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Diplomarbeit

**LONG-TERM OUTCOME AFTER SENNING OR MUSTARD
OPERATION IN PATIENTS WITH D-TRANSPOSITION OF
THE GREAT ARTERIES**

eingereicht von

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zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Kinder- und Jugendheilkunde

Klinische Abteilung für Pädiatrische Kardiologie

unter der Anleitung von

Univ.-Prof. Dr. Andreas Gamillscheg

Graz, am 15. Mai 2008

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Graz, am 15. Mai 2008

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Kristina M. Huber

Foreword

Twenty years from now you will be more disappointed by the things you didn't do than by the ones you did do. So throw off the bowlines. Sail away from the safe harbor. Catch the trade winds in your sails. Explore. Dream. Discover.

[Mark Twain]

Some people never start exploring, and others never stop. A common thread runs through the history of medicine, a curious thread that wends from one explorer to the next. Those who explore and discover in medicine are those willing to challenge the status quo, daring the impossible to become possible. Sometimes it is learning by doing, sometimes an experiment gone wrong, and sometimes it is a cure that we have been waiting for. Not very long ago, a child born with transposition of the great arteries was predestined for a short life, and the brief moment on earth was bonding yet grueling. Though a rare congenital heart condition, a few motivated physicians and surgeons made it their objective to find a treatment for those children – and they did.

As of today, many children have benefited from an atrial switch operation, and some will still undergo a Mustard or Senning procedure in the future – a life-saving operation made possible by the impetus, stamina and inspiration of two scientists!

Thank you!

I would like to thank those who supported me during my time in Graz, and in writing my thesis. Special thanks go to Prof. Andreas Gamillscheg for his never-ending positive challenges and encouragement, and for all the time he sacrificed for this endeavor.

I thank my family Wolfgang, Elisabeth and Claudia for their constant support and patience. I am sure they all have stories to tell about endless phone calls and panic relief conversations.

Thank you to those who encouraged and supported me on my way through medical school. Patrick McGownd and Tina Tomsen, thanks for introducing me to the medical profession and being such wonderful examples and friends. Judy and Glenn Morris, thanks for teaching me the necessities of a doctor's life (golf, cigars and martinis) and much more. Julie Edwards and Kim Snodgrass, thanks for helping me staying grounded, for laughing with me and giving me alternative perspectives of life. Last but not least, Dette Avalon, thank you for your humor, for passionate discussions, challenging medical mysteries, and shared experiences.

Very warm thanks to my landlords Alix and Gerold Frank who have provided the environment, time and everything I could possibly need when I was stuck at my desk writing this thesis. Ms. Planer, Ms. Stoppacher and Ms. Zenzmaier, your time spent on this project and your availability for my questions was well appreciated!

Thank you!

If I have the gift of prophecy and can fathom all mysteries and all knowledge, and if I have a faith that can move mountains, but have not love, I am nothing.

[1 Corinthians 13:2]

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1 ABBREVIATIONS / ABKÜRZUNGEN

AoV	aortic valve	Aortenklappe
ASD	atrial septal defect	Vorhofseptumdefekt
AV block	atrio-ventricular block	atrioventrikulärer Block
BAS	balloon atrioseptostomy	Ballonatrioseptostomie
CHD	congenital heart disease	angeborener Herzfehler
CoA	coarctation of the aorta	Aortenisthmusstenose
CPR	cardio-pulmonary resuscitation	Herz-Lungen-Wiederbelebung
ECG	electrocardiogram	Elektrokardiogramm
JR	junctional rhythm	Knotenrhythmus
LV	left ventricle	linker Ventrikel
LVOTO	LV outflow tract obstruction	LV Ausflusstraktobstruktion
PAC	premature atrial contraction	Vorhofextrasystole
PDA	patent ductus arteriosus	persistierender Ductus arteriosus
PFO	patent foramen ovale	persistierendes Foramen ovale
PGE ₁	prostaglandin E ₁	Prostaglandin E ₁
PM	pacemaker	Schrittmacher
PS	pulmonary stenosis	Pulmonalstenose
PVC	premature ventricular contraction	Kammerextrasystole
PVO	pulmonary venous obstruction	pulmonalvenöse Obstruktion
RV	right ventricle	rechter Ventrikel
SND	sinus node dysfunction	Sinusknotendysfunktion
SR	sinus rhythm	Sinusrhythmus
SVO	systemic venous obstruction	systemvenöse Obstruktion
SVT	supraventricular tachycardia	supraventrikuläre Tachykardie
TGA	transposition of the great arteries	Transposition der großen Arterien
TR	tricuspid regurgitation	Trikuspidalinsuffizienz
VSD	ventricular septal defect	Ventrikelseptumdefekt
VT	ventricular tachycardia	ventrikuläre Tachycardie

2 ZUSAMMENFASSUNG

Hintergrund und Fragestellung: Seit der Einführung Jatenes anatomischer Korrektur bei Transposition der großen Arterien, kommen die Vorhofumkehrverfahren nach Senning und Mustard nur noch selten zum Einsatz. Immer mehr TGA-Patienten nach Vorhofumkehr befinden sich heute im Jugend- bzw. Erwachsenenalter. Diese Arbeit soll Spätkomplikationen nach Vorhofumkehr erfassen bzw. analysieren, um einen Beitrag zur verbesserten Nachsorge zu liefern.

Patienten und Methodik: Daten von 46 Patienten nach Senning- und 33 Patienten nach Mustardoperation wurden retrospektiv in Bezug auf Operation, frühe postoperative Phase und Nachbetreuungszeitraum ausgewertet. Der mittlere Beobachtungszeitraum war $17,5 \pm 8,2$ (0,1-28,4) Jahre, die Patienten sind heute im Mittel $18,7 \pm 8,4$ (0,5-34,75) Jahre alt.

Ergebnisse: Die Spätmortalität 25 Jahre nach Vorhofumkehr war 11,9% für Senning- und 39,3% für Mustardpatienten ($p=0,01$). Eine post-operative Reintervention war in 34,3% unserer Patienten nötig, vorwiegend wegen system- bzw. pulmonalvenösen Obstruktionen. Senningpatienten brauchten weniger häufig Reoperationen als Mustardpatienten (7,1% vs. 46,4%) ($p=0,001$). Insgesamt verzeichneten wir (vorwiegend supraventrikuläre) episodische bzw. permanente Rhythmusstörungen bei 78,6% unserer Patienten, bei 40% waren diese symptomatisch. Die Senninggruppe war meist häufiger, und vor allem früher betroffen ($6,8 \pm 5,3$; 0-15,4 vs. $13,2 \pm 7,5$; 2,8-23,6 Jahre) ($p=0,013$). Antiarrhythmika waren bei insgesamt 21,4% notwendig, 35,7% aller Patienten erhielten einen Schrittmacher. Trikuspidalinsuffizienz war stark mit rechtsventrikulärer Dysfunktion vergesellschaftet ($p=0,006$). Eine moderate bis schwere RV Dysfunktion bestand bei insgesamt 35,7%, supraventrikuläre Arrhythmien erhöhten das Risiko um das Dreifache. Bei der letzten Nachkontrolle wurden 80% unserer Patienten NYHA I zugeordnet, 81,4% hatten einen Ability Index von 1.

Conclusio: Regelmäßige und gründliche Nachuntersuchungen sind nach Vorhofumkehr notwendig, um Komplikationen zu verhindern, oder früh zu entdecken und zu behandeln.

3 ABSTRACT

Background and Objective: Jatene's anatomical correction for transposition of the great arteries has almost entirely replaced Senning's and Mustard's atrial switch techniques. More and more atrial switch patients are now adolescents or adults and require regular follow-up examinations at pediatric or adult cardiology departments. The objective of this thesis is to determine and analyze (late) complications in Senning and Mustard patients, and to make a helpful contribution to improve long-term follow-up.

Patients and Methods: Data for 46 Senning and 33 Mustard patients was analyzed retrospectively pertaining to operation, early post-operative period, and follow-up period. Mean length of follow-up was 17.5 ± 8.2 (0.1-28.4) years. To date, our patients are a mean of 18.7 ± 8.4 (0.5-34.75) years old.

Results: Late mortality 25 years after atrial switch was 11.9% for Senning and 39.3% for Mustard patients ($p=0.01$). Post-operative re-intervention was necessary in 34.3% of patients, mainly for systemic or pulmonary venous pathway obstructions. Senning patients needed fewer re-operations than Mustard patients (7.1% vs. 46.4%) ($p=0.001$). Transient or permanent (mostly supraventricular) arrhythmias were diagnosed in 78.6% of patients, in 40% arrhythmias were symptomatic. Senning patients were generally more often and earlier affected (6.8 ± 5.3 ; 0-15.4 vs. 13.2 ± 7.5 ; 2.8-23.6 years) ($p=0.013$). Pharmacologic anti-arrhythmic therapy was mandatory in 21.4% of all patients, 35.7% needed pacemaker implantation. Tricuspid regurgitation was significantly associated with RV dysfunction ($p=0.006$). Moderate to severe systemic right ventricular dysfunction was diagnosed in 35.7% of our patients, supraventricular arrhythmias increased the risk of RV dysfunction by a factor 3. To date, our patients report good quality of life and functional status, at their latest clinical examination 80% could be assigned to NYHA class I, 81.4% received an Ability Index of 1.

Conclusion: Regular and methodical clinical examinations after atrial switch are paramount to prevent, discover and treat complications early and adequately.

4 INTRODUCTION

Transposition of the great arteries (TGA) is the second most common form of cyanotic congenital heart disease (CHD). With time of follow-up increasing, more and more of the frequent complications of **atrial switch surgery** according to Mustard and Senning surface. Both general medical and medico-technical progress allow for better assessment of outcomes, and the development of more advanced treatment and surgical alternatives. Since the successful introduction of the **arterial switch operation** by Jatene et al and Yacoub in 1975, the techniques of Mustard and Senning have lost some of their importance and now serve as surgical options for some complex TGAs with associated lesions (e.g. hemodynamically relevant ventricular septal defect; VSD), or complicated coronary anatomy. (54) Nonetheless, many of those who were operated on according to Senning or Mustard in the 70s and 80s are still alive and require thorough follow-up schemes for the recognition of late complications of their CHD.

The goal of this study is to evaluate and assess the long-term outcome of TGA patients after atrial switch procedures, admitted to the Division of Pediatric Cardiology/Department of Pediatrics, Medical University Graz, and to compare our patients' results with the long-term results of other children's heart disease centers. This study will statistically illustrate long-term outcomes, early and late complications, and frequencies of various impediments. Two types of atrial switch procedures, Senning and Mustard repair, will be assessed and compared to one another. The effects on sinus rhythm will be of special interest in this study. We expect specific results about rhythmogenic aberrances, which 10 years post-operatively occurred in up to 64% of comparable study populations. (4-6,11-13,21,27,28,31,48,55,59)

This study will also serve as a starting point and basis for further research and evaluation in the field of congenital heart disease, and the treatment thereof. Finally, the chronological registration of complications could be used as an aide in the development of more effective follow-up programs and schemes, designed to

earlier and better uncover problems and complications, and further improve quality of life in patients.

4.1 Definition and Historical Notes

Twenty to 30 out of 100,000 live born children (5-7% of all CHD) suffer from a congenital heart anomaly known as **dextro transposition of the great arteries (d-TGA, henceforth TGA)**, in which the aorta originates from the morphologic right ventricle (RV), while the pulmonary artery has its origin in the left ventricle (LV). (Figures 1 and 2)

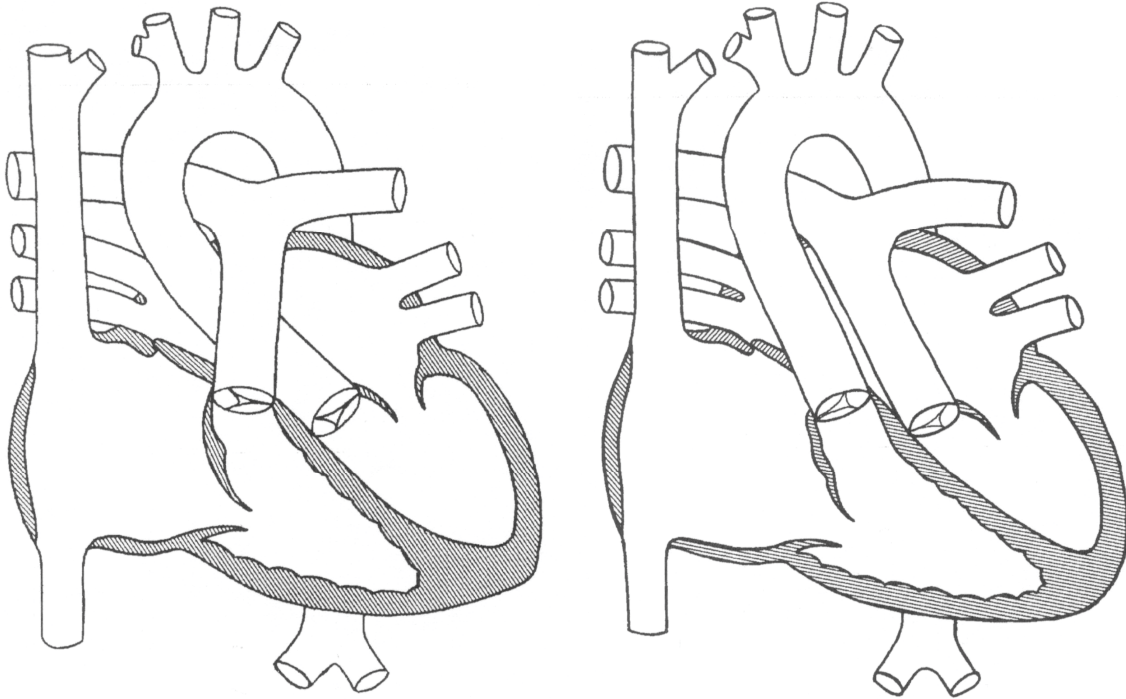


Figure 1 Depiction of normal heart anatomy. (70)

Figure 2 Depiction of d-TGA anatomy. (70)

TGA is the second most common cyanotic heart disease with a male preponderance of 2:1, surpassed only in frequency by Tetralogy of Fallot. Although a rare condition, TGA accounts for 25% of deaths from congenital heart disease in the first year of life. (69)

TGA was first described by Baillie in 1797 and again in 1814 by Farre. (36) Taussig published his first clinical report in 1949, and one year later, Blalock and Hanlon

first performed an interventional surgery on a child born with TGA, an atrioseptectomy. About this time, both Mustard and Senning started their individual efforts to find a surgical cure for the condition. Unfortunately, neither Mustard's arterial re-transpositioning in 1954, nor Senning's atrial switch operation in 1958 were initially successful. (28,36,39,60)

In 1964, Mustard reported a successful operation with a modified version of Senning's technique. Survival of patients could be improved thanks to notable contributions by Rashkind and Miller, who introduced the balloon atrial septostomy (BAS), and the surge continued: Rastelli introduced a new surgical technique which allowed the correction of TGA with associated lesions such as ventricular septal defect (VSD) and left ventricular outflow tract obstruction (LVOTO). To date, morphology and pathophysiology permitting, the most common repair for TGA is the arterial switch operation as first described by Jatene et al and Yacoub in 1975. (28,36,39,60)

4.2 Morphology and Pathophysiology

As a result of the transposition of aorta and pulmonary artery in TGA, the two vessels are positioned parallel to one another. The aorta can be found anteriorly and to the right of the pulmonary artery in 95% of all cases. While the connection between atria and ventricles is concordant, there is ventriculo-arterial discordance, resulting in two separate, parallel circuits: oxygenated blood is pumped back to the lungs through the LV, and non-oxygenated venous blood is pumped back into the systemic circuit by the RV. Survival of the newborn depends on sufficient pre-existent connections between the parallel circuits, such as patent foramen ovale (PFO) or atrial septal defect (ASD) at atrial level, VSD at ventricular level, or patent ductus arteriosus (PDA) at arterial level. Infants who are born without sufficient PDA, PFO and/or VSD need to undergo urgent post-partum interventional cardiac catheterization, or open heart surgery in order to survive. (28,33,36,39,60)

The coronary arteries occasionally show an anomalous origin in patients with TGA, however, it is most common that they originate from the aorta. This and the course of the coronary arteries are relevant for decisions about the type of surgical repair, and will therefore not be discussed in this thesis.

Approximately half of all TGA patients have associated defects, such as VSD (up to 50%), LVOTO (up to 25%) or coarctation of the aorta (CoA, approx. 5%). (28,39,60) TGA can be grouped according to associated defects:

- simple TGA - with PFO, and/or small PDA, but no other defects
- complex TGA - with hemodynamically relevant VSD and/or LVOTO, or CoA

Twenty-five percent of all simple TGAs include a dynamic LVOTO. VSDs are mostly perimembranous or muscular defects in patients with TGA. PDA, one of the imperative cross connections for survival prior to surgical repair, is common in newborns with TGA (75%), however, PDAs show a tendency for spontaneous closure shortly after birth. (28,36,39,60)

Unlike other congenital heart diseases, TGA becomes effective only after birth, when oxygenation of the blood depends exclusively on the lungs of the newborn. Owing to spontaneous closure of a PDA, the baby will show severe signs of hypoxemia and an increase in cyanosis. Left to the natural course of the defect, 80% of patients with simple TGA will die within the first month, and more than 90% will die within the first year of their life. One-year survival for patients with complex TGA ranges from 30% (large VSD) to 70% (large VSD and pulmonary stenosis, PS). Appearance of symptoms decreases with increasing number of cross connections. (28,36,39,60)

4.3 Signs and Symptoms, Diagnosis

Signs and symptoms of TGA generally depend on the size and quantity of cross connections, and the existence of associated defects. Two thirds of all patients are full-term infants with normal birth weight. Moderate to severe cases are termed

"blue babies" because of cyanotic changes noted from minutes to hours after delivery. In addition to central cyanosis, these babies also suffer from metabolic acidosis. If a large VSD is present, cyanosis can be less obvious and more reliable symptoms usually include sucking weakness, tachycardia, tachypnea, and pitting edemas as a result of progressive congestive heart failure. (28,36,39,60)

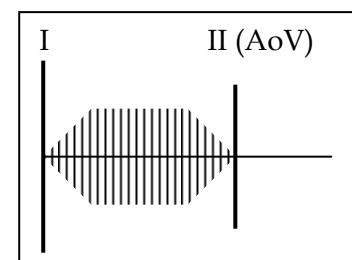
Continuous thorough assessment of the newborn is paramount to develop the most effectual treatment plan. The traditional techniques of inspection, palpation, and auscultation remain standard despite the availability of two-dimensional echocardiography in or near most Austrian hospitals.

4.3.1 Inspection

Upon inspection, dyspnea and cyanosis are noted, the severity depending on cross connections and associated defects.

4.3.2 Palpation and Auscultation

- massive precordial thrill - the RV lies anteriorly and has to maintain systemic pressure
- typically murmurless heart if no associated lesion is present (!)
- second heart sound (aortic valve, AoV) appears single and accented and can be best heard in the III and IV intercostal spaces left parasternally; accentuation can be explained with the position of the AoV closer to the chest wall
- a systolic ejection murmur can be heard in the left II and III intercostal spaces once pressure in the LV has dropped
- a VSD can be heard as regular holosystolic murmur in the III and IV intercostal spaces left parasternally
- a LVOTO most commonly presents as a systolic murmur in the II and III intercostals spaces right parasternally



4.3.3 ECG

A post-partum electrocardiogram (ECG) typically shows a normal right axis deviation and normal right-sided precordial R-potentials.

4.3.4 Chest X-ray

Mediastinal shadow is narrow due to the parallel position of aorta and pulmonary artery. The pulmonary segment is missing. The shadow of the heart appears oval, hence the term "egg-on-side". Pulmonary perfusion is generally increased, with the exception of patients with LVOTO.

4.3.5 Echocardiography

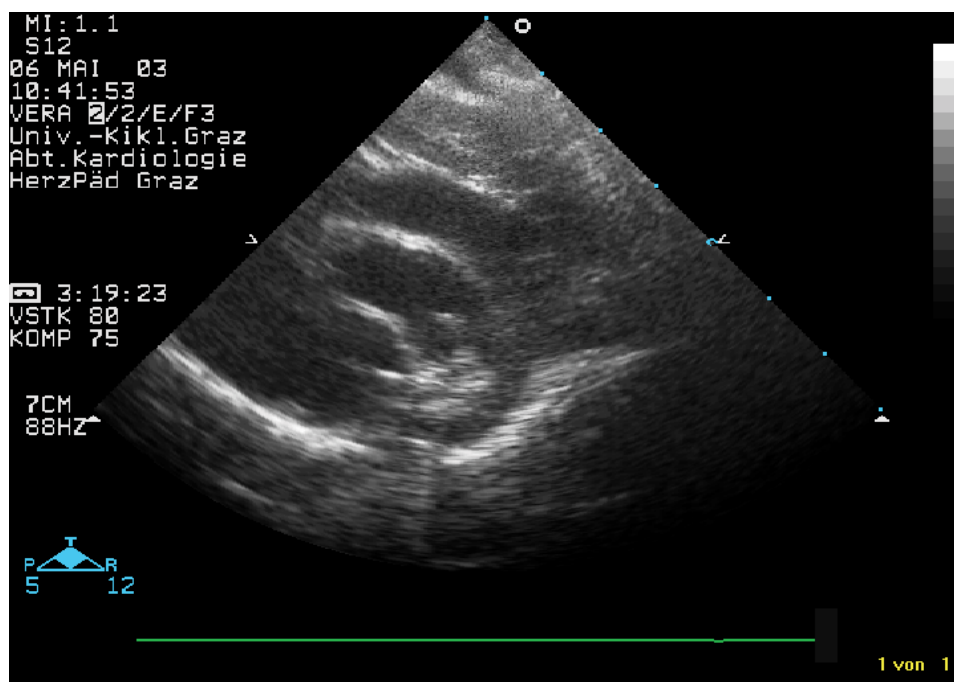


Figure 3 Two-dimensional echocardiography depicting the parallel course of the aorta and pulmonary artery. The bifurcation of the posterior vessel identifies it as pulmonary artery. (Photograph courtesy of Prof. A. Gamillscheg, Medical University Graz)

Two-dimensional echocardiography provides diagnostic certainty. The parasternal long axis allows good imaging of the parallel course of aorta and pulmonary artery with the head and neck vessels branching off of the anterior vessel (aorta), arising from the RV. This axis also allows detection of the LV as

origin of the pulmonary artery. The bifurcation of the posterior vessel serves as main identifier of the pulmonary artery. (Figure 3)

Subcostal and apical planes allow imaging of both ventricles with discordant vessels. Coronary arteries can be employed to identify the aorta.

Color Doppler echocardiography helps reveal an atrial bi-directional shunt; a large PDA as well as associated lesions (VSD, CoA, and LVOTO) can be detected.

Pre-partal ultrasound has made early diagnosis of CHD possible, resulting in most infants with TGA being born in children's heart centers, where early intervention and palliation are available. (39,60)

4.3.6 Cardiac Catheterization

This diagnostic tool may be necessary if intervention, i.e. balloon atrial septostomy (BAS) is intended. Cardiac catheterization is the method of choice for imaging of coronary arteries (origin and course), impossible to visualize in echocardiography, in preparation for arterial switch operation.

4.3.7 Differential Diagnoses

Consider other cyanotic CHD such as Tetralogy of Fallot (with pulmonary atresia), Taussig-Bing complex, uni-ventricular heart, as well as neonatal pulmonary disease such as infant respiratory distress syndrome, persistent fetal circulation syndrome, atelectasis and dystelectasis, and infection or sepsis. Pulse differences can be indicative of juxta-ductal CoA or interrupted aortic arch with PDA and VSD. (60)

4.4 Therapy and Complications

4.4.1 Bridging Therapy

Primary goal is the maintenance or creation of sufficient connections between the systemic and pulmonary circuits. As aforementioned, a PDA is present in most newborns with TGA, but there is a marked tendency for spontaneous closure.

Intravenous prostaglandin E₁ (PGE₁) is mandatory in order to keep an existing PDA open. This reduces the incidence of circulatory and respiratory depression and can, combined with BAS, allow for a bridging to surgery for up to three weeks. (60)

Oxygen (40 to 60%) and correction of metabolic acidosis are additional beneficial treatments. Congestive heart failure may be treated intermittently with catecholamines and diuretics.

In case of severe persistent cyanosis despite an open PDA, Blalock-Hanlon septectomy or Rashkind BAS with Fogarty or Miller-Edwards catheter are indicated. After BAS, hypoxemia usually improves and patients can frequently be extubated.

4.4.2 Corrective Surgical Therapy

Today's treatment of choice is anatomical correction by means of **arterial switch operation**. Ideal time for this surgery is within the first two weeks of life. The longer the period between birth and operation, the less muscle mass is left in the LV by virtue of the physiological post-natal decrease of pulmonary vascular resistance. (28,36,39,60) Consequentially, the LV can no longer accept the afterload of the systemic circulation following an arterial switch operation, and an anatomical repair cannot be successfully completed.

In contrast to Jatene's anatomical repair of TGA, the **atrial switch operation** according to Senning and Mustard redirects blood flow at the atrial level, thus creating two serial circuits. Systemic venous blood is redirected to the mitral valve (the LV remains the pulmonary ventricle), and pulmonary venous blood is redirected to the tricuspid valve, the RV remains the systemic ventricle. (28,36)

Senning actually described his procedure before Mustard, but early attempts had a high mortality. In retrospect, this seems to have been more from factors unrelated to the operation itself, since Senning's patients were generally older and had a high incidence of other complications, including pulmonary hypertension,

and the results of open-heart surgery in small children generally were not good at that time. (33) The Senning technique basically consists of pushing the lateral wall of the right atrium inwards and attaching it to the interatrial septum to divert the superior and inferior vena caval blood to the left atrium, and rotating the posterior part of the interatrial septum to the right to allow the pulmonary veins to drain to the tricuspid valve. In the postoperative course some degree of pulmonary venous congestion is common on the right side and may lead to pleural effusions requiring drainage. (33)

In the course of a **Mustard operation**, the interatrial septum is totally excised and a patch of pericardium [or Gore-Tex (18), Dacron] inserted in such a way that the superior vena caval and inferior vena caval blood is directed to the left atrium and mitral valve and the blood from the pulmonary veins is directed to the tricuspid valve and right ventricle. (33)

Two main types of problems may occur after atrial switch surgery. First, the conducting tissue may be damaged leading to disturbances of cardiac rhythm, often surfacing many years after surgery. The second problem is the development of obstruction at the venous pathways by contraction of the interatrial baffle. This occurs in about 10-15% of all patients and is usually apparent within the first two years after operation, necessitating re-operation or interventional procedures such as balloon dilation with or without stent implantation. (10,33,49)

The postoperative course is similar for Senning's and Mustard's repair. Both operations leave the LV pumping blood into the lungs and, more importantly, the RV taking on systemic circulation, and therefore pumping at a much higher pressure than normal.

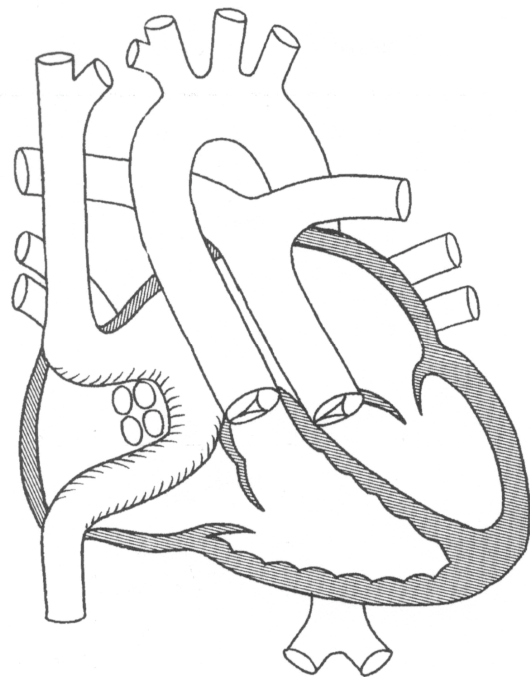


Figure 4 Anatomy after atrial switch operation for d-TGA. (70)

4.4.3 Outcome and Complications after Atrial Switch Operation

Most recent operative mortality rates for **atrial switch operations** have tapered from about 10% (28) to 1-5% (28,60), however, late post-operative mortality and morbidity are still considerable. Most common problems are (2,28,39,60):

- **arrhythmias**, e.g. brady-arrhythmias (loss of sinus node rhythm; junctional escape rhythm) and tachy-arrhythmias (up to 50%; atrial reentry tachycardia, atypical atrial flutter); The incidence of arrhythmias increases with time of follow-up. Arrhythmias in general, but especially atrial flutter, are main risk factors for sudden cardiac death (reported in 7 to 15%). (19)
- **dysfunction of the RV** as systemic ventricle, occurs in about 50% of patients due to altered geometry, differing structure, and progressive tricuspid regurgitation (TR) leading to right ventricular failure.
- **baffle** leaks in up to 25% of patients.
- **obstruction** of the **pulmonary** and/or **systemic venous return**, necessitating re-operation or cardiac interventional procedures.

Outcome after atrial switch is generally satisfying: 70 to 80% of hospital survivors are in good general condition at 20 years of follow-up, however, with reduced exercise tolerance. (60) This is most likely due to chronotropic incompetence and reduced stroke volume response to exercise, a result of ventricular filling rates and tachycardia.

4.5 Follow-up

Because of the potential complications listed above, regular and meticulous check-ups are paramount for TGA patients after atrial switch operation. Depending on the patient's individual condition and health, these check-ups may be spaced as far as one year apart. (28)

4.5.1 Clinical Examination

This examination can reveal useful information about the patient's general condition. Auscultation can provide conclusions about heart function and possible congestive heart failure (note audible splitting of second heart sound). Special attention should be paid to murmurs, e.g. atrio-ventricular regurgitation, and precordial thrills.

4.5.2 ECG and Holter ECG

Presence or absence of sinus rhythm (SR), heart axis (mostly right axis deviation) and RV hypertrophy can be detected in an ECG. A 24-hour recording provides insight into long-term rhythm and conduction of the heart. Heart block or (severe) sinus node dysfunction (SND) can be discovered through the recordings of a Holter ECG.

4.5.3 Chest X-ray

Chest x-ray ideally shows a normal cardio-thoracic ratio.

4.5.4 Echocardiography

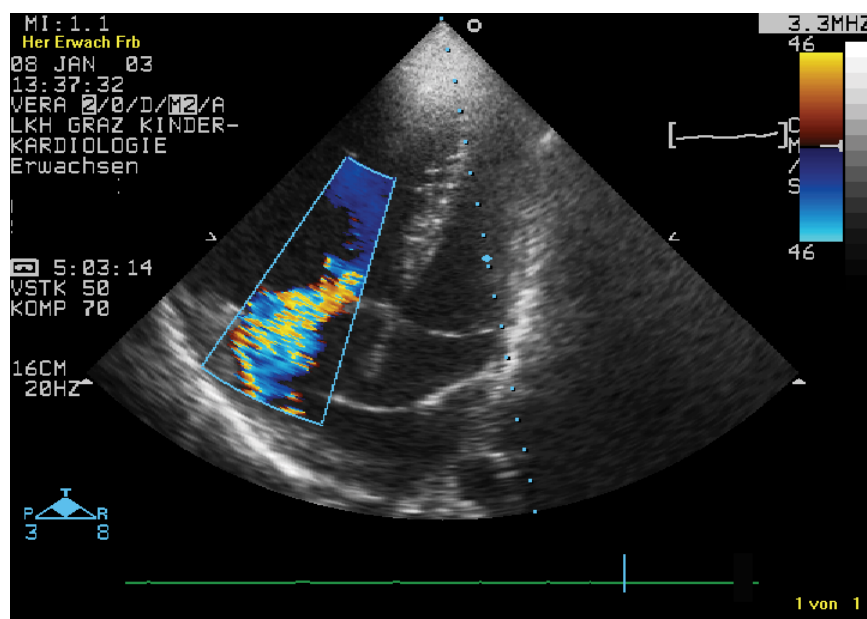


Figure 5 Doppler echocardiography, apical four-chamber view, depicting TR. (Photograph courtesy of Prof. A. Gamillscheg, Medical University Graz)

Two-dimensional and Doppler echocardiography (Figure 5) are clinical routine in the appraisal of systemic RV function, post-operative hemodynamics, and for the detection of TR, stenosis or obstruction of the venous pathways, and baffle leaks.

4.5.5 MRI

MRI is undeniably the best imaging method to assess right ventricular size and function, ejection fraction (EF), or scar tissue, however, it is rarely obtainable for routine clinical examinations.

4.5.6 Radionuclear Ventriculography

This test is useful for the assessment of systemic RV function and can be ordered in lieu of MRI. It additionally allows the evaluation of myocardial perfusion.

4.5.7 Cardiopulmonary Exercise Testing

Most relevant results from this test are chronotropic response and heart rate and rhythm. In patients with or without arrhythmia in a standard ECG, further information about the need for a permanent pacemaker can be obtained.

5 METHODS

All TGA patients of the Division of Pediatric Cardiology/Department of Pediatrics, Medical University Graz, who had undergone atrial switch surgery according to Mustard or Senning, were recruited for this study. Patients operated on at a different hospital were included in the study if sufficient follow-up data could be collected, and a significant amount of follow-up had taken place at our facility in Graz.

Patients were excluded from the study, if they were lost to other hospitals post-operatively and were not followed at our outpatient clinic in Graz, whether they were operated on in Graz or not.

5.1 Statistical Methods

A retrospective review of all relevant patient files and case notes was performed. Pre-operative, operative and early post-operative data including surgical technique, additional repairs during main surgery, post-operative complications, post-operative ECGs, early post-operative treatment and first post-operative catheter were collected and analyzed. Follow-up records were reviewed, including interventional catheterization data, re-operation data, data of last follow-up including pharmacologic treatment, New York Heart Association (NYHA) functional class and Ability index (see attachments), ECGs and 24 hour Holter ECGs, and echocardiograms. Systemic ventricular dysfunction and pulmonary hypertension were recorded and evaluated. Data about ergometer exercise testing and spiro-ergometry was collected and analyzed according to relevance. The following end-points (events) were defined: event free, late death, cardiac syncope, cardio-pulmonary resuscitation (CPR), catheter intervention, pacemaker implantation and re-operation including heart-lung transplantation, and symptomatic arrhythmia necessitating medical treatment. Collected data was entered into a data collection sheet as shown in the attachments.

Descriptive statistics and frequency analysis of data was performed using SPSS 15.0 statistical software for Windows, student version (SPSS Inc., Chicago, Illinois). According to relevance, descriptive statistics are presented as frequencies, median value and range, and/or mean value \pm standard deviation. Variables were compared by χ^2 , Fisher's exact test, Log-Rank test, or Student t-test when appropriate. Relative risk was computed when applicable. For all analyses, level of significance was chosen as $p < 0.05$. Univariate and multivariate analysis was completed using Cox proportional hazards model, stepwise backwards elimination algorithm. The Kaplan-Meier method was used to determine actuarial survival.

6 RESULTS

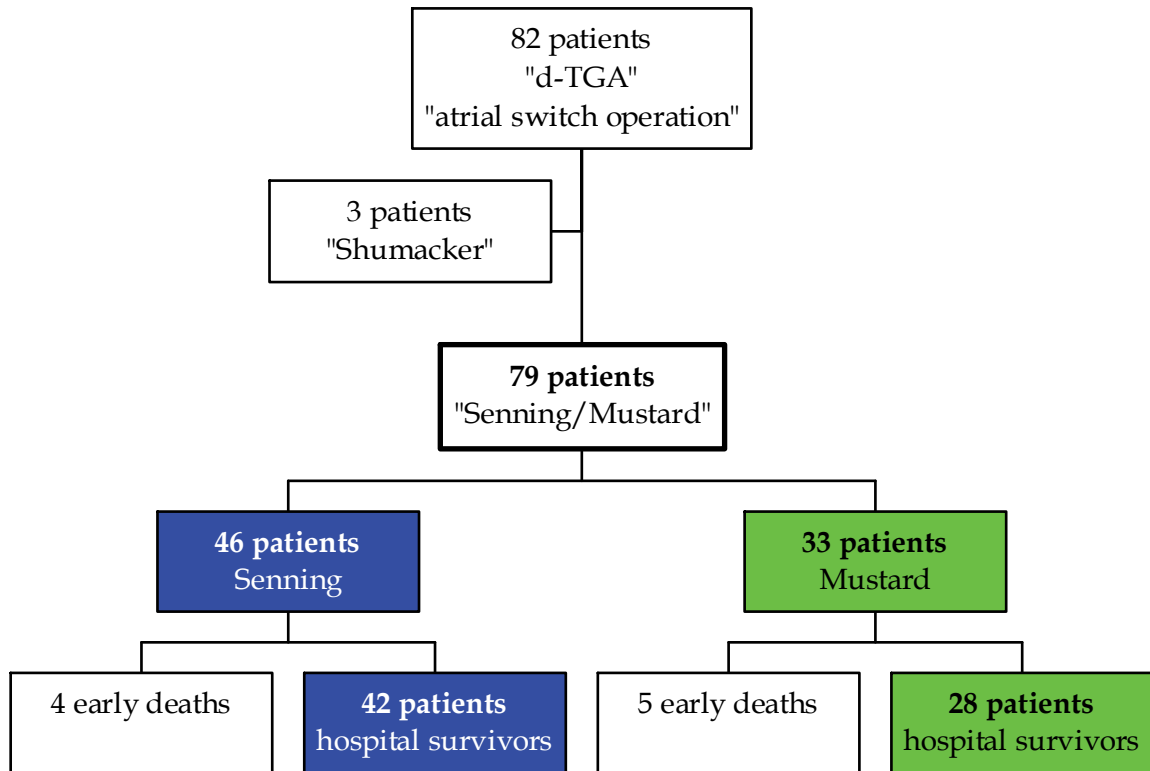


Figure 6 Graph of patients entered into our study. Three patients were excluded as they underwent a Shumacker repair – a modified variation of the Senning technique.

Eighty-two patients matching the following criteria were initially generated by the hospital's administrative computer program: {diagnosis = "(d-)TGA"}, {surgery = "atrial switch operation"}. All but three patients (79 of 82) met the prerequisites mentioned in the description of methods. Of those 79 patients, 56 (70.9%) were male, and 23 (29.1%) female. Forty-six patients underwent atrial switch surgery according to Senning, 33 patients according to Mustard. (Figure 6)

Patients in our collective were born between October 1971 and June 1994 and underwent surgery between January 1974 and May 1995. (Figure 7)

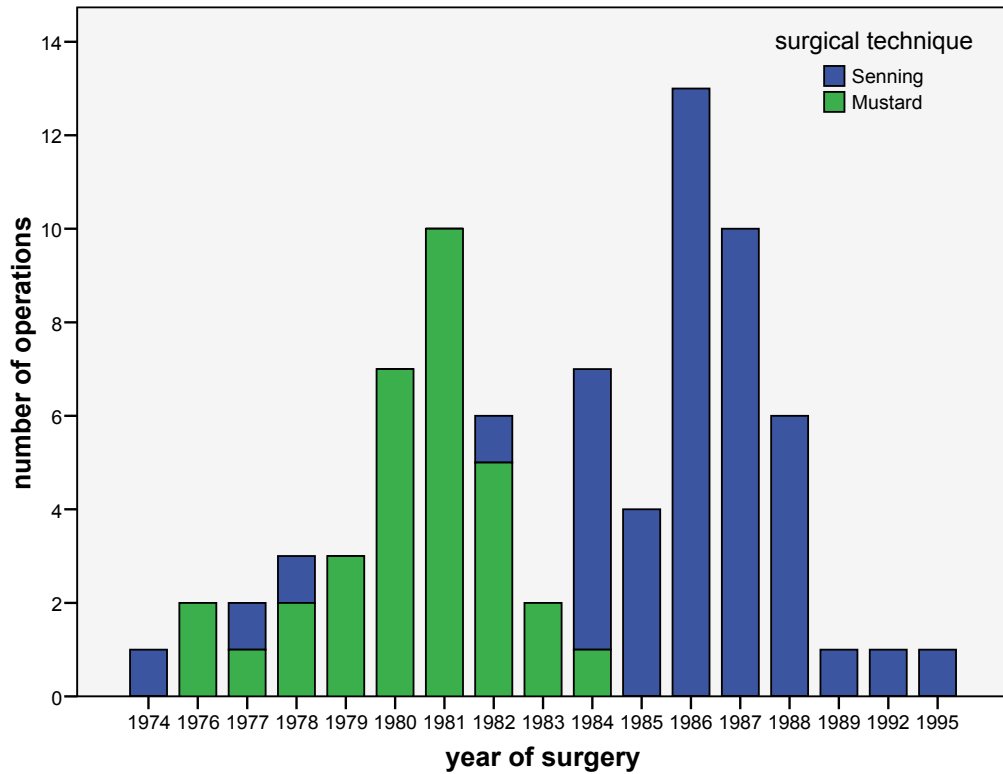


Figure 7 Bar graph depicting linear timeline reflecting use of procedure based on year.

6.1 Associated Defects

Forty-five patients (57%) were initially diagnosed with simple TGA (only PFO and/or small PDA), and 34 patients (43%) with complex TGA (19 patients with one associated defect, 13 patients with two associated defects, and two patients with three associated defects). Associated defects were hemodynamically relevant VSD in 27 patients, PS/LVOTO in 13 patients, and systemic collaterals in two patients.

6.2 Pre-operative Data

6.2.1 Pre-operative Palliative Procedures

Palliative procedures prior to atrial switch operation were performed in all but one patient, born in 1971 with a complex TGA with PFO and large VSD. One palliative procedure was necessary in 62 patients (78.5%), two palliative

procedures were performed in 12 patients (15.2%), and four patients (5.1%) needed three palliative procedures prior to definitive surgery. Palliative procedures included BAS in 75 patients (94.9%), PDA ligation and Blalock-Taussig shunts in 6 patients (7.6%) each, and pulmonary banding and atrial septectomy in five patients (6.3%) each.

6.2.2 Hemodynamic Data

Pre-operative **mean arterial oxygen saturation (SaO₂)** for all patients was 67.3 ± 9.1 (30-87)% with no significant difference between the Senning and Mustard groups. **Mean left ventricular systolic pressure** pre-operatively was 42 ± 23 (15-110) mmHg and significantly lower in the Senning group (34.8 ± 16.7 ; 15-95 mmHg) than in the Mustard group (52.3 ± 26.8 ; 20-110 mmHg) ($p=0.004$). **Pulmonary systolic pressure** was a mean of 23 ± 17.8 (7-100) mmHg with no significant difference between the two study groups. Pulmonary hypertension was detected in 11/79 patients (13.9%).

6.2.3 Pre-operative Rhythm

All but one of 79 patients were in SR, one patient presented with AV-block grade II pre-operatively.

6.3 Operative Data

Forty-six patients (58.2%) underwent a Senning procedure between 1974 and 1995, 33 patients (41.8%) a Mustard procedure between 1976 and 1984. Most of our patients were operated on in Graz, decisions for the type of surgery (Senning or Mustard) were made with the agreement of at least one pediatric cardiologist and a surgeon. Two patients actually underwent surgery in Zurich, Switzerland (Prof. Åke Senning), and a total of 8 patients were operated on in Munich/Germany (n=5), London/Great Britain (n=2), and Vienna/Austria (n=1).

Mean **age at surgery** was 13.5 ± 23.2 (1-180) months, with no significant difference between the Senning and Mustard groups (10.2 ± 26 ; 1-180; vs. 18.2 ± 18 ; 4-83 months). Mean **weight at surgery** was 7.9 ± 4.4 (3.55-36.2) kg and did not differ significantly between groups. In the Senning group, 17/46 patients (37%) were diagnosed with complex TGA, as compared to 17/33 patients (51.5%) in the Mustard group ($p > 0.05$).

Out of 34 patients with complex TGA, 27 (79.4%) needed **additional repairs** such as VSD closure (n=18), pulmonary de-banding (n=5), PDA ligation (n=4), closure of a Blalock-Taussig shunt (n=4), LVOTO resection (n=2), and embolisation of systemic collaterals (n=1) during their atrial switch procedure.

6.4 Early post-operative Data

	frequency	percent %
death	9	11.4
arrhythmia	23	29.1
bleeding	4	5.1
venous pathway obstruction	4	5.1
low cardiac output/multi organ failure	4	5.1
infection	2	2.5
other	11	13.9

Table 1 Early death in 9/79 patients, and early post-operative complications occurring in 27/79 patients, with more than one complication possible per patient.

6.4.1 Early Death

Early death was defined as intra-operative death or death within the first 30 days following atrial switch surgery.

Early death occurred in 9/79 patients (11.4%): four of 46 patients (8.7%) in the Senning group and 5/33 patients (15.2%) in the Mustard group ($p > 0.05$). (Table 1) Causes of death determined by autopsy were low cardiac output (n=5), pulmonary hypertension (n=2), and pulmonary venous obstruction (PVO; n=2). Mean age at surgery of non-survivors did not differ significantly between the Senning and Mustard groups (9 ± 6.8 ; 4-19; vs. 12.2 ± 7.8 ; 4-21 months). There was no

significant difference in age or weight at surgery between survivors and non-survivors. Six out of 9 non-survivors were operated on between the years of 1974 and 1984, the remaining three patients during the later surgical period (1985-1995).

6.4.2 Early Post-operative Complications

A review of anesthesiology, surgical and cardiac ICU protocols showed early **post-operative complications** in 27/79 patients (38.6%). Results are summarized in Table 1.

Early arrhythmias were seen in 23/79 patients (29.1%) and treated with anti-arrhythmic drugs in 7 patients (8.9%), pacemaker (PM) implantation in four patients (5.1%), and cardioversion in one patient. Early arrhythmias occurred significantly more often in the Senning group (19/46 patients, 41.3%) as compared with the Mustard group (4/33 patients, 12.1%) ($p=0.011$). (Table 2)

		surgical technique	
		Senning	Mustard
rhythm postOP (<4weeks)	JR	6	
	AV Block II/III	3	2
	SVT	4	1
	VT		1
	PAC	1	
	SND	5	

Table 2 Post-operative rhythm abnormalities in the Senning and Mustard groups in 23/79 patients ($p=0.011$). [postOP = post-operative; JR = junctional rhythm; AV block II/III = atrio-ventricular block grade II or III; SVT = supra-ventricular tachycardia; VT = ventricular tachycardia; PAC = premature atrial contraction; SND = sinus node dysfunction]

Post-operative bleeding necessitating re-operation occurred in four patients (5.1%). Immediate post-operative **venous obstruction** was detected in four patients (5.1%), all Senning group: one PVO, one systemic venous obstruction (SVO), one PVO/SVO combined, and one undefined obstruction. All patients were re-operated on, one patient died.

Low cardiac output/multi organ failure was observed in four patients (5.1%), all of them recovering consequently.

Other complications (n=11) included pneumothorax, renal venous thrombosis, cerebral stroke, acute renal insufficiency, cerebral atrophy, acute respiratory distress syndrome, pleural effusion, clotting problems, and post-operative intermittent neuro-cognitive deficit.

Please note that starting with chapter 6.5, percentages will be calculated for a total patient number of 70, excluding hospital non-survivors!

6.5 Follow-up Data

Follow-up was defined as time from 30 days after atrial switch operation to latest follow-up appointment or to time of death. Follow-up visits were scheduled every 6 to 12 months, or more frequently if necessary.

Mean length of follow-up was 17.5 ± 8.2 (0.1-28.4) years and did not differ significantly between the Senning and Mustard groups (17.7 ± 6.7 ; 0.1-28.4 vs. 17.2 ± 10.2 ; 0.1-28.3 years; $p > 0.05$).

6.5.1 Late Death

Late death was defined as death of hospital survivors, i.e. survivors of 30 or more days after atrial switch surgery.

To date May 2008, a total of 16/70 (22.9%) patients died during follow-up: 5/42 patients (11.9%) in the Senning, and 11/28 patients (39.3%) in the Mustard group ($p = 0.01$). Death occurred a mean of 9.3 ± 8.5 (0.17-24.4) years post-operatively with no significant time-related difference between the Senning and Mustard groups (10.9 ± 9.4 ; 0.17-20.6 vs. 8.6 ± 8.5 ; 0.33-24.4 years; $p > 0.05$).

Eleven of 16 patients had risk factors or experienced prior events, such as systemic ventricular dysfunction (SVD), pulmonary hypertension, cardiac syncope and history of CPR, PM implantation or re-operation, junctional rhythm (JR), and SND. **Five** patients died unexpectedly with no medical findings prior to death (set off in gray, Table 3).

Patient	Surgical technique	Died	Follow-up interval (years)	Cause of death, patient history
BJ	S	11/10/99	15.3	death after history of severe arrhythmia, SVD
GM	M	9/6/86	6.0	food aspiration during dinner; PM implanted
JF	M	23/1/97	15.6	viral infection (measles); history of SVO dilation and PM
JD	M	16/5/88	5.1	sudden collapse, previously well
KC	M	10/12/88	7.5	pneumonia; history of patch repair, AV block, SVD
KB	M	25/3/03	24.4	death 9 years after HLTX, no F/U after transplantation
KOB	M	11/12/84	4.2	sudden collapse, previously well
KW	S	18/2/89	0.2	sudden collapse, previously well
MR	S	30/5/07	20.6	death after history of severe arrhythmia, PM
PE	M	18/11/80	1.1	heart failure; history of severe pHT, SVD
SF	M	9/11/88	7.6	death after history of re-operation (baffle leak), pHT
SH	M	5/4/81	0.3	pneumonia, previously well
SP	S	19/8/03	16.8	death after history of severe arrhythmia, PM, SVD
SPH	M	24/8/81	0.3	heart failure; previously documented pHT
SM	S	27/4/89	1.4	sudden collapse, previously well
TG	M	27/2/03	22.1	massive pulmonary bleeding; documented Eisenmenger's and severe arrhythmia

Table 3 Causes of death for 16/70 patients. [S=Senning; M=Mustard; SVD=systemic ventricular dysfunction; SVO=systemic venous obstruction; PM=pacemaker; HLTX=combined heart and lung transplantation; F/U=follow-up; pHT=pulmonary hypertension]

Late death occurred to the same extent in the complex (n=7/31, 22.6%) and simple (9/39, 23.1%) TGA groups. (Figure 8)

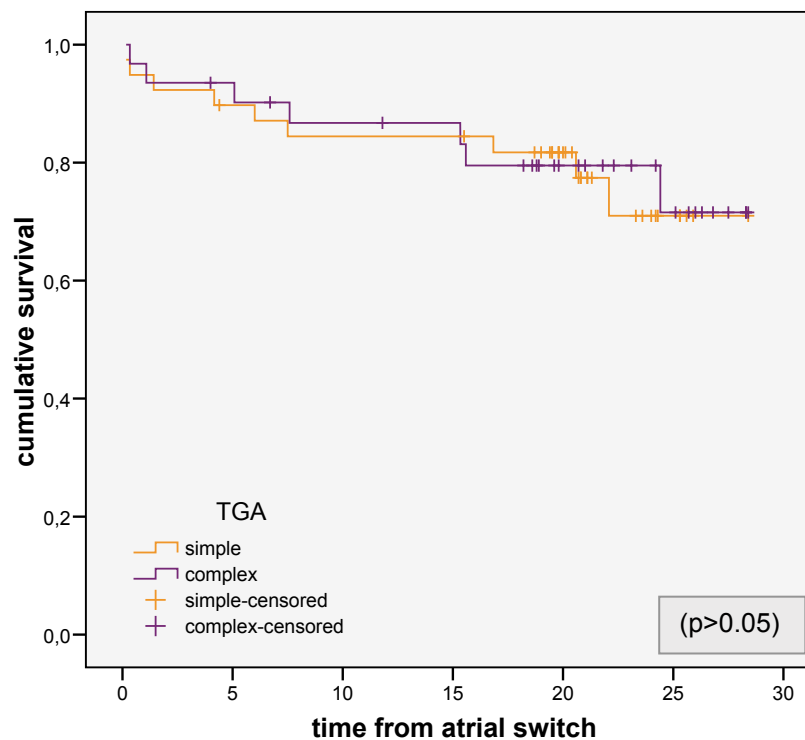


Figure 8 Kaplan-Meier curve for actuarial survival of patients with simple vs. complex TGA.

Overall survival at one, five, 10, 15, 20 and 25 years for the entire group of 70 hospital survivors was 96%, 91%, 86%, 86%, 81% and 77%. In the Senning group, 97.6% (41/42 patients) survived the first post-operative year, 88.1% (37/42 patients) were still alive after 25 or more years. For the Mustard group, corresponding numbers were 92.9% (26/28 patients) and 60.7% (17/28 patients) respectively. (Figure 9)

Mean age of survivors in the Senning and Mustard groups was 19.5 ± 5.3 (4-28.4) and 25.1 ± 2.3 (19.8-28.3) years respectively (overall 21.3 ± 5.3 ; 4-28.4 years).

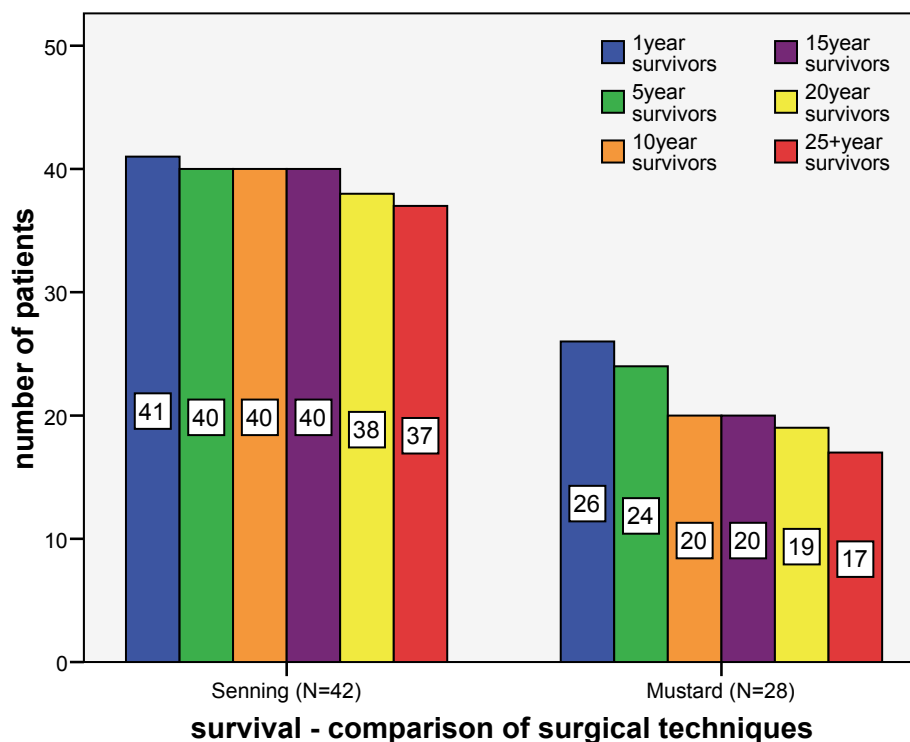


Figure 9 Bar graph depicting survivors in the Senning and Mustard groups plotted as a function of time after atrial switch operation. Actual numbers of survivors at one, five, 10, 15, 20, and 25 years are shown for the two surgical groups.

Actuarial survival in the Senning group at five, 10, 15, 20, and 25 years was 95.2%, 89.9%, 89.9%, 89.9%, and 89.9% respectively. According figures for the Mustard group were 82.1%, 67.9%, 63.9%, 58.5%, and 58.5% respectively ($p=0.033$). (Figure 10)

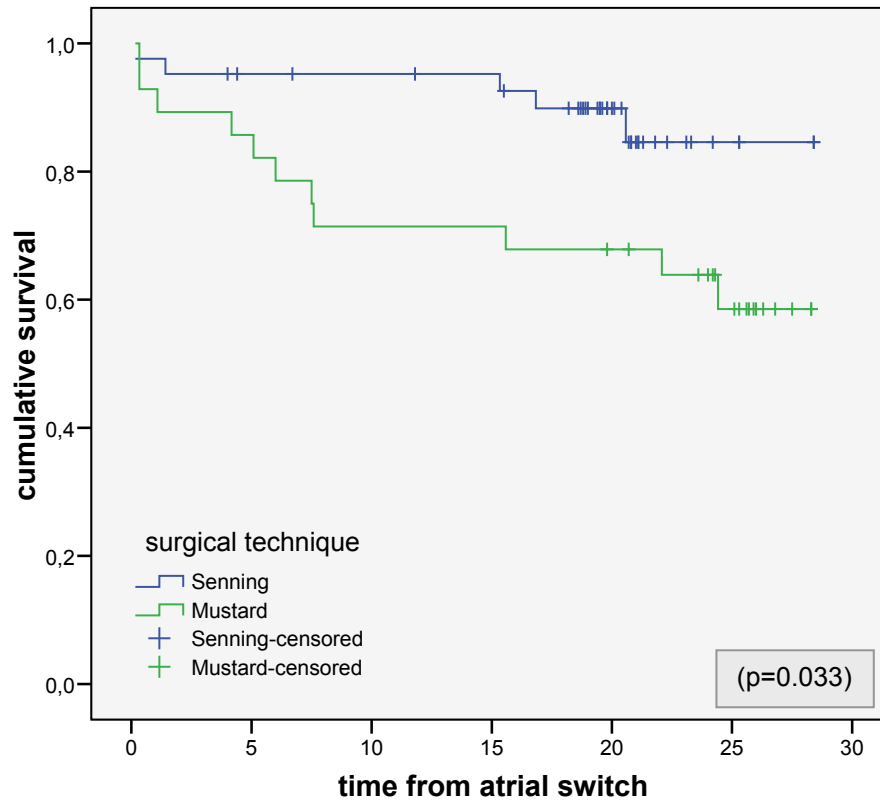


Figure 10 Kaplan-Meier curve for actuarial survival of patients in the Senning and Mustard groups.

6.5.2 Post-operative Procedures

Out of 70 hospital survivors, 46 patients (65.7%) required neither catheter intervention nor re-operation. Twelve patients underwent cardiac catheter interventions, 16 patients needed re-operations. In 6 patients both cardiac catheter intervention and re-operation were necessary.

Cardiac catheterizations and catheter interventions

Cardiac catheterizations (ranging from one to a maximum of 6 per patient) were performed in 60/70 hospital survivors (85.7%).

A total of 22 **cardiac catheter interventions** were performed in 12 individual patients (5 Senning, 7 Mustard) during follow-up (7 patients with one catheter intervention, five patients with three catheter interventions). SVO was observed in 9 patients and treated with dilation (n=5), or dilation and stent implantation (n=4, in three patients multiple times). PVO was treated with dilation in two patients.

Two patients underwent multiple dilations for PVO and SVO, and one patient required occlusion of a baffle leak with a Rashkind occluder.

Catheter interventions took place a mean of 11.3 ± 6.2 (0.3-22.3) years post-operatively, and significantly earlier in Senning (5.9 ± 5.9 ; 0.3-15.8 years) than Mustard patients (13.4 ± 5.1 ; 6.6-22.3 years) ($p=0.008$). Comparatively, there was no significant difference noted between the number of patients requiring cardiac catheter interventions in the Senning (5/42 patients, 11.9%) vs. the Mustard group (7/28 patients, 25%).

Re-operation data

Sixteen of 70 hospital survivors (22.9%) needed a total of 19 re-operations after atrial switch surgery. There was a significant difference between the Senning (3/42 patients, 7.1%) and Mustard groups (13/28 patients, 46.4%) concerning the **individual number of re-operations** ($p=0.001$). The **relative risk (RR)** for re-operation was 10 times as high in the Mustard group ($RR=3$) as compared with the Senning group ($RR=0.3$). Pathologies requiring re-operation included (in order of single frequency) SVO ($n=7$, one patient multiple re-operations), PVO ($n=6$, one patient multiple re-operations), and one case each of baffle leak, LV to pulmonary artery conduit, and resection for LVOTO.

Mean time of re-operation was 6.2 ± 7.0 (0.3-23.6; median=3.5) years after atrial switch operation with no significant difference between the Senning (1.1 ± 0.8 ; 0.6-1.7 years) and Mustard groups (6.9 ± 7.2 ; 0.3-23.6 years).

On a separate account, heart-lung transplantation was performed in one patient in the Mustard group at 15.5 years from atrial switch. This patient died. 9 years later.

6.5.3 Arrhythmias

ECGs were written at every follow-up appointment, Holter ECGs and 48h-event recorders were ordered in case of suspected rhythm abnormality. Over the course of follow-up, a mean of 6.5 ± 5.6 (0-35) **Holter ECGs** were carried out per patient.

Rhythm abnormalities at any point during follow-up, including untreated, transient as well as severe changes, occurred in 55/70 patients (78.6%) with no significant difference between the Senning (34/42 patients, 81%) and Mustard groups (21/28 patients, 75%). Early post-operative arrhythmias had no effect on late arrhythmias ($p=0.21$).

Criteria for SR was considered met if SR was noted more than 90% of Holter ECG monitoring. A permanent or transient **loss of SR** was recorded in 42/70 patients (60%) with no significant difference between the Senning group ($n=28/42$, 66.7%) as compared with the Mustard group ($n=14/28$, 50%). Actuarial survival of continuous SR as estimated by Kaplan-Meier curve delivered a borderline significant difference between groups. (Figure 11)

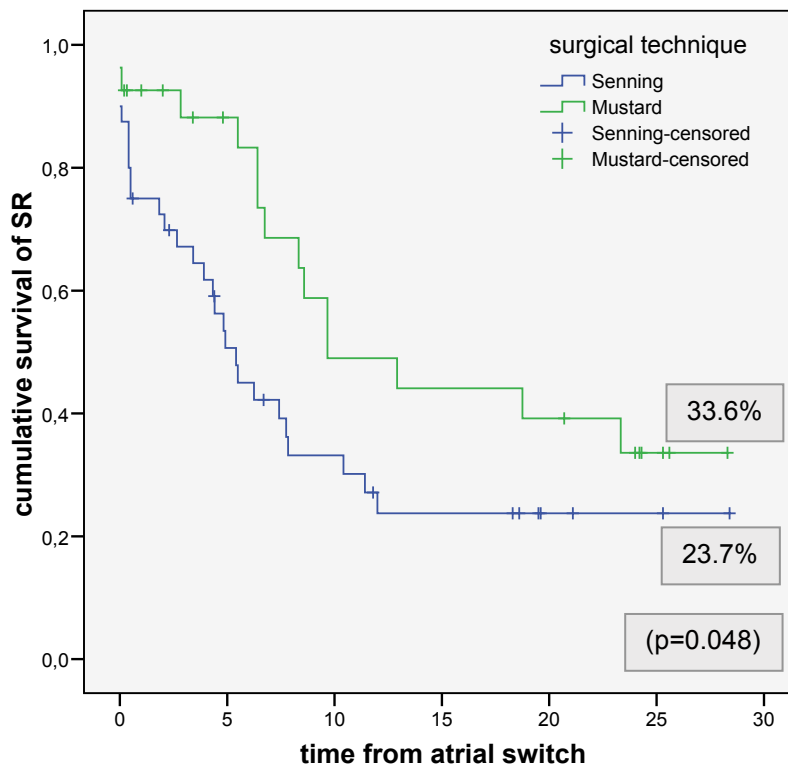


Figure 11 Kaplan-Meier curve for actuarial survival of continuous SR during follow-up in the Senning vs. the Mustard group. Figures at 25 years follow-up are 33.6% and 23.7% respectively.

Loss of continuous SR was detected a mean of 5.4 ± 5.2 (0-23.3) years post-operatively, and significantly earlier in the Senning group (3.9 ± 3.7 ; 0-12 years) as compared with the Mustard group (8.5 ± 6.5 ; 0-23.3 years) ($p=0.005$).

Approximately 15 years after Senning repair, patients tended to stabilize with reference to ECG changes. (Figure 12)

Symptomatic arrhythmias were recorded in 28/70 patients (40%; 17/42 Senning, 11/28 Mustard). Initial incident of those arrhythmias was a mean of 9.3 ± 6.9 (0-23.6) years post-operatively and significantly earlier in the Senning group at 6.8 ± 5.3 (0-15.4) years, than in the Mustard group at 13.2 ± 7.5 (2.8-23.6) years ($p=0.013$). (Figure 12) Twenty-four of 28 patients with symptomatic arrhythmia received a PM shortly after their diagnosis, four patients died subsequently.

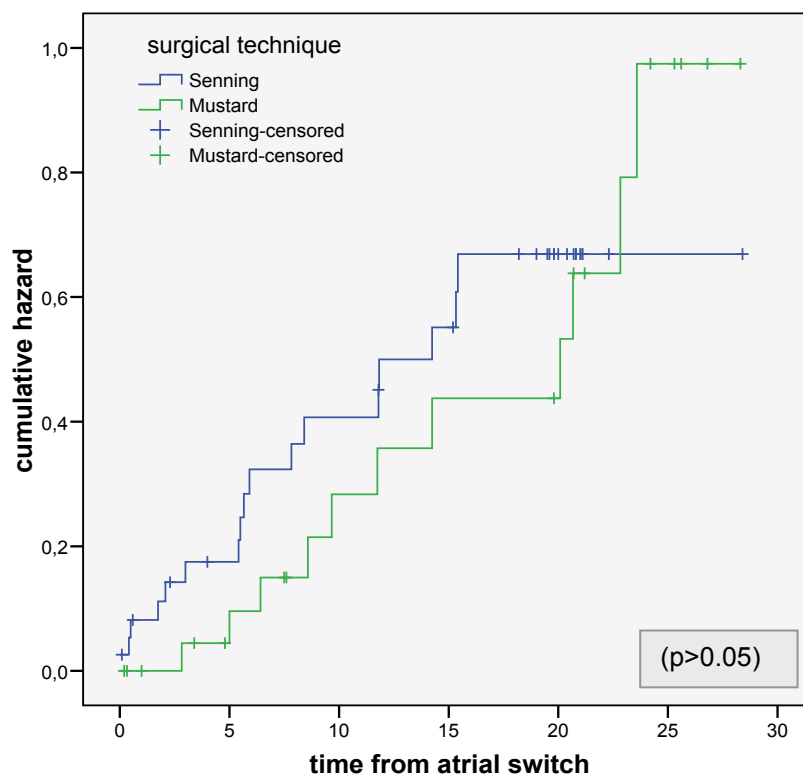


Figure 12 Cumulative hazard for the Senning and Mustard groups to develop a symptomatic arrhythmia during the course of follow-up.

Criteria for **JR** (JR for more than 50% per Holter ECG) was met in 15/70 patients (21.4%; 11 Senning, 4 Mustard) during follow-up. Relative risk for JR was more than twice as high in the Senning ($RR=1.3$) as compared with the Mustard group ($RR=0.6$). JR occurred a mean of 5.4 ± 4.8 (0.1-14.2) years after atrial switch operation with no significant difference noted between the Senning and Mustard groups (4.6 ± 4.9 ; 0.1-14.2 vs. 8.4 ± 4.0 ; 5.5-12.9 years). Treatment with anti-arrhythmic drugs was necessary in 3/15 patients.

SND was diagnosed if one or more of the following criteria were fulfilled (46): sinusatrial block (abnormally low heart rate), sinus arrest, or tachycardia-bradycardia syndrome, with or without asystole between heartbeats.

Criteria for SND were met in 35/70 patients (50%), 25/42 patients (59.5%) in the Senning group compared with 10/28 patients (35.7%) in the Mustard group ($p=0.087$). Relative risk for SND was 2.5 times as high in the Senning group ($RR=1.5$) as compared with the Mustard group ($RR=0.6$). SND was diagnosed at a mean of 8.2 ± 6.1 (0-23.3) years after atrial switch surgery with no significant difference between the Senning group (7.4 ± 5.6 ; 0-19.8 years) vs. the Mustard group (10.3 ± 7.2 ; 0.1-23.3 years). Anti-arrhythmic treatment was necessary in 10/35 patients as single treatment ($n=2$) or combined with PM ($n=8$). Permanent PMs in solitude were implanted in 13/35 patients.

Supra-ventricular tachycardias (SVTs) other than atrial fibrillation or flutter occurred in 15/70 patients (21.4%). On average, SVTs were discovered earlier in the 10/42 (23.8%) Senning patients at 6.9 ± 6.7 (0-16.2) years, as compared with the 5/28 (17.9%) Mustard patients at 15.3 ± 10.8 (2.5-23.9) years ($p>0.05$). Anti-arrhythmic drugs were prescribed for 3/15 patients, permanent PM implantation was necessary in 3/15 patients, and 7/15 patients required a combination of the above.

Atrial fibrillation or flutter was diagnosed in a total of 12/70 patients (17.1%) at a mean of 16.0 ± 4.9 (9.7-23.9) years. Patients in the Senning group (6/42, 14.3%) were diagnosed earlier than patients in the Mustard group (6/28, 21.4%) at a mean of 13.4 ± 2.1 (10.6-15.4) years vs. 18.7 ± 5.6 (9.7-23.9) years respectively ($p=0.07$). Anti-arrhythmic drugs were treatment of choice in 8/12 patients, mostly, however, in combination with permanent PMs ($n=6$). PM implantation was mandatory in a total of 10/12 patients.

AV block was classified as relevant if grade II or III, and was discovered in 9/70 patients (12.9%). Diagnosis was made a mean of 8.9 ± 8.5 (0-22.9) years post-operatively with no significant difference between the 4/42 (9.5%) Senning patients (7.2 ± 8.5 ; 0-16.9 years) as compared with the 5/28 (17.9%) Mustard

patients (10.3 ± 9.2 ; 0-22.9 years). In 7/9 patients diagnosed with AV block, PM implantation was mandatory during follow-up.

Premature ventricular contractions (PVCs) and **ventricular tachycardias (VT)** were detected in 15/70 patients (21.4%) at a mean of 11.2 ± 4.9 (3.0-17.3) years after atrial switch operation. Diagnosis for the 9/42 (21.4%) patients in the Senning group was made a mean of 10.2 ± 5.0 (3.0-17.1) years post-operatively vs. 12.6 ± 4.7 (4.9-17.3) years in the 6/28 (21.4%) Mustard patients ($p>0.05$). Anti-arrhythmic drugs were necessary in 2/15 patients, another four patients required combination therapy (anti-arrhythmic drugs and PM implantation).

Therapy of arrhythmias

Of all patients with rhythm abnormalities at any point during follow-up ($n=55/70$), treatment was mandatory in 30 patients (54.5%).

A total of 15/70 patients (21.4%) were treated with **anti-arrhythmic drugs** first prescribed at a mean of 11.4 ± 7.7 (0.4-23.6) years post-operatively. Comparatively, Senning patients received anti-arrhythmic treatment significantly earlier at 7.4 ± 5.4 (0.4-5.3) years than Mustard patients at 19.5 ± 4.6 (14.3-23.6) years ($p=0.001$). There was no significant difference between the two groups for the number of patients requiring anti-arrhythmic drugs (10/42 Senning patients, 23.8% vs. 5/28 Mustard patients, 17.9%).

Permanent PM implantation was mandatory in a total of 25/70 patients (35.7%), 16/42 in the Senning group (38.1%), and 9/28 patients (32.1%) in the Mustard group ($p>0.05$). Indication for permanent PM implantation was symptomatic arrhythmia in 18/25 patients and AV block in 7 patients. In 5/25 patients, permanent PMs were necessary before, and in 20 patients after age 18. PMs were implanted at a mean of 11.9 ± 6.8 (0-23.0) years post-operatively with no significant difference between the Senning (10.9 ± 6.2 ; 0-19.2 years) and Mustard groups (13.8 ± 7.8 ; 0-23.0 years).

Catheter ablation was performed in 3/70 patients (4.3%), in 2/42 Senning patients (4.8%) at 15.1 and 17.4 years, and 1/28 Mustard patient (3.6%) at 18.6 years after atrial switch operation, all for atrial fibrillation/flutter and SVT.

Cardioversion was necessary in 7/70 patients (10%) because of recurrent episodes of atrial fibrillation or flutter. Four of 42 patients (9.5%) in the Senning, and 3/28 patients (10.7%) in the Mustard group were cardioverted at 14.4 ± 1.3 (13.3-16.2) vs. 16.8 ± 6.2 (9.7-20.7) years respectively ($p > 0.05$). Six of 7 patients ended up with a PM.

6.5.4 Two-dimensional Echocardiography

Two-dimensional echocardiography was performed in all patients at every outpatient follow-up appointment (annually or at least bi-annually).

Systemic RV function was determined semi-quantitatively by experienced pediatric cardiologists. (Figure 13) In 18/70 patients (25.7%) systolic function of the RV was assessed as normal (ejection fraction greater than 50%).

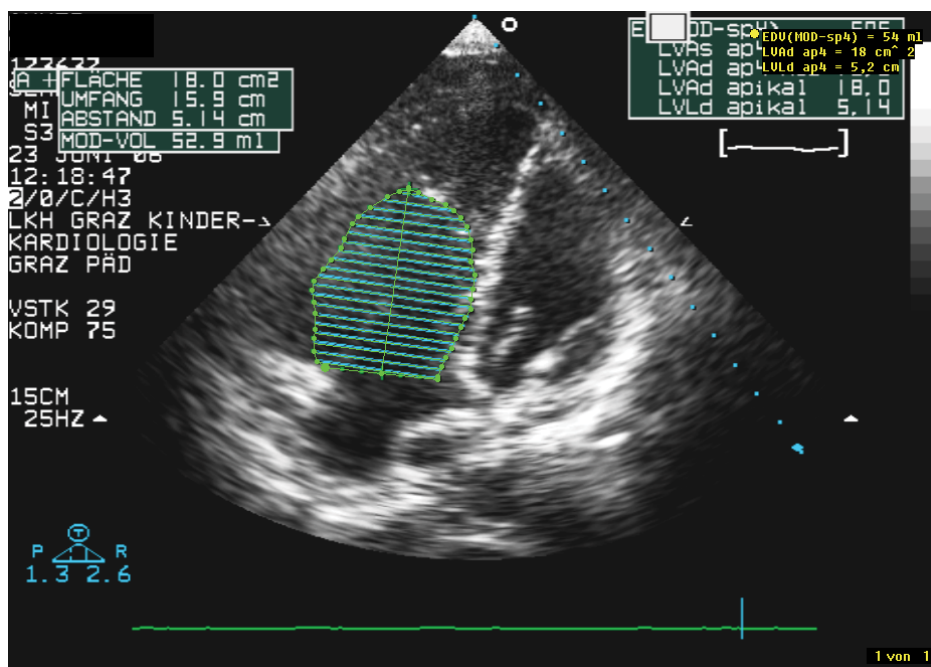


Figure 13 Two-dimensional echocardiography – depicted is a volumetric method to assess size and volume of the RV and ejection fraction as performed at our facility. (Photograph courtesy of Prof. A. Gamillscheg, Medical University Graz)

Impaired ejection fraction was detected a mean of 14.8 ± 5.7 (0.2-28.4) years post-operatively, with no significant difference between the Senning (14.2 ± 4.7 ; 1.7-28.4 years) and Mustard groups (15.4 ± 6.7 ; 0.2-23.8 years). (Table 4)

		surgical technique			
			Senning	Mustard	Combined
RV function	normal (EF>50%)	n (%)	14 (33.3)	4 (14.3)	18 (25.7)
	mildly impaired (EF<50%)	n (%)	12 (28.6)	10 (35.7)	22 (31.4)
	moderately impaired (EF<40%)	n (%)	13 (31.0)	10 (35.7)	23 (32.9)
	severely impaired (EF<30%)	n (%)	1 (2.4)	1 (3.6)	2 (2.9)

Table 4 Systolic right ventricular function in the Senning (42 patients) and Mustard (28 patients) groups ($p>0.05$). Data for 5 patients missing. [RV=right ventricle; EF=ejection fraction]

There was no significant difference between the Senning and Mustard groups concerning onset of decline in systolic RV function. (Figure 14)

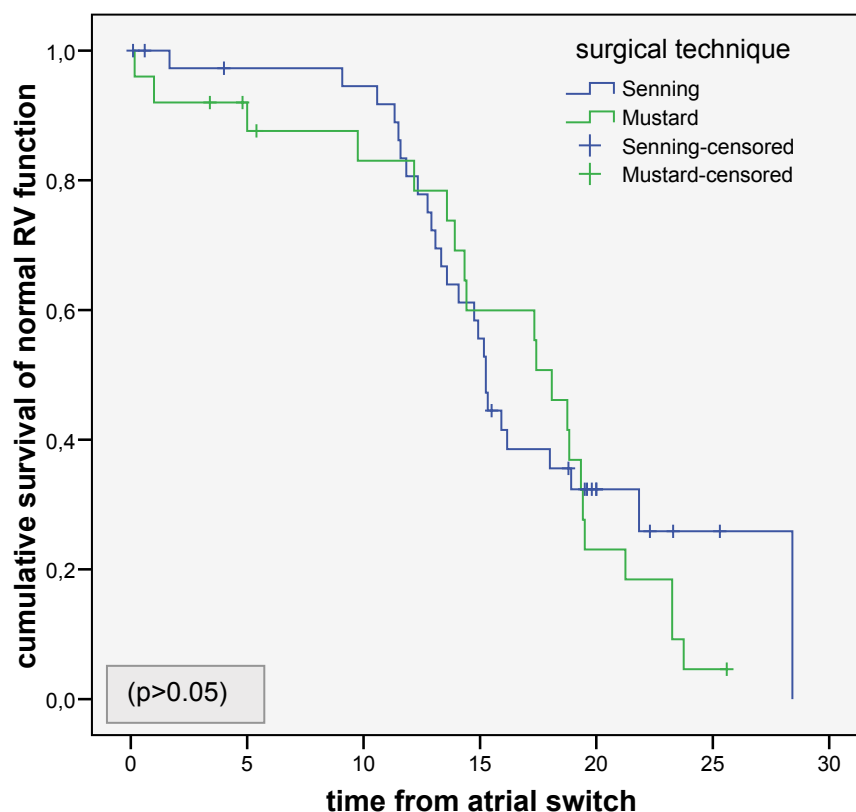


Figure 14 Actuarial survival of normal systolic RV function (ejection fraction > 50%) in the Senning and Mustard groups.

PVCs or VTs (in 15/70 patients) did not significantly affect systemic ventricular function. **Supraventricular arrhythmias** had a borderline not significant influence

on systemic RV function ($p=0.058$). The relative risk for developing systemic ventricular dysfunction was three times as high ($RR=1.5$) in the presence of supraventricular arrhythmias as compared with no supraventricular arrhythmias ($RR=0.5$). (Table 5) Symptomatic arrhythmias resulted in a relative risk 2.5 ($RR=1.7$) that of patients without pathological rhythm findings ($RR=0.7$).

		Systemic right ventricular dysfunction	
		yes	no
		n (%)	n (%)
Supraventricular arrhythmia	yes	32 (45.7%)	10 (14.3%)
	no	12 (17.1%)	11 (15.7%)

Table 5 Function of the right systemic ventricle in the presence and absence of supraventricular arrhythmia ($p=0.058$). [Data for 5 patients missing.]

Patients were significantly more prone to show systemic RV dysfunction if TR was present ($p=0.006$). The relative risk for TR was more than four times as high ($RR=1.7$) in the presence of systemic RV dysfunction as compared with a normally functioning RV ($RR=0.4$).

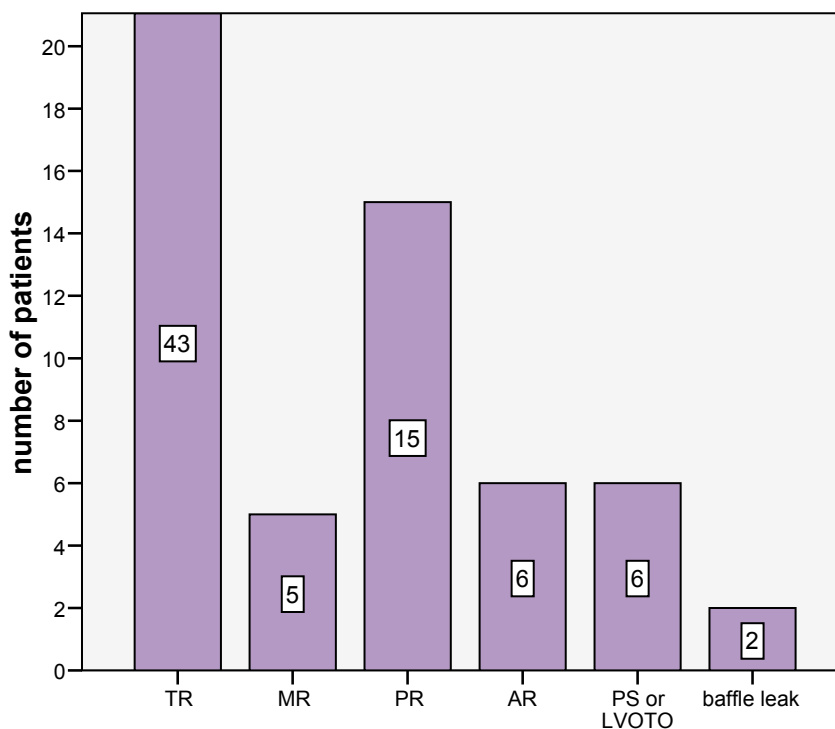


Figure 15 Single occurrences of pathologies detected in two-dimensional echocardiography.

Relevant **TR** was observed in 43/70 patients (61.4%) with no significant difference between the Senning (29/42 patients, 69%) and Mustard groups (14/28 patients, 50%). TR was assessed as mild in 38 patients (88.4%; 27 Senning, 11 Mustard), as moderate in four patients (2 Senning, 2 Mustard), and severe in one patient (Mustard group). There was no significant difference between the TGA simple and complex groups concerning moderate or severe TR ($p>0.05$). On the other hand, patients with TR suffered significantly more often from supraventricular arrhythmias than patients with competent tricuspid valves (74,4% vs. 47,6%) ($p=0.05$).

Mild **mitral regurgitation** occurred in 5/70 patients (3 Senning, 2 Mustard).

Mild **pulmonary regurgitation** and mild **aortic regurgitation** were diagnosed in 15/70 (21.4%; 9 Senning, 6 Mustard) and 6/70 patients (8.6%; 5 Senning, 1 Mustard) respectively.

Mild **pulmonary stenosis** (PS) or LVOTO was diagnosed in a total of 6/70 patients (8.6%). Two of 42 patients (4.8%) in the Senning group were affected, as compared with 4/28 patients (14.3%) in the Mustard group ($p>0.05$).

Two of 42 Senning patients were diagnosed with **affle leaks**, a cardiac catheter intervention was performed on one of them (Rashkind occluder). (Figure 15)

6.6 Evaluation at last Clinical Visit

Last clinical visit was defined as last and therefore most recent outpatient examination of each of our 70 hospital survivors.

Mean age at latest follow-up visit was 18.7 ± 8.4 (0.5-34.75) years with no significant difference between the Senning (18.6 ± 7.1 ; 0.5-34.8 years) and the Mustard group (18.9 ± 10.2 ; 0.7-32.3 years).

6.6.1 Quality of Life, Functional Status

NYHA class and Ability Index

At their latest follow-up appointment, 56/70 patients (80%) were assigned to New York Heart Association (**NYHA**) **functional class I**, 7/70 patients (10%) to NYHA class II, and 7/70 patients (10%) to either NYHA III or IV. Comparatively, there was no significant difference between the Senning (38/42 patients; 90.5%) and Mustard groups (18/28 patients; 62.3%) with reference to NYHA class I ($p=0.052$).

All but 13/70 patients (18.6%) received an **Ability Index (AI)** class 1 ("normal life", see attachments). Four of 42 patients (9.5%) in the Senning group vs. 9/28 patients (32.1%) in the Mustard group ($p=0.048$) were assigned to AI class 2 ("able to work, but experiencing intermittent symptoms and some interference with life"; $n=5$) or AI 3 ("unable to work, frequent symptoms, steady interference with life"; $n=8$).

Exercise Testing

Ergometer exercise (13/70 patients, 18.6%) and spiro-ergometer testing (7/70 patients, 10%) were ordered as evidenced by indication needed. Four patients (5.7%) underwent both tests.

Additional medical findings and employment status

18/70 patients (25.7%) suffered from more or less severe medical conditions other than their underlying heart condition. (Table 6)

	frequency	percent
mental retardation	4	5.7
epilepsy	4	5.7
hemiparesis	2	2.9
Eisenmenger syndrome	2	2.9
psychomotor retardation+Eisenmenger	1	1.4
tetraplegia	2	2.9
hemiparesis+psychomotor retardation	2	2.9
bronchial asthma	1	1.4

Table 6 Additional medical findings in both surgical groups combined at latest follow-up.

Occupation at the last clinical visit ranged from laboratory or kitchen aide to embassy employee or mathematician. Ten patients attended school or college (students) at their latest follow-up, only two patients with tetraplegia were assessed as either unfit for work or disabled. (Figure 16)

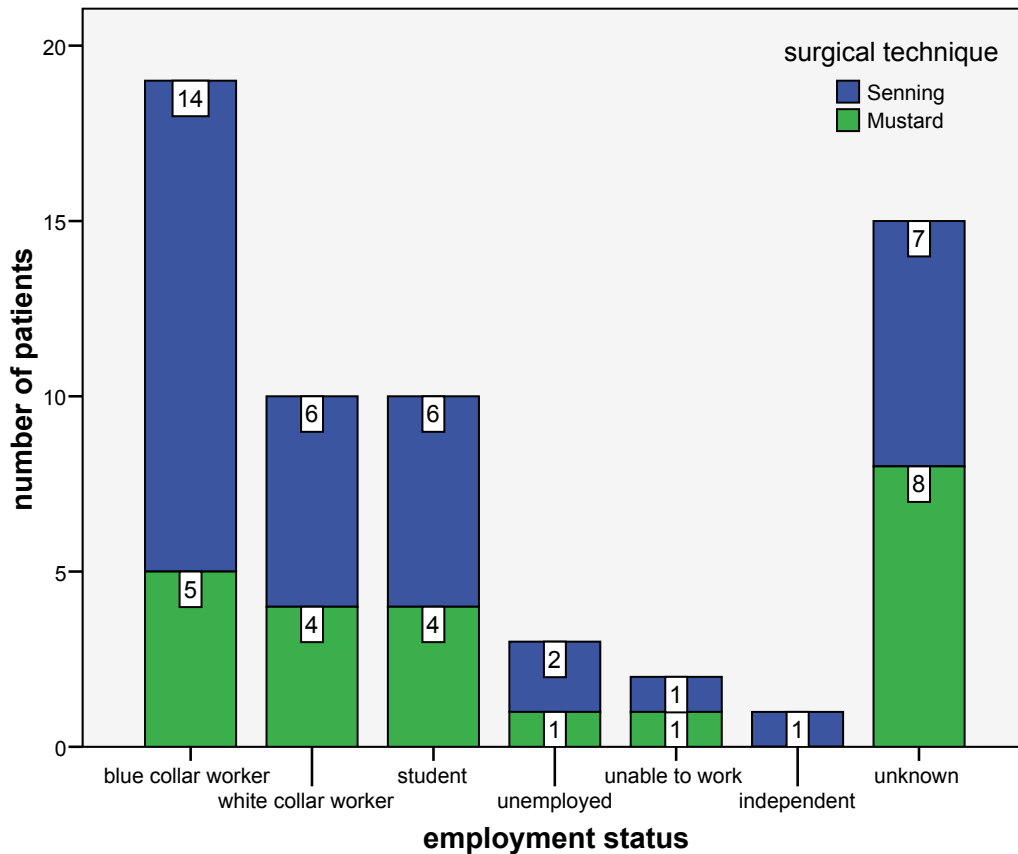


Figure 16 Employment status of patients in the Senning vs. Mustard group at their latest clinical examination. Data about employment status for 10 patients could not be retrieved.

6.6.2 Medications at last Clinical Visit

Twenty-three of 70 patients (32.9%) took **medications at their latest follow-up visit**. Most common was single treatment with beta-blockers (n=6, 8.6%), or beta-blockers in combination with either angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), diuretics, or digitalis (n=6, 8.6%). Other therapies included single treatment with ARBs or ACE inhibitors, digitalis, diuretics, anti-arrhythmic drugs, and combined management therapies. There was no significant difference in pharmacologic treatment between the Senning and Mustard groups (n=10/42; 23.8%; vs. n=13/28; 46.4%) (p=0.076).

6.6.3 ECG and Rhythm at latest Follow-up

Main points of interest were **QRS duration** and **rhythm**. Analysis of QRS duration showed no significant difference between the Senning (117±24; 84-196 ms) and Mustard groups (111±20; 82-154 ms) ($p>0.05$).

Four types of predominant rhythms were differentiated at latest follow-up (for criteria see chapter 6.5.3): SR was found in 27/70 patients (38.6%). JR was diagnosed in two patients (2.9%, both Mustard), SND (46) was diagnosed in 14/70 patients (20%), and significantly more often in the Senning ($n=12/42$) vs. the Mustard group ($n=2/28$) ($p=0.032$). Twenty-five of 70 patients (35.7%) had a PM and presented in PM rhythm. Overall data about rhythms at latest follow-up delivered a significant difference between the Senning and Mustard groups ($p=0.012$). (Table 7)

		surgical technique			
		Senning	Mustard	Combined	
rhythm at F/U	SR ($p=0,078$)	n (%)	12 (28.6)	15 (53.6)	27 (38.6)
	JR	n (%)	0 (0)	2 (7.1)	2 (2.9)
	SND* ($p=0,032$)	n (%)	12 (28.6)	2 (7.1)	14 (20.0)
	pacemaker	n (%)	16 (38.1)	9 (32.1)	25 (35.7)

Table 7 Rhythms found in Holter ECGs at latest follow-up in the Senning vs. Mustard group [Data for 2/70 patients missing]. *Individual results for SND in the Senning vs. Mustard group reached statistical significance ($p=0.032$).

6.6.4 Pulmonary Hypertension

Pulmonary hypertension was defined as an elevation of systolic pulmonary arterial pressure of 30% or more of systemic arterial pressure, as documented in cardiac catheterization or echocardiography protocols. Pulmonary hypertension was present in 11/79 patients (13.9%, 4 Senning, 7 Mustard) **prior** to atrial switch operation. At the most recent follow-up appointment, 12/70 hospital survivors (17.1%) had a diagnosis of pulmonary hypertension. Three of these 12 patients were newly diagnosed post-operatively, in 9 patients pulmonary hypertension initially diagnosed prior to surgery persisted post-operatively. At the latest clinical

examination, patients in the Mustard group were significantly more affected (10/28 patients, 35.7%) than Senning patients (2/42; 4.8%) ($p=0.002$).

6.7 Analysis of Events

6.7.1 Event-free Survival

Event-free survival was defined as time from atrial switch operation to **first** occurring event of the following:

- a) cardiogenic syncope
- b) CPR
- c) late death (of hospital survivors)
- d) cardiac catheter intervention
- e) re-operation, including permanent pacemaker implantation, or heart-lung transplantation (HLTX)
- f) treated, symptomatic arrhythmia

These events occurred in 47/70 patients (67.1%), with some patients suffering each of the 6 events listed.

Primary focus was on **event-free survival**. Over the course of follow-up, 23/70 patients (32.9%) actually remained without any event. A significant difference for event-free survival was noted for patients in the Senning ($n=19/42$, 45.2%) vs. the Mustard ($n=4/28$, 14.3%) group ($p=0.009$). The odds for a patient to remain event-free during follow-up were almost 6 times as high ($RR=1.7$) in the Senning group as compared with the Mustard group ($RR=0.3$).

Time from atrial switch operation to **first** event was a mean of 7.4 ± 7.1 (0-23.6) years, and did not differ significantly between the Senning (6.9 ± 6.6 ; 0-19.2 years) and the Mustard group (7.9 ± 7.6 ; 0-23.6 years) ($p>0.05$). Mean age at first event was 8.5 ± 7.2 (0.3-25.3) with no significant difference for the Senning group as compared with the Mustard group ($p>0.05$).

Percentages for event-free survival at 15 years post-operatively were 41.4% overall, and 47.6% (20/42 patients) for the Senning vs. 32.1% (9/28 patients) for the Mustard group ($p>0.05$). See Figure 17 for actuarial survival.

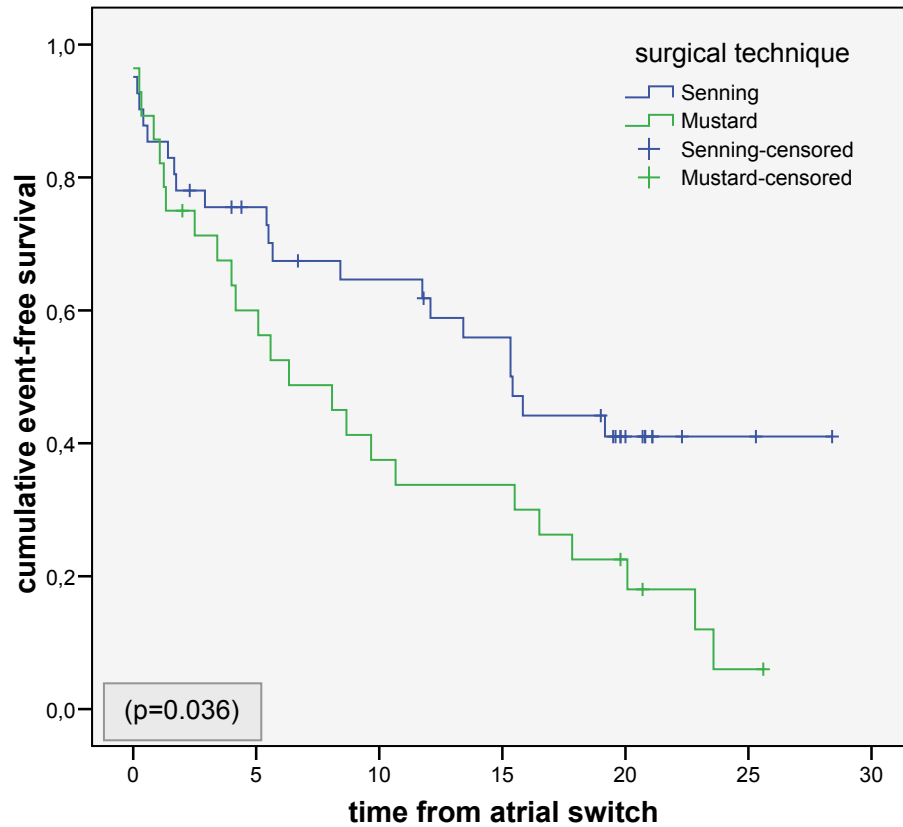


Figure 17 Actuarial event-free survival for patients in the Senning vs. the Mustard group over the course of follow-up.

Results for event-free survival were comparable for simple ($n=14/39$) vs. complex ($n=9/31$) TGA groups ($p>0.05$).

6.7.2 First occurring Event

In 47/70 patients experiencing events, **first occurring events** (out of the 6 events listed above) were re-operation (including pacemaker implantation, HLTX) in 24/70 patients (34.3%), treated arrhythmia in 12/70 patients (17.4%), late death in 6/70 patients (8.6%; five patients died suddenly, one had prior medical findings of pulmonary hypertension and systemic RV dysfunction; Table 3), and catheter intervention in 5/70 patients (7.1%).

6.7.3 Incidence of Events

Cardiogenic syncope affected 6/70 patients (8.6%), 3/42 in the Senning, and 3/28 in the Mustard group. Three patients died subsequently.

CPR was necessary in 6/70 patients (8.6%, 4 Senning, 2 Mustard). Incidences leading to CPR were severe arrhythmia in four patients, cardiogenic syncope in one patient, and PM malfunction in one patient. Three patients died subsequently.

In summary, 16 patients **died** (five Senning, 11 Mustard; $p=0.01$), 12 had **cardiac catheter interventions** (5 Senning, 7 Mustard), 42 needed **re-operations** (19 Senning, 23 Mustard), including 25 PM implantations and one HLTX, and 28 suffered from **symptomatic arrhythmias** (17 Senning, 11 Mustard). Comprehensive results for late death, post-operative cardiac catheter intervention, re-operation, and symptomatic arrhythmias are presented in chapter 6.5.

7 DISCUSSION

Despite a marked reduction in early and late mortality since the introduction of the atrial switch operation for transposition of the great arteries, Senning's and Mustard's procedures have been almost completely abandoned in favor of arterial switch surgery. None the less, most patients who underwent a Senning or Mustard procedure are now young adults, many of them experiencing serious problems directly linked to atrial switch operations, such as arrhythmias, systemic right ventricular dysfunction, and late (sudden) death. (Table 8) The Senning and Mustard cohorts in this study are largely comparable with those of other series in terms of surgical era, length of follow-up, and demographic data. (1,5,12,13,17,19,26,32,35,37,42,47,51-53,59,64,68)

Early Mortality

Nine operative and peri-operative deaths occurred in 79 patients, resulting in an early mortality of 11.4%. In comparable series, early mortality ranged from 3.1% to 16.5% (4,35,50,51). Our Senning group's early mortality rate of 8.7% compares well to other studies with ranges from 4.1% to 15.7%, whereas our Mustard group's early mortality rate of 15.2% falls into the higher ranges of other studies reporting 5% to 21%. (1,12,21,26,42,47,59)

As in most other series, our Mustard patients were operated on during an earlier time-period (1976 to 1984, peaking in 1981) than our Senning patients (grossly 1984 to 1995, peaking in 1986). Consequently, there was more surgical experience in the later surgical era, and Senning patients benefited from surgeons' experience with Mustard repairs. Lower operative mortality may also be attributed to improvements in operative (cardioplegia, hypothermia, heart-lung bypass) and peri-operative management. Accordingly, two thirds of our early deaths fall into the early surgical era (1974 to 1984), and one third into the latter (1985 to 1995).

Follow-up

Both our Senning and Mustard cohort were followed for about 17.5 years, which is comparable with many studies. (1,5,12,13,19,26,32,35,42,47,51-53) Main problems

we registered were late death and rhythm abnormalities on the one hand, and problems associated with the right ventricle as systemic pumping chamber on the other hand. (1,3,5,7,12,13,19,20,35,51-53)

Late Death

Over the course of our follow-up, 16 patients (22.9%) died. In five cases, sudden death occurred in previously well individuals, and general findings validate our assumption, that severe arrhythmia may have been the cause of death in all five patients. It should be noted that two patients died suddenly within a few months from surgery. Sudden death is likely a result of both increased incidence of and sensitivity to tachy-arrhythmias, and decreased atrial and ventricular function. (13,23,26) Accordingly, Sun et al (63) postulated a significantly higher odds ratio for sudden cardiac death in patients with loss of SR. Furthermore, arrhythmias were the most common diagnosis in 11 of our patients with medical findings preceding death. Four patients died of non-cardiac causes but had a history of arrhythmias and cardiac problems. (Table 3)

Late mortality rates have been reported in other series ranging from 5.1% to 25% (5,13,35,50,51,63), our results comparatively fall into the higher ranges. This can be attributed to our Mustard patients' high mortality (39.3%), which exceeds the range of 6.7% to 36% reported in literature (17,21,26,38,42,47,59). Late mortality rate in our Senning cohort was 11.9% and compared well with other studies reporting 2.9% to 16.1% (1,12,26,59). We observed a significantly different actuarial survival for our Senning vs. Mustard cohort at 15 and 20 years after atrial switch of 89.9% vs. 63.9% and 89.9% vs. 58.5% respectively. (Figure 10) We found one study contradicting our results: Khairy et al (35) found a better overall survival for Mustard patients, the majority of studies, however, are in favor of our findings. (5,17,50,51,59) As mentioned above, patients in the later surgical era have lower mortality rates, and this is especially true for our Senning cohort.

There was no difference in actuarial survival between our patients with simple vs. complex TGA, which is contradictory to most other studies with a better outcome in patients with simple TGA. (1,13,26,42,51)

Post-operative Procedures

One third of our patients required post-operative procedures such as cardiac catheter intervention or re-operation.

The majority of our patients (85.7%) had at least one cardiac catheterization during follow up. **Cardiac catheter interventions** were necessary in 12 patients (17.1%) and almost exclusively for venous pathway obstructions (n=11). Patients in the Senning cohort were significantly earlier affected than Mustard patients. This may be in consequence of more experience with catheter interventions in the later follow-up period. Other studies report a greater need for catheter interventions in patients after Mustard repair, mostly for baffle related obstructive problems (SVO and PVO) and rarely for baffle leaks or residual atrial shunts. (1,12,30,35,52) In our study, Senning patients were also less affected than Mustard patients, however, this finding did not reach statistical significance. Khairy et al (35) reported symptomatic and asymptomatic systemic venous obstructions in up to 35.6%.

In our entire cohort, **re-operation** was necessary in 22.9%, which is in keeping with other studies reporting 9.1% to 30% for re-operations. (5,42,51,59) SVO and PVO made up for the majority of operative re-interventions in our study (n=13), as reported in other series. (1,42,51,59,64) Obstructions may be a consequence of scarred tissue, as well as a narrower baffle in the Mustard repair. The use of viable material in the Senning procedure leaves a potential for (better) further atrial and baffle growth and therefore results in fewer complications in the long run. (4,14,34,67) Accordingly, relative risk for re-operation for our Mustard patients was ten times that of our Senning patients. Lastly, we noted a greater need for re-operation for PVO in our study as compared with literature. (1,5,12,30,42,51)

Arrhythmias

Creating an interatrial baffle to redirect systemic and pulmonary venous blood requires extended suture lines partly in close proximity to the sinus node and the sinus node artery respectively. This explains the development of post-operative SND with frequent progressive loss of stable SR after atrial switch. (39,43,45,66) Pathological correlates for abnormal function of the sinus node after atrial switch

surgery are fibrosis of the sinus node and paranodal areas, and compression or thrombosis of the nodal artery. (24) Many authors have determined SND and other supraventricular arrhythmias as main rhythmogenic complication after atrial switch surgery. (1,13,17,19,25,35,40,51-53,59) Supraventricular arrhythmias as risk factor for late death were postulated by Birnie et al (5) and Helbing et al (26).

In our study, 55/70 patients (78.6%) had rhythm abnormalities in at least one Holter ECG during follow-up, and this was true for both the Senning and Mustard cohorts with no significant difference between groups. Hutter et al (32) found ECG changes in 75% of patients. We found a transient or permanent loss of SR in 42 patients (60%), slightly more than Peters et al (52) with 47.5% at 18 years follow-up. Actuarial survival of SR at 25 years follow-up was significantly better in our Mustard (33.6%) than our Senning group (23.7%). Our Senning patients also had a shorter mean survival of SR. (Figure 11) This finding is supported by another study (5), however, other studies (26,35) reported more stable SR in Senning patients. A possible explanation for the ambiguity about continuity of SR may be dissimilar definitions for SR, as well as availability of data about, and frequency of Holter ECGs.

We observed symptomatic arrhythmias in 40% of our patients. This is in agreement with other large series reporting 40% (1,15,19,21,35,40,52,59) or more (13,17,24,30,53). We found patients after Senning or Mustard repair by and large equally affected, however, the onset of symptomatic arrhythmias was significantly earlier in the Senning than the Mustard cohort. (Figure 12)

A JR was diagnosed in 21.4% of our patients, with a relative risk for the Senning cohort twice that of the Mustard cohort. We also noted a trend towards earlier onset in the Senning group. Our results are supported by Gatzoulis et al (19) and Peters et al (52) who found JR in 21.6% respectively 22.5% of their patients. Sarkar et al (59) reported an even higher incidence at 10 years of follow-up (35% in Senning patients, and 29% in Mustard patients).

SND occurred in half of our patients, as previously reported by Haemmerli et al (24). Another study contradicts our results and reports SND in only 17.5% (52). We noted SND more often in our Senning than our Mustard cohort (59.9% vs. 35.7%), and again there was a trend towards earlier onset in the Senning group. Contradictorily, better outcomes for Senning than Mustard patients have been previously reported by Dos et al (13) and Khairy et al (35). Other studies observed SND in the Mustard cohort ranging from 33% to 51% (15,30,40). Twenty-three of our patients with SND (65.7%) needed treatment with anti-arrhythmic drugs, PM implantation, or both.

A review of literature did not convey comprehensive results for SVTs after atrial switch. We found SVTs in 21.4% of our patients (23.8% in the Senning, and 17.9% in the Mustard group), therefore less frequently than in some other studies (17,53), with the exception of one study by Khairy et al (35) who observed fewer SVTs in Senning patients. Onset of SVTs was earlier in our Senning than in our Mustard patients, however, this difference did not reach statistical significance.

Atrial fibrillation and flutter after atrial switch have been reported with an incidence of 8.2% to 22.5% (51,52). We corroborate these results with 17.1% of all patients (Senning cohort 14.3%, Mustard cohort 21.4%). Sarkar et al (59) reported atrial fibrillation or flutter in 6.6% of Senning patients, and results for Mustard patients are generally rather scattered and range from 2.3% (53) to 19.6% (19,21,59). Onset of atrial fibrillation in our study was again earlier in the Senning than in the Mustard cohort. Vetter et al (65) investigated inducible atrial flutter after Mustard repair and postulated a predisposition of TGA patients with atrial flutter and abnormalities of atrial refractoriness to sudden death. Our study did not confirm these findings.

Atrioventricular block type II or III was rather common and occurred in 12.9% of the entire cohort, subsequently necessitating permanent PM implantation in the majority of affected patients. Interestingly, our search of literature delivered no results for AV block after atrial switch.

PVCs and VTs occurred equally in both our study groups (21.4%). We found only one other study (40) commenting on PVCs in 4.2% of Mustard patients at two to 7 years of follow-up.

Ambiguous results for all arrhythmias mentioned above may be a product of a variety of definitions for arrhythmias in different series, availability and frequency of Holter ECGs, as well as different follow-up periods, and variations in the original surgical techniques. In our study, patients after Senning repair were more (JR, SND, SVT) and always earlier affected by rhythm disturbances. (Table 8)

Of our 55 patients diagnosed with ECG changes, only 30 (42.9%) required therapy. One fifth of our patients (21.4%) received anti-arrhythmic drugs in solitude. Other studies reported anti-arrhythmic drugs in 2.9% to 11% of patients (30,47,51,59) with the exception of Puley et al (53) who observed a need for pharmacologic treatment in 39.5%. We purport that our high percentage of pharmacological anti-arrhythmic treatment is a direct result of more frequent diagnoses of arrhythmias in our cohort, especially SND.

Permanent PM implantation after atrial switch has been investigated in several studies, and overall results are ambiguous due to surgical techniques and follow-up periods. In many studies, implantation rates range from 5.5% to 22.5% (13,32,51,52,64). Incidence of PM implantation has been reported as low as 1.5% in the Senning group (59), and from 3.5% to 22% (17,19,21,42,53,59) in the Mustard group. Our outcome clearly exceeds all these figures: overall, permanent PMs were mandatory in 35.7% (Senning group 38.1%, Mustard group 32.1%). Indication for permanent PM implantation was (treated) symptomatic arrhythmia in 18/25 patients and AV block in 7 patients. Of note, in accordance with Puley et al (53) who reported two thirds of PMs implanted after age 18, 80% of our patients needing PMs were older than 18 years. We are prompted to attribute our higher rate of permanent PM implantations to the age of our patients and the individual length of follow-up, however, little data could be found about age of patients at PM implantation in other series. Intention behind permanent PM implantation is

the maintenance of synchronized atrio-ventricular excitation in order to reduce the incidence of systemic RV dysfunction and TR.

Finally, no data could be acquired from other studies concerning catheter ablative therapy and cardioversion.

The RV as Systemic Ventricle

RV volume analysis by two-dimensional echocardiography is a much more controversial technique than LV volume analysis. As Derrick et al (11) postulate about the assessment of the RV: There is no easy model for comparison, and no clear criteria of abnormality. Quantitative assessment of right ventricular function is made difficult by the complex geometry of the RV, and therefore limited. (11,28,62) To date, MRI is the most valuable imaging modality in patients with systemic RVs. (28,41,56) However, mostly due to availability, MRIs are not routine in the follow-up of atrial switch patients. We therefore resorted to two-dimensional echocardiography for the assessment of the RV and found systemic RV dysfunction in 74.3% of the entire cohort. (Table 4) When looking at moderate and severe systemic RV dysfunction, our results are in agreement with many studies reporting on the problems associated with the RV (1,4,6,8,9,12,16,26,31,51,53,59,64): The RV is a one coronary ventricle, and in muscular architecture, structure and thickness not anatomically designed to work as systemic pumping chamber.

As a result of the RV functioning as systemic ventricle and supraventricular arrhythmias, TR is a common observation after atrial switch. Hemodynamically relevant TR may on the other hand perpetuate supraventricular arrhythmias. (5,12,23,26,28,44,51,52,67) In our patients, supraventricular arrhythmias tripled the risk of systemic RV dysfunction, symptomatic arrhythmias increased the risk by a factor 2.5. Accordingly, in our patients with TR, supraventricular arrhythmias occurred significantly more often than in patients with competent tricuspid valves.

Lubiszewska et al (44) found moderate or severe perfusion abnormalities in single-photon emission computed tomography (SPECT) in 33% of patients after atrial switch surgery. These findings worsened under exercise and occurred mostly in

the older patients in the study. Giardini et al (22) found that patients with systemic RVs have areas of abnormal myocardium that can be visualized by gadolinium-enhanced MRI. These areas can be associated with RV dysfunction, arrhythmia, poor exercise tolerance, and clinical deterioration over time, and therefore may be indicative of fibrosis.

Latest Follow-up

At the last clinical examination, 80% of our patients were assigned to NYHA functional class I. Patients after Senning repair were more, however, not significantly more often in NYHA class I (90.5%) as compared with patients in the Mustard cohort (62.3%). NYHA class I results in comparable series ranged from 47.4% to 93% (13,42,50,51), and were generally better for Senning cohorts with 60.7% to 91% (1,26,59) than Mustard cohorts with 63.3% to 89.4% (19,21,26,30). Only one study by Khairy et al (35) delivered contradictory results and reported better NYHA functional class I results for Mustard patients. Overall, 81.4% of our patients met criteria for Ability index class 1, which is supported by Moons et al, (50,51) who observed 85% respectively 86.9% of patients in Ability index class 1. We found Mustard patients significantly more often assigned to Ability index class 2 or 3 than Senning patients.

We observed SR in 38.6% of the entire cohort at the latest clinical examination. This compares well to other studies reporting SR in 25% to 41.2% (5,26,32). In two studies, SR was detected in up to 80% (42,59) in the Senning or Mustard cohort. Our findings in the Senning cohort (SR in 28.6%) are inferior to comparative studies (1,42), whereas 53.6% of our Mustard patients presented in SR at latest follow-up, as reported by Gewillig et al (21) and Puley et al (53).

One third of our patients took medications at their latest follow-up. Other studies reported 16% to 24,3% of patients needing pharmacologic treatment (13,21,58). Permanent PMs were noted in 35.7% of patients at the latest clinical examination. This is once again more than other studies observed, e.g. Helbing et al (26) reported PMs in 7.4% of patients at latest outpatient examination.

In summary, more than three fourths of our patients were in subjectively good condition at their latest follow-up examination, no difference was observed between the study cohorts. Social integration was satisfactory despite a high number of arrhythmias and impaired cardiac parameters. Of note, reduced exercise ability has been reported even in symptom-free children. (6,29,61) Reybrouck et al (57) concluded that serial exercise testing appears useful, because a decreasing exercise tolerance correlated with development of hemodynamic sequels.

Event/Findings	Higher incidence	Comment
Post-operative interventions		
Cardiac catheterization	Mustard	Trend: 11.9% vs. 25%* (p=0.12)
Re-operation	Mustard	7.1% vs. 46.4%* (p=0.002)
Rhythm disturbances		
Loss of sinus rhythm	Senning	Trend: 66.7% vs. 50%* ; Detection earlier in the Senning group (p=0.005)
Symptomatic arrhythmia	Equivalent	significantly earlier in the Senning group (p=0.013)
Junctional rhythm	Senning	Trend towards earlier onset in the Senning cohort
Sinus node dysfunction	Senning	Trend: 59.5% vs. 35.7%*, earlier in the Senning cohort
supraventricular tachycardias	Senning	Trend: 23.8% vs. 17.9%*, earlier in the Senning cohort
Permanent pacemaker	Senning	Trend: 38.1% vs. 32.1%*
Systemic ventricular dysfunction	Mustard	Trend: 61.9% vs. 75%*
NYHA functional class I	Senning	Trend: 90.5% vs. 62.3%* (p=0.052)
Event-free survival	Senning	45.2% vs. 14.3%* (p=0.009)

Table 8 Summary of results for post-operative procedures, rhythm disturbances, systemic ventricular dysfunction, NYHA functional class I, pulmonary hypertension, and event-free survival over the course of follow-up. [*Senning vs. Mustard]

Analysis of events

At a mean follow-up of 17.5 (0.1-28.4) years, 32.9% of patients actually were event-free. (Figure 17) Despite a higher incidence of arrhythmias in our Senning cohort, event-free survival was significantly better in our Senning (45.2%) than our Mustard patients (14.3%). The odds for a patient to remain event-free during follow-up were almost 6 times as high for Senning as compared with Mustard patients. Our results are supported by Birnie et al (5) who reported event-free survival at 15 years follow-up in 39.6% of patients with better results after Senning repair. Event occurrence per patient experience was 10.7±8.6 years, and slightly later in our Senning than our Mustard group. Re-operation, including PM

implantation, ranked first in event incidence, followed by symptomatic arrhythmia and late death, whereas cardiac syncope, cardioversion, and cardiac catheter interventions were rare. Re-operations were common in our study mostly because of a high incidence of PM implantations. With the exception of cardioversion and symptomatic arrhythmia, all events occurred more often in patients after Mustard repair. This may be another effect of surgical era and supports our assumption of better and more comprehensive medical care in the later surgical era.

Conclusion

Most patients after atrial switch surgery are in good general condition and report good quality of life. None the less, regular annual or bi-annual controls of adult patients are imperative to prevent and treat potential long-term complications after atrial switch.

Arrhythmias are a frequent cause of morbidity and mortality in patients of all ages after atrial switch operations. Therefore, scheduled clinical examinations should include thorough evaluation of rhythm in all patients, especially by means of 24h Holter-ECGs. Sudden cardiac death may be prevented by findings in Holter ECGs even in asymptomatic patients. We show clear evidence for complications relating to arrhythmias, especially in patients after age 18.

Obstruction of the pulmonary and systemic venous pathways occurs in both Senning and Mustard patients, but more frequently after Mustard repair. Regular echocardiographic examinations should be focused on venous pathway obstructions, regardless of patients' presenting status. Additionally, two-dimensional echocardiography, in spite of its limitations, may be useful for the assessment of the RV as systemic pumping chamber. Maintenance of synchronized atrio-ventricular excitation through protection of SR or atrio-ventricular pacing may prevent deterioration of systemic RV function. Depending on availability, MRI should be employed as standard imaging modality for the evaluation of the RV.

Cardiac events including sudden death occur even in previously asymptomatic patients. Besides methodical ECG monitoring and evaluation, regular cardiopulmonary exercise testing may help detect cardiac risks in all TGA patients.

Conclusively, comprehensive outpatient examinations remain crucial even or especially after patients enter adulthood.

Limitations

We performed a retrospective query of our data base, therefore data was not always fully available for analyses and assessment. Even though our Senning and Mustard cohorts compare well demographically, they were operated on during different surgical eras: Mustard patients underwent surgery in the first half of the operating period, Senning patients mostly in the second half.

We have to take a learning curve concerning surgical technique, peri-operative management, and post-operative patient care into account. This, as well as medical respectively technical progress, serve as benefit for patients (especially) in the later surgical era, as well as during later follow-up.

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Figure reference

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9 ATTACHMENTS

9.1 Data Collection Sheet

Name:		DOB: / / 19.....	
Sex:	<input type="checkbox"/> M <input type="checkbox"/> F	TGA:	<input type="checkbox"/> simple <input type="checkbox"/> complex
Assoc. defects: (simple = 0/PFO)	<input type="checkbox"/> none <input type="checkbox"/> PFO or ASD <input type="checkbox"/> PDA <input type="checkbox"/> VSD <input type="checkbox"/> CoA <input type="checkbox"/> PS <input type="checkbox"/> syst. coll. <input type="checkbox"/> other		
Palliation preOP: (cath pre-OP)	<input type="checkbox"/> none <input type="checkbox"/> BAS <input type="checkbox"/> atrial septectomy <input type="checkbox"/> pulm. banding <input type="checkbox"/> Blalock-Taussig-Shunt <input type="checkbox"/> subclav. flap plastic <input type="checkbox"/> PDA-lig. <input type="checkbox"/> other		
SaO ₂ preOP (AO):	%	LV pressure preOP:	mmHg
		PA pressure:	mmHg
Rhythm preOP:	<input type="checkbox"/> SR <input type="checkbox"/> JR <input type="checkbox"/> SND <input type="checkbox"/> other		
Surg. technique: (Senning, Mustard)	Age at surgery: mo		
	Weight at surgery: kg		
Add. repair:	<input type="checkbox"/> none <input type="checkbox"/> VSD <input type="checkbox"/> PDA ligature <input type="checkbox"/> other		
PostOP complications:	<input type="checkbox"/> none <input type="checkbox"/> arrhythmia <input type="checkbox"/> bleeding <input type="checkbox"/> cardiac arrest <input type="checkbox"/> obstruction <input type="checkbox"/> infection <input type="checkbox"/> low cardiac output <input type="checkbox"/> other		
Rhythm postOP (<4w):	<input type="checkbox"/> SR <input type="checkbox"/> JR <input type="checkbox"/> Afib/flutt <input type="checkbox"/> AV Block <input type="checkbox"/> SVT <input type="checkbox"/> VT <input type="checkbox"/> PAC <input type="checkbox"/> PVC <input type="checkbox"/> other		
Therapy postOP:	<input type="checkbox"/> none <input type="checkbox"/> pacemaker <input type="checkbox"/> CPR <input type="checkbox"/> re-operation <input type="checkbox"/> anti-arrhythmics		
Post-OP catheter:	mo pOP (/ /) Intervention? <input type="checkbox"/> yes <input type="checkbox"/> no		
	Pathology: <input type="checkbox"/> small restVSD <input type="checkbox"/> small restASD <input type="checkbox"/> pulm. HT <input type="checkbox"/> baffle SV obstr. <input type="checkbox"/> baffle PV obstr.		
1. Cath intervention:	<input type="checkbox"/> yes <input type="checkbox"/> no / /	_____ mo pOP	
2. Cath intervention:	<input type="checkbox"/> yes <input type="checkbox"/> no / /	_____ mo pOP	
3. Cath intervention:	<input type="checkbox"/> yes <input type="checkbox"/> no / /	_____ mo pOP	
1. Re-operation:	<input type="checkbox"/> yes <input type="checkbox"/> no / /	_____ mo pOP	
2. Re-operation:	<input type="checkbox"/> yes <input type="checkbox"/> no / /	_____ mo pOP	
3. Re-operation:	<input type="checkbox"/> yes <input type="checkbox"/> no / /	_____ mo pOP	
Re-intervention (surgery):	<input type="checkbox"/> none <input type="checkbox"/> surgery VSD <input type="checkbox"/> surgery baffle leak (rest ASD) <input type="checkbox"/> surgery SVO <input type="checkbox"/> surgery PVO <input type="checkbox"/> other _____		
Catheterization prior to re-OP or cath intervention: (/ /)	VSD/baffle leak – shunt: %		
	LVOTO – gradient: mmHg (= LV-PA gradient)		
	SV/PV obstr. – grad.: mmHg		
	other:		
① Intervention - Catheterization:	/ /	mo post-OP	
Baffle leak:	% shunt	→ Umbrella	
SV/PV obstruction:	mmHg gradient	→ Dilation/Dil&Stent	
other:		→	

Last Follow-up: / /		Age at last F/U: years	
Length of F/U: years (total)		BNP: (date: / /)	
Type of Meds: start date: / /	<input type="checkbox"/> none <input type="checkbox"/> diuretics <input type="checkbox"/> A + B	<input type="checkbox"/> ACEI/ARB/equiv. <input type="checkbox"/> anti-arrhythmics <input type="checkbox"/> A + D	<input type="checkbox"/> beta-B <input type="checkbox"/> digitalis <input type="checkbox"/> other _____ <input type="checkbox"/> A + Diu <input type="checkbox"/> B + Diu
NYHA class:	Ability index:	Social integration:	
Occupation:		QRS at F/U: ms	
Rhythm at F/U:	<input type="checkbox"/> SR <input type="checkbox"/> SVT	<input type="checkbox"/> JR <input type="checkbox"/> VT	<input type="checkbox"/> Afib/flutt <input type="checkbox"/> PVC <input type="checkbox"/> AV Block <input type="checkbox"/> other
Ergometry?	<input type="checkbox"/> yes <input type="checkbox"/> no	Ergo-Spirometry?	<input type="checkbox"/> yes <input type="checkbox"/> no

Latest 24h Holter: / /		Rate trend: bpm (= mean)	
total # of Holters: _____		Min: bpm	Max: bpm
Type of rhythm:	<input type="checkbox"/> SR <input type="checkbox"/> SVT	<input type="checkbox"/> JR <input type="checkbox"/> VT	<input type="checkbox"/> Afib/flutt <input type="checkbox"/> PVC <input type="checkbox"/> AV Block <input type="checkbox"/> other
Changes discovered:	<input type="checkbox"/> loss of SR	_____ mo pOP (/ /)	Th _x : _____
	<input type="checkbox"/> JR	_____ mo pOP (/ /)	Th _x : _____
	<input type="checkbox"/> Afib/flutt	_____ mo pOP (/ /)	Th _x : _____
Therapy – what, when?	<input type="checkbox"/> SND (+PAC)	_____ mo pOP (/ /)	Th _x : _____
	<input type="checkbox"/> AV-Block	_____ mo pOP (/ /)	Th _x : _____
	<input type="checkbox"/> SVT	_____ mo pOP (/ /)	Th _x : _____
(source: ECG or Holter-ECG)	<input type="checkbox"/> PVC + VT	_____ mo pOP (/ /)	Th _x : _____
	<input type="checkbox"/> ablation	_____ mo pOP (/ /)	Th _x : _____
	<input type="checkbox"/> pacemaker	_____ mo pOP (/ /)	Th _x : _____
	<input type="checkbox"/> cardioversion	_____ mo pOP (/ /)	Th _x : _____
	<input type="checkbox"/> anti-arrhythm.	_____ mo pOP (/ /)	Th _x : _____

Latest TTE: / /		RVEF TTE: %	
RV function:	<input type="checkbox"/> normal <input type="checkbox"/> mildly	<input type="checkbox"/> moderately	<input type="checkbox"/> severely impaired
pulm. hypertension:	<input type="checkbox"/> yes <input type="checkbox"/> no		
AR:	<input type="checkbox"/> none <input type="checkbox"/> mild	<input type="checkbox"/> moderate	<input type="checkbox"/> severe _____%
PR:	<input type="checkbox"/> none <input type="checkbox"/> mild	<input type="checkbox"/> moderate	<input type="checkbox"/> severe _____%
PS/LVOTO:	<input type="checkbox"/> none <input type="checkbox"/> mild	<input type="checkbox"/> moderate	<input type="checkbox"/> severe _____mmHg
TR:	<input type="checkbox"/> none <input type="checkbox"/> mild	<input type="checkbox"/> moderate	<input type="checkbox"/> severe _____mmHg
MR:	<input type="checkbox"/> none <input type="checkbox"/> mild	<input type="checkbox"/> moderate	<input type="checkbox"/> severe _____%
affle leak:	<input type="checkbox"/> none <input type="checkbox"/> mild	<input type="checkbox"/> moderate	<input type="checkbox"/> severe _____%

End points:	<input type="checkbox"/> event free		
	<input type="checkbox"/> syncope	_____ mo post-OP	(/ /)
	<input type="checkbox"/> CPR	_____ mo post-OP	(/ /)
	<input type="checkbox"/> sudden death	_____ mo post-OP	(/ /)
	<input type="checkbox"/> arrhythmia (treated)	_____ mo post-OP	(/ /)
	<input type="checkbox"/> re-operation	_____ mo post-OP	(/ /)
	<input type="checkbox"/> catheter intervention	_____ mo post-OP	(/ /)
	<input type="checkbox"/> systemic RV dysfct ⁿ .	_____ mo post-OP	(/ /)

9.2 Measures of Functional Status

New York Heart Association class and Ability index class were assigned according to a data sheet available at our outpatient clinic:

<u>Patient:</u>				

<u>ABILITY-INDEX</u>				Untersuchungsdatum:
Klasse: (Somerville, Warnes)				
1	Normales Leben Schule ohne Einschränkungen möglich bzw. volle Arbeitsfähigkeit Schwangerschaft problemlos möglich			
2	Arbeit möglich, aber mit Einschränkungen intermittierend Symptome tägliches Leben beeinträchtigt Schwangerschaft möglich			
3	Arbeitsunfähigkeit alle Aktivitäten beeinträchtigt Risikoschwangerschaft			
4	stark beeinträchtigt Abhängigkeit von Pflegepersonen fast völlig ans Haus gebunden			
<u>Stadien der Herzinsuffizienz</u>				Untersuchungsdatum:
<u>Klassifikation der New York Heart Association (NYHA)</u>				
Klasse:				
NYHA I	Patienten mit Herzerkrankung, aber keiner Limitation der physischen Aktivität. Normale physische Aktivität erzeugt keine Dyspnoe, keine Angina, Müdigkeit oder Palpitationen.			
NYHA II	Patienten mit geringer Limitation der physischen Aktivität. Sie sind beschwerdefrei in Ruhe und bei geringer Belastung. Sie werden symptomatisch nur bei vermehrter Belastung.			
NYHA III	Patienten mit deutlicher Einschränkung der physischen Aktivität. Sie sind in Ruhe beschwerdefrei, werden aber selbst bei geringer Aktivität symptomatisch.			
NYHA IV	Patienten, die keine physische Aktivität ohne Beschwerden ausführen können. Symptome der kardialen Insuffizienz oder Angina pectoris können selbst in Ruhe auftreten und verstärken sich bei Belastung.			

10 LEBENS LAUF



Persönliche Angaben

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Ausbildung

10/2002 – 07/2008 Medizinstudium, Medizinische Universität Graz/Österreich
 08/2001 – 05/2002 Auslandsstudium Psychologie, University of North Carolina at Chapel Hill, NC/USA
 10/1999 – 07/2002 Psychologie- und Soziologiestudium, Paris Lodron Universität Salzburg/Österreich
 08/1998 – 05/1999 American Sign Language und Alaska Winter Survival, University of Anchorage/Alaska
 09/1993 – 06/1998 Bundeshandelsakademie I Salzburg/Österreich
 Euroklasse mit Unterricht in englischer Sprache, Vertiefung in Marketing und Biologie; Matura mit „ausgezeichnetem Erfolg“

Praxis

10/2007 – 07/2008 Praktikumsjahr am Universitätsklinikum Graz im Rahmen des Medizinstudiums

- 5 Wochen pädiatrische Kardiologie
- 5 Wochen Allgemeinmedizin (Gasen, Steiermark)
- 10 Wochen Kinderchirurgie mit Notfallmedizin
- 5 Wochen Kardiologie
- 5 Wochen Neurologie Ambulanz

- 10/2007 – 05/2008 Verfassen einer Diplomarbeit in englischer Sprache zum Thema „Long-term outcome after Senning or Mustard operation in patients with d-Transposition of the great arteries“
- 03/2006 – 07/2008 Tutorin für Ethik an der Medizinischen Universität Graz
- Leiten eines Seminars in Ethik für eine Gruppe von ca. 25 Studenten, Erläutern der Thematik, Diskussionsleitung und Mediation
 - Schulung der Studenten zu kritischem Denken in Fragen der Ethik in der Medizin
 - Korrektur und Benotung von Hausarbeiten
- 07/2007 – 08/2007 Famulatur in pädiatrischer Kardiologie mit Neonatologie Intensivstation, Pediatric Cardiology of Alaska, Anchorage/AK; Allen Brauner, DO
- 08/2006 – 09/2006 Famulatur in chirurgischer Gynäkologie, Anchorage Women's Clinic, Anchorage/AK; Tina Tomsen, MD
Famulatur in pädiatrischer Kardiologie, Pediatric Cardiology of Alaska, Anchorage/AK; Allen Brauner, DO
- 07/2006 – 09/2006 Vermessung des subkutanen Fettgewebes mittels Lipometer® für das Anchorage Fire Department, Anchorage/AK
- Vermessung des Körperfettgewebes nach einem patentierten Verfahren (Medizinische Universität Graz)
 - Erläuterung der Testergebnisse, Kurzschulung über Ernährung, Metabolismus und Erkrankungsrisiko für Diabetes mellitus II, koronare Herzkrankheit und metabolisches Syndrom
 - Statistische Auswertung der Testergebnisse für das gesamte Department und einzelne Stationen
- 02/2006 Famulatur allgemeine Chirurgie, Krankenhaus Hallein
- 12/2005 Famulatur Radiologie, Krankenhaus Hallein
- 11/2005 Interviewer am Kongress der European Public Health Association (EUPHA), Graz
- Strukturiertes Interview in Englisch über das Public Health Wesen mit Kongressteilnehmern aus ca. 30 Staaten
- 02/2005 Famulatur Gynäkologie, Krankenhaus Hallein
- 07/2003 – 08/2003 Famulatur Anästhesie, Krankenhaus Hallein
- 01/2002 – 05/2002 Praktikum im Seniorenheim in Chapel Hill/NC

12/2001 – 05/2002	Research Assistant School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill/NC <ul style="list-style-type: none"> • Erheben von Daten über Schule, Freizeit, Alkohol und sexuelle Aktivität bei Schülern im Alter von 10 bis 18 Jahren
03/1997 – 07/2001	aktives Mitglied Rotes Kreuz Hallein

Ferialpraktika und Nebenjobs

09/1999 – 07/2001	Nachhilfelehrerin Studienkreis Hallein <ul style="list-style-type: none"> • Schulbegleitender Einzel- und Gruppenunterricht in Englisch, Mathematik und Französisch, Intensivkurse • Maturavorbereitung für Englisch und Französisch
08/1998 – 09/1999	Au-pair und Studienaufenthalt in Anchorage/Alaska
07/1998 – 08/1998	Freizeitkoordinatorin für das English Institute in Cambridge/GB
Sommer 1996/97	Au-pair in Aylesbury/GB (96) und Rhode St. Gènesse/Belgien (97)
07/1995 – 09/1995	Servicemitarbeiterin bei Restaurant Wienerwald Golling

Zusatzqualifikationen

Sprachen:	ausgezeichnete Englischkenntnisse, inkl. medizinisches Englisch Französisch korrespondenzfähig
EDV-Kenntnisse:	Microsoft Word, PowerPoint, Outlook, Internet Explorer Mac OS Leopard SPSS 15.0, student version Medocs (Kages, Univ.-Klinikum Graz), PACS Radiologie Viewer
Sonstige Kenntnisse:	Führerschein Klassen A und B sehr gute Präsentationsfertigkeiten
Seminare:	Cambridge First Certificate, Grade A Certificate of Spoken English for Industry and Commerce (SEFIC), Pass with Distinction Certificat de Français du Secrétariat, mit Auszeichnung bestanden APIEL – Advanced Placement in English Language, Pass with Distinction Spezielles Studienmodul Notfallmedizin, Medizinische Universität Graz

Persönliche Qualifikationen

Ich arbeite gerne mit Menschen unterschiedlichen Alters und bin es gewöhnt, genau und gewissenhaft zu arbeiten. Ich bin sehr wissbegierig und immer offen für Neues. Ich arbeite gerne selbständig oder auch als Teil einer Gruppe, wobei ich besonderen Wert auf Effizienz und die Zufriedenheit aller Beteiligten lege. Ich setze gerne meine analytischen und kreativen Fähigkeiten ein, insbesondere um auf die individuellen Bedürfnisse anderer Menschen einzugehen.

Spezielle Interessen

Reisen, Sprachen, Sport, Musik

Zukunftsperspektiven

Ich strebe danach, mein theoretisches und praktisches Wissen in einem klinischen Umfeld einzusetzen und auszubauen. Ich begrüße konkrete Möglichkeiten um mein persönliches Ziel einer fachärztlichen Ausbildung in Kinder- und Jugendheilkunde zu erreichen, und beteilige mich mit vollem Einsatz an diesem Vorhaben.

Graz, Mai 2008