“…there is a fountain of youth, it's just that you have to work hard to drink from it.”

Gregg R. Hill

University of Alberta

The effects of twelve weeks of supervised aerobic and resistance training on exercise capacity, muscle strength, quality of life, body composition and cardiovascular disease risk factors in kidney transplant recipients

by

Kenneth James Riess

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

In

Rehabilitation Science

Department of Rehabilitation Medicine

Fall 2011
Edmonton, Alberta

Dedication

I would like to dedicate this thesis to my family who have always been there to support me.

Mom and Dad, you have always believed in me and have never uttered a discouraging word or presented a less than positive attitude for any challenge I decided to attempt. The ethical and moral standards and work ethic you instilled in your 4 boys is something I aspire to with Cooper and Casey.

John, Paul and Timothy, growing up with the three of you truly shaped me into the person I am today. The competitive natures the four of us possess have followed us into adulthood and I thank you for teaching me, in my younger days and now, that nothing is out of reach.

Cooper and Casey, you are two amazing young men. Watching the two of you grow and seeing how hard you work is an inspiration and I could not have done this without the example you set for me.

Jennifer, I love you. This achievement belongs as much to you as it does to me. Your support, understanding and encouragement, especially in the rough patches I went through was essential and will forever be appreciated. Thank you so much.

Abstract

Cardiovascular disease (CVD) is a major cause of mortality in kidney transplant recipients (KTR). The increased CVD risk is due, in part, to reduced cardiorespiratory fitness (VO_{2peak}) associated with inactivity. The role of exercise training to improve overall physical fitness, quality of life (QOL) and CVD risk factors in KTR has not been well studied.

The aim of this thesis is to investigate the effects of a 12 week supervised exercise training (ET) program versus usual care (UC) on VO_{2peak} , muscular strength, QOL, body composition and CVD risk profile in KTR. Further, the mechanisms responsible for the increase in VO_{2peak} will be determined.

Thirty-seven KTR underwent baseline testing consisting of: incremental exercise test with expired gas analysis and impedance cardiography, resting small and large arterial compliance, lower extremity maximal strength, estimation of lean body mass, 24 hour ambulatory blood pressure monitoring, QOL and a 10-year CVD risk score. Subjects were randomized to ET (aerobic exercise 30 – 60 minutes, 3 days/week and strength training 2 days/week) or UC.

Thirty-one subjects (mean age; 55 ± 13 years) were randomized to ET (n=16) or UC (n=15). The changes in VO_{2peak}

(ET 2.6 ± 3.1 vs UC -0.5 ± 2.5 ml·kg^{-1}·min $^{-1}$), peak heart rate (ET 8 ± 14 vs UC – 2.9 ± 11.2 beat· min^{-1}), peak cardiac output (ET 1.7 ± 2.6 vs UC –0.01 ± 0.8 L · min-1), leg press (ET 48.7 ± 34.1 vs UC -10.5 ± 37.7 kg) and leg extension strength (ET 9.5 ± 10.3 vs UC 0.65 ± 5.5 kg) were significantly greater after 12 weeks of ET compared to UC. The change in overall QOL improved significantly after 12 weeks of ET compared to UC. No significant difference was found between groups for 24 hour blood pressure, small and large arterial compliance, lean body mass or 10 year CVD risk score.

The major finding of this thesis is that 12 weeks of supervised ET increased VO_{2peak} secondary to an increase in peak heart rate and cardiac output. A secondary finding is that ET increased lower extremity maximal muscular strength and improved QOL compared to UC.

Acknowledgements

In an undertaking of this magnitude there are so many people who contributed to the final outcome and without whom the completion would not have come to fruition. These people include, but are surely not limited to, the following:

Dr. Mark Haykowsky: A true friend and mentor who, without question, is largely responsible for my successful completion of this PhD. His attention to detail and ability to accept nothing but a best effort did not go unnoticed and will not be forgotten.

Dr. Sita Gourishankar: An amazing clinician and compassionate care giver who instilled in me that the patient is, first and foremost, a person and worthy of my best effort.

Dr. Robert Welsh: A superb clinician and friend whose drive and determination, both academically and athletically, inspired me throughout this process.

Dr. Alex Clark: For instilling in me the notion that science is only one part of the equation. The individual is the greater part.

Dr. Richard Lewanczuk: His insight into scientific method and common sense approach was invaluable in my journey.

Dr. Richard Lawrance: For his unselfish giving of time to help with the collection of data for this project.

Dr. Wayne Tymchak: For his assistance in testing subjects for my study and the input he offered into the design of my research.

Corey Tomzac: Your assistance over the past few years will not go forgotten and was never unappreciated. You are a great friend.

Dr. Ben Esch and Dr. Jessica Scott: Your assistance in collecting data was invaluable and I am fortunate to have had the opportunity to work with you.

Mrs. Leanne Telford and my colleagues at NAIT. Your support and understanding offered to me over the years was very much appreciated.

My mother in law, Jane Percy, your support throughout this process was invaluable.

My parents, Lucian and Therese Riess. You have always believed in me and my abilities and consistently supported me in whatever direction I decided to go.

Finally, and most importantly, to my wife, Jennifer and our two boys, Cooper and Casey. You are the inspiration for all that I do. You make me a better person and have been the motivation for this milestone. Thank you so much for your patience and understanding with all of the activities I missed, whether I was in attendance or not.

Table of Contents

List of Tables

List of Figures

List of Symbols

Symbol	Description
$a\text{-}vO_{2diff}$	Arterio-venous oxygen difference
BMI	Body Mass Index
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
EDV	End Diastolic Volume
EF	Ejection Fraction
ESRD	End Stage Renal Disease
ESV	End Systolic Volume
ET	Exercise Training
HDL	High Density Lipoprotein
HR	Heart Rate
KTR	Kidney Transplant Recipient
LDL	Low Density Lipoprotein
LV	Left Ventricle

MAP	Mean Arterial Pressure
MET	Metabolic Equivalent
Q	Cardiac Output
QOL	Quality of Life
RM	Repetition Maximum
RTC	Renal Transplant Clinic
SBP	Systolic Blood Pressure
SF-36	Medical Short Form 36
SV	Stroke Volume
SVR	Systemic Vascular Resistance
TC	Total Cholesterol
UC	Usual Care
VO_{2peak}	Peak Oxygen Consumption

Definition of Terms

Arterial Compliance

The relationship between volume and pressure in the arteries.

Δ Volume / Δ Pressure.

Arterio-venous Oxygen Difference

A measurement of oxygen extracted from the tissues. It is the difference between the oxygen content in arterial blood and mixed venous blood [1].

Cardiac Output

The product of ventricular stroke volume and heart rate [2, 3].

Ejection Fraction

The fraction of EDV ejected from the ventricle during systole [3].

End Diastolic Volume

The volume of the ventricle at the end of diastole.

End Systolic Volume

The volume of the ventricle at the end of systole.

Mean Arterial Pressure (MAP)

Approximately the sum of one third of the pulse pressure and the diastolic pressure [2].

MAP =

Diastolic Pressure + 1/3 (Systolic Pressure – Diastolic Pressure)

Metabolic Equivalent (MET)

Used to estimate the metabolic cost of activity. One MET is equal to 3.5 ml/Kg/min of Oxygen consumption [1].

Pulse Pressure

The Difference between the systolic pressure and the diastolic pressure [2].

Stroke Volume

The volume of blood ejected from the ventricle during systole. The difference between EDV and ESV [3].

VO_{2peak}

The highest recorded amount of oxygen consumption recorded in a maximal test. Used in clinical setting as maximal values may not be attained due to lack of motivation and / or testing protocol selection [4].

General Introduction

1.1 Background

Kidney transplantation is a lifesaving surgical intervention for select individuals with end stage renal disease (ESRD). Despite improved survival, the leading cause of death in kidney transplant recipients (KTR) with a functioning graft is cardiovascular disease (CVD). The reasons for the increased CVD risk is due to both traditional and novel risk factors present before and after transplantation. Specifically, KTR are at increased risk for hypertension [5], diabetes mellitus [6, 7], hypercholesteremia [8] and obesity [9].

Non-traditional risk factors may also contribute to this increased risk for CVD found in KTR. In particular, arterial compliance has been reported to be lower in KTR. For example, Riess et al. (Appendix A) reported small artery compliance was 31% lower in KTR than age predicted values Further, anti- rejection medication has also been reported to have an negative effect on CVD risk [10]. Also, KTR are more likely to be smokers [6, 11], and are less likely to be active then their age-matched counterparts [12]. A consequence of an inactive lifestyle is that it is associated with a decline in exercise capacity (measured objectively as peak oxygen consumption (VO_{2peak})). As a reduced VO_{2peak} is an important predictor of mortality in healthy [13, 14] individuals and ESRD patients [15], interventions that improve VO_{2peak} may reduce morbidity and mortality in KTR.

1.2 Statement of the Problem and Purpose of this Thesis

Given that KTR are at an increased risk for CVD, interventions that may reduce this cardiovascular risk (such as exercise training) would be of great importance for this population. The aim of this thesis is to investigate the effects of a12 week exercise program on exercise capacity, muscle strength, quality of life (QOL), body composition and CVD risk in KTR. Further, this thesis will explore the possible mechanisms for increases in exercise capacity associated with exercise training.

1.3 Delimitations

1. The subjects were recruited from the University of Alberta Renal Transplant Clinic.
2. Graded exercise testing was performed on a recumbent cycling ergometer.
3. Body composition was assessed with skinfold measurements.
4. Maximal strength was assessed using one repetition maximum (1RM) testing.
5. The supervised training took place over the time course of 12 weeks.
6. Supervised aerobic exercise training was performed 3 days per week with supervised resistance training performed on 2 of these days.

1.4 Limitations

1 Subjects recruited from the University of Alberta Renal Transplant Clinic were volunteers.

2 Subjects recruited for this study were of varying ages and genders.

Review of Literature

2.1 Background

Kidney transplantation is an important surgical intervention for select individuals with end-stage renal disease (ESRD) [16]. Indeed, transplantation has been reported to improve life expectancy [17] and quality of life [18] for those with ESRD. Despite favorable improvements in survival post-transplant, cardiovascular disease (CVD) remains the major cause of morbidity and mortality in kidney transplant recipients (KTR) [16, 19-22]. Specifically, the incidence of heart failure is 5-fold higher in KTR compared to healthy individuals[23]. The increased CVD risk is due to traditional risk factors (i.e. hypertension [24, 25], diabetes [24], sedentary lifestyle [13, 24] and elevated low density lipoprotein and total cholesterol [26]), novel risk factors (i.e. reduced arterial compliance [27]), and risk factors specific to KTR (i.e. loss of graft function [28] and anti-rejection/immunosupression therapy [29] (Figure 1).

2.2 Traditional Risk Factors Contributing to Cardiovascular Disease in Kidney Transplant Recipients

Systemic hypertension and diabetes mellitus are leading CVD risk factors that are prevalent in KTR (Figure 1B and 1C). Hypertension (defined as SBP/DBP >140/90) has been reported to be the most established CVD risk factor in end-stage renal disease[6] and in KTR [5]. Specifically, hypertension, or pharmacologic treatment for hypertension, has been reported in 50% to 90% of KTR [30, 31] compared to 49% in

Canadians 65 years of age and older [32]. In addition, diabetes is the leading cause of renal failure in developed nations [33, 34]. Further, the prevalence of diabetes increases after transplantation as post-transplant diabetes mellitus occurs in 23% of KTR without prior existence of diabetes [35].

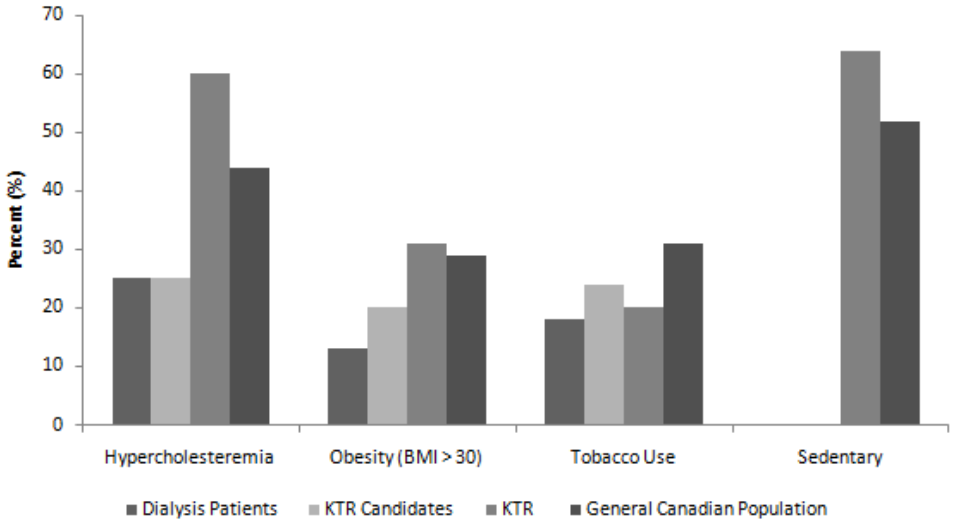
Kidney transplant recipients are at further risk for cardiovascular disease as there is an increased prevalence of dyslipidemia in this population. Indeed, elevated low-density lipoprotein cholesterol and total cholesterol is present in 50% to 70% of KTR [36-38]. This increased risk is likely related to unfavourable cholesterol levels prior to transplant as a major risk factor for post-transplant dyslipidemia is pre-transplant dyslipidemia [36]. Unfortunately, the cardiovascular risks associated with dyslipidemia are enhanced after transplant as the use of anti-rejection drugs post-transplant increases the risk of dyslipidemia in KTR [10].

Smoking and a sedentary lifestyle place KTR at further risk for CVD, as they do for the general population. Although the overall smoking rates in KTR has declined in the last 30 years [39] nearly 20% of KTR continue to smoke after surgery [6, 11]. Ambulatory renal failure patients on dialysis have been reported to have activity levels below the 5th percentile of those reported for the general, age-matched population [12]. Although physical activity levels increase after transplantation, it remains below that of healthy individuals [40]. For example, Gordon et al. [41]

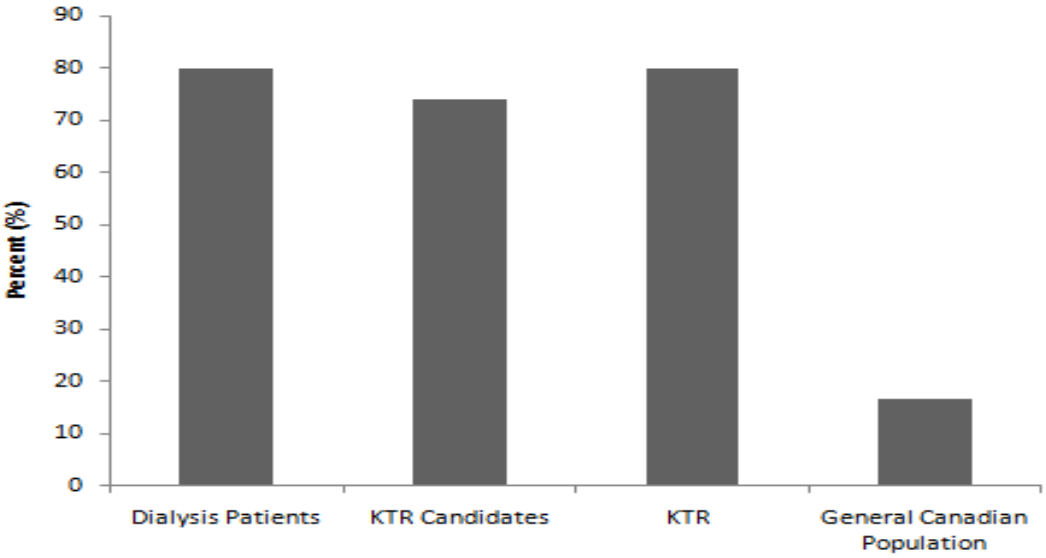
found that 76% of KTR are sedentary while only 11% of KTR reported they were exercised regularly. Consistent with this observation, Painter et al. found that only 36% of transplant recipients performed regular exercise 1-year after transplantation [42].

Figure 1: Prevalence of selected CVD risk factors in KTR and other populations

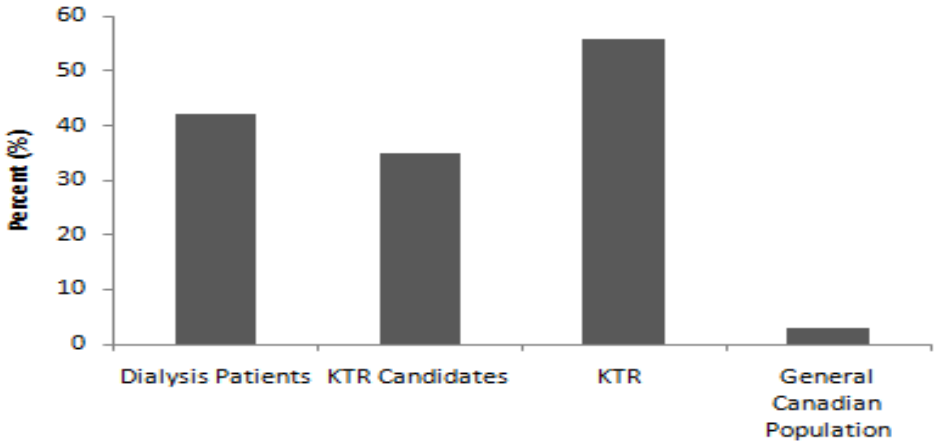
A. Prevalence of specific CVD risk factors in selected populations



B. Prevalence of Systemic Hypertension in selected populations



C. Prevalence of diabetes mellitus in selected populations



Adapted from published data by Young et al.[6], Painter et al. [42] and Statistics Canada [43]. KTR = Kidney Transplant Recipient

Large scale epidemiological studies have consistently demonstrated that reduced exercise capacity (measured objectively on a cardiopulmonary exercise test as VO_{2peak}) is the most important predictor of mortality in healthy individuals and clinical populations [13, 14, 44]. Meyers et al. [13] reported that an increase in VO_{2peak} of 3.5 ml/kg/min (equal to 1 metabolic equivalent or MET) was associated with a 12% improvement in survival in men with or without CVD. Further, Gulati et al. [14] examined the prognostic importance of VO_{2peak} in 5,721 asymptomatic women (mean age = 52 years) subsequently followed for 8 years after initial exercise testing. The main finding was that VO_{2peak} was a major independent predictor of all-cause mortality after adjusting for

traditional cardiovascular risk factors. Specifically, a 1 MET decrease in VO_{2peak} was associated with a 17% increase in mortality. Finally, Sietsema et al. [15] reported that VO_{2peak} was a strong independent predictor of mortality in ESRD. Indeed, they determined that ESRD patients with a $VO_{2peak} < 18$ ml·kg·min^{-1} had a lower 3.5 year survival rate compared to those with a peak VO_{2peak} above this level. Accordingly, VO_{2peak} is an important outcome measure and therapies to improve exercise capacity are warranted in this population.

2.3 Non-Traditional Risk Factors Contributing to Cardiovascular Disease in Kidney Transplant Recipients

Arterial compliance is reduced in ESRD [27] and not fully reversed after kidney transplantation. A pilot study by Riess et al. (Appendix A) recently demonstrated that small artery compliance was 31% lower in clinically stable KTR versus age predicted values. Of note, no difference was found between groups for large artery compliance [45]. Consistent with these results, Yildiz et al. [46] found that small artery compliance was lower in KTR compared to healthy age-matched individuals. These findings have important clinical implications as reduced arterial elastance is an important risk factor for CVD in KTR [47].

Anti-rejection therapy also leads to an increase in the risk of CVD in KTR. A finding due, in part, to these drugs increasing traditional CVD risk factors [10]. Specifically, blood pressure, weight gain and lipid profile are

affected negatively by corticosteroids and Cyclosporin. Tacrolimus has been demonstrated to increase risk of diabetes and Sirolimus and Everolimus both a negative effect on healthy lipid levels [10].

In summary, KTR are at higher risk for CVD than the general population as a result of traditional, novel and / or transplant-specific risk factors. One important modifiable risk factor in this population is reduced physical activity and a reduced VO_{2peak}. The mechanisms for reduced VO_{2peak} may be due to deconditioning associated with a sedentary lifestyle pre / post transplant which may be improved through physical conditioning as a result of exercise training (Table 1).

Table 1: Determinants of exercise capacity with deconditioning, aging, kidney disease / hemodialysis and kidney transplantation

	Deconditioning		Aging		Kidney Disease / Hemodialysis		Kidney Transplantation	
	Rest	Peak Exercise	Rest	Peak Exercise	Rest	Peak Exercise	Rest	Peak Exercise
VO2		↓[48-55]	↓[56]	↓[57, 58]		↓[15, 59-65]		[63, 64]↓[62]
HR	↑[49]	↑[49, 54]		↓[57, 58, 66-68]		↓[61-65, 69]		↓[62]
SV	↓[49, 70]	↓ [49, 51, 52,	↓[56]	↔[57] ↓[58, 68]		↑[62, 65] ↔[59]		↑[62]

		55]						
Q	↔ [70] ↓[49]	↔[49] ↓[51, 55]	↓[56]	↓ [57, 68],index[67]		↔[62, 65]		↑[62]
EF	↔[4 8]	↔[48]		↓ [66, 67]		↓[65]		
EDV	↔[7 0] ↓[49 , 55]			↑ index[67]		↑[65]		
ESV						↑[65]		
LV Diastolic Compliance	↓[70]		↓[56, 71]		↓[72]			

Myocardial Contractility	↔[70]	↔[52]	↔[73, 74]	↓[67]	↓[72]			
a-vO_{2diff}	↔[48, 49]	↔[48, 55]		↓[58] [57, 68, 75]		↓[59, 62]		↓[62]
SVR	↑[49, 70] ↔[48]	↔[48] ↑[52]	↑[76]					↑[77]
MAP	↔[70]	↔ [52]		↑ [67]	↑[78]			
SBP	↓[48]		↑[76]	↑[67]	↑[65]		↑[30, 79]	
DPB	↔		↑[76]	↑[67]	↑[65]			

	[48]							
Blood Volume	↓[48] [49, 50]							
Plasma Volume	↓[49, 50, 54, 70, 80]							
Vasculature Function								
Arterial Elastance	↓[81, 82]		↓[56] [71]		↓[83, 84]		↓ [85, 86]	

large			↓[76, 87]				↔[45]	
small			↓[76]				↓[45]	
Skeletal Muscle Morphology								
Muscle Strength	↓ [88]		↓[89-92]		↓[93, 94]		↓[93]	
Muscle Mass	↓[50 , 88]		↓[95]		↓[94, 96]		↓[97]	
Type 1 fibers	↓ size[98]						↓ [64]	
Type 2 fibers	↔ [98]		size↓[99, 100]				↑[64]	

Capillary Density			↓[101-103]		↓[60, 104]			
Mitochondria			↓ [105, 106]					
O_2 Enzymes	↓[51]		↓[105]		[107, 108]			
Reduced muscle blood flow					↓[109, 110]			

Note: VO2 = Oxygen Consumption, HR = Heart Rate, Q = Cardiac Output, SV= Stroke Volume, EF = Ejection Fraction, EDV = End Diastolic Volume, ESV = End Systolic Volume, A-VO2dif = Arteriovenous Oxygen Difference, SVR = Systemic Vascular Resistance, MAP = Mean Arterial Pressure, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, LV = Left Ventricle

2.4 Reduced Exercise Capacity: Role of Deconditioning

The reduced exercise capacity found in KTR may be secondary to deconditioning associated with a sedentary lifestyle [48-53, 55, 111]. The seminal study by Saltin et al. [55] examined the effects of 20 days of strict bedrest deconditioning on cardiovascular and skeletal muscle function in 5 younger individuals (mean age: 20 years). The main finding was that 20 days of bed rest was associated with a significant and marked decrease in VO_{2peak} (28%). In a long-term follow-up study with the same 5 subjects, the investigators found that the decline in VO_{2peak} after 20 days of bed rest was more detrimental than 3 decades of aging (Figure 2). These findings highlight a number of physiological mechanisms that may account for the reduction in exercise capacity reported in KTR.

In accordance with the Fick Equation oxygen uptake is equal to the product of cardiac output (Q) x arteriovenous oxygen difference (a-vO_{2diff}). Thus, factors reducing VO_{2peak} with disuse / deconditioning may be due to impaired oxygen delivery to and / or utilization by the active muscles. Saltin et al. [55] demonstrated that the decreased VO_{2peak} was primarily due to a reduced peak cardiac output as no significant change in peak a-vO_{2diff} was found after bedrest deconditioning. The reduced peak cardiac output was due to a lower stroke volume as peak heart rate was not altered with extended bed rest. In turn, the blunted peak stroke volume may be due to impaired preload, contractility or afterload. Specifically,

deconditioning is associated with a decrease in size and concomitant decline in LV compliance and stroke volume. Thus the reduced rest / exercise SV may be secondary to impaired preload reserve.

A sedentary lifestyle is also associated with an increase in vascular resistance which, coupled with a decrease in myocardial contractility, may negatively affect SV [52, 55]. Taken together, structural and functional changes in the cardiovascular system occur with a sedentary lifestyle that results in a reduced peak exercise cardiac output. Finally, a sedentary lifestyle is associated with changes in skeletal muscle morphology and function (ie. reduced muscle mass, decreased oxidative (type I) muscle fibers and a decrease in oxidative enzymes) that reduce oxygen utilization by the active muscles during exercise.

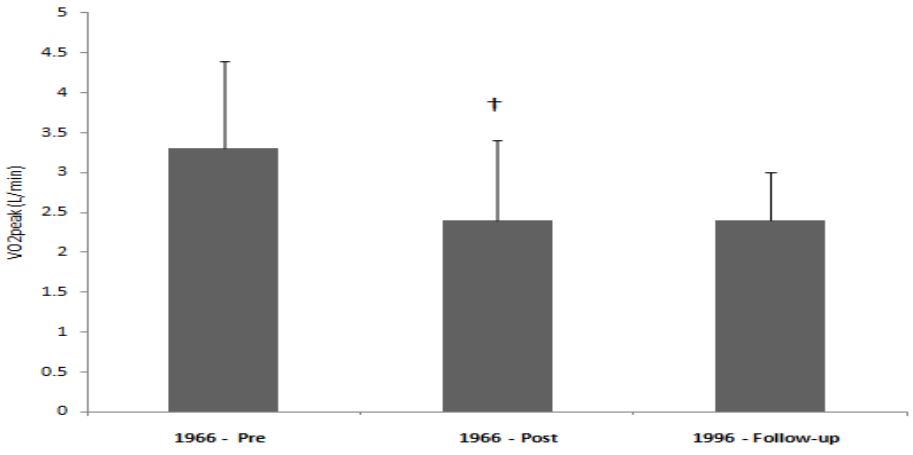
2.5 Reduced Exercise Capacity: Role of Aging

The reduced VO_{2peak} in KTR may also be the result of aging. Specifically, VO_{2peak} decreases by 10% per decade after the age of 25 years [112-114]. Similar to sedentary lifestyle, the reduced VO_{2peak} associated with sedentary aging is related to a reduction in cardiac output [57, 67, 68] secondary to a lower peak heart rate and low stroke volume. Specifically, peak heart declines in early adulthood at a rate of 1 $beat \cdot year^{-1}$ in sedentary, healthy individuals [68, 115]. For example, Ogawa et al. [68] compared cardiac function of sedentary and endurance trained older men and women to that of activity matched younger

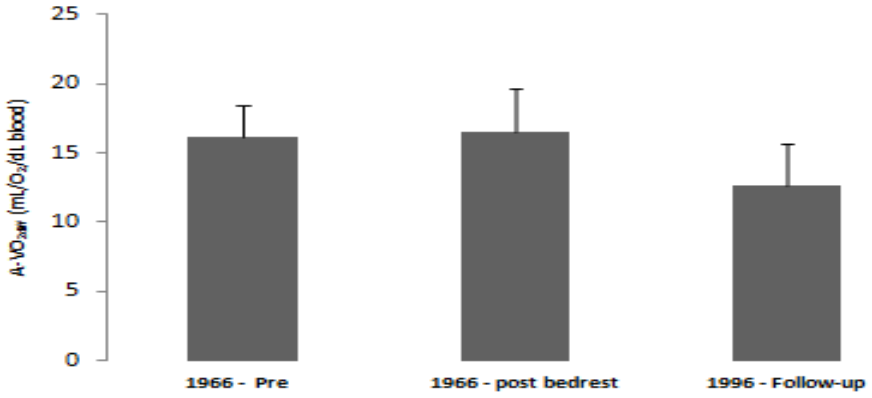
individuals. Cardiac output in the older subjects versus younger was lower as a result of a lower peak heart rate and stroke volume. Notably, the decreased stroke volume accounted for nearly 50% of the age related differences in exercise capacity.

Figure 2: The effects of bedrest and 30 years of aging on peak cardiovascular measurements

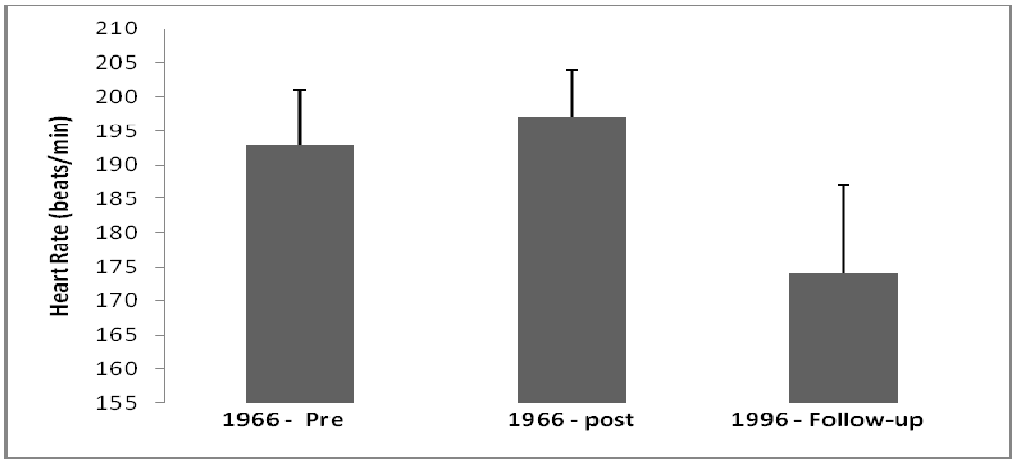
a.



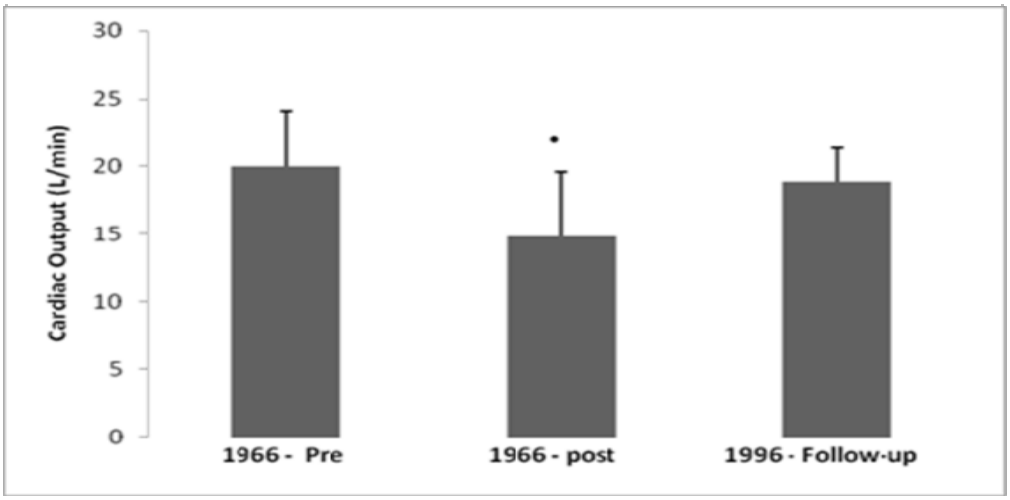
b.



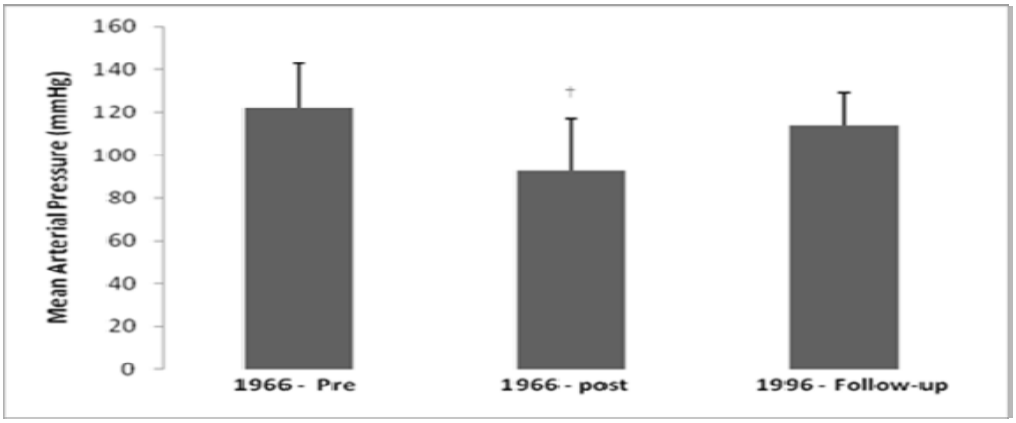
c.

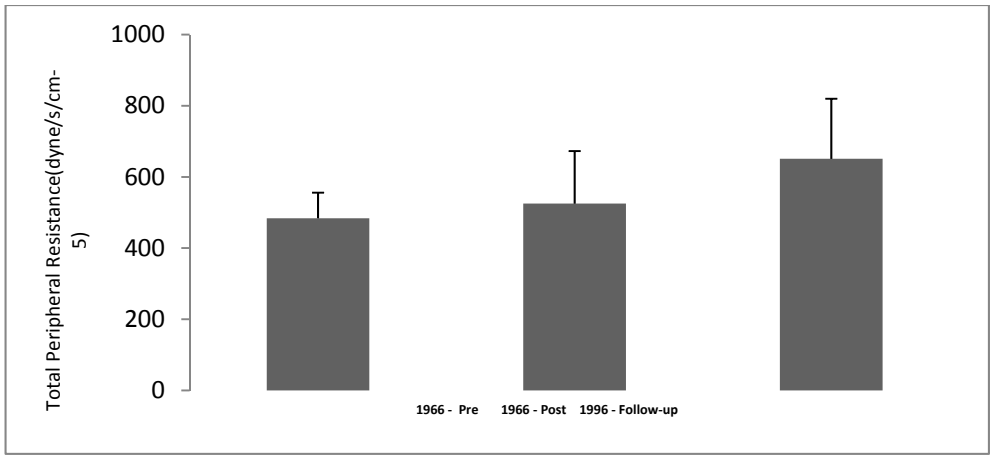

Heart Rate (beats/min)
210
205
200
195
190
185
180
175
170
165
160
155
1966 - Pre
1966 - post
1996 - Follow-up

d.


Cardiac Output (L/min)
30
25
20
15
10
5
0
1966 - Pre
1966 - post
1996 - Follow-up

e.


Mean Arterial Pressure (mmHg)
160
140
120
100
80
60
40
20
0
1966 - Pre
1966 - post
1996 - Follow-up

f. 

Adapted from published data from Saltin et al. [55] and Mcguire et al.[116].

† significant difference vs 1966 Baseline ($p < 0.01$)

• significant difference vs 1966 Baseline ($p < 0.05$)

The underlying mechanism for the reduced stroke volume with sedentary aging may be due to altered preload, vascular or contractile reserve. For example, Arbab-Zadeh et al. [56] reported that reductions in LV compliance in younger sedentary versus older sedentary individuals was associated with an increase in ventricular wall thickness in the latter group [117]. Further, age mediated structural changes in the vascular system results in an increase in vascular resistance and arterial pressure (ie. increased afterload) [56, 71, 76]. Finally, age-mediated decline in myocardial contractility also decreases exercise stroke volume [67].

Similar to an inactive lifestyle, aging results in decreased skeletal muscle capillary [101-103] and mitochondrial volume density [105, 106] resulting in reduced a-vO_{2diff} and exercise capacity [57, 58, 68, 75]. As well, reductions in muscle strength [89-91], muscle mass [95] and a decrease in type 2 muscle fiber size [99, 100] further limit exercise capacity in the aging population. Similar to deconditioning, sedentary aging is associated with impaired skeletal muscle morphology and function (ie. decreased capillary density, mitochondria, muscle mass and oxidative enzymes) that reduces peak exercise VO_2.

Aging and inactivity play a role in reduced peak exercise capacity in the general population. Though the mechanisms may differ, the resulting decrease in peak exercise capacity is similar. Given that KTR are often

sedentary and older, the reduced exercise capacity in this population may be due, in part, to these a sedentary lifestyle and the aging process.

2.6 Reduced Exercise Capacity in End Stage Renal Disease and Kidney Transplant

The reduction in exercise capacity in KTR may be the result of the deleterious effects of ESRD that persist after surgery. Indeed, ESRD patients have lower fitness levels compared to age-matched sedentary individuals [15, 59-65] as their peak exercise capacity has been reported to be between 62% and 68% of age predicted values [62, 65]. Specifically, this reduction in VO_{2peak} is due to a decreased peak cardiac output secondary to a lower peak heart rate [61-65, 69]. The reduced cardiac function may be due to uremic cardiomyopathy [118, 119] or autonomic dysfunction [120, 121] attributed to the uremic state.

Currently, the effect of exercise on cardiac function in ESRD has not been well documented. Moore et al. [59], examined the effects of acute exercise on LV function in 10 ESRD patients compared to age and gender matched predicted values. Although a reduction in peak heart rate was observed, no difference was reported in SV_{peak} between study subjects and previously published data of healthy controls. These findings contrast more recent studies that reported higher SV in ESRD patients during acute exercise compared to healthy controls [62, 65]. Specifically, Painter et al. [62] compared exercise cardiac function between ESRD

patients and healthy controls. While there was no significant difference in peak cardiac output (Q_{peak}), the ESRD patients were reported to have a higher SV_{peak} which compensated for the lower peak heart rate. Although not measured by Painter et al. [62] ESV and EDV have been measured in ESRD. Specifically, Deligiannis et al. [65] reported that ESRD have an increased exercising EDV and ESV compared to sedentary, healthy controls. As such, the increase in SV observed in ESRD is likely due to the higher EDV observed in this group of patients.

The reason for the increase in SV_{peak} in ESRD is likely due to greater exercise EDV [65]. Further, the increase in EDV is the likely outcome of increased extracellular or blood volume that is a hallmark of ESRD [122, 123]. Indeed, fluid retention and the development of volume overload are an expected consequence resulting from loss of renal function [28]. Also, in the presence of an arteriovenous fistula in individuals undergoing hemodialysis there may an additional contributions to the increase in volume overload [28].

The increase in ESV is secondary to a decrease in contractility [124] and / or an increase in afterload [83, 84, 125], both of which have been reported in individuals with ESRD. Individuals with renal failure and uremic patients have less complaint large arteries (including the aorta) [84] than healthy aged matched controls. This contributes to the increased afterload and concomitant increase in ESV [83, 84, 125]. The

increase stiffness found in large arteries in this population is due to arterial calcifications [84, 125] which increase in presence with advancing age and length of time on pre-transplant dialysis. Abnormalities in myocardial contractility may also impair exercise ESV. Zoccali et al. [124] reported on the effect of ESRD on 254 asymptomatic individuals undergoing dialysis. A key finding of this study was that the presence of LV dysfunction in 26% of this population. Further, reduced fractional shortening and lower EF was not only common in ESRD but those with the lowest score were at the greatest risk for cardiovascular events. More recently, Painter et al. [62] reported similar outcomes as patient with ESRD had lower EF then healthy controls. As such, the reduced contractility present in ESRD may be a contributing factor in the reduction of exercise capacity in this group.

2.7 Reduced Exercise Capacity in Kidney Transplant Recipients

Kidney transplantation as a means of renal replacement therapy has been demonstrated to have favourable effects on peak exercise capacities for ESRD [62, 63]. In fact, although some KTR may achieve a level of fitness similar to those of endurance trained subjects [126], the peak exercise capacity in this population does not generally approach those of age matched sedentary individuals [63, 64]. The improvements in exercise capacity as a result of kidney transplantation arise from an increase in peak cardiac output that is the result of increases in peak HR [62, 63, 127]. These increases in peak heart rate are due to removal of

the uremic state[63, 104], as improvement in changes to SV_{peak} have not been observed in the period after transplantation [62]. Specifically, Painter et al. [62] measured peak exercise heart function in 5 KTR (6 months post transplant) and compared the results to healthy controls. The authors reported that the increase in VO_{2peak} observed in this population was attributed to an increased HR_{peak}.

Other central and peripheral limitations may also contribute to reductions in exercise capacity in KTR. Although there is an improvement in hemoglobin levels post-transplant [62], there is not a concomitant widening of peak a-vO_{2dif} [62, 63] indicating a peripheral limitation likely resulting from unresolved declines in muscle function occurring during the pre-transplant period or as a result of anti-rejection therapy. Indeed, Richard et al. reported on a group of well trained KTR compared to age and physical activity matched healthy individuals [126] and determined that while VO_{2peak} was similar between groups, peripheral limitations affected the mechanical efficiency (based on VO_2 versus treadmill speed) of the KTR suggesting this peripheral limitation.

Anti-rejection medication may also play a role in this muscle dysfunction as corticosteroids, a commonly used anti-rejection medication, has been shown to have a negative effect on the muscle function [128]. Further, early reduction of corticosteroids after transplantation improves muscle structure [129]. Finally, the reduction in exercise capacity in KTR

may be the result of unfavorable fiber type distribution. Indeed, Kempeneers et al. [64] reported that their sub-group of the study subjects with, VO_{2peak} values averaging 40.9 $ml \cdot kg^{-1} \cdot min^{-1}$,presented with a preponderance of type 2 muscle fibers, opposite of what would be expected in healthy subjects.

In summary, exercise tolerance is reduced in KTR compared to sedentary individuals [62-64]. Reasons for this reduction may stem from the normal aging process, inactivity and sedentary lifestyle resulting from the lifestyle of ESRD and hemodialysis, or as result of uremia and its effect on the heart and muscle pre transplant. Regardless of the reasons for the decline, improvements in exercise capacity should be a primary consideration for this population.

2.8 Benefits of exercise training in Kidney Transplant Recipients

The role of regular exercise training to improve VO_{2peak} and its determinants in KTR has not been well studied. The few studies performed to date report positive results (Table 2). In an early investigation , Miller et al. [127], found that 6 weeks of supervised exercise training (initiated shortly after transplantation) in a group of 10 KTR resulted in a significant increase (90%) in peak METS. Similarly, Kempeneers et al. [64] found that 6 months of supervised aerobic training increased VO_{2peak} (23%) and isokinetic hamstring and quadriceps muscle

power (45% and 22% respectively) in 16 KTR (mean time from transplant = 62 months).

In a randomized exercise trial, Painter et al. [42] reported on the effects of individualized home exercise training versus usual care in 140 (control = 43, exercise = 97) KTR with VO_{2peak}, muscle strength and body composition follow-up assessments at 6 months and 1 year. Both the control and exercise group in this study realized a similar increase (15%) in VO_{2peak} after 6 months. However, over the course of 12 months home based exercise trained group attained significant increases in $VO2_{peak}$ and muscular strength (25% and 30% respectively, compared to baseline) with no significant improvement in lean body mass or fat mass as measured by dual energy X-ray absorptiometry scans. Similar positive findings showing improved VO_{2peak} (10%), muscular strength (range: 10 – 30%) with no improvement in body composition were reported after 6 months of exercise training in 33 KTR (mean time post transplant = 84 months) by van den Ham et al. [130]. Notably, the improvements in muscle strength and exercise capacity were similar between KTR and healthy control subjects.

Table 2: Review of Role of Exercise Training on KTR in Exercise Studies and Outcomes

Study, Year	Study Sample Time Post-Transplant	Sample Size	Men, %	Mean age (yrs)	Duration of intervention (months)	Training Variables (FITT)	Outcomes	Result
Miller et al., 1987 [127]	Baseline (mean = 17 days post transplant	10	60	Not Reported	1.3	F: 3 / week I: 40% - 60% peak exercise capacity T: 10 to 40	$METS_{peak}$, HR_{peak}	†↑ $METS_{peak}$(90%), † ↑HR_{peak}(12%)

						minutes Ty: Walking		
Kempenees et al., 1990 [64]	Baseline Mean = 62 months post transplant	16	56	33	6	F: 3 / week I: 80 – 90% HR_{max} T: 60 minutes Ty: aerobic training	VO_{2peak}, Leg power	* ↑VO_{2peak}(23%), ↑ isokinetic Leg power - † Quadriceps (22%) - † Hamstring (45%)

Painter et al., 2002 [42]	Baseline one month post transplant	97 KTR CON = 43	62	Con = 44 UC = 40	Follow up at 6 and 12 months	F: 4 / week I: 60 – 80% HR_{peak} T: > 30 min / session Ty: walking, CE	VO2peak, muscular strength, body composition	† ↑ VO_{2peak} at 6 (15%) and 12 months (25%) † ↑ muscle strength at 12 months (30%)
Juskowa et al. 2006 [131]	2-3 days post transplant	69 KTR (32 ET)	61	46	1.25	F: EOD I: NR T: 30 minutes Ty: strength	Hcy, Il-18, and relation to muscle strength	† Inverse relation between Hcy, Il-18 and muscular strength of right upper limb

						training		
Van den Ham et al., 2007 [130]	Mean time from transplant 84 months	33	55	52	3	F:2 / week I:50 – 70% W_{peak},50-70% 1RM T: NR Ty: TM and CE	VO2peak, Muscular Strength, LBM	* ↑VO_{2peak} (10%) † ↑muscle strength (10-3-%), * ↑ LBM (males only)
Romano et al., 2009	(65 ± 25 months) post-transplant	8	50	52	2.5	F:3 / week I: 90% HR_{peak} and 50%	Body Composition, VO_{2peak}	* ↑ VO_{2peak} (13%)

						HR_{peak} T: 15 x 1 minute at 90%, 1 minute @ 50%. Ty: CE, Interval		

CE = Cycle Ergometry, EOD = Every other day, ET = Exercise trained, F = Frquency, Hcy = Homocystein , HR = Heart Rate,I = Intensity, Il = Interleukin, LBM = Lean body mass, METS = Metabolic Equivalent, NR = Not reported, T = Time, TM = Treadmill, Ty = Type, W = Watts.

† $P < 0.01$; * $P < 0.05$; ‡ $P < 0.001$

Romano et al. [132] recently examined the effect of interval training on VO_{2peak}, leg power and fat mass and lean body mass. In this study of 8 KTR (mean time post transplant = 65 months) which lasted 2.5 months, interval training significantly improved VO_{2peak} (13%). Further, this study found that the exercise training contributed to an increase in quality of life, as measure by the SF-36, for the subjects participating. Notably, this study also reported that exercise training of this type also reduces the level of Interleukin-6 (IL-6), a pro-inflammatory cytokine, in KTR.

Other studies have also investigated the effects of exercise training on CVD risk factors in KTR. In a sub-analysis of a previous study [42] Painter et al. [133] reported on the effects of an individualized, home based exercise program on CVD risk factors. The results of this study showed that home based exercise did not reduce the 10-year risk for CVD in KTR. Juskowa et al. [131] detailed the effects of exercise training shortly after kidney transplantation on a 69 KTR randomly assigned to exercise training or UC. The authors reported improvement in Homocystein and IInterleukin-18 levels were inversely related to muscular strength, though exercise training did not have a significant effect on the reduction of these inflammatory markers when compared to usual care.

While the effect of exercise training on KTR has been studied, the reported literature investigating these effects is not without limitations. Few trials were randomized, compliance in the Painter et al.[42, 133] studies

were not well maintained as evident by the finding that at 1 year follow-up 67% of the exercise group was considered active while 36% of the control group met the same criteria. Drop-out rates for the studies were also high as of the 167 subjects that started the study, only 57% completed the subsequent testing sessions. While these studies have shown positive effects on exercise capacity post-kidney transplantation and a positive effect of exercise on KTR [64, 127, 132], they have lacked sufficient sample sizes or control groups. Further, while there have been reported improvements in exercise capacity, the cardiovascular mechanisms for this improvement has not been elucidated [42, 127, 131, 132]. Accordingly, these limitations form the basis of this thesis.

Hypothesis

The primary hypothesis of this study is that twelve weeks of supervised exercise training will significantly improve VO_{2peak} compared to usual care. A secondary hypothesis is that supervised exercise training will improve, large and small arterial compliance, lower body muscular strength, lean body mass, cardiovascular disease risk score and quality of life compared to usual care.

Methods

3.1 Subjects

Ethics approval for this study was obtained from the University of Alberta's Biomedical Board. Subjects were recruited from the University of Alberta's Renal Transplant Clinic (RTC) between June, 2006 and October, 2008. Participants were prescreened by the nursing staff at the RTC to determine their eligibility for the study before being referred for initial contact.

Inclusion criteria for the study included:

1) clinically stable kidney transplant recipients ≥18 years of age.
2) ≥6 months post transplant.

Participants were excluded if they had:

1) uncontrolled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg).

2) type 1 diabetes mellitus.

3) any other condition that would limit exercise testing or training.

3.2 Baseline Assessments

The following baseline tests were performed over a 1 week period (Figure 3).

1) Incremental Exercise Test with Expired Gas Analysis and Impedance Cardiography

The incremental exercise test was performed on an electronically braked cycle ergometer (Lode Medical Technologies, Groningen, NL) during which time a expired gases were collected with a commercially available metabolic measurement system (Parvo-Medics, Salt Lake City, Utah). After collecting two minutes of resting data, the initial workload was set at 15 watts and increased by 15 watts every two minutes until volitional fatigue. Stroke volume (SV) was measured with impedance cardiography (Minnesota Impedance Cardiograph, model 304B; Surcom Inc., Minneapolis MN) in conjunction with a phonocardiogram (Hewlett Packard, model 21050A). Stroke volume was calculated during 20 second sampling periods at the end of each 2 minute exercise stage using Bernstein's equation[134]. Heart rate (HR) and 12 lead ECG waveforms were continuously monitored by a cardiologist for signs of ischemia or dysrhythmia and recorded. Systolic and diastolic blood pressures were obtained manually and recorded every two-minutes. The highest VO_2 measured during a 1 minute period was considered to be the peak score.

2) Small and large arterial compliance

Resting small and large arterial compliance were assessed using computerized arterial pulse waveform analysis (Hypertension Diagnostics, Eagan, MN). This technique involves the use of the applanation tonometry, which requires the placement of a pressure transducer over

the radial artery. The analysis of the 30 second signal averaged arterial pulse wave forms were performed by the tonometry unit and arterial compliance of large and small artery were derived from the analysis of the diastolic waveform decay using the modified Windkessel model of circulation. This technique has been validated previously with arterial waveform measures [76]. Modification of this technique was occasionally required as normally the blood pressure cuff and the surface residing transducer are placed on different arms. For individuals with an arterio-venous fistula the same, non-fistula arm, was used with both devices. This modified procedure has been shown to give similar results as the method normally used in applanation tonometry [135]

3) Lower Extremity Maximal Muscular Strength

Leg-press, leg extension and leg-curl maximal muscular strength were assessed using the one-repetition maximum (RM) test. Specifically, after a brief, low intensity, warm-up on a cycle ergometer the subjects had their standardized joint angle starting points determined. The starting point for the leg press was set with the knee joint at 90 degrees, measured with a goniometer. The starting positions for the leg extension and leg curl assessments were set as close to 90 degrees and 180 degrees, respectively, as the resistance machine would allow. The subjects were then familiarized with the testing maneuvers by performing 2 sub-maximal, multi-repetition lifts. Subsequently, heavier single lifts followed a brief rest period (3-5 minutes) between attempts. The greatest single load lifted by

the subject while adhering to strict form and moving through the entire range of motion was considered their 1 repetition maximum.

4) Anthropometry and Lean Body Mass

Lean body mass was estimated using skinfold measurements. Specifically, the skinfold sites for women included triceps, suprailiac, abdominal and thigh in accordance with the Jackson et al. equation [136]. Male body density was determined using the Jackson and Pollock equation [137] which required measurement of the chest, abdomen and thigh skinfolds. Body density was used to estimate body fat percent using the Brozek equation [138] and lean body mass was then determined. Subject's with a Body Mass Index (BMI) of greater than 30 kg/m^2 were not included in the lean body mass data as skinfolds in this population have been reported to be an unreliable means of assessing body density [139]

5) 24 Hour Ambulatory Blood Pressure Monitoring

Twenty-four hour blood pressure monitoring was assessed with the use of the Spacelab 90207 ambulatory blood pressure monitor (Spacelabs Healthcare, Issaquah, Washington, United States). To maximize patient comfort the monitor was programmed to record blood pressures every 30 minutes during daytime hours (0600hrs to 2200hrs) and every 1 hour during evening hours (2200hrs to 0600hrs). Average daytime, evening and total blood pressures were reported via the Spacelabs Healthcare proprietary software.

6) Cardiovascular Disease Risk Score

Coronary heart disease 10 year risk score was estimated using the Framingham Risk Assessment. Scoring of this assessment has been reported elsewhere [140]. Briefly, points are allotted to increasing degrees of coronary heart disease (CHD) risk factors, including; age (years), total cholesterol ($mmol \cdot L^{-1}$), HDL cholesterol ($mmol \cdot L^{-1}$), systolic blood pressure (mmHg, taken from resting arterial compliance measurement), presence of diabetes and current smoking history. Values were presented as estimated 10 year risk of developing CHD. Subjects who did not have a recent (< 3 months) fasting total (TC) or HDL cholesterol measurement were required to fast for 12 hours (8 hours for type 2 diabetics) prior to having a small sample of blood drawn for assessment of their fasting TC and HDL cholesterol levels.

7) Health Related Quality of Life

Quality of life was assessed with the Short Form 36 (SF-36) [141]. This multi-purpose 36 item questionnaire was used to determine 8 subscales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health) of health. These subscales were also used to determine a physical and mental component summary score.

3.3 Statistical considerations

Statistical analyses were performed using MedCalc for Windows, version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium). Baseline measures between usual care (UC) and exercise trained (ET) were compared using Student T tests. Categorical data was compared for differences with the Chi Squared test. Following 12 weeks of UC or ET the change in outcome measures were assessed for similarity using Levene's Test for Equality of Variance. A one way analysis of variance was used to assess the change in homogeneous groups and Kruskal-Wallis test was used for groups with significant variance. Statistical significance was achieved if a P value of < 0.05 was attained. For the primary outcome (VO_{2peak}), in the absence of a follow-up measurement the initial assessment was carried forward as the final measure and used in the analysis. In the absence of secondary follow-up outcomes pre data was not used in the analysis.

3.4 Sample size, randomization and blinding

The sample size calculation was based on the primary outcome (VO_{2peak}). Based on the findings of Kempeneers et al. [64] an 8mL/kg/min increase in VO_{2peak} was expected with no change in UC. Assuming an attrition rate of 10% and α-level = 0.05, and 80% power, a total of 30 subjects (15 per group) were required for this study.

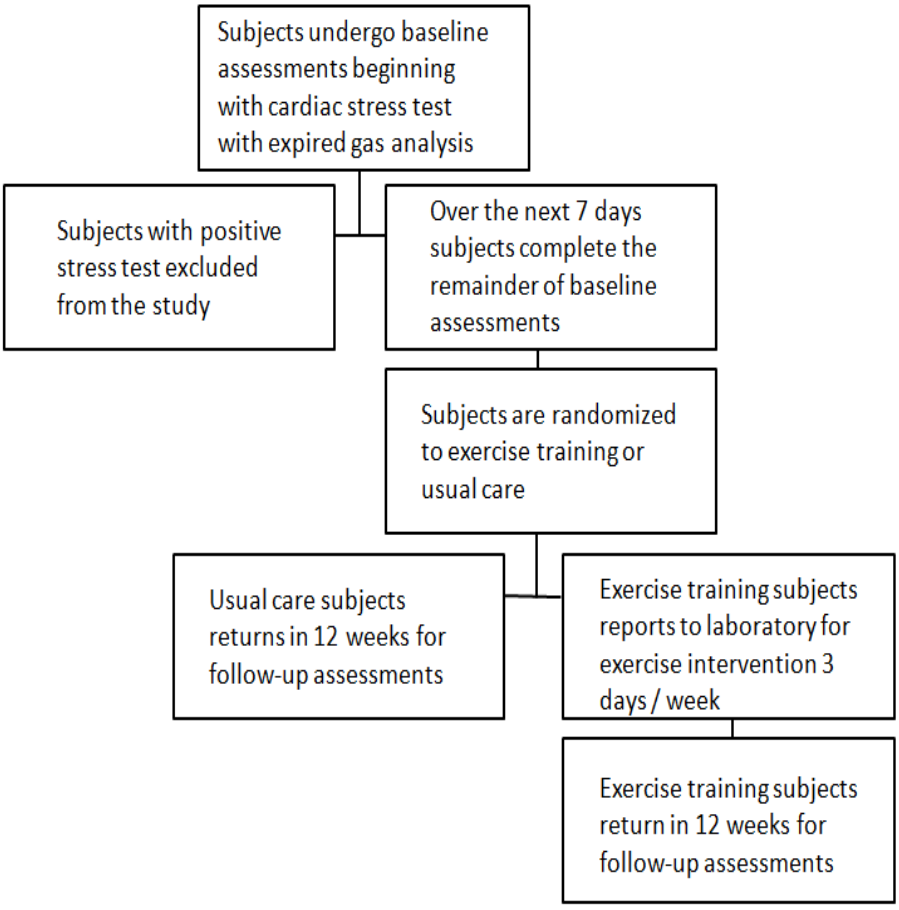
After completing the baseline evaluations the subjects were randomly assigned to UC or ET using computer generated random

number sequences, the results of which were enclosed in sealed envelopes provided by the Epidemiology Coordinating Research Centre , University of Alberta (www.epicore.ualberta.ca). The researches were blinded as to the contents of these envelopes.

3.5 Exercise Intervention

The 12-week exercise intervention consisted of aerobic (3 days/week) and supplemental resistance training (2 days/week) exercise sessions. Aerobic training was performed on a cycle ergometer and motorized treadmill at an exercise intensity between 60% to 80% VO_{2peak} for 30 to 60 minutes per session. Subject accumulated the minimal amount of exercise through shorter intervals if they were unable to complete a continuous 30 minute exercise bout. Lower extremity resistance training was performed at 50% of one RM for 2 sets of 10-15 repetitions with a warm up set of 25%-30% of 1RM. The intensity was gradually increased over the 12 weeks by 5%-10% determined by when the subjects could complete 2 sets of 15 repetitions while adhering to strict technique.

Figure 3: Flow of subjects through study from recruitment to completion.



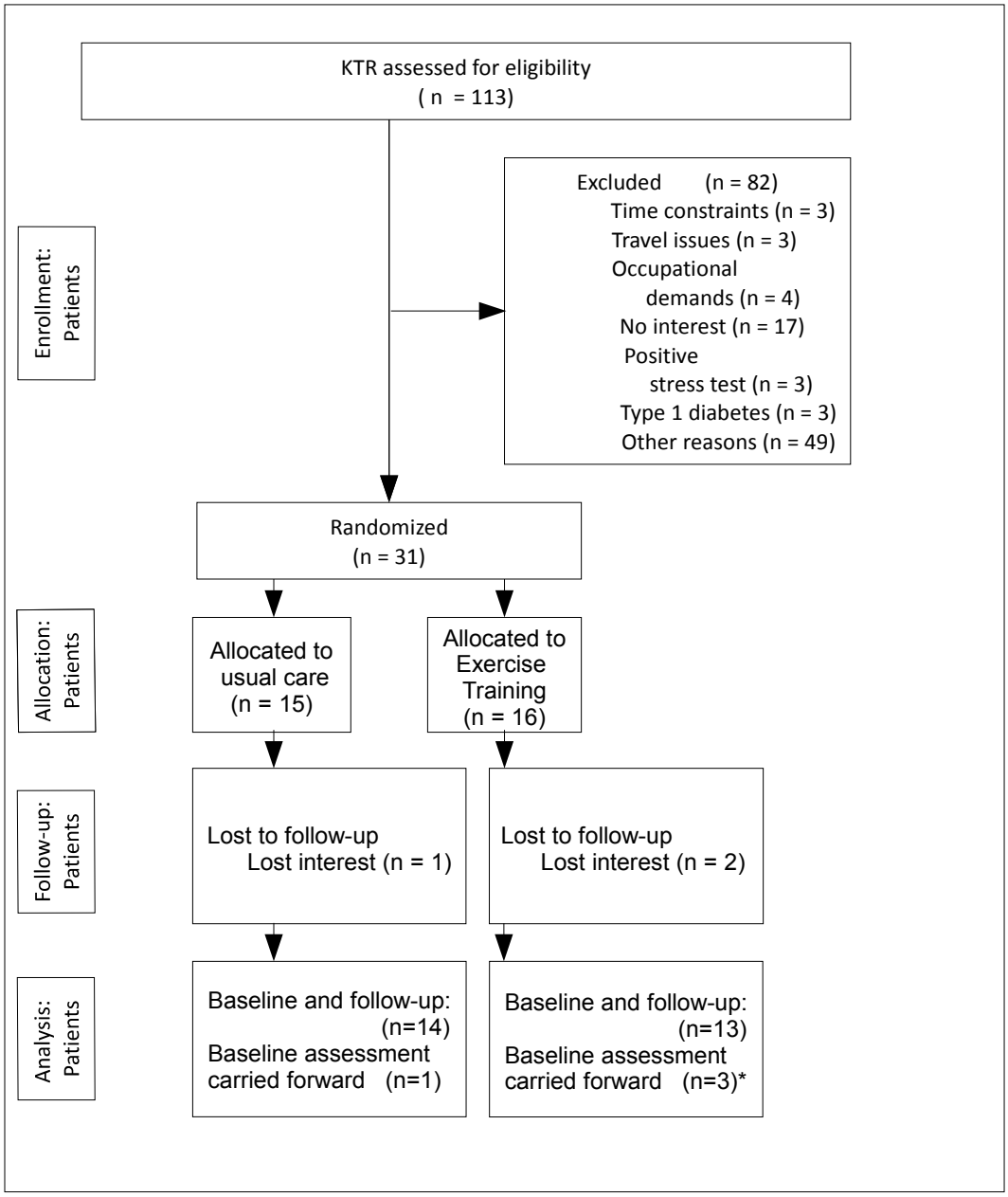
Results

4.1 Baseline

Participant Characteristics

One hundred and thirteen participants were eligible for the study of which 37 performed baseline testing (Figure 4). Six participants were excluded at baseline due to history of type I diabetes (n=3) or a positive stress test (n=3). Accordingly, 31 participants were randomly assigned to ET (n=16) or UC (n=15). Three subjects did not complete the study (1 UC requested not to perform follow-up testing; 2 ET did not attend any exercise sessions or follow-up test assessments).

Figure 4: Flow of participants through the study for the primary outcome (VO_{2peak})



(*Baseline assessment carried forward includes one subject who completed the study but did not complete follow-up primary outcome measure for medical reasons)

Baseline participant characteristics are shown in Table 3. No significant difference was found between groups for age (ET: 56.9 ± 12.2 yrs vs. UC: 52.4 ± 14.3 yrs), height (ET: 166.6 ± 6.3 cm vs. UC: 164.3 ± 6.6 cm), body mass (ET: 79.5 ± 16.2 kg. vs. UC: 75.7 ± 17.0 kg) or time from transplant (ET: 6.4 ± 4.1 yrs vs. UC: 9.1 ± 8.8 yrs). Further, no difference was found between groups for gender, pre-transplant kidney failure etiology or transplant donor type. Except for A2 receptor agonists, no differences were found between groups for cardiovascular or anti-rejection medications (Table 4).

Table 3: Baseline participant characteristics

	UC (n=15)	ET (n=16)
Age (years)	52.4 ± 14.3	56.9 ± 12.2
Gender (m/f)	6 / 9	8 / 8
Time post transplant(years)	9.1 ± 8.8	6.4 ± 4.1
Kidney Donor Type		
Living Donor - Related	6	6
Living Donor - Unrelated	0	1
Deceased Donor	9	9
Etiology of Kidney Failure		
Polycystic	4	4
IgA Nephropathy	1	4
Glomuronalnephritis	2	3
Polynephritis	2	1
Sarcoidosis	0	2
Alports Syndrome	1	0
Diabetes (type II)	1	0
Ureter Reflux	1	0
Unknown	3	2

* $P < 0.05$ vs. UC, data are mean ± SD or as number of subjects

Table 4: Baseline Cardiovascular and Anti-Rejection Medications

Medications		
Cardiovascular Medications		
	UC (n=15)	ET (n=16)
Beta Blocker	4	5
ACE Inhibitor	5	5
Angiotensin2 Receptor Blocker	0	7*
ASA	2	3
Statin	9	9
Diuretic	2	4
Anti-rejection medications		
Imurane	1	2
Prednisone	6	8
Sirolimus	1	1
Cyclosporin	9	8
Mycophenolate Mofetil	11	12
Tacrolimus	4	8

* P < 0.05 vs. UC, data are presented as number of subjects (n)

Exercise Adherence and Training Intensity

Exercise trained subjects completed the study attended 81 ± 31% of their scheduled exercise training sessions at an average intensity of 85 ± 1% of baseline peak heart rate. Lower body resistance training intensities averaged 2 sets of 10 reps at 61 ± 7% of baseline one-repetition maximum.

Baseline Rest and Peak Exercise Cardiopulmonary Performance

No significant difference was found between groups for resting HR (ET: 64.9 ± 11.8 beats·min^{-1} vs. UC: 66.4 ± 8.8 beats·min^{-1}), SBP (ET: 130.4 ± 12.2 mmHg vs. UC: 137.3 ± 18.0 mmHg), DBP (ET: 76.0 ± 7.4 mmHg vs. UC: 76.6 ± 8.9 mmHg), MAP (ET: 97.4 ± 8.8 mmHg vs. UC: 99.5 ± 14.2 mmHg), SVR (ET: 1713.0 ± 681.7 dyn·s·cm^{-5} vs. UC: 1739.1 ± 407.0 dyn·s·cm^{-5}), SV (ET: 60.7 ± 11.0 ml vs. UC: 64.4 ± 14.3 ml), Q_{rest} (ET: 5.3 ± 1.6 L·min^{-1} vs. UC: 4.9 ± 1.2 L·min^{-1}), a-vO_2 diff (ET: 6.9 ± 2.5 ml·dl^{-1} vs. UC: 6.0 ± 1.5 ml·dl^{-1}), VO_2(ET: 0.32 ± 0.08 L·min^{-1} vs. UC: 0.29 ± 0.09L·min^{-1}) or VO_2 indexed to body mass (ET: 4.0 ± 0.9 ml·kg^{-1}·min^{-1} vs. UC: 3.9 ± 1.0 mL·kg^{-1}·min^{-1}).

Peak exercise HR (ET: 133.5 ± 34.3 beats·min^{-1} vs. UC: 137.3 ± 28.0 beats·min^{-1}), SBP (ET: 196.2 ± 25.6 mmHg vs. UC: 198.9 ± 17.8 mmHg), DBP (ET: 85.1 ± 17.9 mmHg vs. UC: 82.4 ± 13.3 mmHg), MAP (ET: 122.2 ± 17.0 mmHg vs. UC: 121.2 ± 10.4 mmHg), SV (ET: 84.0 ± 16.8 ml·beat^{-1} vs. UC: 84.7 ± 20.8 ml·beat^{-1}), Q (ET: 12.3 ± 4.3 mmHg vs.

UC: 12.1 ± 4.2 mmHg), a-vO_2 diff (ET: 13.1 ± 3.7 ml·dl $^{-1}$ vs. UC: 13.4 ± 4.1 ml·dl $^{-1}$), SVR (ET: 905.3 ± 370.3 dyn·s·$^{-1}$cm^{-5} vs. UC: 939.6 ± 432.9 dyn·s^{-1}·cm^{-5}) and VO2 (ET: 1.6 ± 0.7 L·min^{-1} vs. UC: 1.5 ± 0.6 L·min^{-1} and ET: 19.9 ± 22.5 mL·kg^{-1}·min^{-1} vs. UC: 21.3 ± 9.7 mL·kg^{-1}·min^{-1}) were not significantly different between the groups at baseline.

Resting Arterial Compliance and 24 Hour Blood Pressure

Resting small (ET: 5.2 ± 3.0 ml/mmHg x 100 vs. UC: 4.4 ± 1.6 ml/mmHg x 100) and large (ET: 13.9±3.9 ml/mmHg x 10 vs. UC: 12.9 ± 3.9 ml/mmHg x 10) artery compliance and 24 hour SBP (ET: 121.8 ± 8.5 mmHg vs. UC: 128.6 ± 12.7 mmHg) and DBP (ET: 75.0 ± 6.1 mmHg vs. UC: 71.5 ± 8.1 mmHg) were not different between groups at baseline.

Lower Extremity Maximal Muscular Strength

No significant difference was found between groups for the leg press (ET: 204.3 ± 88.8 kg vs. UC: 167.5 ± 70.1 kg), leg extension (ET: 42.2 ± 19.2 kg vs. UC: 39.8 ± 15.6 kg) or leg curl (ET: 28.8 ± 16.4 kg vs. UC: 30.1 ± 17.0 kg) measures of lower body maximal strength.

Lean Body Mass

No significant difference was found for lean body mass between groups (ET: 55.4 ± 11.0 kg vs. UC: 51.2 ± 9.7 kg).

Health Related Quality of Life

Except for the Social Function (ET: 71.1 ± 26.1 vs. UC: 87.5 ± 17.0) subscale, no significant difference was found between groups for health related quality of life measures (Table 5).

Table 5: Baseline comparison of Quality of Life

Domain	Usual care	Exercise Trained
Physical Function	69.0 ± 28.3	71.6 ± 24.6
Role Physical	70.0 ± 44.5	75.0 ± 38.7
Body Pain	67.0 ± 24.8	76.4 ± 58.6
General Health	64.4 ± 22.9	61.8 ± 20.4
Vitality	69.7 ± 17.8	56.9 ± 22.2
Social Function	87.5 ± 17.0	71.1 ± 26.1*
Role Emotional	86.7 ± 35.2	83.3 ± 29.8
Mental Health	81.3 ± 10.1	79.8 ± 12.4
Physical Composite Score	68.0 ± 21.3	67.5 ± 20.0
Mental Composite Score	77.9 ± 16.0	70.6 ± 16.0
Total SF-36 Composite Score	74.4 ± 18.9	71.4 ± 16.4

* $P < 0.05$ vs. UC, data presented as mean ± SD

Cardiovascular Disease Risk Score

No differences were found between the groups for Framingham risk score (ET: 6.0 ± 7.4% vs. UC: 6.6 ± 7.3%).

4.2 Post 12 week intervention

Effects of ET versus UC on Resting Cardiopulmonary Performance

No significant difference was found between groups for change in resting HR (ET: 0.5 ± 6.3 beats/min vs. UC: -0.1 ± 7.2 beats/min, P = 0.815), SBP (ET: - 2.1 ± 13.3 mmHg vs. UC: -4.3 ± 21.2 mmHg, P = 0.745), DBP (ET: 1.2 ± 9.0 mmHg vs. UC: -3.0 ± 8.9 mmHg, P = 0.225), MAP (ET: -1.4 ± 11.3 mmHg vs. UC: -2.1 ± 15.6 mmHg, P = 0.905), SVR (ET: -7.9 ± 848.5 dyn·s·cm^{-5} vs. UC: 168.3 ± 506.2 dyn·s·cm^{-5}, P = 0.585), Q (ET: -0.3 ± 1.4 L/min vs. UC: -0.3 ± 1.3 L/min, P = 0.953) after 12 weeks of UC or ET.

Effects of ET versus UC on Peak Exercise and Cardiopulmonary Performance

No significant difference was found between groups for change in peak exercise SBP, DBP, MAP or SVR. The changes in HR_{peak}, Q_{peak}, VCO_{2peak}, absolute VO_{2peak} (L·min^{-1}) (Figure 5), and VO_{2peak} indexed to body mass was significantly greater after 12 weeks of ET compared to UC (Table 6).

Effect of ET versus UC on arterial compliance and 24 blood pressure

Changes in 24-hour ambulatory SBP (ET: 9.1 ± 12.8 mmHg vs. UC: 1.7 ± 17.2 mmHg, P = 0.351) and DBP (ET: 5.7 ± 6.9 mmHg vs. UC: 1.5 ± 12.8 mmHg, P = 0.424) did not differ between ET and UC after 12 weeks. Further, the change in small (ET: -0.3 ± 2.7 ml/mmHg x 100 vs. UC: 0.9 ±

2.2 ml/mmHg x 100, P = 0.238) and large (ET: 0.2 ± 3.5 ml/mmHg x 10 vs. UC: 0.3 ± 5.0 ml/mmHg x 10, P = 0.941) artery compliance did not differ between groups.

Table 6: Effects of supervised exercise training on cardiopulmonary function during peak exercise

	UC				ET				p
Variable	Pre	Post	Change	n	Pre	Post	Change	n	
VO2($l \cdot min^{-1}$)	1.5 ± 0.6	1.5 ± 0.6	-0.02 ± 0.2 (95% CI: -0.12 - 0.09)†	15	1.6 ± 0.8	1.8 ± 0.8	0.2 ± 0.2 (95% CI: 0.06 – 0.32)	16	0.02*
VO2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	21.2 ± 10.0	20.7 ± 10.2	-0.4 ± 2.5 (95% CI: -1.80 – 0.91)	15	19.9 ± 9.3	22.5 ± 10.2	2.6 ± 3.1 (95% CI: 1.01 – 4.28)	16	0.002*
VCO2($l \cdot min^{-1}$)	1.8 ± 0.8	1.8 ± 0.8	0.01 ± 0.3	14	1.7 ± 0.9	2.0 ± 0.9	0.3 ± 0.3	13	0.005*
VE ($L \cdot min^{-1}$)	55.9 ±	56.9 ±	1.0 ± 16.9	14	61.2 ±	69.9 ±	8.7 ± 13.7	13	0.21

	29.8	26.1			40.7	36.3			7
Power (W)	98.6 ± 56.7	107.1 ± 54.2	8.6 ± 16.3	14	94.6 ± 48.0	113.9 ± 52.1	19.2 ± 14.4	13	0.085
RER	1.1 ± 0.08	1.1 ± 0.1	0.01 ± 0.08	14	1.1 ± 0.2	1.2 ± 0.1	0.1 ± 0.14	13	0.264
HR (beats·min^{-1})	137.3 ± 28.0	134.4 ± 29.6	-2.9 ± 11.2	14	133.5 ± 34.3	141.6 ± 33.1	8.08 ± 14.4	13	0.036*
Percent Predicted Peak HR (%)	81.2 ± 1.5	79.3 ± 1.5	-1.9 ± 6.7	14	81.8 ± 1.8	86.9 ± 1.9	5.1 ± 9.1	13	0.030*
SBP (mmHg)	198.9 ± 17.8	204.6 ± 20.5	5.8 ± 18.9	14	196.2 ± 25.6	199.2 ± 15.7	2.9 ± 23.1	13	0.125
DBP (mmHg)	82.4 ± 10.5	82.8 ± 13.3	0.4 ± 14.0	14	85.1 ± 17.9	86.8 ± 11.3	1.8 ± 14.1	13	0.796
MAP (mmHg)	121.2 ±	123.4 ±	2.2 ± 13.3	14	122.1 ±	124.3 ±	2.2 ± 13.8	13	0.99

	10.0	11.9			17.0	11.1			8
SVR (dyn·s·cm^{-5})	939.6 ± 432.9	967.4 ± 497.9	27.8 ± 146.2	14	905.3 ± 370.3	774.6 ± 231.5	-130.7 ± 264.5	13	0.101
SV (ml)	84.7 ± 20.8	88.1 ± 23.8	3.4 ± 6.3	11	84.0 ± 16.8	90.2 ± 19.9	6.2 ± 17.5	10	0.530
Q (L·min^{-1})	12.1 ± 4.2	12.1 ± 4.6	-0.01 ± 0.8	11	12.3 ± 4.3	13.9 ± 4.2	1.7 ± 2.6	10	0.030*
a-vO2 diff (ml·dl $^{-1}$)	13.4 ± 3.4	13.4 ± 4.1	-0.08 ± 1.8	11	13.1 ± 2.6	13.4 ± 3.6	0.3 ± 3.9	10	0.775

* P < 0.05 vs. UC, data are mean ± SD. † 95% Confidence Interval (CI), reported for primary outcome only.

Effect of ET versus UC on lower body maximal muscular strength

The improvement in leg press and leg extension maximal strength was significantly greater in the ET vs. UC. However, no difference in leg curl maximal strength was observed between the groups (Figure 6).

Effect of ET versus UC on lean body mass

No significant change in lean body mass was found between groups (ET: 0. 9 ± 3.64 kg vs. UC: -0.6 ± 2.69 kg, P = 0.329).

Effect of ET versus UC on cardiovascular disease risk score, low density lipoprotein and total cholesterol

No significant difference was found for Framingham CVD Risk Score between the groups (ET: 0.1 ± 2.0% vs. UC: -0.1 ± 1.2%, P = 0.769). Further, no significant differences were found between groups for changes in HDL cholesterol (ET: -0.013 ± 0.16 vs. UC: 0.80 ± 0.23, P = 0.357) or total cholesterol (ET: 0.28 ± 0.40 vs. UC: 0.0071 ± 0.40, P = 0.203).

Effect of exercise training on Health Related Quality of Life

The ET group demonstrated a significant change in social functioning (ET: 15.2 ± 26.5 vs. UC: -9.82 ± 17.11, P = 0.006), mental composite score (ET: -6.9 ± 42.1 vs. UC: -9.4 ± 23.9, P = 0.004) and overall QOL score (ET: 8.6 ± 13.4 vs. UC: -3.4 ± 12.1, P = 0.02). No other changes in health related QOL were found between groups at the end of 12 weeks (Table 7).

Figure 5: Change in exercise capacity and cardiac performance after 12 weeks of exercise in ET versus UC

Figure 5 A. Changes in VO_{2peak} after 12 weeks of UC or ET

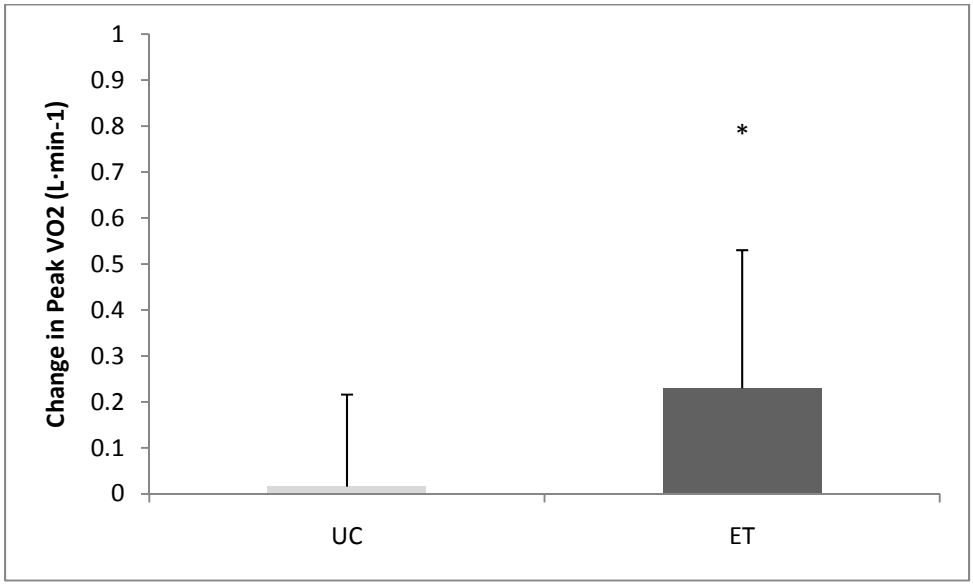


Figure 5 B. Changes in peak SV after 12 weeks of UC or ET

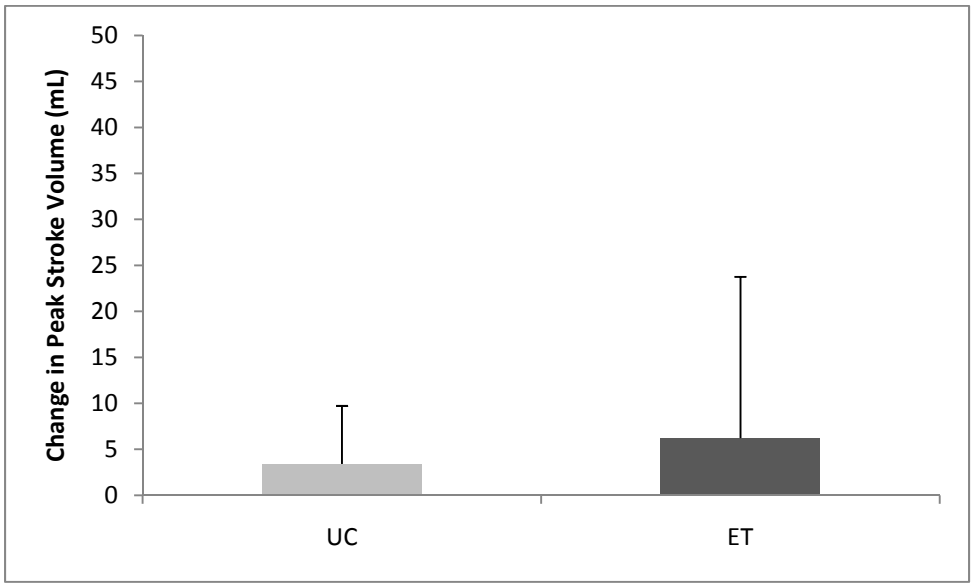


Figure 5 C. Changes in a-$vO2_{diff}$ after 12 weeks of UC or ET

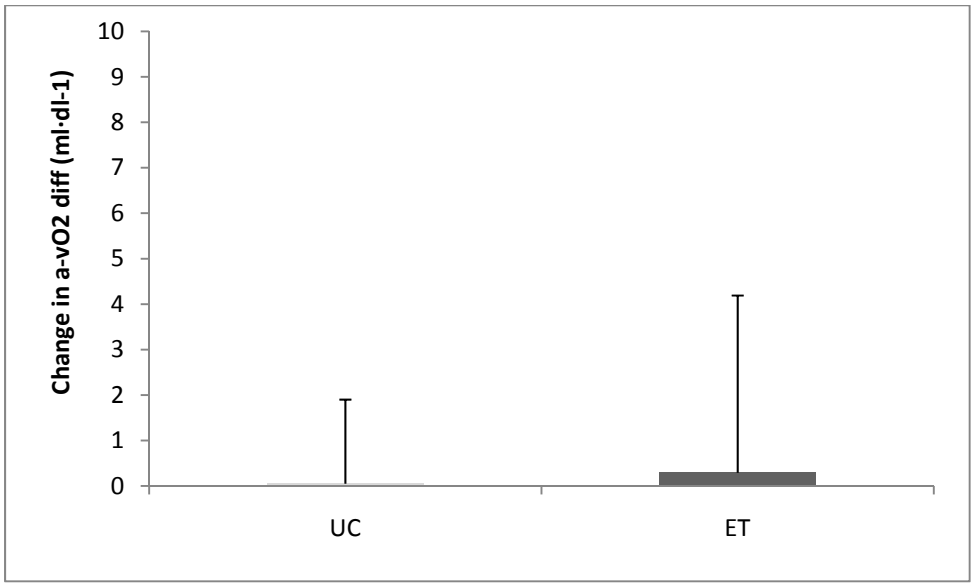
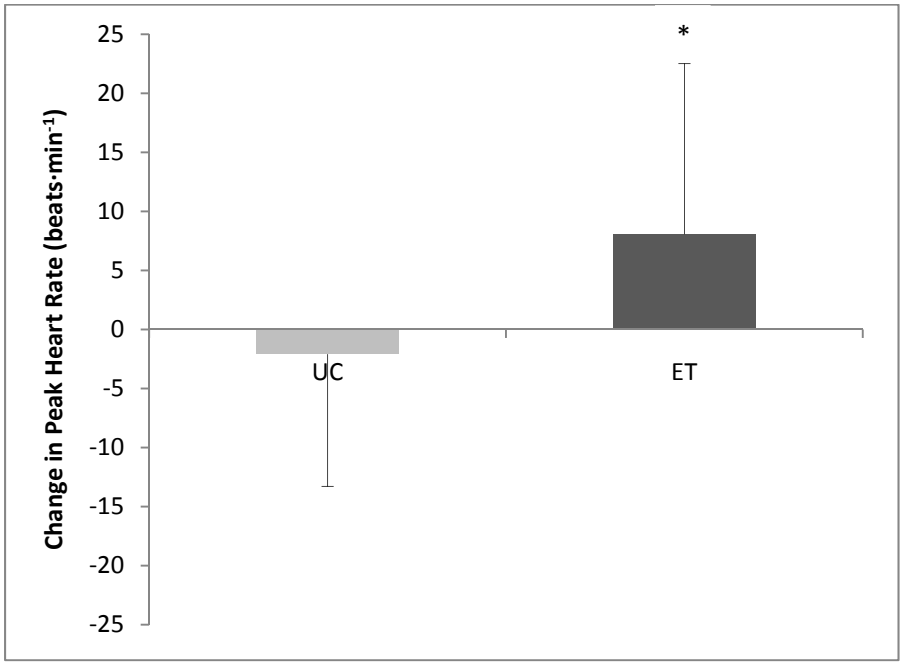
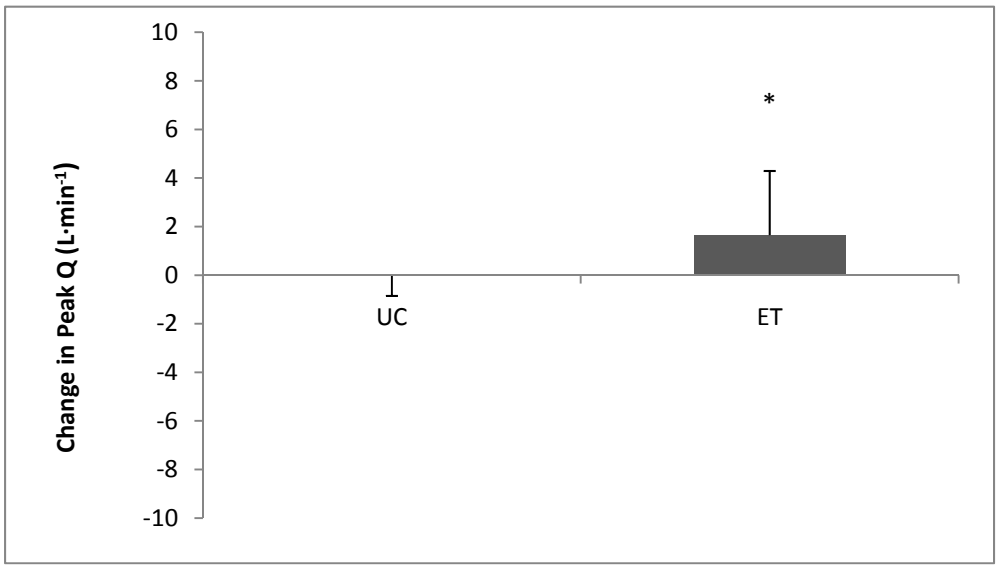


Figure 5 D. Changes in peak heart rate after 12 weeks of UC or ET



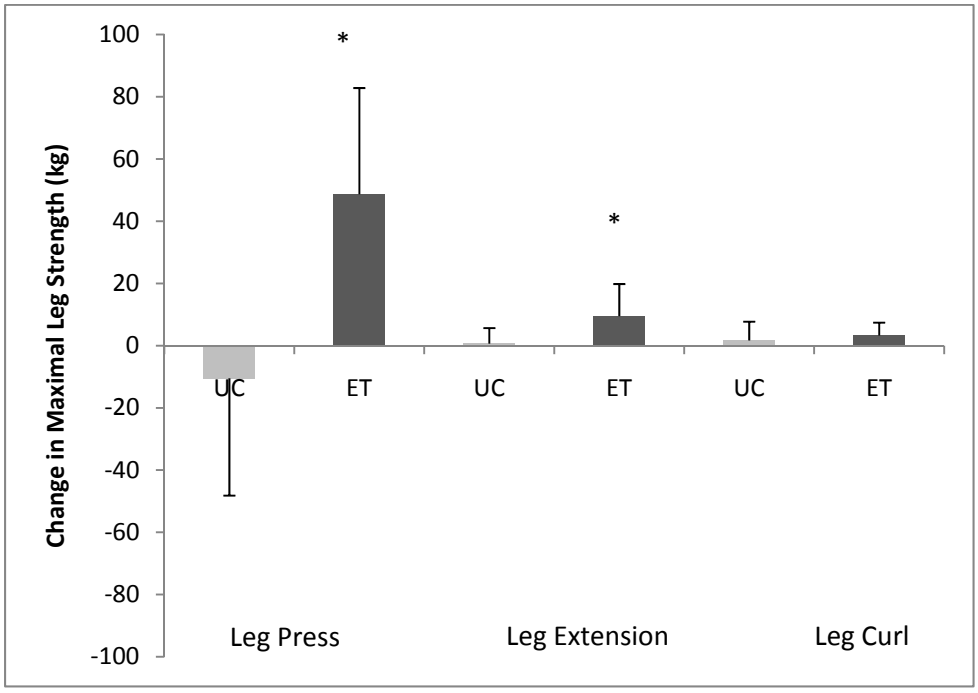
* P < 0.05 vs. UC

Figure 5 E. Changes in Q_{peak} after 12 weeks of UC or ET



* P < 0.05 vs. UC

Figure 6: Change in lower body maximal muscular strength after 12 weeks of UC or ET



* P < 0.05 vs. UC

Table 7: Effects of ET on change in quality of life

Domain	UC	ET
Physical Function	-3.9 ± 22.7	7.71±1.06
Role Physical	-10.7 ± 40.0	12.5 ± 43.6
Body Pain	4.5 ± 14.6	-0.4 ± 22.4
General Health	-5.9 ± 13.2	3.5 ± 11.8
Vitality	7.5 ± 37.5	10.4 ± 9.1
Social Function	-9.8 ± 17.1	15.2 ± 26.5*
Role Emotional	-2.4 ± 40.2	9.5 ± 27.5
Mental Health	-8.0 ± 19.9	2.0 ± 10.6
Physical Composite Score	-7.6 ± 28.0	-7.9 ± 46.9
Mental Composite Score	-9.4 ± 23.9	-6.9 ± 42.1*
Total SF-36 Composite Score	-3.4 ± 12.1	8.64 ± 13.4*

* P < 0.05 vs. UC, mean ± SD

Discussion

5.1 Major Findings

The major finding of this study is that 12 weeks of supervised ET increased VO_{2peak} secondary to an increase in Q_{peak} and HR_{peak}. A secondary finding is that ET improved lower extremity maximal muscular strength and improved in quality of life in KTR compared to UC.

5.2 Improvement in Cardiopulmonary Performance

Currently, only a few studies have examined the effects of exercise training on VO_{2peak} in KTR [42, 64, 127, 133]. In an early study, Miller et al. [127] investigated the effects of 6 weeks of aerobic exercise training on estimated peak METs in 10 recent (mean time post-transplant = 17 days) KTR. The main finding was that short term training improved estimated VO_{2peak} (90%) and peak heart rate (15%). Painter et al. [42] compared 12 months of home based aerobic exercise training, initiated one moth post-surgery, versus usual care (no exercise training) on VO_{2peak}, muscular strength, body composition and QOL in 167 KTR. Outcome measures were examined in both groups at 6 and 12 months post randomization. Both groups improved VO_{2peak} (14%) and muscle strength (ET = 22%; UC = 19%) after 6 months. There was an improvement in VO_{2peak} (7.3%) and muscle strength (9%) from 6 months to 12 months in ET with no change in either VO_{2peak} or muscular strength in UC. Finally, the UC and ET groups had similar improvement in body fat and lean mass over the 12 month period and the SF-36 QOL domain of

Physical Functioning QOL domain demonstrated an increase approaching significance in the ET group. A limitation of this study was that only 68% of the participants randomized to the exercise group adhered to the program. Moreover, 36% of the usual care group reported performing regular exercise, a finding that may explain similar improvement in outcomes during the first 6 months. In a later report, using the same subjects, the investigators found that 12 months of home base exercise training did not improve the 10 year CVD risk over usual care [133]. Further, the measures used to determine 10 year CVD risk (ie. resting SBP and DBP, total cholesterol, HDL-C, presence of diabetes, and self reported tobacco use) were not different between groups after 1 year. Of note, the authors reported that the ET group had an improvement in HDL-C over the UC group that approached significance ($P = 0.07$) despite both ET and UC groups demonstrating an increase in TC versus baseline ($P < 0.0001$).

Kempeneers et al. [64] examined the role of 6 months of aerobic training in KTR (n = 24, mean age = 33 years) and healthy controls (n=6; mean age = 24 years). The mean time post kidney transplant was 5 years. At baseline, VO_{2peak} was 39% lower in KTR versus controls. After training, VO_{2peak} improved by 30% ($P< 0.05$); however, despite this improvement, it remained 22% lower than healthy controls. The mechanism for the favorable change in VO_{2peak} was attributed to peripheral adaptations as quadriceps and hamstring strength improved significantly with training. A sub-analysis on 6 of the “fittest” subjects

revealed reduced type I fiber area suggesting no change in muscle oxygen utilization.

Romano et. al [132] reported on the effects of 10 weeks of interval exercise training (defined as 15 repetitions of 1 minute at 90% of peak heart rate followed by 1 minute of 50% of work interval heart rate) on VO_{2peak}, lean body mass, resting MAP, and QOL in 8 KTR with an average time from transplant of 5.4 years. Short-term training increased VO_{2peak} (13%) and QOL as well as decreased resting MAP (12%) with no change in lean body mass. The present finding that 12 weeks of combined aerobic and strength training improved VO_{2peak}, lower extremity maximal muscular strength and QOL is consistent with prior studies. Moreover, the present results extend previous research by demonstrating that the improvement in VO_{2peak} is primarily due to central factors (i.e. peak exercise Q).

5.3 Effect of Exercise Training on Cardiac Performance

The role of exercise training to improve cardiovascular function in KTR has not been well studied. The increased Q_{peak} found in the current study is due to an increase in HR_{peak}. These findings are in contrast to those of Kempeneers et al. [64] who reported no improvement in HR_{peak}, however it is similar to that of Miller et al. [127]. Further, the percent predicted peak heart rates of our trained subjects increased significantly over the control group. Our ET subjects reached, on average, a peak

heart rate of 87% of predicted (from a baseline of 82%) while the UC had a slight decrease (Pre: 81% vs. Post: 79%) in percent of predicted peak heart rate after 12 weeks. This post training values observed in our study are similar to peak heart rate in active KTR reported by others. Specifically, Richard et al. [126] and Painter et al. [142] reported peak heart rates of 92% and 91% of predicted, respectively, in a group of "fit" KTR (mean VO_{2peak} = 50$ml^{-1}\cdot kg^{-1}\cdot min^{-1}$) [126] and in KTR participating in the United States National Transplant Games[142].

5.4 Effects of ET on systolic and diastolic blood pressure and arterial compliance

Exercise has been shown to have a significant lowering effect on resting blood pressure in hypertensive and normotensive individuals [143, 144] . This reduction in resting blood pressure as a result of exercise has been attributed to a reduction in SVR likely resulting from positive adaptations of the sympathetic and renin-angiotensin systems [144]. The ET subjects demonstrated a slight reduction in resting SVR compared to UC. Despite this finding the 24 hour systolic and diastolic blood pressures and resting systolic and diastolic blood pressures were not altered in ET. This finding is similar prior exercise intervention studies in KTR [64, 127, 133].

Arterial compliance has been shown to be higher (ie. more favourable) in individuals with higher levels of fitness [145]as it responds

favourably to exercise training [146, 147]. Further, Pilot data (appendix A) from our laboratory revealed that KTR have reduced small artery compliance compared to healthy age predicted values and a concomitant reduction in aerobic fitness as measured by 6-minute walk [148].

Arterial stiffness has not been well studied in KTR. However, arterial stiffening has been reported to be an independent predictor of all-cause mortality in end-stage chronic kidney disease [149]. Further, kidney failure has been associated with an increase in arterial stiffening resulting from vascular calcification. This arterial stiffening is directly related to the severity of the kidney failure[150]. Possible reasons for this increase in arterial stiffness in renal failure may be due to the increased prevalence of vascular calcification, aging, male gender and presence of diabetes [150]. Specifically, Sigrist et al. [150]reported that arterial stiffness, as measured by pulse wave velocity, was highest (ie. least complaint) in those CKD subjects with the highest calcification score. This reduction in arterial compliance is improved with transplantation but the use of some immunosupression therapies may limit this improvement [27]. Specifically, Zoungas et al. reported that the use of tacrolimus allowed for greater improvement in arterial function in KTR when compared to cyclosporine [27].

Endurance exercise training is known to have an association with improvements in large and small artery compliance. However, in the

present study no change in either small or large artery compliance occurred with ET. The mechanism for this finding may be due to the type of training performed. For example, by prescribing a 3 month home based walking program (average 5 days per week) to middle age and older sedentary males (average age = 53 years), Tanaka et al.[151] reported a significant improvement in central arterial compliance. However Fjeldstad et al. [152] found that 12 weeks of resistance training did not alter small or large artery compliance in pre-menopausal women. Further, others have demonstrated that resistance training in middle aged men resulted in a negative effect on central arterial compliance [153, 154]. Thus, the deleterious effects of resistance training on arterial compliance may be counteracted with the inclusion of aerobic training in the KTR population.

5.5 Exercise training and muscular strength and lean body mass

Previous studies have consistently shown that that maximal muscular strength is lower in KTR compared to healthy controls [64, 130] . Baseline muscular strength may be lower in KTR as the result of post transplant inactivity [155]. Although improvements in muscular strength occur after supervised training in recent KTR [42], the peak lower body strength attained is 26% lower than reported for healthy controls [130].

The ET subjects in this study had a significant increase in lower body peak maximal strength after the 12 week intervention. An increase in muscular strength has been shown to relate to an concomitant increase

in peak exercise capacity [64] and thus may have contributed to the increase in VO_{2peak}. Although our study did not determine the reasons for increases in peak strength, it is likely that the improvements observed in our ET subjects were the result of improved neuromuscular coordination and, perhaps, an increase in muscle mass.

It has long been accepted that initial improvements in muscular strength are the result of neuromuscular adaptations in healthy subjects [156-158]. As the subjects in this study performed lower body strength training 3 days per week for 12 weeks, it is likely that improvement in muscular strength were the result of neuromuscular adaptations to strength training. It has been suggested that the likely reasons for the increase in force production by the muscle is the result of increased firing rates, increased motor neuron firing rates, increased motor neuron excitability and decreased parasympathetic inhibition [157].

Alternative mechanisms for this increase in peak lower body muscular strength may have been partially due to an increase in, albeit not significant, lean body mass. There is a paucity of data on the effects of exercise training on lean body mass in KTR. Romano et al. [132] reported no significant effect on lean body mass in KTR after 30 cardiovascular training sessions. However, Horber et al. [159] observed a 6.7% increase in thigh muscle area in KTR who trained 21 sessions over 7 weeks. Interestingly, these subjects, who attained similar results to age

matched sedentary controls, were also treated with low-dose prednisone. The ET subjects achieved greater improvement in lean body mass, albeit not significant, as well as improved leg strength. Further, Haykowsky et al. [160] reported heart transplant recipients improved muscular strength and increased leg and total lean body mass through a similar program (ie. 12 weeks) of aerobic exercise and resistance training.

5.6 Exercise and Quality of Life

At baseline, the UC subjects had a significantly higher SF-36 sub-domain score for social function. This trend reversed after 12 weeks of either ET or UC as the UC demonstrated a decrease in social function and a significant increase was observed in UC. Romano et al. [132]reported similar findings after a 10 weeks of interval training. These authors hypothesized that the subject's increase in overall quality of life lead to an increase in self confidence and an concomitant increase in a desire for socialization. Painter et al. [42]observed a significant increase in the *physical functioning* sub-domain of the SF-36 after 12 months of exercise training with no significant change in *social functioning*. This discrepancy between Painter et al. [42] and our subjects may be due to the home based, individual, exercise prescription used by their group versus the supervised, often group based training sessions offered in our study.

5.7 Cardiovascular risk score

The effects of exercise on traditional cardiovascular disease risk factors has long been known to be favourable in both women and men in the general population [161-163]. Further, Painter et al. [133] reported that 12 months of individualized, home based exercise training within one month of transplantation failed to significantly improve 10 year CVD risk based on the Framingham CVD risk score. These authors also reported that there was no improvement in SBP, TC or HDL cholesterol as a result of a year of exercise training. Consistent with these findings, rest SBP, TC or HDL cholesterol were not altered with training in the subset of patients in which this was measured. This study extends the finding of Painter et al. [133] by reporting that KTR who are, on average 6.2 yeas post transplant do not improve CVD risk score with supervised ET. It is likely that the intensity of our exercise intervention was too low for an effect on CVD risk score to be observed. Specifically, intense interval training has been reported to have a greater positive effect on endothelial function [164, 165], mean arterial pressure [165] and mitochondrial function [164] in several populations including heart failure [164] and obese youth [165].

It has been reported that KTR are at an increased risk for CVD compared to the general population [31]. However, this increased risk may be the result of less “traditional” risk factors not accounted for in the

Framingham risk score. Specifically, Diaz et al. [166] reported that along with traditional CVD risks accounted for in the Framingham risk score, hepatitis C virus antibodies, proteinuria, and serum creatinine levels are significantly related to CVD events in KTR. Like Painter et al. [133] this study did not measure these serum markers.

5.8 Health Service Implications

Exercise training has been shown to be a cost effective alternative for both invasive coronary angioplasty [167] and as a treatment for heart failure that reduces hospitalizations and mortality risk [168]. This study did not address the cost effectiveness of ET in KTR; however, it is possible that the improvement in overall physical fitness (VO_{2peak} and maximal muscle strength) with training may have resulted in improved functional independence leading to a reduction in utilization of healthcare services. Future research examining the cost effectiveness of exercise training in KTR versus usual care is required.

5.9 Limitations

This study has limitations. Specifically, participants were recruited from the University of Alberta's Renal Transplant Clinic. As such, those who agreed to take part may have already been eager to exercise and may have been more motivated than the average KTR. Further, the study was statistically powered to determine changes in our primary outcome measure of VO_{2peak}; however, a larger sample size may have been

required to ensure statistical power was present for many of the other outcome measures. Body composition for this study was assessed with the use of measurement of skinfold thickness. While dual energy X-ray absorbtiometry is the gold standard [169], the skinfolds were all performed by the same researcher reduce inter-rater reliability. Exercise logs were not required to be kept by either the control group or the training group and, as such, leisure time physical activities could not be compared between the two groups. The researchers were not blinded to the randomized assignment for the follow-up measures including the follow-up aerobic exercise test. However, maximal RER did not differ between UC and ET during follow-up tests indicating maximal efforts for both groups.

The exclusion criteria of our study included time from transplant, presence of type 1 diabetes and presence of uncontrolled hypertension. As such, this study recruited a wide range of ages (range: 25 – 76 years) and included both genders making the generalizability of you study somewhat limited. Further investigations into more specific KTR populations would be recommended.

5.10 Conclusion and clinical implications

In summary, the present study demonstrated that 12 weeks of supervised exercise training results in significant improvements in VO_{2peak}, lower body maximal leg strength and quality of life in KTR compared to UC. The improvements in VO2peak were primarily due to increase Q and

to a lesser extent to a-vO_{2diff}. Further, the increased Q was due to favorable change in peak exercise HR. Moreover, the increased muscle strength is likely due to increased lean body mass which improved slightly (mean increase: 1%) in ET subjects with a slight reduction in UC lean mass (-0.5%). Finally, ET also improved overall QOL in ET versus UC.

The improved VO2peak may have favorable survival benefits as Myers et al. [13] reported that for each one MET increase in peak exercise there is a 12% increase in survival. Given that the ET improved by close to this 1 MET threshold the subjects who underwent ET may likely have improved their survival by 12%. Future studies need to determine mechanism for favorable change in central and peripheral adaptations as well as optimal exercise intensity to improve CVD risk profile.

General Discussion

The data presented for this thesis contribute important information to the body of knowledge relating to the effects of supervised exercise on CVD risk factors in KTR. Specifically, findings from the pilot study (Appendix A) determined that small artery compliance was reduced in KTR compared to healthy, age matched controls. This is an important finding as small artery compliance is a novel risk factor for cardiovascular events in KTR [170] Further, it was observed that older KTR have lower small and large artery compliance compared to younger KTR, a trend that occurs as part of healthy aging as well [76]and a possible reason for the increased risk for CVD that accompanies aging [171] .

The major study for this thesis demonstrated that was KTR respond favourably to exercise compared to those KTR undergoing usual care. Specifically, KTR demonstrated an improvement in VO_{2peak} (13%) and muscular strength (26% leg press, 33% leg extension) as the result of 12 weeks of supervised exercise training. Improvements in VO_{2peak} and muscular strength in KTR as result of exercise training have been reported by others [42, 127, 130, 132], However, this is the first study to evaluate the likely mechanisms for the improvement in cardiac performance related to the increase in VO_{2peak}. Specifically, it was determined that increases in VO_{2peak} are primarily related to improvements in Q secondary to an increase in HR_{peak}. Accordingly, the mechanisms for the increase in HR_{peak} require further study.

The major finding of this thesis is that KTR who participate in supervised exercise training, 3 days a week for 12 weeks, improve their peak exercise capacity absolutely and relative to body mass. This is an important finding in that improvement in exercise capacity is related to a reduction in mortality. Sietsema et al. [15]reported that patients with ESRD who had a VO_{2peak} < 18 ml/kg/min had a lower 3.5 year survival rate compared to those patients above this score. In addition, Myers et al. [13] found the highest all cause mortality rate was observed in men referred for exercise testing with a peak exercise capacity of similar to that of Sietsema et al. [15] (ie. 17.5 ml/kg/min). Further, Myers et al. [13] reported that an improvement in peak exercise capacity of 3.5 ml/kg/min was associated with a 12% improvement in survival. We reported that our subjects undergoing 12 weeks of supervised exercise training, on average, reported an improvement in peak exercise capacity close to this value (2.6 ml/kg/min). Thus, future studies are required to determine if increases in VO2peak have a favourable effect on survival.

The findings of this thesis extend prior studies in healthy and diseased populations to KTR be demonstrating that short-term ET (combined aerobic and strength training) can increase VO2peak, peak cardiac and skeletal muscle performance and QOL in KTR. Accordingly, KTR should take part in regular physical activity, both aerobic and strength training, not just as part of post-transplant rehabilitation but as a part of a lifelong commitment to improved health.

References

1. Myers, J., *Essentials of Cardiopulmonary Exercise Testing*1996, Champaign Il.: Human Kinetics.
2. Klabunde, R.E., *Cardiovascular Physiology Concepts*. 1 ed2005, Baltimore MD: Lippincott Williams and Wilkins. 235.
3. Lilly, L.S., ed. *Pathophysiology of Heart Disease*. 2003, Lippincott Williams and Wilkens: Philadelphia, PA.
4. Frontera, W.R., ed. *Exercise in Rehabilitation Medicine*. 2 ed. 2006, Human Kinetics: Champaign, Il.
5. Wadei, H.M. and S.C. Textor, *Hypertension in the kidney transplant recipient.* Transplant Rev (Orlando). **24**(3): p. 105-20.
6. Young, J.B., H.H. Neumayer, and R.D. Gordon, *Pretransplant cardiovascular evaluation and posttransplant cardiovascular risk.* Kidney Int. **78 Suppl 118**: p. S1-7.
7. Cowie, C.C., et al., *Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999-2002.* Diabetes care, 2006. **29**(6): p. 1263-8.
8. Eckardt, K.U. and B.L. Kasiske, *Kidney disease: improving global outcomes.* Nat Rev Nephrol, 2009. **5**(11): p. 650-7.

9. Friedman, A.N., et al., *Demographics and trends in overweight and obesity in patients at time of kidney transplantation.* Am J Kidney Dis, 2003. **41**(2): p. 480-7.

10. Marcen, R., *Immunosuppressive drugs in kidney transplantation: impact on patient survival, and incidence of cardiovascular disease, malignancy and infection.* Drugs, 2009. **69**(16): p. 2227-43.

11. Zitt, N., et al., *Cigarette smoking and chronic allograft nephropathy.* Nephrol Dial Transplant, 2007. **22**(10): p. 3034-9.

12. Johansen, K.L., et al., *Low level of self-reported physical activity in ambulatory patients new to dialysis.* Kidney Int.

13. Myers, J., et al., *Exercise capacity and mortality among men referred for exercise testing.* N Engl J Med, 2002. **346**(11): p. 793-801.

14. Gulati, M., et al., *Exercise capacity and the risk of death in women: the St James Women Take Heart Project.* Circulation, 2003. **108**(13): p. 1554-9.

15. Sietsema, K.E., et al., *Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease.* Kidney international, 2004. **65**(2): p. 719-724.

16. Magee, C.C. and M. Pascual, *Update in renal transplantation.* Arch.Intern.Med, 2004. **164**(13): p. 1373-1388.

17. Wolfe, R.A., et al., *Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients*

of a first cadaveric transplant. N Engl J Med, 1999. **341**(23): p. 1725-30.

18. Laupacis, A., et al., *A study of the quality of life and cost-utility of renal transplantation.* Kidney Int, 1996. **50**(1): p. 235-42.
19. Le, A., et al., *Prospective risk stratification in renal transplant candidates for cardiac death*, in *Am J Kidney Dis.*1994. p. 65-71.
20. Braun, W.E. and T.H. Marwick, *Coronary artery disease in renal transplant recipients.* Cleve.Clin.J Med, 1994. **61**(5): p. 370-385.
21. Kjaer, M., et al., *Glucose homeostasis during exercise in humans with a liver or kidney transplant*, in *Am J Physiol*1995. p. E636-E644.
22. Aakhus, S., K. Dahl, and T.E. Wideroe, *Cardiovascular morbidity and risk factors in renal transplant patients.* Nephrol.Dial.Transplant., 1999. **14**(3): p. 648-654.
23. Abbott, K.C., et al., *Hospitalized congestive heart failure after renal transplantation in the United States.* Ann Epidemiol, 2002. **12**(2): p. 115-22.
24. Levey, A.S., et al., *Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease.* Am J Kidney Dis., 1998. **32**(5): p. 853-906.

25. Kasiske, B.L., H.A. Chakkera, and J. Roel, *Explained and unexplained ischemic heart disease risk after renal transplantation.* J Am Soc Nephrol, 2000. **11**(9): p. 1735-43.

26. Jimenez Alvaro, S., et al., *Management of chronic kidney disease after renal transplantation: is it different from nontransplant patients?* Transplant Proc, 2009. **41**(6): p. 2409-11.

27. Zoungas, S., et al., *Arterial function after successful renal transplantation.* Kidney international, 2004. **65**(5): p. 1882-1889.

28. Boudoulas, H., Leifer, C.V., *Renal Disorders and Cardiovascualr Disease*, in *Brunwald's Heqrt Disease. A Textbook of Cardiovascular Medicine*, D.P. Zipes, Editor 2001, W.B. Saunders Co.: Phillidelphia, PA. p. 2280-2297.

29. Colucci, W.S., *Nesiritide for the treatment of decompensated heart failure.* J Card Fail, 2001. **7**(1): p. 92-100.

30. Kasiske, B.L., et al., *Hypertension after kidney transplantation.* Am J Kidney Dis., 2004. **43**(6): p. 1071-1081.

31. Ojo, A.O., *Cardiovascular complications after renal transplantation and their prevention.* Transplantation, 2006. **82**(5): p. 603-11.

32. Canada, S. *High blood pressure, by age group and sex* 2010 [cited 2010 October 15, 2010]; Available from: http://www40.statcan.ca/l01/cst01/health03b-eng.htm.

33. Seaquist, E.R. and H.N. Ibrahim, *Approach to the patient with type 2 diabetes and progressive kidney disease.* J Clin Endocrinol Metab. **95**(7): p. 3103-10.

34. Reilly, R.F.P., M.A., *Nephrology in 30 Days*. First ed2005, New York, NY: McGraw-Hill. 410.

35. Siraj, E.S., et al., *Risk factors and outcomes associated with posttransplant diabetes mellitus in kidney transplant recipients.* Transplant Proc. **42**(5): p. 1685-9.

36. Badiou, S., J.P. Cristol, and G. Mourad, *Dyslipidemia following kidney transplantation: diagnosis and treatment.* Curr Diab Rep, 2009. **9**(4): p. 305-11.

37. Ansell, D., et al., *Chronic renal failure in kidney transplant recipients. Do they receive optimum care?: data from the UK renal registry.* Am J Transplant, 2007. **7**(5): p. 1167-76.

38. Marcen, R., et al., *Achieving chronic kidney disease treatment targets in renal transplant recipients: results from a cross-sectional study in Spain.* Transplantation, 2009. **87**(9): p. 1340-6.

39. Seifi, S., et al., *Posttransplant diabetes mellitus: incidence and risk factors.* Transplant Proc, 2009. **41**(7): p. 2811-3.

40. van den Ham, E.C., J.P. Kooman, and J.P. van Hooff, *Nutritional considerations in renal transplant patients.* Blood Purif, 2002. **20**(2): p. 139-44.

41. Gordon, E.J., et al., *Prevalence and determinants of physical activity and fluid intake in kidney transplant recipients.* Clin Transplant. **24**(3): p. E69-81.

42. Painter, P.L., et al., *A randomized trial of exercise training after renal transplantation.* Transplantation, 2002. **74**(1): p. 42-48.

43. Canada, S. *Physical Activity During Leisure Time*. 2010 [cited 2010 15/Oct/2010]; Available from: http://www40.statcan.gc.ca/l01/cst01/health78b-eng.htm.

44. Blair, S.N., et al., *Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men.* JAMA, 1995. **273**(14): p. 1093-8.

45. Riess, K.J., et al., *Impaired arterial compliance and aerobic endurance in kidney transplant recipients.* Transplantation, 2006. **82**(7): p. 920-3.

46. Yildiz, A., et al., *Arterial elasticity measurement in renal transplant recipients.* Transplant Proc, 2007. **39**(5): p. 1455-7.

47. Barenbrock, M., et al., *Reduced arterial distensibility is a predictor of cardiovascular disease in patients after renal transplantation.* J Hypertens, 2002. **20**(1): p. 79-84.

48. Sullivan, M.J., et al., *Prevention of bedrest-induced physical deconditioning by daily dobutamine infusions. Implications for drug-induced physical conditioning.* J Clin Invest, 1985. **76**(4): p. 1632-1642.

49. Shibata, S., M. Perhonen, and B.D. Levine, *Supine cycling plus volume loading prevent cardiovascular deconditioning during bed rest.* J Appl Physiol. **108**(5): p. 1177-86.

50. Greenleaf, J.E., *Intensive exercise training during bed rest attenuates deconditioning.* Med Sci Sports Exerc, 1997. **29**(2): p. 207-15.

51. Ferretti, G., et al., *The interplay of central and peripheral factors in limiting maximal O2 consumption in man after prolonged bed rest.* J Physiol, 1997. **501 (Pt 3)**: p. 677-86.

52. Bringard, A., et al., *Cardiovascular determinants of maximal oxygen consumption in upright and supine posture at the end of prolonged bed rest in humans.* Respir Physiol Neurobiol. **172**(1-2): p. 53-62.

53. Capelli, C., et al., *Factors determining the time course of VO2(max) decay during bedrest: implications for VO2(max) limitation.* Eur J Appl Physiol, 2006. **98**(2): p. 152-60.

54. Convertino, V.A., et al., *Cardiorespiratory responses to exercise after bed rest in men and women.* Acta Astronaut, 1977. **4**(7-8): p. 895-905.

55. Saltin, B., et al., *Response to exercise after bed rest and after training.* Circulation, 1968. **38**(5 Suppl): p. VII1-78.

56. Arbab-Zadeh, A., et al., *Effect of aging and physical activity on left ventricular compliance.* Circulation, 2004. **110**(13): p. 1799-805.

57. Beere, P.A., et al., *Aerobic exercise training can reverse age-related peripheral circulatory changes in healthy older men.* Circulation, 1999. **100**(10): p. 1085-94.

58. Tanaka, H. and D.R. Seals, *Endurance exercise performance in Masters athletes: age-associated changes and underlying physiological mechanisms.* J Physiol, 2008. **586**(1): p. 55-63.

59. Moore, G.E., et al., *Determinants of VO2peak in patients with end-stage renal disease: on and off dialysis.* Med Sci Sports Exerc, 1993. **25**(1): p. 18-23.

60. Moore, G.E., et al., *Uremic myopathy limits aerobic capacity in hemodialysis patients.* Am J Kidney Dis., 1993. **22**(2): p. 277-287.

61. Painter, P., et al., *Exercise capacity in hemodialysis, CAPD, and renal transplant patients.* Nephron, 1986. **42**(1): p. 47-51.

62. Painter, P., et al., *Effects of Modality Change and Transplant on Peak Oxygen Uptake in Patients With Kidney Failure.* Am J Kidney Dis.

63. Painter, P., et al., *Exercise tolerance changes following renal transplantation.* Am J Kidney Dis., 1987. **10**(6): p. 452-456.

64. Kempeneers, G., et al., *Skeletal muscle limits the exercise tolerance of renal transplant recipients: effects of a graded exercise training program*, in *Am J Kidney Dis.*1990. p. 57-65.

65. Deligiannis, A., et al., *Cardiac effects of exercise rehabilitation in hemodialysis patients.* International journal of cardiology, 1999. **70**(3): p. 253-266.

66. Lakatta, E.G. and D. Levy, *Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part II: the aging heart in health: links to heart disease.* Circulation, 2003. **107**(2): p. 346-54.

67. Stratton, J.R., et al., *Cardiovascular responses to exercise. Effects of aging and exercise training in healthy men.* Circulation, 1994. **89**(4): p. 1648-55.

68. Ogawa, T., et al., *Effects of aging, sex, and physical training on cardiovascular responses to exercise.* Circulation, 1992. **86**(2): p. 494-503.

69. Sietsema, K.E., et al., *Clinical and demographic predictors of exercise capacity in end-stage renal disease.* Am J Kidney Dis, 2002. **39**(1): p. 76-85.

70. Levine, B.D., J.H. Zuckerman, and J.A. Pawelczyk, *Cardiac atrophy after bed-rest deconditioning: a nonneural mechanism for orthostatic intolerance.* Circulation, 1997. **96**(2): p. 517-25.

71. Heckman, G.A. and R.S. McKelvie, *Cardiovascular aging and exercise in healthy older adults.* Clin J Sport Med, 2008. **18**(6): p. 479-85.

72. Mitsnefes, M.M., et al., *Abnormal cardiac function in children after renal transplantation.* Am J Kidney Dis, 2004. **43**(4): p. 721-6.

73. Fujimoto, N., et al., *Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age.* Circulation. **122**(18): p. 1797-805.

74. Scalia, G.M., S.K. Khoo, and S. O'Neill, *Age-related changes in heart function by serial echocardiography in women aged 40-80 years.* J Womens Health (Larchmt). **19**(9): p. 1741-5.

75. McGavock, J.M., et al., *A forty-year follow-up of the Dallas Bed Rest and Training study: the effect of age on the cardiovascular response to exercise in men.* J Gerontol A Biol Sci Med Sci, 2009. **64**(2): p. 293-9.

76. McVeigh, G.E., et al., *Age-related abnormalities in arterial compliance identified by pressure pulse contour analysis: aging and arterial compliance.* Hypertension, 1999. **33**(6): p. 1392-1398.

77. Matteucci, M.C., et al., *Total peripheral vascular resistance in pediatric renal transplant patients.* Kidney international, 2002. **62**(5): p. 1870-1874.

78. Hornum, M., et al., *Pre-diabetes and arterial stiffness in uraemic patients.* Nephrol Dial Transplant. **25**(4): p. 1218-25.

79. Paoletti, E., et al., *Association of arterial hypertension with renal target organ damage in kidney transplant recipients: the predictive*

role of ambulatory blood pressure monitoring. Transplantation, 2009. **87**(12): p. 1864-9.

80. Perhonen, M.A., J.H. Zuckerman, and B.D. Levine, *Deterioration of left ventricular chamber performance after bed rest : "cardiovascular deconditioning" or hypovolemia?* Circulation, 2001. **103**(14): p. 1851-7.

81. Terenzi, T.J., *An alteration in arterial compliance associated with elevated aerobic fitness.* J Manipulative Physiol Ther, 2000. **23**(1): p. 27-31.

82. Arena, R., et al., *Maximal aerobic capacity and the oxygen uptake efficiency slope as predictors of large artery stiffness in apparently healthy subjects.* J Cardiopulm Rehabil Prev, 2009. **29**(4): p. 248-54.

83. Ueno, H., et al., *Skin autofluorescence, a marker for advanced glycation end product accumulation, is associated with arterial stiffness in patients with end-stage renal disease.* Metabolism, 2008. **57**(10): p. 1452-7.

84. Blacher, J., et al., *Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease.* Hypertension, 2001. **38**(4): p. 938-42.

85. Strozecki, P., et al., *Factors associated with increased arterial stiffness in renal transplant recipients.* Med Sci Monit. **16**(6): p. CR301-6.

86. Verbeke, F., et al., *Arterial stiffness and wave reflections in renal transplant recipients.* Nephrol Dial Transplant, 2007. **22**(10): p. 3021-7.

87. Greenwald, S.E., *Ageing of the conduit arteries.* J Pathol, 2007. **211**(2): p. 157-72.

88. Jones, S.W., et al., *Disuse atrophy and exercise rehabilitation in humans profoundly affects the expression of genes associated with the regulation of skeletal muscle mass.* FASEB J, 2004. **18**(9): p. 1025-7.

89. Bassey, E.J., et al., *Leg extensor power and functional performance in very old men and women.* Clin Sci (Lond), 1992. **82**(3): p. 321-7.

90. Brown, M., D.R. Sinacore, and H.H. Host, *The relationship of strength to function in the older adult.* J Gerontol A Biol Sci Med Sci, 1995. **50 Spec No**: p. 55-9.

91. Hvid, L.G., et al., *Effects of aging on muscle mechanical function and muscle fiber morphology during short-term immobilization and subsequent retraining.* J Appl Physiol.

92. Janssen, I., et al., *Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr.* J Appl Physiol, 2000. **89**(1): p. 81-8.

93. van den Ham, E.C., et al., *Similarities in skeletal muscle strength and exercise capacity between renal transplant and hemodialysis patients.* Am J Transplant, 2005. **5**(8): p. 1957-1965.

94. Johansen, K.L., et al., *Muscle atrophy in patients receiving hemodialysis: effects on muscle strength, muscle quality, and physical function.* Kidney international, 2003. **63**(1): p. 291-297.

95. Lakatta, E.G., *Hemodynamic adaptations to stress with advancing age.* Acta Med Scand Suppl, 1986. **711**: p. 39-52.

96. Brodin, E., et al., *Physical activity, muscle performance and quality of life in patients treated with chronic peritoneal dialysis.* Scand J Urol Nephrol, 2001. **35**(1): p. 71-8.

97. Painter, P., et al., *Exercise capacity and muscle structure in kidney recipient and twin donor.* Clin Transplant, 2003. **17**(3): p. 225-230.

98. Berg, H.E., L. Larsson, and P.A. Tesch, *Lower limb skeletal muscle function after 6 wk of bed rest.* J Appl Physiol, 1997. **82**(1): p. 182-8.

99. Larsson, L., *Morphological and functional characteristics of the ageing skeletal muscle in man. A cross-sectional study.* Acta Physiol Scand Suppl, 1978. **457**: p. 1-36.

100. Lexell, J., *Human aging, muscle mass, and fiber type composition.* J Gerontol A Biol Sci Med Sci, 1995. **50 Spec No**: p. 11-6.

101. Coggan, A.R., et al., *Histochemical and enzymatic characteristics of skeletal muscle in master athletes.* J Appl Physiol, 1990. **68**(5): p. 1896-901.

102. Parizkova, J., et al., *Body composition, aerobic capacity, and density of muscle capillaries in young and old men.* J Appl Physiol, 1971. **31**(3): p. 323-5.

103. Proctor, D.N., et al., *Oxidative capacity of human muscle fiber types: effects of age and training status.* J Appl Physiol, 1995. **78**(6): p. 2033-8.

104. Diesel, W., et al., *Morphologic features of the myopathy associated with chronic renal failure.* Am J Kidney Dis, 1993. **22**(5): p. 677-84.

105. Crane, J.D., et al., *The effect of aging on human skeletal muscle mitochondrial and intramyocellular lipid ultrastructure.* J Gerontol A Biol Sci Med Sci. **65**(2): p. 119-28.

106. Gianni, P., et al., *Oxidative stress and the mitochondrial theory of aging in human skeletal muscle.* Experimental Gerontology, 2004. **39**(9): p. 1391-1400.

107. Nakao, T., et al., *Impaired lactate production by skeletal muscle with anaerobic exercise in patients with chronic renal failure. A possible consequence of defective glycolysis in skeletal muscle.* Nephron, 1982. **31**(2): p. 111-5.

108. Metcoff, J., et al., *Cell metabolism in uremia.* Am J Clin Nutr, 1978. **31**(9): p. 1627-34.

109. Bradley, J.R., et al., *Impaired nutritive skeletal muscle blood flow in patients with chronic renal failure.* Clin Sci (Lond), 1990. **79**(3): p. 239-245.

110. Marrades, R.M., et al., *Effects of erythropoietin on muscle O2 transport during exercise in patients with chronic renal failure.* J Clin Invest, 1996. **97**(9): p. 2092-100.

111. Convertino, V., et al., *Cardiovascular responses to exercise in middle-aged men after 10 days of bedrest.* Circulation, 1982. **65**(1): p. 134-40.

112. Tanaka, H., et al., *Greater rate of decline in maximal aerobic capacity with age in physically active vs. sedentary healthy women.* J Appl Physiol, 1997. **83**(6): p. 1947-53.

113. Heath, G.W., et al., *A physiological comparison of young and older endurance athletes.* J Appl Physiol, 1981. **51**(3): p. 634-40.

114. Pimentel, A.E., et al., *Greater rate of decline in maximal aerobic capacity with age in endurance-trained than in sedentary men.* J Appl Physiol, 2003. **94**(6): p. 2406-13.

115. Astrand, I., et al., *Reduction in maximal oxygen uptake with age.* J Appl Physiol, 1973. **35**(5): p. 649-54.

116. McGuire, D.K., et al., *A 30-year follow-up of the Dallas Bedrest and Training Study: I. Effect of age on the cardiovascular response to exercise.* Circulation, 2001. **104**(12): p. 1350-7.

117. Lakatta, E.G., *Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part III: cellular and molecular clues to heart and arterial aging.* Circulation, 2003. **107**(3): p. 490-7.

118. Hung, J., et al., *Uremic cardiomyopathy--effect of hemodialysis on left ventricular function in end-stage renal failure.* N Engl J Med, 1980. **302**(10): p. 547-51.

119. Ianhez, L.E., J. Lowen, and E. Sarbaga, *Uremic myocardiopathy.* Nephron, 1975. **15**(1): p. 17-28.

120. Rockel, A., et al., *Uraemic sympathetic neuropathy after haemodialysis and transplantation.* Eur J Clin Invest, 1979. **9**(1): p. 23-7.

121. Soriano, G. and R.P. Eisinger, *Abnormal response to the Valsalva maneuver in patients on chronic hemodialysis.* Nephron, 1972. **9**(4): p. 251-6.

122. Cannella, G., et al., *Blood pressure control in end-stage renal disease in man: indirect evidence of a complex pathogenic mechanism besides renin or blood volume.* Clin Sci Mol Med, 1977. **52**(1): p. 19-21.

123. de Planque, B.A., E. Mulder, and E.J. Mees, *The behaviour of blood and extracellular volume in hypertensive patients with renal insufficiency.* Acta Med Scand, 1969. **186**(1-2): p. 75-81.

124. Zoccali, C., et al., *Prognostic value of echocardiographic indicators of left ventricular systolic function in asymptomatic dialysis patients.* J Am Soc Nephrol, 2004. **15**(4): p. 1029-37.

125. Guerin, A.P., et al., *Arterial stiffening and vascular calcifications in end-stage renal disease.* Nephrol.Dial.Transplant, 2000. **15**(7): p. 1014-1021.

126. Richard, R., et al., *Exercise limitation in trained heart and kidney transplant recipients: central and peripheral limitations.* J Heart Lung Transplant, 2005. **24**(11): p. 1774-80.

127. Miller, T.D., et al., *Graded exercise testing and training after renal transplantation: a preliminary study.* Mayo Clin Proc., 1987. **62**(9): p. 773-777.

128. Horber, F.F., et al., *Evidence that prednisone-induced myopathy is reversed by physical training.* J Clin Endocrinol Metab, 1985. **61**(1): p. 83-8.

129. Topp, K.S., et al., *Alterations in skeletal muscle structure are minimized with steroid withdrawal after renal transplantation.* Transplantation, 2003. **76**(4): p. 667-73.

130. van den Ham, E.C., et al., *The functional, metabolic, and anabolic responses to exercise training in renal transplant and hemodialysis patients.* Transplantation, 2007. **83**(8): p. 1059-68.

131. Juskowa, J., et al., *Physical rehabilitation and risk of atherosclerosis after successful kidney transplantation.* Transplant Proc, 2006. **38**(1): p. 157-60.

132. Romano, G., et al., *Physical training effects in renal transplant recipients.* Clin Transplant, 2009.

133. Painter, P.L., et al., *Effects of exercise training on coronary heart disease risk factors in renal transplant recipients.* Am J Kidney Dis., 2003. **42**(2): p. 362-369.

134. Bernstein, D.P., *A new stroke volume equation for thoracic electrical bioimpedance: theory and rationale.* Crit Care Med, 1986. **14**(10): p. 904-909.

135. Alavi, H., et al., *Comparison of arterial elasticity measured in left and right arms using the HDI/Pulsewave CR-2000 Research System.* Blood Press Monit, 2002. **7**(5): p. 277-80.

136. Jackson, A.S., M.L. Pollock, and A. Ward, *Generalized equations for predicting body density of women.* Med Sci Sports Exerc, 1980. **12**(3): p. 175-181.

137. Jackson, A.S. and M.L. Pollock, *Generalized equations for predicting body density of men.* Br J Nutr, 1978. **40**(3): p. 497-504.

138. Brozek, J., *Body composition: models and estimation equations.* Am J Phys Anthropol, 1966. **24**(2): p. 239-46.

139. Durnin, J.V. and J. Womersley, *Body fat assessed from total body density and its estimation from skinfold thickness: measurements*

on 481 men and women aged from 16 to 72 years. Br J Nutr, 1974. **32**(1): p. 77-97.

140. Grundy, S.M., et al., *Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology.* Circulation, 1999. **100**(13): p. 1481-92.

141. Ware, J.E., Jr. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**(6): p. 473-83.

142. Painter, P.L., et al., *Health-related fitness and quality of life in organ transplant recipients.* Transplantation, 1997. **64**(12): p. 1795-1800.

143. Kelley, G.A., K.A. Kelley, and Z.V. Tran, *Aerobic exercise and resting blood pressure: a meta-analytic review of randomized, controlled trials.* Prev.Cardiol., 2001. **4**(2): p. 73-80.

144. Fagard, R.H. and V.A. Cornelissen, *Effect of exercise on blood pressure control in hypertensive patients.* Eur J Cardiovasc Prev Rehabil, 2007. **14**(1): p. 12-7.

145. Maldonado, J., et al., *Modulation of arterial stiffness with intensive competitive training.* Rev Port Cardiol, 2006. **25**(7-8): p. 709-14.

146. Westhoff, T.H., et al., *The cardiovascular effects of upper-limb aerobic exercise in hypertensive patients.* J Hypertens, 2008. **26**(7): p. 1336-42.

147. Maeda, S., et al., *Acute exercise increases systemic arterial compliance after 6-month exercise training in older women.* Hypertens Res, 2008. **31**(2): p. 377-81.

148. Riess, K.J., et al., *Impaired arterial compliance and aerobic endurance in kidney transplant recipients.* Transplantation, 2006. **82**(7): p. 920-923.

149. London, G.M., et al., *Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality.* Nephrol Dial Transplant, 2003. **18**(9): p. 1731-40.

150. Sigrist, M., et al., *Vascular calcification and cardiovascular function in chronic kidney disease.* Nephrol Dial Transplant, 2006. **21**(3): p. 707-14.

151. Tanaka, H., et al., *Aging, habitual exercise, and dynamic arterial compliance.* Circulation, 2000. **102**(11): p. 1270-1275.

152. Fjeldstad, A.S., M.G. Bemben, and D.A. Bemben, *Resistance training effects on arterial compliance in premenopausal women.* Angiology, 2009. **60**(6): p. 750-6.

153. Miyachi, M., et al., *Unfavorable effects of resistance training on central arterial compliance: a randomized intervention study.* Circulation, 2004. **110**(18): p. 2858-63.

154. Miyachi, M., et al., *Greater age-related reductions in central arterial compliance in resistance-trained men.* Hypertension, 2003. **41**(1): p. 130-5.

155. Gordon, E.J., et al., *Longitudinal analysis of physical activity, fluid intake, and graft function among kidney transplant recipients.* Transpl Int, 2009. **22**(10): p. 990-8.

156. Gabriel, D.A., G. Kamen, and G. Frost, *Neural adaptations to resistive exercise: mechanisms and recommendations for training practices.* Sports Med, 2006. **36**(2): p. 133-49.

157. Aagaard, P., *Training-induced changes in neural function.* Exerc Sport Sci Rev, 2003. **31**(2): p. 61-7.

158. Carroll, T.J., S. Riek, and R.G. Carson, *Neural adaptations to resistance training: implications for movement control.* Sports Med, 2001. **31**(12): p. 829-40.

159. Horber, F.F., et al., *Impact of physical training on the ultrastructure of midthigh muscle in normal subjects and in patients treated with glucocorticoids.* J Clin Invest, 1987. **79**(4): p. 1181-90.

160. Haykowsky, M., et al., *Exercise training improves aerobic capacity and skeletal muscle function in heart transplant recipients.* Am J Transplant, 2009. **9**(4): p. 734-9.

161. Berlin, J.A. and G.A. Colditz, *A meta-analysis of physical activity in the prevention of coronary heart disease.* Am J Epidemiol, 1990. **132**(4): p. 612-28.

162. Lee, I.M., C.C. Hsieh, and R.S. Paffenbarger, Jr., *Exercise intensity and longevity in men. The Harvard Alumni Health Study.* JAMA, 1995. **273**(15): p. 1179-84.

163. Powell, K.E., et al., *Physical activity and the incidence of coronary heart disease.* Annu Rev Public Health, 1987. **8**: p. 253-87.

164. Wisloff, U., et al., *Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study.* Circulation, 2007. **115**(24): p. 3086-94.

165. Tjonna, A.E., et al., *Aerobic interval training reduces cardiovascular risk factors more than a multitreatment approach in overweight adolescents.* Clin Sci (Lond), 2009. **116**(4): p. 317-26.

166. Diaz, J.M., et al., *Risk factors for cardiovascular disease after renal transplantation.* Transplant Proc, 2003. **35**(5): p. 1722-4.

167. Hambrecht, R., et al., *Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial.* Circulation, 2004. **109**(11): p. 1371-8.

168. Georgiou, D., et al., *Cost-effectiveness analysis of long-term moderate exercise training in chronic heart failure.* The American Journal of Cardiology, 2001. **87**(8): p. 984-8; A4.

169. Lee, S.Y. and D. Gallagher, *Assessment methods in human body composition.* Curr Opin Clin Nutr Metab Care, 2008. **11**(5): p. 566-72.

170. Grey, E., et al., *Reduced small artery but not large artery elasticity is an independent risk marker for cardiovascular events.* Am J Hypertens., 2003. **16**(4): p. 265-269.

171. Najjar, S.S., A. Scuteri, and E.G. Lakatta, *Arterial aging: is it an immutable cardiovascular risk factor?* Hypertension, 2005. **46**(3): p. 454-462.

Appendix A

Ethics Approval

Health Research Ethics Board

2J2.27 Walter Mackenzie Centre
University of Alberta, Edmonton, Alberta T6G 2R7
p.780.492.9724
p.780.492.0459
p.780.492.0839
f.780.492.7303
ethics@med.ualberta.ca

ETHICS APPROVAL FORM

Date: January 2005

Name(s) of Principal Investigator(s): Dr. Sita Gourishankar

Department: Medicine

Title: **Evaluating the effects of a supervised exercise training program versus usual lifestyle on exercise capacity, cardiovascular function and outcomes, skeletal muscle mass and quality of life in kidney transplant recipients: A randomized control trial**

The Health Research Ethics Board (Biomedical Panel) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation.

Specific Comments:

The Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. Subject consent for access to identifiable health information is required for the research described in the ethics application, and appropriate procedures for such consent have been approved by the REB Panel. The REB has also reviewed and approved the patient information material and consent form.

D. W. Morrish, M.D.
Chairman, Health Research Ethics Board
Biomedical Panel

Jan 28-05
Date of Approval Release

This approval is valid for one year

Issue #5770

UNIVERSITY OF ALBERTA Capital Health CARITAS HEALTH GROUP

Appendix B

Supporting Publication

Impaired arterial compliance and aerobic endurance in kidney transplant recipients

A version of this chapter has been published in

Transplantation, 82: 920-923, 2006

Note: This chapter was completed as a pilot project for the major study of this thesis. Credit was received for this chapter as partial completion of REHAB 899 in the Fall 2004 semester. It has been included as an appendix to this thesis as its findings are important to the direction in which the major study's efforts were directed.

ABSTRACT

Background: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in kidney transplant recipients (KTR). Two risk factors for CVD that have not been examined in this population are arterial compliance and aerobic capacity.

The primary objective was to determine small and large artery compliance and aerobic endurance in KTR. A secondary objective was to explore the relationship between aging and arterial compliance and aerobic endurance in KTR.

Methods: Sixty-two clinically stable KTR were recruited from the University of Alberta Renal Transplant Clinic. Small and large artery compliance was assessed using computerized arterial pulse waveform analysis. Aerobic endurance was determined using the six-minute walk test. Age-matched normative data from healthy individuals was used for comparison.

Results: Small arterial compliance was lower in KTR (5.5 ± 3 ml/mmHg x 100) compared to age-matched healthy individuals' predicted values (7.9 ± 0.9 ml/mmHg x 100, $p<0.0001$). No difference was found for large artery compliance between KTR (16.0 ± 6.6ml/mmHg x 10) and age-matched healthy predicted values (15.2 ± 1.3 ml/mmHg x 10, $p=0.5$). Small and large artery compliance were 35% ($p=0.026$) and 36% ($p=0.005$) higher in

younger (<51 years) versus older (>51 years) KTR, respectively. The six-minute walk distance was 28% lower in KTR (495 ± 92 m) compared to healthy age-predicted values (692 ± 56 m $p<0.0001$).

Conclusions: Compromised arterial compliance and poor aerobic endurance may partially explain the high incidence of CVD in KTR. Interventions demonstrated to improve these parameters may afford substantial clinical benefit in this population.

INTRODUCTION

Kidney transplantation is the treatment of choice for individuals with end stage kidney disease (1). Despite the improvements in graft and patient survival after transplant, approximately 40% of kidney transplant recipients die with a functioning graft (2). Although death with a functioning graft may be an indication of successful transplantation and the goal of kidney transplant programs, death from cardiovascular disease is the leading cause of mortality and morbidity in KTR (1). This increased cardiovascular risk has primarily been attributed to “traditional” risk factors (hypertension, dyslipidemia, diabetes, smoking, renal failure and obesity) present before and/or after transplantation (3). However, increased attention is being paid to other risk factors associated with a sedentary lifestyle such as low aerobic capacity and peripheral vascular endothelial dysfunction. Indeed, Sietsema et al. (4) found that decreased exercise capacity was the strongest predictor of mortality in patients with end-stage renal disease. Further, Blacher et al. (5) found that increased arterial stiffness was an independent predictor of cardiovascular and all cause mortality in end-stage renal disease. Despite this evidence in end stage renal failure patients, no study to date has examined the global cardiovascular function (i.e. aerobic endurance and arterial compliance) of patients who have undergone kidney transplantation. As a crucial first step in this area of investigation, we conducted a pilot study to examine the arterial compliance and aerobic endurance of KTR.

MATERIALS AND METHODS

Subjects

This study was conducted between July and September, 2004. Ethics approval for this investigation was obtained from the University of Alberta Hospital Health Research Ethics Board and informed consent was obtained prior to commencement of any study-related procedures. The participants for this study included 62 randomly selected, clinically stable, outpatient KTR who attended the Renal Transplant Clinic. The Renal Transplant Clinic provides comprehensive follow-up care for approximately 900 KTR from urban and rural northern Alberta. Subjects were not considered for this study if orthopedic limitations prevented them from performing the six minute walk test or if they were unable to understand english and a suitable translator was not readily available.

Assessment of large and small arterial compliance

Resting systolic and diastolic blood pressure and small and large artery compliance were assessed non-invasively using computerized arterial pulse waveform analysis (Hypertension Diagnostics, Eagan, MN). This technique involves the use of applanation tonometry which requires the placement of a transducer over the radial artery. The analysis of the 30-second signal averaged arterial pulse wave forms was performed by the tonometry unit and arterial compliance of the large and small arteries

were derived from the analysis of the diastolic waveform decay using the modified Windkessel model of circulation. This technique has been validated previously with invasive arterial waveform measurements(6). The mean of two measurements was used for analysis. Age-predicted values were determined based on a regression equation for 164 healthy individuals between 21 and 56 years of age studied previously in our laboratory.

Aerobic endurance

Aerobic endurance was determined using the six-minute walk test which has been used to assess aerobic endurance in several different clinical populations(7-9). The six minute walk test was performed on a flat 20m corridor during which time the participants were asked to "cover as much distance as possible" in the six-minute period. Healthy age-predicted six-minute walk distance values were determined from the regression equation published by Gibbons et al.(10).

Statistical Analysis

Comparison between KTR and age-predicted healthy values for heart rate, blood pressure, arterial compliance and distance walked in six-minutes was performed with one way analysis of variance (ANOVA) using MedCalc (Mariakerke, Belgium) software. In order to examine the effect of aging on arterial pressure and compliance, KTR were categorized into

two groups based on median age (ie, ≤ 51 years versus > 51 years) and compared using one-way ANOVA. Finally, correlation analysis was performed to assess the relationship between time since transplant and small and large artery compliance. The alpha level was set “a priori” at $p<0.05$. Data are presented as mean ± SD.

RESULTS

Participant Characteristics

During the three-month study period we recruited 62 eligible KTR (41 males). Participant characteristics are described in Table 1. The mean age was 51 ± 14 years, ranging between the ages of 21 and 73 years. The mean time since transplantation was 7.3 ± 6.5 years (range: 0.004 to 27.9 years). Notably, 25% of participants were diabetic requiring treatment with oral hypoglycemics or insulin (Table 1).

Cardiovascular function

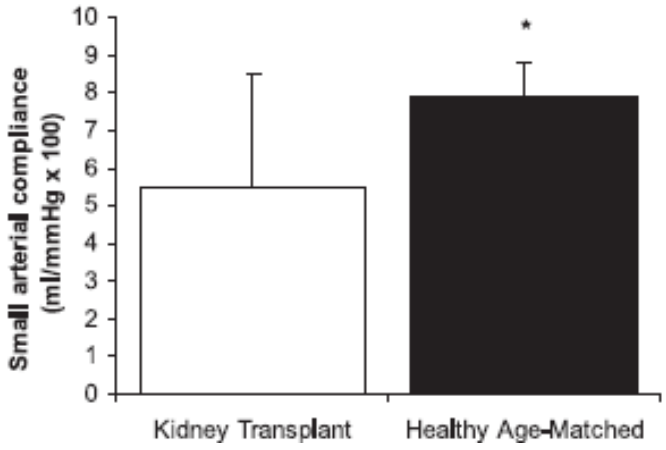
Resting heart rate was significantly higher in KTR (72 ± 3 beats/min) compared to healthy age-matched predicted values (67 ± 3 beats/min, $p=0.0016$). No significant difference was found for systolic (SBP) or diastolic (DBP) blood pressure between KTR (SBP: 133 ±14 mmHg and DBP: 78 ± 8 mmHg) and healthy age-matched predicted values (SBP: 129 ± 7 mmHg and DBP: 77 ± 6 mmHg, $p=0.150$ and 0.626 respectively). Small artery compliance was 30% lower in KTR (5.5 ± 3

ml/mmHg x 100) compared to healthy age-predicted values (7.9±0.9 ml/mmHg x 100, $p<0.0001$, Figure 1) with no difference for large artery compliance between groups (KTR: 16.0 ±7.0 ml/mmHg x 10 vs. age-predicted healthy values: 15 ±1 ml/mmHg x 10, $p=0.4$). No significant correlation was found between the time since transplant and small or large artery compliance.

Table 1. Participant Characteristics

Age (years)	51 ± 14
Time to transplant (years)	7.3 ± 6.5
Height (cm)	170±10
Weight (Kg)	79 ±18
Resting systolic blood pressure(mmHg)	136±15
Resting diastolic blood Pressure (mmHg)	77±8
Resting heart rate (beats/min)	70±12
Diabetic	n = 14
Non-diabetic	n = 47
Unknown diabetic diagnosis	n = 1

Figure 1.



Small artery compliance in kidney transplant recipients and age-matched predicted values for healthy individuals.

(*, p<0.0001 vs. Kidney Transplant)

Effect of aging on cardiovascular function in KTR

Systolic blood pressure was significantly higher in older KTR (141 ± 16 mmHg) compared to younger KTR (133 ± 13 mmHg, p=.05). No difference was found between groups for DBP (older KTR: 78 ± 7 mmHg vs. younger KTR: 78 ± 8 mmHg, p=0.85) or heart rate (older KTR: 69 ± 11 beats/min vs. younger KTR: 71 ± 13 beats/min, p=.47). Older KTR had significantly lower small (old: 4.4 ± 2.1 mmHg/ml x 100 vs. young: 5.9 ± 3.0 mmHg/ml x 100, p=0.026) and large artery compliance (old: 12.5 ± 5.8 ml/mmHg x 10 vs. young: 17.0 ± 6.4 ml/mmHg x 10, p=0.005) compared to younger KTR.

Aerobic endurance

The distance walked in 6 minutes was 28% lower in KTR (495 ± 92m) compared to age-predicted values (692 ± 56m, $p<0.0001$). Also, the distance walked in six-minutes was significantly lower in older KTR (466 ± 76m) versus younger KTR (523 ± 98m, $p= 0.013$).

DISCUSSION

This study reports for the first time that KTR have a significantly lower small artery compliance and aerobic endurance compared to age-matched healthy individuals. The second key finding is that older KTR have significantly lower small and large artery compliance and aerobic endurance compared to younger KTR.

Kidney transplantation and aerobic endurance

Our finding that KTR had severely reduced aerobic endurance may be secondary to deleterious effects of pre-transplant end stage renal disease as well as post-transplant deconditioning coupled with normal aging. Specifically, increased age and a sedentary lifestyle are known to be associated with alterations in cardiovascular function that result in a decline in oxygen delivery to the working muscle (11;12). Consistent with this hypothesis, we found that older KTR had the greatest impairment in arterial compliance and aerobic endurance. Thus, the abnormal exercise capacity found in our KTR may be due to their impaired peripheral

vascular function. Of greater concern, a consequence of the decreased fitness is that it may be an important risk factor for future CVD. For example, Myers et al.(13) found peak exercise capacity was the strongest predictor of cardiovascular and all-cause mortality even when controlling for established cardiovascular risk factors in healthy males with or without underlying cardiovascular disease. Sietsema et al. (4) demonstrated that reduced exercise capacity was a powerful predictor of mortality in individuals with end-stage kidney disease. Accordingly, the increased cardiovascular mortality that occurs after kidney transplantation may be worsened by the reduced fitness associated with adhering to a sedentary lifestyle. Thus, exercise rehabilitation is an important area to direct future research toward and nephrologists and rehabilitation specialists should confidently encourage KTR to perform regular physical activity to reduce the negative cardiovascular effects of a sedentary lifestyle.

Kidney transplantation and arterial compliance

Previous investigators (14-16) have shown that small artery compliance is reduced in individuals with hypertension, diabetes mellitus and/or smokers. Given that these cardiovascular risk factors are prevalent in KTR our finding of a significant decline in small artery compliance in these individuals is not surprising. The consequence of the impaired vascular function is that it may be an important prognostic indictor for future cardiovascular events. Specifically, Grey et al.(17) reported that a 2-

unit decline in small artery compliance was associated with a significant increase in a future cardiovascular event in individuals between 25 and 89 years of age. Notably, our KTR small artery compliance was 2.4 units lower than expected for age-matched healthy individuals studied in our laboratory. The mechanism responsible for the post-transplant abnormality in small artery compliance was not examined in this study, however, it may be secondary to abnormalities in endothelial function associated with hypertension, diabetes, obesity, pre-transplant renal failure, post-transplant immunosuppression therapy or as a consequence of a sedentary lifestyle. Consistent with this hypothesis, our diabetic KTR small and large artery compliance was 20 to 30% lower than non-diabetic KTR.

Arterial compliance in older KTR

Advancing age has been shown to result in a significant and marked decline in small and large artery compliance (6). Similarly, we found that small and large artery compliance was 25% lower in older compared to younger KTR. The age-mediated decline in arterial stiffness is secondary to the increase in collagen content and concomitant decline in elastin (18). A serious consequence of the increased arterial stiffness and ventricular afterload is concentric cardiac hypertrophy which, if not alleviated, may over time lead to chronic heart failure. Exercise training has been shown to improve arterial compliance in different aging

populations including middle aged and older sedentary men (19), postmenopausal women (20) and patients with congestive heart failure (21) so future research in this area as it relates to KTR is an important step.

Limitations

A limitation of this study is the absence of a record of current medications taken by the subjects at the time of the study. For example older subjects may have been taking beta blockers which could reduce their heart rate and exercise capacity.

Summary

We have demonstrated that KTR have severely reduced aerobic endurance and small and large artery compliance. Interventions, such as exercise training, that can improve exercise capacity and arterial compliance may play a central role in reversing the cardiovascular morbidity and mortality in KTR.

References

1. Magee CC, Pascual M. Update in renal transplantation. *Arch Intern Med* 164:1373-1388, 2004

2. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. *Kidney Int* 57:307-313, 2000

3. Bostom AD, Brown RS, Jr., Chavers BM et al. Prevention of post-transplant cardiovascular disease--report and recommendations of an ad hoc group. *Am J Transplant* 2:491-500, 2002

4. Sietsema KE, Amato A, Adler SG, Brass EP. Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. *Kidney Int* 65:719-724, 2004

5. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 99:2434-2439, 1999

6. McVeigh GE, Bratteli CW, Morgan DJ et al. Age-related abnormalities in arterial compliance identified by pressure pulse

contour analysis: aging and arterial compliance. *Hypertension* 33:1392-1398, 1999

7. Haykowsky M, Riess K, Figgures L et al. Exercise training improves aerobic endurance and musculoskeletal fitness in female cardiac transplant recipients. *Curr Control Trials Cardiovasc Med* 6:10, 2005

8. Guyatt GH, Sullivan MJ, Thompson PJ et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 132:919-923, 1985

9. Hung C, Daub B, Black B, Welsh R, Quinney A, Haykowsky M. Exercise training improves overall physical fitness and quality of life in older women with coronary artery disease. *Chest* 126:1026-1031, 2004

10. Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. *J Cardiopulm Rehabil* 21:87-93, 2001

11. Sullivan MJ, Binkley PF, Unverferth DV et al. Prevention of bedrest-induced physical deconditioning by daily dobutamine

infusions. Implications for drug-induced physical conditioning. *J Clin Invest* 76:1632-1642, 1985

12. Saltin B, Blomqvist G, Mitchell JH, Johnson RL, Jr., Wildenthal K, Chapman CB. Response to exercise after bed rest and after training. *Circulation* 38:VII 1-78 1968

13. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 346:793-801, 2002

14. McVeigh GE, Burns DE, Finkelstein SM et al. Reduced vascular compliance as a marker for essential hypertension. *Am J Hypertens* 4:245-251, 1991

15. McVeigh G, Brennan G, Hayes R, Cohn J, Finkelstein S, Johnston D. Vascular abnormalities in non-insulin-dependent diabetes mellitus identified by arterial waveform analysis. *Am J Med* 95:424-430, 1993

16. McVeigh GE, Morgan DJ, Finkelstein SM, Lemay LA, Cohn JN. Vascular abnormalities associated with long-term cigarette smoking identified by arterial waveform analysis. *Am J Med* 102:227-231, 1997

17. Grey E, Bratteli C, Glasser SP et al. Reduced small artery but not large artery elasticity is an independent risk marker for cardiovascular events. *Am J Hypertens* 16:265-269, 2003

18. Najjar SS, Scuteri A, Lakatta EG. Arterial aging: is it an immutable cardiovascular risk factor? *Hypertension* 46:454-462, 2005

19. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. *Circulation* 102:1270-1275, 2000

20. Sugawara J, Inoue H, Hayashi K, Yokoi T, Kono I. Effect of low-intensity aerobic exercise training on arterial compliance in postmenopausal women. *Hypertens Res* 27:897-901, 2004

21. Parnell MM, Holst DP, Kaye DM. Exercise training increases arterial compliance in patients with congestive heart failure. *Clin Sci (Lond)* 102:1-7, 2002

Appendix C

Kidney Transplantation in Exercise (KITE) Data Forms

LETTER OF INFORMATION

Evaluating the effects of a supervised exercise training program versus usual lifestyle on exercise capacity, cardiovascular function and outcomes, skeletal muscle mass and quality of life in kidney transplant recipients: a randomized control trial

Principal Investigator: Dr. Sita Gourishankar

Sub-Investigators: Dr. Mark Haykowsky

Dr. Robert Welsh

Dr. Richard Lewanczuk

Dr. Wayne Tymchak

Kenneth Riess, Ph.D. Candidate

Background:

You are being asked to consider participating in this study because you have had a kidney transplant. Kidney transplantation is an important and effective treatment for chronic kidney failure. Once someone has received a new kidney, our goals are to keep the kidney functioning well and to keep the recipient healthy and enjoying an improved quality of life.

Today, the leading cause of death of kidney transplant recipients is cardiovascular disease. We know that a major risk factor for cardiovascular disease in people without a transplant is lack of exercise. Many studies have been done on the general population to show that exercise reduces cholesterol (the amount of fat in the blood), blood pressure, weight and the chance of developing diabetes, as well reducing deaths from cardiovascular events (such as heart attacks and strokes). Currently, the effect that exercise training has on heart and muscle function, exercise capacity and quality of life in kidney transplant recipients has not been well studied.

Purpose:

The purpose of this research study is to see if 3-months of supervised exercise training of kidney transplant recipients can increase

their exercise ability, improve heart and skeletal muscle structure and function, reduce the risk factors for heart disease, and improve their quality of life.

Description of the study

Forty kidney transplant recipients at the University of Alberta Kidney Transplant Program will be invited to participate in this study. Participants will be in the study for about 3.5 months. The study consists of a set of baseline assessments done over a 1- week period, then the 3-month study time followed by a repeat of the baseline assessments.

If you agree to participate, you will undergo the following baseline assessments during 2 visits over the 1-week period:

- **Visit 1:** Exercise Laboratory, Division of Cardiology, University of Alberta Hospital
  Duration: 1 hour and 30 minutes

- Quality of Life Questionnaire. You will be asked to fill out a brief questionnaire that will ask a number of questions about your quality of life. This will take about 10 minutes to complete.
- Framingham Risk Profile questionnaire: You will be asked a series of questions regarding your heart health history and risk factors for heart disease.
- Blood Vessel Test: A special blood pressure machine will be placed on your arm and wrist to measure the "stiffness" of your blood vessels.
- Supervised exercise bicycle test. Before you start the test, 10 electrodes (electrical contacts) will be placed on your chest to measure you heart rate, and a blood pressure cuff will be placed on your arm to measure your blood pressure throughout the study. You will start the test with easy pedaling that will become a little more difficult every 2 minutes. A special mouthpiece and nose clip will be used to measure your oxygen uptake. The exercise test usually lasts 10 to 15 minutes and a specially trained health care worker will supervise the test.
- Heart Function Test. During the bicycle exercise test, electrodes will be placed on your chest and on the side of your neck. These electrodes will be attached to computers that will monitor the electrical activity of your heart and the amount of blood your heart pumps with each beat.

- **Visit 2:** Renal Transplant Clinic, University of Alberta Hospital and Cardiac/Therapeutic Exercise Research Laboratory, Corbett Hall, University of Alberta.
  Duration: 2.5 hours

  - Cardiovascular risk profile. You will be asked to come in after an overnight fast (no food or drinks for 12 hours) and the following tests will be performed:
    1. Breath test: Your sensitivity to insulin will be used to measure your metabolism. First, you will be asked to blow into a special test tube through a straw. You will then be given 100 ml (3 ounces) of a harmless, sweet, orange-flavoured drink. Ninety minutes later you will be asked to blow through a straw into another small test tube.
    2. Blood (cholesterol) Test: You will be asked to come the University of Alberta Hospital during which time a needle will be inserted into a vein in your arm and a small amount (1 to 3 tablespoons) of blood will be withdrawn to measure your lipid (cholesterol) profile.
    3. 24-Hour Blood Pressure test: You will be sent home with a 24 hour blood pressure monitor. This consists of a blood pressure cuff on your arm that is attached to a recording device that you carry over your shoulder in a case. The blood pressure monitor takes blood pressure measurements every 20 – 30 minutes during regular activities throughout the day and night.
  - Lean Body Mass. Lean body mass will be estimated with skinfold measurements. This will involve lightly "pinching" the skin at several pre-determined, easily accessible, areas on the body. With the use of a measurement device called a caliper, the thickness of this skinfold will be obtained.
  - Lower Extremity Strength. You will perform a series of tests that will assess the strength of your leg muscles. Initially, you will lift a very light weight. Then the weight will become progressively heavier until you can lift a specific weight one time.

Once you have completed all the baseline assessments, you will be randomly assigned (like the flip of a coin) to one of 2 groups:

Group 1: Supervised Exercise Training group

Group 2: Usual Lifestyle (no exercise training) group.

Group 1:

If you are assigned to the "Supervised Exercise Training" group, you will participate in a three-month aerobic and resistance exercise program. You will come to the Cardiac/Therapeutic Exercise Research Laboratory (Corbett Hall, University of Alberta Campus) 3 days per week for 3-months to exercise under supervision. The aerobic training will be performed on a stationary bicycle and a treadmill for 30 to 60 minutes per session. You will be asked to perform a 5 to 10 minute warm up before you start and a 5 to 10 minute cool down after completing the aerobic exercises. The resistance training will be performed during 2 of your 3 weekly visits. It will consist of 1 or 2 sets of 10 to 15 repetitions to strengthen your legs. The intensity will be increased according to your performance.

Group 2:

If you are assigned to Group 2, you will be asked to continue with your normal daily activities during the time of the study. You will see your transplant care team members on a regular basis and be given the usual care and recommendations that we give to all our transplant patients.

For all participants, some information will be collected from your medical charts to help us understand the differences between the volunteers assigned to each group. We will collect such information as your age, date of transplant, cause of renal failure, medications, dialysis history, some information about your donor, and blood work and urine tests that are done as part of your standard of care. We may collect other information not listed here as well.

Possible Risks:

The exercises that you will perform are generally regarded as very safe. All testing and exercise sessions will be performed under appropriate supervision. Data from individuals with or without heart disease suggests that the likelihood of having a heart attack or dying during a bicycle test is 1 in 10,000 tests. You may experience temporary muscle soreness after the initial exercise test and during the first weeks of exercise training. The blood test may cause some local pain and bruising. Finally, you may feel some mild nausea after the breath test.

Possible Benefits:

The possible benefit to you of participating in this study is you might improve your overall health if you are assigned to the exercise group. No benefit is guaranteed, so you may or may not benefit directly from participating in this study. However, you will be helping us to understand how exercise can change exercise capacity and heart and muscle structure and function in individuals who have received a kidney transplant.

Confidentiality:

Personal records relating to this study will be kept confidential. Only the investigators and their study staff will have access to your records. Information concerning your participation in this study may be reviewed by the Health Research Ethics Board (HREB). Any report published as a result of this study will not identify you by name.

By signing the consent form you give permission to the study staff to access any personally identifiable health information which is under the custody of other health care professionals as deemed necessary for the conduct of the research.

Voluntary Participation:

You do not have to be in this study. If you choose not to participate, it will not affect your current medical care or future relations with your transplant physician or the transplant team.

If you do choose to participate, you are free to change your mind and withdraw from this study at any time, and your continuing medical care will not be affected in any way. If you withdraw your consent, the researchers may only use and disclose the protected health information already collected for this research study. No further health information about you will then be collected by, or disclosed to, the researchers for this study.

If the study is not undertaken or if it is discontinued at any time, the quality of your medical care will not be affected. If knowledge gained from this study or any other study becomes available which could influence your decision to continue, you will be promptly informed.

Reimbursement of Expenses:

You will not incur any costs as a result of participation in this study. You will not be paid for participation in this study.

Compensation for Injury:

If you become ill or injured as a direct result of participating in this study, medical treatment will be available to you at no additional cost. By signing this consent form, you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

Contacts:

Please contact any of the individuals listed below if you have any questions and concerns.

Dr. Sita Gourishankar	407-3627 (after hours: 407-8822)
Dr. Mark Haykowsky	492-5970

If you have any questions or concerns about any aspect this study or your rights as a study participant, you may contact the Patient Concerns Office of Capital Health, at 407-1040. This office has no affiliation with the study investigators.

SUBJECT CONSENT

Evaluating the effects of a supervised exercise training program versus usual lifestyle on exercise capacity, cardiovascular function and outcomes, skeletal muscle mass and quality of life in kidney transplant recipients: a randomized control trial

Principal Investigator:	Dr. Sita Gourishankar	407-3672
Sub-Investigators:	Dr. Mark Haykowsky	492-5970
	Dr. Robert. Welsh	407-6452
	Dr. Richard. Lewanczuk	407-6277
	Dr. Wayne Tymchak	407-1574
	Kenneth Riess, Ph.D. candidate	492 7336

YES NO

Do you understand that you have been asked to be in a research study?
☐ ☐

Have you read and received a copy of the attached Letter of Information?
☐ ☐

Do you understand the benefits and risks involved in taking part in this research?

☐ ☐

Have you had an opportunity to ask questions and discuss this study?
☐ ☐

Do you understand that you are free to withdraw from the study at any time

without having to give a reason and without affecting your future medical care?

☐ ☐

Has the issue of confidentiality been explained to you?

☐ ☐

Do you understand who will have access to your medical records including personally identifiable health information?

☐ ☐

Do you want the investigator(s) to inform your family doctor that you are participating in this research study?

☐ ☐

If so, give his/her name: _____

Who explained this study to you? _____

I agree to take part in this study. Yes ☐ No ☐

Subject's Signature: _____ Date: _____

Printed Name: _____

Witness: _____ Date: _____

Relationship: _____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Investigator/Designee: _____ Date: _____

Subject Contact Information

Patient Name: _____ Date: _____

Patient Code: _____

Address _____

_____

_____

_____

Telephone **Home ( ) _____**

Work ( ) _____

Cell ( ) _____

Preferred Contact Time **AM _____** **PM _____**

Secondary Contact Person

Name _____

Relationship _____

Telephone ( ) _____

Subject Information Sheet

Patient Code: _____ Date: _____

☐ Pre ☐ Post

Group Training / Control

Gender Male / Female

Date of Birth _____/_____/_____

Day Month Year

Date of Kidney Transplant

_____/_____/_____

Time From Transplant :_____ days

Day Month Year

Transplant Type: □CDV □LURD □LRD

Etiology _____

Medications

Medication Name	**Total Daily Dose**

Maximal Exercise Testing Data Collection Form

Patient Code: _____
Date: _____

☐ Pre ☐ Post

Height: _____ cm

Weight: _____ kg

MAXIMAL TESTING PROTOCOL:

Time (min)	Work Rate (W)	BP	HR	RPE	VO2 (ml/kg/min)
2:00	0				
4:00	15				
6:00	30				
8:00	45				
10:00	60				
12:00	75				
14:00	90				
16:00	105				
18:00	120				
20:00	135				
22:00	150				
24:00	165				
26:00	180				

Arterial Compliance and Resting Blood Pressure

Patient Code: _____ Date: _____

☐ Pre ☐ Post

Height: _____

Weight: _____

	Measure 1	Measure 2	Measure 3	Measure 4	Average
Heart Rate					
SBP					
DBP					
MAP					
PP					
SVR					
TVI					
LAE					
SAE					
CO					
CI					

Body Composition and Insulin Sensitivity

Patient Code:_____ Date: _____

☐ ☐Pre Post

Height: _____ cm

Weight: _____ kg

Males	**Measure 1**	**Measure 2**	**Measure 3**	**Average**
Chest				
Abdominal				
Thigh				

Females	**Measure 1**	**Measure 2**	**Measure 3**	**Average**
Tricep				
Suprailiac				
Abdominal				
Thigh				

Insulin Sensitivity Result

Test Date _____

Absolute ^{13}C Increase _____

1 RM Strength Testing Form

Patient Code: _____ Date: _____

☐ Pre ☐ Post

Height: _____ cm

Weight: _____ kg

Leg Press Weight
Reps

Leg Press 1 Rep Max _____

Leg Curl Weight
Reps

Leg Curl 1 Rep Max _____

Leg Extension Weight
Reps

Leg Extension 1 Rep Max _____

Randomization Form

Patient Code: _____ Date: _____

- ☐ **Consent** **Date:_____**
- ☐ **VO2 Peak** **Date: _____ Date: _____**
- ☐ **Impedance**
  - **Cardiography** **Date: _____ Date: _____**
  - **Arterial Compliance** **Date: _____ Date: _____**
  - **SF36** **Date: _____ Date: _____**
- ☐ **Strength** **Date: _____ Date: _____**
- ☐ **Body Composition** **Date: _____ Date: _____**
- ☐ **Insulin Sensitivity** **Date: _____ Date: _____**
- ☐ **Randomized** **Date: _____**

Patient I.D. _____

Daily Supervised Exercise Log

Study ID_____ Initials_____

Date_____/_____/_____

D M Y

	Time	HR	Kp / Speed	RPM / %	RPE
Rest	0:00				
Warm-up	5:00				
Treadmill	5:00				
	10:00				
	15:00				
	20:00				
Bike	5:00				
	10:00				
	15:00				
	20:00				
	25:00				
Cool Down	5:00				

Exercise	Ideal Weight	Actual Weight	# Sets	# Reps
Leg Press				
Leg Extensions				
Leg Curls				