like truncus arteriosius, interruption of the aortic arch, pulmonary atresia, ventricular septal defect and tetralogy of Fallot.

4. Genomic imprinting
For many congenital heart defects the risk for offspring to get the same disorder is higher if the mother than if the father has a heart defect.[5] Probably this is caused by a phenomenon called genomic imprinting. Genomic imprinting means that a certain part of the genome is modified in the germ cells with an “imprint” that turns certain

genes on or off, dependent on the gender of the person. This imprint is reversible in the next generation.

Recurrence risks and prenatal diagnosis

Recurrence risks for offspring of patients with a congenital heart defect depend on the cause of the defect. (Table1)

Table 1

Specific lesion	Recurrence rate	Associated syndromes
Atrial septal defect	3-5% familial ASD with long PR higher	Holt Oram-upper limb deformity autosomal dominant
Ventricular septal defects	2-5% occasionally familial	Down's syndrome
Atrio-ventricular septal defect (complete)	10-14% in affected mother	Down's syndrome in > 50%
Pulmonary stenosis	3-5%	Noonan, congenital rubella, Williams, Alagille
Tetralogy of Fallot	3-5% 22q11 deletion with 50% recurrence risk in 16%	Deletion of chromosome 22q11 (16%)
Aortic valve stenosis	12-20% in affected mother Bicuspid valve may be familial	Recurrence rate may be higher in syndromes
Subaortic stenosis	Familial cases described	Shone's syndrome (left heart abnormalities)
Coarctation	May be familial Association with bicuspid aortic valve	22q11 deletion
Patent arterial duct	No information	Congenital rubella
Ebstein's anomaly	6% in affected mother familial occurrence documented	rare
Marfan's syndrome	50% autosomal dominant	
Complete transposition of the great arteries	2% rare familial recurrence	none
Congenitally corrected transposition	3-5%	none

Most patients with a chromosomal defect are not reproductive, although some women with Turner syndrome and men with Klinefelter syndrome do have the possibility of having children. The recurrence risks of these chromosomal defects depend on the precise diagnosis and exceeds the scope of this paper.
The offspring of patients with mendelian or single gene disorders (autosomal dominant, autosomal recessive or X-linked recessive) have increased recurrence risks. For autosomal dominant traits the risk to be a mutation carrier for the offspring is 50%. Because of reduced penetrance and variable expression the true risk of a heart defect may be lower. For autosomal recessive disorders the offspring risk will be low if the carrier frequency is low. In X-linked disease the offspring risk may vary

as it depends on the gender of the parent and the level of expression in female carriers.
In multifactorial inheritance the recurrence rate of heart defects in the offspring of an affected parent may vary between 1.5% and 14 % with higher rates if the affected parent is a female and if more family members are affected.[4] Several studies have recently reported large families with congenital heart defects with high risks of recurrence.[11-20] To estimate the recurrence risk for an individual couple it is essential to perform a thorough family investigation.

Cardiac structural anomalies and functional problems in the fetus can be detected by prenatal echocardiography from 16 weeks of gestation or earlier. Many defects are already visible at that time, although not all defects will be detected.[21] Only in cases with a known chromosomal or mendelian (single gene) defect prenatal diagnosis by chorion villus biopsy or amniocentesis is an option.

The future is nearby….

Dividing causes of congenital heart defects in chromosomal, mendelian (single gene) and multifactorial disease is a simplification. The possibility that phenotype variability of single gene disorders is due to complex interactions between other genetic factors and/or environmental factors is a logical extension of the concept that simple Mendelian traits are, in fact, complex traits. On the other hand presumed complex traits may sometimes be due to a single gene disorder with low penetrance. Considerable interest has developed in identifying the modifying genetic and environmental factors. Identification of the factors that modify the phenotype of single gene disorders will enhance our appreciation of the clinical diversity of congenital heart defects.[22-25] More genetic research is necessary for further identification of the genes. Many studies suggest a long list of (candidate) genes. Environmental factors such as maternal smoking, maternal exposition to drugs and supplements of folic acid and other nutritional factors are also subject of extensive research.

In conclusion

The interactions of genetic and environmental factors in patients with congenital heart defects are still a topic of research. Hopefully this will lead to a better understanding of the etiology of these defects and consequently to the availability of better information to patients about the risk of their offspring. In the end this may lead to prevention of a substantial part of these defects in the future. Further research in this field is necessary.

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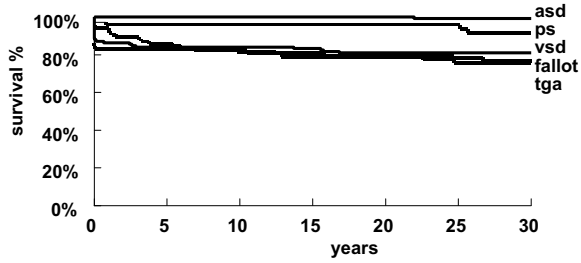
Chapter 15

Summary and discussion

Adult congenital heart disease is an intriguing new cardiovascular speciality. The advent of cardiac surgery and more recently catheter-based intervention has transformed the outlook for patients with congenital heart disease. Fifty percent or more of those currently alive and well, would have died before reaching adulthood had it not been for (surgical) intervention.[1] Survival rates have improved dramatically and, dependant on the type of defect, 70 to 100% of the patients operated upon between 1968 and 1980 are still alive (Figure 1). However, in later live new problems arise in part of these patients. Accordingly, a major concern in the next decades will be the care of patients with congenital heart disease reaching adult life. In particular indications for and timing of reintervention are important.[2,3]

Figure 1 Survival after congenital surgery



Establishment of specialist centres to manage the complex grown-up heart disease population is a priority. These centres will provide the basis for research as well as for training into this new area of cardiology. Although most adult patients with congenital heart disease live a normal live, many have residua or sequelae requiring close observation or treatment. The spectrum of complexity increases in adult life, because rhythm disturbances, atherosclerosis and heart failure become apparent in addition to the already complex pathophysiology of the congenital defect.

A major part of this thesis describes the outcome of patients operated in the era before 1980 with a mean of 25 years follow-up. In a way, we are studying a “moving target”, because since then, many changes have taken place in surgical techniques and catheter interventions for the treatment of specific abnormalities in these patients have been introduced. Thus, the long-term outcome of the patients undergoing surgery or catheter interventions nowadays will be different from that of 25 years ago. Nevertheless, by prospectively studying long-term outcome of these patients, growing insight in the perspectives of the different patient-groups becomes available and will provide feedback to the (paediatric) cardiologists and cardiac

surgeons. For the patients, information on the long-term prognosis becomes available.

Most congenital cardiac patients require life-long specialised cardiac care. Many of them need further surgery, percutaneous intervention, arrhythmia intervention or treatment for heart failure. Table 1 shows the morbidity in the different diagnosis groups as investigated in our longitudinal follow-up study 25 years after surgery. We focussed on 5 groups of patients.

Table 1

	Early mortality (<30days)	Late CV-mortality (30d-25yrs)	Reoperation	Pacemaker	Exercise capacity	SV-arrhythmia
ASD	0%	0%	0%	5%	95%	8%
VSD	11%	4%	6%	4%	91%	1%
PS	2%	4%	15%	5%	90%	8%
Mustard	5%	17%	46%	28%	72%	11%
Fallot	16%	7%	28%	5%	83%	12%

ASD = Atrial septal defect, VSD = Ventricular septal defect, PS = Pulmonary valve stenosis, Mustard = Transposition of the great arteries corrected with a Mustard repair, Fallot = Tetralogy of Fallot, Late CV-mortality = Cardiovascular mortality from 30 days until 21-33 years after operation, SV-arrhythmias = Supraventricular arrhythmia

The outcome of patients with surgical repair of **atrial septal defect** during childhood is excellent.[4] Over 21-33 years of follow-up there was no cardiovascular death and only 1 patient needed a reoperation. There are minor ongoing concerns regarding post-repair arrhythmias and right atrial dilatation, but these were not associated with significant morbidity and no episodes of heart failure, stroke, or pulmonary hypertension were observed. This outcome compares favourably with results of ASD patients at adult age, who often encounter supraventricular arrhythmias both without and after successful surgery at adult age. It is presumed that longstanding adverse haemodynamics with volume overload as well as atrial and perhaps pulmonary venous wall stretch lead to slow, inhomogeneous atrial activation and refractoriness which in turn causes reentry tachycardias.[5] The issue of how defects should be closed is unresolved. Device closure in selected patients is a new safe and effective method of closing septal defects and is associated with reduced morbidity, shorter hospital stay and reduced costs, when compared to surgery.[6]
However, at present there are no outcome studies with follow-up of much more than 24 months and it is speculative, whether device closure will reduce the incidence of post-procedural rhythm disturbances. Early intervention, be that surgical or device closure, of all sizeable atrial septal defects is clearly indicated.[5] One might conclude that patients with successfully closed ASD at young age do not need routine medical supervision other than dedicated to complaints. However, although the outcome is favourable after surgical ASD-closure, our study revealed that of the female patients only half of the expected number became pregnant compared to the normal Dutch population. The reason for this low number of pregnancies was not assessed, but psychological barriers in starting a family (for example due to fear for negative effects of pregnancy, and fear for heart disease in their children) may have played a role. This topic needs further attention. Perhaps, an appointment with the cardiologist at

the beginning of adulthood may help to give optimal information about the long-term prognosis of the disease, issues as family planning, career possibilities, and insurance matters might than be discussed. Although patients perform well on objective scales, attention for subjective health and quality of life is warranted.[7]

Patients with **ventricular septal defect** closure at young age are often discharged from routine control, but an access mortality have been observed in a subgroup of these patients, especially those with high pulmonary resistance, in whom several cases of sudden death occurred (Figure 1).[8] Reoperation was necessary in 6% of the patients and some patients developed sinus node disease late after repair of VSD, requiring pacemaker implantation. Supraventricular rhythm disturbances were rare in this group. Thus, specialised cardiological care is warranted in patients after VSD closure perhaps at 5 year intervals.

Follow-up of patients operated upon because of a relative "simple" lesion: **valvular pulmonic stenosis**, is not so "simple". We found 7% late mortality and 15% reintervention in this group after 25 years. Pulmonary regurgitation was present in almost all patients after surgical repair. Especially the patients operated with the transannular patch technique frequently needed a reintervention. Supraventricular arrhythmias were associated with severe pulmonary regurgitation and these rhythm disturbances disappeared after reoperation.[9]

The surgical management of patients with **complete transposition of the great arteries** has changed substantially. Nowadays the arterial switch operation is being used, but until the mid 1980's most patients were operated upon using the atrial switch technique (Mustard or Senning procedure). Late follow up after the **Mustard operation** shows a 17% mortality rate and as high as a 46% rate of reintervention after 25 years.[10] Our longitudinal study provides hard evidence for the inability of the anatomic right ventricle to sustain the systemic circulation for a prolonged period. Deterioration of ventricular function occurs over time, which was expected already on theoretical grounds. The clinical condition of our patients late after Mustard repair is declining and we may expect more deaths and need for heart transplantation in the next decade. Attention to baffle obstruction with a low threshold for treatment, surgical or by means of catheter intervention, may be a first step, but further research towards other treatment options (medication, biventricular pacing) is clearly warranted for these patients. Supraventricular arrhythmias are often found in this group of patients (11%).

Late mortality after repaired **tetralogy of Fallot** is comparable with that of after surgery for pulmonary valve stenosis (7% in 25 years), although periprocedural mortality was higher. The need for reintervention is higher after correction of tetralogy of Fallot (Table 1). As in the patients with a pulmonic stenosis the Fallot patients operated with the transannular patch technique are particularly at risk for reintervention. Whether changes in surgical approach will prevent these problems in the future is speculative. The timing of reoperation for pulmonary regurgitation is still under debate, but our study showed that surgery should not be postponed too long.[10] Many of these adult patients lead unrestricted lives and seem asymptomatic at follow-up. Residual significant pulmonary regurgitation however, is common and gradually results in right ventricular dilatation and dysfunction with consequently diminished exercise capacity and rhythm disturbances.[11,12] Although ventricular

arrhythmias are important, because they are a risk factor for sudden death in these patients, these do not occur very frequently.[2] Supraventricular rhythm disturbances, on the other hand, play a major role in the morbidity of these patients.[12]

The **Fontan operation** is used for patients with complex heart disease with only one functioning ventricle, for example patients with tricuspid atresia. In our adult Fontan patients we found a high mortality (28%) and also a very high morbidity, up to 100% in 10 years after operation. Particularly reoperations, supraventricular arrhythmias, and thromboembolic events were common. Quality of life assessment showed physical functioning, mental health and general health perception to be significantly lower for Fontan patients compared to the normal Dutch population.[13] These patients comprise a small proportion of our adult congenital patient population, but they are responsible for the majority of major problems encountered in our daily practise. These patients need particularly intensive follow-up in a specialised centre for congenital heart disease. An aggressive approach towards rhythm disturbances, heart failure and cyanosis is necessary with an extensive diagnostic work-up, including (transoesophageal) echocardiography, magnetic resonance imaging and cardiac catheterization and angiography.

Coarctation repair is associated with hypertension and recoarctation. Less well known is the high incidence of problems related to a **bicuspid aortic valve**, which was found in 63 % of our adult coarctation patients.[14] Furthermore, aortic stenosis as well as aortic regurgitation occurred, requiring intervention in a third of these patients. Some form of ascending aorta pathology (aorta dilatation and aortic arch abnormalities) was found in half of the coarctation patients. A surprisingly high number of patients showed kinking of the aortic arch. The bicuspid aortic valve is correlated with ascending aortic wall abnormalities, due to media degeneration, comparable with the abnormalities found in Marfan's syndrome. This may lead to ascending aorta dilatation with the risk of aortic dissection. It is not clear whether these media degenerative changes are also present in the pulmonary artery and thus whether the **Ross-operation** is a good choice for these patients. In our patients we did not find additional problems after the Ross-procedure in patients with a bicuspid aortic valve, but longer follow-up is certainly necessary.[15]

Quality of life was studied in 350 patients with congenital heart disease. Most patients lead normal lives and are well capable of finding a job and building a career. In our study 85% of the patients had a paid job.[16] However, the wish to have a child of their own, may cause insecurities, especially for young female patients.

Pregnancy leads to an increase in cardiac output of 40%, and during pregnancy all females have a higher risk of rhythm disturbances and thrombo-embolic events. Most grown-ups with congenital heart disease, who have a normal functional capacity can tolerate pregnancy, but pre-pregnancy counselling is mandatory, including a review of medication to avoid any drugs that may be deleterious to the foetus, like ACE inhibitors and A-II antagonists.[17] The risks to the mother of morbidity and mortality and, when appropriate, the impact of pregnancy on long-term survival should be discussed. In addition, the risks to the foetus of inheriting congenital heart disease should be considered.[18]

Implications: An expert multidisciplinary team for adult congenital heart disease is necessary for this special patient group and should be associated with a strong paediatric cardiac group and cardiac surgical group. Expert skills should be available in diagnostic and interventional cardiac catheterisation, echocardiography, electrophysiology, cardiac imaging (3-dimensional echocardiography, magnetic resonance imaging) as well as management of high-risk pregnancies and reproductive counselling.[19] Motivation, trained staff and adequate diagnostic and therapeutic techniques are the first requirements to deliver good clinical care. At the moment, motivation is present, but definitely more doctors and nurses should be trained to deal with this growing population and finally, healthcare resources should be allocated to provide better access to 3-D echocardiography, magnetic resonance imaging, electrophysiology and cardiac catheterisation (device closure and stenting). It is therefore appreciated that the Netherlands Society of Cardiology has recognised adult congenital heart disease as one of the six area's of expertise or 'subspecialisation' within cardiology.

Many congenital patients can be followed in an appropriate general adult cardiac service. Yearly follow-up in the general hospital, in combination with visits once every 3-5 years in a specialist centre is well possible.

However, we recommend that all patients should be seen for initial consultation at least once in a specialised adult cardiac centre to establish the diagnosis and need for follow-up care. Patients who should be seen frequently and perhaps exclusively in the specialist centre include those with the prospect of premature death, reintervention or complications of their condition and those, whose condition is unfamiliar to general cardiologists. Any patient who develops a new clinical problem related to their congenital heart defect should be referred for re-evaluation in the specialist centre. Furthermore, consultation should be requested with the specialist unit prior to any intervention in adults with congenital heart disease.[19] All surgical and percutaneous interventions in these patients should be performed by surgeons and interventional cardiologists, who are trained in this highly specialised area, in centres with experience in this field.

Long-term follow-up of patients with congenital heart disease is "life-long follow up" and continuous research in this field is mandatory. This thesis is but a step in this proces.

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Samenvatting

Tot het begin van de zestiger jaren hadden kinderen die geboren werden met een aangeboren hartafwijking slechte vooruitzichten en vaak overleden deze kinderen op jonge leeftijd. Sinds de introductie van open hart chirurgie met behulp van de hart-long machine (in Rotterdam in 1968) is het mogelijk deze patiëntjes te opereren en sindsdien bereikt ongeveer 85% van deze kinderen de volwassen leeftijd. Er onstaat hierdoor een groeiende groep volwassenen met een aangeboren hartafwijking. In Nederland zijn dat er ongeveer 25.000. Er is echter weinig bekend over de lange termijn prognose van deze mensen. Het is niet goed bekend of zij een normale levensverwachting hebben of toch vroeger dan gemiddeld overlijden. Vaak zijn er restafwijkingen waarvoor nieuwe operaties of andere ingrepen nodig zijn en er is een verhoogde kans op ritmestoornissen en hartfalen. Eerdere studies naar de lange termijn resultaten waren vaak gericht op de mensen met problemen, waardoor er een selectie kan zijn opgetreden van de ziekste patiënten. Het is dan ook de vraag of deze eerdere studies representatief zijn voor de hele groep van geopereerde mensen. Tenslotte is er weinig bekend over de kwaliteit van leven van deze mensen en of zij een leven leiden zoals hun leeftijdsgenoten op het gebied van sport, werk, relatie en kinderen. Om deze reden hebben we een systematisch na-onderzoek georganiseerd van patiënten die in ons ziekenhuis op jonge leeftijd zijn geopereerd aan aangeboren hartafwijkingen.

In deze studie hebben we de hele groep patiënten bestudeerd die in Rotterdam op de kinderleeftijd een open hart operatie heeft ondergaan tussen 1968 en 1980. Er heeft geen selectie plaatsgevonden. De 5 grootste groepen patiënten met verschillende diagnoses zijn opgeroepen voor onderzoek. Het betreft de mensen met een gaatje in het tussenschot tussen de boezems van het hart (ASD), met een gaatje in het kamertussenschot (VSD), de mensen met een verkeerde aansluiting van de grote slagaders die geopereerd zijn met een zogenaamde Mustard operatie (Mustard), mensen met een vernauwing van de klep naar de longslagader (PS=pulmonaal stenose) en mensen met een tetralogie van Fallot, een combinatie van een gaatje in het kamertussenschot, een vernauwing van de longslagader en verplaatsing van de grote lichaamsslagader (TOF). Al deze mensen werden opgeroepen om mee te doen aan de studie. Het onderzoek bestond uit een bezoek aan de cardioloog, een ECG, een echo van het hart, een fietstest, een 24-uurs ritme registratie en een 2.5 uur durend psychologisch interview. Het onderzoek werd verricht in 1990 en opnieuw in 2001, om het verloop in de tijd te registreren.

In hoofdstuk 2 tot en met 6 worden de resultaten van de 5 verschillende groepen beschreven. Alle patiënten zijn op jonge leeftijd geopereerd (<15 jaar) en zijn in 2001 tussen de 20 en 50 jaar oud. (Tabel 1)

De patiënten met een gaatje in het tussenschot tussen de boezems (ASD) doen het uitstekend. Zij hebben een normale levensverwachting, hebben geen nieuwe operaties of andere ingrepen gehad en hebben een normale inspanningscapaciteit. Uit andere studies is bekend dat mensen met een ASD dat niet, of pas op volwassen leeftijd gesloten is een grote kans hebben op ritmestoornissen. Uit ons onderzoek is

gebleken dat het belangrijk is deze gaatjes op jonge leeftijd te sluiten, omdat daarmee het optreden van ritmestoornissen grotendeels voorkomen kan worden.

De patiënten met een gaatje in het tussenschot van de kamers (VSD) hadden rondom de operatie op jonge leeftijd een forse sterfte zien (20% in het eerste jaar). Dit is tegenwoordig gelukkig beduidend verbeterd. De 'late' overleving is goed, maar toch minder dan in de algemene bevolking. Vooral de mensen met een hoge druk in de longen blijken, zo blijkt uit dit onderzoek, een fors verhoogde kans op overlijden te hebben. Wij vonden weinig late restafwijkingen zoals kleplekkage, infectie in het hart of rest-gaatjes. Een opvallende bevinding is, dat 4% van de mensen een pacemaker nodig had meer dan 15 jaar na de operatie. Het is daarom nuttig deze mensen af en toe nog voor controle bij de cardioloog te laten komen. De helft van de mensen met een VSD ondervond problemen bij het afsluiten van levensverzekeringen, terwijl de levensverwachting goed is en er weinig late problemen optreden. Mogelijk kunnen de resultaten van deze studie bijdragen aan het vaststellen van meer objectief gemeten en geïndividualiseerde richtlijnen voor het afsluiten van levensverzekeringen.

Bij de mensen met een Mustard operatie moet de rechter hartkamer al het bloed naar het lichaam pompen. Deze is daarvoor niet gebouwd, want normaal doet de linker hartkamer dat. In 1990, gemiddeld 15 jaar na de operatie, waren de bevindingen eigenlijk verbazingwekkend goed en leek de rechter kamer dit goed vol te houden, alhoewel de patiënten wel vaak nieuwe operaties en pacemakers nodig hadden. Tussen 1990 en 2001 zien we echter een duidelijke achteruitgang. Dit uit zich in hartfalen bij 9% van de mensen, een duidelijk slechtere pompfunctie van de rechter hartkamer op echo bij bijna alle mensen, veranderingen op het ECG en een afname van inspanningscapaciteit. Dit zijn zeer verontrustende bevindingen en als deze ontwikkeling zich voortzet zal een groot deel van deze patiënten binnen 10 a 20 jaar hartfalen krijgen met het risico van overlijden, dan wel een harttransplantatie moeten ondergaan. We concluderen dan ook dat bij deze groep patiënten intensief gezocht moet worden naar verdere behandelingsmogelijkheden.

De mensen met een vernauwing van de klep naar de longslagader hebben een goede levensverwachting, die slechts iets lager ligt dan bij de algemene bevolking. Bij deze groep werden weinig problemen gezien in 1990, echter tussen 1990 en 2001 heeft ongeveer 10% van de mensen een nieuwe hartklep nodig en waarschijnlijk komen daar de komende jaren meer mensen bij. Bij de eerste operatie wordt de vernauwing van de klep opgeheven, veelal met behulp van een inzetstukje. De hieruit voortvloeiende lekkage van de hartklep wordt jaren goed verdragen, maar deze belasting gaat op de lange duur toch een probleem vormen voor het hart. Dit is tot nu toe niet beschreven in de literatuur, omdat veel mensen met deze afwijking niet meer door een cardioloog worden gecontroleerd. Hieruit blijkt wel het belang de hele geopereerde groep op te roepen voor onderzoek. Onze conclusie luidt dat de chirurgische techniek op dit punt moet worden aangepast.

Bij de mensen met een tetralogie van Fallot is de levensverwachting redelijk, maar niet geheel normaal. Ook deze mensen hebben vaak een nieuwe hartklep nodig vanwege lekkage van de longslagaderklep. Het is moeilijk het optimale moment te kiezen voor deze tweede operatie. Te lang wachten kan lijden tot schade aan het hart, terwijl een nieuwe klep ook maar weer een beperkt aantal jaren meegaat (12-15 jaar) en voorkomen moet worden dat deze mensen te vaak geopereerd moeten

worden. In onze studie hebben we het echo-onderzoek van 1990 als uitgangspunt genomen, waarna de mensen goed vervolgd en in 2001 opnieuw bekeken zijn. Hierdoor zijn er adviezen voor deze moeilijke problematiek mogelijk geworden. Nieuwe diagnostische methoden, zoals MRI zijn ook belangrijk voor de bestudering van de kleplekkage, maar er zijn (nog) geen studies die dit over de tijd hebben kunnen vervolgen. Ook blijken de mensen met een tetralogie van Fallot op de volwassen leeftijd regelmatig last van hartritmestoornissen te hebben. Frequente controle in een gespecialiseerd centrum is voor deze patiënten zeker gewenst.

De operatie volgens Fontan wordt uitgevoerd bij mensen die maar 1 werkende hartkamer hebben in plaats van 2. Deze operatie biedt patiënten de mogelijkheid volwassen te worden. Omdat deze operatie nog niet zolang wordt uitgevoerd waren er nog geen resultaten bekend van mensen die met deze operatie de volwassen leeftijd hebben bereikt. Uit ons onderzoek blijkt dat het merendeel van deze patiënten problemen krijgt. Hartfalen, ritmestoornissen, re-operaties, longembolieen en een beperkte levensverwachting komen bij bijna al deze mensen op de volwassen leeftijd aan de orde. Deze groep mensen blijkt ook minder goed in staat een normaal leven te leiden en de “kwaliteit van leven” is minder dan bij hun leeftijdsgenoten. Deze patiënten moeten intensief begeleid worden in een gespecialiseerd centrum. Deze groep behelst slechts een paar procent van onze patiënten populatie, maar vormt meer dan 50% van de problemen die we bij de dagelijkse praktijk tegenkomen.

Bij patiënten die geopereerd zijn aan een vernauwing in de grote lichaamsslagader (coarctatie) is het bekend dat zij op latere leeftijd opnieuw een vernauwing kunnen krijgen en dat zij een verhoogde kans hebben op hoge bloeddruk. Bij ons onderzoek van de patiënten met een coarctatie vonden we naast deze bekende problemen, dat meer dan de helft van de mensen een afwijking krijgt aan de aortaklep. Dit is de klep tussen de linker hartkamer en de grote lichaamsslagader (aorta). Bij sommigen gaat de klep lekken, bij anderen treed een vernauwing op. Verder zagen we ook regelmatig een verwijding van het eerste stukje van de grote lichaamsslagader ontstaan. Dit is uitermate belangrijk, want hierdoor ontstaat de kans op een scheur in de grote lichaamsslagader, met meestal fatale uitkomst. Ook verderop in de grote lichaamsslagader werden afwijkingen gezien. Een coarctatie blijkt niet alleen een lokaal probleem maar een veel uitgebreidere ziekte van de hele aorta. Het is belangrijk ook deze patiënten levenslang te vervolgen, met speciale aandacht voor afwijkingen aan de aortaklep en het eerste deel van de aorta. Het onderliggende proces en de erfelijke factor hierin moeten nader onderzocht worden.

Wat betreft de “Kwaliteit van leven” heeft de studie bij de 350 volwassenen die op jonge leeftijd geopereerd zijn aangetoond, dat de meesten een normaal leven leiden en dat zij prima in staat zijn een baan te krijgen en een carrière op te bouwen. In onze studie had 85% van de mensen een betaalde baan. Ook op het gebied van sport en vrijetijdsbesteding en het hebben van een relatie wijken zij niet af van de algemene bevolking. Een opvallende bevinding is dat er echter minder zwangerschappen in deze groep worden gezien. Dit zou verklaard kunnen worden uit angst dat de eigen gezondheid zal lijden onder een zwangerschap en angst voor aangeboren hartafwijkingen bij de kinderen. Of andere oorzaken, zoals verminderde fertiliteit, bijvoorbeeld ten gevolge van de hartziekte of ondergane behandelingen een rol spelen moet verder onderzocht worden.

Zwangerschap vormt een belasting voor het hart. Tijdens de zwangerschap neemt namelijk het rond-te-pompen bloedvolume met 40% toe. Dit wordt door vrouwen met een normaal hart meestal goed verdragen, alhoewel ook zij tijdens de zwangerschap meer kans hebben op hartritmestoornissen en vocht vasthouden. Bij vrouwen met een hartaandoening kan zwangerschap tot problemen lijden. Vooraf moet er met de individuele patiënt gesproken worden over de risico's. Een aantal medicijnen die vaak door hartpatiënten worden gebruikt (bloedverdunners, ACE-remmers, A-II antagonisten) zijn absoluut verboden tijdens de zwangerschap, omdat deze een verhoogde kans op afwijkingen bij het kind geven en ook dit moet bijtijds besproken worden. Tenslotte moet er aandacht zijn voor het risico een kind met een hartafwijking te krijgen, dit kan variëren van 2 tot 50%.

Een gespecialiseerd team is nodig voor de behandeling van de volwassenen met een aangeboren hartafwijking. Gespecialiseerde cardiologen moeten nauw samenwerken met kindercardiologen en hartchirurgen. Expertise op het gebied van diagnostische onderzoeksmethoden zoals echocardiografie en MRI-beeldvorming, op het gebied van electrofysiologie (diagnostiek en behandeling van ritmestoornissen) en interventie-catheterisatie en op het gebied van hoog-risico zwangerschappen en erfelijkheid moet voorhanden zijn. Meer cardiologen zullen opgeleid moeten worden om aan de groeiende vraag naar specialistiche hulp te kunnen voldoen.

Concluderend gaat het goed met de meeste volwassenen met een aangeboren hartafwijking, maar bij sommige groepen komen nog frequent late problemen voor, waarbij levenslange controle aangewezen is.

Tabel 1 Resultaten 25 jaar na open hartchirurgie op de kinderleeftijd

	Lange termijn-overleving (>25jr)	Re-operaties	Pacemaker	Inspannings-vermogen
ASD	uitstekend	niet	5%	goed
VSD	goed	6%	4%	goed
PS	goed	15%	5%	goed
Mustard	redelijk	46%	28%	matig
Fallot	goed	28%	5%	redelijk

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Curriculum Vitae

The author of this thesis was born on September 27, 1961, in Winterswijk, the Netherlands. She graduated in 1979 at the Hamaland College in Winterswijk: VWO-B certificate.
From 1979 to 1986 she studied medicine at the University of Utrecht. In 1982 she spent several months as a student trainee in the Charing Cross Hospital in London. In 1984, during a research fellowship she has described the first results of a new treatment: "Percutenous Transluminal Coronary Angioplasty (PTCA)" in Utrecht under supervision of Prof.Dr. T. van der Werf. The topic of her final essay for medical school was the occurrence of myocardial infarction during pregnancy.
As part of the training in cardiology she studied internal medicine from March 1987 to March 1989 at the Groene Hart Hospital in Gouda (chairman dr. K.J. Heering). In April 1989 the speciality training cardiology started at the Department of Cardiology of the Universitair Medisch Centrum Utrecht (chairman Prof.dr. E.O. Robles de Medina and dr. P.W. Westerhof). She was registered as a cardiologist on May 1, 1992.
Since 1992 the author is working as cardiologist at the department of Cardiology at the Thoraxcenter, Erasmus MC in Rotterdam, the Netherlands (chairman Prof.dr. J.R.T.C. Roelandt and from 2003 Prof.dr. M.L. Simoons). Together with dr. Folkert Meijboom she manages the Program for adult congenital heart disease.
From 2000 to 2003 she performed a large follow-up study in adults with congenital heart disease with a grant from the Netherlands Heart foundation.
She is a member and co-founder of the working group on congenital heart disease of the Netherlands Society of Cardiology.
The author of this thesis is married to Frank Roos and they have 4 children: Leontien (1993), Michiel (1995), Evianne (1999) and Sietske (2002).