FACTORS THAT LIMIT EXERCISE PERFORMANCE
AND THE USE OF ANGIOTENSIN CONVERTING
ENZYME INHIBITORS IN ADULT SURVIVORS OF THE
MUSTARD PROCEDURE

Sloane Hechter

A thesis submitted in conformity with the requirements for the degree of Masters of
Science in the field of Cardiovascular Science,
Graduate Department of Institute of Medical Science,
University of Toronto

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0-612-58704-5
FACTORS THAT LIMIT EXERCISE PERFORMANCE AND THE USE OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS IN ADULT SURVIVORS OF THE MUSTARD PROCEDURE

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Masters of Science
Graduate Department of Institute of Medical Science
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February 2001

Abstract:

Objectives: The aim of this study is to describe resting and exercise hemodynamics in a large adult population of patients with the Mustard procedure and to determine whether angiotensin converting enzyme (ACE) inhibitors improve exercise power. Methods: Eighty-four adults with the Mustard procedure who have had cardiopulmonary exercise tests were identified. Magnetic resonance imaging and echocardiographic studies were obtained in order to assess right ventricular size, function and hemodynamics. Results: Patients achieved lower maximum oxygen uptake (VO2peak), maximum heart rate, forced vital capacity, forced expiratory volume in 1 second and oxygen saturations at maximal exercise compared to a healthy population. Within the ACE group, there were trends indicating an improvement in VO2peak and a reduction in maximum systolic blood pressure pre and post ACE initiation. Conclusion: Patients after the Mustard procedure have subnormal exercise capacities. Within the ACE group, some patients improved their VO2peak and reduced their maximum blood pressure.
Acknowledgements

I am most thankful to my supervisors, Dr. Gary Webb and Dr. Peter Liu, and my advisors, Dr. Per Morten Fredriksen, Dr. Sam Siu, Dr. Lee Benson and Dr. Jack Goodman for their invaluable support and leadership. I am also indebted to Dr. Naeem Merchant for teaching me everything I know about cardiac imaging and for his patience while I flooded his department with MRI requisitions. I also am particularly grateful to Drs. Gary Webb and Peter Liu for their expert advice.

I wish to express my sincere gratitude and appreciation to:

-The University of Toronto Congenital Cardiac Centre for Adults for all their help in booking patients, retrieving patient charts and organizing tests.

-Dr. Gruschen Veldtman for his encouragement, advice and friendship.

-Dr. Michael Connelly for reviewing my thesis.

-Eleanor, Donna and Judy for keeping me organized and in-line.

-Mickey who introduced me to the cardiac chart room at the Hospital for Sick Children and then to the bowels of the hospital.

-Mohammed Ali Warsi, MSc for blazing a clear trail for me to follow as I worked toward my MSc.

-Gideon De Marche for introducing me to my first Mustard baby and for suffering through the formaldehyde as we examined a post Mustard heart.
This thesis is dedicated to Dr. Per Morten Fredriksen who is an extraordinary role model for me; acting as a scientist, mentor and a true friend.
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<tr>
<td>MRI</td>
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<td>VO\textsubscript{2peak}</td>
<td>Maximum Oxygen Uptake</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced Vital Capacity</td>
</tr>
<tr>
<td>FEV\textsubscript{1}</td>
<td>Forced Expiratory Volume in 1 Second</td>
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<td>TGA</td>
<td>Transposition of the Great Arteries</td>
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<td>EDV</td>
<td>End Diastolic Volume</td>
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<td>ACE</td>
<td>Angiotensin Converting Enzyme</td>
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<td>PDA</td>
<td>Patent Ductus Arteriosus</td>
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<td>VSD</td>
<td>Ventricular Septal Defect</td>
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<tr>
<td>AV</td>
<td>Atrioventricular</td>
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<tr>
<td>RVEF</td>
<td>Right Ventricular Ejection Fraction</td>
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<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
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<td>LVOTO</td>
<td>Left Ventricular Outflow Tract Obstruction</td>
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<td>CHF</td>
<td>Congestive Heart Failure</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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Chapter 1

General Introduction and Purpose of the Study
Transposition of the Great Arteries (TGA) is a congenital cardiovascular anomaly in which the aorta arises entirely or in large part from the right ventricle, and the pulmonary artery arises entirely or in large part from the left ventricle (1). TGA accounts for 7-8% of all congenital heart disease (1). Prior to the advent of effective treatments like the Mustard procedure, at least 16% of deaths due to congenital heart disease in childhood were due to TGA (1). The Mustard procedure results in a systemic right ventricle subjected to abnormal pressure loading. Right ventricular myocardial fiber distribution differs from that of the left ventricle and may render the right ventricle less able to function as a systemic ventricle (2). The increased end diastolic volume (EDV) (3,4) and systemic pressure demands that the right ventricle be subjected to higher wall tensions throughout contraction. As a result, the right ventricle will have a higher oxygen consumption than the systemic left ventricle in almost all patients with the Mustard procedure (5,6).

The greater right intraventricular pressures promote an increase in the size of myocytes (5,6) and results in ventricular hypertrophy. This may lead to diastolic dysfunction, and pave the way for systolic dysfunction. The ability of the right ventricle to sustain systolic function may be crucial to the patient's functional status. Most patients are asymptomatic at rest, but have reduced exercise tolerance as evidenced by a lower VO\textsubscript{2peak}. While most patients with the Mustard procedure are now reaching adulthood, there have been few reports on resting and exercise performance in this emerging population. Ensing's group reported that during maximal exercise, marked abnormalities occur in nearly all indexes of cardiovascular function (7). Sagin-Saylam's group found similar results (8). Exercise tolerance is an important contributor to a patient's quality of
life. Depending on the range of limitation in functional status, a patient could be exhausted while running to a bus or may tire after a brisk walk in the park.

There are some studies in the literature which report oxygen desaturation with exercise in the Mustard cohort. However, there is no evidence in these reports to elucidate the cause of desaturation. Gilljam's group describes exercise arterial oxygenation in patients (mean age 15 years) and suggests that ventilation-perfusion inequalities, extrapulmonary shunts and diffusion limitations may be responsible (9). Matthews et al described exercise arterial desaturation in patients (mean age 13 years) and assumed small interatrial baffle leaks were responsible which became more significant with exercise (10). Bowyer et al report desaturation with exercise in patients 10 years of age and attribute their result to baffle leakage (11).

While these studies describe oxygen desaturation with exercise, the cause of such desaturation has not been shown. Our study aims to describe exercise limitations and oxygen desaturation in adult Mustard patients and seeks to answer why some of these patients desaturate on exertion.

This study also investigates the use of ACE inhibitors prescribed to ameliorate exertional limitations, protect the right ventricle, and to improve the quality of life for these patients. ACE inhibitors have demonstrated beneficial hemodynamic responses on exercise and improved resting cardiac function in patients with CHF and morphological systemic left ventricles (3,12,13). In addition, ACE inhibitors have been shown to reduce changes in left ventricular volume, shape, and wall structure (ventricular remodeling) in patients with systemic left ventricular dysfunction (14,15). Ventricular remodeling is thought to be a key factor for the progression toward CHF (14).
There is no literature available on treatment of ACE inhibitors in patients with TGA after the Mustard procedure. Koutali et al have described no treatment effect in a group of patients with a Fontan circulation on ACE inhibitors (16). However, we hypothesize that, since ACE inhibitors have been shown to improve ventricular remodeling and hemodynamic responses to exercise in patients with systemic left ventricular dysfunction, adults after the Mustard procedure demonstrating systemic right ventricular dysfunction will also benefit from ACE inhibitor therapy.
Chapter 2

Introduction
Background of Transposition of the Great Arteries

The malformation in TGA consists of the origin of the aorta arising from the morphological right ventricle and the origin of the pulmonary trunk arising from the morphological left ventricle (figure 1). The origin of the aorta is usually to the right of and anterior to, but may be lateral to, the main pulmonary artery (17). This anatomical arrangement renders 2 separate circulations, without the potential for mixing. However, most patients have an interatrial communication. In its absence, all unoxygenated systemic venous return is directed to the systemic circulation and oxygenated pulmonary venous blood is directed to the pulmonary circulation. Thus, with no communication, the individual would die soon after birth upon closure of the arterial duct. Two-thirds of patients with TGA have a patent ductus arteriosus (PDA), and about one half have an associated ventricular septal defect (VSD) (see table 1 for associated anomalies) (17). Without treatment, about 30 percent of patients die within the first week of life, 50 percent within the first month, 70 percent within 6 months, and 90 per cent within the first year (figure 2) (18).
Figure 1. Transposition of the Great Arteries

Legend:
1. Transposition of the great arteries
2. Ventricular septal defect
3. Overriding pulmonary artery

Ao=aorta, PA=pulmonary artery, RA=right atrium, LA=left atrium, RV=right ventricle, LV=left ventricle
Table 1. Associated Anomalies in a Surgical Series of Patients with TGA

(The data are from a series of 260 patients undergoing operation at Green Lane Hospital in Auckland, New Zealand, 1964-1984. The totals are not cumulative (1)).

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<td>36</td>
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<tr>
<td>VSD</td>
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<td>Moderate</td>
<td>30</td>
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<tr>
<td>Large</td>
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<td>Multiple</td>
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VSD=ventricular septal defect, PDA=patent ductus arteriosus, LVOTO=left ventricular outflow tract obstruction.
Figure 2. Age at Survival and Life Expectancy Without Correction

Actual survival and life expectancy of 655 children with TGA, all of whom died between 1957 and 1964. The group is heterogeneous in that about 15% of the total had either single ventricle, hypoplasia of the left ventricle with mitral stenosis or atresia, or hypoplasia of the right ventricle with tricuspid stenosis or atresia. However, the trends are representative of patients with TGA (18).
Embryology

The embryogenesis of TGA is highly controversial. There is consensus that the development of a straight rather than a spiral infundibulotruncal septum precedes development of the reversed ventricular origin of the great arteries (17). This occurs if the subpulmonary, rather than the subaortic, infundibulum is absorbed (17). Transposition appears to result from a shift of the pulmonary artery rather than the aorta from the heart tube's outlet zone to the left ventricle (17). This movement may be the result of a maldevelopment of the infundibulum, or a combination of infundibular maldevelopment and truncal malseptation (17).

Diagnostic Echocardiography

Conotruncal abnormalities can be diagnosed by prenatal echocardiography with a high degree of accuracy (19). Determining the exact spatial relationship of the great arteries is difficult though in some fetuses on echocardiography.

Hereditary Factors

TGA occurs more often in males than females: moreover, there is reportedly an excess of males among the unaffected relatives of probands. This is construed as evidence that maternal intrauterine hormone levels play a role in the manifestation of this malformation (20).
**Right Ventricular Morphology**

The right ventricle in TGA is normally positioned and its sinus and inflow portions are normal in their architecture. However, the right ventricle is hypertrophied and unusually large in infants with TGA. In about 90% of cases, there is an infundibulum, with the aorta positioned anteriorly and rightward (1). The posterior and leftward pulmonary artery runs parallel to the aorta. This morphology also includes an infundibular septum which joins normally with the ventricular septum (in the absence of a VSD) (1). In normal hearts, the infundibulum deviates to the left, however in hearts with TGA, the infundibulum extends superiority from the ventricular sinus (1).

The atrioventricular (AV) valves may be at the same level and the interventricular septum is usually smaller than in normal hearts.

In 10% of hearts with TGA without a VSD, the aorta is either directly anterior or anterior and leftward of the origin of the pulmonary artery (21). In rare cases, the aorta is positioned posteriorly.
Figure 3. Interior View of the Right Ventricle in Transposition of the Great Arteries

Specimen showing the interior of the right ventricle in a heart with TGA with an intact ventricular septum. The conal (infundibular) septum inserts in a normal way between the 2 divisions of the septal band (trabecula septomarginalis.) These structures and the right ventricular free wall are hypertrophied. The infundibulum projects directly superiorly from the sinus portion of the ventricle rather than superiorly, anteriorly, and leftward, as in the normal heart, and gives origin to the aorta and the aortic valve.
Figure 4. Exterior View of the Heart with Transposition of the Great Arteries

Ao=aorta, PA=pulmonary artery, RAA=right atrial appendage, LAA=left atrial appendage, RV=right ventricle, LV=left ventricle

Specimen showing the external appearance of a heart with TGA. The infundibulum of the morphologically right ventricle extends directly superiorly from the sinus portion to give rise to a rightward anterior aorta. The pulmonary trunk lies parallel to the aorta in a posterior leftward position and arises from the morphologically left ventricle. The arrow points to the left anterior descending coronary artery.
Ventricular Wall Thickness, Cavity Shape, and Function

The morphological right ventricle in the setting of TGA has anatomic features similar to the morphological left ventricle in normal hearts. The right ventricular wall in TGA is thicker than the left ventricular wall from birth and increases in thickness with age proportional to the growth of the child. The left ventricular wall is of normal thickness at birth. However, it becomes progressively thinner with age (assuming there is no VSD or pulmonary stenosis) (22). In contrast, the left ventricular wall in normal hearts is born thicker than the right ventricular wall and progressively thickens with age proportional to the growth of the child.

The systemic right ventricle late after Mustard repair is thicker than the systemic left ventricle in a normal individual. This may be due to the right ventricle’s spherical shape which is less suited to a high pressure system than the ellipsoid systemic left ventricle. As well, the systemic right ventricle may adapt through hypertrophy and hyperplasia.

In TGA, the absence of a VSD or pulmonary stenosis allows left ventricular wall thickness to remain within the normal range within the first year of life. If the pulmonary stenosis is severe, left ventricular wall thickness may exceed right ventricular wall thickness.

Infants born with TGA present with a normal ellipsoid shaped left ventricle that evolves into an unusual banana shape soon after birth (23). This change is accompanied by functional modifications such as reduced left ventricular ejection fractions.

Right ventricular EDV increases while right ventricular ejection fraction (RVEF) decreases after the perinatal period (1). The increase in end diastolic volume is
likely due to an increased afterload. Since stroke volume is maintained, ejection fraction will fall (4). Left ventricular EDV is increased, and left ventricular ejection fraction (LVEF) is normal in hearts with TGA (4,24). The ratio of right ventricular EDV to left ventricular EDV is increased from a normal value of 1 to 1.46± 0.33 (1).

**Hemodynamics**

The amount of blood exchanged between the systemic and pulmonary circulations by intercirculatory shunts will determine the systemic arterial oxygen saturation. The effective systemic blood flow is ascertained by the amount of left to right shunting (blood passing from the pulmonary to systemic circulation). Conversely, the pulmonary blood flow is ascertained by the amount of right to left shunting. There is equal net volume exchange between the 2 circulations per unit time at rest (17). Static muscle work will increase systemic blood pressure resulting in systemic flow less than pulmonary flow. Dynamic exercise causes vasodilation yielding an increase in systemic blood flow greater than that of pulmonary flow.

Intercirculatory communications, the presence of associated obstructive intracardiac and extracardiac anomalies, the extent of the bronchopulmonary circulation, and the relation between pulmonary and systemic vascular resistance will all modify the magnitude of intercirculatory mixing (17).

**Preoperative Clinical Findings**

There is a spectrum of clinical findings ranging from cyanosis and rapidly progressive hypoxemia if there is no intracardiac communication and the duct closes to early heart
failure and minimal cyanosis with a large intracardiac communication (17). For example, a patient with a persistent PDA or a large VSD may present with minimal cyanosis but experience heart failure after the first few weeks of life (25).

Right axis deviation, right atrial enlargement, and right ventricular hypertrophy, are among the most common electrocardiographic findings (17). Fifty percent of chest x-rays may appear normal in the first days of life, particularly in infants with an intact ventricular septum (17). Subsequently, roentgenographic findings are highly diagnostic of TGA (26). However, these findings involve (1) progressive cardiac enlargement; (2) a characteristic egg-shaped or oval cardiac configuration in the anteroposterior view, and (3) a narrow vascular pedicle created by superimposition of the aortic and pulmonary artery segments; and (4) increased pulmonary vascular markings (17).

**Surgical History**

The first morphological description of TGA is attributed to Baillie in 1797 (27). The term *transposition of the aorta and pulmonary artery* was coined by Farre when he described the third known case of this anomaly in 1814 (28). The recognition of TGA during life resulted from the observations of Fanconi and Taussig in 1932 and 1938 respectively (29). In 1950 Blalock and Hanlon at the Johns Hopkins Hospital described a closed method of atrial septectomy directed at providing mixing of systemic and pulmonary venous return at the atrial level (30). In 1953, Lillehei and Varco described a partial physiological correction in which anastomosis of the right pulmonary veins to the right atrium and the inferior vena cava to the left atrium became a technique known as the Baffes operation (31).
Rashkind and Miller introduced balloon atrial septostomy in 1966, which revolutionized the palliation of TGA (32).

Throughout the 1950's there were surgical attempts to correct TGA either at the atrial or great artery levels. In 1959, Senning developed the first corrective procedure at the atrial level by refashioning the walls of the right atrium and the atrial septum (33). The Mayo Clinic used the Senning procedure between 1960 and 1964 with some successes but with many disappointing results (34). In 1963, Dr. Mustard introduced his procedure at The Hospital for Sick Children in Toronto (35). This procedure (later known as the Mustard procedure) was devised in order to create larger atria than was achieved with Senning's operation by excising the atrial septum and using a pericardial baffle to channel venous return. The Mustard technique was embraced by cardiac surgical centers around the world.

Several years after successful Mustard procedures began, when balloon atrial septostomy was established, it became common practice to delay the operation for 12 to 24 months after balloon atrial septostomy (1). TGA with large VSDs remained a dilemma throughout this early period due to the rapid onset of pulmonary vascular disease in many of these patients (1). In 1972, Lindesmith and colleagues introduced the concept of a palliative Mustard procedure in which the VSD is left unclosed for patients with severe pulmonary hypertension (36).

There were not many operative successes in patients with TGA, VSD, and LVOTO in this early period of cardiac surgery for TGA (1). However, in 1969, Rastelli and colleagues combined the intraventricular tunnel repair (which consisted of joining the left ventricle to the aorta) with a rerouting valve extracardiac conduit (creating a connection
between the right ventricle and the pulmonary artery). In addition, he closed the origin of the pulmonary artery from the left ventricle to yield an anatomic repair of TGA, VSD, and LVOTO (37,38).

Dr. Mustard originally attempted the arterial switch, transposing only the left coronary artery. However, his attempts were unsuccessful and he abandoned the procedure in favour of what is now the Mustard operation. It was not until Jatene described successful arterial switch in 1975 that this procedure was adopted (39). The atrial switch operation is now rarely carried out since the advent of the arterial switch procedure for TGA. However, throughout the world there remains a population of patients with TGA after an atrial switch whose circulation depends upon a systemic right ventricle. Literature regarding the ability of the right ventricle to function systemically is currently evolving.

**Indications for Mustard Operation**

Traditionally, the mere presence of TGA in the absence of important LVOTO or pulmonary vascular disease was an indication for operation. A balloon atrial septostomy was usually performed if symptoms were severe and operation could not be performed immediately (1). The patient was preferably 6 months to 1 year of age for more elective operations. Sometimes for very ill babies, the operation would also be done on an emergency basis.
Chapter 3

The Mustard Procedure
Operative Technique

The Mustard technique involves intraatrial redirection by excision of the interatrial septum and creating a new partition with a pericardial baffle diverting the systemic venous return into the left ventricle through the mitral valve (40). Systemic venous return thence continues from the left ventricle through the pulmonary valve and into the pulmonary circulation (40). Pulmonary venous blood is diverted through the tricuspid valve to the right ventricle, and onward to the aorta.

“The suture lines are close to the pulmonary venous orifices, but are generally away from the caval orifices, with the suture bites being relatively shallow, especially near the tricuspid valve. The coronary sinus is left intact and the patch is sutured so the coronary sinus drains with the systemic venous return.

Pericardium is removed between phrenic nerves. A rectangle is cut from the pericardium, to be used for the intraatrial baffle, and retraction sutures are placed in each corner. The remaining portion of pericardium is fashioned into a triangle to be used as the patch on the new left atrium.” (41).

The most appropriate material, configuration, and size of the atrial baffle have been controversial throughout the years. Autologous pericardium is usually recommended because of the higher prevalence of baffle complications when Dacron is used (1). One method is to use a very small pericardial baffle and sew it snugly in place away from the caval orifices so that more of the caval pathways is atrial wall rather than baffle (1). However, another concept derived from the Toronto technique uses a larger baffle that is sewn into place around the caval orifices, with a redundancy of the baffle around the
cavae to minimize the chance of narrowing the superior or inferior vena cava pathways
(42).

Figure 5. The Mustard Technique
Atrial Switch operation by the Mustard technique.

A) (1) The usual oblique atriotomy is made,
or (2) V-Y incision is used.
B) After excising the atrial septum, the coronary
sinus is cut down.
C) The pericardial baffle is made from pericardium.
In one technique, the Toronto-type baffle is used
and is sewn around the caval orifices. The
dimensions in the large diagram and in (C1) are
for a 5-kg infant. Dimensions of 7x4 cm are used
for 10-kg child, and proportionately larger ones for
larger children. The main drawing represents the
shape and dimensions of this pericardial baffle as it is
initially excised. In the other technique, the patch does
not reach to the orifices of the cavae but rather to the
atrial wall and proximal to the cavae and thus can be
smaller (C2).

(1) The Toronto baffle for a 5-kg child.
(2) The alternate baffle for a 5-kg child.

D) The baffle is first sutured over the left pulmonary veins. The small circles show the suture line, and the dashed lines show an alternative one with the small baffle. Stay sutures may be inserted to aid in placement of the suture line.

E) Continuation of the baffle suture line

(1) With the larger patch, the suture line is continued around the orifices of the superior and inferior vena cavae.

(2) With the smaller patch, the suture line is kept well away from the caval orifices. Each stitch in the atrial wall penetrates the wall completely and gathers the wall down onto the pericardial patch.

F) (1) Simple closure of the right atriotomy

(2) Closure of the V-Y plasty to enlarge the pulmonary venous atrium. Note the desired purse-string effect of the baffle suture line in the atrial wall near the superior and inferior vena cava.
Modes of Death Early Postoperatively

Low cardiac output is the most common mode of death early postoperatively (within one year) after the Mustard procedure. This is due to relatively small atria which results in a lower ventricular filling pressure than would otherwise pertain (43). Other modes of death early after the Mustard procedure include high pulmonary vascular resistance, baffle obstruction, respiratory complications and arrhythmias (43).
Chapter 4

Late Post Operative Results
Overview

The quality of life of late survivors after the Mustard procedure is good; most achieving a normal level of education and employment (44,45). The well known late complications of the Mustard procedure include supraventricular brady-tachyarrhythmias, dilatation and failure of the systemic ventricle, tricuspid valve incompetence, obstruction of either systemic or pulmonary venous return, LVOTO and baffle leaks (46). Most patients remain asymptomatic despite hemodynamic or arrhythmic problems. However, many children have reduced exercise tolerance evidenced by a lower VO\textsubscript{2peak} compared with normal values (7). Adult survivors are also at risk for premature death, congestive heart failure (CHF), and supraventricular tachyarrhythmia (44). Puley et al reported that pulmonary hypertension and right ventricular dysfunction were independent risk factors for death or CHF (44). These abnormalities usually coincide with an older age at operation and are often accompanied by rhythm disturbances (44).

Right Ventricular Dysfunction

Both early and late right ventricular dysfunction are common in patients with TGA after the Mustard procedure. There are many reasons potentially responsible for poor right ventricular performance as the systemic pump in these patients. (1) Almost all of these patients have been subjected to perinatal hypoxia, but it is unknown whether “hypoxic injury” involving the right ventricle alone could be responsible for dysfunction as a late sequela (47). (2) The embryologic origin of the right ventricle results in a less efficient pumping chamber although this is difficult to prove (47). (3) There may be a mismatch between the right ventricular blood supply and demand which contributes to right ventricular dysfunction among these patients (47). Lubiszewska et al reported
moderate or severe perfusion abnormalities at rest which worsened with exercise in some patients with the Mustard procedure (48). (4) The right ventricle is more susceptible to injury during cardiopulmonary bypass at the time of surgery than the left ventricle so that what might be a minor stress for a left ventricle at open heart surgery may be a major insult for the right ventricle for the child with TGA at the time of a Mustard operation. Most of these procedures were carried out in the 1960’s and 1970’s when myocardial protection was certainly not as sophisticated as the current era (47). (5) The presence of significant tricuspid insufficiency early in life also may be the cause rather than the result of late right ventricular dysfunction (47). (6) Chronic tachyarrhythmias may contribute to poor myocardial function in some patients (47). (7) Finally, the question of the intrinsic limitation of the long-term capacity of the right ventricle to function as a systemic ventricle must be addressed. The spherical shape of the right ventricle may not be well suited to high pressure demands of systemic circulation (47). It is of note that the left ventricle adopts a more spherical shape after mitral valve replacement without chordal preservation and is thus less efficient.

**Electrophysiological Disturbances**

Arrhythmias are common following the Mustard procedure (49). Electrophysiological irregularities arise in part because Mustard's operation disturbs 1 or more of the 3 components of the specialized atrial conducting tissues (sinus node, internodal tracts and AV node) (50). Of these tissues, the sinus node can be particularly affected. Acute changes in sinus node function can result from direct trauma from the interatrial baffle, or direct surgical damage to the artery which supplies the nodal tissue. Necrosis or
infarction of the sinus node itself with interstitial hemorrhage and edema of the nodal tissue has been observed (1). Edwards and Edwards found that, among 9 cases with sinus node artery compression, the sinus node showed acute infarction in 7 (51). Chronic changes include fibrosis in the node and paranodal tissue, such that in some cases, the sinus node can no longer be recognized (1). The surgical techniques responsible for this damage includes incorrect methods for superior vena cava cannulation and damage to the sinus node artery by excessive excision of the limbus which leads to reendothelialization of the resultant exposed area. Additionally, direct suture involving the sino atrial node may occur (1). Although these abnormalities are associated with dysrhythmias and are present in a significant number of individuals with late sudden death, it is unlikely that these mechanisms account for all the arrhythmias arising late after the Mustard procedure. The extensive suture lines within the atria itself, as well as excision of virtually the entire atrial septum, may also contribute to late arrhythmias (52,53).

Preservation of the anterosuperior portion of the limbus decreases the incidence of dysrhythmia (54). In contrast, division of the free wall of the coronary sinus does not predispose to arrhythmogenesis (54).

Junctional rhythm becomes progressively more prevalent as the patients age (1). About 10% of patients in junctional rhythm display a varying sinus-junctional rhythm, and a small few show a pure junctional rhythm (1). From the time a patient leaves the hospital, there is a decrease in the incidence of sinus rhythm as follow-up lengthens (55,56).

In patients with slow junctional rhythm, there is a relatively normal chronotropic response to exercise as reversion to sinus rhythm is common (57). Rapid (accelerated)
junctional rhythm, as well as supraventricular tachycardias or atrial flutter are uncommon in patients with slow junctional rhythm (50). These arrhythmias may result in reduced cardiac output and require active measures for rate control, if reversion to normal sinus rhythm is not possible (50).

**Rhythm Monitoring**

Twenty-four hour Holter monitoring following the Mustard procedure may reveal infrequent dysrhythmias that are overlooked on standard 12 lead ECGs (58). Holter studies allow rhythm disturbances to be categorized as normal or probably abnormal, studies that fail to make this differentiation overstate the incidence of arrhythmia (55).

Postoperative Holter monitoring does expose additional dysrhythmias, especially when the patient is in junctional rhythm. Rhythm monitoring during maximal exercise testing may disclose additional information. Mathews and associates noted that of 15 patients in sinus rhythm at rest who underwent exercise testing a mean of 9 years after the Mustard procedure, 9 developed either premature atrial or ventricular contractions or junctional rhythm during exercise stress (10).

**Sudden Death**

During the early development of the Mustard procedure, Aberdeen emphasized that some of these dysrhythmias may predispose the patients to sudden death (59). Sudden death occurs in about 5% of hospital survivors over a period of 10-20 years (1). However, sudden death is rare in patients who remain in sinus rhythm postoperatively (57,60). In a
collaborative study of 372 patients, junctional rhythm was a very minor risk factor for sudden death, while no other risk factors were found (57,60).

The Baffle

Minor leakage at the baffle suture line occurred in 15% to 29% of 390 reported cases (61-69). Severe leakage occurred in only 0.8% to 4% of the same cases and required reoperation (61-69). These studies reported on patients 6 months to 11 years post Mustard procedure.

Pulmonary Vascular Disease

When an atrial switch operation is performed within the first 3 months of life for patients with TGA, pulmonary vascular disease is rare. Gilljam et al found that in a few patients with the Mustard procedure the pulmonary venous channels were narrowed, leading to increased pulmonary venous pressure during exercise, which may contribute to abnormal gas exchange (9). Mahony et al did not find any cases of pulmonary vascular disease in 28 patients who underwent the Mustard procedure within the first 100 days of life (62). When the procedure is performed after 3 months of age, 5-10% of patients develop pulmonary vascular disease postoperatively (70,71).

Vena Caval and Pulmonary Venous Obstruction

Systemic venous obstruction is a well-known complication following the Mustard procedure (72). Obstruction of the systemic and pulmonary venous pathways after the Mustard procedure is associated with an increased risk of arrhythmia and sudden death.
Superior vena cava obstruction appears late postoperatively in 5-10% of survivors after the Mustard procedure (74). Mazzei and Mulder first described superior vena caval obstruction in 1971 (75). Baffle shape, size, composition, and positioning of the suture lines within the atrium all contribute to its production. The fact that it has proved impossible to eliminate this problem many years after the Mustard procedure suggests that the precise mechanism is not well understood (figure 6) (75).

Inferior vena caval obstruction is much less frequent than superior vena caval obstruction, occurring in only 1%-2% of patients (4,63). Reoperation with insertion of a new baffle is usually indicated for inferior vena caval obstruction, since mortality is high if untreated.

Pulmonary venous obstruction is less common but even more serious, and tends to occur more commonly when a Dacron baffle is used (76).
Figure 6. Obstructed Superior Vena Cava

Cineangiogram after injection into the superior vena cava in 20° left anterior oblique projection. The heavy arrow marks the site of obstruction. The fine dotted lines (small arrows) outline that portion of the original right atrial appendage that lies in the upper venous compartment beneath the baffle and above the site of obstruction. There is retrograde flow into the azygous vein.

A=azygous vein, LAA=left atrial appendage, LV=left ventricle, SVA=systemic venous atrium, SVC=superior vena cava.
Chapter 5

Management After the Mustard Procedure
Overview

Recent advances in surgical and medical management have dramatically altered the outlook for patients with congenital heart disease (77). As a result, ever-increasing numbers of such patients survive to adulthood. Longitudinal follow up is now strongly recommended due to the number of late complications that are common in these patients after the Mustard procedure (78). The patients at our Centre are followed annually and regularly have: cardiopulmonary exercise studies to assess cardiopulmonary function at maximal exertion; echocardiography to assess right ventricular function at rest and tricuspid valve function; MRI to evaluate several variables; chest x-rays; and electrocardiography.

Magnetic Resonance Imaging

There are 3 aspects of right ventricular anatomy which render it difficult to assess function with the echocardiographic approach. The first is the complex shape of the right ventricle which is pyramidal and becomes significantly distorted with pathology. The shape thus defies simple geometric representation, and ideally requires orthogonal biplane imaging and computer reconstruction of the volume (79). The second difficulty of right ventricular volume assessment is the heavy trabeculation of the free wall (79) which makes edge detection difficult. Finally the close overlap between the right ventricular chamber and other neighboring cardiac chambers such as that right atrium and the left ventricle makes it difficult to measure volume reliably with many conventional imaging techniques (79). Currently used non-invasive techniques to study right ventricular function such as echocardiography or radionuclide studies, have several
limitations, particularly in patients with abnormal right ventricular shape (79-81). Recently, MRI has successfully been applied to quantify ventricular function and large vessel and intracardiac volumetric flow (82). Due to the fact that this is a non-invasive technique devoid of radiation, serial measurements are readily feasible. Access to structures in the chest and choice of imaging planes are practically unlimited. A contiguous set of image sections encompassing the ventricle of interest provides a 3-dimensional data set that allows volume calculations without geometric assumptions (81). The contrast between blood and myocardial tissue is high which eliminates the need for contrast reagents (83). Considering these characteristics, MRI is a particularly suitable method for serial assessment of right ventricular function in patients with the Mustard procedure.

Several MRI techniques can be applied to assess various aspects of a post Mustard operation heart. Multislice spin echo MRI is commonly used to define cardiac morphology, and has been used to evaluate baffle function in patients after the Mustard procedure (79). However, spin echo MRI lacks the temporal resolution to provide adequate functional information. By applying short repetition times, short echo-times and small flip angles, gradient echo MRI provides higher temporal resolution than spin echo sequences, adequate to isolate end-diastolic and end-systolic time points (84). With tomographic gradient echo MRI, ventricular volumes can be measured from a stack of multiphase images, usually with a time frame of +30 ms between the phases and a varying number of time frames, depending on heart rate (85). From these images biventricular size and function may be derived simultaneously. Orientation of the image plane has not been standardized. For right ventricular volume measurements, several
MRI plane strategies have been reported (85). Images aligned with the left ventricle short axis are often used (86). Since the right ventricle has no clearly definable axis, transverse sections are also used for right ventricular measurements. With current MRI techniques, image acquisition is not real time but requires up to 256 cardiac cycles to optimize the signal to noise ratio (83). Acquisition of a complete set of gradient echo tomographic images requires approximately 30-40 minutes with conventional techniques (83). High-speed MR sequences have been introduced, providing real-time images (87). Currently these techniques have not yet found widespread use due to hardware limitations.

MR velocity mapping is a technique that can be used for quantification of blood. MR velocity mapping is a modified gradient echo sequence that uses a velocity-encoding magnetic field gradient in the direction of flow (88). When magnetic spins of intravascular protons flow along the magnetic field gradient, they acquire a phase shift proportional to their velocity. Thus, MR velocity mapping provides a 2-dimensional map of velocity distribution across the imaging plane (83). To calculate volumetric flow the imaging plane is oriented perpendicular to the direction of flow, and through-plane velocity is encoded in the phase of the MR signal. A fundamental difference with tomographic gradient echo MRI is that velocity mapping uses the phase information of the MR signal rather than the amplitude (88).

Analysis of MR images requires dedicated software packages. Ventricular volumes are calculated by summation of ventricular cavity area, assessed by manually assisted semi-automated tracing of the endocardial outline on a stack of multisection gradient echo MR image sections of a specific time frame, and multiplied by section thickness.
On end-systolic frames epicardial contours are drawn to determine ventricular wall mass. Ventricular wall volume is calculated as myocardial area multiplied by the sum of slice and interslice gap thicknesses. A specific gravity of 1.05 g/ml is used for calculation of ventricular mass (83).

Despite some practical limitations MRI is a useful imaging method in patients after the Mustard procedure. Information on baffle function, right and left ventricular size, ejection fraction and wall mass, intracardiac and large vessel flow velocities and flow volumes can be obtained non-invasively in a single examination. Serial measurements are feasible, allowing close monitoring of these patients during follow-up after the Mustard procedure.

**Pharmacological Management**

A standard protocol for pharmacological management does not exist for patients after the Mustard procedure. Patients with the Mustard procedure are at a greater risk for CHF (44) and may benefit from medications that prevent the development of this condition. ACE inhibition has been shown to have a protective effect on systemic ventricular function in patients with CHF (89). ACE inhibitors function by inhibiting angiotensin II thereby decreasing peripheral vascular resistance and reducing cardiac hypertrophy.

**Renin-Angiotensin System**

Angiotensin I, a decapeptide (90) is the main product of the interaction of renin on angiotensinogen. Renin is an acid protease, which is stored and secreted from the renal juxtaglomerular cells located in the wall of the afferent arteriole, and is contiguous to the macula densa (12,13). Angiotensin I does not have vasoconstrictive activity. Renin
secretion exerts a pressor effect only if angiotensin I is metabolized by the angiotensin converting enzyme to the octapeptide pressor hormone angiotensin II (90). Accordingly, inhibition of this key intermediate enzyme provides an opportunity to block the effector arm of the renin-angiotensin cascade. The availability of relatively specific antagonists of the renin-angiotensin system has had many important effects on modern cardiovascular medicine. First, the antagonists have provided a tool for exploring and later establishing the importance of the renin-angiotensin system in cardiovascular homeostasis. It is commonly known that the renin-angiotensin system is one of the key mechanisms involved in blood pressure regulation (90).

There are many ways to assess the potential for a drug to inhibit ACE activity. One way is to show blockade of the pressor response to exogenous angiotensin I. This method allows for direct evidence of the efficacy of any ACE inhibitor. However, this method necessitates pharmacological doses of angiotensin I be injected. A more convenient way to evaluate ACE activity is to measure plasma ACE activity (91). In the case of the ACE inhibitor captopril, enzyme activity must be determined immediately after drawing blood because, in vitro, the captopril-ACE complex tends to dissociate, which may lead to underestimation of the extent to which ACE is inhibited (92) (figure 7 shows the response of the renin-angiotensin system to ramipril). ACE in the endothelium (non-circulating ACE), is responsible for the bulk of the conversion of angiotensin I to angiotensin II, thus, its activity should be corroborated by simultaneous determinations of plasma angiotensin II (93). Plasma angiotensin II can be determined, however, the assay remains difficult and there are potentially interfering cross-reacting precursors and metabolites and in vitro production of angiotensin II have to be taken into account (94).
Response of the renin-angiotensin-aldosterone system to short-term ACE inhibition with a single oral dose of ramipril (HOE 498, 10 or 20 mg) in 4 normal volunteers. Ang-(1-8) octapeptide (true angiotensin II) virtually disappeared from plasma, whereas immunoreactive angiotensin II decreased by only 44%. PRA, plasma renin activity (14).
Angiotensin II

Angiotensin II maintains high blood pressure by stimulating receptors of vascular smooth muscle cells. Other factors are involved however, and a given level of circulating angiotensin II may indeed cause different degrees of blood vessel contraction. For example, increasing total body sodium is known to enhance blood pressure responsiveness to this peptide (95). Vascular hyperactivity to angiotensin II is also present in hypertensive patients in whom blood vessels have undergone structural changes (96). It is also possible that a vasodilating prostaglandin, such as prostacyclin synthesized in the vascular wall, blunts the pressor effect of angiotensin II (97). ACE inhibitors decrease the breakdown of bradykinin. As well, since angiotensin II blocks the vasodilating effects of bradykinin, ACE inhibitors are also beneficial in preventing bradykinin inhibition (98).

Angiotensin II stimulates aldosterone secretion (99). Therefore, it is also probable that the rate of aldosterone production is decreased during ACE inhibition (100) (see figure 8). This effect may be of great benefit to hypertensive patients. After closely studying plasma aldosterone and angiotensin II levels after long-term ACE inhibition, investigators found that both parameters were still markedly reduced and that changes in these parameters were closely correlated (101).

The Renin-Angiotensin System in Heart Failure

The renin-angiotensin system is acknowledged to be important in the pathogenesis of CHF (102). The circulating renin-angiotensin system has well-characterized hemodynamic effects in CHF that, although initially beneficial (103), are ultimately
deleterious (104,105). The tissue renin-angiotensin system has autocrine and paracrine effects that have not been characterized fully; however, there is a growing awareness that angiotensin II may have important properties related to cellular growth and hypertrophy, in addition to its pressor and sodium retentive characteristics (see below).

The system is one of several tightly integrated neuroendocrine systems that are activated in response to a decrease in cardiac output (106). Reduced cardiac output is associated with the activation of an enzymatic cascade leading to the formation of angiotensin II (107). Among the effects of angiotensin II is the mediation of an increase in preload via sodium retention and an increase in afterload by systemic vasoconstriction (108). Increases in preload cannot enhance systolic function in the failing heart because of reduced preload reserve (109).

In response to an increase in afterload, the healthy heart could increase contractility to maintain cardiac output. The failing heart is less able to do so, and the increased afterload may lead to a decrease in cardiac output (110,111). Therefore, the circulating renin-angiotensin system may accelerate worsening of myocardial function and progression of heart failure.

Speculation has arisen regarding the existence of a local renin-angiotensin system with autocrine and paracrine effects. *In vitro* molecular studies have subsequently confirmed the presence of the components of the renin-angiotensin cascade in cardiac tissue (112). Thus, angiotensin II can be produced in cardiac tissue, in which it is possible to exert an array of local effects. *In vitro* studies suggest that, among its other effects, angiotensin II may advance hypertrophy of cardiac myocytes (113). Work done in vascular smooth muscle cells has helped to clarify the supposed mechanism by which angiotensin II
promotes cell growth. Angiotensin II by way of increased intracellular calcium levels and activation of protein kinase C, stimulates increased transcription of proto-oncogenes (such as c-fos and c-myc), which, in turn, may code for a variety of proteins essential to the growth and hypertrophy of cells (114-117). This mechanism may be critical to understanding the role of the local renin-angiotensin system in promoting ventricular remodeling and progression of heart failure. Therefore, by inhibiting angiotensin II formation with ACE inhibitors, cardiac hypertrophy may be prevented.

In summary, the renin-angiotensin system is a complex dual system: a circulating classic hormonal system and a local autocrine and paracrine system localized to a variety of tissues including cardiac tissue. Its ongoing activation may contribute to the pathogenesis of CHF by locally promoting growth and hypertrophy of cardiac tissue.

The Survival Trials

Over the last decade, several large prospective clinical trials have assessed the efficacy of ACE inhibitors in prolonging the lives of patients with CHF.

Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

CONSENSUS was the first large study to examine the effects of ACE inhibition in CHF (118). The trial was designed to evaluate the effects of enalapril versus placebo on survival in patients with severe CHF (New York Heart Association class IV). This study was terminated prematurely after 18 months because of the marked reduction in mortality seen in patients treated with enalapril. Enalapril reduced mortality by 40% at 6 months
and by 31% at 12 months. As well, there was a significant reduction (50%) in the number of deaths due to pump failure in the treatment group.

Subsequent assessment of neuroendocrine activation in patients participating in CONSENSUS showed a positive association between baseline levels of neuroendocrine substances (including angiotensin II) and subsequent mortality (119). These results support the use of ACE inhibitors in patients with the most pronounced abnormalities of the neuroendocrine system. Such patients are most likely to derive a survival benefit from ACE inhibitors.

Studies Of Left Ventricular Dysfunction (SOLVD)

Prior to the publication of SOLVD, data were not available to assess the survival benefits of ACE inhibitors in patients with mild heart failure or asymptomatic left ventricular dysfunction. SOLVD was therefore designed to evaluate the effects of enalapril on mortality and morbidity in patients with New York Heart Association class II and III heart failure (120). SOLVD consisted of a prevention arm (patients without overt CHF) and a treatment arm (patients with overt CHF). The prevention arm of SOLVD demonstrated that patients with left ventricular dysfunction in the absence of overt heart failure derived no survival benefit from treatment with enalapril, although enalapril appeared to forestall the development of overt heart failure and the need for subsequent hospitalization. Thus, the results of SOLVD are consistent with those of CONSENSUS: interference with neuroendocrine systems such as the renin-angiotensin system confers survival benefit to patients with heart failure.
Subgroup analysis of baseline neuroendocrine activation in the SOLVD patients revealed normal plasma renin activity in patients entering both arms of the study (121). This lack of activation of circulating renin-angiotensin system in the baseline state suggests that the beneficial effect of ACE inhibition may be related to interference with the tissue renin-angiotensin system.

The Heart Outcomes Prevention Evaluation Study Investigators (HOPE)

The HOPE study evaluated the effects of ramipril in a high-risk population in preventing the primary outcome, which was a composite of death from cardiovascular causes, myocardial infarction, or stroke, as well as each outcome separately. Secondary outcomes included death from any cause, the need for revascularization, hospitalization for unstable angina or heart failure and complications related to diabetes. Results demonstrated that ramipril is beneficial in a broad range of patients without evidence of left ventricular systolic dysfunction or heart failure who are at high risk for cardiovascular events. Treatment with ramipril reduced the rates of death, myocardial infarction, stroke, coronary revascularization, cardiac arrest and heart failure (122).

Summary

A review of recent survival trials underscores the progress that has been made in the past decade in the treatment of patients with CHF. Direct vasodilators were the first therapy demonstrated to prolong life in patients with CHF. Subsequent trials have demonstrated the superiority of ACE inhibitors in prolonging life when compared with direct vasodilators. This superiority reflects the dual mechanism of action of ACE
inhibitors: neuroendocrine activation and direct cellular hypertrophy and remodeling.

Many aspects of the use of ACE inhibitors, including potential cardiac conditions which may benefit from ACE therapy and mechanism of action, remain unexplored.

Nonetheless, these agents have emerged as the preeminent therapy for CHF.
Chapter 6

Exercise and Cardiac Function in Healthy Adults
Overview

The cardiac response to exercise is complex and involves the interaction of heart rate, contractility, preload, and afterload. Dynamic exercise results in an increase in sympathetic tone thus stimulating an increase in heart rate and myocardial contractility. The vascular response is an increase in venous return and a decrease in afterload. This results in a preservation or increase in stroke volume by the Frank Starling mechanism (123).

Early in this century, Starling suggested that ventricular preload may regulate cardiac function during exercise (124). During exercise, there is also an increased ventricular filling rate which occurs at the expense of diastasis. The increased rate is due to an almost 2-fold increase in the pressure gradient that exists between the atria and ventricles (125). It has also been shown that there is reduced cardiac filling during intense exercise whereupon contractility is the key determinant in maintaining stroke volume (126). During maximal exercise, total body oxygen consumption may increase to 10-12 fold, and cardiac output 4-5 fold (17). There is a redistribution of blood flow from non-exercising areas, with an enormous increase in blood flow to the exercising muscles. Despite this redistribution, oxygen extraction by exercising muscles still increases to very high levels.

Pulmonary Circulation

The basic function of the pulmonary circulation is the uptake of oxygen and the liberation of carbon dioxide by the blood. This function is efficiently accomplished by the pulmonary circuit, which normally carries all the cardiac output through the lungs at
pressure in the adult approximately one-sixth that of the systemic circulation. It is obvious, therefore, that its resistance to blood flow is one-sixth that of the systemic circulation (127).

A mismatch in ventilation and perfusion might cause oxygen desaturation. When there is actually no perfusion, the ventilation is wasted insofar as gas exchange is concerned, and the region affected is considered dead space. At the other extreme, when there is no ventilation and perfusion is maintained, a shunt exists where oxygenation of blood does not occur. In this case, hemoglobin is still desaturated when it leaves the pulmonary capillary (128).
Chapter 7

Left vs. Right Heart Anatomy in Healthy Adults:

Possible Explanations for Why the Left Side is Better

Suited to Systemic Circulation
The Ventricles

The striking difference in configuration between the 2 ventricles in normal individuals is depicted by a transverse section throughout the chest (figure 8). The left ventricular chamber is an ellipsoid surrounded by relatively thick musculature of 8-10 mm at autopsy (127). This arrangement is well suited to ejecting blood against the high resistance characteristic of systemic circulation. The right ventricle, which contracts against a low resistance in the normal population has a crescent-shaped chamber and a thin outer wall, measuring 4-5 mm in thickness (129). The anterior right ventricular wall curves over the ventricular septum, which normally bulges into the right ventricular cavity (127). Although the ventricular septum forms the medial wall of both ventricles, it seems to contribute predominantly to left ventricular function in normal subjects. Muscle bundles called the trabeculae carneae line the anterior and inferior walls of the right ventricular cavity, which often form ridges along the inner surface of the wall (127).
Figure 8. Transverse section through the heart at approximately the level of the 8th thoracic vertebra. The plane of the atrial and ventricular septa slants approximately 45° to the left of the midline.

RA=right atrium, LA=left atrium

The left ventricle is naturally suited in configuration and thickness as the systemic pump. The left ventricle is thicker, ellipsoid in shape and benefits more from the ventricular septum than the right ventricle.

The right ventricle with its thin walls and crescent shape is not adapted to functioning under systemic loads. Since the *trabeculae carneae* form ridges along the inner surface of the right ventricular wall, these muscle bundles reduce the volume of the ventricle and may result in a lesser EDV.
The Atria in the Normal Heart

The right atrium forms the right lateral cardiac border and is above, behind, and to the right of the right ventricle. Most of the right atrium is to the right and anterior to the left atrium. On the posterior external surface of the right atrium a ridge, the *sulcus terminalis*, extends vertically from the superior to the inferior vena cava. The sinus node is usually located at the lateral margin of the junction of the superior vena cava with the right atrium and the atrial appendage beneath or near the *sulcus terminalis* (127). The inner surfaces of the posterior and medial (septal) walls of the right atrium is smooth, while the surfaces of the lateral wall and of the right atrial appendage are composed of parallel muscle bundles, the *pectinate* muscle (130). The right atrial wall measures about 2 mm in thickness (127). The medial wall of the right atrium includes the atrial septum and is also important because of its proximity to several structures (130). The atrial septum is found in the posteroinferior portion of the medial wall of the right atrium and extends obliquely forward from right to left (131).

The left atrium is located superiorly, in the midline, and posterior to other cardiac chambers. The left ventricle is to the left, anterior, and inferior to the left atrium. The posterior position of the left atrium makes it impossible to palpate externally unless it is massively dilated (127).

The wall of the left atrium is 3 mm, slightly thicker than that of the right atrium (127). Two pulmonary veins enter posterolaterally on each side, conveying oxygenated blood from the lungs. Though there are no true valves at the junction of the pulmonary veins and the left atrium, sleeves of atrial muscle extend from the left atrial wall around the
pulmonary veins for 1-2 cm and may exert a partial sphincter-like influence, tending to lessen reflux during atrial systole or mitral regurgitation (127).

There are 2 main functions of the atria: a transport, or pump, function, and a reservoir function to collect blood available for rapid ventricular filling (132). Like the ventricles, the atria respond to an increase in fiber length by an increased force of contraction. Increased atrial contractility may be produce by increased sympathetic stimulation, by inotropic agents such as digitalis or catecholamines, or by decreased vagal stimulation (132). Each of these causes the atrium to pump a greater amount of blood forward into the ventricle, with a resultant increase in ventricular end-diastolic fiber length and pressure (the *atrial kick*), thereby causing the ventricle to increase its force of contraction (133). When the atrial transport function is lost in a person with an otherwise normal heart, the normal circulatory reserve mechanisms are able to maintain the cardiac output at rest within normal limits. However, when subjected to strenuous exercise, cardiac output is usually diminished (133).

The atria also have an endocrine function. In response to atrial distention and/or a sodium load, the atria produce atrial natriuretic peptide, a hormone responsible for excretion of sodium and water by augmenting glomerular filtration rate, inhibiting sodium reabsorption in the proximal tubule and inhibiting release of renin and aldosterone. Atrial natriuretic peptide also causes arteriolar and venous dilation by antagonizing the vasoconstrictor actions of angiotensin II and sympathetic stimulation. Thus atrial natriuretic peptide has the capacity to oppose sodium retention and arterial pressure elevation in hypervolemic states (134).
The left and right atria have significant differences, which render them suited to their respective circulatory functions. Accordingly, systemic right atria are less well adapted to high-pressure demands of the systemic circulation. While atrial remodeling occurs, the thinner right atrial wall is not as well equipped to participate in a high-pressure systemic circuit. Additionally, the papillary muscles of the left ventricle help maintain its ellipsoidal shape. The tricuspid valve apparatus does not do this and hence the ventricle becomes more spherical which may be more inefficient. Further, Wolff et al reported that irrespective of the alpha adrenergic receptor (alpha$_1$-AR) subtype, the total number of alpha$_1$-AR transcripts is dramatically lower in the right atrium than in the left atrium (134). Since atrial contractility may be increased by sympathetic stimulation it would follow that if there were less adrenergic receptors in the right atrium, there would be less opportunity for sympathetic stimulation and less opportunity to increase contractility.

These points suggest that right atria may not be suited to producing the strong *atrial kick*, required by systemic atrium.

**Myocardial Blood Supply**

In the most common "normal" coronary artery pattern, the left main coronary artery travels anteriorly, slightly inferiorly, and leftward from the left coronary sinus to emerge behind the pulmonary trunk (127). The left main stem divides into 2 or more major branches of nearly equal diameter - the left anterior descending, and the left circumflex (127). These larger branches branch out to form smaller vessels throughout the left ventricle.
The right coronary artery leaves the coronary sinus and descends into the right AV groove curving posteriorly at the acute margin of the right ventricle (127). This sole blood supply divides to form smaller vessels throughout the right ventricle. The left ventricle has 2 major arteries while the right ventricle only has one. Perhaps, this greater blood supply achieved by the left ventricle is influential in rendering its performance as a systemic pump. The oxygen demand of the normal systemic left ventricle is greater than that of the right ventricle as it pumps against a greater resistance, hence working harder. The left ventricle thus requires superior delivery of blood to its tissues. It may follow that a systemic right ventricle might not have an appropriate supply of blood to meet systemic circulatory demands. Celermajer’s group reported reversible and fixed perfusion defects with concordant regional wall motion abnormalities in the systemic right ventricle 10-20 years after Mustard repair (135).

The Atrioventricular Valves

The mitral valve, which is normally located between the left atrium and left ventricle, is composed of 2 leaflets. The fibroelastic valvular tissue, which is attached to the annulus fibrosus, completely encircles the orifice, providing a cone-shaped funnel extending into the left ventricular cavity (127). The leaflets of the mitral valve are described as anteromedial and posterolateral (127). The anteromedial leaflet is continuous with supporting tissues from the noncoronary and left coronary aortic cusps, which lie above them. The posterolateral leaflet is less mobile and restricted in its movement. It is attached superiorly to the annulus fibrosus and has approximately the same surface area as the anteromedial leaflet (127).
The tricuspid valve is normally found between the right atrium and right ventricle. The tricuspid valve is oriented in its plane in a semivertical axis, and directs the right atrial blood anteriorly, inferiorly, and to the left (127). There are 3 tricuspid leaflets which differ from the mitral leaflets in being thinner, more translucent, and less easily separate into distinct leaflets (127).

The mitral leaflets are more resilient than the tricuspid leaflets and seem ideal for the larger pressure demands of the systemic left ventricle than the pulmonary right ventricle. When a right ventricle has the responsibility of a systemic high pressure pump, the thin and translucent tricuspid leaflets may not be well adapted for this situation.
Chapter 8

Methods
Hypotheses

- Adults with the Mustard procedure have reduced aerobic capacities during exercise due to a reduced maximal heart rate and systemic RVEF.
- Echocardiographic and MRI variables such as RVEF and right ventricular volumes are abnormal when compared to a healthy population.
- Oxygen desaturation with exercise is due to right-to-left shunts as a result of baffle leakage.
- ACE inhibitors will benefit resting and exercise systemic right ventricular ejection fraction and ameliorate adverse right ventricular remodeling in patients with the Mustard procedure.

Patient Population

Between 1963 and 1980 the Mustard procedure was performed on 435 patients at the Hospital for Sick Children, Toronto, Canada. Survival to age 18 years was 79% (344 patients). Of these adult patients, 152 (44%) are followed at the University of Toronto Congenital Cardiac Centre for Adults. Late mortality after age 18 was 10% (15 patients) and 33 patients were lost to follow up. The remaining 119 patients were all consecutively recruited to undergo cardiopulmonary testing. Of the 119 patients, 84 (71%) had undergone a cardiopulmonary exercise study as part of this evaluation, and are the subject of this study. The remaining 35 patients (16 males, 19 females) without exercise tests were not different from those with exercise tests (study patients: 56 males and 28 females) (table 2).
Table 2. Study Mustard patients with exercise cardiopulmonary studies (CPS) vs. Mustard patients without CPS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mustards with CPS</th>
<th>N</th>
<th>Mustards w/o CPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>80</td>
<td>23 (18-38)</td>
<td>35</td>
<td>25 (9-49)</td>
</tr>
<tr>
<td>Age at Mustard (years)</td>
<td>61</td>
<td>2 (1-10)</td>
<td>32</td>
<td>1.5 (1-13)</td>
</tr>
<tr>
<td>% with BAS</td>
<td>56</td>
<td>39</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>% with BHS</td>
<td>56</td>
<td>38</td>
<td>23</td>
<td>52</td>
</tr>
<tr>
<td>% with SEP</td>
<td>56</td>
<td>13</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>% with more than one</td>
<td>56</td>
<td>11</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>% with complex lesions</td>
<td>62</td>
<td>47</td>
<td>30</td>
<td>53</td>
</tr>
<tr>
<td>% with no syst AVV regurg</td>
<td>65</td>
<td>18</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>% with mild syst AVV regurg</td>
<td>65</td>
<td>39</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td>% with moderate syst AVV regurg</td>
<td>65</td>
<td>29</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td>% with severe syst AVV regurg</td>
<td>65</td>
<td>14</td>
<td>29</td>
<td>14</td>
</tr>
</tbody>
</table>

w/o=without, CPS=cardiopulmonary exercise studies, BAS=balloon atrial septostomy, BfS=Blalock Hanlon septectomy, SEP=Sterling Edwards procedure, syst=systemic, AVV=atrioventricular valve, regurg=regurgitation.

Ten patients without exercise tests have died and 5 with exercise tests are dead but were included in the study.

Of the 84 patients with cardiopulmonary exercise studies, 14 (17%) were on ACE inhibitors and had undergone cardiopulmonary exercise tests pre and post ACE initiation. These patients had been placed on ACE inhibitors by their attending cardiologists at the Centre, usually in the belief that ACE inhibitors might be helpful, and in a few to alleviate dyspnea or documented high blood pressure.

The mean age of the patients on ACE inhibitors (2 females and 12 males) was 31 years (range 26-42 years). The mean age at Mustard repair was 3 years (range 1-8 years).
and the mean age at ACE inhibitor therapy initiation was 26 years (range 20-37 years). This group was older than the remainder of the Mustard cohort whose mean age was 23 years (range 18-35 years). Mean age at Mustard repair for the patients who were not placed on ACE inhibitors was 2 years (range 1-10 years).

A control group of 12 age matched adults (7 males and 5 females) without any clinical evidence of heart disease and at low probability of cardiovascular events were randomly chosen to act as controls in this study. They all underwent MRI imaging and the standard MRI variables of their pulmonary right ventricles were assessed. The median age of this group at the time of MRI was 23 years (range 16-53 years).

**Cardiopulmonary Exercise Studies**

FVC and FEV₁ were performed according to American Thoracic Society standards prior to cardiopulmonary exercise testing (136). Values obtained for FVC and FEV₁ were compared to those predicted for healthy adults in the same age group (137).

Cardiopulmonary exercise studies were conducted using an electronically braked upright ergometer cycle (Elema, Sweden). For warm up, all patients began exercising at 20 watts during the first minute of the protocol. The workload was increased by 20 watts every 2 minutes until exhaustion, the point that defined their VO₂\textsubscript{peak}. Measurements of expired gases were performed by an oxygen analyzer (Amtech Oxygen Analyzer S-3A/I) every 30 seconds. The analyzer was calibrated prior to testing using known values of oxygen and carbon dioxide standard gases. Blood pressure was measured at one-minute intervals during exercise using a sphygmomanometer and heart rate and rhythm were determined using a cardiac monitor. Oxygen saturations were obtained continuously
using a finger probe (Nellcor Puritan Bennett, model: NPB290). VO\textsubscript{2peak} results were compared to those from an age matched healthy population (138).

To measure ejection fraction radiopharmaceutical 750 MBq \textsuperscript{99mTc}O\textsubscript{4}\textsuperscript{+} was injected prior to exercise. The images were acquired using ADAC gamma detector camera (model Transcam). The images were analyzed using a semi-automated algorithm. The results were analyzed by 2 independent observers and averaged. The error of reproducibility of the left ventricular ejection fraction in our laboratory is $< 2\%$.

The following were examined from the cardiopulmonary exercise study data:

- FVC (L)
- FEV\textsubscript{1} (L)
- Exercise time (min)
- Resting heart rate (bpm)
- Resting systolic blood pressure (mmHg)
- Resting diastolic blood pressure (mmHg)
- Maximum systolic blood pressure (mmHg)
- Maximum diastolic blood pressure (mmHg)
- Maximum heart rate (bpm)
- VO\textsubscript{2peak} (L/min)
- VO\textsubscript{2peak} (mL/Kg/min)
- Ventilation, (L/min)
- Resting LVEF (%)
- Resting RVEF (%)
Exercise LVEF (%)  
Exercise RVEF (%)  
Exercise right ventricular EDV (L)

**Magnetic Resonance Imaging**

MRI performed within 18 months of cardiopulmonary exercise studies were examined in 23 adults in the Mustard group. MRI was studied for RVEF and right ventricular volume.

**Protocol**

- Axial T1 weighted images used for anatomical imaging.
- 10 mm slices, interleaved with 10 mm slices, effectively contiguous 5 mm slices.
- Matrix 256 x 192 pixels.
- 2 NEX (number of excitations).
- Superior/inferior saturation pulses (to decrease slow flow signal).
- Minimum time to repetition (TR) = 1 r-to-r wave interval.
- Time to echo (TE) = 20 msec.

- Cine gradient-echo images for functional studies.
- Multiple axial segmented K space (box in which echo signals are reconstructed)
- FMPGR (fast multiplanar gradient echo)
- 10 mm contiguous slices
- 256 x 128 pixels
- 6 NEX
2D Echocardiography

Cross sectional 2D transthoracic echocardiography was performed within 1 year of cardiopulmonary exercise studies. Standard parasternal long and short axis, apical 4 chamber and subcostal views were used. Assessment of right ventricular size and function was made on parasternal long and short axis and apical 4-chamber views. The degree of systemic AV valve regurgitation was assessed on apical 4-chamber and modified parasternal long axis views, using standard color Doppler techniques. Systemic AV valve regurgitation was graded in 65 patients according to broadness and size of regurgitant jet as well as right atrial size, into mild, moderate and severe.

Operative Data

The database of the Division of Cardiology at the Hospital for Sick Children was reviewed for Mustard operative reports for the 84 patients in this study. Fifty-one operative reports were found and examined.

Angiotensin Converting Enzyme Inhibitor Dosage

The dosage of ACE inhibitors was categorized as low, medium or high according to reference values for equivalent doses (139). Using enalapril as an example, a low dose is 5-9 mg·day⁻¹, a medium dose is 10-40 mg·day⁻¹ and a high dose is ≥40mg·day⁻¹. There were 6 patients in the low dose group, 7 in the medium dose group and 1 patient in the high dose group. Compliance was unknown; however, all patients confirmed by telephone or in person that they were taking the medication as prescribed.
Statistics

The data was analyzed using SPSS 9.0 for Windows. Descriptive data was expressed as medians with ranges, and measured data was presented as means with standard deviations. Differences across age groups were analyzed using ANOVA. A linear regression model (backward elimination selection procedure) was used to reveal the impact of pre operative catheterization and operative data, as well as MRI and cardiopulmonary exercise results on VO$_{2peak}$. The correlation between the presence of sinus rhythm and VO$_{2peak}$ was determined using the Spearman Rank Correlation Test. The correlation between percent change in right ventricular ejection fraction and VO$_{2peak}$ was determined using the Pearson Correlation Test. Depending on whether or not the variables were normally distributed, MRI variables between the Mustard and control groups were compared using the Student t-test or the Mann-Whitney test. Variables continuous for the same groups were compared using the paired Student t-test or the Wilcoxon Signed Ranks test. Relationships between the degree of systemic AV valve regurgitation and VO$_{2peak}$ were determined using the Kruskal-Wallace test. In the ACE group a multiple linear regression model (backward elimination selection procedure) was used to demonstrate the impact of descriptive variables. A p value of <0.05 was regarded as statistically significant.
Chapter 9

Results: Cardiopulmonary Exercise Studies in

Adult Survivors of the Mustard Procedure
Cardiopulmonary Exercise Performance in Adult Survivors with the Mustard Procedure

Results

Cardiopulmonary Exercise Studies

Resting data are presented in table 3 and exercise data are presented in table 4. Adults after the Mustard procedure achieved a lower VO$_{2peak}$ in each age group for both males and females (n=53, range 41-49% of reference values and n=26, range 36-41% of reference values, respectively) (figure 10). Mean resting systemic RVEF with standard deviation was (n=54) 47 ±14% and mean pulmonary LVEF was (n=71) 55 ±13% (table 3). Patients achieved an 11 ±19% increase in their systemic RVEF from rest to exercise (table 4). No gender differences were found between systemic RVEF (p=0.328). There was also no correlation between VO$_{2peak}$ and percent change in RVEF (r=0.168, p=0.234).

Values obtained for FVC (n=79, mean 3.75 ±0.95) and FEV$_1$ (n=79, mean 3.16 ±0.85) were depressed compared to predicted values (figure 11).

Maximum heart rates (table 4) were lower in the Mustard cohort (n=81, mean 147 ±25SD bpm) than predicted values (140), patients achieving on average 75% of their predicted maximum heart rate (table 4). Fifty-three of 67 patients (79%) were in sinus rhythm during exercise testing and there was no relationship between the presence of sinus rhythm and VO$_{2peak}$.

Mean oxygen saturation was normal at rest (n=19, mean 97 ±3%) compared with a healthy population (97-100%). At maximal exercise however, mean oxygen saturations
were depressed (n=41, mean 88 ±5%) (table 4). All 41 patients who were tested for oxygen saturations at maximal exercise demonstrated subnormal values. The mean age of these patients was 25 ±7 years, mean age at Mustard repair was 25 ±19 months, mean exercise time was 7 ±2 minutes, mean RVEF was 59 ±12% and mean VO2peak was 21 ±7ml/kg-min⁻¹.

Magnetic Resonance Imaging

MRI noted significantly lower resting RVEFs (n=27, 43 ±8%, p ≤0.001) and larger right ventricular volumes (n=22, 132.2 ±49.7 ml, p≤0.001) than healthy control subjects also analyzed with MRI (table 5). Right ventricular free-wall thickness could not be measured accurately as surgical artifacts would have obscured the results.

Echocardiography

Fifty-three patients (82%) demonstrated systemic AV valve regurgitation. There were 12 patients with no systemic AV valve regurgitation, 26 patients with mild systemic AV valve regurgitation, 18 with moderate, and 9 with severe systemic AV valve regurgitation. No relationship was found between severity of systemic AV valve regurgitation at rest and VO2peak.

Operative Data

There were no relationships between operative variables (including age at surgery) (table 6).
Table 3. Resting Cardiopulmonary Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mustard</th>
<th>%Predicted</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (liters)</td>
<td>79</td>
<td>3.75 (±0.95)</td>
<td>81 (±12)</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (liters)</td>
<td>79</td>
<td>3.16 (±0.85)</td>
<td>86 (±16)</td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>76</td>
<td>74 (±16)</td>
<td>75*</td>
<td></td>
</tr>
<tr>
<td>Sys BP (mmHg)</td>
<td>76</td>
<td>120 (±18)</td>
<td>120*</td>
<td></td>
</tr>
<tr>
<td>Dias BP (mmHg)</td>
<td>76</td>
<td>72 (±13)</td>
<td>80*</td>
<td></td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>19</td>
<td>97 (±3)</td>
<td>97-100*</td>
<td></td>
</tr>
<tr>
<td>CPS RVEF (%)</td>
<td>54</td>
<td>47 (±14)</td>
<td>≥ 35**</td>
<td></td>
</tr>
<tr>
<td>CPS LVEF (%)</td>
<td>71</td>
<td>55 (±13)</td>
<td>≥50**</td>
<td></td>
</tr>
</tbody>
</table>

FVC=forced vital capacity, FEV₁=forced expiratory volume in 1 second, HR=heart rate, bpm=beats per minute, Sys/Dias BP=systolic/diastolic blood pressure, mmHg=millimeters of mercury, SaO₂=oxygen saturation, CPS=cardiopulmonary exercise studies, LVEF=left ventricular ejection fraction, RVEF=right ventricular ejection fraction.

*=Reference (141), **= Nuclear Cardiology, Toronto General Hospital
Table 4. Maximal Exercise Cardiopulmonary Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mustard</th>
<th>% Predicted</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise time (sec)</td>
<td>82</td>
<td>386 (±179)</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>HR max (bpm)</td>
<td>81</td>
<td>147 (±25)</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Sys BP max (mmHg)</td>
<td>75</td>
<td>170 (±29)</td>
<td></td>
<td>197 (±28)*</td>
</tr>
<tr>
<td>Dias BP max (mmHg)</td>
<td>75</td>
<td>86 (±23)</td>
<td></td>
<td>89 (±12)*</td>
</tr>
<tr>
<td>SaO₂ max (%)</td>
<td>41</td>
<td>88 (±5)</td>
<td></td>
<td>97-100**</td>
</tr>
<tr>
<td>VO₂peak (ml·kg⁻¹·min⁻¹)</td>
<td>81</td>
<td>20.0 (±6.3)</td>
<td></td>
<td>42-48***</td>
</tr>
<tr>
<td>VO₂peak (ml·min⁻¹)</td>
<td>79</td>
<td>1375.8 (±544.7)</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>RVEF max (%)</td>
<td>55</td>
<td>53 (±15)</td>
<td></td>
<td>69 (±6) ****</td>
</tr>
<tr>
<td>LVEF max (%)</td>
<td>68</td>
<td>62 (±14)</td>
<td></td>
<td>68 (±8)*</td>
</tr>
<tr>
<td>% Change in RVEF</td>
<td>52</td>
<td>11 (±19)</td>
<td></td>
<td>≥5%****</td>
</tr>
</tbody>
</table>

Exercise time=duration of exercise, HR max=maximum heart rate, bpm=beats per minute, Sys/Dias BP=systolic/diastolic blood pressure, mmHg=millimeters of mercury, SaO₂ max=oxygen saturation at maximal exercise, VO₂peak=maximum oxygen uptake, LVEF=left ventricular ejection fraction, RVEF=right ventricular ejection fraction, N/A=not applicable.

* = Reference (140), ** = Reference (141), *** = Reference (138), **** = Reference (142).
Table 5. Control vs. Patient Magnetic Resonance Imaging Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Patient RV</th>
<th>N</th>
<th>Control RV</th>
<th>p-value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEF (%)</td>
<td>23</td>
<td>44 (±8)</td>
<td>12</td>
<td>63 (±8)</td>
<td>&lt;0.0001</td>
<td>47-76*</td>
</tr>
<tr>
<td>RV volume (cc)</td>
<td>18</td>
<td>126.58 (±51.23)</td>
<td>12</td>
<td>70.00 (±30.03)</td>
<td>&lt;0.0001</td>
<td>74 (±2)*</td>
</tr>
</tbody>
</table>

RVEF=right ventricular ejection fraction, RV=right ventricle.
*=(143).
Table 6. Operative Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mustard</th>
<th>N</th>
<th>Males</th>
<th>N</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Mustard (mo)</td>
<td>80</td>
<td>17 (1-252)</td>
<td>53</td>
<td>17 (1-252)</td>
<td>27</td>
<td>17 (6-102)</td>
</tr>
<tr>
<td>Mustard CR temp (deg)</td>
<td>31</td>
<td>20.1 (±4.0)</td>
<td>19</td>
<td>19.9 (±4.0)</td>
<td>12</td>
<td>20.4 (±4.1)</td>
</tr>
<tr>
<td>Mustard CE temp (deg)</td>
<td>36</td>
<td>17.7 (±6.5)</td>
<td>22</td>
<td>16.7 (±4.6)</td>
<td>14</td>
<td>19.2 (±8.6)</td>
</tr>
<tr>
<td>Cardiac output (l)</td>
<td>47</td>
<td>1.7 (±1.0)</td>
<td>31</td>
<td>1.6 (±0.8)</td>
<td>16</td>
<td>1.8 (±1.3)</td>
</tr>
<tr>
<td>Post op stay (days)</td>
<td>42</td>
<td>17 (8-120)</td>
<td>29</td>
<td>17 (8-120)</td>
<td>13</td>
<td>15 (14-76)</td>
</tr>
<tr>
<td>Age at first palliation (days)</td>
<td>50</td>
<td>11 (1-1825)</td>
<td>34</td>
<td>11 (1-1500)</td>
<td>16</td>
<td>10 (1-1825)</td>
</tr>
</tbody>
</table>

Mustard=Mustard procedure, mo=months, temp=temperature, deg=degrees, CR=colorectal, CE=coloesophageal, l=liters, Flow=blood flow during surgery, Post op stay=post operative stay in hospital.
Figure 10. VO$_{2\text{peak}}$ in Mustard patients and healthy adults in different age groups

- Healthy male
- Healthy female
- Mustard male
- Mustard female

$\bullet, \Delta = $ Reference values for healthy males and females are from (138).
Figure 11. Percent predicted forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) and obtained values over age.
Discussion

Cardiopulmonary exercise data from the present study showed that adult patients after a Mustard repair for TGA achieved a lower VO$_{2peak}$ than a healthy population, in agreement with previous reports (7,9,144). There is no perfect control group for the systemic right ventricle. We elected to use the morphologic pulmonic right ventricle in healthy persons as opposed to the morphologic systemic left ventricle since they differ with respect to fiber orientation, blood supply and nerve supply. This study also showed that resting mean ejection fractions were within the normal range and the increase in systemic RVEF from rest to maximum exercise was within normal limits. Patients demonstrated low mean FVC and FEV$_1$ values as well as depressed maximum heart rates compared to predicted values. Mean oxygen saturation was normal at rest, however, diminished during maximal exercise.

MRI demonstrated significantly lower RVEFs and larger right ventricular volumes than the control group. Resting RVEF determined by MRI agreed closely with resting RVEF determined by radionuclide angiography at 47% and 44% respectively.

Echocardiography showed systemic (tricuspid) AV valve regurgitation in most patients.

Pediatric operative data (table 6) including age at surgery, showed no significant relationships to adult cardiopulmonary exercise results.
Chapter 10

Results: Right-to Left Shunts and Exertional Desaturation
Right-to-Left Shunts and Exertional Desaturation in Adult Patients After the Mustard Procedure

Introduction

Our previous report showed significantly depressed oxygen saturations at maximal exercise in a cohort of adults with the Mustard procedure (n=41, 88 ±5%, p≤0.001), despite no echocardiographic evidence of a significant shunt. The aim of this prospective pilot study is to determine whether baffle leaks in a Mustard cohort was the cause of reduced oxygen saturations with exercise.

Methods

Patient Population

Six patients (3 females and 3 males), with the largest decline in oxygen saturations at maximal exercise were chosen to perform a resting and exercise quantitative right-to-left shunt study in order to investigate the possibility of a right-to-left shunt. The median age was 27 years (range 21-32) years and median age at Mustard repair was 1 year (range 1-4 years).

Statistical analysis illustrated no significant differences between this cohort and the remaining 78 patients who had undergone cardiopulmonary exercise studies with respect to age (p=0.195), age at Mustard repair (p=0.447), weight (p=0.486), pre Mustard repair palliation (p=0.988), body surface area at the time of Mustard repair (p=0.760), post Mustard repair complications (p=0.934) or duration of hospital stay post Mustard repair (p=0.577).
Post Mustard repair catheter reports examined from the database of the Division of Cardiology at the Hospital for Sick Children showed no differences for morphological systemic right ventricular oxygen saturations ($p=0.457$), or morphological pulmonic left ventricular oxygen saturations ($p=0.888$) between the 6 patients who performed shunt studies and the remaining 78 who did not. Of the 84 patients, all received a pericardial baffle except for 1 patient, who received a Dacron conduit and is not one of these 6 patients studied.

Resting Nuclear Quantitative Right-to-Left Shunt Study

To measure right-to-left shunting, 40 MBq of $^{99m}$Tc MAA (macro aggregated albumin) was injected intravenously into the right arm while patients were sitting upright. Immediately after, while still at rest, patients were imaged using the Elscint camera in a posterior supine position. Hot markers were placed at both supraclavicular fossa. The lungs, kidneys and right or left lateral brain were viewed for 3 minutes each. The Apex SP4 computer processor was used to process the images. MAAQ (macro aggregated albumin quantitation) was preset to quantitative shunting and CPPQ (cardiopulmonary perfusion quantitation) was preset to quantitative perfusion.

The radioactive material in the kidney and brain was calculated and compared to that of the lungs by a technician blinded to the patient’s status. A significant shunt was defined as any value greater than the control range (0.003–0.005). Images of a brain, kidney and lungs perfused with radioactive material at rest and after peak exercise are illustrated in figure 12.
Exercise Nuclear Quantitative Right-to-Left Shunt Study

Patients were exercised on a Quinton 55 treadmill and monitored using an ECG, blood pressure cuff (Quinton 412) and operating system (Quinton 5000). Patients followed the Bruce Protocol (145) and were injected with 40 MBq immediately after peak exercise (the point at which VO₂ plateaued) was reached. Patients were imaged 15 minutes after injections following the same protocol outlined for the resting nuclear study.

Statistics

The data was analyzed using SPSS 9.0 for Windows. Descriptive data was expressed as medians with ranges. Measured data was presented as means with standard deviations. Variables continuous for the same groups were compared using the Wilcoxon Signed Ranks test. A p value of <0.05 was regarded as statistically significant.

Results

At rest, the nuclear study showed a mean shunt (kidney + brain: lung) of 0.005 (±0.003). Exercise nuclear studies showed a mean shunt of 0.05 (±0.11). The increase in shunting from rest to exercise was significant (p=0.028) (figure 13). (When 1 outlying patient was excluded from statistical analysis, the increase in shunting remained significant {p=0.043}). The percent increase in shunting from rest to exercise is demonstrated in figure 14.
Discussion

Baffle leaks are well-known late sequelae of the Mustard procedure (146). This study demonstrates that nuclear exercise studies are a powerful tool in detecting shunting during exercise. Bink-Boelkens et al reported that baffle leaks confirmed with cardiac catheterization, were missed with 2D echocardiography when shunts were less than 25% of the pulmonary circulation (147). Despite the fact that baffle leaks were not detected on routine echocardiography examination in these 6 patients, baffle leaks can be detected with this more sensitive radionuclide technique. This uncovered a hitherto unsuspected shunting that occurs or greatly increases during exercise in these Mustard patients. This is suspected to be subclinical baffle leakage, even though shunting at the pulmonary or other levels cannot be ruled out.
Figures

Figure 12. Images of a brain, kidney and lungs perfused with radioactive material at rest and at peak exercise.

Baseline Shunt Study

Exercise Shunt Study
Figure 13. Shunting at rest and at peak exercise.
Figure 14. The percent increase of shunting from rest to peak exercise.
Chapter 11

Results: Angiotensin Converting Enzyme Inhibitors
Angiotensin Converting Enzyme Inhibitors in Adults after the Mustard Procedure

Results

Resting Data

There were no significant differences for resting variables determined by cardiopulmonary exercise studies pre and post ACE initiation (table 7).

MRI noted significantly lower resting RVEFs (n=12, 41 ±7, p ≤0.001) and larger right ventricular volumes (n=8, 132 ±47 ml, p≤0.001) than healthy control subjects also analyzed with MRI (table 8).

Exercise Data

There were no statistically significant differences in the pre and post ACE cohort for exercise variables (table 9). However, VO_{2peak} increased by a mean of 27% in 10 patients (64%) (figure 15) and maximum systolic blood pressure decreased by a mean of 19% in 7 patients (36%) (figure 16). Six patients (43%) increased their exercise duration by a mean of 29% and 3 patients stayed the same.

Age, Dosage and Gender Effects

Within the ACE group, current age, age at surgery, age at ACE inhibitor initiation, dosage of ACE inhibitors and gender showed no effect on the cardiopulmonary exercise results (including VO_{2peak}, blood pressure and heart rate at maximal exercise, or systemic
RVEF at maximal exercise). There was also no effect on MRI study variables (including systemic RVEF or systemic right ventricular volume).
Table 7. Pre and post angiotensin converting enzyme (ACE) inhibitor therapy resting cardiopulmonary study data (minimum of 6 months on ACE inhibitors).

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Pre ACE</th>
<th>Post ACE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (liters)</td>
<td>14</td>
<td>4.2 (±0.85)</td>
<td>4.1 (±0.91)</td>
<td>0.310</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>14</td>
<td>80 (±8)</td>
<td>78 (±9)</td>
<td>0.214</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>14</td>
<td>75 (±13)</td>
<td>77 (±15)</td>
<td>0.970</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>14</td>
<td>114 (±11)</td>
<td>120 (±13)</td>
<td>0.340</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>14</td>
<td>68 (±8)</td>
<td>72 (±12)</td>
<td>0.290</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>14</td>
<td>58 (±10)</td>
<td>59 (±12)</td>
<td>0.609</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>14</td>
<td>47 (±11)</td>
<td>45 (±11)</td>
<td>0.608</td>
</tr>
</tbody>
</table>

FVC=forced vital capacity, HR=heart rate, bpm=beats per minute, BP=blood pressure, mmHg=millimeter of mercury, LVEF=left ventricular ejection fraction, RVEF=right ventricular ejection fraction.
Table 8. Control vs. patient on ACE (Angiotensin Converting Enzyme) inhibitor magnetic resonance imaging (MRI) variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Patient RV</th>
<th>N</th>
<th>Control RV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEF (%)</td>
<td>12</td>
<td>41 (±7)</td>
<td>12</td>
<td>63 (±8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV volume (cc)</td>
<td>8</td>
<td>132 (±47)</td>
<td>12</td>
<td>70.00 (±30.03)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

RVEF=right ventricular ejection fraction, RV=right ventricle.
Table 9. Pre and post angiotensin converting enzyme (ACE) inhibitor therapy maximal exercise cardiopulmonary study data (minimum of 6 months on ACE inhibitors).

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Pre ACE</th>
<th>Post ACE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise time (minutes)</td>
<td>14</td>
<td>6.6 (±1.8)</td>
<td>7.0 (±1.9)</td>
<td>0.58</td>
</tr>
<tr>
<td>HR&lt;sub&gt;max&lt;/sub&gt; (bpm)</td>
<td>14</td>
<td>148 (±21)</td>
<td>144 (±27)</td>
<td>0.340</td>
</tr>
<tr>
<td>Systolic BP&lt;sub&gt;max&lt;/sub&gt; (mm Hg)</td>
<td>14</td>
<td>178 (±16)</td>
<td>166 (±28)</td>
<td>0.148</td>
</tr>
<tr>
<td>Diastolic BP&lt;sub&gt;max&lt;/sub&gt; (mm Hg)</td>
<td>14</td>
<td>84 (±14)</td>
<td>85 (±16)</td>
<td>0.740</td>
</tr>
<tr>
<td>VO&lt;sub&gt;2peak&lt;/sub&gt; (ml·kg&lt;sup&gt;-1&lt;/sup&gt;·min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>14</td>
<td>16.7 (±5.1)</td>
<td>18.5 (±5.4)</td>
<td>0.360</td>
</tr>
<tr>
<td>Ventilation (l·min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>14</td>
<td>61.4 (±18.6)</td>
<td>63.9 (±23.9)</td>
<td>0.554</td>
</tr>
<tr>
<td>LVEF max (%)</td>
<td>14</td>
<td>58 (±10)</td>
<td>59 (±12)</td>
<td>0.609</td>
</tr>
<tr>
<td>RVEF max (%)</td>
<td>14</td>
<td>47 (±11)</td>
<td>45 (±11)</td>
<td>0.608</td>
</tr>
</tbody>
</table>

bpm=beats per minute. BP<sub>max</sub>=maximum blood pressure. Exercise time=duration of exercise. HR<sub>max</sub>=maximum heart rate. LVEF=left ventricular ejection fraction. mm Hg=millimeter of mercury. RVEF=right ventricular ejection fraction. Ventilation=maximum air expired during exercise. VO<sub>2peak</sub>=maximum oxygen uptake.
Figure 15. Maximum oxygen uptake ($VO_{2peak}$) pre and post angiotensin converting enzyme (ACE) initiation.
Figure 16. Maximum systolic blood pressure pre and post angiotensin converting enzyme (ACE) initiation.
Discussion

To our knowledge this is the first report to describe the use of ACE inhibitors in adults after the Mustard procedure. Results from the present study, although preliminary, showed that ACE inhibitor therapy for 6 months or longer did not significantly affect exercise tolerance, resting hemodynamics or ventricular remodeling. However, some patients improved their VO$_{2peak}$, exercise duration and lowered their blood pressure at maximum exercise post ACE inhibitor initiation. These findings show that although there were no statistically significant overall changes, some patients did, however, have a positive effect and this data should be considered as important pilot data, and that there is a significant variation in response of this population to ACE inhibitors.

Lester et al reported preliminary results showing improvements in exercise times and right ventricular ejection fractions in similar patients treated with an angiotensin-2 receptor antagonist (148).

Despite the fact that patients in the present study were most often clinically asymptomatic at rest, exercise intolerance was evidenced by lower VO$_{2peak}$; findings which are in agreement with previous reports (7,9,144).
Chapter 12

Discussion
Through our studies, we have demonstrated that patients with TGA following the Mustard procedure on average showed impaired aerobic power, a normal resting RVEF measured by RNA, which increased normally with exercise. As well, we found oxygen desaturation during exercise, in many, which may be related to potential baffle leakage. We have shown that ACE inhibitors improve VO₂peak and decreased exercise systolic blood pressure in a subset of patients (although there was no overall difference).

A right ventricle in the systemic position is present in patients with TGA after the Mustard procedure. There are no acceptable standards to compare and describe right ventricular function in these patients. We elected to use the morphological pulmonic right ventricle in healthy adults without congenital heart disease as a comparison group for these patients. We realize that this may not truly serve as an appropriate control for the study population. However, in the absence of other more established reference controls, this at least allowed a standard against which the performance can be measured.

Many investigators have reported that adult Mustard patients demonstrate subnormal responses to exercise (7,9,149-152). There are many possible bases for this observation including right ventricular dysfunction, peripheral deconditioning, rhythm disturbances, chronotropic incompetence and impaired lung function. Paul and colleagues report that diminished exercise performance is related to a diminished cardiac output, resulting from diminished stroke volume and also related to a blunted heart rate response (152). Murphy et al demonstrated that even in a group of asymptomatic patients, a substantial number have either a decreased resting RVEF or a subnormal response to exercise (150). Similarly, Gilljam’s group reported that VO₂peak and heart rate were low at maximal exercise (9). Ensing and colleagues found that heart rate, oxygen saturation and stroke
volumes were reduced at maximal exercise compared with control values (7). As well, Warnes et al reported right ventricular dysfunction and tricuspid regurgitation in several patients (153).

Abnormal right ventricular responses to exercise in the patient group described in the present study may be attributed to myocardial hypoxia (pre operative and intraoperative) and to the right ventricle’s geometry which may be ill-suited mechanically as the systemic pump faces arterial pressures. Benson and colleagues have also noted that right ventricular fiber array differs from that of the left ventricle and may render the right ventricle less able to function systemically (144).

Peripheral deconditioning may also contribute to depressed exercise performance in this cohort. This may be due to a sedentary lifestyle adopted since childhood resulting in peripheral large limb muscles being unable to maximize oxygen extraction, rendering a depressed VO2peak. This observation was noted by Fredriksen et al in male adolescents with congenital heart disease who are less physically active than an age matched normal population (154). Heart failure studies have also shown similar effects upon peripheral musculature (155).

Abnormal heart rate responses to exercise may also contribute to subnormal exercise power in this cohort. Gillette’s group has suggested that abnormalities in rhythm found in this patient population have been attributed to surgical sinoatrial node damage (156).

Chronotropic incompetence likely has an important role in the low maximum oxygen uptake achieved by this cohort. Notably, Paul et al reviewed many studies on similar cohorts and reported that diminished exercise performance was related to a blunted heart rate response (152). Clearly, if heart rate responses to exercise are subnormal, cardiac
output (without a concomitant increase in stroke volume) will not rise to the degree expected and thus the cardiac contribution to maximum oxygen uptake will be abnormally low.

Reduced pulmonary function may also contribute to decreased exercise performance. Some patients have subnormal FVC and FEV₁ and may have restrictive or obstructive lung disease. This may result in reduced oxygen saturation and delivery to tissues. With increased oxygen demand on exertion, compromised lung function may not deliver enough oxygen to meet the demands of peripheral tissue yielding a reduced VO₂peak. In heart failure studies, exercise power correlates nicely with the increased ventilatory response (157). Possible pulmonary causes have been explored, including increased dead space ventilation, abnormal airway function, and abnormal diffusion capacity. Clark et al report that it is more likely that excessive ventilation is not due to a primary pulmonary pathology but rather the increase in dead space is likely to be a response to increased ventilation (158).

Another important finding in our cohort was that oxygen saturations at maximal exercise were lower than expected. This is in agreement with observations made by Sagin-Saylam and colleagues (8).

Gilljam et al found abnormally low exercise oxygen saturations in a similar adult cohort and noted that half of this population also had baffle gaps (9). Despite confirming baffle gaps in 50% of their patients, this group attributed their findings of depressed oxygen saturations in part to intrapulmonary shunts especially in patients with pulmonary hypertension (9).
Matthews and colleagues suspected inter-atrial baffle leaks in a pediatric population. They found that many of their patients desaturated during exercise despite cardiac catheterization documented normal oxygen saturations at rest and apparent absence of shunting (10). Bowyer et al also showed similar findings, which they attributed to a potential baffle leak (11).

Baffle leaks with exercise-induced or augmented right to left shunts may be largely responsible for diminished oxygen saturations at maximal exercise found in the present cohort. While echocardiography did not detect shunting at rest in patients tested in this study, nuclear studies showed a significant shunt in 3 patients at rest (0.008 ±0.003) and in all 6 patients tested during maximal exercise. These findings suggest that echocardiography may not be sensitive enough to determine potentially important inter-atrial shunts. Bink-Boelkens et al reported that baffle leaks confirmed with cardiac catheterization, were missed with echocardiography when shunts were less than 25% of the pulmonary circulation (147). However, this study demonstrates that nuclear exercise studies are a more powerful tool and particularly useful to detect shunting during exercise. In an effort to confirm that shunting was due to baffle leakage, the investigators are in the process of performing stress echocardiography with contrast in these 6 patients.

A possible reason for baffle leakage includes degenerative changes associated with long-term baffle placement.

Significant baffle leaks, which limit activities of daily living, can be repaired. Minor baffle leakage may not require repair if patients report normal activities of daily living and shunting is not apparent at rest.
Angiotensin Converting Enzyme Inhibitors

Results from the present study, although preliminary, showed that ACE inhibitor therapy for 6 months or longer did not significantly affect exercise tolerance, resting hemodynamics or ventricular remodeling in a cohort of Mustard adults. However, some patients improved their VO$_{2peak}$, exercise duration and lowered their blood pressure at maximum exercise post ACE inhibitor initiation. These findings show that although there were no statistically significant overall changes, some patients did, however, have a positive effect and this data should be considered as pilot data.

For baseline values of VO$_{2peak}$, oxygen saturation at maximal exercise and time on ACE inhibitors, there appears to be no differences between responders and non-responders to ACE inhibition therapy.

An important question to consider is whether the dosage of ACE inhibitors was substantial enough to achieve quantitative changes in the right ventricle. The Studies On Left Ventricular Dysfunction (SOLVD) investigators demonstrated a reduction in the incidence of heart failure in patients with acquired left ventricular dysfunction using a maximum dosage of 20 mg·day$^{-1}$ of enalapril (159,160). Stevenson suggested the need for higher doses of ACE inhibitors to achieve maximal benefit in patients with severe CHF (161).

In the present study, 8 patients were treated with enalapril using a mean dosage of approximately 20 mg·day$^{-1}$. This dosage may not be large enough to affect right ventricular remodeling or increase exercise tolerance in many adults after the Mustard procedure.
Although ACE inhibitors have proven to be effective in patients with systemic left ventricular dysfunction (12,15,159,160), their effectiveness has never been assessed for the human systemic right ventricle. Thus, we have not ascertained whether the systemic right ventricle and systemic left ventricle respond similarly to ACE inhibitors. It has been postulated that there is differential expression of angiotensin II receptors in the right and left ventricles. While few studies have examined localized expression of angiotensin II receptors on the systemic right ventricle, Heymes et al reported up-regulation of angiotensin II receptor (AT1a and AT1b) mRNA levels in the morphologic left ventricles in 3-month-old rats but not in the morphologic right ventricles (162). Another group reported that angiotensin II does not contribute to the development of pressure overload-induced morphologic right ventricular hypertrophy. The authors showed that the expression of angiotensin receptors was not altered by increased afterload in the ovine fetus (163). Further, Black et al determined that ACE inhibitors prevented the development of morphologic left ventricular hypertrophy but did not influence growth of the morphologic right ventricle in rats with spontaneous hypertension (164). These findings suggest that the morphologic right ventricle may not rely as heavily upon angiotensin II as the morphologic left ventricle does. It may be that other systems may play a more significant role in morphologic right ventricular dysfunction and remodeling.

A further uncertainty exists as to whether the initiation of ACE inhibitor therapy was early enough to achieve beneficial results in all patients. ACE inhibitors have been examined in the literature based on their ability to treat patients with acquired left ventricular dysfunction, with a relatively short time lapse between onset of left ventricular failure and initiation of ACE inhibitor therapy. Kramer et al reported
hemodynamic benefits in CHF patients who started ACE inhibitor therapy after a mean of 4.2 ±2.8 years after the evidence of heart failure (165). Creager et al described patients with CHF who initiated ACE inhibitor therapy after a mean of 2.1 ±2.4 years after presenting with heart failure with similar results (166). In the present study, the mean time interval between the surgical correction with the Mustard procedure and ACE inhibitor initiation was 24 ±5 years. There thus exists the possibility that the extended high-pressure demands on the morphological systemic right ventricle cannot be rescued by "late" use of ACE inhibitor therapy in these patients.

Finally, those patients who responded well to ACE inhibition may have had a more activated renin-angiotensin system initially. As well, patients may have been taking other medications which acted synergistically with ACE inhibitors.
Chapter 13

Conclusion
The present study showed that patients with TGA after the Mustard procedure have subnormal exercise capacities while maintaining normal mean systemic RVEF at rest and during maximal exercise. Factors such as right ventricular dysfunction, peripheral deconditioning, rhythm disturbances, chronotropic incompetence and impaired lung function may be responsible for these results. As well, patients demonstrated oxygen desaturation with exercise (with some displaying a right-to-left shunt increasing with exertion), which from preliminary data is attributable to baffle leakage.

There were no statistically significant differences pre and post ACE initiation for the cardiopulmonary exercise study and MRI determined variables. However, findings in VO$_{2\text{peak}}$ and blood pressure at maximum exercise showed a positive impact of ACE inhibitors in some patients warranting the need for further studies on a larger population.
Chapter 14

Acknowledgements
Per Morten Fredriksen has been supported by The Norwegian Association for Children with Congenital Heart Disorders (FFHB), The Norwegian Lung- and Heart Association and The National Foundation of Public Health in Norway.

Gruschen Veldtman has been supported by the National Heart Research Fund, UK.
Chapter 15

Future Research
Directions for Future Studies

We have shown that there is a significant increase in right to left shunting from rest to exercise but some questions remain:

1. Where is the exact location of the shunt?
2. What are the clinical implications of a right to left shunt in these patients?

In order to answer these questions, the same 6 patients will be studied with a stress echocardiogram using bubbles to visualize the exact location of the shunt. We will then correlate the presence and degree of shunting on exertion with oxygen saturations on exertion.

It has also been demonstrated that ACE inhibitors have a positive effect in some patients. However, it is not clear as to whether or not angiotensin II is activated in these patients. A larger prospective study should examine ACE enzyme activity and angiotensin II levels from blood samples taken pre and post ACE inhibitor initiation. As well, MRI may be used to examine ventricular remodeling and CPS studies to describe exercise tolerance pre and post ACE inhibitor initiation.
Appendices

Pre Operative Catheter Data

The database of the Hospital for Sick Children was used to identify patients currently followed up at TCCCFA with pre operative catheter and operative reports. Fifty-one patients were found and reports were examined.

The following were included as pre operative catheter variables (Table 10):

Table 10. Pre Operative Catheter Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mustard</th>
<th>N</th>
<th>Males</th>
<th>N</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV saturation (%)</td>
<td>50</td>
<td>68 (±13)</td>
<td>34</td>
<td>67 (±13)</td>
<td>16</td>
<td>70 (±13)</td>
</tr>
<tr>
<td>RV sys pressure (mmHg)</td>
<td>51</td>
<td>90 (±21)</td>
<td>34</td>
<td>92 (±19)</td>
<td>17</td>
<td>86 (±25)</td>
</tr>
<tr>
<td>RV dias pressure (mmHg)</td>
<td>48</td>
<td>7 (±3)</td>
<td>32</td>
<td>6 (±3)</td>
<td>16</td>
<td>7 (±3)</td>
</tr>
<tr>
<td>RA O₂ sat (%)</td>
<td>49</td>
<td>63 (±14)</td>
<td>34</td>
<td>62 (±15)</td>
<td>5</td>
<td>66 (±11)</td>
</tr>
<tr>
<td>RA A pressure (mmHg)</td>
<td>25</td>
<td>9 (±5)</td>
<td>17</td>
<td>9 (±5)</td>
<td>8</td>
<td>9 (±3)</td>
</tr>
<tr>
<td>RA V pressure (mmHg)</td>
<td>27</td>
<td>8 (±4)</td>
<td>17</td>
<td>8 (±5)</td>
<td>10</td>
<td>8 (±3)</td>
</tr>
<tr>
<td>RA mn pressure (mmHg)</td>
<td>45</td>
<td>5 (±2)</td>
<td>31</td>
<td>5 (±2)</td>
<td>14</td>
<td>6 (±3)</td>
</tr>
<tr>
<td>LA saturation (%)</td>
<td>49</td>
<td>91 (±10)</td>
<td>32</td>
<td>91 (±10)</td>
<td>17</td>
<td>91 (±12)</td>
</tr>
<tr>
<td>LA A pressure (mmHg)</td>
<td>28</td>
<td>8 (±3)</td>
<td>19</td>
<td>8 (±3)</td>
<td>9</td>
<td>9 (±3)</td>
</tr>
<tr>
<td>LA V pressure (mmHg)</td>
<td>29</td>
<td>8 (±2)</td>
<td>19</td>
<td>8 (±2)</td>
<td>10</td>
<td>9 (±2)</td>
</tr>
<tr>
<td>LA mn pressure (mmHg)</td>
<td>49</td>
<td>5 (±2)</td>
<td>32</td>
<td>5 (±2)</td>
<td>17</td>
<td>5 (±3)</td>
</tr>
<tr>
<td>LV saturation (%)</td>
<td>51</td>
<td>85 (±13)</td>
<td>34</td>
<td>85 (±7)</td>
<td>17</td>
<td>84 (±20)</td>
</tr>
<tr>
<td>LV sys pressure (mmHg)</td>
<td>50</td>
<td>48 (±28)</td>
<td>33</td>
<td>44 (±25)</td>
<td>17</td>
<td>56 (±31)</td>
</tr>
<tr>
<td>LV dias pressure (mmHg)</td>
<td>47</td>
<td>6 (±3)</td>
<td>31</td>
<td>6 (±3)</td>
<td>16</td>
<td>6 (±3)</td>
</tr>
<tr>
<td>PA saturation (%)</td>
<td>31</td>
<td>83 (±8)</td>
<td>19</td>
<td>84 (±7)</td>
<td>12</td>
<td>82 (±9)</td>
</tr>
<tr>
<td>PA sys pressure (mmHg)</td>
<td>29</td>
<td>40 (±34)</td>
<td>20</td>
<td>38 (±34)</td>
<td>9</td>
<td>46 (±35)</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value 1</td>
<td>Value 2</td>
<td>Value 3</td>
<td>Value 4</td>
<td>Value 5</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
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<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
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</tr>
<tr>
<td>PA dias pressure (mmHg)</td>
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<td>10 ±12</td>
<td>20</td>
<td>12 ±14</td>
<td>9</td>
<td>7 ±2</td>
</tr>
<tr>
<td>PA mn pressure (mmHg)</td>
<td>29</td>
<td>15 ±9</td>
<td>18</td>
<td>15 ±8</td>
<td>11</td>
<td>15 ±10</td>
</tr>
<tr>
<td>Ao saturation (%)</td>
<td>47</td>
<td>70 ±11</td>
<td>30</td>
<td>70 ±11</td>
<td>17</td>
<td>72 ±13</td>
</tr>
<tr>
<td>Ao sys pressure (mmHg)</td>
<td>42</td>
<td>91 ±15</td>
<td>28</td>
<td>91 ±16</td>
<td>14</td>
<td>90 ±12</td>
</tr>
<tr>
<td>Ao dias pressure (mmHg)</td>
<td>42</td>
<td>54 ±10</td>
<td>28</td>
<td>54 ±11</td>
<td>14</td>
<td>54 ±10</td>
</tr>
<tr>
<td>Ao mn pressure (mmHg)</td>
<td>40</td>
<td>70 ±13</td>
<td>25</td>
<td>70 ±12</td>
<td>15</td>
<td>69 ±15</td>
</tr>
<tr>
<td>SVC saturation (%)</td>
<td>49</td>
<td>49 ±14</td>
<td>33</td>
<td>46 ±15</td>
<td>16</td>
<td>55 ±11</td>
</tr>
<tr>
<td>IVC saturation (%)</td>
<td>40</td>
<td>53 ±13</td>
<td>28</td>
<td>53 ±13</td>
<td>12</td>
<td>53 ±14</td>
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<tr>
<td>Pulm flow (l·min⁻¹·m²⁻¹)</td>
<td>27</td>
<td>4.8 ±3.1</td>
<td>17</td>
<td>8.7 ±6.1</td>
<td>10</td>
<td>5.9 ±2.4</td>
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<tr>
<td>Sys flow (l·min⁻¹·m²⁻¹)</td>
<td>28</td>
<td>2.3 ±2.1</td>
<td>19</td>
<td>4.8 ±3.6</td>
<td>9</td>
<td>4.8 ±1.4</td>
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<tr>
<td>Pulm:sys flow</td>
<td>21</td>
<td>7.6 ±5.2</td>
<td>14</td>
<td>2.7 ±2.5</td>
<td>7</td>
<td>1.4 ±0.5</td>
</tr>
</tbody>
</table>

RV=right ventricular, saturation=oxygen saturation, LV=left ventricular, sys pressure=systolic pressure, dias pressure=diastolic pressure, PA=pulmonary artery, Ao=Aortic, Pulm flow=pulmonary circulation blood flow, sys flow=systemic circulation blood flow
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