CEREBRAL BLOOD FLOW IN HEART TRANSPLANT RECIPIENTS AT REST AND DURING INCREMENTAL EXERCISE

by

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Abstract

Pathological impairments to cardiac output may impact cerebral blood flow (CBF). Prior studies on heart transplant recipients (HTR) have reported increases of 25-53% in CBF, 1-6 months following transplant. It is currently unknown if CBF is chronically altered in the years following transplant or during progressive exercise stress, when compared with aged-matched controls (AM). Donor population controls (DC) were included to determine if the responses observed in HTR are related to the age of the donor rather than the individual. The aim of this thesis was to examine the influence of long-term heart transplantation on the regulation of CBF velocity (CBFv) at rest and during incremental exercise. Two hypotheses were tested: 1) CBFv would be similar in HTR when compared to AM, but lower than DC; 2) that during incremental exercise, the HTR would have reduced elevations in CBFv compared with AM and DC.

To address these hypotheses, HTR were tested who have a reported inability to acutely increase cardiac output during exercise. Seven male clinically stable HTR (62 ± 9 yrs of age, 9 ± 7 yrs post-transplant), seven male AM (62 ± 7 yrs), and seven male DC (22 ± 3 yrs) were recruited for this study. Bilateral middle cerebral arteries were insonated using transcranial Doppler ultrasound to obtain an index of CBFv. Data were obtained while seated and during an incremental cycling test to volitional exhaustion. A repeated measures ANOVA was applied to identify differences across exercise intensity. Comparisons between groups were performed with Fisher's LSD *post hoc* test.

The main findings were: 1) Rest: CBFv was comparable between HTR and AM (40 *vs*. 41 cm/s), as expected, CBFv was 68% higher in the DC compared with the HTR and AM

groups ($P<0.05$). 2) Incremental exercise: mean CBFv was not significantly different between the HTR and AM groups across any of the exercise intensities.

In conclusion, the CBFv of long-term HTR are comparable to AM both at rest and during incremental exercise that despite a suppressed $VO_{2\ Peak}$ (and likely Q) CBFv is well maintained during incremental exercise in long – term HTR.

Preface

This study was approved by the University of British Columbia Clinical Research Ethics Board (H11-02576 – CBF in HTR) and the University of Alberta Clinical Research Ethics Board. (Pro00011560).

Chapters three, four and five are based on data collected in the Mazankowski Alberta Heart Institute at the University of Alberta by Dr. Philip Ainslie, Dr. Mark Haykowsky, Dr. Luis Altamirino-Diaz, Dr. Helen Jones, Kit Marsden, Mike Nelson and Jonathan Smirl. The data were analyzed in the cardiovascular physiology laboratory at the University of British Columbia by Jonathan Smirl. Dr. Ainslie and Dr. Haykowsky were responsible for the overall design and concept of the study, technical assistance, data collection, equipment acquisition, subject recruitment, and funding for the study. Dr. Altamirino-Diaz was responsible for the collection and analysis of the echocardiograph images. Dr. Jones, Kit Marsden and Mike Nelson assisted in the collection of the data. Jonathan Smirl was responsible for assisting in the overall study design and study concept. Jonathan coordinated the data collection involved in this study, and analyzed all of the data, including statistical analyses and writing.

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List of Abbreviations

ACA	-	Anterior Cerebral Artery
ACE	-	Angiotension-Converting Enzyme
AM	-	Age-Matched Control
BP	-	Blood Pressure
BPM	-	Beats Per Minute
BMI	-	Body Mass Index
CA	-	Cerebral Autoregulation
CBF	-	Cerebral Blood Flow
CHF	-	Congestive Heart Failure
CO_2	-	Carbon Dioxide
CPP	-	Cerebral Perfusion Pressure
CVP	-	Central Venous Pressure
CVR	-	Cerebrovascular Resistance
DC	-	Donor Population Control
ECG	-	Electrocardiogram
PET CO_2	-	Partial Pressure of End Tidal Carbon Dioxide
HF	-	Heart Failure
HR	-	Heart Rate
HR_{peak}	-	Heart Rate Peak
$HR_{reserve}$	-	Heart Rate Reserve
HT	-	Heart Transplant
HTR	-	Heart Transplant Recipient

ICP	-	Intra-cranial Perfusion Pressure
IHD	-	Ischaemic Heart Disease
LVEF	-	Left Ventricular Ejection Fraction
MABP	-	Mean Arterial Blood Pressure
MCA	-	Middle Cerebral Artery
MCAv	-	Middle Cerebral Artery Velocity
O_2	-	Oxygen
PCA	-	Posterior Cerebral Artery
$PaCO_2$	-	Partial Pressure of Arterial Carbon Dioxide
PI	-	Pulsitility Index
PNS	-	Parasympathetic Nervous System
Q	-	Cardiac Output
SNS	-	Sympathetic Nervous System
SV	-	Stroke Volume
TOR	-	Target of Rapamycin
VO_{2peak}	-	Peak Oxygen Consumption

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“The only place where success comes before work is in the dictionary.”

~Vince Lombardi

Chapter One: Introduction and Review of the Literature

The heart transplant recipient (HTR) population represents a unique opportunity to observe the effects of cardiac output (Q) on cerebral blood flow (CBF) because the cerebrovasculature and cardiovasculature systems differ in chronological age. The cerebrovasculature is left intact and is therefore the same age as the HTR, where as the donor heart will typically be younger. This unique population provides an opportunity to examine some of the conflicting results in the Q and CBF literature (refer to section 1.2.2.) Namely, studying this population should enable the determination as to which is the key component of CBF: is it the age of the brain and its cerebrovasculature or is it the age of the heart and its cardiovasculature?

The following literature review describes a brief background on heart transplantation (HT) along with the factors associated with the regulation of CBF. The influences of cardiac function, aging and cardiac disease on CBF as it relates to the healthy human, congestive heart failure (CHF) and HTR populations are also considered. Thereafter, there is also a brief summary of the sparse literature that has directly assessed CBF in HTR.

1.1. Brief Background on Heart Transplantation

The first successful heart transplant was performed by Christiaan Barnard in 1967. The initial survival outcome was not very promising; the recipient, Louis Washkansky, survived for just 18 days[1]. However, the 2nd heart transplant recipient (HTR) had a much better outcome and survived for 19 months[1]. With improved surgical techniques and better medications, survival rates have continued to improve. During the 1980s the median survival

was up to 8.3 years; by the 2000s it had increased to approximately 10.5 years[2]. With improved survival rates, heart transplantation has moved beyond being an experimental medical procedure and is now an accepted therapy for extending end-stage heart failure patients' lives[3]. Coinciding with the improved survival rates of HTR, there is an increased desire by the patients to return to a functional lifestyle and experience a good quality of life.

However, pre-operatively many of the HTR have CHF and, because of this, undergo extended pre-transplant hospitalization. During this time of bed-rest, their cardiovascular parameters - such as peak oxygen consumption ($VO_{2\ peak}$) - decrease approximately 26%[3], typically ranging from 10 to 14 mL/kg/min[4, 5]. Yet, after HT, ventricular systolic function is improved to normal levels [6,7] as a result of the donor heart. Furthermore, through regular endurance training, peak heart rate (HR_{peak}) and $VO_{2\ peak}$ can improve to 95% of age-matched norms[3]. As extreme examples; there has been a case of a HTR who completed Ironman™ Canada[8]; and a group of 14 HTR successfully competing in a 4-day 600km running relay from Paris to La Plagne[9]. Despite this potential for improvement, many HTR experience $VO_{2\ peak}$ values approximately 50-70% of their predicted age-matched counterparts[3, 10]. Possible reasons for the reduced $VO_{2\ peak}$ include; depression[11-14], fatigue[12, 14-16], abnormal vascular function[17, 18], diastolic dysfunction[19, 20], post-transplant immunosuppressive therapy[3, 21, 22], cardiac allograft de-innervation[5, 7, 10, 23], skeletal muscle dysfunction[24] associated with the pre-transplant/post-transplant de-conditioning [3, 21], and physical pain[12-14].

The increased longevity after successful heart transplantation[2] has led to a change in the long-term outcomes of HTR. For example, neurological complications eventually develop in approximately 60-80% of all HTR[14, 25, 26]. Tung *et al.*[12], have reported that this may be due to side effects from the life-long post-operative use of anti-rejection

immunosuppressant therapies. Over the course the post-transplant survival period, there is approximately a 14-18% occurrence rate of a cerebrovascular event, such as cerebral haemorrhage or ischaemic stroke occuring[14, 26, 27]. Zierer *et al.*[28], have suggested another possible reason for the cerebrovascular events that are experienced in the HTR populations - that the cerebrovasculature in HTR may have a limited range of tolerance for changes in systemic blood pressure (BP). This risk of a cerebrovascular events may be due to cerebral vessel remodeling in the face of chronic cerebral hypoperfusion that has been associated with heart failure (HF)[25, 26, 28, 29]. However, with the possible increase in CBF associated with cardiac transplantation[30-32] (refer to section 1.5.) there is a trade-off; an increased risk of hyper-perfusion related complications occurring over the short-term post-transplant[28, 30]. In addition over the long-term, there is an increased likelihood that an ischaemic stroke will occur as a complication of cardiac transplantation[25-27]. The end result for HTR is that they ultimately require extremely sensitive hemodynamic management and it is suggested they should be cautious of both hypo- and hyper-tensive episodes[28]. This avoidance is troublesome, since changes in BP occur in a myriad of everyday activities; postural change, coughing, laughing, defecation, exercise, and sexual activity, etc...

1.2. Regulation of CBF

The human brain has a mass of approximately 1400g which equates to ~2% of the total mass of an average 70kg male[33]. At rest, normal cerebral oxygen (O_2) consumption is 3.5mL/100g brain tissue per minute[34] equating to ~49mL O_2 per min, or approximately 20% of the ~250mL O_2 per min the body consumes at rest. Thus, the brain has placed itself very prominently in the hierarchical positioning of organ demands[35]. With particular emphasis on

the integrative perspective, the following section provides an overview of the factors that regulate of CBF in humans.

1.2.1. Neurogenic Control of CBF

Neurogenic control refers to the influence on CBF of the sympathetic nervous system (SNS) [Figure 1.1. (1)] and parasympathetic nervous system (PNS) [Figure 1.1. (2)]. The cerebral vasculature is extensively innervated by sensory and autonomic neurons[36-38]. Sensory neurons have been implicated in the transmission of afferent activity produced by the nociceptors to the central nervous system; however, their role in cerebral vasomotor control is unclear[39]. Autonomic neurons from the SNS and PNS nervous systems innervate the cerebral vasculature. The SNS innervations arise from the superior cervical ganglia[40]; PNS innervations arise from the sphenopalatine and otic nerves[41].

The functional role for SNS and PNS control of the cerebral vasculature is controversial[42-47]. The SNS contribution to CBF regulation is dependant on the rate of change in arterial blood pressure[42], a response that has an important role in dynamic cerebral autoregulation (CA)[48, 49]. As BP can surge during REM sleep, it has been suggested that elevations in SNS activity may act in a shielding/protective role and prevent cerebral hyperperfusion during the periods of increased BP[50-52]. Although SNS control of CBF is not fully understood, it appears it may have a functional role during extreme hypo and hypertension.

The role of the PNS in CBF regulation is also still largely unknown, especially in humans. However, a recent study; has implied that the PNS may have a role in

cerebrovascular system regulation during exercise[53], a finding that was further discussed in a companion editorial[41].

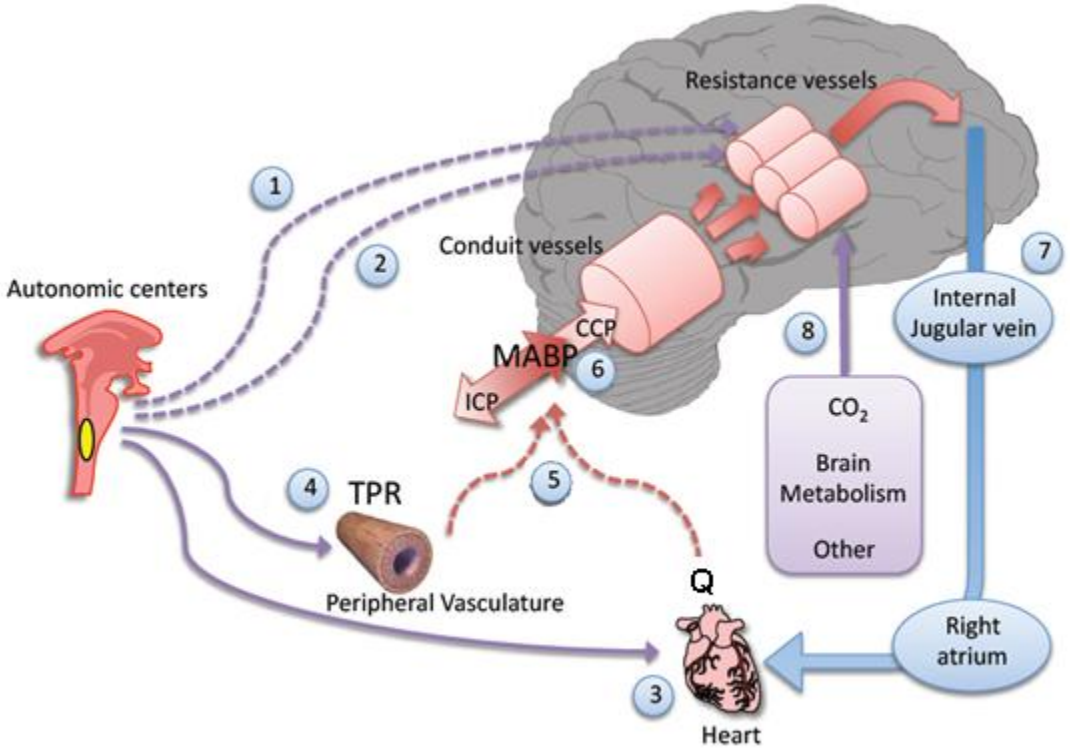

Figure 1.1. Factors and pathways that regulate CBF control. Control of cerebrovascular tone through neurogenic means is controversial, however sympathetic (1) and parasympathetic (2) inputs have been implicated. The quotient of cardiac output (Q; 3) and total peripheral resistance (TPR; 4) of the circulatory system is mean arterial blood pressure (MABP; 5). The peripheral vasculature has an impact on CBF regulation by way of MABP. Cerebral perfusion pressure (CPP; 6) is the pressure gradient difference between MABP and intra-cranial pressure (ICP) under conditions where the central venous pressure (CVP), as measured at the jugular vein (7), is lower than ICP and is the driving force behind cerebral perfusion. Cerebral autoregulation is under the influence of modulating factors such as CO_2 and brain metabolism (8). (adapted from[47]).

1.2.2. Influences of Cardiac Function on CBF

The primary function of the heart is to adequately perfuse the organs of the body with blood. The heart provides this function by contracting its muscular walls, increasing the pressure in the closed chamber (i.e. ventricle), when the internal pressure is greater than that of the attached artery (pulmonary or aorta), the blood is expelled through the valve and into the circulatory system. The intrinsic rate of the sino-atrial node of the heart is approximately 100 beats per minute (bpm). In healthy humans the sino-atrial node is also extrinsically regulated by the PNS and SNS[54]. Increased parasympathetic tone slows the heart rate (HR) below the basal rate whereas enhanced sympathetic tone increases HR towards peak levels with the secondary assistance of catecholamines[54]. Heart transplant recipients represent a unique population to study the effects of cardiac function because, during the transplantation process, the nerve fibres to the heart are transected, resulting axonal degeneration and complete denervation of the heart (Figure 1.2)[55, 56]. Surgical denervation results in the heart having increased sensitivity to the neurotransmitters that were lost, resulting in the transplanted heart being highly sensitive to norepinephrine and epinephrine[55]. The end result is that the transplanted heart is, at least initially, completely denervated and dependent upon hormones (e.g. catecholamines) to control increases in HR. This hormone dependence following transplant results in a delayed and blunted HR response and creates a greater reliance upon the pre-load to increase stroke volume (SV) and thus Q, especially during exercise[7, 10, 57]. However, over time, re-growth of transected nerves can take place and result in some re-innervation of the heart[56]. More rapid and complete re-innervation of the heart can occur if the allograft heart comes from a younger donor and if the transplantation procedure is fast and uncomplicated[56].

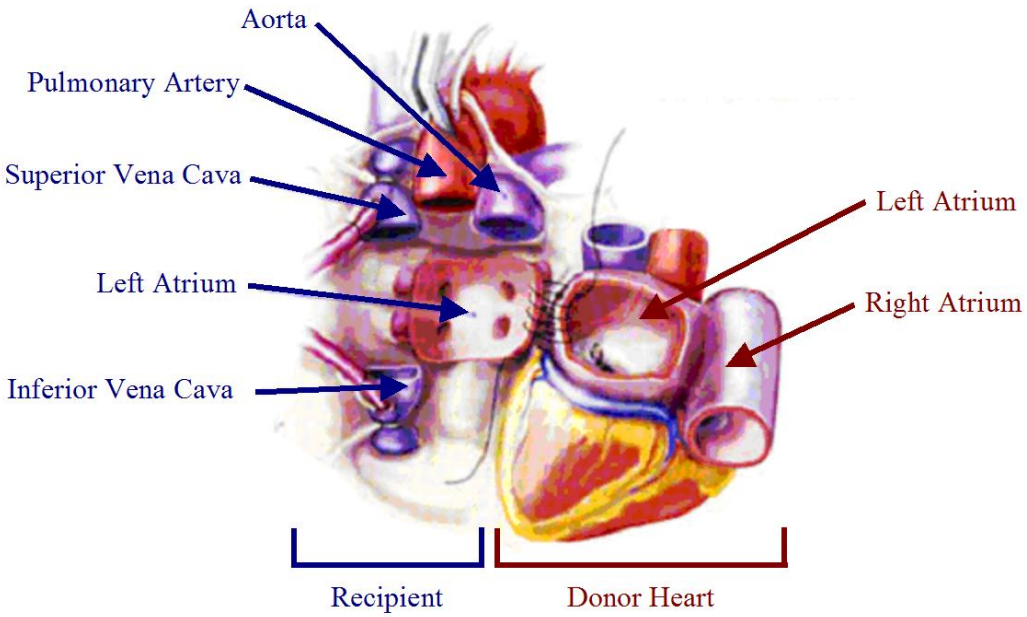

Figure 1.2. The de-innervated donor heart (red) is being sutured in the recipient (blue) during cardiac transplantation surgery. The major blood vessels of the pulmonary and systemic circuits are labeled for identification and orientation.

Cardiac output [Figure 1.1. (3)] is the total volume of blood expelled per minute and is determined by the quotient of HR and SV[5, 58]. At rest in the healthy human population, SV is approximately 70-80 mL and is influenced by 3 main factors: diastolic stretch, contractility and BP[58]. Diastolic stretch and contractility are influenced by the total peripheral resistance (TPR) [Figure 1.1. (4)] which is the sum of the vascular resistance across the entire circulatory system and as such has an impact on SV by way of the diastolic stretch[58]. Alterations in BP influence venous return and thus will also have an affect on SV[58], for example: an increase in TPR will lead to an increase in diastolic stretch.

The relationship between Q and CBF is unclear in the current literature (Table 1.1. – Appendix IV). From the 31 studies reviewed in Table 1.1., 9 studies showed no Q-CBF relationship, 9 studies showed a Q-CBF relationship and 5 studies showed conflicting results. The Q-CBF relationship occurs under certain conditions [e.g., changes in body temperature, blood volume or alterations in BP and venous return due to increases in lower body negative pressure or medications] while other conditions do not show a relationship at all.

A possible reason for some of this confusion in the literature on the Q-CBF relationship is the counterintuitive nature of this concept. For example, neither of the mechanisms that mediate Q [SV or heart rate] are represented in Poiseuille's law. Poiseuille's law is a major concept in the determination of CBF and is represented in the following equation:

$$F = (P_1-P_2)\pi r^4/8\mu L \qquad \textbf{Equation 1.}$$

Where: *F=flow, P_1=inflow pressure, P_2=outflow pressure, r=radius, μ= viscosity of the fluid, L=length*

The inflow pressure is BP; out flow pressure is the pressure in the internal jugular vein [Figure 1.1. (7)]. The length of the cerebral vasculature is not a physiological variable that changes or can be altered as it is consistent within each individual[87]. So if those are not responsible for the observed changes in Q and CBF, what does and is there a population we could observe that may better assist us in understanding this relationship?

1.2.3. Autoregulatory Control of CBF

A critical intrinsic response of the mammalian brain is known as cerebral autoregulation (CA) – the process by which adjustments are made to the cerebrovascular resistance to ensure that the CBF levels are matched to metabolic needs[88]. There are two main components to CA: static and dynamic. Static CA describes the tendency of CBF to be chronically maintained over a wide range of BP changes[89] [Figure 1.1. (5)]; and dynamic CA describes the ability of the cerebral vasculature to resist acute changes in perfusion pressure, due to changes in BP over a short time-course of less than five seconds[48]. If CA fails, the brain is put at risk of ischaemic damage (during low blood pressures) and of haemorrhage (during high blood pressure). Impairment of CA has been associated to the risk of stroke[90].

The classic description by Lassen[91], and further re-emphasized in a review by Paulson *et al.*[92], was that CBF has an autoregulatory range that is maintained over a wide range of BP (50-150 mmHg); however, this has been challenged by recent evidence that CBF is also dependant upon alterations to BP[89]. Lucus *et al.*[89] have reported that MCAv changes ~8% per 10 mmHg shift in BP across both hypo- and hypertension, suggesting that arterial baroreflex regulation of BP [Figure 1.1. (4)] may have a greater role in CBF control than traditionally thought. Moreover, an inverse relationship between cardiac baroreflex

sensitivity and dynamic CA, suggests the presence of compensatory interactions between peripheral blood pressure and central CBF control mechanisms, that optimize CBF control has been reported[93]. Such interactions may account for the divergent changes in CA and baroreflex sensitivity seen with normal aging, and in clinical conditions such as spontaneous hypertension[94], autonomic failure[95], and chronic hypotension[96]. Because of related alterations in heart rate variability[97, 98] and baroreceptor sensitivity[99] following heart transplantation, unstable control of blood pressure may ensue. Thus, dynamic CA may be a particularly important mechanism to protect the brain from alterations in BP. However, to date no studies have assessed CBF or dynamic CA over the longer term (i.e. years) in HTR.

1.2.4. Regulation of CBF by $PaCO_2$

The downstream cerebral arterioles [Figure 1.1. (8)] are highly sensitive to changes in the partial pressure of arterial CO_2 ($PaCO_2$)[100]. Respiratory-induced changes in $PaCO_2$ are tightly coupled with CBF and therefore play an important role in the regulation of CBF[101, 102]. Cerebrovascular reactivity is the CBF response to changes in $PaCO_2$ and is of vital homeostatic importance as it helps regulate, influence and maintain central pH [33, 101, 103, 104]. When there is an elevation in $PaCO_2$ (hypercapnia) there is a corresponding increase in the CBF as a result of the vasodilation of the cerebral arteriole bed [Figure 1.1. (8)][33]. Conversely, when there is a reduction in $PaCO_2$ (hypocapnia), vasoconstriction of the cerebral arteriole bed occurs and there is a subsequent reduction in the CBF[33]. However, there are differences in the amplitude of CBF response to hyper- and hypocapnic events[100], with hypercapnic events demonstrating a larger response over a wider array of CO_2

challenges[105]. This is possibly due to a large release of nitric oxide in the brain that coincides with hypercapnia, where as this response is not present in hypocapnia[106].

Studies have shown that there is a link between cerebrovascular endothelial dysfunction and impairment in the reactivity of cerebral vascualture[107-109] as well as cognitive decline[109-111]. These findings suggest that alterations in the peripheral vasculature, may also affect cerebrovascular function, including cognitive outcomes. Congestive heart failure (CHF), which is one of the primary precursors to heart transplantation, is characterized by decreasing cardiac function[112, 113]. This reduction in cardiac function along with cerebrovascular endothelium dysfunction and impaired reactivity may relate to the observed cognitive declines associated with this population[114, 115].

1.2.5. Effects of Cerebral Metabolism on CBF at Rest and During Exercise

Oxygen delivery to the brain is reliant upon the arterial O_2 content and CBF. Resting cerebral O_2 consumption is maintained throughout a variety of $PaCO_2$ alterations, as typically experienced during cerebrovascular reactivity challenges[116-118], via increases in O_2 extraction[33].

It has been well- reported that CBF is elevated by 10-20% during sub-maximal exercise (reviewed in: [100, 119]). These increases in CBF are likely driven via the increased O_2 requirements of the brain[100, 120]. After the aerobic threshold (60-70% of VO_{2Peak}), CBF returns toward baseline (and possibly lower) values due to hyperventilation-induced hypocapnia, regardless of increasing O_2 demands within the brain[120, 121]. Exercise-induced hyperventilation (and related hypocapnia) therefore appears to be a stronger regulator of CBF than cerebral metabolism at exercise intensities above aerobic threshold (~70% VO_{2max})[122].

1.3. Cognitive Impairment in CHF

Clinical populations with severe cardiovascular disease and end-stage heart failure have also been shown to have impaired cognitive function[30, 31, 114, 123-128]. Approximately 25-50% of CHF patients experience cognitive impairment, which is associated with a 5-fold increase in mortality among older adult hospitalized patients[114, 129]. Structural and functional brain changes, including discrete losses in gray matter, brain volume, areas of silent stroke, and decreased CBF[31, 130-133], have also been observed in CHF patients. End-stage HF patients who have undergone heart transplantation have shown significant rapid improvements in cognitive functioning soon after transplants that were stable within 3 months[127, 134, 135]. These studies indicate that a higher stroke volume, higher cardiac and lower right atrial pressure are all correlated with better cognitive function[135].

Gruhn *et al.*[31], argued that the neurological impairment in the CHF patients was due cerebral hypoperfusion associated with a CBF 30% below normal resting values[31]. These conclusions are hindered, as there were no neuropsychological testing pre- or post-transplant[31]. The 30% reductions in CBF are above the aggregate experimental and human study data, which showed that non-human primates have a 22 mL/100g per min (40% below normal resting values) threshold before neuronal function is impaired[136]. In humans, electroencephalography activity decreases if mean CBF falls below 23 mL/100g per min (54% below normal resting values) during carotid clamping[137]. Ackerman noted clinical cognitive dysfunction is not necessarily related to a CBF threshold. Rather, these studies support the notion that the brain may be more tolerant to hypoperfusion than early investigators had implied[138]. However, a review paper by Roman[139] concluded that circulatory conditions, such as cerebral hypoperfusion due to CHF, result in localized brain

injuries that lead to undiagnosed forms of cognitive decline in older adults. Thus, further research with prospective studies and experimental models are still needed to determine the pathogenesis of cognitive dysfunction in end-stage HF patients and HTR.

1.4. Influences of Cardiac Disease on CBF

According to the 2008 cardiac transplant update from the Canadian Cardiovascular Society Consensus Conference[140]:

> *Cardiac transplantation is the treatment of choice for patients who have severe end-stage heart failure despite maximal medical therapy and/or complex congenital heart disease not amenable to surgical palliation at reasonable risk.*

In the 27th official adult heart transplant report by the Registry of the International Society for Heart and Lung Transplantation[2], CHF represents 51.4% of all pre-transplant diagnosis, Ischaemic heart disease (IHD) 39.9%, re-transplant 2.4% and other causes making up the remaining diagnosis[2].

1.4.1. Congestive Heart Failure

The major reductions in deaths from cardiovascular diseases (hypertension, coronary diseases and damage to the cardiac valves) have led to more and more people living with HF[112, 113]. There are an estimated 5.7 million people living with HF and almost 300 000 annual deaths from HF complications in the United States of America alone[113]. End-stage HF occurs after the myocardium has exhausted all of its reserve capacity and compensatory

mechanisms, leaving the possibility for salvage limited leading to terminal CHF[112]. The greatest survival outcome for end-stage HF patients is a cardiac transplant. However, the supply of donor hearts is limited, with only 3000-5000 heart transplants take place worldwide each year [2, 113].

Reduced CBF has been reported in older adult males with CHF[32, 141-144]. However, there are conflicting opinions in the literature on the root cause of the reduced CBF. Loncar *et al.*[141] reported that older adult males with mild to moderate CHF have reduced CBF values independently associated with reduced left ventricular ejection fraction (LVEF). Conversely, Choi *et al.*[32] have shown that in cases of severe HF there is no correlation between LVEF and CBF. This discrepancy could be due to experimental differences in the assessment of CBF and related complications associated with the functional classification of CHF, such as neurohormonal activation, having an influence on CBF[141]. Regardless of the cause of the reduced CBF, both groups acknowledge a myriad of negative outcomes associated with reduction in CBF. For instance, the authors speculated that the reduced CBF may result in structural changes occurring within the brain[32, 141, 144]; this effect could manifest in negative outcomes such as impaired cognitive function (as previously described), and autonomic nervous system dysfunction[141]. Whilst speculative, these outcomes might be the reason for the increased risk of CHF patients also developing cognitive disorders such as Alzheimer disease or dementia[141].

1.4.2. Ischemic Heart Disease

Ischemic heart disease (IHD) is one of the major causes of death in the western world and will result in over 150 000 deaths in the United Kingdom in the next year[145, 146]. IHD

involves a complex interaction between haematological, biochemical, immunological and physiological factors[145, 146]. All of these combine to elevate certain clotting factors, such as fibrinogen, which result in paralyzing the heart due to the blocking blood flow to one or more of the major coronary arteries eventually resulting in coronary artery thrombosis and resultant myocardial ischemia[146, 147]. Over time, the blockages build-up and lead to cellular death of the localized myocardial tissue resulting in a reduced ejection fraction and possible rupture of the myocardial wall[147]. The two most effective and viable long-term treatments for end-stage IHD are cardiac surgery and heart transplantation[146, 147].

Reduced CBF has been observed in approximately 75% of IHD patients[148, 149], which may possibly explain why one of the major complications of cardiac surgery is ischemic stroke[148, 149]. With the increased risk of ischemic stroke associated with cardiac surgery, Kawabori *et al.*[148], have recommended that IHD patients should be preoperatively screened for MCA and internal carotid artery occlusion.

1.5. Changes in CBF in HTR

Heart transplantation is a life saving surgical intervention for select individuals with end-stage HF. Despite normal resting left ventricular systolic function after surgery, HTR have reduced Q during exercise[6, 10]. The mechanism responsible for post-transplant impairment in Q reserve [6, 10] is attributed to surgical denervation of the transplanted heart[10], diastolic dysfunction[10], and peripheral vascular dysfunction[10]. A consequence of a blunted Q reserve is that it may result in decreased CBF (refer to section 1.2.2.). Currently, there have been only three studies that have examined CBF at rest in HTR[30-32]. Moreover, to date, no studies have reported how CBF might be altered during exercise. The following section will

provide an overview of the salient methodological and experimental findings from these three studies.

It was reported[150] that CBF might be reduced in patients with CHF, resulting in cognitive impairments, memory problems, confusion, lethargy and dizziness. Many of these conditions were improved after heart transplantation[127]. On this basis, Gruhn *et al.* [31] reasoned that CBF alterations may be occurring in patients with CHF who undergo heart transplantation.

In their study, CHF patients had reported CBF baseline values of 35 ± 3 mL/min per 100g rising to 50 ± 3 mL/min per 100g using Xenon gas inhalation (Figure 1.3.) one month after undergoing successful heart transplantation ($P<0.05$), and the after transplantation the HTR were not significantly different from the control values 52 ± 5 mL/min per 100g (Figure 1.4.). Thus, leading to the conclusion that CBF rapidly normalizes after heart transplantation. A small subset of the HTR were re-examined at 6 months post transplant and it was reported that the CBF and MCAv values did not differ from those at one month[31].

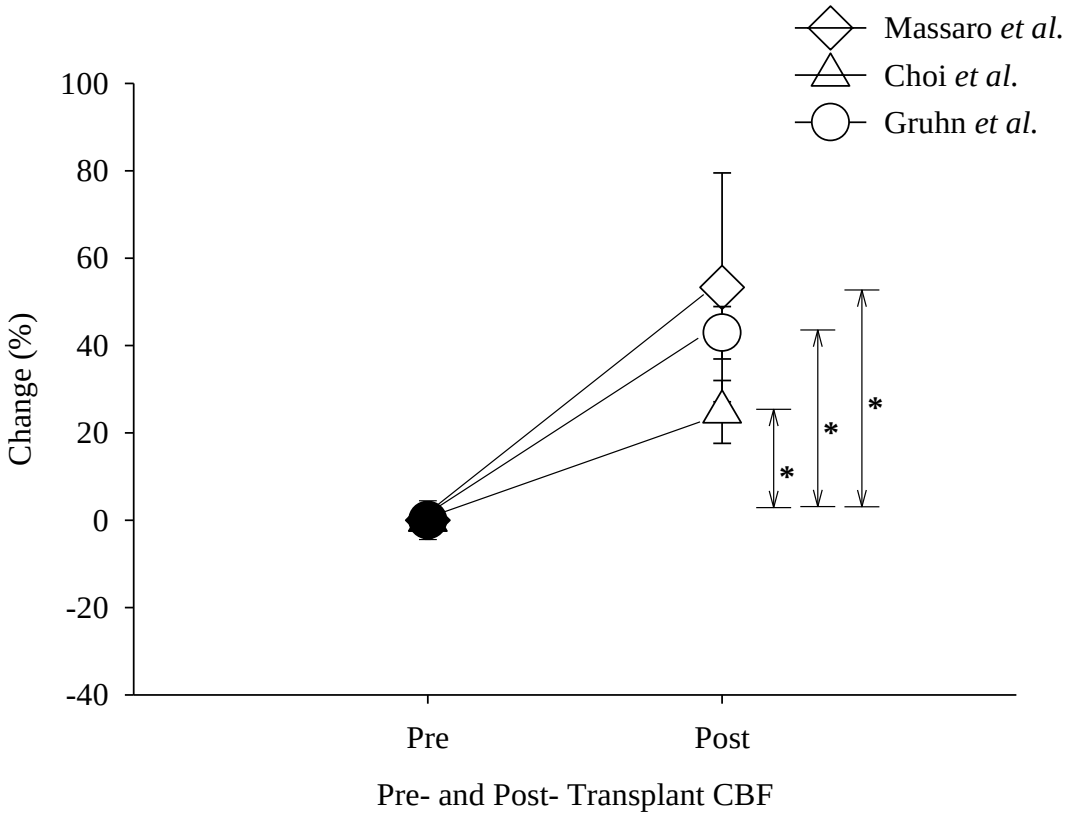

Figure 1.3. Summary of the percent change in pre- and post-transplant cerebral blood flow (CBF) observed in studies of heart transplant recipients (HTR). All three HTR studies[30-32] reported statistically significant CBF increases post-transplant of between 25 and 53% (*denotes, $P < 0.05$).

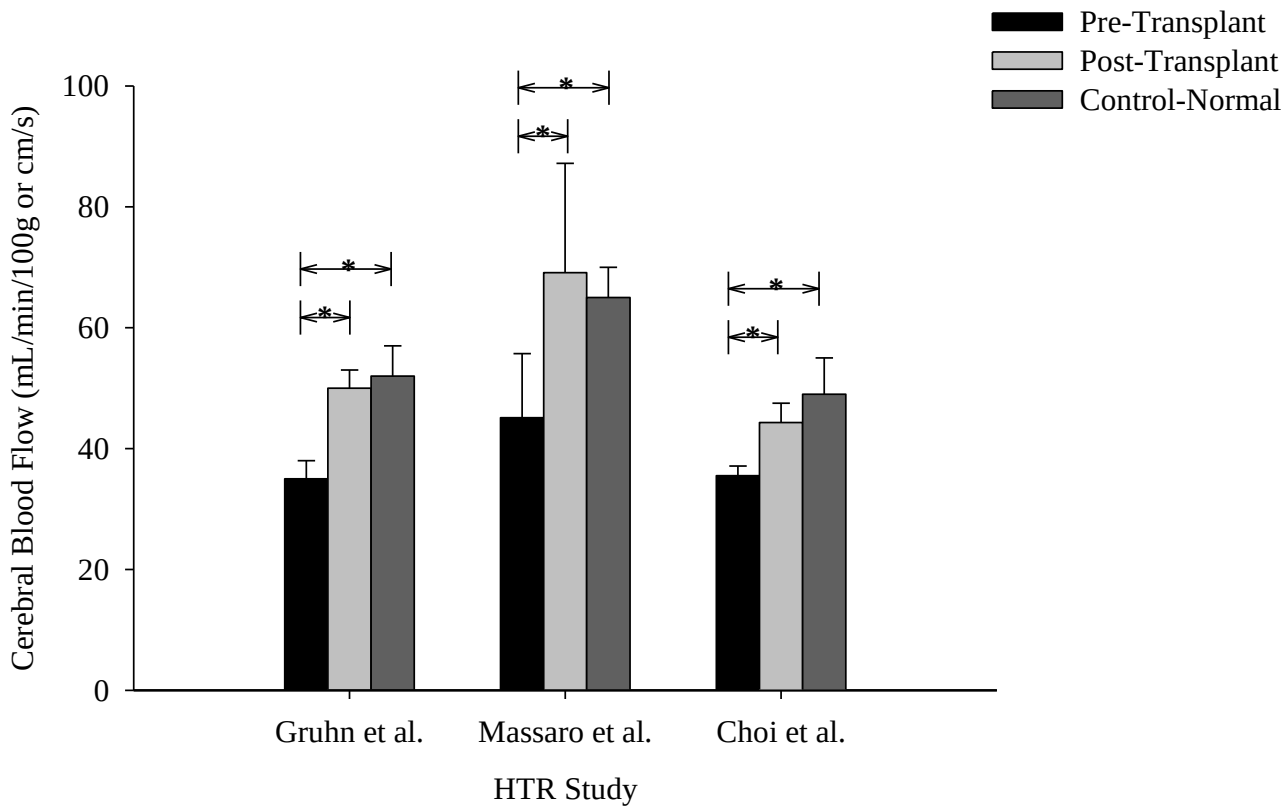

Figure 1.4. Summary of pre- and post-transplant and control/normal cerebral blood flow (CBF) values in the studies with heart transplant recipients (HTR). CBF values were reported as mL/min/100g brain mass (Xenon inhalation) by Gruhn *et al.*[31] and Choi *et al.*[32], and as cm/s (transcranial Doppler) by Massaro *et al.*[30]. Gruhn *et al.*[31], and Choi *et al.*[32], reported age-matched (AM) control values, Massaro *et al.*[30], did not provide this information, instead AM normal values were obtained from Ainslie *et al.* [151]. All studies reported statistically significant differences pre- and post-transplant as well as between HTR and AM comparison groups. No statistically significant differences were reported between post-transplant and AM comparison groups. (*denotes, $P < 0.05$)

One difference noted was the end-stage HF patients had significantly (P<0.05) lower end tidal carbon dioxide (PET CO_2) concentrations (34.5 ± 1.5 mmHg) than their control groups (39.0 ± 0.8 mmHg) [31]. Assuming normal cerebrovascular CO_2 reactivity[33], the 4.5 mmHg reduction in PET CO_2 would account for approximately 18% of the observed 30% reduction in CBF. Hypocapnia is a well known condition associated with congestive heart failure (CHF) patients[152-155], and chronic hypocapnic exposure can result in cerebral hemodynamic maladaptation [156]. Gruhn *et al.*[31] reported that the increase in CBF following HT being strictly caused by the marked hypercapnia was questionable. Therefore, they concluded that the decreases in CBF for patients with severe CHF may contribute to the neurological symptoms they experience[31].

Another possibility to explain Gruhn's findings was noted in a companion Editorial[138]. This editorial suggested that the reported 30% increase in CBF following HT was perhaps due to a perisurgical fall in hematocrit, as well as putting forth the notion that the pre-surgery reduction in CBF may not be sufficient to cause neurological impairment. Although Gruhn *et al.* [31] did not provide the hematocrit data for their subjects, it was estimated that net hematocrit levels fell by 8.3% 30 days post transplant[138]. A reduction in hematocrit levels from 0.57 to 0.24 can result in an increase in red blood cell velocity of more than 50% due to the reduction in red blood cell viscosity[157]. Such changes may explain the CBF changes found by Gruhn *et al.* [31] could have occurred due to blood viscosity changes as noted in Poiseuille's law (Equation 1.)[138].

In the second study, Massaro *et al.*[30] reported changes in CBF velocity (as index by transcranial Doppler - TCD) in CHF patients before and after heart transplantation in order to evaluate the intracranial hemodynamic features that are associated with the improvement of

cardiac output. Twenty-six patients were preoperatively selected for their study. Upon completion of neuroimaging examinations (cranial CT or MRI), 4 patients were excluded because of silent ischaemic brain lesions and 20 for signs of cerebral atrophy[30]. The twenty-two patients included in the study had a mean age of 45.3 years, MCAv of 45.1 ± 10.6 cm/s (Figure 1.3.), and a mean hematocrit of 38.8 ± 5.5%[30]. Fourteen patients underwent successful heart transplantation. Findings showed a 53.3% increase in MCAv (P<0.0001) in MCAv of 53.3% (Figure 1.2.) and a lower mean hematocrit levels (31.2 ± 2.0%) was observed[30]. Pre-operative and post-operative neuropsychological evaluations were not performed during the study[30].

When evaluating their data for the 53.3% improvement in MCAv the authors were unable to observe any MCAv-hematocrit correlation[138]. The lack of correlational data in the pre- and post-transplant measures of MCAv and hematocrit, led Massaro *et al.* [30] to conclude that the CBF increases observed in their studies were probably not due to the changes in hematocrit levels. Overall, these findings allowed the authors to report that the main mechanism for the increase in MCAv after successful heart transplantation was most likely due to the improved Q. In support, Baufreton et al.[158] have recently confirmed in healthy humans there is no MCAv - hematocrit relationship.

The focus of the final study by Choi *et al.* [32] was to investigate factors that represent the chronicity and level of severity of HF, but not associated with exercise capacity or the LVEF, in respect to global CBF changes observed in CHF patients, rather than the effects of heart transplantation on CBF. Overall, fifty-two CHF patients took part in their study, four of which underwent heart transplantation. In these four, it was noted that global CBF at rest increased (35.5 ± 1.6 to 44 ± 3.2 mL/100g per min: Figure 1.3.) and left ventricular ejection

fraction (LVEF) normalized (19.8 ± 6.8% to 66.8 ± 3.3%) for these subjects[32]. However, the authors did not expand upon or make any reference to these findings in their discussion. These results, in conjunction with the findings by Gruhn *et al.* [31], support the conclusion by Massaro *et al.* [30], in that the main mechanism for the increase in CBF post-transplant is likely due to the increased Q that the 'new' heart provides.

Chapter Two: Purpose, Aims and Hypotheses

2.1. Purpose of Thesis

A limitation of the prior studies of CBF in HTR[30-32], is that CBF was only examined at rest during the acute post-transplant time period (up to 6 months), and was also not examined during exercise stress, when Q reserve is challenged[6, 21].

The HTR population has a reported inability to increase Q during exercise due to cardiac denervation[159-161]. However, it has also been reported that the exercise HR response will vary with the length of time after transplant and this may be due to the possible re-innervation of the heart[6]. Furthermore, the role that this possible cardiac re-innervation and concomitant improvement in exercise Q associated with heart transplantation has on CBF is unknown[100].

How these possible alterations in the long-term HTR (cardiac re-innervation and improvements in exercise Q) will affect CBF at rest and during exercise stress is currently unknown.

2.2. Aims

The aim of this thesis was enhance the current literature of CBF in HTR by being the first study to examine the influence of long-term heart transplantation on the regulation of CBF at rest as well as being the first study to assess the effects of exercise stress on CBF in HTR.

2.3. Hypotheses

1. That CBF (indexed using TCD) would be similar in HTR when compared to age and activity-matched controls, but CBF would be attenuated relative to donor population controls.
2. During incremental cycling exercise, to exhaustion, HTR would have reduced elevations in CBF compared with age and activity-matched controls (AM) and donor population controls (DC).

Chapter Three: Methods

3.1. Participants

Seven male clinically stable HTR (62 ± 9 yrs), years post transplant (9 ± 7 yrs), from the University of Alberta Heart Transplant Clinic, seven male AM (62 ± 7 yrs), and seven male DC (22 ± 3 yrs) were recruited for this study (Table 3.1). All of the HTR subjects were clinically stable and had no clinical or biopsy evidence of rejection.

The AM were recruited to match with the HTR on an individual basis for both age and activity level, as there is a decrease in MCAv of approximately 1% per year across the aging spectrum, and a 17% increase in MCAv that is associated with long-term endurance training, irrespective of aging[151]. The DC were included in the study to offset a study limitation of Kao *et al.*[10], which indicated that the exercise response observed in HTR may be more closely related to the age of the donor rather than the age of the individual. The age of the DC group was chosen to represent the most common heart transplant donor group. For example, in North America over 50% of all donors are between the ages of 18-34[2].

All subjects were asked to abstain from caffeine, smoking and alcoholic beverages for a period of 12 hours prior to the study and all medications were maintained for the study. Each subject underwent a familiarization of the laboratory and testing protocols before the initiation of the incremental peak exercise protocol. This study and was approved by the University of Alberta Health Research Ethics Board (Pro00011560), and all participants provided written informed consent before the experiment.

Included in the study was the only HTR to have successfully completed the Ironman™ endurance race (subject #02)[8]. This subject was also the only HTR participant to have a non-ischemic pre-surgery etiology.

Statistical analysis were performed with and without HTR subject #02 in order to establish if the increased fitness and training levels associated with completion of an Ironman Triathlon and/or the effects of the non-ischemic pre-surgery etiology influenced the main findings of the study (Table 3.2).

Table 3.1. Participant Characteristics (all subjects)

	HTR (n=7)	**AM (n=7)**	**DC (n=7)**
Age (years)	62 ± 9	62 ± 7	22 ± 3 †‡
Body Mass Index (kg/m^2)	27 ± 5	26 ± 4	25 ± 3
Resting BP (mmHg)	99 ± 4	99 ± 15	91 ± 6
Resting Mean MCAv (cm/s)	40 ± 12	41 ± 7	69 ± 9 †‡
Resting Cerebrovascular Resistance (mmHg/cm/s)	2.6 ± 0.7	2.5 ± 0.5	1.3 ± 0.2 †‡
Resting Pulsitility Index (AU)	0.9 ± 0.2	1.1 ± 0.3	1.1 ± 0.2
Peak O_2 Consumption (ml/kg/min)	25 ± 10	35 ± 9	51 ± 7 †‡
Years after transplantation	9 ± 7		
Medications			
Corticosteroid	2		
Antiproliferative agent	4		
Calcinerurin inhibitor	4		
mTOR inhibitor	4		
Ca^{2+} channel blocker (diltiazem)	5	1	
ACE inhibitor	4	1	
Diuretic	3	1	
Aspirin	6	1	
Lipid –lowering agent	4		

Values are means ± SD. All subjects were ischemic pre-surgery etiology except HTR subject #02 who was non-ischemic etiology. Heart transplant recipient (HTR); age-matched (AM); donor population control (DC); blood pressure (BP); target of rapamycin (TOR); angiotensin-converting enzyme (ACE). Statistical significance was set at $P < 0.05$, †denotes significance between HTR *vs.* DC, ‡denotes significance between AM *vs.* DC.

Table 3.2. Participant Characteristics (without HTR subject #02 and matched controls)

	HTR (n=6)	AM (n=6)	DC (n=6)
Age (years)	64 ± 8	63 ± 7	21 ± 2 †‡
Body Mass Index (kg/m^2)	28 ± 4	26 ± 4	26 ± 2
Resting BP (mmHg)	98 ± 3	98 ± 16	90 ± 7
Resting Mean MCAv (cm/s)	41 ± 13	42 ± 8	67 ± 7 †‡
Resting Cerebrovascular Resistance (mmHg/cm/s)	2.6 ± 0.7	2.5 ± 0.4	1.4 ± 0.3 †‡
Resting Pulsitility Index (AU)	0.9 ± 0.3	1.1 ± 0.3	1.0 ± 0.2
Peak O_2 Consumption (ml/kg/min)	22 ± 4	33 ± 8*	50 ± 7 †‡
Years after transplantation	7 ± 4		
Medications			
Corticosteroid	2		
Antiproliferative agent	4		
Calcinerurin inhibitor	4		
mTOR inhibitor	4		
Ca^{2+} channel blocker (diltiazem)	4	1	
ACE inhibitor	4	1	
Diuretic	3	1	
Aspirin	6	1	
Lipid –lowering agent	4		

Values are means ± SD. All subjects were ischemic pre-surgery etiology. Heart transplant recipient (HTR); age-matched (AM); donor population control (DC); blood pressure (BP); target of rapamycin (TOR); angiotensin-converting enzyme (ACE). Statistical significance was set at $P < 0.05$, *denotes significance between HTR *vs.* AM, †denotes significance between HTR *vs.* DC, ‡denotes significance between AM *vs.* DC.

3.2. Instrumentation

Whenever possible, both the right and left middle cerebral arteries were insonated by placing a 2-MHz Doppler probe (Spencer Technologies, Seattle, WA, USA) to obtain bilateral CBF velocity and are securely locked in place with an adjustable head-band (Spencer Technologies, Seattle, WA, USA), enabling continuous measures of CBFv throughout the incremental cycling test. Heart rate was recorded with a three-lead electrocardiogram (ECG). Blood pressure was monitored in the arm by electrosphygmomanometry (SunTech Medical, Morrisville, NC, USA), with a microphone placed over the brachial artery and the Korotkoff sounds gated to the ECG. Expired O_2 and CO_2 gases were measured by an online gas analyzer (Sensormedics Metabolic Cart, 2900BZB, Sensormedics Corporation, Homestead, FL, USA and Vmax Encore VIASYS Healthcare Inc. Yorba Linda, CA, USA) and were calibrated with standard gas of a known concentration before each exercise test. All data were recorded and stored for subsequent analysis using commercially available software (LabChart version 7.0, ADInstruments, Colorado Springs, CO, USA).

Echocardiograph images (Vivid-*i*, GE Healthcare, USA) were recorded and assesed by a cardiologist in order to directly compare the Q with the CBFv. Unfortunately upon assessment of the recorded images, the data were deemed unacceptable for valid measurement due to subject movement during the incremental exercise test.

An example of the instrumentation setup for the incremental exercise protocol is shown in Figure 3.1.

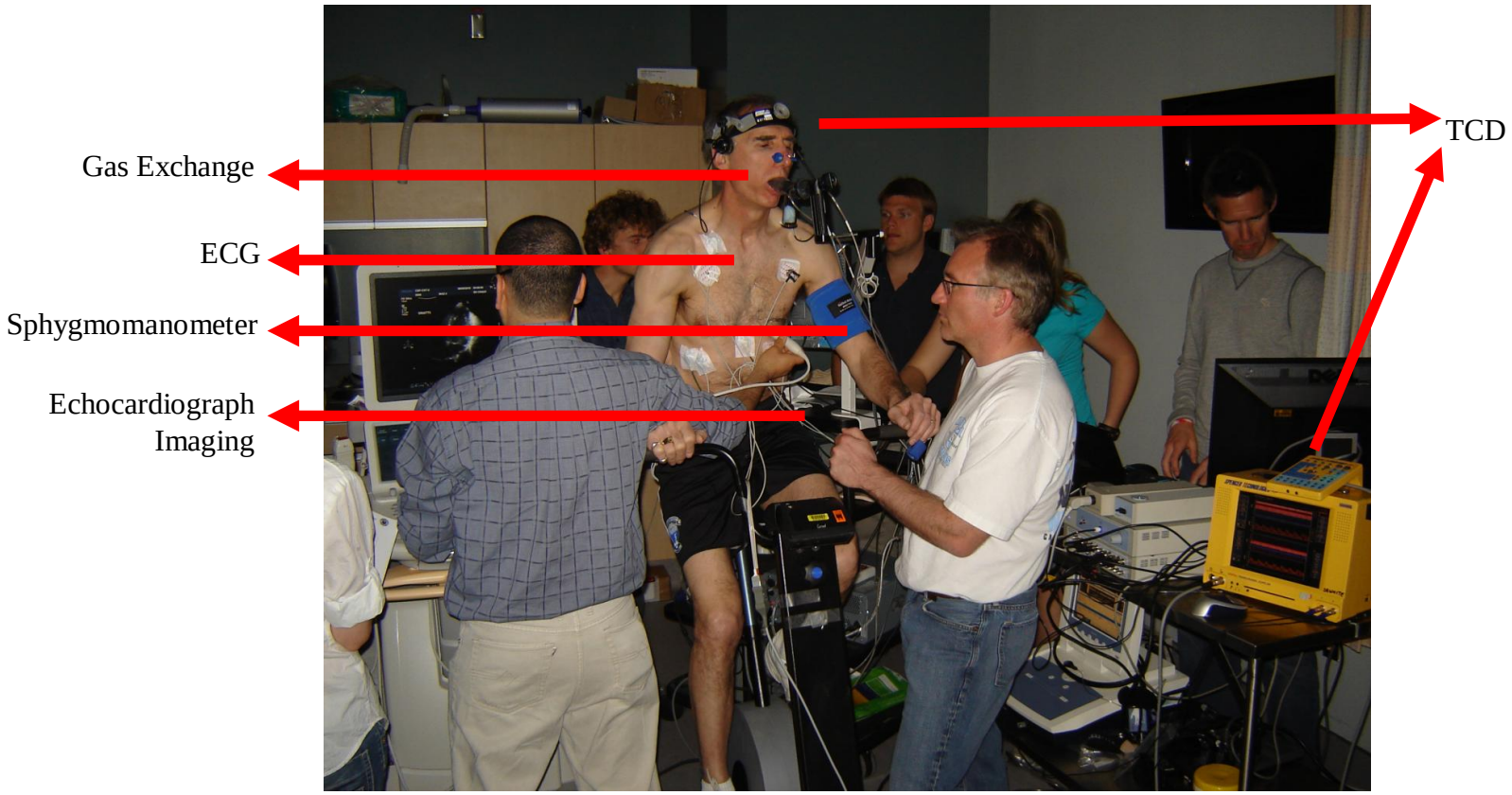

Figure 3.1. Instrumentation setup on subject during the incremental cycling exercise protocol. Transcranial Doppler ultrasound (TCD), Electrocardiograph (ECG).

3.3. Transcranial Doppler Ultrasound

Transcranial Doppler ultrasound (TCD) was first introduced into the clinical and research areas by Aaslid[162] in 1982. This technique has several advantages for the assessment of measuring CBF velocities in humans; it is non-invasive, has high resolution, allows for continuous monitoring, and repeated measures[101, 163]. Transcranial Doppler ultrasound functions are based on the principle of Doppler shift; as such, TCD is able to detect the red blood cell flow velocities in a variety of cerebral vessels (MCA, anterior cerebral artery, posterior cerebral artery). This study utilized the MCA as it is readily available through the temporal acoustic window, has a trajectory that is parallel with the insonation probe[101, 162] (Figure 3.2.) and has been shown to carry approximately 70-80% of the blood volume into the respective hemisphere[164]. It is key to be aware that TCD gives a measure of blood flow velocity (cm/s) and not blood flow (mL/min/100g) per se. However, provided that the insonated vessel remains constant in diameter, these two principles are closely related as shown by the following equation[163]:

Cerebral blood flow velocity = blood flow volume / blood vessel diameter **Equation 2.**

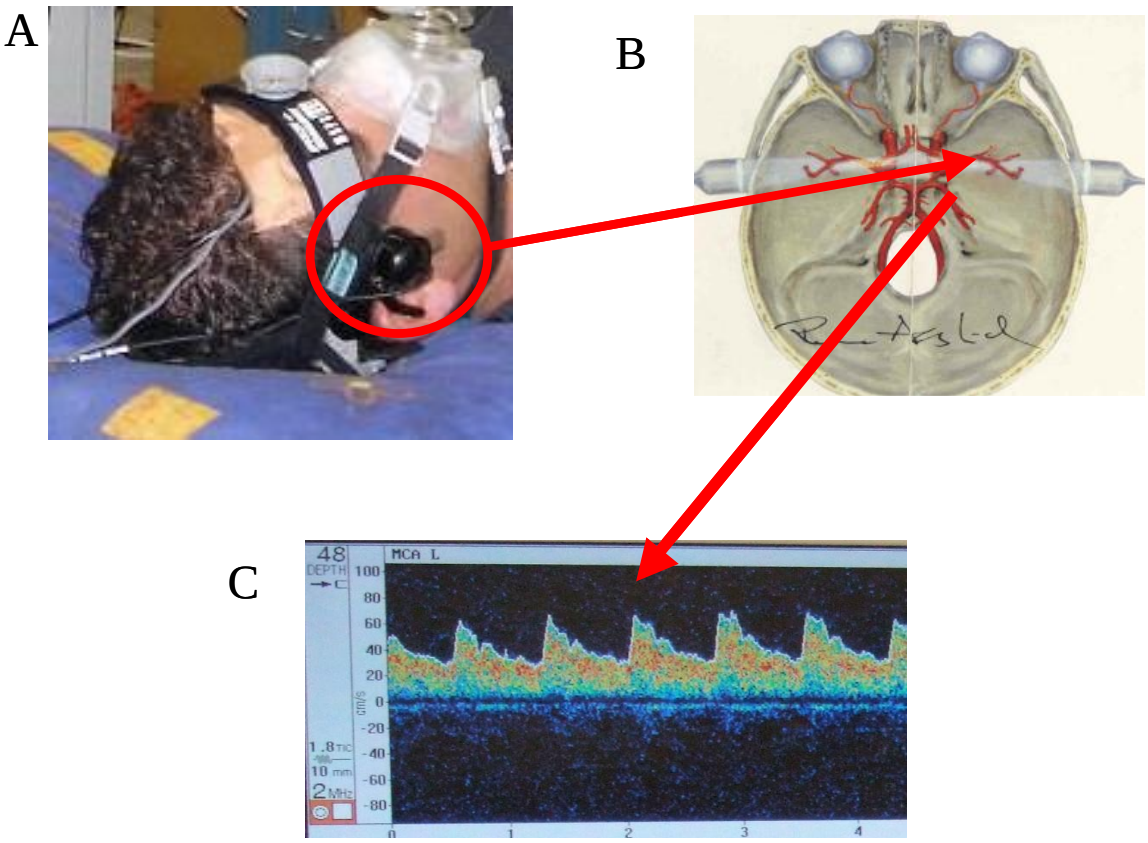

Figure 3.2. Image of the transcranial Doppler ultrasound (TCD) probe being held in place with the headband (A), a frontal view of the insonation of the middle cerebral artery (MCA) (B), image of the MCA velocity waveform and envelope (C).

3.3.1. Validity of TCD

In the literature it has been shown that the diameter of the MCA remains relatively unchanged over a range of 23-60 mmHg for $PaCO_2$[163, 165-167]. Additionally, there have been several studies on humans that have compared TCD estimates of MCAv with several other measures of CBF: Kety-Schmidt method[168], magnetic resonance imaging [167] and the Fick principle[169]. All of these studies have shown a good correlation between the measures of CBF with the assessment of MCAv via TCD; as such the findings of these studies collectively support the use and validity of MCAv as an indirect measure of CBF.

3.3.2. Principle of TCD

The basic principle of TCD is that a transmitter inside a Doppler probe emits a 2 MHz pulsed-Doppler ultrasound beam through the thin bone acoustic window to a given target vessel. Some of the ultrasound beam is then reflected off of the red blood cells and recorded by the receiver in the Doppler probe. The Doppler shift is the difference between the transmitted and received signals and determines the velocity of the red blood cells in the target vessel and is calculated in the following equation[170]:

$$\text{Doppler frequency shift} = 2 \times V \times Ft \times \cos\theta / C \qquad \textbf{Equation 3.}$$

Where: *V=velocity of the reflector (red blood cells), Ft=transmitted frequency (2 MHz), cosθ=correction factor based on the angle of insoniation, and C=speed of sound in the blood (1540m/s)*

In TCD, since both the transmitted frequency and speed of sound in the blood are constants, the frequency of the Doppler shift is ultimately dependant upon the velocity of the red blood cells and the angle of insonation of the Doppler probe[170]. The angle of insonation is vital to the accuracy of the measure. It is recommended that the angle of insonation is kept less than 30°; as the cosine will vary between 1 and 0.86 in this range, thus giving a maximum error of less than 15%[162]. An advantage to measuring the MCA, as opposed to other cerebral vessels is that the angle of insonation is that the flow of the vessel is parallel to the probe (Figure 3.2.-B), thus resulting in a lower insonation angle and therefore less error[170].

The final Doppler signal is the summation of all of the signals reflected from the velocity of each of the red blood cells within the sample volume of the target vessel[170]. The processing unit in the TCD uses spectral analysis to extract the 3-dimensional Doppler data into a 2-dimensional Doppler waveform (Figure 3.2.-C)[170]. This waveform and its subsequent spectral envelope are used to determine the MCAv, which is recorded for future analysis.

3.3.3. Technique of TCD

The approach to insonating a cerebral vessel has been described in detail elsewhere[101, 162, 170] and is summarized as follows. First, acoustic gel is placed on the probe and temporal window, this aids in signal conduction. Second, the Doppler probe is positioned over the acoustic window and held in place with an adjustable headband. Lastly, the MCAv signal is obtained and secured by an experienced research technician using search methods that have been previously described[101, 162].

The flow-volume MCAv waveform was obtained from the spectral envelope and displayed in LabChart in real time. From the flow-volume waveform, systolic and diastolic MCAv were obtained. Mean MCAv was calculated as follows:

Mean MCAv = 1/3 Systolic MCAv + 2/3 Diastolic MCAv **Equation 4.**

Where: *Mean MCAv = mean middle cerebral artery velocity (cm/s), Systolic MCAv = systolic middle cerebral artery velocity (cm/s), Diastolic MCAv = diastolic middle cerebral artery velocity (cm/s).*

In addition, Cerebrovascular Resistance (CVR) was calculated as: MAP/MCAv. MCAv Pulsitility Index (PI) was calculated as: (Systolic MCAv-Diastolic MCAv)/Mean MCAv.

3.4. Incremental Cycling Exercise Protocol

An electrically braked cycle ergometer (Monark 894E, Varberg, Sweden) was utilized for the incremental cycling exercise test. Baseline measures were recorded in a seated position on the cycle ergometer, after the subjects began the exercise protocol. The first stage was begun at 50 watts (W) and the workload for all subsequent stages was increased 25W every 2 min until the respiratory exchange ratio exceeded 1.00, subsequently the workload increased 25W every minute until volitional exhaustion. Upon completion of the protocol VO_{2peak} was determined from the highest 20-second average expired O_2 value. This protocol was modified for the HTR to begin at 25W due to the lower expected VO_{2peak} values as described by Scott *et al.*[6].

The criteria for completing the exercise protocol were: leveling off of VO_2, respiratory exchange ratio greater than 1.15, a rate of perceived exertion of 20 (on the 6-20 Borg scale), or heart rate at age-predicted maximal values.

3.5. Statistical Data Analysis

Statistical analyses were performed using PASW version 18.0 for Windows (PASW, Inc. Chicago, Illinois). A one-way repeated measures ANOVA with group by intensity comparisons was applied to identify differences across intensity. Upon establishing the normality of the data using a skewness-kurtosis normality test, comparisons between groups were performed with Fisher's LSD *post hoc* test. Linear Regression was used to determine the relationship between heart rate reserve ($HR_{reserve}$) and age, and years post transplant. Data are presented as means ± standard deviation (SD), and significance was set at $P < 0.05$. All statistical tests were run with and without HTR subject #02.

Chapter Four: Results

4.1. Participant Characteristics

Participant characteristics are shown in Table 3.1. There were no statistical significances in body mass index (BMI), resting BP or resting pulsitility index (PI). By design the DC were younger than the HTR and AM groups. Differences were observed between the HTR and DC as well as the AM and DC groups for resting MCAv and cerebrovascular resistance (CVR). The HTR (inclusive of subject #02) had a lower VO_{2peak} than the AM and DC comparison groups by 27% and 50% respectively (Table 3.1.). When subject #02 and matched controls were excluded, the HTR had a lower VO_{2peak} than the AM and DC comparison groups by 34% and 56% respectively (Table 3.2.). Removal of this subject, however, did not influence any other variables.

4.2. Incremental Exercise Test

Cerebrovascular, cardiovascular and pulmonary responses at rest and during the incremental exercise test are summarized in Table 3.3. (all subjects) and Table 3.4. (without HTR subject #02 and matched controls).

Table 4.1. Cardiovascular, Pulmonary and Cerebrovascular responses at rest and during the incremental exercise test at 50%, 70%, 90% and peak VO_2 (all subjects)

	$MCAv_{mean}$ (cm/s)	$MCAv_{sys}$ (cm/s)	$MCAv_{dia}$ (cm/s)	HR (bpm)	$HR_{reserve}$ (bpm)	BP_{mean} (mmHg)	BP_{sys} (mmHg)	BP_{dia} (mmHg)	PET CO_2 (mmHg)	CVR (mmHg/cm/s)	PI (AU)
Rest											
HTR	40 ± 12	63 ± 20	28 ± 10	93 ± 9	0 ± 0	99 ± 4	123 ± 5	87 ± 7	28 ± 5	2.7 ± 0.7	0.9 ± 0.2
AM	41 ± 7	70 ± 12	27 ± 7	74 ± 10*	0 ± 0	104 ± 19	134 ± 26	82 ± 12	29 ± 3	2.6 ± 0.6	1.0 ± 0.3
DC	69 ± 9†‡	119 ± 18†‡	45 ± 7†‡	72 ± 13†	0 ± 0	91 ± 6	117 ± 11	78 ± 8	37 ± 4†‡	1.3 ± 0.2†‡	1.0 ± 0.2
50% VO_{2peak}											
HTR	46 ± 10	80 ± 19	28 ± 7	107 ± 8	14 ± 5	107 ± 6	149 ± 12	86 ± 7	33 ± 3	2.5 ± 0.6	1.1 ± 0.2
AM	52 ± 10	97 ± 16	29 ± 9	100 ± 10	26 ± 19	110 ± 12	169 ± 21*	81 ± 10	37 ± 3	2.2 ± 0.3	1.3 ± 0.3
DC	84 ± 11†‡	159 ± 23†‡	47 ± 9†‡	122 ± 19†‡	51 ± 7†‡	99 ± 6‡	143 ± 11‡	77 ± 8	43 ± 4†‡	1.2 ± 0.2†‡	1.3 ± 0.2
70% VO_{2peak}											
HTR	47 ± 11	87 ± 22	28 ± 7	125 ± 3	32 ± 11	118 ± 12	176 ± 24	88 ± 10	34 ± 2	2.6 ± 0.8	1.2 ± 0.2
AM	54 ± 8	107 ± 12*	27 ± 8	125 ± 19	51 ± 28	120 ± 13	197 ± 28	81 ± 10	37 ± 2*	2.2 ± 0.4	1.5 ± 0.3*
DC	84 ± 11†‡	162 ± 18†‡	45 ± 10†‡	164 ± 13†‡	92 ± 7†‡	105 ± 6†‡	163 ± 13‡	76 ± 8†	44 ± 4†‡	1.3 ± 0.3†‡	1.4 ± 0.2
90% VO_{2peak}											
HTR	46 ± 11	88 ± 24	25 ± 7	142 ± 7	49 ± 11	126 ± 11	196 ± 17	91 ± 12	32 ± 2	3.0 ± 1.0	1.4 ± 0.3
AM	54 ± 6	112 ± 8*	25 ± 8	143 ± 19	69 ± 28	127 ± 11	214 ± 20	83 ± 10	35 ± 5	2.4 ± 0.4	1.6 ± 0.3
DC	75 ± 8†‡	148 ± 20†‡	38 ± 6†‡	185 ± 8†‡	113 ± 15†‡	109 ± 7†‡	178 ± 9†‡	74 ± 8†	36 ± 4†	1.5 ± 0.2†‡	1.5 ± 0.2
100% VO_{2peak}											
HTR	45 ± 11	88 ± 25	23 ± 7	152 ± 10	60 ± 15	128 ± 9	202 ± 16	91 ± 13	28 ± 3	3.1 ± 1.0	1.4 ± 0.3
AM	53 ± 8	109 ± 13	24 ± 7	154 ± 18	80 ± 28	129 ± 13	221 ± 17*	84 ± 17	32 ± 4	2.5 ± 0.5	1.6 ± 0.2
DC	63 ± 9†	132 ± 24†	28 ± 8	196 ± 5†‡	124 ± 12†‡	111 ± 7†‡	187 ± 12‡	73 ± 8†	28 ± 5	1.8 ± 0.2†	1.7 ± 0.3

Values are means ± SD. Heart transplant recipient (HTR); age-matched (AM); donor population control (DC); middle cerebral artery velocity (MCAv); heart rate (HR); blood pressure (BP); end tidal CO_2 (PET CO_2); cerebrovascular resistance (CVR) and pulsitility index (PI). Statistical significance was set at $P < 0.05$, *denotes significance between HTR *vs.* AM, †denotes significance between HTR *vs.* DC, ‡denotes significance between AM *vs.* DC.

Table 4.2. Cardiovascular, Pulmonary and Cerebrovascular responses at rest and during the incremental exercise test at 50%, 70%, 90% and peak VO_2 (without HTR subject #02 and matched controls)

	$MCAv_{mean}$ (cm/s)	**$MCAv_{sys}$** (cm/s)	**$MCAv_{dia}$** (cm/s)	**HR** (bpm)	**$HR_{reserve}$** (bpm)	**BP_{mean}** (mmHg)	**BP_{sys}** (mmHg)	**BP_{dia}** (mmHg)	**PET CO_2** (mmHg)	**CVR** (mmHg/cm/s)	**PI** (AU)
Rest											
HTR	41 ± 13	64 ± 22	29 ± 10	93 ± 10	0 ± 0	98 ± 3	124 ± 5	85 ± 6	27 ± 5	2.6 ± 0.7	0.9 ± 0.3
AM	42 ± 8	71 ± 12	27 ± 8	76 ± 10*	0 ± 0	98 ± 16	133 ± 28	80 ± 12	29 ± 3	2.5 ± 0.4	1.1 ± 0.3
DC	67 ± 7†‡	113 ± 13†‡	44 ± 7†‡	71 ± 14†	0 ± 0	90 ± 7	117 ± 12	77 ± 9	37 ± 4†‡	1.4 ± 0.3†‡	1.0 ± 0.2
50% VO_{2peak}											
HTR	46 ± 11	79 ± 21	28 ± 8	106 ± 9	13 ± 5	106 ± 7	150 ± 13	84 ± 7	33 ± 3	2.5 ± 0.7	1.1 ± 0.2
AM	51 ± 11	97 ± 18	28 ± 9	99 ± 10	24 ± 19	106 ± 7	165 ± 20	78 ± 5	36 ± 3	2.1 ± 0.4	1.4 ± 0.3
DC	82 ± 10†‡	154 ± 20†‡	46 ± 9†‡	120 ± 20‡	50 ± 7†‡	98 ± 6	143 ± 12‡	76 ± 8†	43 ± 4†‡	1.2 ± 0.2†‡	1.3 ± 0.2
70% VO_{2peak}											
HTR	47 ± 12	85 ± 24	28 ± 7	125 ± 3	32 ± 12	117 ± 13	174 ± 25	90 ± 10	33 ± 2	2.7 ± 0.8	1.2 ± 0.2
AM	54 ± 9	107 ± 13*	27 ± 8	123 ± 20	48 ± 30	118 ± 13	195 ± 30	79 ± 7*	37 ± 2	2.2 ± 0.4	1.5 ± 0.3*
DC	82 ± 11†‡	159 ± 17†‡	44 ± 11†‡	163 ± 14†‡	92 ± 8†‡	104 ± 6	163 ± 14‡	75 ± 8†	43± 4†‡	1.3 ± 0.3†‡	1.4 ± 0.2
90% VO_{2peak}											
HTR	46 ± 13	86 ± 26	25 ± 7	142 ± 8	49 ± 12	125 ± 12	203 ± 18	92 ± 12	32 ± 2	3.0 ± 1.1	1.3 ± 0.2
AM	55 ± 7	113 ± 8*	25 ± 8	143 ± 21	66 ± 30	127 ± 12	218 ± 17	83 ± 11	34 ± 5	2.3 ± 0.4	1.6 ± 0.3*
DC	75 ± 9†‡	149 ± 22†‡	38 ± 7†‡	186 ± 9†‡	115 ± 15†‡	109 ± 7†‡	179 ± 10‡	74 ± 9†	36 ± 4	1.5 ± 0.3†‡	1.5 ± 0.2
100% VO_{2peak}											
HTR	45 ± 12	85 ± 26	24 ± 7	151 ± 10	59 ± 16	130 ± 8	203 ± 17	94 ± 12	28 ± 2	3.2 ± 1.1	1.4 ± 0.2
AM	53 ± 8	111 ± 14	24 ± 7	152 ± 20	77 ± 29	124 ± 6	218 ± 17	78 ± 8*	32 ± 5	2.4 ± 0.3	1.6 ± 0.2
DC	64 ± 9†	136 ± 25†	28 ± 8	195 ± 6†‡	125 ± 13†‡	111 ± 8†‡	187 ± 14‡	73 ± 8†	29 ± 5	1.8 ± 0.2†	1.7 ± 0.3†

Values are means ± SD. Heart transplant recipient (HTR); age-matched (AM); donor population control (DC); middle cerebral artery velocity (MCAv); heart rate (HR); blood pressure (BP); end tidal CO_2 (PET CO_2); cerebrovascular resistance (CVR) and pulsitility index (PI). Statistical significance was set at $P < 0.05$, *denotes significance between HTR *vs.* AM, †denotes significance between HTR *vs.* DC, ‡denotes significance between AM *vs.* DC.

4.3. Rest

Resting mean (Figure 4.1.-A), systolic and diastolic MCAv were not significantly different between the HTR and AM groups; however, these variables were lower in the HTR and AM groups when compared to DC (Table 4.1.). At rest, HR (Figure 4.1.-B) was significantly different for the HTR as compared to both the AM and DC. No significant differences were reported in any of the resting mean, systolic or diastolic BP (Figure 4.1.-C). The DC had higher ($P<0.05$) PET CO_2 levels and lower CVR than both the HTR and AM. No other significant differences were found at rest between the groups (Table 4.1.). When subject #02 was excluded from the analysis, all of the previous findings were unchanged (Table 4.2.).

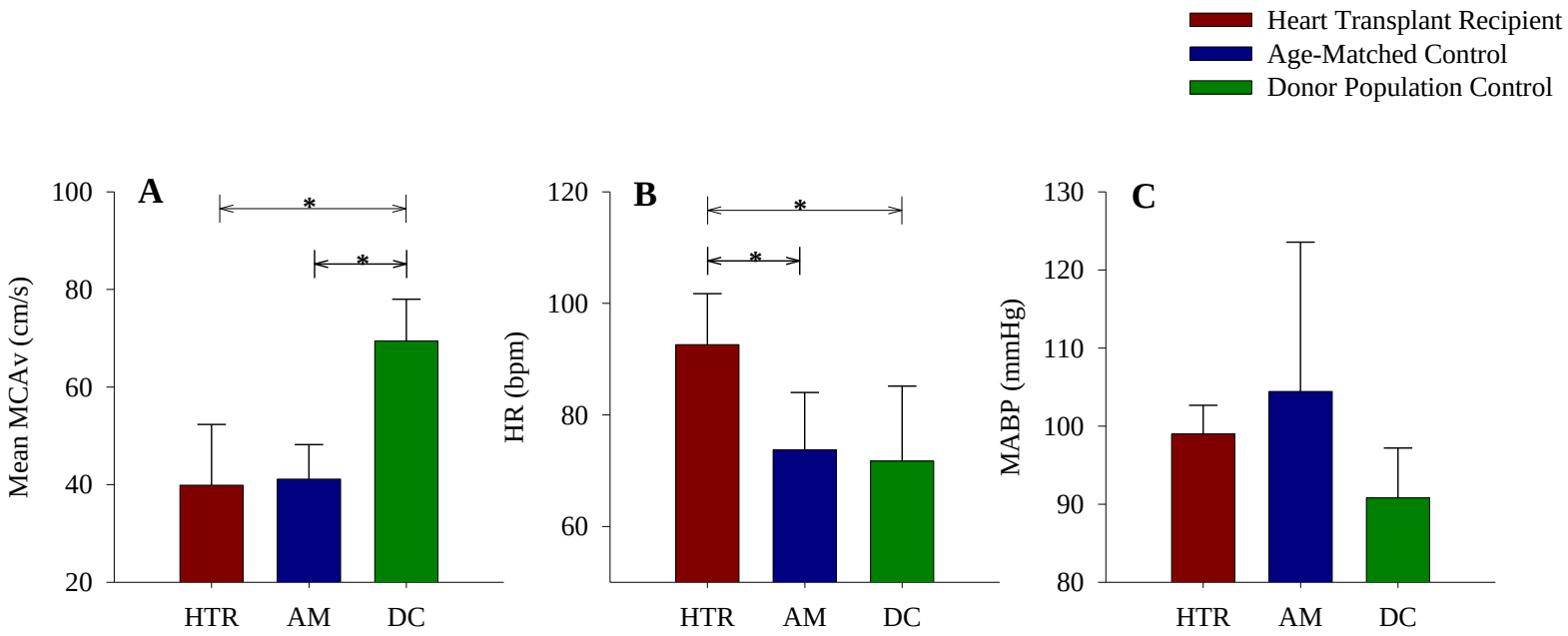

Figure 4.1. Resting values for (**A**) mean middle cerebral artery velocity (MCAv), (**B**) heart rate (HR) and (**C**) mean arterial blood pressure (MABP) for the heart transplant recipient (HTR), age-matched (AM) and donor population control (DC) groups. Statistical significant differences between HTR *vs.* DC and AM *vs.* DC were observed in MCAv and HR, no statistical differences were noted between HTR *vs.* AM for any condition, nor between any of the HTR, AM or DC groups MABP. (Values are means ± SD. *denotes, $P < 0.05$)

4.4. VO_{2peak}

Relative VO_{2peak} for all subjects (Figure 4.2.-A; Table 3.1) values for the HTR (25.4 ± 10.4 mL/kg/min) and AM (35.0 ± 8.7 mL/kg/min) were significantly lower than the DC (50.6 ± 6.7 mL/kg/min) (Table 3.1.). The HR_{peak} (Figure 4.3.-A) and $HR_{reserve}$ (Figure 4.3.-B) for the DC were significantly higher than both the HTR and AM groups, and there was a trend toward lower relative VO_{2peak} and $HR_{reserve}$ between HTR and AM ($P = 0.055$, and $P = 0.071$ respectively). When subject #02 was excluded from the analysis, there was a significant difference observed in the VO_{2peak} between the HTR and AM groups (Figure 4.2.-B; Table 3.2.).

At VO_{2peak}, mean and systolic MCAv were significantly lower in the HTR as compared to the DC, but not significantly different from the AM. The DC had lower MABP than both the HTR and AM ($P<0.05$). Systolic BP was higher in the AM group, compared with both the HTR and DC. The only other significant difference in BP at VO_{2peak} was the lower diastolic BP for the DC when compared with the HTR. The DC also had lower ($p<0.05$) CVR when compared to the HTR. All other cerebrovascular, cardiovascular and cardiorespiratory VO_{2peak} responses were not different between the HTR, AM and DC groups with all subjects included (Table 4.1.). The exclusion of subject #02 resulted in the same findings except the significant differences observed between the HTR and AM groups in BP did not occur in the mean BP; rather, they occurred in both diastolic BP at both 70%and 100% of VO_{2peak} (Table 4.2.).

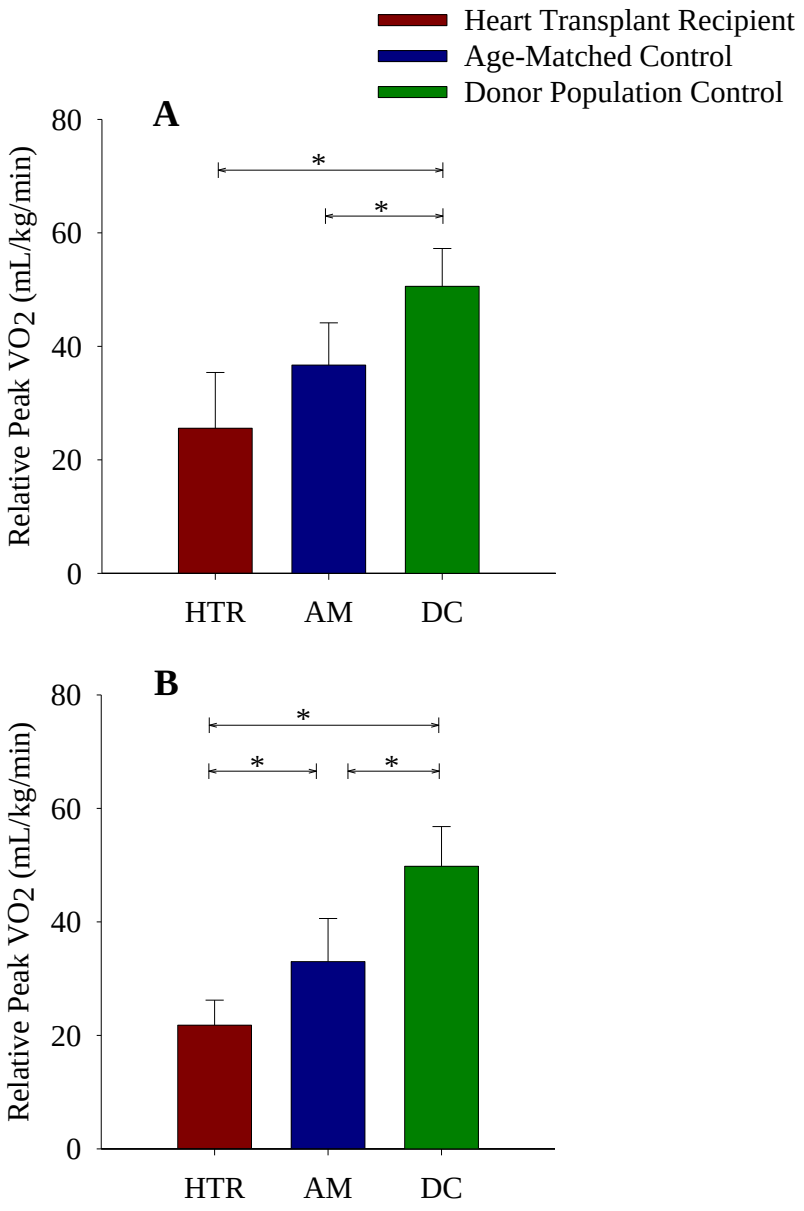

Figure 4.2. Relative VO_{2peak} for the heart transplant recipient (HTR), age-matched (AM) and donor population control (DC) groups. (**A**) Data shown with the inclusion of all subjects, (**B**) Data shown with the exclusion of HTR subject #02. Statistical significant differences were observed between HTR *vs.* DC and AM *vs.* DC. Values are means ± SD. *denotes, $P < 0.05$.

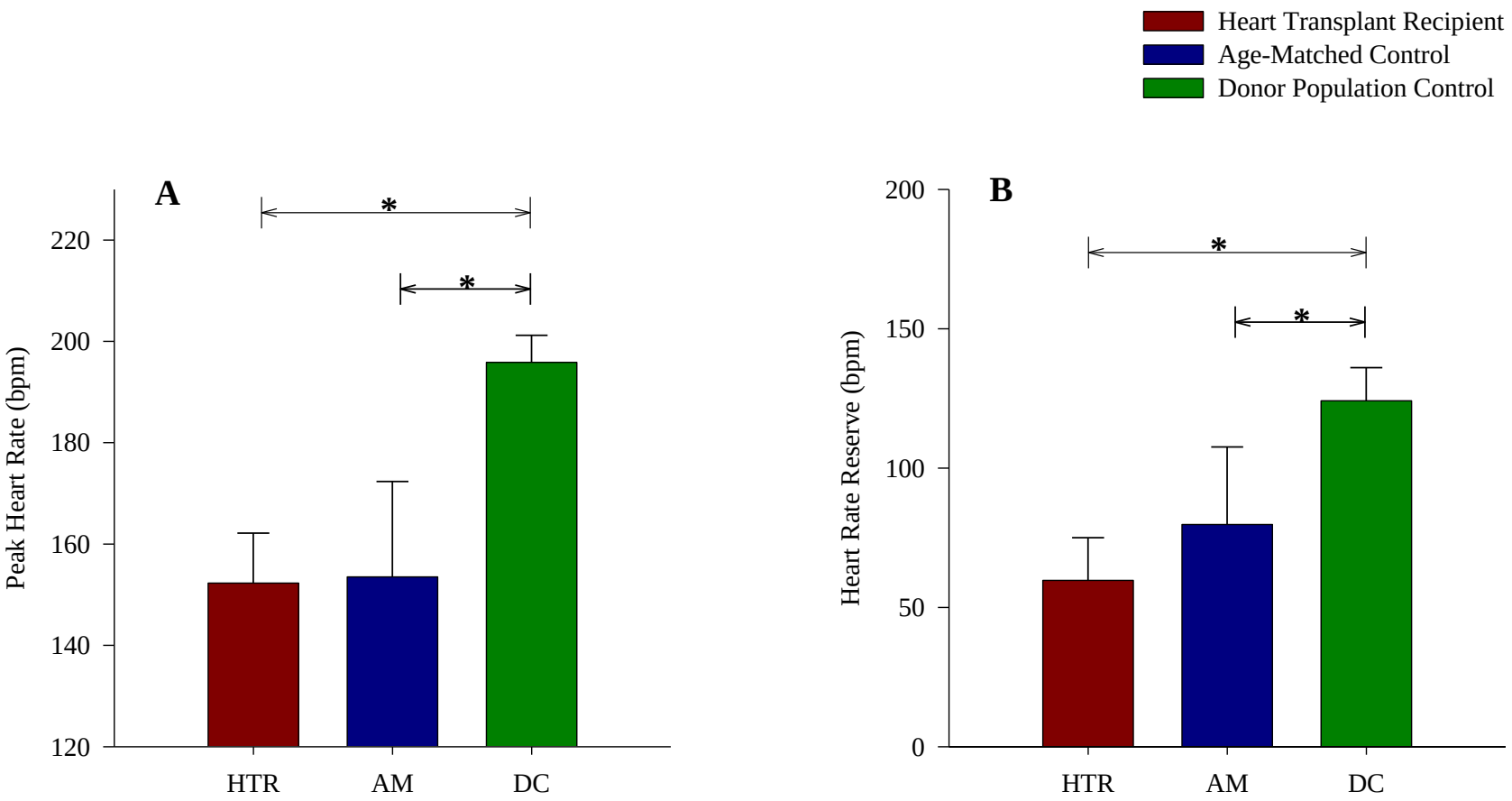

Figure 4.3. (**A**) Peak heart rate (HR_{peak}) and (**B**) heart rate reserve ($HR_{reserve}$) for the heart transplant recipient (HTR), age-matched (AM) and donor population control (DC) groups. Statistically significant differences observed between the HTR *vs.* DC and AM *vs.* DC in both HR_{peak} and $HR_{reserve}$. Although there were no statistically significant differences for either condition between HTR *vs.* AM, a lower trend was observed in $HR_{reserve}$ (P = 0.071). Significance between the HTR *vs.* AM groups was not reached upon the exclusion of subject #02 (not shown). Values are means ± SD. *denotes, $P < 0.05$.

4.5. $HR_{reserve}$ Relationships

There was a significant negative relationship associated with $HR_{reserve}$ and age for the life-span of the entire subject pool (Figure 4.4.-A). There was also a significant individual group relationship between $HR_{reserve}$ and age for the AM group ($R^2 = 0.79$, $P = 0.008$; data not shown). There was no $HR_{reserve}$ relationship for either the HTR ($R^2 = 0.13$, $P = 0.429$) or DC ($R^2 = 0.02$, $P = 0.778$). The $HR_{reserve}$ for the DC were significantly higher than both the HTR and DC throughout the incremental exercise test (Table 4.1. and Table 4.2.). The HTR also showed a lower trend in $HR_{reserve}$ as compared to the AM during the test; however significance was never reached (mild, $P = 0.080$; moderate, $P = 0.070$; intense, $P = 0.075$). There was no evident relationship between $HR_{reserve}$ with years after transplant (Figure 4.4.-B) with or without HTR subject #02.

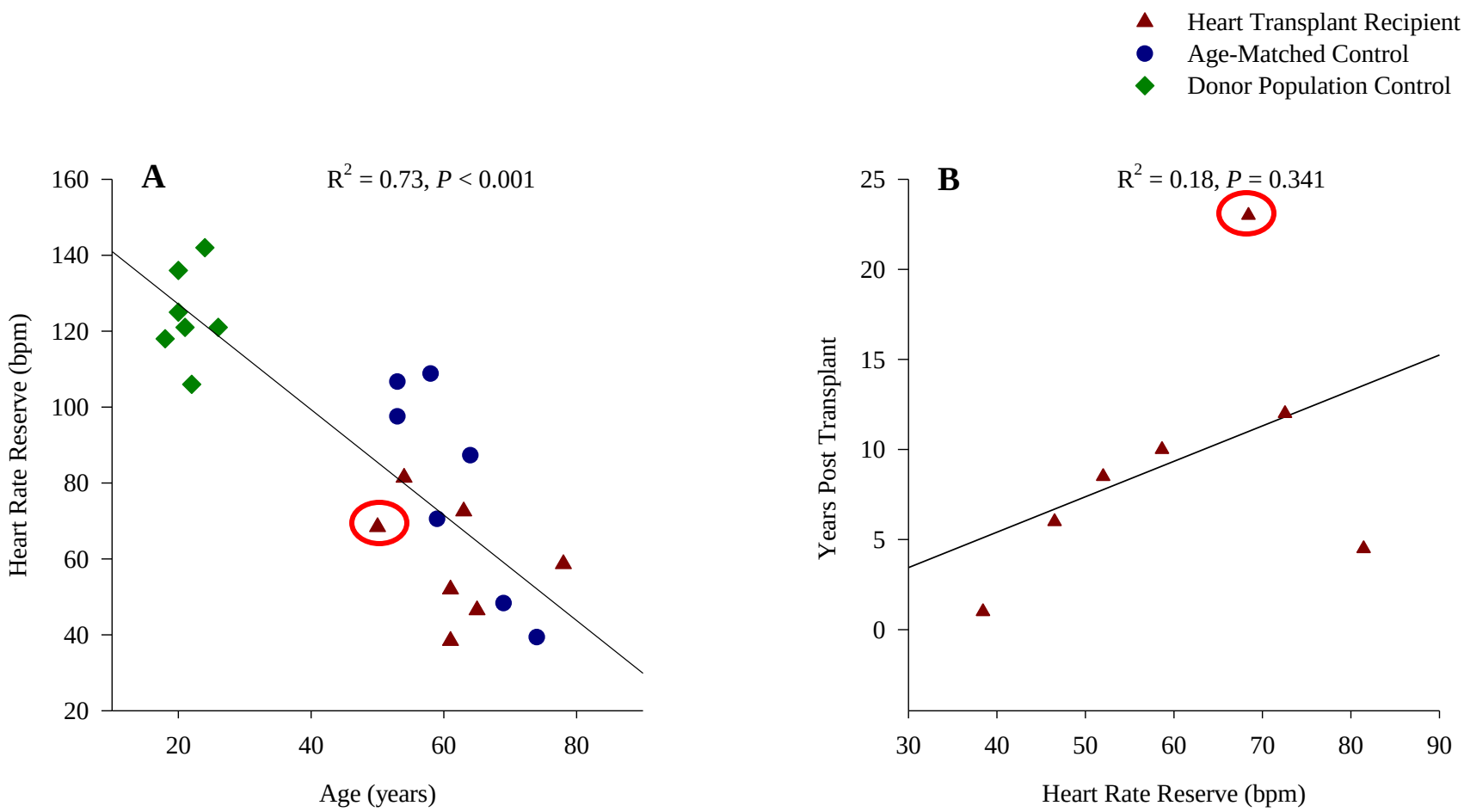

Figure 4.4. (**A**) Overall relationship between heart rate reserve ($HR_{reserve}$) and age of all subjects - heart transplant recipients (HTR), age-matched (AM) and donor population controls (DC); and (**B**) the relationship between $HR_{reserve}$ and years post transplant. Although not plotted, the relationship between age and $HR_{reserve}$ for each group (A) are as follows: HTR ($R^2 = 0.13$, $P = 0.429$), AM ($R^2 = 0.79$, $P = 0.008$), DC ($R^2 = 0.02$, $P = 0.778$). Red circle indicates subject #02.

4.6. Mild, Moderate and Intense Exercise

During mild (50% of VO_{2peak}), moderate (70% of VO_{2peak}) and intense (90% of VO_{2peak}) exercise, $MCAv_{mean}$ (Figure 4.5.-A) was higher ($P<0.05$) in the DC compared to both the HTR and AM. However, $MCAv_{mean}$ was not significantly different between the HTR and AM groups. From rest to mild exercise the $MCAv_{mean}$ for the DC demonstrated a large increase, plateaued as intensity increased to the moderate level, followed by a sharp decline as peak intensity was reached. The HTR and AM groups demonstrated a different trend; both groups had a steady increase in $MCAv_{mean}$ up to the moderate intensity level, after which a plateau was obtained that continued to the end of the test to VO_{2Peak} (Figure 4.5.-A).

The HTR, AM and DC groups all demonstrated a trend of BP increasing with exercise intensity (Figure 4.5.-B). During mild exercise the AM was significantly higher than the DC; however, HTR was not significantly different from either the AM or the DC. In moderate exercise, intense and peak exercise the HTR and AM group were not different in BP; however, they were higher than the DC.

The PET CO_2 response (Figure 4.5.-C) for all three groups showed a similar trend to one another from rest to mild exercise, at which point the DC were significantly higher than both the HTR and AM. All three groups experienced a small increase during moderate exercise and were significantly different from each other with DC and HTR having the highest and lowest values respectively. The DC group experienced a sharper decline in PET CO_2 during intense exercise than the HTR and AM groups; the only significant difference during intense exercise was between the HTR and DC. There were no differences in PET CO_2 during peak exercise (Table 4.1. and Table 4.2.).

Across majority of the incremental exercise test spectrum, the CVR of the HTR and AM were higher than the DC (Figure 4.5.-D; $P<0.05$). Only at peak exercise intensity did this change, at which point only the CVR of the HTR was significantly higher than the DC; there were no differences between the HTR and AM groups. There where no significant changes to the results when subject #02 was excluded from the analysis (Table 4.2.).

During mild exercise, systolic MCAv (Figure 4.6.-A) for the DC was significantly higher than the HTR and AM. All three groups were different during moderate and intense exercise; DC was higher than AM, and the HTR were lower than AM. There was a slightly different pattern demonstrated in the diastolic MCAv (Figure 4.6.-B). For example, throughout the entire incremental exercise test, there were no differences between HTR and AM; however, the diastolic MCAv for DC was higher ($P<0.05$). Only at peak exercise did the diastolic MCAv for the DC decrease enough that there was no longer any significant differences amongst the groups. The only difference in PI throughout the incremental exercise test occurred during moderate exercise. At which point the HTR were lower ($P<0.05$) than the AM (Figure 4.6-C; Table 4.1).

When subject #02 was removed from the analysis, there were no significant changes in the systolic or diastolic MCAv data (Table 4.2.). However, during the analysis of the PI there were two changes to the significance findings: a difference between the HTR and AM at 90% VO_{2peak} and between the HTR and DC at 100% of VO_{2peak}.

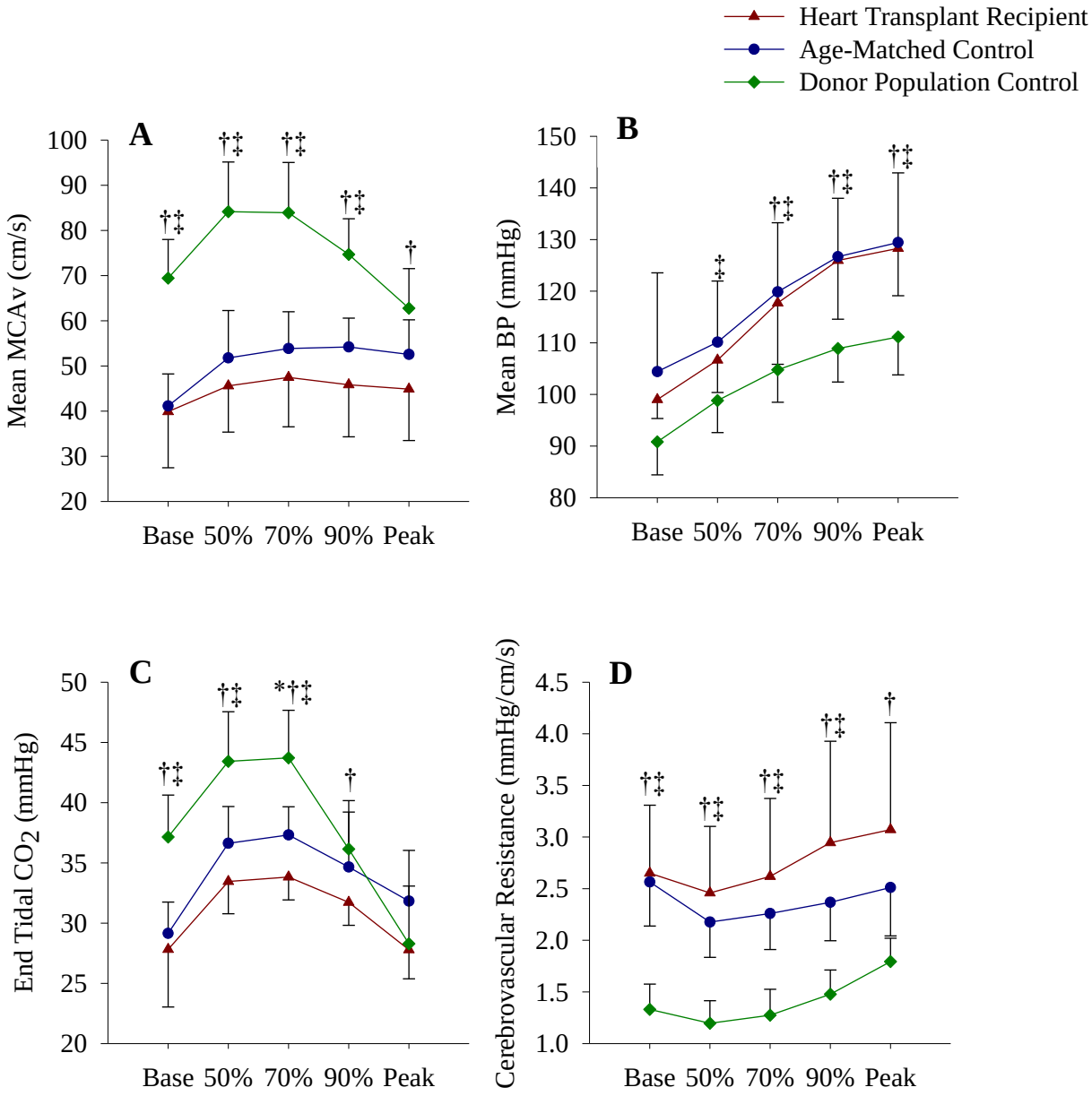

Figure 4.5. (**A**) Mean middle cerebral artery velocity (MCAv), (**B**) mean blood pressure (BP), (**C**) end tidal CO_2 (PET CO_2), and (**D**) cerebrovascular resistance (CVR) values for the heart transplant recipient (HTR), age-matched (AM) and donor population control (DC) groups across the incremental exercise test. (Values are means ± SD. *denotes between HTR *vs.* AM, †denotes significance between HTR *vs.* DC, ‡denotes significance between AM *vs.* DC. Statistical significance was set at $P < 0.05$). Data shown is for all subjects.

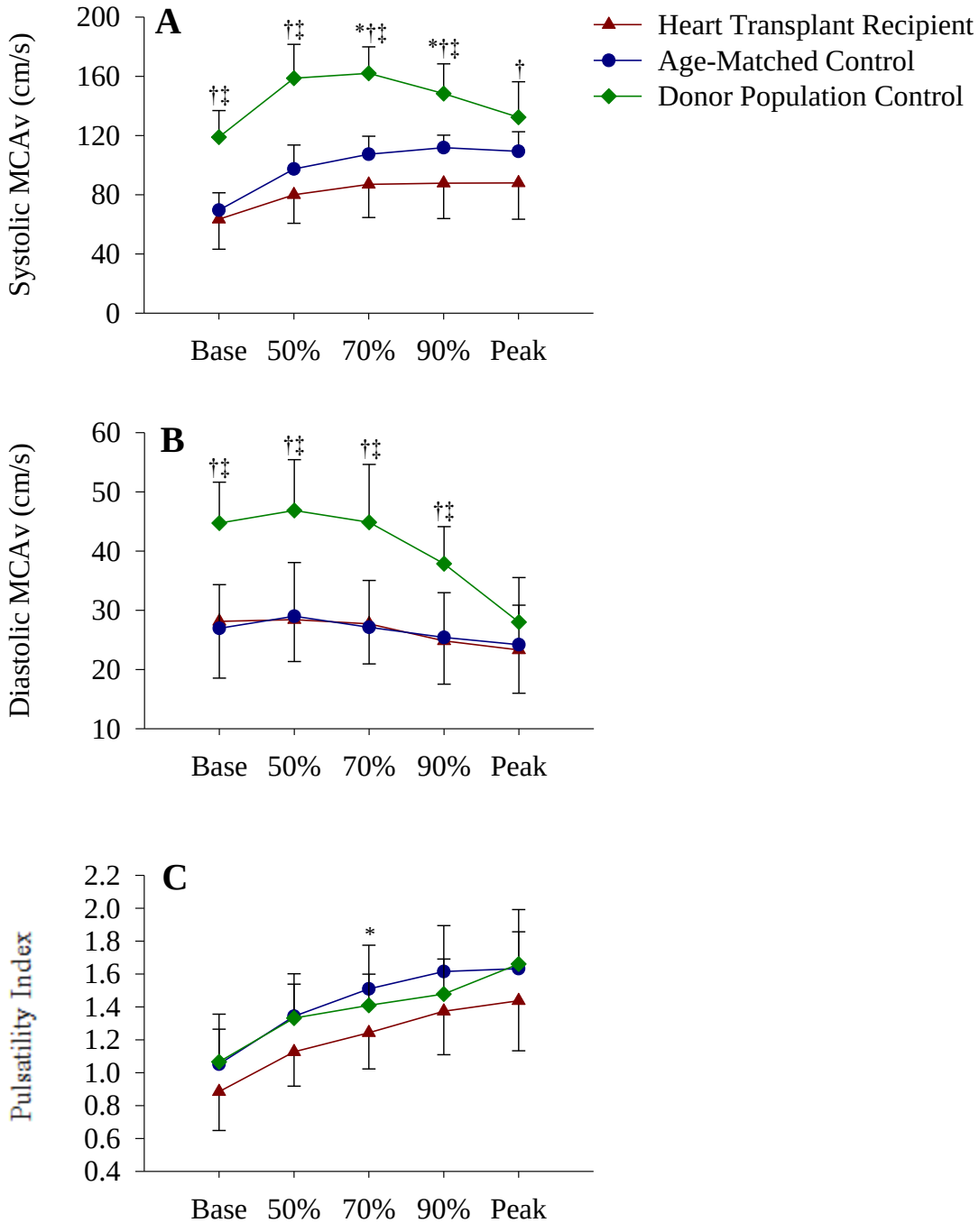

Figure 4.6. **(A)** Systolic middle cerebral artery velocity (MCAv), (**B**) Diastolic MCAv, and (**C**) Pulsatility Index (PI) values for the heart transplant recipient (HTR), age-matched (AM) and donor population control (DC) groups across the incremental exercise test. (Values are means ± SD. *denotes between HTR *vs.* AM, †denotes significance between HTR *vs.* DC, ‡denotes significance between AM *vs.* DC. Statistical significance was set at $P < 0.05$). Data shown is for all subjects.

Chapter Five: Discussion and Conclusion

5.1. Principle Findings

The two novel principle findings of this study were: 1) Although the general pattern of change in mean MCAv was comparable during exercise in HTR compared to AM, systolic MCAv was selectively reduced in the HTR during moderate and intense exercise; and 2) When compared to DC, a comparable 'relative' elevation in mean MCAv was evident from rest to light intensity exercise; however, HTR and AM controls did not display comparable declines in MCAv at exercise intensities 70% of VO_{2peak} and greater. At these higher intensities the HTR and AM MCAv declines were similar to each other but blunted when compared to the DC. These findings were unaltered with and without the inclusion of the highly trained HTR; subject #02 (Table 4.1. and 4.2.). Collectively, the similarities in the CBF response between HTR and AM during exercise are remarkable and highlights that a 'younger' denervated donor heart does not adversely impact on CBF at rest or during exercise, even with the presence of immunosuppressive therapy and likely stiffer vasculature in HTR. Nevertheless, the influence of medication and/or arterial stiffness in the HTR may underpin the apparent differences in systolic MCA velocity and pulsation.

5.2. Influence of HT on CBF at Rest - Comparison with Previous Studies

To date, as mentioned, only three studies have quantified CBF following HT[30-32]. Gruhn *et al.*[31] reported that CBF was reduced in patients with severe chronic heart failure by approximately 30% and that these levels were normalized with heart transplantation one month after transplant. When the patients were re-examined at six months post transplant,

the CBF values did not differ from those observed one-month post. Ackerman[138] wrote an editorial in response to the 2001 Gruhn *et al.*[31] study and criticized the lack of data on hematocrit levels, as they have observed that hematocrit levels are lower in HTR – it was suggested that the lower hematocrit levels would reduce the viscosity in the blood and be able to account for virtually all of the increase in CBF. Massaro *et al.*[30] did report increases in CBF in all 14 of their subjects one month after receiving the HT; however, they were unable to correlate the 53% increase in CBF to the lower mean hematocrit levels. In the final study, Choi *et al.* [32] presented data on four patients with chronic heart failure that underwent heart transplantation; global CBF was raised by 25% two to four months post surgery. Our study is the first report of how CBF is altered over the longer term (i.e. years – 1 to 22 years) following HT. Our findings show that CBF (as indexed by TCD) in HTR is similar to age-matched controls at rest (Table 4.1. and Table 4.2.). Based on the lack of correlational data between hematocrit and MCAv in the findings by Massaro *et al.*[30] (HTR) and the confirmation by Baufreton *et al.*[158] (healthy humans), we feel that MCAv values that were observed in the current study were not influenced by the hematocrit levels of either the HTR or their controls.

5.3. Young Heart, Old Brain: Influence of Aging on CBF

Over the course of normal human aging, physiological and psychological changes occur that result in the structural and functional alterations of the cardiovascular and cerebrovascular systems[171, 172]. These alterations result in observed decreases in CBF over that possibly reflect a global decrease in cerebral perfusion[151]. Ainslie *et al.*[151], quantified this decline in CBF as a decrease in MCAv of approximately 1% per year through a

comprehensive study of 307 healthy male subjects. Another key finding from this study was that regular endurance exercise training results in an increase in MCAv of approximately 17% across the aging spectrum[151]. It was speculated that the underlying mechanisms for these improvements in CBF were due to the numerous cardiovascular benefits that are associated with regular physical training[151]. These results also demonstrate that 'normal' is really only a point of reference for comparison as living a healthy and active lifestyle can potentially delay pathological disorders that result in age-associated cerebrovascular related brain diseases[151]. With healthy aging, CBF declines 25-30% between 20 and 80 years of age[151, 173]. Similarly, a longitudinal study by Fotenos *et al.*[174] has shown there to be a reduction of 0.45% per year in total brain volume after 30 years of age.

As expected, resting MCAv (Figure 4.1.-A; Table 4.1. and Table 4.2.) was higher in the DC compared with the AM and HTR participants[173]. Interestingly, despite a 'younger' heart, the HTR had comparable declines in CBF as the AM controlled (Figure 4.5.-A). Thus, this apparent reduction in resting MCAv with age is likely due to the reduction in brain volume[174] and therefore metabolism and blood flow[175] rather than age- and HTR-related differences in cardiac function. In other words, an 'old brain' is the fundamental cause of cerebral hypoperfusion rather than a 'young heart' as the CBF in the HTR are responding in a similar fashion to the AM, even though their heart is more similar in age to the DC.

5.4. Influence of HTR on CBF Alterations During Exercise

$MCAv_{mean}$ was elevated ~20% in response to sub-maximal exercise in the young and older individuals with and without HT (Figure 4.5.-A). This magnitude of increase is similar to that observed by other authors in young participants[100] and recently in old[176]. It is well

established, at least in healthy young humans, that MCAv is intensity dependent up until ~70% of VO_2 max, after which it declines to near resting levels due to hyperventilation-induced hypocapnia[120, 121]. Below the ventilatory threshold the increase in CBF with exercise is likely driven by increases in $PaCO_2$ and cerebral metabolism, as a result of increased functional activation with motor activity[100]; however, above this intensity, the large disproportional increase in ventilation results in a reduction in $PaCO_2$ and concomitant reductions in CBF despite progressive elevations in the cerebral metabolism.

In contrast, in both HTR and age matched controls, we did not observe comparable declines in MCAv at maximal exercise intensity as evident in the AM (Figure 4.5.-A, Table 4.1. and Table 4.2.); thus, this influence seems to be due to age *per se* rather than related autonomic and vascular changes associated with HT. The mechanisms by which older adults are less able to exhibit comparable levels of hypocapnia (mediated via exercise-induced hyperventilation) are not clear, but may be as a result of factors such as reduced lung and chest wall compliance[177, 178], respiratory muscle fatigue[179], and differences in age-related chemosensitivity[180, 181].

5.5. Influence of Aging on End-Tidal PCO_2

A number of factors may explain the apparently age-related reductions in PET CO_2 (Table 4.1. and Table 4.2.). Fundamentally, arterial PCO_2 can be altered via respiratory mechanisms (alveolar ventilation) and renal (or acid-base) mechanisms (bicarbonate filtration/reabsorbtion). In the respiratory system, arterial PCO_2 diffuses from the blood stream into the alveoli where it can be expelled directly from the body. In the renal system, bicarbonate is filtered by the glomeruli into the renal tubules, when bicarbonate levels are

below 24 mM/L, virtually all of the bicarbonate is reabsorbed, when bicarbonate levels exceed 28 mM/L, the excess above this value is expelled in the urine[182].

With aging, there is decrease in the steady-state bicarbonate ion concentration and an increase in steady-state blood proton concentration[183]. Decreases in $PaCO_2$ with aging can be attributed to the progressive metabolic acidosis occurring due to the normal decline in renal function: reduction in size and number of glomeruli, impairments in electrolyte transfer in the renal tubules, and a decrease in renal blood flow[184] which result in less bicarbonate filtration occurring. As well as the subsequent respiratory adaptations: less compliant chest wall, decrease in strength of respiratory muscles, alveoli dilatation, enlargement of airspaces, decrease in exchange surface area which combine to result in a decrease in air exchange within the lungs[185]. These myriad of factors, alone or in combination, would seems to explain the higher baseline PET CO_2 in DC as compared with the HTR and AM populations (Figure 4.5-C).

5.6. Differential Changes in Systolic MCA Velocity and Pulsatility Index

The superior location of the brain with respect to the heart means that a higher pressure, pulsatile flow may be more effective at overcoming the effect of gravity and maintaining CBF[186]. Systolic MCAv was generally lower in the HTR across all exercise intensities but only reached statistical significance with the AM at 70% and 90% of the VO_{2peak} (Table 4.1. and Table 4.2.; Figure 4.6.-A) i.e., a intensity close to or above the aerobic threshold. However, when subject #02 was removed from the analysis, the PI of the AM controls was also significantly higher than the HTR at 70% and 90% (Table 4.2.). The higher trends shown systolic BP for the AM (Table 4.1. and Table 4.2.) in conjunction with

the PI and systolic MCAv indicate that there may be a stiffening of the vasculature that is responsible for these changes. Alternatively, the related reductions in BP at the higher exercise intensities in HTR were similar to the findings of Braith *et al.*[3]. These reductions may be explained by the structural alternations experienced in the HTR during their low-flow state of CHF[3]; such changes may have led to an impairment in peripheral vasoconstrictor responsiveness post transplant[3].

Recently, Laurent *et al.*[187], when observing the effects of systolic blood pressures in the circulatory system it is best to utilize propagative models (i.e. the Moens-Korteweg equation) as they assume the velocity at which the pulse wave travels along the vessel will have a finite value. Laurent *et al.*[187] suggested that applying propagative models will represent a more realistic approach to how the arterial tree functions as a propagative model that is composed of a simple distensible vessel that terminates at the peripheral resistance and has elastic properties, which allow for the generation of pressure waves. Using this notion, it is possible to understand how the increase in arterial stiffness would increase the cerebral perfusion pressure, and result in an increase in the systolic BP which would most likely influence the systolic MCAv and PI as noted in Table 4.1. and Table 4.2.

Furthermore, the PI (Figure 4.6.-C) was increased in response to exercise in the all of the groups (HTR, AM and DC). These increases in PI may be a result of changes in vascular tone that are due to the increased systolic BP and/or alterations in PET CO_2 which indirectly influences this variable (Table 4.1. and Table 4.2.). A decreased resistance/higher compliance system is beneficial, reducing the capacity of the vascular bed to respond to transient alterations in blood flow. It appears as though the HTR are well adapted to maintain

cerebral perfusion during exercise as well as both the AM and DC (Table 3.3.). This is a novel finding and warrants further investigation.

5.7. Limitations

5.7.1. TCD Ultrasound

A limitation of TCD ultrasound is that it only measures CBF velocity (cm/s) and is not a measure of true CBF volume (mL/min/100g). However, numerous studies have shown that the cross-sectional area of the conduit vessels in the brain remain constant[163, 165-167] and as such the changes that are observed in CBFv are directly proportional to the global CBF both at rest and during exercise[100,101]. It is recognized that changes in vessel diameter will significantly alter blood flow (radius to the fourth power, Equation 1.). However, several studies have measured vessel diameter directly measured in humans, over a wide range of mean arterial pressures and PET CO_2, with diameter remaining relatively stable[163, 165-167].

The quality of the TCD ultrasound signal is also dependant upon sufficient penetration of the temporal acoustic window. As we age, there is a general reduction in the quality of the acoustic window, Marinoni *et al.*[188] have suggested that over time there may be changes to the reflection, scattering and absorption qualities, due to the effects of osteoporosis resulting in an increase in the amount of inadequate windows from 3.0% of males younger than 30 to 7.6% of males over 60 years old[188].

5.7.2. Activity Matching

The HTR and AM controls were matched for BMI and activity levels; however, the young controls were recruited from a university based population and were not matched based on activity; they were only matched with BMI. This may have resulted in a slight portion of the elevated MCAv values reported for the DC, as previous studies have shown that there can be up to a 17% increase in MCAv associated with long-term endurance training, irrespective of age[151]. However, subject #02 did not show an increased MCAv as compared with the rest of the HTR and AM which is probably due to a sample size issue as a larger *N* (>45) is typically needed to show a fitness influence on CBF[189].

5.8. Implications

5.8.1. MCAv at Rest

The MCAv at rest in the HTR is comparable with their age and activity matched controls. When compared with the DC, the MCAv in both the HTR and AM groups were significantly lower, suggesting that the 'older' brain and cerebrovasculature of the HTR plays a greater role than that of the 'younger' heart.

5.8.2. MCAv During Incremental Exercise

During the incremental exercise test, the MCAv in HTR responded in a similar fashion as that of the AM, with and without the inclusion of subject #02.

The MCAv responses in both the HTR and AM did not decrease at the same rate as the DC during the higher exercise intensities (90% and 100% of VO_{2peak}). During the incremental exercise test there was very little variation in the PET CO_2 and MCAv for both the HTR and AM. However, the DC responded in a similar fashion up to aerobic threshold; at higher exercise intensities, the DC experienced a dramatic decrease in both the PET CO_2 and MCAv (Figure 4.5.; Table 4.1. and Table 4.2.). This finding highlights the powerful role of PaCO2 on MCAv, irrespective of the age of the brain or heart.

5.8.3. MCAv in HTR With and Without Subject #02

The removal of the 'fit' HTR did not alter any of the main MCAv findings of this study. Unfortunately, with only one highly fit HTR, it is not possible to examine the long-term training effects on MCAv in HTR as there was simply not a large enough sample size (n>45; [189]) to show the training effects on MCAv. A further study should be conducted with a much larger n to determine the effects of long-term training in HTR on MCAv.

5.9. Future Studies

To further understand the relationship between CBF and HTR, the following studies are proposed:

5.9.1. Effects of Long-Term Endurance Training on CBF in HTR

This study is proposed because the removal of the long-term trained HTR did not alter any of the main MCAv findings of this study. This was most likely due to the

extremely low n (1) and a larger sample (n>45) would be most likely to show the training effects of HTR on MCAv.

5.9.2. Longitudinal Study of CBF in HTR

This study only provides a cross-sectional insight in the effects of long-term HT on CBF. A study that follows a group of HTR throughout their post-transplant experience would enable a broader picture of the true long-term effects of HT on CBF regulation.

5.9.3. Effects of Incremental Exercise on CBF in End-Stage Heart Failure Patients

This study is proposed because the literature has shown that there is a known decrease in CBF in patients with end-stage heart failure[32, 141-144]. Also, a VO_{2peak} of less than 15.0 mL/kg/min is one of the criteria for receiving a HT. It would be interesting to compare the CBF results of a population with a greatly reduced VO_{2peak} to the HTR individuals in this study. This could provide more insight into the benefits of HT on CBF.

5.10. Conclusion

During both rest and throughout the incremental exercise test, the HTR and AM had similar responses in their CBF, and these responses were different from DC. These findings held true with and without the inclusion of subject #02. Thus leading to the conclusion, that despite a suppressed $VO_{2\ Peak}$ (and likely Q) cerebral blood flow is well maintained during incremental exercise in long – term heart transplant recipients.

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Appendices

Appendix I: Participant Information Sheet

INFORMATION SHEET

CARDIAC FUNCTION, CEREBRAL BLOOD FLOW AND ARTERIAL BLOOD PRESSURE DURING VENTILATORY CHALLENGE, CARDIAC UNLOADING AND CYCLE EXERCISE, IN HEART TRANSPLANT RECIPIENTS

INVESTIGATORS

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BACKGROUND AND PURPOSE

Heart transplant recipients have reduced cardiac output (pumping capacity of the heart) during exercise or cardiac (un)loading (as occurs when going from lying to standing position quickly). The effect that reduced cardiac output reserve has on blood flow to the brain (called cerebral blood flow) has not been studied in heart transplant recipients. The aim of this study is to assess the acute effect of a ventilator challenge, cardiac unloading, and cycle exercise on cardiac function, cerebral blood flow and arterial blood pressure in heart transplant recipients and age-matched healthy individuals.

DESCRIPTION OF THE STUDY

If you decide to participate in this study, the total time commitment will be one extra visit (4 hours) at the Alberta Cardiovascular and Stroke Research Centre in the Mazankowski Alberta Heart Institute. Refusal to participate in this study will not affect your treatment at the University of Alberta Hospital.

RESEARCH PROCEDURES

Assessment of cardiac function, cerebral blood flow and arterial blood pressure during ventilatroy challenge.

Prior to this test, we will measure your height and weight. A number of electrodes (electrical contacts) will be placed on your chest and connected to a computer to measure your heart rate. A small cuff will be placed on your finger to measure your blood pressure. A special headpiece with an ultrasound probed attached to it that will be positioned on your head to measure the blood flow to your brain. Some gel and an ultrasound probe will be placed on your chest to measure your cardiac function. You will also be fitted with a nose clip and will breathe through a special mask that will be attached to a computer that will analyze your oxygen uptake and carbon dioxide (CO_2) production. After resting measures are obtained, you will breathe a gas mixture (5% CO_2 in 21% O_2) for 3 min, followed by a brief recovery. You will then be asked to increase your breathing rate and depth for 3 minutes.

Assessment of cardiac function, cerebral blood flow and arterial blood pressure during cardiac unloading tests.
After a 10-15 minute rest period of lying flat on your back, you will be instructed to sit up and stand as quickly as possible (within 3 seconds) during which time your heart rate, blood pressure and cerebral blood flow will be measured.

After a brief rest period, you to lie on your back in a comfortable, relaxed position with your legs inside a custom built lower body pressure chamber. The chamber will be sealed snuggly around your waist. During the test, the pressure inside the chamber will be reduced with a household vacuum to alter the amount of blood returning to the heart. After a 5-miunte rest period, you will undergo three (-10 mmHg, -20mmHg and -40 mmHg for 10 minutes at each stage) levels of decreased pressure during which time your heart rate, blood pressure, heart function and cerebral blood flow will be measured. If you become lightheaded, dizzy, or your blood pressure begins to drop the test will be stopped.

Assessment of cardiac function, cerebral blood flow and arterial blood pressure, during cycle exercise. After resting measures of your heart rate, blood pressure, cardiac function, cerebral blood flow and oxygen uptake (using a special mouthpiece and collection tube attached to a computer that measures your O_2 consumption) are obtained, you will begin cycling at a comfortable speed and the resistance that you will pedal against will become more difficult every two minutes until you feel you are no longer able to continue cycling. This test will be test will be completed in 10-15 minutes.

A specially trained health care worker will supervise the above tests.

POSSIBLE BENEFITS
This study will determine your heart function, cerebral blood flow and blood pressure during a ventilatory challenge, cardiac unloading and during cycle exercise.

POSSIBLE RISKS
During the lying to stand test you may feel lightheaded. During the lower body negative pressure test you may feel lightheaded or become unconscious, however, your heart rate, blood pressure, cardiac function and cerebral blood flow will be carefully monitored to prevent this from occurring. In addition, the pressure will be returned to normal immediately to reduce the feeling of light-headedness. The inflated finger cuff used to measure your blood pressure may result in a numb feeling that will disappear when the cuff is removed. The exercise that you will perform is considered safe. All testing and exercise sessions will be performed under appropriate supervision. Data from individuals with/without heart disease suggests that the likelihood of having a heart attack or dying during an exercise test is 1 in 10,000 tests. The mouthpiece that is used during the exercise test may make your mouth feel dry. You may also experience temporary muscle soreness after exercising. There are no adverse effects associated with cardiac or cerebral ultrasound.

COSTS
You will not have to pay for the tests that you will perform in this study. However, you may be coming to the University of Alberta more often than if you were not participating in this study. You will be reimbursed for your parking and food costs associated with participating in the study**.**

CONTACTS
Please contact the investigators listed below if you have any questions or concerns:
M. Haykowsky, PhD at (780) 492-5970 W. Tymchak, MD FRCPC (780) 407-1574

CONFIDENTIALITY

Personal records will be kept confidential. Only the persons listed above will have access to your data. Any report published as a result of this study will not identify you by name.

For this study, the researchers will need to access your personal health records for health information such as medical history and test results. The health information collected as part of this study will be kept confidential unless release is required by law, and will be used only for the purpose of the research study. 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.

In addition to the investigators listed, the Health Research Ethics Board may have access to your personal health records to monitor the research and verify the accuracy of study data.

By signing the consent form you give permission for the collection, use and disclosure of your medical records. Study information is required to be kept for 7 years. Even if you withdraw from the study, the medical information which is obtained from you for study purposes will not be destroyed. You have a right to check your health records and request changes if your personal information is incorrect.

VOLUNTARY PARTICIPATION

You are free to withdraw from this study at any time without giving a reason. If knowledge gained from this study or any other study becomes available which could influence your decision to continue, you will be promptly informed. If you have any questions or concerns about any aspect this study, you may contact the Health Research Ethics Board at 492-9724. This office has no affiliation with the study investigators.

Appendix II: Participant Consent Form

CONSENT FORM
CARDIAC FUNCTION, CEREBRAL BLOOD FLOW AND ARTERIAL BLOOD PRESSURE DURING VENTILATORY CHALLENGE, CARDIAC UNLOADING AND CYCLE EXERCISE, IN HEART TRANSPLANT RECIPIENTS

INVESTIGATORS

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P. Ainslie, Ph.D.	UBCO, Human kinetics	(250) 807-8089

Please answer the following questions:

	Yes	**No**
Do you understand that you are being asked to be in a research study?	___	___
Have you read and received a copy of an attached information sheet?	___	___
Do you understand the benefits and risks in taking part in this research study?	___	___
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, and do you understand who will have access to your medical records?	___	___
Do you want the investigators to inform you family doctor that you are participating in this study?	___	___

Who explained this study to you? _____

	Yes	**No**
I agree to take part in this study:	___	___

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

_____ _____
Signature of Witness Date

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

_____ _____
Signature of Investigator or Designee Date

Appendix III: Literature Review of Cardiac Output on Cerebral Blood Flow

Table 1.1. Summary of the current literature observing effects of cardiac output on cerebral blood flow

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Schienberg 1950[59]	CHF (14) (patients with anaemia were excluded)	Kety and Schmidt[60] N_2O technique	General observations	CHF patients when compared with normal population showed: CBF ↓ 39% (40 vs 65 mL/min/100g), a-v O_2 difference ↑ 41% (8.6 vs 6.1 volumes per cent). The Author noted: the means may not be directly comparable as the CHF mean age was 40 Male and female and normal were all under 30 and healthy males.	NF
Schieve et al. 1951[61]	Human subjects of varying health (14)	Kety and Schmidt [60] N_2O technique	Adrenocorto -tropic Hormone intake	With Adrenocortotropic Hormone intake: CBF ↓ 18% (61 to 50 mL/min/100g), MABP ↑ 9% (90 to 98 mmHg), CVR ↑ 32% (1.6 to 2.1 units).	NF
Sensen-bach et al. 1960[62]	CHF (37): mild to moderate (24), severe (13) (patients with anaemia, pulmonary disease, renal disease or cerebral arteriosclerosis were excluded)	Kety and Schmidt[60] N_2O technique	Observation of CBF as compared to CHF classification state in lucid patients	CHF patients as compared to normal data: Mild to moderate CHF: ↔ CBF (51 vs 48 mL/min/100g), MABP ↑ 30% (121 vs 94 mmHg), CVR ↔ (2.49 vs 2.35 units). Severe CHF: ↓ 21% CBF (39 vs 48 mL/min/100g), MABP ↔ (100 vs 94 mmHg), CVR ↑ 13% (2.66 vs 2.35 units).	NF

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Einsberg et al. 1960[63]	Severe CHF (24) (patients with mental disease, pulmonary disease, renal disease or cerebral arterio-sclerosis were excluded)	Kety and Schmidt[60] N_2O technique	Observation of CBF as compared to CHF classification state in confused patients	Confused severe CHF patients as compared to; normal controls and lucid severe CHF patients: CHF vs normal: ↓ 46% CBF (26 vs 48 mL/min/100g), MABP ↔ (98 vs 94 mmHg), CVR ↑ 54% (3.61 vs 2.35 units). Confused vs Lucid: ↓ 40% CBF (26 vs 43 mL/min/100g), MABP ↑ 15% (106 vs 92 mmHg), CVR ↑ 62% (3.54 vs 2.18 units).	NF
Andrews et al. 1969[64]	Unanesthet-ized Rats (14); Anesthetized Rats (14)	Fractional uptake of Iodo-antipryrine -^{133}I	Temperature change	Unanesthetized Rats showed a 50% ↓ in CBF with temperature ↓: 0.77 (37°C) to 0.38 mL/min (25°C), Hematocrit values were reported to ↑ from 0.45 (37°C) to 0.59 (25°C), Q ↓ 48% from 286 (37°C) to 149 mL/kg/min (25°C); Anesthetized Rats showed a small ↓ in CBF with temperature ↓: CBF, Hematocrit and Q values were not reported.	+
Shapiro and Chawla 1969[65]	Human patients with complete heart block (5)	Kety and Schmidt[60] N_2O technique	Cardiac pacemaker controlled HR set at 30-40, 60, 70, 90 and 100 beats per minute	HR 30-40: Q (2.8 L/min), CBF control (100%), CVR control (100%), $PaCO_2$ (38 mmHg) HR 60: Q (3.6 L/min), CBF control (118%), CVR control (88%), $PaCO_2$ (41 mmHg) HR 70: Q (3.4 L/min), CBF control (118%), CVR control (94%), $PaCO_2$ (40 mmHg) HR 90: Q (3.4 L/min), CBF control (118%), CVR control (93%), $PaCO_2$ (41 mmHg) HR 100: Q (3.6 L/min), CBF control (124%), CVR control (98%), $PaCO_2$ (39 mmHg)	+

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Davis and Sundt 1980[66]	Cats (70)	^{133}Xenon washout	Hypovolumic (10); Propanol (10); Isoproterenol (10); Hypervolumic (10); Angiotension (10); Propanolol-Angiotension (10); Phenoxybenzamine-angiotension (10)	Hypovolumic: Q ↓ 32%, CBF ↓ 24%, MABP ↓ slightly Propanol: HR ↓ 28%, Q ↓ 23%, CBF ↓ 30%, MABP not reported Isoproterenol: HR ↑ 20%, Q ↑ 38%, CBF ↔, MABP not reported Hypervolumic: HR ↓ slightly, Q ↓ 7%, CBF ↓ 22%, MABP ↓ slightly Angiotension: induced changes in MABP had varied results in CBF, overall a slight ↑ in CBF and ↓ in Q with ↑ in MABP (changes less than 10%) Propanolol-Angiotension: MABP ↓ 6%, Q ↓ 26%, CBF ↓ 12% Phenoxybenzamine-angiotension: MABP ↓ 24%, Q ↔, CBF ↓ 15%	+ / -
Moustafa and Hopewell 1981[67]	Female rats (28)	^{125}Iodo-antipyrine extraction technique	Age Changes: 6 months (6) 9 months (4) 12 months (6) 15 months (6) 18 months (6)	6 months (6): Q 257 mL/min/kg body weight, CBF 6.7 mL/min/kg body weight; 9 months (4): Q 183 mL/min/kg body weight, CBF 6.0 mL/min/kg body weight; 12 months (6): Q 208 mL/min/kg body weight, CBF 4.8 mL/min/kg body weight; 15 months (6): Q 163 mL/min/kg body weight, CBF 4.1 mL/min/kg body weight; 18 months (6): Q 157 mL/min/kg body weight, CBF 3.5 mL/min/kg body weight	+

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Cook et al. 1983[68]	Healthy males (7)	^{133}Xenon inhalation	Intravenous admin-istration of Epoprostenol	Pre infusion: ABP_{sys} 123 mmHg, ABP_{dia} 76 mmHg, HR 73 bpm, Q 4.2 L/min, CBF 46.0 mL/min/100g 15 minutes post: ABP_{sys} 122 mmHg, ABP_{dia} 73 mmHg, HR 79 bpm, Q 4.4 L/min, CBF 40.7 mL/min/100g 30 minutes post: ABP_{sys} 123 mmHg, ABP_{dia} 73 mmHg, HR 79 bpm, Q 4.1 L/min, CBF 38.9 mL/min/100g	-
Hermansen et al. 1984[69]	Newborn dogs (13)	Radioactive microsphere reference organ technique	Metabolic Acidosis	With increasing acidosis, there was a 27% ↓ in Q, ↔ in HR, ↔ in CBF. Concluded that decrease in Q due to ↓ in SV and had no effect on CBF.	-
Barrington et al. 1987[70]	Adult monkeys (6)	^{133}Xenon clearance	Negative pressure ventilation via external high frequency oscillation	Control (mechanical ventilation) vs. external high frequency oscillation: ↔ Q (2.83 vs 3.03 L/min) ↔ CBF (43.9 vs 39.0 mL/min/100g) ↔ MABP (119 vs 113 mmHg)	NF

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Mutch et al. 1990[71]	New Zealand white Rabbits (16)	Summing weighted flows in all brain regions and comparing to brain weight of the decapitated rabbit	Isoflurane injection (8); Halothane injection (8)	Isoflurane vs. Halothane at each injection stage: Baseline: MABP (64.3 vs 67.2 mmHg), Q (472 vs 506 mL/min), CBF (0.7 vs 0.9 mL/g/min), PE injection (N/A), ICP (2.9 vs 2.1), CPP (61.4 vs 65.5) Flow 2: MABP (79.2 vs 81.5 mmHg), Q (385 vs 363 mL/min), CBF (0.9 vs 1.1 mL/g/min), PE injection (8.5 vs 15.3 µg/kg/min), ICP (3.1 vs 2.4 mmHg), CPP (76.1 vs 79.5 mmHg) Flow 3: MABP (89.6 vs 94.7 mmHg), Q (388 vs 263 mL/min), CBF (1.0 vs 1.8 mL/g/min), PE injection (12.8 vs 28.6 µg/kg/min), ICP (3.4 vs 3.6 mmHg), CPP (86.2 vs 91.5 mmHg) Flow 4: MABP (105.4 vs 106.6 mmHg), Q (341 vs 226 mL/min), CBF (1.2 vs 2.5 mL/g/min), PE injection (16.9 vs 63.5 µg/kg/min), ICP (3.7 vs 5.1 mmHg), CPP (101.7 vs 102.0 mmHg) Flow 5: MABP (116.6 vs 115.8 mmHg), Q (325 vs 150 mL/min), CBF (1.4 vs 3.8 mL/g/min), PE injection (21.1 vs 137.3 µg/kg/min), ICP (5.0 vs 6.7 mmHg), CPP (111.7 vs 109.8 mmHg)	-
van der Giessen et al. 1990[72]	Conscious cross-breed pigs (14)	Inspection of the brain during dissection	Nimodipine injection	Highest nimodipine dosage as compared to baseline data: HR ↑ 42%, Q ↑ 54%, CBF ↔, CVR ↔, MABP ↓ 9%	-

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Bouma and Muizelaar 1990[73]	Human patients with intact or impaired cerebral autoregulation (35)	^{133}Xenon inhalation or ^{133}Xenon injection	Phenyl-ephrine, Arfonad and Mannitol admin-istration	Pre-drug vs pos-drug comparison for intact and impaired cerebral autoregulation: (Absolute values not reported for Q) Intact cerebral autoregulation: Phenylephrine: CBF (36 vs 35 mL/100g/min, ↓ 1%), MABP (96 vs 127 mmHg, ↑ 32%), ICP (18 vs 20 mmHg, ↑ 11%), Q (↑ 7%) Arfonad: CBF (41 vs 40 mL/100g/min, ↓ 2%), MABP (111 vs 86 mmHg, ↓ 23%), ICP (18 vs 21 mmHg, ↑ 17%), Q (↓ 10%) Mannitol: CBF (37 vs 37 mL/100g/min, ↔), MABP (101 vs 100 mmHg, ↓ 1%), ICP (18 vs 13 mmHg, ↓ 28%), Q (↑ 17%) Impaired cerebral autoregulation: Phenylephrine: CBF (21 vs 32 mL/100g/min, ↑ 53%), MABP (92 vs 123 mmHg, ↑ 34%), ICP (18 vs 16 mmHg, ↓ 11%), Q (↑ 15%) Arfonad: CBF (66 vs 46 mL/100g/min, ↓ 31%), MABP (108 vs 77 mmHg, ↓ 29%), ICP (16 vs 18 mmHg, ↑ 13%), Q (↑ 22%) Mannitol: CBF (20 vs 27 mL/100g/min, ↑ 40%), MABP (94 vs 90 mmHg, ↓ 4%), ICP (17 vs 16 mmHg, ↓ 6%), Q (↑ 1%)	-

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Levine et al. 1994[74]	Healthy males (13)	MCAv via TCD	Orthostatic challenge (lower body negative pressure)	Arrows indicate changes from rest at –15, -30, -40 and –55 mmHg Rest: Q (5.7 L/min), non-fainter MCAv (58 cm/s), fainter MCAv (52 cm/s), HR (58 bpm), SV (98 mL), MABP (82 mmHg) -15 mmHg: Q (5.7 L/min, ↔), non-fainter MCAv (61 cm/s, ↔), fainter MCAv (52 cm/s, ↔), HR (63 bpm, ↑ 9%), SV (90 mL, ↓ 9%), MABP (83 mmHg, ↔) -30 mmHg: Q (5.0 L/min, ↓ 12%), non-fainter MCAv (56 cm/s, ↔), fainter MCAv (50 cm/s, ↔), HR (68 bpm, ↑ 17%), SV (73 mL, ↓ 11%), MABP (83 mmHg, ↔) -40 mmHg: Q (4.2 L/min, ↓ 24%), non-fainter MCAv (55 cm/s, ↔), fainter MCAv (45 cm/s, ↓ 14%), HR (76 bpm, ↑ 31%), SV (55 mL, ↓ 33%), MABP (84 mmHg, ↔) -55 mmHg: Q (3.5 L/min, ↓ 39%), non-fainter MCAv (50 cm/s, ↓ 14%), fainter MCAv (N/A), HR (90 bpm, ↑ 55%), SV (90 mL, ↓ 57%), MABP (88 mmHg, ↑ 6%)	-

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Ide et al. 1998[75]	Healthy human volunteers (9)	MCAv via TCD	Effect of reducing the ability to change Q at rest, during handgrip and cycling exercise with metroprolol (β_1 adrenergic blockade)	Control vs Metroprolol at rest and during Handgrip and cycling at (83, 113, 147, and 186 watts) Rest: MCAv (59 vs 56 cm/s), percent change in Q (100 vs 92 %), HR (67 vs 65 bpm), MABP (94 vs 86 mmHg), $PaCO_2$ (5.1 vs 4.9 kPa) Handgrip: MCAv (67 vs 63 cm/s), percent change in Q (116 vs 100 %), HR (77 vs 71 bpm), MABP (106 vs 100 mmHg), $PaCO_2$ (5.1 vs 5.0 kPa) 83 watts: MCAv (72 vs 64 cm/s), percent change in Q (218 vs 185 %), HR (113 vs 99 bpm), MABP (105 vs 96 mmHg), $PaCO_2$ (5.2 vs 5.3 kPa) 113 watts: MCAv (72 vs 66 cm/s), percent change in Q (260 vs 222 %), HR (135 vs 114 bpm), MABP (112 vs 103 mmHg), $PaCO_2$ (5.1 vs 5.2 kPa) 147 watts: MCAv (69 vs 64 cm/s), percent change in Q (315 vs 258 %), HR (158 vs 128 bpm), MABP (119 vs 106 mmHg), $PaCO_2$ (4.9 vs 4.9 kPa) 186 watts: MCAv (66 vs 62 cm/s), percent change in Q (349 vs 293 %), HR (169 vs 130 bpm), MABP (122 vs 112 mmHg), $PaCO_2$ (4.4 vs 4.6 kPa)	+
Larsen et al. 2000[76]	Fulminant hepatic failure patients (9)	MCAv via TCD	Norepin-ephrine infusion	Measurements before and during Norepinephrine infusion: MCAv (49 vs 63 cm/s, ↑ 30%), Q (5.7 vs 7.1 L/min, ↑ 25%), MABP (75 vs 97 mmHg, ↑ 32%), SV (59 vs 71 mL, ↑ 20%)	+

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Gruhn et al. 2001[31]	Congestive heart failure (12); Heart transplant recipients (5)	^{133}Xenon inhalation	Pre- and post- heart transplant-ation	Measurements taken pre- and post-transplant: CBF (36 vs 50 mL/min/100g, ↑ 39%), CI (2.5 vs 2.4 L/min/m^2, ↔), MABP (76 vs 93 mmHg, ↑ 22%)	NF
Van Lieshout et al. 2001[45]	Healthy young adult humans (10)	MCAv via TCD	5 minutes of Standing, followed by 2 minutes of leg tensing and 2 final minutes of standing	Stand 1: Q (4.2 L/min), MCAv (58 cm/s), MABP (75 mmHg), $PaCO_2$ (4.7 kPa) Tensing: Q (4.5 L/min), MCAv (64 cm/s), MABP (79 mmHg), $PaCO_2$ (5.0 kPa) Stand 2: Q (4.2 L/min), MCAv (58 cm/s), MABP (77 mmHg), $PaCO_2$ (4.7 kPa)	+
Wilson et al. 2002[77]	Healthy humans (9)	MCAv via TCD	Normo-thermic tilt and whole body heating tilt (with and without pre-cooling)	Measures are pre and during experimental condition: Normothermic – no cooling: MCAv (62 vs 54 cm/s), Q (6.5 vs 5.2 L/min), MABP (87 vs 82 mmHg), HR (57 vs 72 bpm) Normothermic – pre-cooling: MCAv (61 vs 60 cm/s), Q (6.3 vs 5.8 L/min), MABP (86 vs 93 mmHg), HR (57 vs 63 bpm) Heating – no cooling: MCAv (55 vs 43 cm/s), Q (8.0 vs 5.7 L/min), MABP (83 vs 71 mmHg), HR (88 vs 126 bpm) Heating – pre-cooling: MCAv (54 vs 59 cm/s), Q (8.2 vs 5.2 L/min), MABP (88 vs 93 mmHg), HR (87 vs 72 bpm)	+ / -

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Joseph et al. 2003[78]	Human patients with vasoplasm after subarachnoid hemorrhage (16)	Xenon CT system	Hyper-volemia: Phenyl-ephrine to ↑ MABP (5); Dobutamine to ↑ Q (5)	Measures are pre and post treatment: Phenylephrine: CBF (19.2 vs 33.3 mL/100g/min, ↑ 73%), MABP (103.4 vs 132.0 mmHg, ↑ 28%) Dobutamine: CBF (24.8 vs 35.7 mL/100g/min, ↑ 44%), CI (4.0 vs 6.0 L/min/m^2, ↑ 50%)	+
Brown et al. 2003[79]	Human Adults (13)	MCAv via TCD	Orthostatic challenge: Lower body negative pressure	Lower body negative pressure settings of 0, -10, -20, -30, -40, -50 mmHg (% change to baseline measure) 0 mmHg: $MCAv_{mean}$ (71 cm/s), Q (6.86 L/min), SV (116 mL), HR (60 bpm), MABP (86 mmHg) -10 mmHg: $MCAv_{mean}$ (67 cm/s, ↓ 6%), Q (6.37 L/min, ↓ 7%), SV (109 mL, ↓ 6%), HR (59 bpm, ↔), MABP (90 mmHg, ↑ 5%) -20 mmHg: $MCAv_{mean}$ (70 cm/s, ↔), Q (5.60 L/min, ↓ 18%), SV (93 mL, ↓ 20%), HR (61 bpm, ↔), MABP (89 mmHg, ↔) -30 mmHg: $MCAv_{mean}$ (70 cm/s, ↔), Q (4.65 L/min, ↓ 32%), SV (74 mL, ↓ 36%), HR (65 bpm, ↑ 8%), MABP (86 mmHg, ↔) -40 mmHg: $MCAv_{mean}$ (61 cm/s, ↓ 14%), Q (4.19 L/min, ↓ 39%), SV (63 mL, ↓ 44%), HR (71 bpm, ↑ 18%), MABP (89 mmHg, ↑ 3%) -50 mmHg: $MCAv_{mean}$ (57 cm/s, ↓ 20%), Q (3.80 L/min, ↓ 45%), SV (48 mL, ↓ 59%), HR (83 bpm, ↑ 38%), MABP (91 mmHg, ↑ 6%)	+ / -
Kusaka et al. 2005[80]	Newborn infant humans (17)	Mulitchannel Near infrared spectroscopy	Observa-tional	Significant positive relation between Q and CBF: Linear regression line equation: CBF = 0.03Q + 8.71, R^2 = 0.70, *P* = 0.002	+

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Ogoh et al. 2005[81]	Healthy human males (7)	MCAv via TCD	Rest and Exercise with: infusions of albumin to ↑ Q; lower body negative pressure to ↓ Q	Rest and exercise values for: lower body negative pressures at 8 Torr and 16 Torr, albumin infusion 1 and 2. (% changes are to control values). Rest: 8 Torr: MCAv (63 cm/s, ↓ 5%), Q (5.8 L/min, ↓ 11%), HR (70 bpm, ↑ 6%), MABP (96 mmHg, ↔), $PaCO_2$ (39 mmHg, ↔) 16 Torr: MCAv (62 cm/s, ↓ 6%), Q (5.3 L/min, ↓ 18%), HR (74 bpm, ↑ 12%), MABP (99 mmHg, ↔), $PaCO_2$ (40 mmHg, ↔) Albumin 1: MCAv (71 cm/s, ↑ 8%), Q (8.2 L/min, ↑ 26%), HR (82 bpm, ↑ 24%), MABP (92 mmHg, ↓ 4%), $PaCO_2$ (41 mmHg, ↔) Albumin 2: MCAv (73 cm/s, ↑ 11%), Q (8.5 L/min, ↑ 31%), HR (84 bpm, ↑ 27%), MABP (91 mmHg, ↓ 5%), $PaCO_2$ (41 mmHg, ↔) Exercise: 8 Torr: MCAv (70 cm/s, ↔), Q (14.1 L/min, ↔), HR (123 bpm, ↑ 8%), MABP (104 mmHg, ↓ 5%), $PaCO_2$ (42 mmHg, ↔) 16 Torr: MCAv (68 cm/s, ↔), Q (13.7 L/min, ↔), HR (130 bpm, ↑ 14%), MABP (106 mmHg, ↔), $PaCO_2$ (41 mmHg, ↔) Albumin 1: MCAv (74 cm/s, ↔), Q (16.5 L/min, ↑ 12%), HR (129 bpm, ↑ 13%), MABP (105 mmHg, ↓ 4%), $PaCO_2$ (41 mmHg, ↔) Albumin 2: MCAv (74 cm/s, ↔), Q (18.5 L/min, ↑ 26%), HR (133 bpm, ↑ 17%), MABP (106 mmHg, ↔), $PaCO_2$ (41 mmHg, ↔)	+ / -
Massaro et al. 2006[30]	Congestive heart failure humans (22), heart transplantation subset (14)	MCAv via TCD	A subset (14) under heart transplant-ation	Pre and 2-4 month post transplant measures: CBF (45.1 vs 69.1 cm/s, ↑ 53%), MABP (75.2 vs 94.6 mmHg, ↑ 26%), hematocrit (38.8 vs 31.2 %, ↓ 20%)	NF

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Choi et al. 2006[32]	Advanced heart failure humans (52), underwent heart transplant-ation (4)	Radionuclide angiography	small subset (4) under heart transplant-ation	Pre and 2-4 month post transplant measures: CBF (35.5 vs 44.3 mL/100g/min, ↑ 25%) LVEF (19.8 vs 66.8 %, ↑ 237%)	NF
Drombrowski et al. 2006[82]	Adult male dogs (31)	Stable isotope labeled microspheres with post mortem tissue evaluation	Induced chronic obstructive hydro-cephalus	Average CBF and Q for baseline, 2 weeks, 4-6 weeks, 8-12 weeks and 16+ weeks (% change is in relation to current measure vs baseline) Chronic Hydrocephalus: CBF (mL/min/g): base (0.587), 2 weeks (0.317, ↓ 46%), 4-6 weeks (0.298, ↓ 49%), 8-12 weeks (0.384, ↓ 34%), 16+ weeks (0.242, ↓ 59%) Q (mL/min): base (4.97), 2 weeks (3.52, ↓ 29%), 4-6 weeks (3.46, ↓ 30%), 8-12 weeks (3.91, ↓ 21%), 16+ weeks (3.06, ↓ 38%) Surgical Control: CBF (mL/min/g): base (0.661), 2 weeks (0.312, ↓ 53%), 4-6 weeks (0.403, ↓ 39%), 8-12 weeks (0.408, ↓ 38%), 16+ weeks (0.582, ↓ 12%) Q (mL/min): base (4.10), 2 weeks (2.86, ↓ 30%), 4-6 weeks (2.62, ↓ 36%), 8-12 weeks (3.35, ↓ 18%), 16+ weeks (3.77, ↓ 8%)	+

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Ogoh et al. 2007[83]	Healthy males (8)	MCAv via TCD	Moderate and heavy exercise before and after cardio-selective β_1-adrenergic blockade (metro-prolol)	Effects of rest, moderate and heavy exercise under control and metropolol conditions. (Q and SV data are presented as % change from control rest, other values are absolute measures) Control: Rest: MCAv (60 cm/s), Q (0 %), SV (0 %), HR (66 bpm), MABP (92 mmHg), $PaCO_2$ (5.2 kPa) Moderate: MCAv (75 cm/s), Q (182 %), SV (40 %), HR (130 bpm), MABP (104 mmHg), $PaCO_2$ (5.7 kPa) Heavy: MCAv (67 cm/s), Q (276 %), SV (46 %), HR (171 bpm), MABP (115 mmHg), $PaCO_2$ (5.4 kPa) Metropolol: Rest: MCAv (52 cm/s), Q (-5 %), SV (-6 %), HR (67 bpm), MABP (85 mmHg), $PaCO_2$ (5.1 kPa) Moderate: MCAv (59 cm/s), Q (146 %), SV (35 %), HR (117 bpm), MABP (93 mmHg), $PaCO_2$ (5.4 kPa) Heavy: MCAv (56 cm/s), Q (235 %), SV (46 %), HR (163 bpm), MABP (109 mmHg), $PaCO_2$ (5.1 kPa)	-

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Ogawa et al. 2007[84]	Healthy human males (12)	MCAv via TCD	Orthostatic challenge: lower body negative pressure; ↑ central blood volume with saline injections	Data for baseline, lower body negative pressure (-15 and –30 mmHg), saline injection (15 and 30 mL/kg), (% changes are to baseline): Baseline: MCAv (67 cm/s), Q (4.16 L/min), SV (72.9 mL), HR (58 bpm), MABP (80 mmHg), PET CO_2 (41 mmHg) -15 mmHg: MCAv (67 cm/s, ↔), Q (3.64 L/min, ↓ 12%), SV (64.3 mL, ↓ 12%), HR (61 bpm, ↔), MABP (80 mmHg, ↔), PET CO_2 (40 mmHg, ↔) -30 mmHg: MCAv (68 cm/s, ↔), Q (2.80 L/min, ↓ 33%), SV (44.2 mL, ↓ 39%), HR (68 bpm, ↑ 17%), MABP (77 mmHg, ↔), PET CO_2 (40 mmHg, ↔) 15 mL/kg: MCAv (72 cm/s, ↑ 7%), Q (4.73 L/min, ↑ 14%), SV (78.0 mL, ↔), HR (61 bpm, ↔), MABP (86 mmHg, ↔), PET CO_2 (40 mmHg, ↔) 30 mL/kg: MCAv (73 cm/s, ↑ 9%), Q (5.08 L/min, ↑ 22%), SV (75.5 mL, ↔), HR (68 bpm, ↑ 17%), MABP (82 mmHg, ↔), PET CO_2 (40 mmHg, ↔)	+ / -
Ogoh et al. 2010[85]	Healthy human males (9)	MCAv via TCD	Acute hypotension by releasing thigh cuffs before and after; metropolol and glycol-pyruvate plus metropolol	Data for control, metropolol, and glycopyruvate plus metropolol, (% changes are to control): Control: MCAv (73 cm/s), Q (6.8 L/min), SV (103 mL), HR (67 bpm), MABP (85 mmHg), PET CO_2 (39.7 mmHg) Metropolol: MCAv (70 cm/s, ↔), Q (6.0 L/min, ↓ 12%), SV (105 mL, ↔), HR (58 bpm, ↓ 13%), MABP (85 mmHg, ↔), PET CO_2 (39.8 mmHg, ↔) Glycopyruvate+: MCAv (72 cm/s, ↔), Q (8.6 L/min, ↑ 27%), SV (92, ↓ 11%), HR (95 bpm, ↑ 42%), MABP (86 mmHg, ↔), PET CO_2 (39.1 mmHg, ↔)	-

Study[a]	Population (n)	CBF Technique	Intervention (n)	Findings	Q-CBF Relationship
Deegan et al. 2010[86]	Healthy human volunteers (19)	MCAv and ACAv via TCD	Transient systemic hypoper-fusion induced by thigh cuff deflation (supine and seated)	Supine and Seated data (% changes are to condition baseline): Supine: Baseline: MCAv (81.7 cm/s), ACAv (62.2 cm/s), Cardiac Index (2.2 L/min/m^2), HR (64 bpm), MABP (90 mmHg) Pre-release: MCAv (83.7 cm/s, ↑ 3%), ACAv (62.8 cm/s, ↑ 1%), Cardiac Index (2.7 L/min/m^2, ↑ 17%), HR (73 bpm, ↑ 14%), MABP (101 mmHg, ↑ 12%) Post-release: MCAv (79.2 cm/s, ↓ 3%), ACAv (58.5 cm/s, ↓ 6%), Cardiac Index (3.0 L/min/m^2, ↑ 36%), HR (78 bpm, ↑ 22%), MABP (84 mmHg, ↓ 7%) Seated: Baseline: MCAv (75.2 cm/s), ACAv (59.7 cm/s), Cardiac Index (2.5 L/min/m^2), HR (73 bpm), MABP (91 mmHg) Pre-release: MCAv (77.6 cm/s, ↑ 3%), ACAv (60.3 cm/s, ↑ 1%), Cardiac Index (3.0 L/min/m^2, ↑ 20%), HR (78 bpm, ↑ 7%), MABP (98 mmHg, ↑ 8%) Post-release: MCAv (71.1 cm/s, ↓ 5%), ACAv (52.9 cm/s, ↓ 11%), Cardiac Index (3.2 L/min/m^2, ↑ 28%), HR (88 bpm, ↑ 21%), MABP (79 mmHg, ↓ 13%)	-

[a] Studies are in chronological order.

n = number; CHF = congestive heart failure; CBF = cerebral blood flow; a-v O_2 = atrial-venous Oxygen difference; MABP = mean arterial blood pressure; ABP_{sys} = systolic arterial blood pressure; ABP_{dia} = diastolic arterial blood pressure; N_2O = Nitrogen Oxide; CVR = cerebrovascular resistance; Q = cardiac output; HR = heart rate; SV = stroke volume; CI = cardiac index; $PaCO_2$ = partial pressure of arterial Carbon Dioxide; ICP = intracranial pressure; LVEF = left ventricular ejection fraction; MCA = middle cerebral artery; MCAv = middle cerebral artery velocity; ACA = anterior cerebral artery; ACAv = anterior cerebral artery velocity; TCD = transcranial Doppler.

↑ indicates increase; ↓ indicates decrease; ↔ indicates no change.
+ indicates positive Q-CBF relationship; - indicates no Q-CBF relationship; NF = no findings for Q-CBF relationship.

Appendix IV: Raw Data – Output from LabChart

		MCAv						
		Systolic (cm/s)	Relative (%)	**Diastolic** (cm/s)	Relative (%)	**Mean** (cm/s)	Relative (%)	Change to Baseline
AM 1	Base	69.450	0.000	35.490	0.000	46.810	0.000	0.000
AM 2	Base	71.120	0.000	30.630	0.000	44.127	0.000	0.000
AM 3	Base	84.700	0.000	18.830	0.000	40.787	0.000	0.000
AM 4	Base	69.090	0.000	21.580	0.000	37.417	0.000	0.000
AM 5	Base	51.770	0.000	19.200	0.000	30.057	0.000	0.000
AM 6	Base	58.600	0.000	26.590	0.000	37.260	0.000	0.000
AM 7	Base	82.080	0.000	36.220	0.000	51.507	0.000	0.000
HTR 1	Base	50.980	0.000	26.050	0.000	34.360	0.000	0.000
HTR 2	Base	57.400	0.000	23.770	0.000	34.980	0.000	0.000
HTR 3	Base	63.680	0.000	33.860	0.000	43.800	0.000	0.000
HTR 4	Base	78.720	0.000	22.110	0.000	40.980	0.000	0.000
HTR 6	Base	101.270	0.000	47.500	0.000	65.423	0.000	0.000
HTR 7	Base	43.550	0.000	21.100	0.000	28.583	0.000	0.000
HTR 8	Base	48.480	0.000	22.440	0.000	31.120	0.000	0.000
DC 1	Base	123.000	0.000	43.000	0.000	69.667	0.000	0.000
DC 2	Base	91.000	0.000	38.000	0.000	55.667	0.000	0.000
DC 3	Base	105.000	0.000	54.000	0.000	71.000	0.000	0.000
DC 4	Base	149.000	0.000	49.000	0.000	82.333	0.000	0.000
DC 5	Base	120.000	0.000	40.000	0.000	66.667	0.000	0.000
DC 6	Base	119.000	0.000	37.000	0.000	64.333	0.000	0.000
DC 7	Base	125.000	0.000	52.000	0.000	76.333	0.000	0.000
AM 1	50%	87.490	0.260	32.500	-0.084	50.830	0.086	4.020
AM 2	50%	88.600	0.246	27.160	-0.113	47.640	0.080	3.513
AM 3	50%	103.290	0.219	17.800	-0.055	46.297	0.135	5.510
AM 4	50%	82.340	0.192	21.160	-0.019	41.553	0.111	4.137
AM 5	50%	91.790	0.773	26.260	0.368	48.103	0.600	18.047
AM 6	50%	97.380	0.662	32.590	0.226	54.187	0.454	16.927
AM 7	50%	130.550	0.591	45.450	0.255	73.817	0.433	22.310
HTR 1	50%	60.560	0.188	27.970	0.074	38.833	0.130	4.473
HTR 2	50%	86.990	0.516	25.470	0.072	45.977	0.314	10.997
HTR 3	50%	75.830	0.191	28.790	-0.150	44.470	0.015	0.670
HTR 4	50%	98.290	0.249	25.670	0.161	49.877	0.217	8.897
HTR 6	50%	105.690	0.044	41.330	-0.130	62.783	-0.040	-2.640
HTR 7	50%	51.760	0.189	18.130	-0.141	29.340	0.026	0.757
HTR 8	50%	80.640	0.663	31.510	0.404	47.887	0.539	16.767
DC 1	50%	172.000	0.398	48.000	0.116	89.333	0.282	19.667
DC 2	50%	132.000	0.451	36.000	-0.053	68.000	0.222	12.333
DC 3	50%	145.000	0.381	57.000	0.056	86.333	0.216	15.333
DC 4	50%	189.000	0.268	52.000	0.061	97.667	0.186	15.333

DC 5	50%	131.000	0.092	46.000	0.150	74.333	0.115	7.667
DC 6	50%	165.000	0.387	35.000	-0.054	78.333	0.218	14.000
DC 7	50%	177.000	0.416	54.000	0.038	95.000	0.245	18.667

		MCAv						
		Systolic (cm/s)	Relative (%)	**Diastolic** (cm/s)	Relative (%)	**Mean** (cm/s)	Relative (%)	Change to Baseline
AM 1	70%	98.140	0.413	32.670	-0.079	54.493	0.164	7.683
AM 2	70%	104.360	0.467	24.550	-0.198	51.153	0.159	7.027
AM 3	70%	111.220	0.313	15.620	-0.170	47.487	0.164	6.700
AM 4	70%	95.700	0.385	21.820	0.011	46.447	0.241	9.030
AM 5	70%	103.330	0.996	24.950	0.299	51.077	0.699	21.020
AM 6	70%	105.830	0.806	30.490	0.147	55.603	0.492	18.343
AM 7	70%	132.450	0.614	39.790	0.099	70.677	0.372	19.170
HTR 1	70%	63.870	0.253	26.980	0.036	39.277	0.143	4.917
HTR 2	70%	100.080	0.744	25.590	0.077	50.420	0.441	15.440
HTR 3	70%	81.930	0.287	27.590	-0.185	45.703	0.043	1.903
HTR 4	70%	113.120	0.437	27.500	0.244	56.040	0.367	15.060
HTR 6	70%	109.550	0.082	37.280	-0.215	61.370	-0.062	-4.053
HTR 7	70%	54.210	0.245	15.660	-0.258	28.510	-0.003	-0.073
HTR 8	70%	85.960	0.773	33.300	0.484	50.853	0.634	19.733
DC 1	70%	176.000	0.431	53.000	0.233	94.000	0.349	24.333
DC 2	70%	133.000	0.462	30.000	-0.211	64.333	0.156	8.667
DC 3	70%	156.000	0.486	54.000	0.000	88.000	0.239	17.000
DC 4	70%	183.000	0.228	48.000	-0.020	93.000	0.130	10.667
DC 5	70%	146.000	0.217	42.000	0.050	76.667	0.150	10.000
DC 6	70%	168.000	0.412	34.000	-0.081	78.667	0.223	14.333
DC 7	70%	172.000	0.376	53.000	0.019	92.667	0.214	16.333
AM 1	90%	115.990	0.670	37.290	0.051	63.523	0.357	16.713
AM 2	90%	108.430	0.525	19.450	-0.365	49.110	0.113	4.983
AM 3	90%	117.720	0.390	14.720	-0.218	49.053	0.203	8.267
AM 4	90%	107.490	0.556	22.450	0.040	50.797	0.358	13.380
AM 5	90%	104.580	1.020	25.100	0.307	51.593	0.717	21.537
AM 6	90%	102.430	0.748	26.990	0.015	52.137	0.399	14.877
AM 7	90%	126.000	0.535	31.830	-0.121	63.220	0.227	11.713
HTR 1	90%	61.990	0.216	22.440	-0.139	35.623	0.037	1.263
HTR 2	90%	97.650	0.701	18.520	-0.221	44.897	0.283	9.917
HTR 3	90%	87.420	0.373	27.020	-0.202	47.153	0.077	3.353
HTR 4	90%	117.530	0.493	25.960	0.174	56.483	0.378	15.503
HTR 6	90%	112.250	0.108	33.800	-0.288	59.950	-0.084	-5.473
HTR 7	90%	53.460	0.228	13.500	-0.360	26.820	-0.062	-1.763
HTR 8	90%	84.440	0.742	32.540	0.450	49.840	0.602	18.720
DC 1	90%	182.000	0.480	41.000	-0.047	88.000	0.263	18.333
DC 2	90%	127.000	0.396	28.000	-0.263	61.000	0.096	5.333
DC 3	90%	129.000	0.229	47.000	-0.130	74.333	0.047	3.333
DC 4	90%	142.000	-0.047	38.000	-0.224	72.667	-0.117	-9.667

DC 5	90%	147.000	0.225	38.000	-0.050	74.333	0.115	7.667
DC 6	90%	168.000	0.412	32.000	-0.135	77.333	0.202	13.000
DC 7	90%	143.000	0.144	41.000	-0.212	75.000	-0.017	-1.333

		MCAv						
		Systolic (cm/s)	Relative (%)	**Diastolic** (cm/s)	Relative (%)	**Mean** (cm/s)	Relative (%)	Change to Baseline
AM 1	Peak	108.090	0.556	28.910	-0.185	55.303	0.181	8.493
AM 2	Peak	107.340	0.509	21.720	-0.291	50.260	0.139	6.133
AM 3	Peak	120.620	0.424	15.550	-0.174	50.573	0.240	9.787
AM 4	Peak	101.220	0.465	22.460	0.041	48.713	0.302	11.297
AM 5	Peak	95.520	0.845	20.520	0.069	45.520	0.514	15.463
AM 6	Peak	99.160	0.692	23.860	-0.103	48.960	0.314	11.700
AM 7	Peak	133.070	0.621	36.330	0.003	68.577	0.331	17.070
HTR 1	Peak	60.610	0.189	20.730	-0.204	34.023	-0.010	-0.337
HTR 2	Peak	105.170	0.832	15.390	-0.353	45.317	0.296	10.337
HTR 3	Peak	91.080	0.430	24.520	-0.276	46.707	0.066	2.907
HTR 4	Peak	115.070	0.462	25.900	0.171	55.623	0.357	14.643
HTR 6	Peak	110.540	0.092	32.260	-0.321	58.353	-0.108	-7.070
HTR 7	Peak	52.070	0.196	13.190	-0.375	26.150	-0.085	-2.433
HTR 8	Peak	81.450	0.680	31.100	0.386	47.883	0.539	16.763
DC 1	Peak	178.000	0.447	32.000	-0.256	80.667	0.158	11.000
DC 2	Peak	118.000	0.297	27.000	-0.289	57.333	0.030	1.667
DC 3	Peak	109.000	0.038	41.000	-0.241	63.667	-0.103	-7.333
DC 4	Peak	113.000	-0.242	30.000	-0.388	57.667	-0.300	-24.667
DC 5	Peak	127.000	0.058	17.000	-0.575	53.667	-0.195	-13.000
DC 6	Peak	147.000	0.235	23.000	-0.378	64.333	0.000	0.000
DC 7	Peak	134.000	0.072	26.000	-0.500	62.000	-0.188	-14.333

		Pulsitility Index	MAP					
			Systolic (mmHg)	Relative (%)	**Diastolic** (mmHg)	Relative (%)	**Mean** (mmHg)	Relative (%)
AM 1	Base	0.725	120.000	0.000	80.000	0.000	99.000	0.000
AM 2	Base	0.918	129.000	0.000	87.000	0.000	101.000	0.000
AM 3	Base	1.615	183.000	0.000	92.000	0.000	122.333	0.000
AM 4	Base	1.270	104.000	0.000	62.000	0.000	76.000	0.000
AM 5	Base	1.084	117.000	0.000	70.000	0.000	85.667	0.000
AM 6	Base	0.859	140.000	0.000	95.000	0.000	110.000	0.000
AM 7	Base	0.890	143.000	0.000	87.000	0.000	105.667	0.000
HTR 1	Base	0.726	121.000	0.000	88.000	0.000	99.000	0.000
HTR 2	Base	0.961	120.000	0.000	97.000	0.000	104.667	0.000
HTR 3	Base	0.681	120.000	0.000	92.000	0.000	101.333	0.000
HTR 4	Base	1.381	129.000	0.000	76.000	0.000	93.667	0.000
HTR 6	Base	0.822	131.000	0.000	83.000	0.000	99.000	0.000
HTR 7	Base	0.785	120.000	0.000	90.000	0.000	100.000	0.000
HTR 8	Base	0.837	120.000	0.000	83.000	0.000	95.333	0.000
DC 1	Base	1.148	124.000	0.000	78.000	0.000	93.333	0.000
DC 2	Base	0.952	129.000	0.000	89.000	0.000	102.333	0.000
DC 3	Base	0.718	106.000	0.000	74.000	0.000	84.667	0.000
DC 4	Base	1.215	117.000	0.000	83.000	0.000	94.333	0.000
DC 5	Base	1.200	109.000	0.000	80.000	0.000	89.667	0.000
DC 6	Base	1.275	103.000	0.000	78.000	0.000	86.333	0.000
DC 7	Base	0.956	131.000	0.000	62.000	0.000	85.000	0.000
AM 1	50%	1.082	150.000	-0.351	82.000	0.025	104.667	-0.197
AM 2	50%	1.290	168.000	0.302	83.000	-0.046	111.333	0.102
AM 3	50%	1.847	195.000	0.066	78.000	-0.152	117.000	-0.044
AM 4	50%	1.472	136.000	0.308	72.000	0.161	93.333	0.228
AM 5	50%	1.362	171.000	0.462	70.000	0.000	103.667	0.210
AM 6	50%	1.196	191.000	0.364	101.000	0.063	131.000	0.191
AM 7	50%	1.153	170.000	0.189	80.000	-0.080	110.000	0.041
HTR 1	50%	0.839	154.000	0.273	93.000	0.057	113.333	0.145
HTR 2	50%	1.338	140.000	0.167	95.000	-0.021	110.000	0.051
HTR 3	50%	1.058	169.000	0.408	82.000	-0.109	111.000	0.095
HTR 4	50%	1.456	135.000	0.047	74.000	-0.026	94.333	0.007
HTR 6	50%	1.025	149.000	0.137	82.000	-0.012	104.333	0.054
HTR 7	50%	1.146	138.000	0.150	89.000	-0.011	105.333	0.053
HTR 8	50%	1.026	157.000	0.308	84.000	0.012	108.333	0.136
DC 1	50%	1.388	138.000	0.113	77.000	-0.013	97.333	0.043
DC 2	50%	1.412	159.000	0.233	86.000	-0.034	110.333	0.078
DC 3	50%	1.019	138.000	0.302	73.000	-0.014	94.667	0.118
DC 4	50%	1.403	143.000	0.222	84.000	0.012	103.667	0.099
DC 5	50%	1.143	137.000	0.257	79.000	-0.013	98.333	0.097
DC 6	50%	1.660	128.000	0.243	78.000	0.000	94.667	0.097
DC 7	50%	1.295	156.000	0.191	61.000	-0.016	92.667	0.090

		Pulsitility Index	MAP					
			Systolic (mmHg)	Relative (%)	**Diastolic** (mmHg)	Relative (%)	**Mean** (mmHg)	Relative (%)
AM 1	70%	1.201	176.000	-0.238	85.000	0.063	115.333	-0.115
AM 2	70%	1.560	208.000	0.612	83.000	-0.046	124.667	0.234
AM 3	70%	2.013	205.000	0.120	72.000	-0.217	116.333	-0.049
AM 4	70%	1.591	156.000	0.500	69.000	0.113	98.000	0.289
AM 5	70%	1.535	241.000	1.060	83.000	0.186	135.667	0.584
AM 6	70%	1.355	211.000	0.507	98.000	0.032	135.667	0.233
AM 7	70%	1.311	182.000	0.273	79.000	-0.092	113.333	0.073
HTR 1	70%	0.939	170.000	0.405	94.000	0.068	119.333	0.205
HTR 2	70%	1.477	193.000	0.608	82.000	-0.155	119.000	0.137
HTR 3	70%	1.189	162.000	0.350	82.000	-0.109	108.667	0.072
HTR 4	70%	1.528	141.000	0.093	77.000	0.013	98.333	0.050
HTR 6	70%	1.178	213.000	0.626	87.000	0.048	129.000	0.303
HTR 7	70%	1.352	166.000	0.383	91.000	0.011	116.000	0.160
HTR 8	70%	1.036	189.000	0.575	106.000	0.277	133.667	0.402
DC 1	70%	1.309	167.000	0.347	75.000	-0.038	105.667	0.132
DC 2	70%	1.601	178.000	0.380	85.000	-0.045	116.000	0.134
DC 3	70%	1.159	152.000	0.434	72.000	-0.027	98.667	0.165
DC 4	70%	1.452	165.000	0.410	82.000	-0.012	109.667	0.163
DC 5	70%	1.357	145.000	0.330	78.000	-0.025	100.333	0.119
DC 6	70%	1.703	156.000	0.515	77.000	-0.013	103.333	0.197
DC 7	70%	1.284	179.000	0.366	60.000	-0.032	99.667	0.173
AM 1	90%	1.239	193.000	-0.165	86.000	0.075	121.667	-0.066
AM 2	90%	1.812	221.000	0.713	94.000	0.080	136.333	0.350
AM 3	90%	2.100	209.000	0.142	65.000	-0.293	113.000	-0.076
AM 4	90%	1.674	206.000	0.981	75.000	0.210	118.667	0.561
AM 5	90%	1.541	244.000	1.085	92.000	0.314	142.667	0.665
AM 6	90%	1.447	233.000	0.664	87.000	-0.084	135.667	0.233
AM 7	90%	1.490	190.000	0.329	83.000	-0.046	118.667	0.123
HTR 1	90%	1.110	185.000	0.529	97.000	0.102	126.333	0.276
HTR 2	90%	1.762	193.000	0.608	82.000	-0.155	119.000	0.137
HTR 3	90%	1.281	180.000	0.500	81.000	-0.120	114.000	0.125
HTR 4	90%	1.621	181.000	0.403	80.000	0.053	113.667	0.214
HTR 6	90%	1.309	226.000	0.725	87.000	0.048	133.333	0.347
HTR 7	90%	1.490	199.000	0.658	96.000	0.067	130.333	0.303
HTR 8	90%	1.041	211.000	0.758	112.000	0.349	145.000	0.521
DC 1	90%	1.602	183.000	0.476	76.000	-0.026	111.667	0.196
DC 2	90%	1.623	191.000	0.481	86.000	-0.034	121.000	0.182
DC 3	90%	1.103	167.000	0.575	70.000	-0.054	102.333	0.209
DC 4	90%	1.431	172.000	0.470	78.000	-0.060	109.333	0.159
DC 5	90%	1.466	169.000	0.550	76.000	-0.050	107.000	0.193
DC 6	90%	1.759	176.000	0.709	76.000	-0.026	109.333	0.266
DC 7	90%	1.360	187.000	0.427	59.000	-0.048	101.667	0.196

		Pulsitility Index	MAP					
			Systolic (mmHg)	Relative (%)	**Diastolic** (mmHg)	Relative (%)	**Mean** (mmHg)	Relative (%)
AM 1	Peak	1.432	212.000	-0.082	83.000	0.038	126.000	-0.033
AM 2	Peak	1.704	220.000	0.705	89.500	0.029	133.000	0.317
AM 3	Peak	2.078	225.000	0.230	68.000	-0.261	120.333	-0.016
AM 4	Peak	1.617	206.000	0.981	80.000	0.290	122.000	0.605
AM 5	Peak	1.648	247.000	1.111	70.000	0.000	129.000	0.506
AM 6	Peak	1.538	235.000	0.679	119.000	0.253	157.667	0.433
AM 7	Peak	1.411	200.000	0.399	77.000	-0.115	118.000	0.117
HTR 1	Peak	1.172	183.000	0.512	97.000	0.102	125.667	0.269
HTR 2	Peak	1.981	199.000	0.658	76.000	-0.216	117.000	0.118
HTR 3	Peak	1.425	203.000	0.692	82.000	-0.109	122.333	0.207
HTR 4	Peak	1.603	190.000	0.473	88.000	0.158	122.000	0.302
HTR 6	Peak	1.341	234.000	0.786	83.000	0.000	133.333	0.347
HTR 7	Peak	1.487	204.000	0.700	99.000	0.100	134.000	0.340
HTR 8	Peak	1.052	203.000	0.692	114.000	0.373	143.667	0.507
DC 1	Peak	1.810	202.000	0.629	79.000	0.013	120.000	0.286
DC 2	Peak	1.587	200.000	0.550	82.000	-0.079	121.333	0.186
DC 3	Peak	1.068	172.000	0.623	71.000	-0.041	104.667	0.236
DC 4	Peak	1.439	189.000	0.615	76.000	-0.084	113.667	0.205
DC 5	Peak	2.050	173.000	0.587	72.000	-0.100	105.667	0.178
DC 6	Peak	1.927	180.000	0.748	74.000	-0.051	109.333	0.266
DC 7	Peak	1.742	194.000	0.481	58.000	-0.065	103.333	0.216

		HR	Et CO2		CVR		Yrs Post	Age
		Absolute	**Absol**	Relative	**Absolute**	Relative		
		(bpm)	(mmHg)	(%)	(mmHg/cm/s))	(%)		
AM 1	Base	75.500	30.700	0.000	2.784	0.000		59.00
AM 2	Base	65.100	30.700	0.000	2.289	0.000		53.00
AM 3	Base	83.500	26.200	0.000	2.999	0.000		74.00
AM 4	Base	90.580	32.500	0.000	2.031	0.000		69.00
AM 5	Base	71.920	25.200	0.000	2.850	0.000		64.00
AM 6	Base	62.050	29.000	0.000	2.952	0.000		53.00
AM 7	Base	67.500	29.700	0.000	2.052	0.000		58.00
HTR 1	Base	90.580	31.900	0.000	2.881	0.000	12.0	63.00
HTR 2	Base	90.580	31.300	0.000	2.992	0.000	23.0	50.00
HTR 3	Base	96.120	27.400	0.000	2.314	0.000	6.0	65.00
HTR 4	Base	105.700	23.000	0.000	2.286	0.000	1.0	61.00
HTR 6	Base	87.260	30.300	0.000	1.513	0.000	8.5	61.00
HTR 7	Base	100.240	31.200	0.000	3.499	0.000	10.0	78.00
HTR 8	Base	77.670	19.600	0.000	3.063	0.000	4.5	54.00
DC 1	Base	75.000	37.000	0.000	1.340	0.000		20.00
DC 2	Base	83.000	32.000	0.000	1.838	0.000		21.00
DC 3	Base	53.000	42.000	0.000	1.192	0.000		24.00
DC 4	Base	78.000	39.000	0.000	1.146	0.000		26.00
DC 5	Base	74.000	34.000	0.000	1.345	0.000		18.00
DC 6	Base	86.000	40.000	0.000	1.342	0.000		22.00
DC 7	Base	53.000	36.000	0.000	1.114	0.000		20.00
AM 1	50%	109.170	36.200	0.179	2.059	-0.260		59.00
AM 2	50%	109.170	36.400	0.186	2.337	0.021		53.00
AM 3	50%	93.550	32.400	0.237	2.527	-0.157		74.00
AM 4	50%	83.090	33.100	0.018	2.246	0.106		69.00
AM 5	50%	95.670	38.400	0.524	2.155	-0.244		64.00
AM 6	50%	105.070	39.900	0.376	2.418	-0.181		53.00
AM 7	50%	105.470	40.000	0.347	1.490	-0.274		58.00
HTR 1	50%	103.790	36.200	0.135	2.918	0.013	12.0	63.00
HTR 2	50%	111.060	36.100	0.153	2.393	-0.200	23.0	50.00
HTR 3	50%	115.420	32.900	0.201	2.496	0.079	6.0	65.00
HTR 4	50%	114.340	28.500	0.239	1.891	-0.173	1.0	61.00
HTR 6	50%	95.300	32.100	0.059	1.662	0.098	8.5	61.00
HTR 7	50%	111.490	33.500	0.074	3.590	0.026	10.0	78.00
HTR 8	50%	97.620	34.900	0.781	2.262	-0.262	4.5	54.00
DC 1	50%	125.000	45.000	0.216	1.090	-0.187		20.00
DC 2	50%	142.000	38.000	0.188	1.623	-0.117		21.00
DC 3	50%	97.000	49.000	0.167	1.097	-0.080		24.00
DC 4	50%	135.000	46.000	0.179	1.061	-0.074		26.00
DC 5	50%	129.000	39.000	0.147	1.323	-0.016		18.00
DC 6	50%	134.000	46.000	0.150	1.209	-0.099		22.00
DC 7	50%	94.000	41.000	0.139	0.975	-0.124		20.00

		HR	Et CO2	CVR	Yrs Post	Age		
		Abs	Abs		Rel		Abs	Rel
		(bpm)	(mmHg)	(%)	(mmHg/cm/s))	(%)		
AM 1	70%	122.50	37.200	0.212	2.116	-0.240		59.00
AM 2	70%	151.54	34.900	0.137	2.437	0.065		53.00
AM 3	70%	100.35	34.000	0.298	2.450	-0.183		74.00
AM 4	70%	100.80	36.500	0.123	2.110	0.039		69.00
AM 5	70%	128.48	39.000	0.548	2.656	-0.068		64.00
AM 6	70%	132.20	39.500	0.362	2.440	-0.174		53.00
AM 7	70%	136.01	40.100	0.350	1.604	-0.218		58.00
HTR 1	70%	126.48	36.600	0.147	3.038	0.054	12.0	63.00
HTR 2	70%	122.41	36.300	0.160	2.360	-0.211	23.0	50.00
HTR 3	70%	124.03	32.000	0.168	2.378	0.028	6.0	65.00
HTR 4	70%	124.80	33.600	0.461	1.755	-0.232	1.0	61.00
HTR 6	70%	123.21	32.000	0.056	2.102	0.389	8.5	61.00
HTR 7	70%	122.69	32.800	0.051	4.069	0.163	10.0	78.00
HTR 8	70%	130.49	33.500	0.709	2.628	-0.142	4.5	54.00
DC 1	70%	171.00	46.000	0.243	1.124	-0.161		20.00
DC 2	70%	181.00	41.000	0.281	1.803	-0.019		21.00
DC 3	70%	154.00	47.000	0.119	1.121	-0.060		24.00
DC 4	70%	174.00	46.000	0.179	1.179	0.029		26.00
DC 5	70%	160.00	38.000	0.118	1.309	-0.027		18.00
DC 6	70%	167.00	48.000	0.200	1.314	-0.021		22.00
DC 7	70%	142.00	40.000	0.111	1.076	-0.034		20.00
AM 1	90%	138.00	33.500	0.091	1.915	-0.312		59.00
AM 2	90%	167.23	25.700	-0.163	2.776	0.213		53.00
AM 3	90%	111.31	33.300	0.271	2.304	-0.232		74.00
AM 4	90%	130.43	35.600	0.095	2.336	0.150		69.00
AM 5	90%	140.05	39.000	0.548	2.765	-0.030		64.00
AM 6	90%	147.80	36.700	0.266	2.602	-0.119		53.00
AM 7	90%	164.54	38.800	0.306	1.877	-0.085		58.00
HTR 1	90%	155.30	34.200	0.072	3.546	0.231	12.0	63.00
HTR 2	90%	142.39	32.200	0.029	2.651	-0.114	23.0	50.00
HTR 3	90%	134.31	30.800	0.124	2.418	0.045	6.0	65.00
HTR 4	90%	138.97	32.300	0.404	2.012	-0.120	1.0	61.00
HTR 6	90%	137.37	30.500	0.007	2.224	0.470	8.5	61.00
HTR 7	90%	146.98	28.600	-0.083	4.860	0.389	10.0	78.00
HTR 8	90%	138.84	33.500	0.709	2.909	-0.050	4.5	54.00
DC 1	90%	189.00	36.000	-0.027	1.269	-0.053		20.00
DC 2	90%	192.00	33.000	0.031	1.984	0.079		21.00
DC 3	90%	194.00	40.000	-0.048	1.377	0.154		24.00
DC 4	90%	182.00	38.000	-0.026	1.505	0.313		26.00
DC 5	90%	187.00	32.000	-0.059	1.439	0.070		18.00
DC 6	90%	180.00	42.000	0.050	1.414	0.054		22.00
DC 7	90%	171.00	32.000	-0.111	1.356	0.217		20.00

		HR	Et CO2		CVR		Years Post Transplant	Age
		Absolute	**Absolute**	Relative	**Absolute**	Relative		
		(bpm)	(mmHg)	(%)	(mmHg/cm/s))	(%)		
AM 1	Peak	146.000	32.000	0.042	2.278	-0.182		59.00
AM 2	Peak	171.750	23.400	-0.238	2.646	0.156		53.00
AM 3	Peak	122.850	31.100	0.187	2.379	-0.207		74.00
AM 4	Peak	138.900	35.100	0.080	2.504	0.233		69.00
AM 5	Peak	159.180	31.700	0.258	2.834	-0.006		64.00
AM 6	Peak	159.550	32.900	0.134	3.220	0.091		53.00
AM 7	Peak	176.300	36.600	0.232	1.721	-0.161		58.00
HTR 1	Peak	163.140	31.400	-0.016	3.694	0.282	12.0	63.00
HTR 2	Peak	159.000	25.400	-0.188	2.582	-0.137	23.0	50.00
HTR 3	Peak	142.630	28.500	0.040	2.619	0.132	6.0	65.00
HTR 4	Peak	144.120	27.800	0.209	2.193	-0.040	1.0	61.00
HTR 6	Peak	139.260	29.400	-0.030	2.285	0.510	8.5	61.00
HTR 7	Peak	158.900	24.200	-0.224	5.124	0.465	10.0	78.00
HTR 8	Peak	159.100	27.800	0.418	3.000	-0.021	4.5	54.00
DC 1	Peak	200.000	23.000	-0.378	1.488	0.110		20.00
DC 2	Peak	204.000	26.000	-0.188	2.116	0.151		21.00
DC 3	Peak	195.000	35.000	-0.167	1.644	0.379		24.00
DC 4	Peak	199.000	27.000	-0.308	1.971	0.720		26.00
DC 5	Peak	192.000	27.000	-0.206	1.969	0.464		18.00
DC 6	Peak	192.000	35.000	-0.125	1.699	0.266		22.00
DC 7	Peak	189.000	25.000	-0.306	1.667	0.497		20.00

AM – Age Matched, HTR – Heart Transplant Recipient, DC – Donor Population Control, MCAv – Middle Cerebral Artery Velocity, MAP - Blood Pressure, Et CO_2 – End Tidal Carbon Dioxide, CVR – Cerebrovascular Resistance, YRS Post – Years Post Transplant

Data is presented as raw data output from LabChart and recorded in Excel, subsequent analysis was preformed in PASW 18.0 and graphs were produced in Sigma Plot.