Evaluation of impedance cardiography (ICG) for assessing hemodynamic parameters in Fontan patients

By
S.-Pedram Hassan-Tash

A Thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

in partial fulfilment of the requirements of the degree of

MASTER OF SCIENCE

Department of Physiology and Pathophysiology

Max Rady College of Medicine

University of Manitoba

Winnipeg, Manitoba, Canada

Abstract

Introduction: Hemodynamic assessment using currently available methods is particularly challenging in the Fontan population. Patients with Fontan circulation are generally described to have chronically low cardiac output (CO) and high central venous pressure (CVP). Reduced exercise capacity is amongst many adverse effects associated with Fontan circulation. We set to firstly examine accuracy and reproducibility of a non-invasive technology in hemodynamic assessment and, secondly to evaluate resting, and post-exercise hemodynamics in patients with Fontan circulation using this non-invasive means. Amongst available non-invasive hemodynamic assessment technologies, whole body impedance cardiography (ICG) has been gaining popularity. Amongst available ICG devices, Non-invasive Cardiac System (NICaS, NI Medical) had performed well throughout various validation studies.

Material and method: In the first part of the project, forty-one patients undergoing cardiac magnetic resonance imaging (CMR), as part of their standard of clinical care, were investigated using NICaS 10 minutes prior to undergoing CMR. The stroke volume (SV) generated by NICaS was compared to aortic forward flow volume measured by CMR. To evaluate the reproducibility of NICaS, 10 of the participants chosen at random were re-investigated by NICaS 15 min post-CMR. In the latter part, twenty-one patients with Fontan circulation and 21 age and sex matched healthy participants were assessed by cardiopulmonary exercise testing (CPET) using treadmill ergometer and breath gas analyzer. Their resting and post-exercise hemodynamic parameters were also measured using NICaS.

Results: Data from 39 patients was available for comparison of CMR to ICG. 15/39 (39%) were female; mean ± SD age and body mass index (BMI) were 54 ± 15 years (range: 27 - 86 years) and 28.6 ± 5.5 kg/m^2 (range: 20.5 - 41.9 kg/m^2) respectively. NICaS derived SV strongly correlated

with aortic forward flow measured by CMR, with Pearson correlation factor (r) of 0.78, and significance (p) of < 0.05. The Bland-Altman limits of agreement between NICaS and CMR were -22 and 36 ml, and bias found to be 7 ml. Repeat NICaS measurements of SV pre- and post-MRI in 10 subjects were markedly similar (pre: 80 ± 18 ml (range: 51 - 102 ml) vs. post: 76 ± 17 ml (range: 50 - 99 ml); Kappa = 1). In our CEPT part, the mean ± SD age amongst Fontan and control groups was 28 ± 10, and 29 ± 6 years old respectively. Sex ratio of male/female was 14/7 in both groups. Fontan group showed a significantly lower mean peak oxygen consumption (peak VO_2) compared to control (23.6 ± 5.5 vs. 43.2 ± 9 ml/Kg/min; $p < 0.05$). Fontan had a significantly higher ventilatory efficiency which is demonstrated as minute ventilation to carbon dioxide production ratio (VE/VCO_2) (40 ± 5 vs. 32 ± 4; $p < 0.05$). Fontan participants on average had a significantly lower resting SV, CO, and significantly higher resting HR when compared to control (respectively: 50.7 ± 16.4 vs. 88 ± 20 ml, $p < 0.05$; 3.9 ± 1.6 vs. 5.6 ± 1.1 l/min, $p < 0.05$; 77 ± 14 vs. 65 ± 11 beats/min, $p < 0.05$).

Conclusion: NICaS derived SV demonstrated strong correlation with aortic forward flow volume assessment of CMR. NICaS additionally exhibited excellent reproducibility. Additionally, in later part of our work we found that our CPET and ICG assessments are in keeping with previously published data in the Fontan population. As such we believe it would be feasible to incorporate use of NICaS in clinical research and routine clinical care of patients with Fontan circulation.

Table of contents

Table of Abbreviations:

AC	Alternating Current
ACE	Angiotensin Converting Enzyme
ACHD	Adult Congenital Heart Disease
Ao	Aorta
ARB	Angiotensin Receptor Blocker
ASA	Acetylsalicylic Acid
ASD	Atrial Septal Defect
BP	Blood Pressure
B-T	Blalock-Taussig shunt
CCB	Calcium Channel Blocker
CHD	Congenital Heart Disease
CMR	Cardiac Magnetic Resonance Imaging
CO	Cardiac Output
CPET	Cardiopulmonary Exercise Test
CVP	Central Venous Pressure
ECG	Electrocardiogram
Echo	Echocardiography
HF	Heart Failure
HLV	Hypoplastic Left Ventricle
HRV	Hypoplastic Right Ventricle
ICG	Impedance Cardiography
IVC	Inferior Vena Cava
LA	Left Atrium
LV	Left Ventricle
NICaS ™	Non-Invasive Cardiac System
NOAC	Novel Oral Anticoagulation
PA	Pulmonary Artery
PDE	Phosphodiesterase
PS	Pulmonary Stenosis

PV	Pulmonary Vein
PVR	Pulmonary Vascular Resistance
RA	Right Atrium
RV	Right Ventricle
SSFP	Steady-State Free Precession
SV	Stroke Volume
SVC	Superior Vena Cava
SVR *	Systemic Vascular Resistance
TA	Tricuspid Atresia
TPR*	Total Peripheral Resistance
TPRI	Total Peripheral Resistance Index
Tx	Transplant
UVH	Univentricular Heart
VCO_2	Carbon Dioxide Production
VE	Minute Ventilation
VO_2	Oxygen Consumption
VSD	Ventricular Septal Defect

* These two terms are used interchangeably.

List of Figures

List of Tables

List of Equations

Chapter 1: Literature review

Introduction to Fontan

Documentations of cyanosis due to congenital heart disease (CHD) go back to about 200 years ago. Discoloration and hasty deterioration of infants, only a few weeks old, prompted the observant physicians to report their autopsy findings. Various CHDs were described in the first half of the 19th century. One such congenital cardiac anomaly is tricuspid atresia (TA). Although the term TA was coined in the early 1860s, it did not appear in English literature until the early 20th century.[1–3] Campbell believed most patients suffering from TA would benefit from a shunt creation until the day comes when a more curative method is pioneered.[1,4] Later on, a handful of great physicians aspired that healing a "blue baby" with congenital TA should not be beyond the reach of science, and as a result of their work the foundation to Fontan's procedure was set.[5] In 1971, Fontan and Baudet published the first series of their techniques in early "Fontan" procedures. Such a procedure overall included superior vena cava to be directly connected to pulmonary circulation whereas inferior vena cava will connect to pulmonary arteries through right atrial appendage (classic Fontan circulation) leading to passive filling of the pulmonary circulation. Then Patient's anatomical/functional single ventricle was placed such that it would pump blood through the systemic circulation. This created a systemic venous circulation that is connected directly to pulmonary circulation without a sub-pulmonary ventricle.[6]

Left uncorrected, a defect resulting in functionally univentricular heart (UVH) can lead to hypoxemia and early heart failure. The small percent of those surviving childhood suffer from very poor quality of life during teenage years and rarely enter adulthood. Retrospective review of patients treated with Fontan procedures, performed between 1973 and 1998 at Mayo clinic,

demonstrated improved longevity.[7] Although originally intended to treat patients with TA, the Fontan procedure has remained the standard of care in treating patients born with a range of CHDs, not amenable to bi-ventricular repair. This method has been refined over recent time, resulting in various sub-classes of Fontan patient population such as classic Fontan circulation (right atrial appendage connected to the pulmonary artery), lateral tunnel Fontan (a baffle created with either prosthetic material or atrial tissue connecting inferior vena cava (IVC) to the pulmonary circulation), and extra-cardiac Fontan (incorporating a prosthetic tube that connects the IVC to the pulmonary circulation).[8]

In Figure 1we have elected to depict TA, a subset of congenital heart abnormality requiring Fontan operation (on the left), and one of the subtypes of Fontan repair, extra cardiac Fontan (on the right). (These figures are produced by author through hand drawing and are influenced by Dorland's illustrated medical dictionary and Kojima et al., 2020. [9,10])

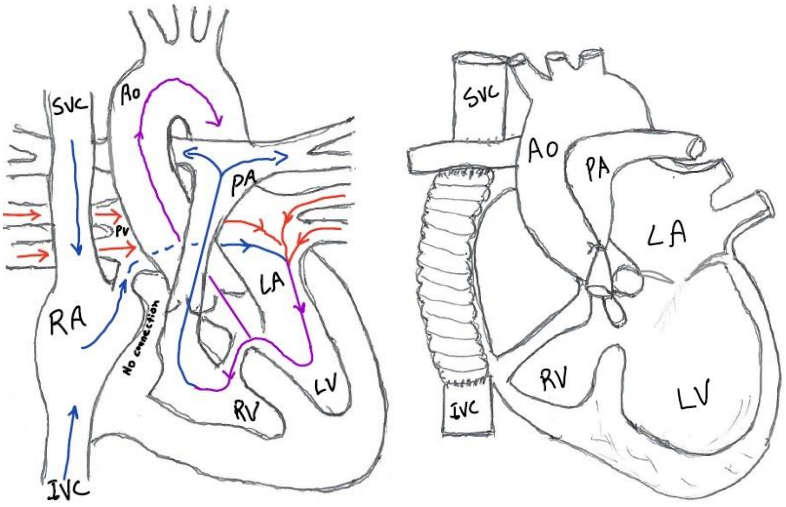

Figure 1 - Tricuspid atresia (left) and extracardiac Fontan (right)

On the left: demonstrating TA in which blood from vena cavae system flows to RA. Given the lack of connection between RA and RV, blood flows through congenital shunt to PV and then to LA. Hence bypassing pulmonary circulation. On the right: Extra cardiac Fontan, where IVC is attached to PA via a conduit. This enables the systemic venous blood to flow through the pulmonary system.
SVC: superior vena cava, RA: right atrium, IVC: inferior vena cava, PV: pulmonary vein, LA: left atrium, LV: left ventricle, RV: right ventricle, Ao: aorta, PA: pulmonary artery

Epidemiology

Marelli estimated prevalence of CHD to be around 11.9/1000 amongst children in year 2000, with 1.5/1000 being a severe form of CHD. With improvements of medical and surgical management, more children with CHD survive childhood and enter adulthood. Between 1985 and 2000, the average age of a CHD patient increased by 6 years owing to an 85% increase in adult congenital heart disease (ACHD) population as a result of better survival outcome in affected children.[11]

Fontan is a sub-population of CHD. Despite its shortcomings, the Fontan physiology is still the main palliation used for management of certain patients born with a range of complex CHDs. Nowadays, most patients who undergo Fontan procedure survive childhood and adolescence and

their care is subsequently transitioned to ACHD specialists. In 2019, the global population of Fontan patients was estimated to be about 70,000, with predicted doubling time of about 20 years.[12]

Long-term outcomes in Fontan circulation

The Fontan procedure improves longevity and quality of life in patients with complex CHD. Fontan physiology has been shown to deteriorate relatively faster compared to normal cardiovascular circulation. Limited knowledge and the short time elapsed since refinements of Fontan technique, makes it challenging to be certain about long-term consequences of Fontan circulation.[13]

Despite satisfactory initial outcomes, Fontan circulation inherently has (1) low cardiac output (CO), and (2) chronically elevated central venous pressure (CVP) that lacks pulsativity; both aforementioned factors contribute to long-term complications of Fontan circulation.[14,15]

Long-term complications associated with the Fontan circulation include (1) liver damage eventually leading to cirrhosis, (2) atrial tissue stretch (especially in the patients with classical Fontan) leading to arrhythmias, (3) renal dysfunction (secondary to chronic low CO state and chronic venous congestion, affecting trans-renal perfusion pressure), (4) protein loosing enteropathy (perhaps due to increased mesenteric vascular resistance), (5) venous stasis and increased thrombogenicity (likely secondary to sluggish flow), (6) muscle wasting (7) immunological, and (8) metabolic derangements.[12,14]

Current clinical assessment

The growing population of adult patients with Fontan circulation demands a directed multidisciplinary approach.[16] Assessment of Fontan is a comprehensive approach that includes multisystem assessment with particular attention to cardiovascular system. Currently, adult

patients with Fontan circulation are seen in adult congenital heart clinic and undergo a historically accepted series of evaluations with in-depth history and physical examination, blood work, electrocardiogram (ECG), cardio-pulmonary exercise stress test, echocardiogram (echo), CMR and cardiac catheterization. These tests are aimed at evaluating Fontan circulation, and various specific organ functionality, mainly liver, kidney, and endocrine.[12]

Amongst the commonly used clinical assessments we would like to mention and briefly discuss the following means:

Electrocardiography (ECG):

Used to assess underlying heart rhythm, to identify sinus or atrio-ventricular conduction abnormalities.

Trans-thoracic echocardiography (TTE):

Amongst well-established non-invasive hemodynamic assessment approaches, echocardiography (echo) uses geometrical assumptions and velocity time integral, is not always accurate and is heavily dependent on the operator's skills. Geometrical assumptions used in constructing and interpreting TTE reports, do not always hold true in instances of all CHDs.[17,18] Decrease quality of acoustic window due to multiple previous thoracic surgeries in this population, or its poor accuracy in assessment of shunts are amongst other drawbacks of this modality.[19]

TTE is often performed annually with the aim of identifying any interval change in ventricular function, atrio-ventricular valvular pathology, and flow patterns.

Cardiopulmonary exercise test (CPET):

Cardiopulmonary exercise test is an in-depth test of functional capacity. Such test, when performed at regular intervals, can demonstrate any real interval change that is usually difficult to perceive

otherwise. CPET can also help differentiate limitations due to cardiovascular, respiratory, or musculo-skeletal systems. CPET has been deemed a prognostication gold standard in the Fontan population. It is the changes of peak oxygen consumption (VO_2) over time that is informative of outcome and not a onetime baseline assessment.[20] CPET is not without shortcomings: requiring specialized facility and staff, costly, difficult to undergo for frail patients.[21]

Cardiac magnetic resonance (CMR):

Cardiac magnetic resonance (CMR) is considered to be a gold standard investigational tool for assessment of ventricular function and SV measurement.[22] Although essential in care of patients with CHD, routine CMR has its own limitations. Claustrophobic patients or those with metal or device implants may not be able to undergo CMR. Additionally, issues such as portability, cost, and a lengthy and uncomfortable procedure, limit its utility. Stainless steel artifacts, consequence of Fontan's multiple previous sternotomies, lowers imaging quality.[23,24] Furthermore, hemodynamic assessment during exertion while undergoing CMR is only possible in a few specialized centers around the world as it requires an MRI safe ergometer, and skilled operators.[22,25] This method's reproducibility in certain heart conditions (such as valvular pathologies and …) has also been questioned. [26]

Cardiac catheterization:

Gold standard for CO measurement is invasive cardiac catheterization. This method only became widely used after development of relatively safer and specialized instruments for the task.[27] This modality is utilized for more accurate pressure and flow characterization. In addition to its invasive nature, it includes undesirable contrast and radiation exposure.[19] Besides the obvious unattractiveness of an invasive procedure, cardiac catheterization for CO calculation has the following disadvantages: requires specialized facility and staff, costly, not suitable for frequent

and continuous monitoring, it was never challenged against a previously universal gold standard, and particularly relevant to CHD is that extra and intracardiac shunts affect the accuracy of CO measurement.[27,28]

As we gain more insight into Fontan circulation, it is becoming clearer that some traditional ways of assessing a biventricular failure may not necessarily be suitable to this population.

Current patient management

Current management of Fontan patients is mainly targeted at symptomatic relief. Despite many similarities to acquired heart failure, none of the conventionally accepted heart failure therapies have shown prognostic benefit in patients with Fontan circulation. At later stages of clinical deterioration patients may present with a range of symptoms, described under the umbrella term "failing Fontan" (also known as Fontan failure). These patients are considered for risky treatment options such as heart and liver transplantation.[29–32]

Transplant (Tx):

Despite improved surgical techniques and outcome, heart failure remains a common cause of death in Fontan patients. Factors such as male gender, atrio-ventricular valve insufficiency, arrhythmia, or systemic right ventricle adversely affect the overall outcome in Fontan.[33]

Although heart transplantation improves longevity and quality of life for the majority of Fontan patients, these patients still remain at higher risk of mortality post successful heart transplantation, in comparison to those undergoing heart transplantation for non-Fontan indications.[34] Factors such as multiple blood product transfusions, may negatively affect outcome of Tx.[35] In cases of Fontan failure, by the time of need for heart Tx there has been forced adaptations in anatomy that may be significant enough to increase the risks of the operation. By

the time of heart Tx, the majority of Fontan patients have developed liver dysfunction ranging from fibrosis to cirrhosis and even hepatocellular carcinoma and would require a work up by the liver transplant team as well.[36,37].

Introduction to Fontan exercise hemodynamics

A physiological system's ability to augment CO during exertion is vital to its survival. CO is determined by chronotropy, inotropy, preload and afterload. If ventricular function is not severely impacted, Fontan's CO is heavily reliant on preload. Due to lack of adequate preload reserve, when a Fontan heart rate (HR) is augmented in the physiologic range, the CO is not augmented as much. CO in the patients with Fontan circulation is more pre-load dependent than the patients with bi-ventricular circulation. A determining element of Fontan preload is pulmonary vascular resistance (PVR).[38] In Fontan circulation, energy provided by the systemic ventricle must work through not only the systemic vascular resistance (SVR), but also the PVR. Fontan circulation surprises experts in terms of longevity it provides in reality, versus what is expected based on baseline exercise capacity. Given the constellation of comorbidities associated with Fontan circulation, and diminished cardiopulmonary exercise capacity as a result of Fontan physiology, experts were not expecting the longevity benefit that is observed in this population in real life.[14]

Fontan exercise capacity and hemodynamic assessment

As more individuals with Fontan palliation live long enough to transition into ACHD clinics, the demand is higher than ever to clinically follow these patients. Despite poor baseline hemodynamic performance compared to "norm", it is estimated that about 80% of Fontan patients will survive into the fourth decade of life. Some of this success may be owed to refined and

improved Fontan operation.[33] Such patients are investigated by CPET at a regular interval to identify any interval change.

Oxygen consumption (VO_2) is dependent on SV, HR, lung oxygenation and tissue extraction. Peak VO_2 is achieved when VO_2 reaches a plateau after initial increase in response to exercise (external stress). The role of peak VO_2 assessment in prognostication of certain heart diseases has been established.[21]

A marker of ventilation efficiency measured during CPET, VE/VCO_2, uses minute ventilation (VE) and carbon dioxide production (VCO_2) ratio to convey information regarding the individual's need to breathe a certain volume of air in exchange for a given unit of CO_2.[21,39]

Attempts to expand monitoring benefits of CPET in the general CHD or HF populations to the Fontan population have been made. CPET interpretation is not as well understood in Fontan as it is in HF.[40]

Treadmill CPET is overall a safe and reproducible study. During treadmill CPET a breath-by-breath analyzer calculates VO_2, using Fick's principle as the foundation. This method's inclusivity of both CO (representing cardiac health) and oxygen delivery and use (representing cellular and pulmonary health), makes it an ideal holistic clinical tool.[41] Its prognostication ability has been well studied and established in different cardiac patients including Fontan.[20,42–45] Although the predictive value of baseline CPET in CHD has been praised before, it is its trend over time that is of value in Fontan and not the one-time base-line assessment. Adverse events can very well be predicted based on serial CPET and monitoring peak VO_2 changes over time.[40,45–47]

In considering exercise-limiting factors, inability to sufficiently augment CO is amongst the main contributing factors to Fontan's below average exercise performance.[48]

Factors such as inability to augment SV have been deemed a key limiting factor in Fontan's poor CO augmentation (i.e., inadequate flow reserve relative to biventricular heart).and peak VO_2 performance. Chronotropic incompetence, although observed, is not a major player in poor CPET performance of Fontan.[49–51]

Characteristics of an ideal SV assessment tool

As discussed above Peak VO_2 has demonstrated to be of value in terms of clinical prognostication. Peak VO_2 obtained during CPET has been used as a surrogate for SV.[50] This prompted us to further consider the study of a non-invasive SV monitoring device with certain predefined characteristics. An ideal tool for monitoring SV must possess the following qualities: cost effective, non-invasive, quick, operator independent, reproducible, accurate, precise, continuous, easy to set up and use.

ICG

The need for non-invasive hemodynamic monitoring in the clinical setting has been demonstrated and discussed above. HR, SV, CO and SVR are amongst highly desirable parameters amongst clinicians. From guiding real time therapy in critically ill patients to determining long term prognosis, these hemodynamic parameters provide a wealth of clinical information. Although there are physical examination techniques that aid clinicians to estimate these values, accuracy of estimates obtained this way has been questioned.[52]

Modern day user friendly, cheap, non-invasive and continuous HR monitoring has roots in the late 1800s, when the first human heart electrocardiogram (ECG) was recorded.[53] Nowadays ECG is a widely utilized technology in hospitals and clinical settings for rate and rhythm monitoring. When it comes to SV and CO monitoring, the available clinical standards lack

qualities such as ease of use, cost effectiveness and/or being non-invasive. The use of more invasive methods are limited to deteriorating or very sick patients, and the use of more costly method of CMR is spaced out in time and lacks continuity due to the nature of this assessment tool, as it is not possible to undergo such assessment continuously.[54]

Direct SVR measurement in a clinical setting is inherently challenging. However, with the aid of physiology of hemodynamics and understanding of Fick's principle, it has been shown that CO can be estimated from HR and SV; and SVR from CO and BP.[55–58]

Given the excellent accessibility of ECG and BP machines in the clinical setting, and the central role of SV in estimating CO and SVR, efforts have been made to non-invasively assess SV. Amongst the available methods, impedance cardiography (ICG) has attracted clinical researchers. A variety of prototypes and commercial versions have been produced. From those using only thorax to others using whole body, they all rely on similar principal. An external low alternating current (AC) at high frequency is sent through the body, the change in this AC is caused by the body hindering the flow of electricity and causes a change in voltage between two points on the body. The cause of this change is known as bioimpedance, and depends on resistance (determined by body composition) and reactance (determined by cellular composition).[59,60] The use of bioimpedance in assessing SV is known as ICG. Backed by The National Aeronautics and Space Administration, Kubicek et al.'s published method of SV calculation, based on regional body impedance was amongst the first to put this idea into practice.[54,61] Later modifications of his algorithm by different scientists and companies have led to overall improvement of ICG technology.[62]

Integration of ICG in research and intensive care settings has been gaining popularity. This assessment tool takes advantage of recognizing changes in the conductance of the body as SV is

pumped through the vasculature. The change in diameter of vasculature (as SV passes through) changes the body's resistance to AC. Impedance is non-invasively measurable; based on body's impedance when given certain patient characteristics such as sex, age, height, weight, hemoglobin level, and electrolyte levels ICG devices are able to calculate SV. The whole body impedance variations of this technology have demonstrated excellent agreement with thermodilution (TD).[63,64]

Non-invasive cardiac system (NICaS), produced by NIMedical, is a whole body ICG technology. This tetrapolar tool, uses two electrodes (one special sticker) placed preferably on a wrist and another special sticker on the contralateral ankle. It takes advantage of formulae discussed in patents authored by Tsoglin and Frinerman at the end of the 1990s. The formula takes into account body habitus, age, sex, and other factors affecting electrical conductance of blood and body. [65,66]

Many devices utilizing ICG exist on the market. Although concepts utilized are alike, each device uses a different correction factor based on assumptions set by the producers. The correction factors utilized in the estimation of SV affect the accuracy. NICaS has done an acceptable job developing their algorithm yielding an SV in close agreement with reference methods. [67–73] Despite a few reports of poor correlation between ICG and a reference method, numerous other studies were satisfied with the agreeability of ICG and reference methods. The studies showing poor correlation used the less desirable thoracic ICG technique and not NICaS per se; later, studies similar in design were not able to confirm the reported lack of agreement.[67–73]

Whole body ICG, when incorporated into clinical practice, has the potential to provide clinicians with additional information vital to patient care. Monitoring a variety of conditions, as

well-known as hypertension to complex congenital heart diseases, can immensely benefit from integration of this technology into clinical practice.[67,74]

At first we set to investigate how well the SV measured by NICaS agrees with CMR. This inexpensive, easy to use tool is ideal for continuous hemodynamic monitoring. If it demonstrates acceptable agreement with CMR, then we will use it during Fontan CPET assessment.

Commonly used concepts

Here we provide a brief review of certain values and concepts frequently used in this project. Awareness of the following concepts provides a better understanding of the underlying theme here:

The fascination with measuring CO and SV goes back to times of Eugen Fick. Fick's principle states VO_2 is a product of CO and arteriovenous oxygen difference.[75]

VO_2 = CO x arteriovenous oxygen difference

Equation 1 - Fick's Principle

CO is the volume of blood pumped through the body over time. The relationship between CO and other hemodynamic values is shown in a mathematical format in **Equation 2** and **CO =** MAP/TPR **Equation 3**.[57]

CO = HR x SV

Equation 2 - Cardiac output (CO) as a product of heart rate (HR) and stroke volume (SV)

CO = MAP/TPR

Equation 3 - Cardiac output (CO) equals mean arterial pressure (MAP) divided by total peripheral resistance (TPR)

At times CO and flow, and systemic vascular resistance (SVR) and TPR may be used interchangeably. Fundamentally all ICG devices can detect and measure changes in body impedance (ΔZ) and use it to calculate SV. Based on Ohm's law, when considering direct current (DC), voltage (V) is a product of current (I) and resistance (R). When considering alternating current (AC) R is replaced with the term impedance (Z, measure of material's hinderance to AC). If a known current is applied throughout the assessment, $\mathbf{\Delta V} = I \times \Delta Z$

Equation 4 demonstrates how measuring the change in voltage (ΔV) across a circuit can provide sufficient input to calculate change in impedance.[76] The human body is a conductor of electricity and can act as a circuit. ICG devices apply a known low amplitude current across two points on the body and are capable of measuring the voltage difference across 2 points on the body.

$$\Delta V = I \times \Delta Z$$

Equation 4 - Ohm's law, change in voltage (ΔV) is a product of current (I) and change in impedance (ΔZ)

The body's ability to conduct electricity depends on factors such as: electrolyte balance, cell membrane make up, blood content, direction of red blood cell movement, temperature, length and diameter of the body section acting as a circuit, amount of gas, fluid or solid in said circuit. Fundamentally impedance is a function of conduction path length (L) divided by its surface area (SA); considering volume (V) is a product of SA and L the classical formula to calculate value of impedance is shown in $\mathbf{Z} = \rho (L2/V)$

Equation 5.[76]

$$Z = \rho (L^2/V)$$

Equation 5 - Impedance (Z) equals to resistivity of conduction material (ρ) multiplied by the value obtained by dividing length (L) squared by volume (V)

After many years and numerous modifications by different scientists and scientific groups, Tsoglin and Frinerman in 1992 produced a finely tuned semi-empirical formula that is very close to the formula employed by NICaS today. This formula is shown in **SV =** (Hctcorr / $Ksex_{, age}$) x kel x Kwt x IB x (H2 x ΔR / R) x (α + β / β)

Equation 6.[77]

$SV = (Hct_{corr} / K_{sex, age}) \times k_{el} \times K_{wt} \times IB \times (H^2 \times \Delta R / R) \times (\alpha + \beta / \beta)$

Equation 6 - Stroke volume (SV) is calculated based on Hct_{corr} (hematocrit correction factor proportional to measured hematocrit), K_{el} (coefficient related to blood electrolytes), K_{wt} (coefficient related to participant's weight), IB (index balance which is equal to measured extracellular fluid / the expected extracellular fluid volume), $K_{sex,age}$ (coefficient depending upon a patient's sex and age), H is individual's height, ΔR is the change in the resistance portion of the bioimpedance during cardiac cycle, R is the baseline whole body bioresistance and α + β / β is the ratio of the systolic time plus diastolic time / the diastolic time.

Further minor modification of SV = (Hctcorr / $Ksex_{, age}$) x kel x Kwt x IB x (H2 x ΔR / R) x (α + β / β)

Equation 6 by incorporating a hydration factor has yielded a formula that is used by NICaS, which allows this device to calculates SV via measuring impedance.[78]

Chapter 2: Study rationale and methods

Rationale

There is a need for a hemodynamic assessment tool that is cost effective, operator independent, portable, non-invasive, quick, with continuous monitoring ability in clinical research and clinical settings. Amongst the available methods of hemodynamic monitoring, the ICG technique has been drawing scientists' attention. Once available, SV can be used to derive a range of hemodynamic parameters. Determining HR and SV allows for the calculation of CO. Furthermore, given the availability of non-invasive BP devices, from CO and BP it is possible to calculate TPR (used interchangeably with SVR).

NICaS, approved by US Food and Drug Administration (FDA) 510(K) No. K080941 (July 2009)[78] and Health Canada, has shown promising performance over the years. However, like other assessment tools and tests in medicine its approved use is limited. To be able to expand the use of this device to more general scenarios (i.e., "off label" use until enough evidence is collected for approval) further studies to monitor its behaviour in different medical conditions and under different settings is still required.[63,69,77,79–81]

First, we set to assess the precision and accuracy of NICaS against CMR. Then we assessed the utility of NICaS in a clinical research setting with particular focus on Fontan hemodynamic assessment.

Hypothesis

(i) NICaS SV assessment is comparable with aortic forward flow volume obtained from CMR. (Inter-device/method agreement)

(ii) SV measured by NICaS closely resembles itself when repeated on the same person shortly after. (Intra-device/method agreement)

(iii) The CPET obtained peak VO_2 values measured at our lab in Fontan, are comparable with that that of previously published values.

(iv) ICG is suitable to detect differences in hemodynamics of normal cardiovascular system and Fontan circulation

(v) SV at rest measured by ICG, correlates well and significantly with peak VO_2.

Expected outcomes

(i) ICG derived SV will resemble aortic forward flow measured by the systemic ventricular assessment gold standard, CMR.

(ii) ICG technology will demonstrate good intra-device consistency.

(iii) Peak VO_2 in Fontan using CPET at our lab will be in keeping with that measured at other institutions.

(iv) Fontan will have a lower SV compared to Control.

(v) SV at rest measured by NICaS, can predict peak VO_2 in both Fontan and Control.

Methods

Approval from both The University of Manitoba Research Ethics Board and the St. Boniface Hospital's Office of Clinical Research was obtained before the start of each project. Both parts A and B were prospective observational clinical studies combined with retrospective medical chart review.

Study population

ICG Vs. CMR Validation cohort

Forty-one adult patients who presented to St. Boniface Hospital MRI center in Winnipeg to undergo CMR as ordered by their physicians for their own medical indication, consented to partake in our study. Their characteristics are shown in **Table 1**.

CPET and ICG hemodynamic values

For the Fontan arm of the study, twenty-one adult Fontan patients followed up by Manitoba Adult Congenital Heart Clinic agreed to participate in our study. For the control arm, information flyers were displayed around St. Boniface Hospital and University of Manitoba Active Living Center. Applicants were enrolled after a screening process, ensuring they are free of any known cardiovascular disease or comorbidities and to age and gender match them with the Fontan group.

NICaS Analysis

ICG Vs. CMR Validation

Prior to CMR, participants were placed in a quiet section to relax in supine position for 10 minutes. Then, a NICaS special electrode (sticker) was placed over the radial artery of left wrist and a second one over posterior tibialis artery of right ankle. In occasions where this configuration was not possible (e.g. amputation, overlying infection) right wrist/left ankle or wrist/wrist configurations were used. Given there is a correction factor built into the NICaS algorithm for these configuration adjustments, ideally these modifications should only have an insignificant effect on measurements. Participants were asked to relax and maintain their supine position. Five to ten minutes of measurements were recorded. Afterwards, patients proceeded to CMR. Radiologists interpreting CMR were blinded to SV measured by NICaS.

Ten of the participants were randomly selected and agreed to undergo NICaS measurements both before and after their CMR; this was done to evaluate intra-device reproducibility. After the completion of their CMR, and allowing 10 minutes for the participants to relax again, they underwent NICaS SV assessment in the same manner as pre-CMR.

CPET and ICG hemodynamics

Participants were scheduled to attend an assessment session at Active Living Center (ALC) of University of Manitoba. During this session, they underwent NICaS assessment once pre-CPET to assess resting SV and associated hemodynamics and again immediately after their CPET while their body was still in an excited state from the CPET. Pre-CPET, participants were placed in a supine position and NICaS special electrodes (stickers) were applied the wrist/contra lateral ankle or wrist/wrist in a similar manner as described above. Post-CPET, participants underwent NICaS assessment within one minute.

Detail on MRI protocol

Participants in the ICG vs. CMR validation group underwent CMR assessment as part of their standard medical care. The CMR protocol has been put in place by St. Boniface Hospital MRI center and Department of Radiology and utilizes 1.5 Tesla MRI scanners, following standard protocols.[82,83] Patients are placed in the CMR machine in supine position and breath hold techniques are performed while acquiring images. Radiologists use semi-automated recognition of features to make adjustments manually to the contour to be used in stacked disc (i.e. Simpson's method) to assess left ventricle. Radiologists' assessment was then reported as part of the patient's medical record. We reviewed these reports and extracted the stated left ventricular forward flow to be used in our study for comparison to NICaS reported SV.

Out of the 41 patients, due to CMR technical issues, 2 of the patients' CMRs were deemed inadequate and their SV were not reported. Hence the data from 39 study participants was used for analysis.

Exercise session

During the CPET sessions, participants were taken to the assessment area of University of Manitoba Active Living Center. Their height and weight were measured and recorded. A body composition assessment using InBody 570 body composition device was carried out for each participant, then participant's BP was measured using a manual sphygmomanometer and a stethoscope. Participants were then directed to a bed set up near the treadmill and breath by breath gas analyzer used. While relaxed and lying supine, NICaS assessment was performed. Participants were then asked to stand next to the bed for NICaS evaluation of postural changes in hemodynamics. Participants then transferred on to a treadmill and were fitted with the breathalyzer mask. The well-established modified Bruce protocol (a standard test in cardiopulmonary exercise testing), suitable for those with lower exercise capacity, was used to carry out our CPET.[84,85] In certain instances, particularly amongst Fontan arm, the treadmill test had to be stopped early before reaching maximal effort, due to claudication, significant dyspnea, chest discomfort, or reaching maximal HR.

Statistical analysis

All statistical analysis, correlation graphs and tables were done using Microsoft Excel 2016 and Office 365. Bar graphs are constructed using GraphPad Prism V9.

ICG Vs. CMR Validation

SV calculated by NICaS was compared to aortic forward flow volume measured by CMR, using correlation analysis. Where applicable values are reported as mean ± SD.

Further, we analyzed the agreement between CMR and NICaS by plotting a Bland-Altman graph and calculated bias, and limits of agreements as per literature.[78,86,87]

For the ten participants used to assess intra-device reproducibility, Pearson correlation and Cohen statistics were used, with Cohen value between 0.81 to 1 showing perfect reproducibility.[88]

CPET and ICG hemodynamics

Demographics and body composition values of both Fontan and Control arms are displayed in mean ± SD where appropriate. These values were compared between the two groups using two tailed student t-test ($p < 0.05$ showing significant difference).

CPET and NICaS hemodynamic values in the two groups of Fontan and Control were compared using a two tailed student t-test.

Peak VO_2 obtained during CPET and SV measured at rest immediately prior to the CPET were used in a regression analysis conducted using Microsoft Excel. Based on the assumption that 0 SV has oxygen consumption of 0, the intercept was set to 0 for this regression analysis ($p < 0.05$ denoting significant correlation).

Chapter 3: Results

ICG Vs. CMR Validation

A total of 41 individuals underwent ICG and CMR assessment of their SV. All 41 participants successfully underwent ICG SV assessment. In 2 individuals due to poor imaging quality, the CMR study was voided by the clinical radiologist. Data from 39 individuals who successfully underwent both ICG and CMR assessment were used for comparison. 70% of participants were males, average age of participants was 54 ± 15 years (yr), with average BMI of 28.6 ± 5.5 kg/m^2. Their demographic and anthropometric information is shown in Table 1. This table also lists most frequent indications for CMR and includes noteworthy medical indications for CMR. Amongst these, hypertrophic cardiomyopathies and arrhythmogenic right ventricular dysplasia were the most frequent indications, followed by CHDs.

Table 1 - Participants' information and most frequent reasons for CMR referral.

Total participants (n)	39
Females (%)	15 (30)
Age (yr ± SD)	54 ± 15
BMI (Kg/m2) (mean ± SD)	28.6 ± 5
Most frequent and of note reasons for referral	n
Hypertrophic cardiomyopathy	12
Arrhythmogenic right ventricular dysplasia	4
Tetralogy of Fallot	3
Abnormal EF%	3
Hemochromatosis	3

Ventricular septal defect	2
Previous Ross procedure	1

Data from 39 participants was used for comparison. %Female, average age, average BMI is shown. Indications for CMR are also displayed. Hypertrophic cardiomyopathy was the most frequent indication for CMR request. Amongst the participants, a previous Ross operation, and tetralogy of Fallot were amongst noteworthy mentions.

Using NICaS, participants' average SV ± SD was found to be 77 ± 20.45 ml amongst the 39 participants. The reported aortic forward flow by the clinical radiologist based on CMR assessment had an average ± SD of 84 ± 23.07 ml. (Table 2)

Table 2 – SVs measured by ICG and CMR.

	SV (ml) (mean ± SD)	**Range ml (min - max)**
CMR	84 ± 23	47 - 132
ICG	77 ± 20	31 - 123

This table summarizes the average SV measured by the two modalities of CMR and ICG in 39 participants.

SV measured by ICG device NICaS was compared with SV assessment using CMR as reported by radiologist in 39 participants. SV of participants assessed by ICG showed a strong and statistically significant correlation with that of assessment by CMR, yielding Pearson correlation factor of $r = 0.79$, $p < 0.05$. (**Figure 2**). In **Figure 2** the dotted line ($x = y$) represents most ideal scenario where a dynamic parameter (here SV) assessed by two different modalities would return the same value.

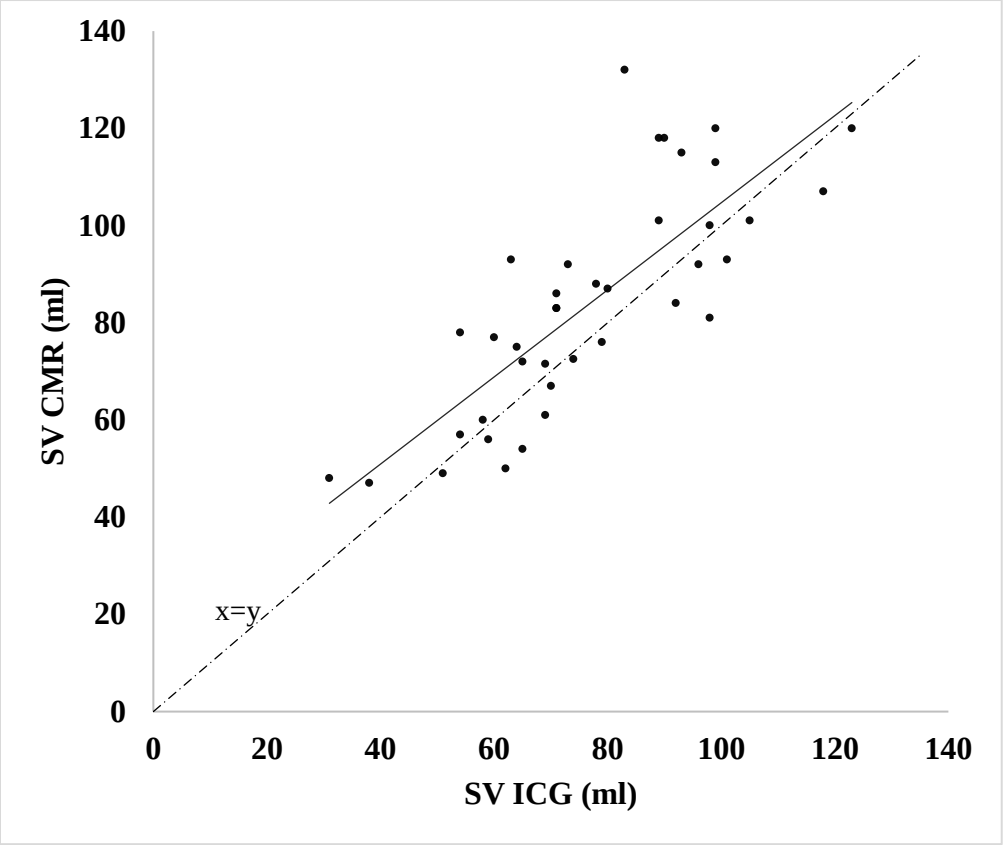

Figure 2 - Pearson correlation between SV measured by CMR vs. ICG. SV in ml measured in 39 participants using two different modalities of CMR and ICG are plotted for each participant. The solid line represents the trend line. Pearson correlation was calculated to be $r = .79$ ($p < 0.05$). The dotted line represents the line of best fit $y = x$.

As part of our investigation into precision of NICaS, its intra-device validity was assessed using 10 randomly selected participants amongst the 39 individuals in our study. Their SV was assessed shortly before and after their CMR session. The average SV measured by NICaS in these 10 individuals before CMR was 80 ± 18 ml, and after CMR 76 ±17 ml. Utilizing Cohen kappa analysis[88], NICaS demonstrated excellent reproducibility with kappa of 1. (Error! Reference s ource not found.)

Table 3 – Assessment of ICG device NICaS' intra-device reliability

Pre-CMR SV (ml) (SV ± SD)	**Post-CMR SV (ml) (SV ± SD)**
80 ± 18	76 ± 17
Pre-CMR SV range (ml) (min. - max.)	**Pre-CMR SV range (ml) (min. - max.)**
51 - 102	50 - 99
Pre- and post-CMR Pearson correlation coefficient (r)	**p**
0.9	0.0007
Cohen's kappa coefficient	
1	

10 individuals were randomly selected to undergo ICG assessment of SV shortly before and after their CMR session. The mean SV measured shortly before and after CMR are reported as Pre-CMR and Post-CMR in this table.

As seen in **Figure 3**, Bland-Altman analysis was chosen for further graphical illustration of differences between the values measured using the two independent techniques of ICG and CMR. On the y-axis the difference between SV measured by ICG and CMR is plotted against the average SV measured by ICG and CMR for each one of the 39 participants. Bias represents the average differences in SV measured by CMR and ICG. Upper (U LOA) and lower (L LOA) limits of agreement were calculated by first calculating two-tailed inverse of the Student's t-distribution of CMR and ICG SV differences, then this value was multiplied by standard deviation of these

differences, and at last the resulting number was added to bias (for U LOA) and subtracted from bias (for L LOA).

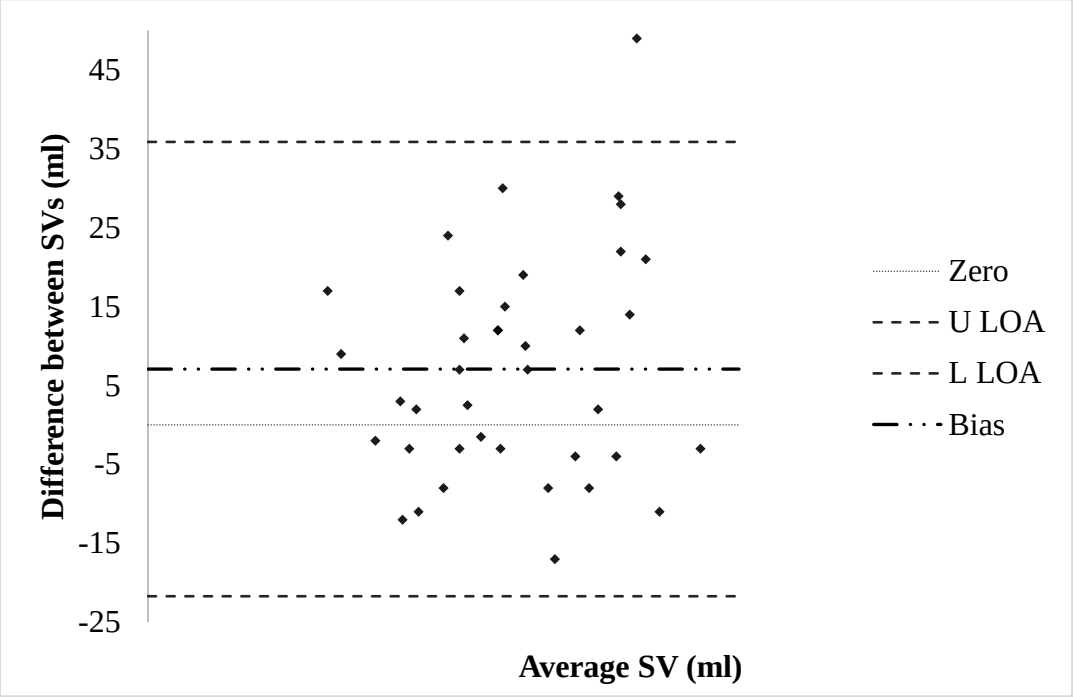

Figure 3 – Bland-Altman graph: Difference between SV measured by the two modalities of CMR and ICG is plotted on the y-axis. This is calculated by subtracting each participant's SV measure by ICG from SV measured by CMR ($SV_{CMR} - SV_{ICG}$). The x-axis represents the average of SV measured by CMR and ICG in each participant.

The values for the elements of this Bland-Altman graph such as bias, upper limit of agreement (U LOA), and lower limit of agreement (L LOA) were calculated to be 7 ml, 36 ml, and -22 ml respectively, these values are summarized in **Table 4**.

Table 4 – Elements of Bland-Altman plot.

Bias (ml)	7
U LOA (ml)	36
L LOA (ml)	-22

CPET and ICG hemodynamics

For this part of the project, 21 participants with Fontan palliation and 21 healthy age- and sex- matched Controls were recruited. Available etiologies necessitating Fontan palliation were obtained through retrospective chart review. These etiologies necessitating Fontan procedure are reported in **Table 5**. Amongst these etiologies, tricuspid atresia and transposition of great vessels tops the list in terms of frequency. Information regarding the type of established Fontan circulation in individuals was also obtained during retrospective medical chart review, and are listed in second part of **Table 5**. Medications taken by the Fontan group and the number of individuals taking the medication is listed in alphabetical order in **Table 5**.

Table 5 - Original diagnosis, Fontan procedure type, and list of medications.

Original Diagnosis:	**n**
Tricuspid atresia	10
Transposed vessels	9
HRV	7
HLV	5
PS	4
VSD	4
Double outlet right ventricle	3
Double Inlet LV	2
Double Inlet RV	2
Hypoplastic aortic arch	2
Mitral atresia	1
Aortic atresia	1
Situs solitus, right hand ventricular topology	1
Juxta-arterial ventricular septal defect (bilateral conus)	1

Double outlet left ventricle	1
Epstein	1
ASD	1
Fontan Type:	**n**
Extracardiac	14
Lateral Tunnel	4
Bjork	1
Atrio-pulmonary	1
Unknown	1
Age of Fontan Circulation at time of study (year) (mean ± SD)	22 ± 6
Medication	**n**
ACE Inhibitors	7
Allopurinol	1
Amiodarone	1
ARBs	1
ASA	13
Beta Blocker	2
CCB	1
Digoxin	1
Diuretic	2
Endothelin Receptor Antagonist	1
NOACs	2
PDE-5 Inhibitor	1
Spironolactone	2
Statin	1
Warfarin	1

Some participants suffered from multiple congenital heart conditions coexisting simultaneously. At the time of our study on average (± SD) 22 ± 6 years had elapsed from the participants' Fontan procedure completion.

Both cohorts had 16 males. Their demographic and anthropometric data were compared using a student t-test, with threshold of significance set at $p < 0.05$. The Fontan and Control groups' average age, height, BMI and body fat did not significantly differ. The two groups'

weight, muscle mass, and resting blood pressure were amongst values that significantly differed between the two groups. The averages and the p values (using 2 tailed student t-test) are shown in **Table 6**. We found that on average Fontan group, despite no significant difference in height, has a significantly lower muscle mass.

Table 6 - Fontan and Control demographics and anthropometric information.

	Fontan (n=21)	**Control** (n=21)	p
Males (%) (mean ± SD)	14(67)	14(67)	-
Age (yrs) (mean ± SD)	28 ± 10	29 ± 6	0.65
Height (cm) (mean ± SD)	170 ± 9	172 ± 9	0.54
Weight (Kg) (mean ± SD)	70 ± 14	78 ± 14	0.047
Body Fat Mass (Kg) (mean ± SD)	19 ± 9	18 ± 8	0.69
Skeletal Muscle Mass (Kg) (mean ± SD)	28 ± 6	34 ± 8	0.01
BMI (Kg/m2) (mean ± SD)	24 ± 4	26 ± 3	0.06
%Body Fat (mean ± SD)	27 ± 10	24 ± 9	0.21
Lean Body Mass (Kg) (mean ± SD)	51 ± 10	60 ± 13	0.01
Dry Lean Mass (Kg) (mean ± SD)	13 ± 3	29 ± 6	0.01
Systolic BP (mmHg) (mean ± SD)	114 ± 11	123 ± 11	0.01

P-value of < 0.05 denotes significant difference between the two groups.

Exercise capacity of both Fontan and Control were assessed during CPET, using a breath by breath gas analyzer. Fontan peak VO_2 was significantly lower than Control, as expected. Average Fontan and Control peak VO_2, $\%VO_2$ max (peak VO_2/Expected peak VO_2 for age, sex, weight, and height), VE/VCO_2, maximum heart rate (HR max) during exercise are reported in Figure 4. As expected, Fontan compared (2 tailed student t-test) to Control, significantly ($p < 0.05$) underperformed in all the aforementioned categories.

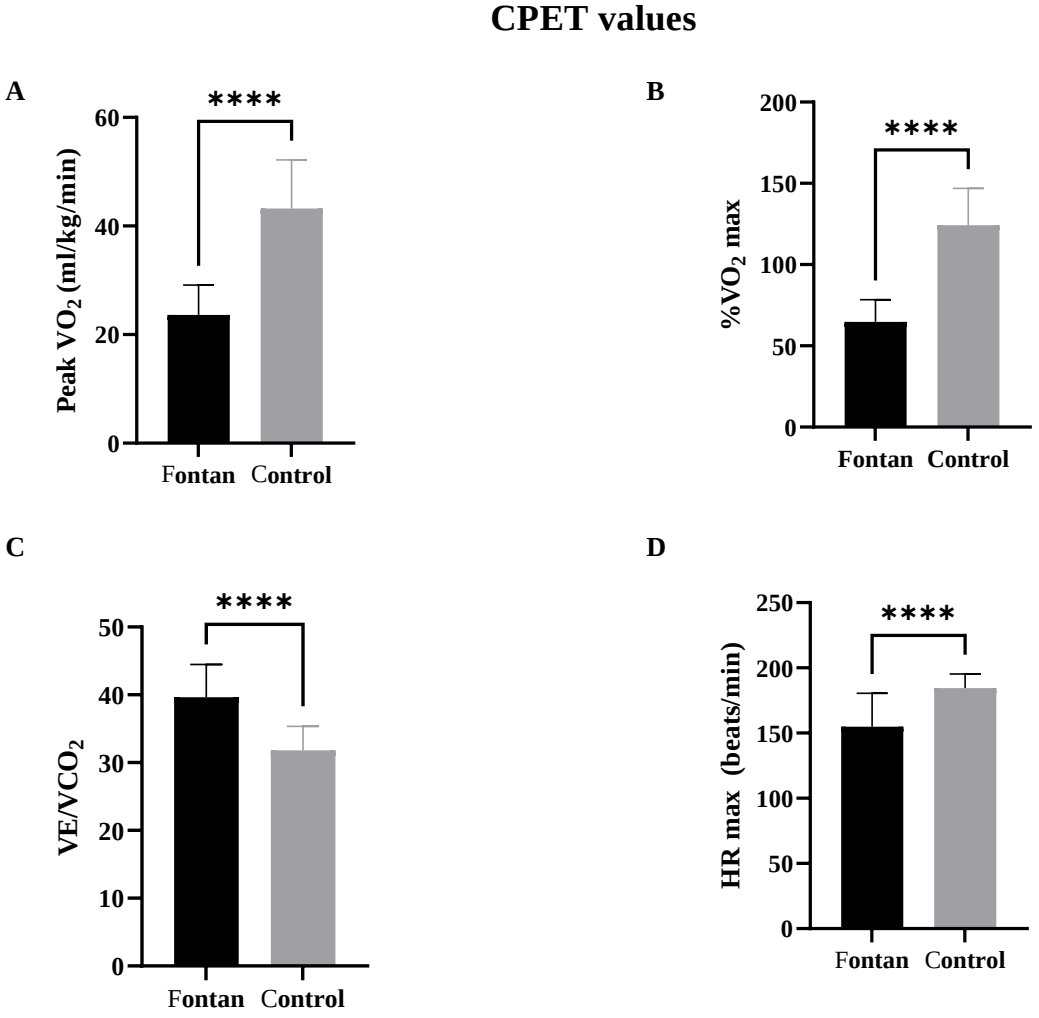

Figure 4 - Hemodynamic parameters obtained during CPET

A. Peak oxygen consumption (Peak VO_2) Fontan 23.63 vs. Control 43.20 ml/kg/min **B.** Percent predicted oxygen consumption obtained (%VO_2 max) Fontan 64.71% vs. Control 124.24% **C.** ventilatory efficiency (VE/VCO2) Fontan 39.64 Vs Control 31.83 **D.** Maximum heart rate achieved at peak exercise (HR max) Fontan 154.81 Vs Control 184.38. **** denotes $p \leq 0.0001$, when the averages of the two groups were compared using a 2-tailed student t-test ($p < 0.05$). The error bars represent SD for corresponding bar.

Prior to the treadmill exercise session, participants underwent ICG evaluation of their resting hemodynamics using NICaS. Fontan group on average had a significantly lower resting SV and CO despite having higher resting HR. Averages of HR, SV, SI, CI, CO and TPRI at rest in both groups, and significance of their comparison (2 tailed student t-test) are reported in Figure 5. $P < 0.05$ was used as threshold for significance.

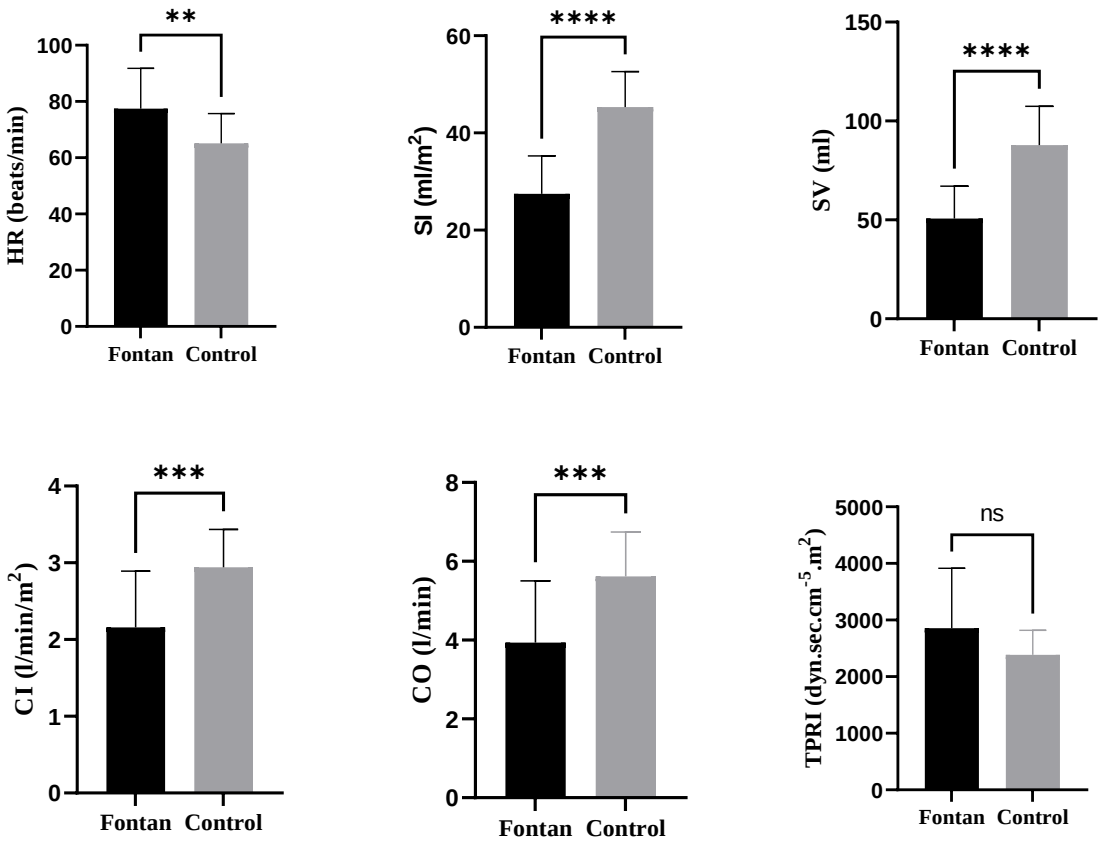

Figure 5 - ICG hemodynamic parameters derived using NICaS at rest, compared in Fontan vs. Control.

A. Heart rate (HR) Fontan 77.48 vs. Control 65.10 beats/min **B.** Stroke index (SI) Fontan 27.48 vs. Control 45.33 ml/m^2 **C.** Stroke volume (SV) Fontan 50.71 vs. Control 87.81 ml **D.** Cardiac index (CI) Fontan 2.16 vs. Control 2.94 l/min/m2 **E.** Cardiac output (CO) Fontan 3.94 vs. Control 5.62 l/min **F.** Total peripheral resistance index (TPRI) Fontan 2855 vs. Control 2384 dyn.sec.cm^{-5}.m^2. ns denotes $p > 0.05$, ** denotes $p \leq 0.01$, *** denotes $p \leq 0.001$, **** denotes $p \leq 0.0001$ when the averages of the two groups were compared using a 2-tailed student t-test. The error bars represent SD for the corresponding bar graph.

To assess participants' hemodynamic status while still in an exercise induced physiologically excited state, participants underwent ICG hemodynamic evaluation within 1 minute after the treadmill exercise session (post exercise). There was no significant difference between post exercise HR amongst the two groups. Fontan group on average had a significantly lower post exercise SV and CO despite having a HR at par with Control. Averages of HR, SV, SI, CI, CO and TPRI post exercise derive from ICG method using NICaS in both groups, and significance of their comparison (2 tailed student t-test) are reported in Figure 6. $P < 0.05$ was used as threshold for significance.

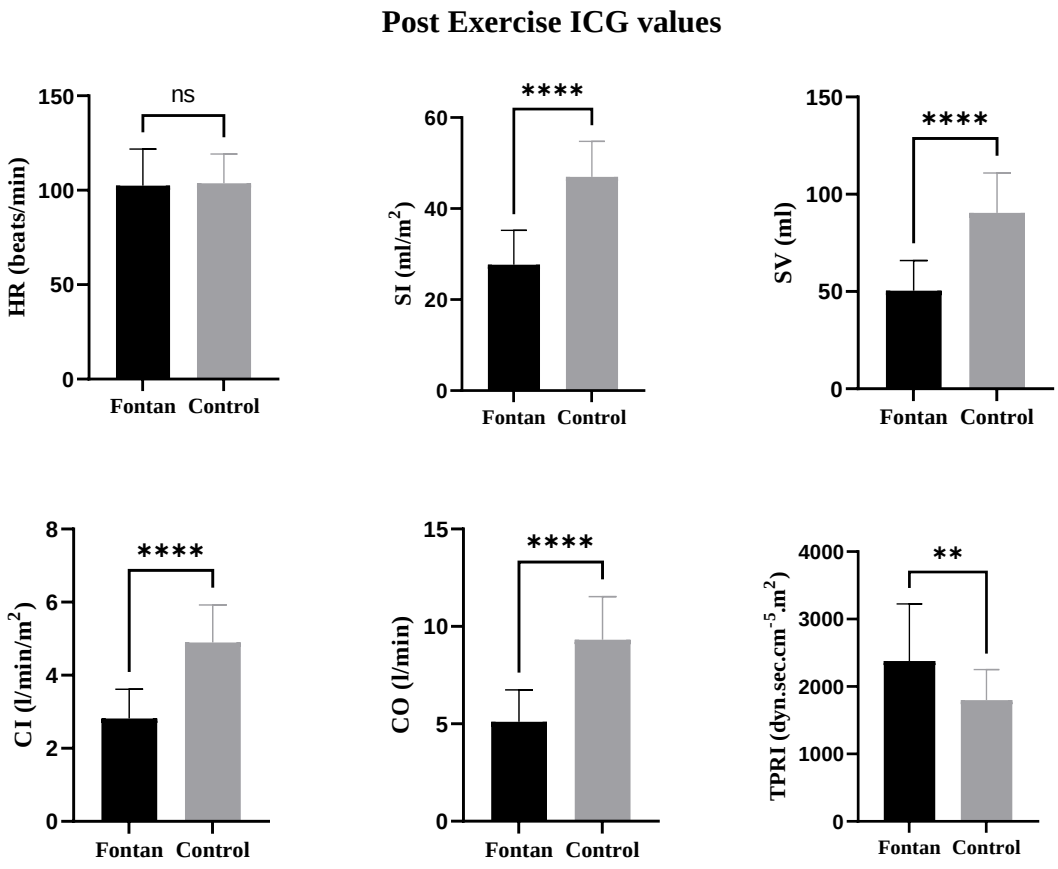

Figure 6 - ICG hemodynamic parameters derived using NICaS within 1 min post treadmill exercise session (post exercise), compared in Fontan vs. Control.

Post exercise averages for Fontan vs. Control are reported. **A.** Heart rate (HR) Fontan 102.48 vs. Control 103.71 beats/min. HR post exercise did not differ significantly between the two groups **B.** Stroke index (SI) Fontan 27.67 vs. Control 46.95 ml/m^2 **C.** Stroke volume (SV) Fontan 50.43 vs. 90.43 Control 87.81 ml **D.** Cardiac index (CI) Fontan 2.82 vs. Control 4.90 l/min/m2 **E.** Cardiac output (CO) Fontan 5.10 vs. Control 9.32 l/min **F.** Total peripheral resistance index (TPRI) Fontan 2379 Vs Control 1799 (dyn.sec.cm^{-5}.m^2). ns denotes $p > 0.05$, ** denotes $p \leq 0.01$, **** denotes $p \leq 0.0001$ when the averages of the two groups were compared using a 2-tailed student t-test. The error bars represent SD.

Assuming there is no oxygen consumption at SV of 0 ml and given that peak oxygen consumption (peak VO_2) is a function of cardiac output, we performed a regression analysis between these two parameters, with intercept of 0. Correlation of r = 0.92 with $p<0.05$ was discovered between peak VO_2 measured during CPET and the independently measured SV by NICaS when considering all participants. Regression analysis between these two independently assessed values amongst the two groups separately was also performed. In all cases ICG derived resting SV exhibited excellent linear correlation with peak VO_2. These findings are summarized in Figures 7 to 9.

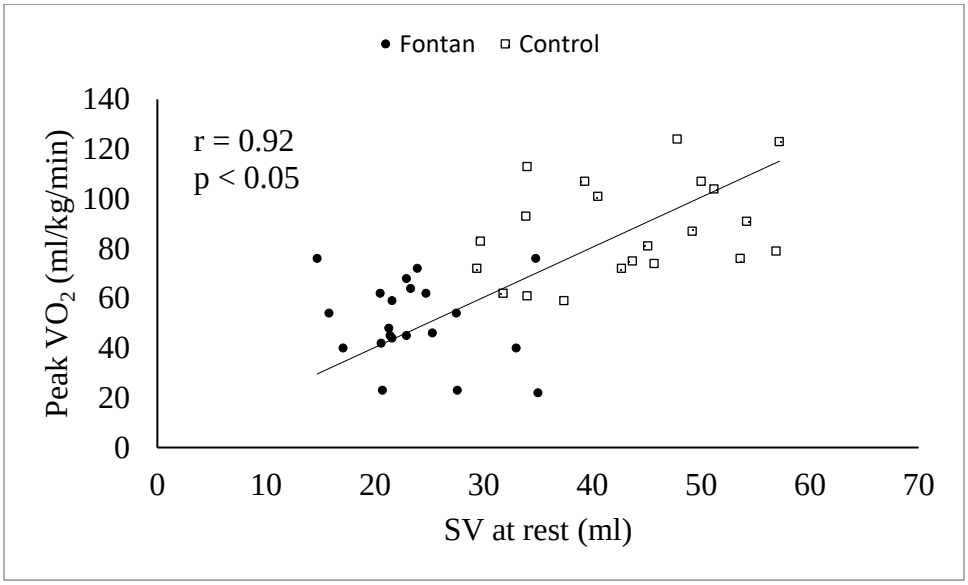

Figure 7 - Correlation between peak oxygen consumption (peak VO_2) obtained from breath gas analyzer during CPET and resting SV obtained from NICaS during resting ICG measurements in all participants combined

are demonstrated. The resting SV showed a significant correlation with peak VO_2. r = 0.92, $p < 0.05$.

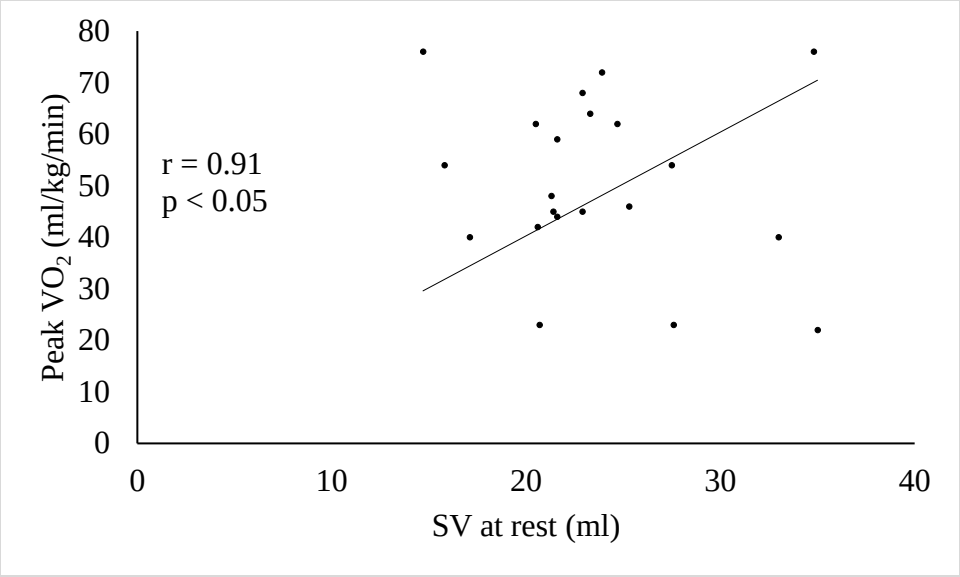

Figure 8 - Correlation between peak oxygen consumption (peak VO_2) obtained from breath gas analyzer during CPET and resting SV obtained from NICaS during resting ICG measurements in only Fontan participants

are demonstrated. The resting SV showed a significant correlation with peak VO_2. $r = 0.91$, $p < 0.05$.

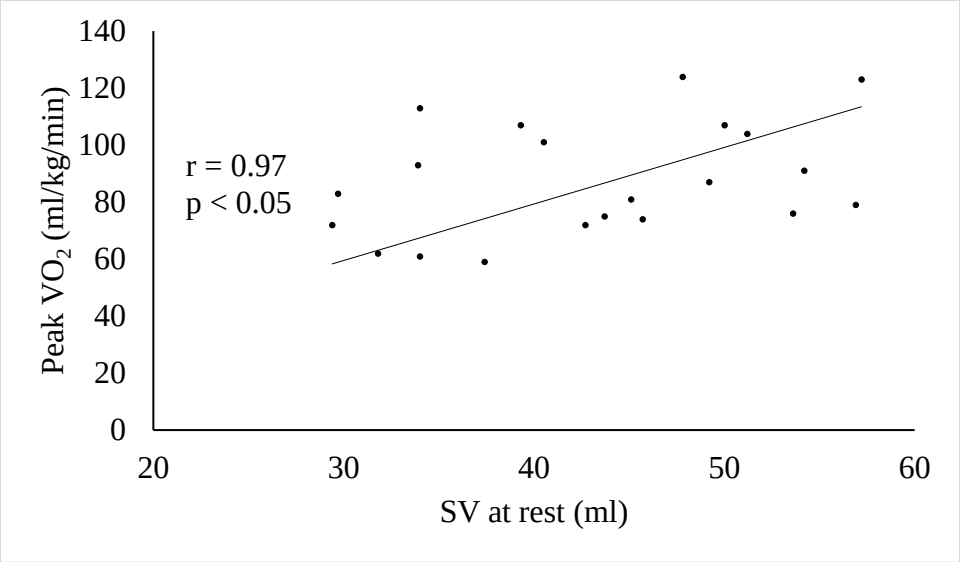

Figure 9 - Correlation between peak oxygen consumption (peak VO_2) obtain from breath gas analyzer during CPET and resting SV obtained from NICaS during resting ICG measurements in only Control participants

are demonstrated. The resting SV showed a significant correlation with peak VO_2. $r = 0.97$, $p < 0.05$.

Chapter 4: Discussion

Need for non-invasive hemodynamic assessment

The need for hemodynamic assessment in intensive care, perioperative care and trauma setting has been well established.[89,90] Amongst the essential hemodynamic parameters, HR (utilizing ECG) and non-invasive BP are monitored readily, however without SV or a surrogate of it the picture is incomplete. Invasive methods are losing popularity and being replaced with less invasive alternatives.[91] This has paved the way for utilizing non-invasive methods of estimating SV. Lack of a clear definition of absolute clinical gold standard or disagreement over methods of statistical analysis to gauge a new medical device against an already accepted method, has made adaptation to novel clinical devices slow.[92] This evolving technology has had its share of criticism as well.[93] Keeping in mind continuous improvement of this method, the need for more observational studies and need for more data gathering in different conditions is clearly required.

Patient populations requiring highly specialized care such as heart failure and Fontan benefit from regular hemodynamic assessment.[94,95] Utilization of non-invasive hemodynamic monitoring in the clinical setting may have prognostication and preventative value. Amongst available non-invasive options, ICG has been gaining momentum in popularity.

ICG as an option

Using electrodes applied to the skin in form of stickers, ICG technology carries out its function by sending a small alternating current (AC) through organic matter and measuring potential difference between two points. The measure of resisting AC through organic matter is impedance. Changes in the diameter of blood vessels when receiving the SV results in changes in

their AC opposing characteristics and creates a change in impedance. Being able to measure this change in impedance provides us with enough input to estimate SV.[96] Employing the same fundamental concepts, entities developing ICG devices incorporate their own correction factors and at times proprietary modifications in hopes of refining the accuracy of estimated hemodynamic parameters they measure. Amongst the available variety of options, we took an interest in NICaS. This ICG device, uses two skin stickers, is easy to set up, cheap, operator independent and has been observed to generate reproducible data.[81,97,98] Its two limb lead and total body impedance set up are amongst ICG modifications that have been praised.[63,81]

Initially, we showed a significantly strong correlation between NICaS assessment of SV with CMR generated aortic forward flow volume. Our study cohort included patients with varying underlying heart conditions, including those with CHDs and surgically managed CHDs. We were content with the ICG device's performance against the gold standard of systemic ventricle assessment, CMR.

NICaS not only exhibited good inter-device reliability, but it also has excellent intra-device reliability. Collected ICG measurements in 10 participants both shortly before and after their CMR, exhibited perfect kappa of 1. This finding is reassuring since in many situations trending the change in hemodynamic parameters is more important than knowing the accurate absolute baseline. We were pleased with NICaS' reproducibility and ability to continuously generate real time hemodynamic parameters.

Although objectively not assessed, the majority of participants voluntarily voiced their satisfaction with comfort, and short duration of the assessment. Given the clinical importance of hemodynamic trending over time in almost any population, and lack of convenient means to assess

a full hemodynamic picture of a sub-specialized populations such as HF and Fontan, we set to use NICaS during CPET sessions.[74,99–101]

Population and participation

As mentioned in chapter 1, the global population of Fontan in 2019 has been estimated to be around 70,000 with doubling time of 20 years.[12] The participation of 21 Fontan patients in this study is a strength of this project. At the time of the study, this represented more than half of known adult Fontan patients in the province of Manitoba and western part of Ontario. Studies of similar nature at more populous centers, for example collaboration between France and Belgium had 25 Fontan participants, and to put the matter into perspective, a multinational study involving 24 cardiology centers and 15 countries had a total of 435 participants (this was a quality of life questionnaire study with less physical exertion required by design).[102,103]

CPET hemodynamic assessment

Although exercise capacity and oxygen consumption improve after Fontan completion compared to before it, the increased exercise capacity is still suboptimal in comparison to healthy subjects.[104,105] Cardiopulmonary exercise testing is shown to be a valuable prognostication tool over time and is regularly used as part of accepted standard medical care for this population.[12] Of note, the exercise capacity of different Fontan subtypes has not been shown to significantly differ, as such all Fontans regardless of their repair subtype are treated as one cohort in our study.[106] Different studies have reported CPET parameters in Fontan and some examples of the reported numbers are as follow: peak VO_2 of 26.3 ml/kg/min (65% of predicted for age and gender)(Cross sectional study, 411 subjects) [50], median peak VO2 of 21.9 ml/kg/min [107], 60 to 64% of predicted peak VO2 [106]. Poirier et al. lists more than 10 studies that reported lower peak VO_2 in Fontan

compared to healthy, and about 5 studies showing higher VE/VCO_2 in Fontan compared to healthy.[108]

In our study we observed lower exercise capacity in Fontan compared to control. This is in keeping with previously published results from other institutions. We found the average peak VO_2 in Fontan to be 23.6±5.5 ml/kg/min and in control 43.2±9 ml/kg/min. These numbers correspond to %peak VO_2 predicted, averages were 65%±14% and 124%±23% respectively. Our findings reaffirm lower peak VO_2 in Fontan compared to healthy population. Congruent with other studies, we report higher mean of VE/VCO_2 in the Fontan group than control (40±5 and 32±4.respectively). This indicates worse ventilatory efficiency. Simply put, VE/VCO_2 indicates volume of air needed to be displaced by lungs to expel given volume of CO_2.[109] The prognostic significance of this value in the unique population of Fontan is not well understood.

ICG hemodynamic parameters

Although Fontan has higher resting HR and smaller HR reserve, chronotropy has not been identified as a limiting factor to peak exercise tolerance.[50,110,111] An objective surrogate of exercise capacity is peak VO_2. VO_2 can be broken down to two fundamental parts, oxygen delivery and oxygen consumption. We believe that Fontan's chronically low CO state is dictated by low SV which in turn is limited by decreased preload This leads to subnormal oxygen delivery. In those with chronically low CO state, this can lead to poor muscle mass development. As per such causative assumption, it is reasonable to deduce that improving oxygen delivery (i.e. improving SV in case of Fontan leading to CO improvement) over time may improve muscle growth and as a result oxygen uptake will improve.[110] This emphasizes the need for regular SV assessment in this population.

It has been previously shown that Fontan circulation generates a smaller SV and CO. Some instances of these values reported in the limited number of studies available are: in one study, median resting SV of 64 ml, resting CO 3.9 l/min was reported;[107] in another study 8 Fontan patients underwent cardiac catheterization for hemodynamic assessment and their reported values are resting mean CI was 2.3±0.6 l/ min/ m^2, SI 28.3±8.7 ml/m^2,[111] in another study on 25 Fontan patients using bioimpedance resting CI was 2.91 l/ min/ m^2. [102] Utilizing ICG, our measured average resting SV for Fontan and control were 50.7±16.4 and 88±20 ml, respectively. Despite having a higher resting HR, the Fontan group also demonstrated lower CO in our study. We report mean CO of 3.9±1.6 l/min for Fontan group and 5.6±1.1 l/min for control. This further reconfirms that Fontan circulation's inherent low SV is the main driver of low CO state in this population. By measuring resting BP during CPET session, it is possible to calculate TPR. Our reported total peripheral resistance index (TPRI) provides further proof that Fontan's peripheral vasculature is chronically constricted to maintain a normal BP. Fontan physiology's attempt to adapt and maintain near normal BP by increasing peripheral vascular resistance to compensate for low CO (caused by low SV in this population), comes at the price of reduced oxygen delivery and its sequels as mentioned in the previous section.

This is the ideal place to mention and entertain the idea that contrary to classical belief, perhaps if conditioned from early ages, a persistent exercise regimen may be of benefit to the overall health of the Fontan population.[108] More longer-term studies are needed to shed light on the effect of different types of exercise and conditioning regimens on outcomes in this population. ICG has the potential to be an important component of such studies assessing the effect of long term exercise programs on Fontan outcomes.

Limitations

Due to ethical reasons, comparison of ICG in every patient population, with invasive or semi-invasive gold standards of care, is not possible. There is much to be learned in terms of ICG's reliability and accuracy in different patient populations. Certain underlying pathologies affecting the blood composition (e.g. abnormal proteins), or different cardiac anatomies can affect the data generated by ICG. As such there is still a need to further observe ICG devices in different patient populations. In the first part of our study (comparing ICG with CMR), we did observe that two of our participants with underlying amyloidosis exhibited the largest SV difference with CMR. Although, such observed difference could be just by chance, larger studies are required to verify any such limitations.

Although every effort was made to perform ICG measurements as close to the CMR measurements; due to incompatibility of ICG device with MRI, simultaneous measurements were not possible. As shown in the result section, our study demonstrated a bias of 7 ml. This means that on average NICaS underestimated the SV by 7 ml compared to CMR. Although this is not of grave clinical significance, one way to further assess ICG technology would be to develop MRI safe cables that have the capability of being utilized simultaneously with CMR.

It has repeatedly been reported that ICG devices are prone to motion artifacts. As a result, they ideally require patients to be motionless or the limbs used for the assessment to be in minimal motion.[112] During the later part of our study (CPET), we encountered the same problem. Due to the nature of treadmill ergometer testing, all body limbs are in a state of motion. This made it difficult to carry out ICG measurements during peak exercise. However, given the NICaS' ability to generate one data point every 20 seconds we were able to assess our participants immediately after exercise, when their bodies were still somewhat in an excited state. For future studies of

similar nature, we propose using a bike ergometer. When using the wrist-wrist configuration on a bike ergometer, hands can be kept steady for the short duration required to obtain ICG measurement.

Future direction

Demonstrated suitability of ICG in trending SV makes it suitable for follow up studies. Observational studies, following patients over time to assess the changes in their SV will be of great value. This type of study will enable us to construct prognostication algorithms based on SV changes in a given patient population.

The realms of genomics, proteomics, metabolomics and lipidomics studies that utilize biomarker assessment have become commonplace in the world of clinical research. Given the extent of observed and hypothesized metabolic derangement in the Fontan population, studies aiming to correlate biochemical findings with ICG hemodynamic assessment are of great value. The aim of this kind of study will be to detect relationships between information provided from ICG assessment about hemodynamic adaptations and its effect on adaptations at the cellular level and their mutual effect on one another. As such, collection of plasma samples during these observational follow up studies would provide an immense amount of practical data.

Given the quick, non-invasive and relative operator independent ICG modality, we foresee its use in acute situations such as heart attack or during hemodynamically altering procedures to gain popularity. The road has been paved for a prospective follow up study of a unique population as Fontan, to see the effects of long-term exercise and conditioning programs in this population. NICaS can be utilized to assess their hemodynamic status over a period of years at fixed intervals

and trend hemodynamic values in response to such programs in this population at our cardiac center. [108]

Chapter 5: Study conclusion

We found a strong correlation between NICaS and CMR when assessing SV, additionally we observed consistent measurements of SV by ICG in Fontan during our study with previously reported findings in this population in other studies. We also found a strong correlation between resting SV assessed independently by ICG with peak VO_2 values obtained during CPET.

As such, an FDA and Health Canada approved device such as NICaS that utilizes whole body impedance technology can be used to monitor SV (and other hemodynamic parameters deriving from it). ICG may reliably be used in clinical or clinical research settings. Employing such a non-invasive tool in clinical and research settings is the next step to improve our understanding of different cardiovascular conditions.

References

1. Rashkind WJ. Tricuspid atresia: A historical review. *Pediatr Cardiol*. 1982;2(1):85-88. doi:10.1007/BF02265624

2. Brown JW. Congenital tricuspid atresia. *Arch Dis Child*. 1936;11(66):275-280. doi:10.1136/adc.11.66.275

3. Elster SK. Congenital Atresia of Pulmonary and Tricuspid Valves. *Arch Pediatr Adolesc Med*. 1950;79(4):692. doi:10.1001/archpedi.1950.04040010707010

4. Campbell M. Tricuspid atresia and its prognosis with and without surgical treatment. *Br Heart J*. 1961;23(6):699-710. doi:10.1136/hrt.23.6.699

5. Blalock A. The Surgical Treatment of Malformations of The Heart. *J Am Med Assoc*. 1945;128(3):189. doi:10.1001/jama.1945.02860200029009

6. Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax*. 1971;26(3):240-248. doi:10.1136/thx.26.3.240

7. Mair DD, Puga FJ, Danielson GK. The Fontan procedure for tricuspid atresia: early and late results of a 25-year experience with 216 patients. *J Am Coll Cardiol*. 2001;37(3):933-939. doi:10.1016/S0735-1097(00)01164-5

8. van der Ven JPG, van den Bosch E, Bogers AJCC, Helbing WA. State of the art of the Fontan strategy for treatment of univentricular heart disease. *F1000Research*. 2018;7. doi:10.12688/f1000research.13792.1

9. Anderson Dorland, William Alexander Newman., DM. *Dorland's Illustrated Medical Dictionary*. Saunders; 2000.

10. Kojima T, Taki M, Toda K, et al. Hepatocyte growth factor predicts failure of Fontan circulation. *ESC Hear Fail*. 2020;7(6):3738-3744. doi:10.1002/ehf2.12943

11. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation*. 2007;115(2):163-172. doi:10.1161/circulationaha.106.627224

12. Rychik J, Atz AM, Celermajer DS, et al. Evaluation and Management of the Child and Adult With Fontan Circulation: A Scientific Statement From the American Heart Association. *Circulation*. 2019;140(6):CIR0000000000000696. doi:10.1161/CIR.0000000000000696

13. de Leval MR, Deanfield JE. Four decades of Fontan palliation. *Nat Rev Cardiol*. 2010;7(9):520-527. doi:10.1038/nrcardio.2010.99

14. Gewillig M. THE FONTAN CIRCULATION. *Heart*. 2005;91(6):839-846. doi:10.1136/hrt.2004.051789

15. Rychik J. The Relentless Effects of the Fontan Paradox. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2016;19(1):37-43. doi:https://doi.org/10.1053/j.pcsu.2015.11.006

16. Schilling C, Dalziel K, Nunn R, et al. The Fontan epidemic: Population projections from the Australia and New Zealand Fontan Registry. *Int J Cardiol*. 2016;219:14-19. doi:10.1016/j.ijcard.2016.05.035

17. Lang MD, FASE, FESC RM, Badano MD, PhD, FESC LP, Mor-Avi PhD, FASE V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European

Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1-39.e14. doi:10.1016/j.echo.2014.10.003

18. Egbe AC, Wajih Ullah M, Afzal A, et al. Feasibility, reproducibility and accuracy of electrical velocimetry for cardiac output assessment in congenital heart disease. *IJC Hear Vasc*. 2020;26:100464. doi:https://doi.org/10.1016/j.ijcha.2019.100464

19. Hauser JA, Taylor AM, Pandya B. How to Image the Adult Patient With Fontan Circulation. *Circ Cardiovasc Imaging*. 2017;10(5). doi:10.1161/CIRCIMAGING.116.004273

20. Udholm S, Aldweib N, Hjortdal VE, Veldtman GR. Prognostic power of cardiopulmonary exercise testing in Fontan patients: a systematic review. *Open Hear*. 2018;5(1):e000812. doi:10.1136/openhrt-2018-000812

21. Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. *Postgrad Med J*. 2007;83(985):675 LP - 682. doi:10.1136/hrt.2007.121558

22. Gerche A La, Claessen G, Van de Bruaene A, et al. Cardiac MRI. *Circ Cardiovasc Imaging*. 2013;6(2):329-338. doi:10.1161/CIRCIMAGING.112.980037

23. Yeong M, Loughborough W, Hamilton M, Manghat N. Role of cardiac MRI and CT in Fontan circulation. *J Congenit Cardiol*. 2017;1(1):8. doi:10.1186/s40949-017-0010-x

24. Pennell DJ. Cardiovascular magnetic resonance: twenty-first century solutions in cardiology. *Clin Med J R Coll Physicians*. 2003;3(3):273-278. doi:10.7861/clinmedicine.3-3-273

25. Grothues F, Smith GC, Moon JCC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal

subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol*. 2002;90(1):29-34. doi:https://doi.org/10.1016/S0002-9149(02)02381-0

26. Mathew RC, Löffler AI, Salerno M. Role of Cardiac Magnetic Resonance Imaging in Valvular Heart Disease: Diagnosis, Assessment, and Management. *Curr Cardiol Rep*. 2018;20(11):119. doi:10.1007/s11886-018-1057-9

27. Pugsley J, Lerner AB. Cardiac Output Monitoring: Is There a Gold Standard and How Do the Newer Technologies Compare? *Semin Cardiothorac Vasc Anesth*. 2010;14(4):274-282. doi:10.1177/1089253210386386

28. Nishikawa T, Dohi S. Errors in the measurement of cardiac output by thermodilution. *Can J Anaesth*. 1993;40(2):142-153. doi:10.1007/BF03011312

29. Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M. Protein-losing enteropathy after the Fontan operation: an international multicenter study. PLE study group. *J Thorac Cardiovasc Surg*. 1998;115(5):1063-1073. doi:10.1016/s0022-5223(98)70406-4

30. Egbe AC, Connolly HM, Niaz T, et al. Prevalence and outcome of thrombotic and embolic complications in adults after Fontan operation. *Am Heart J*. 2017;183:10-17. doi:10.1016/j.ahj.2016.09.014

31. Mahnke CB, Boyle GJ, Janosky JE, Siewers RD, Pigula FA. Anticoagulation and incidence of late cerebrovascular accidents following the Fontan procedure. *Pediatr Cardiol*. 26(1):56-61. doi:10.1007/s00246-003-0684-z

32. Lasa JJ, Glatz AC, Daga A, Shah M. Prevalence of arrhythmias late after the Fontan operation. *Am J Cardiol*. 2014;113(7):1184-1188. doi:10.1016/j.amjcard.2013.12.025

33. Dennis M, Zannino D, du Plessis K, et al. Clinical Outcomes in Adolescents and Adults

After the Fontan Procedure. *J Am Coll Cardiol*. 2018;71(9):1009-1017. doi:https://doi.org/10.1016/j.jacc.2017.12.054

34. D. B, D. N, C. C, et al. Outcome of Listing for Cardiac Transplantation for Failed Fontan. *Circulation*. 2006;114(4):273-280. doi:10.1161/CIRCULATIONAHA.105.548016

35. McCormick AD, Schumacher KR. Transplantation of the failing Fontan. *Transl Pediatr*. 2019;8(4):290-301. doi:10.21037/tp.2019.06.03

36. Bhama JK, Shulman J, Bermudez CA, et al. Heart transplantation for adults with congenital heart disease: Results in the modern era. *J Hear Lung Transplant*. 2013;32(5):499-504. doi:10.1016/j.healun.2013.01.1047

37. Egbe AC, Poterucha JT, Warnes CA, et al. Hepatocellular Carcinoma After Fontan Operation. *Circulation*. 2018;138(7):746-748. doi:10.1161/CIRCULATIONAHA.117.032717

38. Gewillig M, Brown SC, Eyskens B, et al. The Fontan circulation: who controls cardiac output? *Interact Cardiovasc Thorac Surg*. 2010;10(3):428-433. doi:10.1510/icvts.2009.218594

39. Ferreira AM, Tabet J-Y, Frankenstein L, et al. Ventilatory efficiency and the selection of patients for heart transplantation. *Circ Heart Fail*. 2010;3(3):378-386. doi:10.1161/CIRCHEARTFAILURE.108.847392

40. Fernandes SM, Alexander ME, Graham DA, et al. Exercise testing identifies patients at increased risk for morbidity and mortality following fontan surgery. *Congenit Heart Dis*. 2011;6(4):294-303. doi:10.1111/j.1747-0803.2011.00500.x

41. Marco G, Francesco B, Cemal O, David S, Ross A. Cardiopulmonary Exercise Testing. *J*

Am Coll Cardiol. 2017;70(13):1618-1636. doi:10.1016/j.jacc.2017.08.012

42. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary Exercise Testing in Heart Failure. *JACC Hear Fail*. 2016;4(8):607-616. doi:10.1016/j.jchf.2016.03.022

43. Lang CC, Agostoni P, Mancini DM. Prognostic Significance and Measurement of Exercise-Derived Hemodynamic Variables in Patients With Heart Failure. *J Card Fail*. 2007;13(8):672-679. doi:10.1016/j.cardfail.2007.05.004

44. Fernandes SM, McElhinney DB, Khairy P, Graham DA, Landzberg MJ, Rhodes J. Serial Cardiopulmonary Exercise Testing in Patients with Previous Fontan Surgery. *Pediatr Cardiol*. 2010;31(2):175-180. doi:10.1007/s00246-009-9580-5

45. Inuzuka R, Diller G-P, Borgia F, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. *Circulation*. 2012;125(2):250-259. doi:10.1161/CIRCULATIONAHA.111.058719

46. Egbe AC, Driscoll DJ, Khan AR, et al. Cardiopulmonary exercise test in adults with prior Fontan operation: The prognostic value of serial testing. *Int J Cardiol*. 2017;235:6-10. doi:10.1016/j.ijcard.2017.02.140

47. Diller G-P, Dimopoulos K, Okonko D, et al. Heart Rate Response During Exercise Predicts Survival in Adults With Congenital Heart Disease. *J Am Coll Cardiol*. 2006;48(6):1250-1256. doi:10.1016/j.jacc.2006.05.051

48. Ohuchi H, Arakaki Y, Hiraumi Y, Tasato H, Kamiya T. Cardiorespiratory response during exercise in patients with cyanotic congenital heart disease with and without a Fontan operation and in patients with congestive heart failure. *Int J Cardiol*. 1998;66(3):241-251.

doi:10.1016/S0167-5273(98)00249-6

49. Cortes RG, Satomi G, Yoshigi M, Momma K. Maximal hemodynamic response after the Fontan procedure: Doppler evaluation during the treadmill test. *Pediatr Cardiol*. 1994;15(4):170-177. doi:10.1007/BF00800671

50. Paridon SM, Mitchell PD, Colan SD, et al. A Cross-Sectional Study of Exercise Performance During the First 2 Decades of Life After the Fontan Operation. *J Am Coll Cardiol*. 2008;52(2):99-107. doi:https://doi.org/10.1016/j.jacc.2008.02.081

51. van den Bosch AE, Roos-Hesselink JW, van Domburg R, Bogers AJJC, Simoons ML, Meijboom FJ. Long-term outcome and quality of life in adult patients after the Fontan operation. *Am J Cardiol*. 2004;93(9):1141-1145. doi:10.1016/j.amjcard.2004.01.041

52. Eisenberg PR, Jaffe AS, Schuster DP. Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients. *Crit Care Med*. 1984;12(7):549-553. doi:10.1097/00003246-198407000-00001

53. Barold SS. Willem Einthoven and the Birth of Clinical Electrocardiography a Hundred Years Ago. *Card Electrophysiol Rev*. 2003;7(1):99-104. doi:10.1023/A:1023667812925

54. Van De Water JM, Miller TW, Vogel RL, Mount BE, Dalton ML. Impedance Cardiographya: The Next Vital Sign Technology? *Chest*. 2003;123(6):2028-2033. doi:https://doi.org/10.1378/chest.123.6.2028

55. Roguin A. Adolf Eugen Fick (1829-1901) – The Man Behind the Cardiac Output Equation. *Am J Cardiol*. 2020;133:162-165. doi:https://doi.org/10.1016/j.amjcard.2020.07.042

56. Trammel JE, Sapra A. *Physiology, Systemic Vascular Resistance*.; 2021.

http://www.ncbi.nlm.nih.gov/pubmed/32310535

57. King J, Lowery DR. *Physiology, Cardiac Output*.; 2021. http://www.ncbi.nlm.nih.gov/pubmed/29262215

58. Hill LK, Sollers Iii JJ, Thayer JF. Resistance reconstructed estimation of total peripheral resistance from computationally derived cardiac output - biomed 2013. *Biomed Sci Instrum*. 2013;49:216-223. https://pubmed.ncbi.nlm.nih.gov/23686203

59. Tang WHW, Tong W. Measuring impedance in congestive heart failure: current options and clinical applications. *Am Heart J*. 2009;157(3):402-411. doi:10.1016/j.ahj.2008.10.016

60. Khalil SF, Mohktar MS, Ibrahim F. The theory and fundamentals of bioimpedance analysis in clinical status monitoring and diagnosis of diseases. *Sensors (Basel)*. 2014;14(6):10895-10928. doi:10.3390/s140610895

61. Woltjer HH, Bogaard HJ, de Vries PM. The technique of impedance cardiography. *Eur Heart J*. 1997;18(9):1396-1403. doi:10.1093/oxfordjournals.eurheartj.a015464

62. Sageman WS, Riffenburgh RH, Spiess BD. Equivalence of bioimpedance and thermodilution in measuring cardiac index after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2002;16(1):8-14. doi:https://doi.org/10.1053/jcan.2002.29635

63. Cotter G, Schachner A, Sasson L, Dekel H, Moshkovitz Y. Impedance cardiography revisited. *Physiol Meas*. 2006;27(9):817-827. doi:10.1088/0967-3334/27/9/005

64. Raaijmakers E, Faes TJ, Scholten RJ, Goovaerts HG, Heethaar RM. A meta-analysis of published studies concerning the validity of thoracic impedance cardiography. *Ann N Y Acad Sci*. 1999;873(1):121-127. doi:10.1111/j.1749-6632.1999.tb09458.x

65. Tsoglin A, Frinerman E. Methods and system for non-invasive determination of the main cardiorespiratory parameters of the human body. Published online 1998:55.

66. Tsoglin A, Frinerman E. METHOD AND SYSTEM FOR NON NWASIVE DETERMINATION OF THE MAIN CARDORESPRATORY PARAMETERS OF THE HUMAN BOOY. Published online 1998.

67. Mansouri S, Alhadidi T, Chabchoub S, Salah R Ben. Impedance cardiography: Recent applications and developments. *Biomed Res*. 2018;29(19):3542-3552. doi:10.4066/biomedicalresearch.29-17-3479

68. Noda K, Endo H, Kadosaka T, et al. Comparison of the measured pre-ejection periods and left ventricular ejection times between echocardiography and impedance cardiography for optimizing cardiac resynchronization therapy. *J arrhythmia*. 2017;33(2):130-133. doi:10.1016/j.joa.2016.08.003

69. Germain MJ, Joubert J, O'Grady D, Nathanson BH, Chait Y, Levin NW. Comparison of stroke volume measurements during hemodialysis using bioimpedance cardiography and echocardiography. *Hemodial Int*. 2018;22(2):201-208. doi:10.1111/hdi.12589

70. McIntyre JPR, Ellyett KM, Mitchell EA, et al. Validation of thoracic impedance cardiography by echocardiography in healthy late pregnancy. *BMC Pregnancy Childbirth*. 2015;15:70. doi:10.1186/s12884-015-0504-5

71. Burlingame J, Ohana P, Aaronoff M, Seto T. Noninvasive cardiac monitoring in pregnancy: impedance cardiography versus echocardiography. *J Perinatol*. 2013;33(9):675-680. doi:10.1038/jp.2013.35

72. Kaszuba E, Scheel S, Odeberg H, Halling A. Comparing impedance cardiography and

echocardiography in the assessment of reduced left ventricular systolic function. *BMC Res Notes*. 2013;6:114. doi:10.1186/1756-0500-6-114

73. Faini A, Omboni S, Tifrea M, Bubenek S, Lazar O, Parati G. Cardiac index assessment: validation of a new non-invasive very low current thoracic bioimpedance device by thermodilution. *Blood Press*. 2014;23(2):102-108. doi:10.3109/08037051.2013.817121

74. Ebrahim M, Hegde S, Printz B, Abcede M, Proudfoot JA, Davis C. Evaluation of Impedance Cardiography for Measurement of Stroke Volume in Congenital Heart Disease. *Pediatr Cardiol*. 2016;37(8):1453-1457. doi:10.1007/s00246-016-1456-x

75. Acierno LJ. Adolph Fick: mathematician, physicist, physiologist. *Clin Cardiol*. 2000;23(5):390-391. doi:10.1002/clc.4960230519

76. Summers RL, Shoemaker WC, Peacock WF, Ander DS, Coleman TG. Bench to bedside: electrophysiologic and clinical principles of noninvasive hemodynamic monitoring using impedance cardiography. *Acad Emerg Med Off J Soc Acad Emerg Med*. 2003;10(6):669-680. doi:10.1111/j.1553-2712.2003.tb00054.x

77. Cohen AJ, Arnaudov D, Zabeeda D, Schultheis L, Lashinger J, Schachner A. Non-invasive measurement of cardiac output during coronary artery bypass grafting. *Eur J Cardio-Thoracic Surg*. 1998;14(1):64-69. doi:10.1016/S1010-7940(98)00135-3

78. Giavarina D. Understanding Bland Altman analysis. *Biochem Medica*. 2015;25(2):141-151. doi:10.11613/BM.2015.015

79. Bhavya G, Nagaraja PS, Singh NG, et al. Comparison of continuous cardiac output monitoring derived from regional impedance cardiography with continuous thermodilution technique in cardiac surgical patients. *Ann Card Anaesth*. 2020;23(2):189-

192. doi:10.4103/aca.ACA_1_19

80. Goldkorn R, Naimushin A, Rozen E, Freimark D. Early post-stress decrease in cardiac performance by impedance cardiography and its relationship to the severity and extent of ischemia by myocardial perfusion imaging. *BMC Cardiovasc Disord*. 2020;20(1):354. doi:10.1186/s12872-020-01639-2

81. Paredes OL, Shite J, Shinke T, et al. Impedance cardiography for cardiac output estimation: reliability of wrist-to-ankle electrode configuration. *Circ J*. 2006;70(9):1164-1168. doi:10.1253/circj.70.1164

82. Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP, Sivananthan MU. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. *J Magn Reson Imaging*. 2003;17(3):323-329. doi:https://doi.org/10.1002/jmri.10262

83. Chavhan GB, Babyn PS, Jankharia BG, Cheng H-LM, Shroff MM. Steady-State MR Imaging Sequences: Physics, Classification, and Clinical Applications. *RadioGraphics*. 2008;28(4):1147-1160. doi:10.1148/rg.284075031

84. Panithaya C, Askew JW. Exercise ECG testing: Performing the test and interpreting the ECG results - UpToDate. *https://www.uptodate.com/contents/exercise-ecg-testing-performing-the-test-and-interpreting-the-ecg-results?search=modified%20bruce%20protocol&sectionRank=1&usage_type=default&anchor=H674890&source=machineLearning&selectedTitle=1~150&display_rank=1#H67489*. Published online 2020.

85. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of

functional aerobic impairment in cardiovascular disease. *Am Heart J*. 1973;85(4):546-562. doi:https://doi.org/10.1016/0002-8703(73)90502-4

86. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet (London, England)*. 1986;1(8476):307-310.

87. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res*. 1999;8(2):135-160. doi:10.1177/096228029900800204

88. McHugh ML. Interrater reliability: the kappa statistic. *Biochem medica*. 2012;22(3):276-282. https://pubmed.ncbi.nlm.nih.gov/23092060

89. Saugel B, Cecconi M, Wagner JY, Reuter DA. Noninvasive continuous cardiac output monitoring in perioperative and intensive care medicine. *Br J Anaesth*. 2015;114(4):562-575. doi:10.1093/bja/aeu447

90. Kuster M, Exadaktylos A, Schnüriger B. Non-invasive hemodynamic monitoring in trauma patients. *World J Emerg Surg*. 2015;10(1):11. doi:10.1186/s13017-015-0002-0

91. Teboul J-L, Saugel B, Cecconi M, et al. Less invasive hemodynamic monitoring in critically ill patients. *Intensive Care Med*. 2016;42(9):1350-1359. doi:10.1007/s00134-016-4375-7

92. Saugel B, Reuter DA. III. Are we ready for the age of non-invasive haemodynamic monitoring? *Br J Anaesth*. 2014;113(3):340-343. doi:https://doi.org/10.1093/bja/aeu145

93. Wang DJ, Gottlieb SS. Impedance cardiography: more questions than answers. *Curr Heart Fail Rep*. 2006;3(3):107-113. doi:10.1007/s11897-006-0009-7

94. Jain CC, Borlaug BA. Hemodynamic assessment in heart failure. *Catheter Cardiovasc*

Interv Off J Soc Card Angiogr Interv. 2020;95(3):420-428. doi:10.1002/ccd.28490

95. Bradley EA, Berman D, Daniels CJ. First implantable hemodynamic monitoring device placement in single ventricle fontan anatomy. *Catheter Cardiovasc Interv*. 2016;88(2):248-252. doi:https://doi.org/10.1002/ccd.26498

96. Sherwood(Chair) A, Allen MT, Fahrenberg J, Kelsey RM, Lovallo WR, van Doornen LJP. Methodological Guidelines for Impedance Cardiography. *Psychophysiology*. 1990;27(1):1-23. doi:https://doi.org/10.1111/j.1469-8986.1990.tb02171.x

97. Beck R, Milella L, Labellarte C. Continuous non-invasive measurement of stroke volume and cardiac index in infants and children: comparison of Impedance Cardiography NICaS® vs CardioQ® method. *Clin Ter*. 2018;169(3):e110-e113. doi:10.7417/T.2018.2064

98. Taniguchi Y, Emoto N, Miyagawa K, et al. Noninvasive and simple assessment of cardiac output and pulmonary vascular resistance with whole-body impedance cardiography is useful for monitoring patients with pulmonary hypertension. *Circ J*. 2013;77(9):2383-2389. doi:10.1253/circj.cj-13-0172

99. Medina-Lezama J, Narvaez-Guerra O, Herrera-Enriquez K, et al. Hemodynamic Patterns Identified by Impedance Cardiography Predict Mortality in the General Population: The PREVENCION Study. *J Am Heart Assoc*. 2018;7(18):e009259. doi:10.1161/JAHA.118.009259

100. Milton P, T. AW, R. MM, et al. Utility of Impedance Cardiography for the Identification of Short-Term Risk of Clinical Decompensation in Stable Patients With Chronic Heart Failure. *J Am Coll Cardiol*. 2006;47(11):2245-2252. doi:10.1016/j.jacc.2005.12.071

101. Weipert J, Koch W, Haehnel JC, Meisner H. Exercise capacity and mid-term survival in patients with tricuspid atresia and complex congenital cardiac malformations after modified Fontan- operation. *Eur J Cardio-thoracic Surg*. 1997;12(4):574-580. doi:10.1016/S1010-7940(97)00220-0

102. Legendre A, Guillot A, Ladouceur M, Bonnet D. Usefulness of stroke volume monitoring during upright ramp incremental cycle exercise in young patients with Fontan circulation. *Int J Cardiol*. 2017;227:625-630. doi:https://doi.org/10.1016/j.ijcard.2016.10.087

103. Holbein CE, Fogleman ND, Hommel K, et al. A multinational observational investigation of illness perceptions and quality of life among patients with a Fontan circulation. *Congenit Heart Dis*. 2018;13(3):392-400. doi:10.1111/chd.12583

104. Driscoll DJ, Danielson GK, Puga FJ, Schaff H V, Heise CT, Staats BA. Exercise tolerance and cardiorespiratory response to exercise after the Fontan operation for tricuspid atresia or functional single ventricle. *J Am Coll Cardiol*. 1986;7(5):1087-1094. doi:10.1016/s0735-1097(86)80227-3

105. Zellers TM, Driscoll DJ, Mottram CD, Puga FJ, Schaff H V, Danielson GK. Exercise tolerance and cardiorespiratory response to exercise before and after the Fontan operation. *Mayo Clin Proc*. 1989;64(12):1489-1497. doi:10.1016/s0025-6196(12)65704-8

106. Rhodes J, Garofano RP, Bowman FO, Grant GP, Bierman FZ, Gersony WM. Effect of right ventricular anatomy on the cardiopulmonary response to exercise. Implications for the Fontan procedure. *Circulation*. 1990;81(6):1811-1817. doi:10.1161/01.CIR.81.6.1811

107. Larsson ES, Eriksson BO. Haemodynamic Adaptation During Exercise in Fontan Patients at a Long-Term Follow-Up. *Scand Cardiovasc J*. 2003;37(2):107-112.

doi:10.1080/4017430310001221

108. Brassard P, Bédard E, Jobin J, Rodés-Cabau J, Poirier P. Exercise capacity and impact of exercise training in patients after a Fontan procedure: a review. *Can J Cardiol*. 2006;22(6):489-495. doi:10.1016/s0828-282x(06)70266-5

109. Habedank D, Reindl I, Vietzke G, et al. Ventilatory efficiency and exercise tolerance in 101 healthy volunteers. *Eur J Appl Physiol Occup Physiol*. 1998;77(5):421-426. doi:10.1007/s004210050354

110. Goldberg DJ, Avitabile CM, McBride MG, Paridon SM. Exercise capacity in the Fontan circulation. *Cardiol Young*. 2013;23(6):824-830. doi:10.1017/S1047951113001649

111. Shachar GB, Fuhrman BP, Wang Y, Lucas R V, Lock JE. Rest and exercise hemodynamics after the Fontan procedure. *Circulation*. 1982;65(6):1043-1048. doi:10.1161/01.CIR.65.6.1043

112. Staelens A, Tomsin K, Grieten L, et al. Non-invasive assessment of gestational hemodynamics: benefits and limitations of impedance cardiography versus other techniques. *Expert Rev Med Devices*. 2013;10(6):765-779. doi:10.1586/17434440.2013.853466