NON-INVASIVE CARDIAC OUTPUT OF CHILDREN IN HEALTH AND DISEASE:
Respiratory Gas Techniques

by

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A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy
Graduate Department of Exercise Sciences
University of Toronto

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Abstract

Cardiac output (Q) is an important determinant of the cardiovascular system’s ability to meet the oxygen needs of the body. This dissertation addresses the non-invasive measurement of Q, in healthy children and those with heart and lung disease. 1) The correction factors for collision broadening, downstream difference and end tidal CO₂ (PetCO₂), used in the CO₂ rebreathe (equilibrium) method, were evaluated. In lung disease, one is unable to assume a normal dead space to estimate arterial CO₂ (PaCO₂), and the use of any of these correction factors alone should be used with caution as they each exert a profound effect on the Q measurement. 2) A new equation to predict PaCO₂ from PetCO₂ in patients with CF was derived via multiple regression analysis, taking into account disease severity. 3) The validity and reliability of Q measures via the inert gas rebreathing technique (Innocor™ device) were evaluated. The highest intraclass correlation coefficients were attained during exercise (0.7-0.98), indicating excellent reliability of the device. Comparisons of Q measures from the Innocor™ (Q_{inn}) to the AMIS mass spectrometer system (Q_{Amis}) were made to assess validity. The bias (Q_{inn} - Q_{Amis}) and limits of agreement (±2SD) were 0.45 ± 1.9 L.min⁻¹ and 0.27 ± 2.1 for children with congenital heart disease and healthy controls respectively, with no systematic differences between the
two methods. 4) Assessment of cardiac output in Fontan patients demonstrated that an individualized, atrioventricular (AV) delay optimization was required. Moreover, there was a small but significant improvement in heart function with AV synchronized pacing (DDI) versus ventricular pacing (VVI), suggesting that further study with a larger sample of patients is warranted. The limitations and strengths of the measurement of non-invasive cardiac output in children, primarily via respiratory gas analysis, were delineated and recommendations were made for their use.
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Abbreviations

a-$\bar{v}$O$_2$diff arterio-venous oxygen difference (mL.100mL$^{-1}$)
CaCO$_2$ arterial content of carbon dioxide (mL.100mL$^{-1}$)
Ca-$\bar{C}$vCO$_2$ arterio-mixed venous oxygen content difference (mL.100mL$^{-1}$)
EDV end diastolic volume (mL)
EF ejection fraction (%)
ESV end systolic volume (mL)
HR heart rate (b.min$^{-1}$)
PaCO$_2$ partial pressure of arterial carbon dioxide (mmHg)
P$\bar{v}$CO$_2$ partial pressure of mixed venous carbon dioxide (mmHg)
Q cardiac output (L.min$^{-1}$)
RR respiratory rate (breaths.min$^{-1}$)
SVR systemic vascular resistance (mmHg.L$^{-1}$.min$^{-1}$)
SV stroke volume (mL)
$V_A$ alveolar ventilation (L.min)
$V_E$ minute ventilation (BTPS, mL)
$V_D$ dead space (mL)
$V_T$ tidal volume (BTPS, mL)
VCO$_2$ carbon dioxide production (L.min$^{-1}$)
VO$_2$ oxygen consumption (L.min$^{-1}$)
Chapter 1: Introduction

Children have been described as naturally active beings, who, given the opportunity, will discover and operate within their own physical limits (Strong, 1999). Although there has been a recent focus on the increasingly sedentary lifestyle of children (Tremblay and Willms, 2003) compared to their adult counterparts, we will still consider children to be ‘active beings’. Children with chronic illness are often less physically active than their healthy peers, due to a variety of factors such as disease specific physical limitations, time consuming treatments, and overprotection of caregivers. These factors may lead to a spiral of deconditioning and inactivity, resulting in further reductions in participation, culminating in prolonged disability (Bar-Or, 1983). Indeed, the mounting evidence of health impairments in sedentary children highlights how important it is to facilitate their ability to participate in an active life. It is the belief that health impairments can be ameliorated if we can equip children with the ability to engage in regular physical activity, while striking a balance between effectiveness and safety.

The response to exercise in healthy children provides a framework for our understanding of the physiological mechanisms of the cardiorespiratory system, comprised of the cardiovascular and respiratory systems, in health and disease. Prior to devising a new treatment one must be able to quantify the functioning of this system in a feasible, reproducible manner and make a diagnosis. While one would test the functioning of a machine while under the stress of a load, so too must we stress the body in order to be able to evaluate its limitations. In the clinical setting, exercise has been commonly used as a probe to test the reserve of physiological mechanisms. In addition it has been employed therapeutically, as a stressor to induce increased capacity through adaptation to the stress, in a variety of disease conditions (Bar-Or, 1983).

Cardiac output (Q), or the amount of blood pumped by the heart per minute, is an important determinant of the cardiovascular system’s ability to meet the oxygen needs of
the body. From a cardiologist’s perspective, the heart is easily accessible and measurable, which allows them the ability to intervene, based on an extensive knowledge of function.

Most of our understanding of cardiac output has been derived from invasive studies in animals and adult humans. Since children are not small adults, they require investigations tailored to their unique ages and sizes. Though childhood may be broken down into several categories including infant, child, youth and adolescent, for the purposes of this dissertation research a child will be defined as any individual less than 18 years of age and an adult, 18 years and older.

The ethics and practicality of invasive forms of testing in children have necessitated an improvement in our abilities to measure cardiac output non-invasively. On-going monitoring of children requires techniques that are feasible for frequent and repeatable measures. Methodological studies are required to assess and enhance our ability to measure cardiac output non-invasively.

This dissertation research was a quest to improve our understanding of cardiac output determination in healthy children as well as those with cardiac or lung disease, to challenge the integral components of the cardiorespiratory system. It was believed that practical, feasible measures of cardiac output would contribute useful information to the management of certain diseases and health impairments.

This dissertation begins with a review of the non-invasive methods for measuring cardiac output considered appropriate for use in the pediatric setting, as well as the original invasive work that laid the foundation for these methods. Next, a research projects chapter, beginning with a methods development section, outlines three projects undertaken to refine the CO₂ rebreath method of cardiac output determination, addressing the challenges of using this method in patients with lung disease. Recommendations have been made to enhance those techniques.

The original research continues with two major application investigations, including the assessment of the reliability and validity of the Innocor™ device to measure cardiac output via the inert gas rebreathing technique, and an evaluation of
pacemaker optimization in patients with Fontan repair, using cardiac output as the outcome variable. Prior to a submission to a scientific journal, these two papers will be revised by eventual co-authors and their names will be added at that point.

Two clinical populations were selected for these investigations. The first was patients with cystic fibrosis, as they represent an example of pediatric lung disease, and thus present a challenge to non-invasive methods that rely on gas exchange that may be disrupted as a result of their lung disease. The second was patients with congenital heart disease, as they represent a population in which we expect cardiac output to be altered, due to the nature of their disease.

The discussion chapter is divided into two main sections; the first summarizes the comprehensive, systematic evaluation of resident and non-resident respiratory gas methods of cardiac output evaluation, outlining strengths, limitations and recommendations for improvement. The second section provides an exercise science perspective for understanding pediatric cardiac output determination, providing a physiological context within which to apply the research findings.

Lastly, the dissertation concludes with a summary of limitations and future directions to further advance our knowledge in the area of non-invasive pediatric cardiac output.
Chapter 2: Background and Review of Literature

The first part of this chapter provides background information for the following topics: normal responses to exercise, with a special focus on children and how their response differs from adults’, limitations to exercise (a theoretical construct to provide a framework to understand limitations in disease), definitions, physiological and clinical relevance of cardiac output. The second part of this chapter deals with the methods of cardiac output determination, beginning with the original, invasive, ‘gold standard’ techniques, followed by respiratory gas analysis methods (both resident and non-resident gas), a brief review of impedance cardiography and echocardiography. Common methods of comparison of the various techniques are assessed. The relevant pathophysiology and functional status of the two clinical populations included in this dissertation are then introduced. The chapter concludes with a statement of the research problem and a list of research hypotheses.

2.1 Normal Response to Exercise

2.1.1 Introduction

The human body has an impressive functional reserve, or ability to respond to increasing demand. As adults increase their level of dynamic, aerobic exercise, oxygen consumption (VO₂), a measure of cardiopulmonary function, may reach 20 times the resting value. This may be accompanied by an increase in cardiac output (Q) of up to seven times the resting value for athletes (Saltin, 1967), vastly improving the delivery of oxygen to the muscles.

The main role of the cardiovascular system during exercise is to transport additional O₂ to the exercising muscles and CO₂ away from this area. This delivery of oxygen can best be described by Fick’s principle:
\[ \text{VO}_2 = Q \cdot (\text{CaO}_2 - \text{C\O}_2) \]  \hspace{1cm} \text{(equation 1)}

Knowing that \( Q = \text{HR} \cdot \text{SV} \), this equation becomes,

\[ \text{VO}_2 = \text{HR} \cdot \text{SV} \cdot (\text{CaO}_2 - \text{C\O}_2) \]  \hspace{1cm} \text{(equation 2)}

During exercise, both \( Q \) and arterio-venous oxygen content difference (\( a-\text{\O}_2\text{diff} \)) rise, the former by an increase in \( \text{HR} \) and \( \text{SV} \), and the latter by an increased extraction of oxygen by the working muscles. Heart rate response to exercise is initially the result of increased sympathetic and reduced parasympathetic stimulation.

The three main determinants of cardiac output are preload (influenced by venous return and heart rate), afterload (depends on systolic BP) and myocardial contractility (enhanced by catecholamine release in exercise). During dynamic exercise preload increases with intensity and facilitates an enhanced stroke volume, total peripheral resistance falls as a result of dilation of the muscle vasculature, and arterial systolic pressure rises and diastolic pressure remains nearly unchanged.

Increases in \( \text{SV} \) during exercise result from a greater end diastolic volume (EDV) and a more complete emptying of the heart; this results in a reduced end systolic volume (ESV). The relationship between these two measures, or the ejection fraction (\( \text{EF} = ((\text{EDV}-\text{ESV})/\text{EDV}) \cdot 100 \)), is sometimes used as a measure of heart function, although its usefulness is somewhat limited due to the fact that it is influenced by both loading (preload and afterload) and contractile state of the heart. Sample values for \( \text{EF} \) in adults at rest could be \( ((120-50)/120) \cdot 100 = 58\% \) while during dynamic exercise they may rise to \( ((168-38)/120) \cdot 168 = 77\% \) (Rowell, 1986). In children, ejection fractions have been reported from 63\% at rest to 81\% at maximal exercise, using gated nuclear angiography (DeSouza et al., 1984).

Starling’s law of the heart is most apparent when the body is moved from upright to supine position or in the abrupt change from rest to exercise. Although at rest, in the upright position, approximately 40\% of the EDV (50-70ml) remains after ventricular
contraction, this amount decreases with increasing exercise intensity due to catecholamine enhanced myocardial contractility. In the supine position, the removal of the effect of gravity enables a greater venous return, increasing EDV and allowing SV to be at almost its highest at rest (McArdle et al., 2001).

Unlike dynamic exercise, resistance or strength training causes vascular compression and an increase in total peripheral resistance. The body responds with an increase in sympathetic nervous system activity, Q and mean arterial blood pressure (MAP). However compared to dynamic exercise, resistance exercise leads to a smaller rise in Q and a larger rise in MAP in part due to increased diastolic BP.

As workrate increases more oxygen is extracted from the blood and the arteriovenous oxygen content difference, \((\text{CaO}_2 - \text{CvO}_2)\), widens. Eriksson et al. found that the maximum \(\Delta\text{VO}_2\text{diff}\) in their study of exercising children was \(145 \text{ ml.L}^{-1}\) (Eriksson, 1971; Eriksson and Koch, 1973), compared to previous reports of \(181 \text{ ml.L}^{-1}\) in adults (Ekblom, 1969).

The other main contributor to cardiopulmonary function is the respiratory system. The rise in alveolar ventilation maintains \(\text{PaO}_2\) and removes \(\text{CO}_2\) and is achieved by increases in respiratory frequency and tidal volume \((\text{Ve} = \text{Vt} \cdot \text{RR})\). Tidal volume, however, must be greater than the dead space in order for the fresh air to reach the alveoli \((V_A = (\text{Vt} - \text{Vd}) \cdot \text{RR})\). This becomes an issue for individuals with very small tidal volumes, such as small children with lung disease, where there will be an increased dead space.

In health, the energy cost of breathing is estimated at 3-5% of the total oxygen consumption and therefore the relationship of \(\text{VO}_2\) and work rate is fairly consistent. In heavy exercise the respiratory muscles can receive as much as 15% of the total cardiac output, which explains why an increased work of breathing in lung disease can lead to a competition for blood flow, with a resultant vasoconstriction in the locomotor muscles and a limitation to work capacity (Dempsey et al., 1996).
2.1.2 Differences Between Children and Adults in Cardiopulmonary Response to Exercise

In comparing children to adults the concept of ‘relative’ amounts of work is noteworthy. As Godfrey at al. (1974b) stated, the work involved in taking a full feed during infancy is probably equivalent to about the amount of work an adult would perform running 1500m. If children are able to maintain similar levels of gas exchange, blood gases and cardiac output for equivalent work rates, Godfrey suggests that certain biological norms or relationships must be established early in development. For example, as the child develops and the dimensions of the heart and lungs increase, the need for tachypnea and tachycardia will decrease, however the relationship between the changing mechanics of circulation and ventilation will be closely integrated, laying the basis for cardiopulmonary interactions throughout life. Table 1 illustrates the differences between adults and children in central and peripheral response to exercise.

Table 1. Central and peripheral hemodynamic responses to exercise; a comparison between children and adults

<table>
<thead>
<tr>
<th>Function</th>
<th>Children’s Response (compared with adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate - submax</td>
<td>Higher, especially after first decade</td>
</tr>
<tr>
<td>Heart rate - max</td>
<td>Higher</td>
</tr>
<tr>
<td>Stroke volume – submax and max</td>
<td>Lower</td>
</tr>
<tr>
<td>Cardiac output – submax</td>
<td>Somewhat higher</td>
</tr>
<tr>
<td>Arterio-mixed venous O₂ difference-submax</td>
<td>Somewhat higher</td>
</tr>
<tr>
<td>Blood flow to active muscle</td>
<td>Higher</td>
</tr>
<tr>
<td>Systolic and diastolic blood pressure-submax</td>
<td>Lower</td>
</tr>
</tbody>
</table>

(Bar-Or, 1983)

*Heart Rate.* Resting heart rate declines during childhood. Unlike adults, HRmax is age-independent until 18 years, at which point there is a decline of approximately 0.7-0.8 beats/min per year (Bar-Or and Buskirk, 1974). Higher submaximal heart rates compensate for the lower SV of younger children.
**Stroke Volume.** Resting and maximal SV increase proportional to left ventricular size and body size. Since Qmax increases in parallel with VO₂max and HRmax does not change with size, SVmax is the major determinant of increasing Q in the growing child (Rowland, 1996).

**Cardiac Output.** The capacity to increase Q is to a very small degree a function of size in children. Gadhoke et al. (1969) reported a difference of only one litre/min of Q between the largest and smallest child for a given VO₂ in a group of 9-15 year old boys.

**VO₂max.** While VO₂max is characterized in adults by a plateau of VO₂, whereby a further increase in exercise intensity will not elicit a further increase in VO₂, in children it is rare to elicit such a plateau (Bar-Or, 2000). More often VO₂peak is used to define the highest VO₂ achieved in children.

The debate continues regarding the most appropriate way to express VO₂max in children. If presented in absolute terms, L/min, VO₂max increases as the child grows, similarly in boys and girls until adolescence, at which point males begin a steeper increase while females begin to plateau. The relative VO₂max, (mL·kg⁻¹·min⁻¹), remains constant for males throughout childhood, but in females, begins to decline gradually, by approximately 0.8 mL·kg⁻¹·min⁻¹·yr⁻¹ at puberty (Bar-Or, 1983). In adults there is a steady decline in VO₂ max of approximately 10% with each decade of life (Hawkins and Wiswell, 2003).

**Q:VO₂ relationship.** The slope of the Q:VO₂ relationship, also termed the ‘exercise factor’ by Rowland (1996) describes the “ratio of change in cardiac output to change in VO₂, and is used as a marker of cardiac performance” (Table 2). This ratio is approximately 5.5-6.0 for children, similar to adults.
Table 2. Exercise factor (change in Q relative to VO$_2$) in studies of children

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>Delta Q/VO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bar-Or et al. (1971)</td>
<td>CO$_2$ rebreathing</td>
<td>5.7</td>
</tr>
<tr>
<td>Marx et al. (1987)</td>
<td>Doppler</td>
<td>6.0</td>
</tr>
<tr>
<td>Edmunds et al. (1982)</td>
<td>CO$_2$ rebreathing</td>
<td>6.0</td>
</tr>
<tr>
<td>Godfrey et al. (1971)</td>
<td>CO$_2$ rebreathing</td>
<td>5.7</td>
</tr>
<tr>
<td>Locke et al. (1978)</td>
<td>Direct Fick</td>
<td>6.5</td>
</tr>
<tr>
<td>Rowland et al. (1992)</td>
<td>Bioimpedance</td>
<td>4.4</td>
</tr>
</tbody>
</table>

(Rowland, 1996).

Figure 1. Cardiac output of the exercising child. This figure shows that the Q vs VO$_2$ relationship of adults has a similar slope but a slightly higher intercept than children. Individual values for boys performing upright submaximal and maximal cycle-ergometer exercise: Closed circles: data by Godfrey et al. (Godfrey et al., 1971) on boys with body height of 110 to 154 cm, tested by CO$_2$ rebreathing. Closed triangles: data by Eriksson on boys 13-14 years old, tested by dye dilution (Eriksson, 1971). The shaded area represents young adults performing upright exercise. Compiled from the literature by Bar-Or et al. (1971).

Unlike others who reported no differences between children and adults (Gadhoke and Jones, 1969; Godfrey et al., 1971; Jacob et al., 1997), Turley et al. (1997b) found that children had a lower Q for a given VO$_2$, which was compensated for by a higher a–vDO$_2$. They also reported a higher HR and total peripheral resistance and lower SV in children compared to adults, on both cycle and treadmill exercise. They attributed the lower SV to
a smaller left ventricular mass and a smaller muscle mass performing relatively greater amounts of work.

Bar-Or (1983) compiled the differences in respiratory function between adults and children, indicating an overall higher respiratory effort for a given submaximal workload (Table 3).

Table 3. Respiratory function during exercise: A comparison between children and adults.

<table>
<thead>
<tr>
<th>Function</th>
<th>Children’s Response (compared with adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation per kilogram body weight - max</td>
<td>Same</td>
</tr>
<tr>
<td>Ventilation per kilogram body weight - submax</td>
<td>Higher</td>
</tr>
<tr>
<td>Ventilatory “breaking point”</td>
<td>Earlier or same</td>
</tr>
<tr>
<td>Respiratory rate – max and submax</td>
<td>Higher</td>
</tr>
<tr>
<td>Tidal volume/vital capacity - max</td>
<td>Lower</td>
</tr>
<tr>
<td>Tidal volume/vital capacity – submax</td>
<td>Same or lower</td>
</tr>
<tr>
<td>Ventilatory equivalent – max and submax</td>
<td>Higher</td>
</tr>
<tr>
<td>Dead space/tidal volume</td>
<td>Same</td>
</tr>
<tr>
<td>Partial pressure of arterial CO₂</td>
<td>Somewhat lower</td>
</tr>
</tbody>
</table>

(Bar-Or, 1983)

2.1.3 Limitations to Exercise

An understanding of what limits performance provides us with a context within which to understand pathology and disease. Jones and Killian (2000) have reviewed numerous potential limiting factors, one example being an inadequate oxygen (O₂) delivery to the working muscle. While the debate continues, there is consensus of the maximum oxygen consumption (VO₂ max) as the prime indicator of exercise capacity. “The physiological significance of the VO₂max relates to its dependence upon the functional capacity and integration of systems required for oxygen supply, transport, delivery, and use” (McArdle et al., 2001). Much research has centered on the exploration of variables that might influence the delivery of O₂ to the muscle.
Following this idea, Lindstedt (1988) offers an explanation for the limitation of oxygen uptake. They describe the respiratory system as a series of structures, each offering a degree of resistance to gas transport. These structures are comprised of pulmonary ventilation, transportation through the circulatory system, and finally diffusion between the blood and tissue. Unlike previous suggestions of a rate-limiting step in the transport of O₂, this view suggests that one cannot manipulate one part of the system in isolation because the resistance of each area will depend upon other points in the cascade. Resistors can be structurally fixed or adaptable. Of the latter, the step that offers the greatest resistance is often the area that is the most able to be trained. The relationship between Q and VO₂ would be such that a high O₂ delivery would be compensated by a lower extraction, and vice versa. While the answer to what limits performance continues to be debated, the use of this conceptual approach can help us to understand the pathophysiology of disease. These concepts may be applied to children as well as to adults.

It is likely most useful to combine the above two approaches to understand pathophysiology. While one method stresses the search for a limiting factor of an individual’s response to a maximal load, the other suggests compensatory mechanisms working in concert with each other in response to the underlying pathology.

2.2 Cardiac Output

2.2.1 Introduction

The ability of children to participate in an active lifestyle with ease is reflected in their cardiorespiratory fitness. An understanding of one’s cardiorespiratory fitness or functional capacity has long been a focus of exercise physiology research. Once the VO₂max was accepted as the best measure of one’s functional capacity it became important to understand what limited this parameter and how this limitation could lead to functional impairment in patients.
Cardiac output may be viewed as both a determinant (‘ruler’) of the cardiovascular system’s ability to meet the oxygen needs of the body, (via changes in myocardial contractility), as well as a ‘slave’, or a consequence of the state of the rest of the system (due to preload, afterload). In either case, the study of the human body under physical stress is able to reveal information unattainable in the resting condition. The next section will discuss the physiological and clinical relevance of cardiac output.

2.2.2 Clinical Relevance

What additional clinical information do measurements of Q provide, if one already has values of oxygen consumption, ventilation and/or anaerobic threshold for an exercising child? We know that \( V_O_2 \) gives us feedback on the transport and utilization of oxygen, while ventilation gives us a measure of the body’s ability to move air in and out of the lungs, and an indication of increasing metabolic acidosis. Lastly, anaerobic threshold may indicate when energy liberation from anaerobic metabolism increases to a level where acid base balance and ventilation are perturbed. While a measure of Q is related to VO\(_2\), it also gives us detailed feedback on the functioning of the heart itself, through inference of myocardial performance (stroke volume), coordination of the myocardium to eject the blood and the anatomical flow pathway for blood (shunt). These factors, together with arterio-venous oxygen difference (a-\( \bar{V}_O_2 \)diff), may offer insight into cardiovascular factors that limit the transport of oxygen. This is of particular interest to exercise physiologists and clinicians, and applies to a broad range of individuals (adults and children) from elite athletes to patients with chronic disease.

It has been suggested that the limitation to exercise in cardiovascular disease is a reduced exercise capacity (VO\(_2\)max). Conversely, however, a normal VO\(_2\)max does not necessarily indicate a normal Q. For example, if Q is suboptimal in the face of a normal VO\(_2\), the body may be compensating to allow for increased O\(_2\) extraction and this information would be missed if one did not measure Q. This information might point to a more detailed study of cardiac function. Additionally, with an apparently normal Q one may be able to maintain SV as a result of cardiac dilation, in the face of a reduced left ventricular ejection fraction (LVEF) (Driscoll et al., 1989). Thus, similar to the idea
offered by Lindstedt (1988), the evaluation of Q cannot be performed in isolation and must be viewed in context of the cardiorespiratory system response to exercise, as changes in one area of the body will cause compensation in another.

Although a measure of Q can further our insight into the pathophysiology of disease, sometimes the attainment of a predicted maximum heart rate is used instead, as a marker of having reached a cardiovascular limitation. How do we resolve this in children, however, when there is no well-documented age-related maximum heart rate in this age group? An accurate measure of Q could offer some insight into whether the cardiovascular system is limiting the response to exercise in children.

Measures of Q are useful in that they can provide feedback on disease progression and treatment, especially within groups of patients (Driscoll et al., 1989). If clinically, a measure of cardiac reserve is defined by “the ability of the Q to increase from rest values to meet the oxygen demands of exercise” (Jones, 1997), then a Q value could be evaluated against the corresponding value of oxygen consumption for a given workload. Normal values for adults (Jones, 1997) and children (Godfrey, 1974a) have been published, which are specific to the techniques and calculations from which they were derived.

2.3 Methods of Cardiac Output Determination

This section will briefly review the invasive ‘gold standard’ technique to determine cardiac output, Direct Fick, followed by two other invasive techniques, dye dilution and thermodilution. A detailed review of the respiratory gas analysis techniques, both resident and non-resident gases, will follow, as these have been the most commonly performed non-invasive methods employed in children. The section will conclude with a brief review of echocardiography and impedance cardiography methods.
2.3.1 “Gold Standard” Invasive Methods

Cardiac catheterization and the use of either the direct Fick equation or dye-dilution principle are considered to be the gold standard techniques for Q determination. The thermodilution procedure is often included in this category (Warburton et al., 1999a). These techniques have been previously used to validate non-invasive or indirect measures of Q.

The original Fick theory (Guyton, 1977) states that the amount of oxygen arriving at the right side of the heart (Q x CvO$_2$), plus the amount of oxygen that enters via the lungs (VO$_2$), must equal the amount of oxygen transported away from the left side of the heart (Q x CaO$_2$). This technique to measure Q requires an arterial blood sample to be drawn and VO$_2$ and VCO$_2$ to be determined while the subject is in a steady state condition. In addition, a sample of pulmonary arterial blood is required as it represents a measure of well-mixed venous blood, and avoids the heterogeneous samples of venous blood that could arise from the varied metabolic rates occurring around the body.

While the direct Fick may be indicated for anaesthetized patients in the intensive care unit, the technical difficulty and inherent risk involved to perform this test make it impractical and unethical for routine testing of children, even with its low rate of error (5% at rest) (Warburton et al., 1999a).

Another invasive method of Q determination, dye dilution, is often used for the validation of indirect methods (Eriksson and Koch, 1971). Rather than determine VO$_2$, a measure is made of the downstream concentration of a dye that has been injected into venous circulation either via the pulmonary artery or a central venous line. A higher Q will result in more rapid dilution of the dye. Arterial blood is then sampled to attain a measure of the concentration of dye over time, which will be related to Q (Warburton et al., 1999a). Warburton et al. (1999a) compiled an extensive review of Q research and found the reliability and reproducibility for the dye dilution technique to be comparable to those of the direct Fick method (coefficients of variation of 5-10% at rest and during submaximal exercise). Validation studies comparing these two methods reported correlation coefficients ($r$) of 0.73 (Doyle et al., 1953) to 0.96 (Taylor and Shillingford,
1959). Of the invasive direct techniques, dye dilution is the one most commonly reported in children (Zeidifard et al., 1972; Eriksson and Koch, 1971; Sekelj et al., 1958).

The third invasive technique of Q determination is thermodilution. It follows a similar principle to dye dilution, but instead employs the injection of a cold fluid of saline into the pulmonary artery. The degree of cooling is inversely related to Q (Bowdle et al., 1991). Although thermodilution has been used in both clinical and exercise physiology settings, its use as a gold standard has been highly questioned due to numerous reports of overestimation of Q by this technique compared to the dye dilution and direct Fick (Warburton et al., 1999a; Espersen et al., 1995).
Table 4. Research investigations involving invasive determination of cardiac output in healthy children

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Method</th>
<th>Condition</th>
<th>Sample values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sproul (1964)</td>
<td>n = 21</td>
<td>Direct Fick</td>
<td>Rest, supine</td>
<td>Q: 4.4 L. min⁻¹, SV: 46.92 mL. a-(\bar{\text{O}}_2)diff: 4.1 mL.100mL⁻¹</td>
</tr>
<tr>
<td></td>
<td>6-16 yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erikson et al.</td>
<td>n = 9 B 13-14 yrs</td>
<td>Dye dilution</td>
<td>Rest, submax, max ex cycle</td>
<td>Qmax: 17.4 L.min⁻¹, SVmax : 87 mL max a-(\bar{\text{O}}_2)diff max :14.5 mL.100mL⁻¹; VO₂max 2.5 L.min⁻¹</td>
</tr>
<tr>
<td>(1971)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eriksson et al.</td>
<td>n = 9 B 11-13 yrs</td>
<td>Dye dilution</td>
<td>Rest, submax, max ex cycle</td>
<td>Qmax: 12.5 L.min⁻¹, SVmax : 67 mL a-(\bar{\text{O}}_2)diff max :14.2 mL.100mL⁻¹; VO₂max 2.5 L.min⁻¹</td>
</tr>
<tr>
<td>(1973)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumming (1978)</td>
<td>n = 31 B, 9.5-15.5 yrs</td>
<td>Dye dilution</td>
<td>Rest, submax, max ex Supine</td>
<td>Peak CI : B :10.1 L. min⁻¹ per M²; G :8.6 L. min⁻¹ per M² Peak SVI : B :72.2 mL per M²; G :64. mL per M²</td>
</tr>
<tr>
<td></td>
<td>n = 31 G, 8.7-14.9 yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lock et al. (1978)</td>
<td>n = 10 11.6 yr</td>
<td>Direct Fick</td>
<td>Cycle ex</td>
<td>Peak CI : 8.4 L. min⁻¹ per M²; Peak SVI : 59.3 mL per M²</td>
</tr>
</tbody>
</table>

B = boys; G = girls; CI = cardiac index; SVI = stroke volume index; a-\(\bar{\text{O}}_2\)diff = arterio-venous oxygen difference; Upright exercise unless specified otherwise.
2.3.2 Respiratory gas analysis: Resident Gas (CO₂)

Carbon dioxide is the resident gas used to determine Q via respiratory gas analysis. The two main techniques of CO₂ rebreathing were introduced by Collier (1956) and Defares (1958), and differ primarily in how mixed venous CO₂ (P̅vCO₂) is determined. As an extension of the direct Fick principle, Q can be solved for with the use of CO₂ instead of O₂ by what is then termed the Indirect Fick: \( Q = \frac{VCO_2}{(CvCO_2 - CaCO_2)} \). Carbon dioxide production is routinely determined via respiratory gas measurements and a variety of recommendations have been proposed for the determination of CO₂ in mixed venous and arterial blood, as well as for the conversion of partial pressure to content.

Collier: CO₂ Rebreathe Equilibrium Technique (Collier, 1956)

The subject rebreathes a mixture of a high concentration of CO₂ from a closed bag (10-15% in balance O₂) while at a steady state. During the rebreathing, the lung acts as a tonometer and the concentration in the lung-rebreathing bag approaches the partial pressure of mixed venous CO₂ (P̅vCO₂). If both the volume of the rebreathing bag and the concentration of CO₂ have been chosen correctly, equilibrium is reached before recirculation occurs. End tidal CO₂ is measured continuously during the rebreathe and the concentration at equilibrium is accepted as the P̅vCO₂. The high background concentration of oxygen in the CO₂ mixture ensures complete saturation of pulmonary blood, thus allowing for the calculation of mixed venous CO₂ content via the CO₂ dissociation curve (McHardy, 1967).

Cumming et al. (1978) have suggested that recirculation times in children are as fast as 4.5 seconds, however their work was collected on children who were exercising supine and has not been repeated since. Godfrey (1974a) and others have maintained that recirculation times in children are approximately 10 seconds during exercise and slightly longer at rest. All data must be collected prior to this time to avoid the confounding effect of recirculation on P̅vCO₂ measurements; once recirculation has occurred, the initial rebreathed CO₂ has returned to the heart and will artificially raise the P̅vCO₂, thus lowering the Q.
This technique is well validated in children and adults, with (Coates et al., 1988; Mahler et al., 1985) and without (Godfrey and Davies, 1970) (Lands et al., 1992b) lung disease. Considered the most technical of the rebreathing protocols, the equilibrium method has been widely studied and reported over the past 50-60 years.

**Bag [CO₂] and Volume Selection, Rate of Rebreathing**

To obtain a proper equilibrium plateau from the rebreathe manoeuvre one must select the appropriate concentration of CO₂ for the rebreathing bag. Jones et al. (1973) have provided both a table based on a given power output, O₂ uptake and end tidal PCO₂ in adults, and provided the equation, \( P_{bag}CO₂ (\text{ideal}) = 48.5 + 0.007 VCO₂ + 0.7 PetCO₂ \) for this purpose. The applicability of this relationship for children has yet to be determined. Generally the volume in the bag is set at 1.5 times the tidal volume of the subject. With increasing intensity of exercise the CO₂ concentration in the bag must be raised, as reflected by the increasing PeCO₂, VCO₂ or VO₂ of the subject.

The ideal tracing is one where a plateau is achieved between 8 and 12 seconds of rebreathing at rest, prior to recirculation. If the concentration in the bag is inaccurate it will cause an equilibrium tracing to rise (bag concentration is too low) or fall (bag concentration is too high) to more than ±2 mmHg of the starting concentration. In this case, Denison (1968) demonstrated that one can extrapolate the line to 20 seconds and achieve reliable results for \( P\bar{v}CO₂ \). An experienced technician should be able to obtain an acceptable equilibrium with 1-2 attempts of the manoeuvre.

Recommended ventilatory rates while rebreathing have been reported in the range of 20-25 (Mahler et al., 1985) 30 (Jones and Rebuck, 1973; Jones et al., 1966) or 30-40 breaths per minute (Heigenhauser and Jones, 1979). An optimal rebreathing frequency for children has yet to be determined.

**End Tidal Estimate of Arterial CO₂ (PaCO₂)**

The need for a correction for end tidal CO₂ (PetCO₂) is based on the observation that there is a difference between PetCO₂ and PaCO₂. PaCO₂ is approximately 2 mmHg greater than
PetCO\textsubscript{2} at rest, due to dilution from poorly perfused alveoli at the top of the lung, in the upright position. With exercise, there is an increased perfusion and recruitment of alveoli, reducing alveolar dead space, bringing the mean alveolar CO\textsubscript{2} closer to the mean arterial CO\textsubscript{2}. PetCO\textsubscript{2} increases relative to PaCO\textsubscript{2} because of the increased rate of delivery of CO\textsubscript{2} to the lung, increasing the slope of the alveolar phase of the CO\textsubscript{2} expiratory curve. The difference between these two variables, P(a-et)CO\textsubscript{2}, is approximately 2 mmHg at rest and falls to approximately –4.0 mmHg during exercise (Wasserman et al., 1994).

Disagreement continues as to whether PetCO\textsubscript{2} is an accurate estimate of PaCO\textsubscript{2} in lung disease. Mahler et al. (1985) compared cardiac output, as determined by direct Fick and CO\textsubscript{2} rebreathing methods, in patients with obstructive lung disease, in a regularly cited study. These authors concluded that there was a significant correlation between the two methods (r = 0.70) at rest, only when an arterial measure of PCO\textsubscript{2} was measured. Stronger significant correlations were found between the two methods during exercise using arterial PCO\textsubscript{2} (r = 0.79) compared to PetCO\textsubscript{2} (r = 0.63). Respiratory rates in this study were as low as 20-25 breaths per minute.

Jones et al. (1979) reported a relationship between PetCO\textsubscript{2} and PaCO\textsubscript{2} (determined via arterial catheter) in adults of PaCO\textsubscript{2} = 5.5 + 0.90 PetCO\textsubscript{2} – 0.0021 V\textsubscript{T}. This well accepted and often-employed correction equation was originally derived from a sample of five healthy adult males, confirmed in previously collected data in 10 men, and later reconfirmed by others (Robbins et al., 1990) in six healthy adult males. Jones et al. (1979) cautioned that the use of their correction equation should be reserved for healthy subjects and avoided in those with abnormal pulmonary function due to lung areas with high time constants for gas exchange. Others have suggested that there should be a different prediction equation used for patients with cardiopulmonary disease compared to healthy individuals (Brutinel, 1983). In addition they reiterated a conclusion of Godfrey and Davies (1970) (based on earlier results of Jones (1966)) to avoid the application of this correction to children’s data, since smaller lungs might lead to greater fluctuations in alveolar gas concentrations and children’s respiratory rates are higher than in adults.

Though many researchers have recommended that the use of end tidal PCO\textsubscript{2} to estimate arterial PCO\textsubscript{2} be reserved only for individuals with normal pulmonary function (Davis et al.,
1978; Heigenhauser and Jones, 1989; Franciosa et al., 1976; Jones et al., 1979; Jones et al., 1966; Mahler et al., 1985; Pianosi and Hochman, 1996; Driscoll et al., 1989; Muiesan et al., 1968), in fact the difference between estimated (Jones corrected end tidal) and directly sampled \( \text{PaCO}_2 \) in patients with advanced lung disease (Coates et al., 1988) was reported to be \( 0.8 \pm 3.5 \text{ mmHg} \), and not significant. While the actual power of this test may have been low to be able to detect the difference, the fact remains that the estimated and directly sampled \( \text{PaCO}_2 \) were very similar in this group of patients, and the difference would likely have been within the measurement error of the technique.

Lands et al. (1996) later reported similar results in 19 patients with CF with severe airflow limitation. Although end tidal estimates produced \( \text{PaCO}_2 \) values that were lower than the actual \( \text{PaCO}_2 \) derived from an indwelling arterial catheter, this made little difference to the calculated \( \text{CO}_2 \) content values. Coefficients of variation for \( Q \) of 13.5-14.6\% were considered acceptable by the authors, comparing \( Q \) via end tidal to arterial, and they recommended that the use of end tidal \( \text{CO}_2 \) gives an acceptable estimate of \( \text{PCO}_2 \) and leads to reasonable values of \( Q \).

Pianosi et al. (1996) concluded that \( \text{PetCO}_2 \) was not a valid alternative to \( \text{PaCO}_2 \) in CF patients with moderately severe lung disease, in contrast to the above study. Unlike Lands et al. (1996) however, this group relied on arterialized capillary blood samples to estimate \( \text{PaCO}_2 \). It is of interest to note that this group sampled the end tidal \( \text{CO}_2 \) simultaneous to the blood sampling. Given that meticulous technique is essential to ensure a good quality, free flowing capillary blood gas sample, void of air bubbles, a potential source of error may have been hyperventilation, associated with the normal apprehension of children of blood sampling, which could have reduced \( \text{PetCO}_2 \) values.

Based on these results, Pianosi et al. (1996) derived a new equation (\( \text{PaCO}_2 = 0.647 \cdot \text{PetCO}_2 + 12.4 \)) to predict \( \text{PaCO}_2 \) in healthy children, following an earlier recommendation of Paterson et al. (1982). This equation was derived in 23 healthy children and confirmed in nine more. They concluded that their equation was not reliable in children with moderately severe pulmonary disease due to CF, but gave results that were superior to other bloodless methods, for the calculation of \( Q \) by the indirect Fick (\( \text{CO}_2 \)) method.
Summary

Disagreement remains as to which is the most acceptable method of determining PaCO$_2$ non-invasively in children, for the use in Q calculations, and especially for children with lung disease; namely, whether to use PetCO$_2$ as a surrogate for PaCO$_2$, or to employ one of the previously described prediction equations (Jones et al., 1979; Pianosi and Hochman, 1996).

PaCO$_2$, P$i$CO$_2$ and the Conversion from Partial Pressure to Content

Given the lack of consensus for calculation of Q in children, an extensive comparison was performed of different methods of calculating Q by the indirect (CO$_2$) Fick method in various populations (Paterson, 1972). A total of sixteen methods of calculations were evaluated, based on different choices made for the determination of arterial PCO$_2$ (Jones end tidal correction, and four different dead space prediction equations with the solution of the Bohr equation ($V_D = (PaCO_2 - PeCO_2 / PaCO_2) \cdot V_T$)), mixed venous PCO$_2$ (downstream corrected or not) and the conversion of these tensions to veno-arterial content differences (Jones equations for the description of the CO$_2$ dissociation curve (Jones, 1997) or Godfrey’s mathematical equations to describe McHardy’s relationships for the CO$_2$ dissociation curve (Godfrey, 1970)).

Three different female populations were included (young, trained swimmers, pre-adolescent non-athletic girls and adult females) in order to compare values to males. Cycle ergometry was performed at 25-80% max capacity during steady state exercise.

Selection of the best method was based on the following criteria: a) correlation between Q and VO$_2$, b) comparison of PaCO$_2$ and P$i$CO$_2$ values to direct measures in the literature, c) confirmation that the calculated dead space increased and the dead space to tidal volume ratio decreased with increasing VO$_2$ and d) comparison to dye dilution or direct Fick.

The author found that for both samples of girls the most reasonable calculations of Q were derived from dead space predictions (Godfrey and Davies, 1970) and the solution of the Bohr equation to predict PaCO$_2$, and that Q could vary by 15-20%, depending on which estimate of PaCO$_2$ was employed. They suggested that their method of end tidal sampling may not have been able to separate the breaths at higher workloads, due to slow analyzer performance.
available at that time, however, possibly causing both their end tidal CO₂ and Q values to be low. Currently this can easily be accomplished with rapid infrared analysis or via mass spectrometry.

The limitation of the study by Paterson (1972) was that it involved a very small number of subjects (n=9 girls; some competitive swimmers, others healthy controls and n=6 adult women) and the regression equations formulated to predict Q must be viewed within this context.

The correlation coefficient was used as criteria for selection of one method of calculation over another. A stronger approach to the comparison of different methods would involve absolute measures of variability of each method (Atkinson and Nevill, 1998) (i.e. standard error, confidence limits) rather than simply a relative measure such as a correlation coefficient (r-value). The correlation coefficient does not indicate whether or not there was systematic bias between the methods and the absolute measures offer a context within which to understand the measures.

This group (Paterson and Cunningham, 1976) later published the following recommendations for the calculation of Q in children: Use of the ‘Andrew’ V D equation for children (V D = -21.8 + 0.77 height (cm) + 0.11 V T (ml) to calculate PaCO₂, downstream correction for P vCO₂ (discussed below), and use of a modified McHardy conversion to calculate arterial and mixed venous content values.

*Downstream Correction*

It has been documented that the PCO₂ measured in the bag during rebreathing was higher than in simultaneously measured arterial blood (Coates, 1992;Jones et al., 1967;Paterson, 1972), and the difference increased at higher workloads. The alveolar-to-blood PCO₂ difference became known as the “downstream difference” because the blood was sampled ‘downstream’ from the lungs. Suggestions were made that ‘there was incomplete equilibration of CO₂, either between alveolar gas and pulmonary capillary blood, or between the plasma and the red cell’ (Jones, 1997). This resulted in an empirically derived downstream correction factor: P vCO₂ = P EQCO₂ – ((0.24 P EQCO₂) – 11), where P EQCO₂ is equal to the equilibrium PCO₂ derived from rebreathing (Jones, 1997). Although debate continues over its use, convention thus far has been
to apply a downstream correction with the equilibrium method in adults only to correct for this

gas to blood difference, and to leave children’s data uncorrected, to preserve the Q:VO₂

relationship, used as a measure of criterion validity (Godfrey, 1974a).

Paterson et al. (1976) also evaluated the method of conversion of CO₂ from partial

pressure to content, the final step required for the calculation of Q via the indirect Fick method. Valid results were obtained when gas tensions were converted to content differences by

equations based on McHardy (1967) relationships. When the use of the Godfrey (1970)
dissociation curve led to content values that were 20ml/l lower than the McHardy’s (1967) curve

(which led to higher Q values), Paterson and coworkers questioned whether perhaps this explained why Godfrey et al. (1974a) had chosen not to apply the downstream correction in children. Disagreement remains as to whether or not the downstream correction factor should be applied to children’s data, and whether or not it is applicable in the equilibrium or exponential methods of CO₂ rebreathe.

Collision Broadening

Subsequent to this work, the problem of collision broadening (Hornby et al., 1995) was identified by comparing infrared analysis to mass spectrometry. When an infrared analyzer is used to analyze CO₂ gas in the presence of a high background of O₂, (such as that used in the equilibrium method), an underestimation of the PᵥCO₂ and overestimation of Q will result. A collision broadening correction factor must therefore be applied to CO₂ data collected in such a high O₂ environment. This will not affect the PetCO₂ reading since it is not measured in a background of high O₂. The Paterson (1976) data was not corrected for collision broadening.

Validity, Reliability

When Q primarily reflects the metabolism of brain activity (such as at rest), PᵥCO₂ will be only slightly higher than PaCO₂. However, when Q is reflective of an increased metabolism (such as an increased physical activity or compensation to heart failure), PᵥCO₂ and thus the CᵥCO₂ - CaCO₂, may rise. Use of the CO₂ rebreathe technique is not advisable under conditions of low metabolic activity in children or adults as the small veno-arterial PCO₂ difference may act to magnify analytical error (Godfrey and Davies, 1970). The larger the veno-arterial PCO₂
difference the less will be the effect of small errors. Similar problems were identified in a small group of older males (mean age of 59.7 ± 7.5 yrs) with moderate (n=6) to severe (n=9) obstructive lung disease where the coefficient of variation for repeated measurements of CO₂ rebreathing was 21.9-27.5% at rest and 7.8-17.2% in exercise (Mahler et al., 1985). Nonetheless, many researchers continue to report Q results via CO₂ rebreathing at rest (Mahler et al., 1985; Musewe et al., 1998; Franciosa et al., 1976; Perrault et al., 1992; Falkner et al., 1977; Espersen et al., 1995).

Ranges of variability have been reported for Q measurements, determined with the CO₂ rebreathe technique. Cardiac output results using the CO₂ rebreathe technique in critically ill adult patients were within ± 20% of direct Fick values (Davis et al., 1978). The authors reasoned that while this appears to be large variability, in fact comparisons of thermodilution with direct Fick yielded values within ±17% (Branthwaite and Bradlet, 1968). Normal variation of ±10% for VO₂ and VCO₂, ±2% for P\\text{\textsubscript{a}}CO₂ and ±3 % for PaCO₂ was reported for these data. While these results are larger than normal variation for VO₂ and VCO₂ (±5%), this sample population included critically ill patients at rest in the critical care unit. A similar comparison of techniques in healthy subjects, using end tidal PCO₂ to estimate arterial CO₂, resulted in a 6% systematic underestimation of Q and a difference with direct Fick of ±13% (Muiesan et al., 1968).

Most of the Q data collected from direct techniques were collected in adults. Where possible, it is important to verify that children’s non invasive Q data are compared to direct data derived from children (Eriksson and Koch, 1971; Zeidifard et al., 1972; Sekelj et al., 1958). Since directly derived Q data are scarce in children, an alternative example was suggested by Paterson et al. (1982), who investigated the consistency of the CO₂ rebreathe equilibrium technique in 12 boys. They found that regression analysis of repeat tests produced prediction equations of Q from VO₂ that were in close agreement with dye dilution studies performed in children, by Eriksson et al. (1971). While it may not be as reproducible as the Direct Fick and thermodilution, dye dilution is often the comparison of choice as it is the closest to a clinical measure.
Summary of CO₂ Rebreathe – Equilibrium Technique

An automated system that continuously sampled ventilatory parameters as the subject was achieving steady state, then calculated the bag CO₂ concentration based on an empirical estimation outlined previously (Jones and Rebuck, 1973) and automatically filled the bag, would avoid some of the trial and error on the part of the technician in making the proper selection of the bag volume and concentration. One of the challenges of commercially designed exercise systems however, is the inflexibility of the software to meet the specifications of the researcher. Factors such as the timing of switching the participant into the rebreathing bag, the length of time for the rebreathing manoeuvre, the option to abort the manoeuvre should the child do something unexpected, which is not unusual, are all examples of pediatric specifications which must be addressed. As a result, many researchers have chosen the laborious task of creating their own software, and/or performing much of the procedure manually.

Although the optimal rebreathing frequency for children has not yet been determined, experience with children in the Cardiopulmonary Exercise Laboratory at the Hospital for Sick Children (HSC) would suggest that approximately 40 breaths per minute avoids shallow hyperventilation and ensures adequate mixing prior to recirculation.

Questions of which correction factors are most appropriate for calculation of Q in children, i.e. estimation of PaCO₂ from end tidal sampling, downstream correction, collision broadening, and conversion of partial pressure to content, remain to be clarified.

Defares: CO₂ Rebreathe Exponential Technique

The second well accepted method of Q determination via CO₂ rebreathe is the exponential technique. Described by Defares et al. (1958) this method involves rebreathing an initially low concentration of CO₂ (4-5%). The PetCO₂ increases with subsequent rebreathing until an asymptote is reached, that point being the P̄VCO₂. The rise in PetCO₂ was originally described as a monoexponential function. More recently Alves da Silva et al. (1985) have suggested that the PetCO₂ follows an exponential trend that is characterized by the function PetCO₂ (t) = PasymCO₂ (1 - K₀ e⁻ⁿᵗ). This group evaluated four different procedures to mathematically derive the asymptote of the exponential rise in the P_eCO₂ using a variety of CO₂
mixtures (2-6%), bag volumes and frequency of breathing. They concluded that the most accurate solution was an iterative method in which a least squares regression analysis was performed on the logarithmically transformed data of PCO$_2$ of breath with time of rebreathing. PVCO$_2$ is then taken as the point at 20 seconds on the curve, and is assumed to be equivalent to the asymptote. Results of this work demonstrated that the PVCO$_2$ derived in this manner was similar to that obtained by the equilibrium method with downstream correction in children (Jacob et al., 1997), and that the Q values were within the expected range of previous published results (Falkner et al., 1977).

The exponential method has several significant advantages over the equilibrium method. The subject rebreathes a low concentration of CO$_2$ (4-5%) from a bag, which is virtually unnoticed by the subject when they are switched into the rebreathing bag. As well, since this method does not require a steady state condition it is possible to acquire multiple measurements of Q during a progressive exercise protocol, allowing for the evaluation of stroke volume recruitment. With the equilibrium method one can obtain at most 2-3 workloads as each workload requires approximately 5 minutes to reach steady state, and approximately one further minute to clear out the inhaled CO$_2$ and dead space of the system. For some individuals, the higher [CO$_2$] is not as well tolerated at high exercise intensity. With the exponential method all that is required between manoeuvres, is the time necessary to clear out the inhaled CO$_2$ and the dead space of the system. This will occur rapidly with increasing levels of exercise intensity. While the original work of Alves da Silva (1985) arrived at the recommendation of defining the PVCO$_2$ as the value of the PetCO$_2$ at 20 seconds, the question has been posed if a quadratic function may more appropriately fit the data, indicating more work may be needed in this area.

Of specific concern is whether ventilation-perfusion mismatching may compromise proper equilibration, which is necessary to determine PVCO$_2$. Lands et al. (1992a) performed a critical study to validate the exponential method in young adults with lung disease. Fourteen patients with CF and 14 controls were evaluated for Q first via the exponential technique (during incremental exercise) then via both the equilibrium and exponential techniques (during steady state exercise). The authors combined the mild CF group with the controls and compared them to the moderate and severe CF group. They concluded that there was no difference between the groups for the Q:VO$_2$ relationship based on where the data fell in relation to the 95% confidence
limits of Falkner et al. (1977). A statistical test of the difference between the slopes of the two groups may have offered a more definitive conclusion than the above comparison simply to a set of confidence limits from separate data.

The most salient observations in this study were the lack of difference in $P\tilde{V}CO_2$ between the two groups, between the exponential and equilibrium (downstream corrected) methods derived during steady state, nor in the derived $Q$. This would imply that the exponential method is valid in patients with CF. As a result, the collection of exponential $CO_2$ rebreath data on healthy children would be a valuable addition to these findings.

Stroke volume (SV) has generally been reported to plateau early (approximately 40% of $VO_2$ max) during cycling exercise (McArdle et al., 1981) whereas others have reported no plateau with treadmill exercise in elite cyclists (Gledhill et al., 1994). Findings of $Q$ data collected on children via the exponential method suggest that the SV response to progressive exercise in children may be different to that in adults. Similar to previously reported results of Turley et al. (1997a), thus far we have observed only a minimal increase in SV with progressive exercise (Trachsel et al., 2006), suggesting the presence of a plateau in the early stages of exercise in children. As well, girls appear to have less of an increase in SV than boys. These preliminary data suggest that children may have little SV reserve and instead rely on an increase in HR to meet the increasing exercise demands.

While Stringer et al. (1997) have recommended the prediction of $Q$ from an assumed $a-\tilde{V}DO_2$ based on an assumed linear relationship between $VO_2$ and $Q$, it has been reported that children have a higher $a-\tilde{V}DO_2$ to make up for a lower SV (Turley and Wilmore, 1997a). In order to confirm the consistency of this $Q:VO_2$ relationship in children over a progressive exercise protocol, there must be preliminary methodological studies to assess the error of the exponential technique for the determination of $Q$.

**Quality control in resident gas techniques**

In order to produce valid and reproducible $Q$ data, attention must be paid to details of methodology, especially since small errors can seriously affect the results in children (Godfrey, 1974a). Factors such as temperature, pressure and saturation factors, collision broadening if
using an infrared analyzer, choice of arterial sample or an estimate for PaCO₂, downstream correction, volume and concentration in the rebreathing bag, quality of equilibrium plateau or exponential tracings, must all be carefully accounted for to avoid the accumulation of a cascade of errors and accounted for in the final calculations of Q in children.

2.3.3 Non-Resident Gas: N₂O and C₂H₂

This method is based on the use of a gas that is perfusion limited and diffuses readily across the lung surface into the blood. The rate at which the gas is taken up by the blood will be directly related to the rate of pulmonary blood flow. The most commonly used non-resident gases for the determination of Q are nitrous oxide (N₂O) and acetylene (C₂H₂). Of the two, the latter has been more commonly used, and is the method most recommended for the determination of Q at maximal exercise (Warburton et al., 1999a). The recent availability of a commercially designed N₂O system to measure cardiac output is currently gaining more acceptability, however. The non-resident gas technique commonly includes the addition of an insoluble tracer gas to the rebreathing bag, such as Argon, Helium, or more recently, SF₆. The tracer gas is used to calculate total systemic volume, which is the combination of the lung volume at end expiration, the dead space volume of the rebreathing valve, the residual volume of the bag when empty and the volume of the rebreathing bag. The total systemic volume can be determined by the dilution of the insoluble gas, and is used to correct the soluble gas concentration prior to any calculations, to compensate for incomplete mixing. As well, a display of the insoluble gas during rebreathing provides evidence of adequate mixing, the absence of which will indicate a loss of gas into poorly ventilated areas of the lung (Innocor, 2007).

A measure of oxygen saturation is used to calculate oxygen content, and along with oxygen consumption and Fick’s principle used on the pulmonary circulation, cardiac output is calculated. The shunt fraction is then calculated, and if the saturation is less than 98% effective pulmonary blood flow will be less than total cardiac output (Innocor, 2007).

While one can mathematically account for loss due to poor mixing, the fundamental assumption of this technique is complete mixing of all intrapulmonary gas within 3-4 seconds, and therefore the use of these methods is generally reserved for patients free of lung disease.
Total cardiac output ($Q_t$) should be equivalent to effective pulmonary blood flow ($Q_{\text{eff}}$) in the absence of a shunt, or, blood that enters the arterial blood without passing through ventilated areas of the lung (West, 1995). Nonetheless, a very small degree of shunt is normal due to collection of some of the bronchial artery blood in the pulmonary vein and the draining of a small portion of the coronary venous blood directly into the left ventricle (West, 1995). Patients with congenital heart disease or severe lung disease may have a significant degree of shunt due to abnormal routing of blood flow or a diffusion limitation of the respiratory membrane, respectively. Therefore in this case, $Q_{\text{eff}}$ would be equivalent to $Q_t$ minus the amount of shunt.

*Acetylene ($C_2H_2$) Rebreathe*

Based on the findings of an equilibrium of $C_2H_2$ within 3 breaths of the rebreathing manoeuvre (Triebwasser et al., 1977) (suggesting the tracer gas could thus be eliminated) and of the more accurate fit of a linear rather than a curvilinear function to the $C_2H_2$ decay tracing (Smyth et al., 1984), Warburton et al. (1999a) have recommended the use of the following equation to calculate $Q$:

$$Q = \frac{VO_2 \cdot (C_2H_2)_{\text{diff}}}{(O_2)_{\text{diff}} \cdot xC_2H_2 \cdot P_b \cdot 47 \cdot 0.00974} = \frac{VO_2}{a\bar{\nabla}O_2_{\text{diff}}},$$

(equation 3)

where $(C_2H_2)_{\text{diff}}$ is the amount of acetylene absorbed per litre of blood during the time of sampling (Warburton et al., 1998), $(O_2)_{\text{diff}}$ is the amount of oxygen absorbed during the time of sampling, $xC_2H_2$ is the average concentration of acetylene during the time of sampling, $P_b$ is the barometric pressure, 47 is the assumed vapour pressure of water in the lungs (mmHg), 0.00974 is the numerical constant derived by combining the constants 760 and 100, and using 740 as the solubility coefficient for $C_2H_2$ in blood at body temperature. Nonetheless $Q$ is still calculated by some groups with the use of a monoexponential curve to fit the decay of $C_2H_2$, and the use a tracer gas to confirm adequate mixing (Rosenthal et al., 1995).

A range of solubility coefficients has been suggested for acetylene 0.710 (Chapman et al., 1950), 0.740 (Grollman, 1929), and 0.768 (Meyer and Schied, 1980). Smyth et al. (Smyth et al., 1984) determined that using the coefficient of Chapman et al. (0.710) was most appropriate as it
yielded Q values via the acetylene technique that most closely approximated Q via dye dilution. Long-term derangement of lung structure leading to an altered tissue mixing in the lung may likely warrant an adjusted solubility coefficient. The need for a unique solubility coefficient for children has not been identified thus far.

Rosenthal et al. have published a group of research studies employing the C₂H₂ rebreathe technique in children (Rosenthal et al., 1995; Rosenthal and Bush, 1997; Rosenthal and Bush, 1998; Rosenthal and Bush, 1999) and express most of their outcome variables per m². This limits comparison and evaluation of their results to other studies which have expressed results in a similar relative unit.

Acetylene has also been used in a single breath hold (intrabreath) technique to measure effective pulmonary blood flow in school-aged survivors of bronchopulmonary dysplasia (BPD) compared to healthy premature and normal healthy children (Mitchell et al., 1998). This measure is normalized for body surface area and termed the effective cardiac index (ECI). The reported coefficient of variation for repeat intrabreath measurements of ECI on the same day from this lab was 17%. This value was based on resting data from children with a wide range of obstructive airway disease. As an acceptable value should be more in the range of 5-8%, one questions the ability to discern differences of ECI values between groups or as a follow-up to treatment. In addition, experience with children would suggest that normal breathing irregularities would render a single breath technique less reliable than a rebreathing technique in this age group.

Comparison of Resident versus Non-Resident Gas Methods

Rosenthal et al. (1997) concluded that the CO₂ rebreathe was not reliable enough to be used in children in favour of the C₂H₂ technique. However this group made significant methodological compromises to the original CO₂ rebreathe manoeuvre, in order to allow simultaneous calculation of effective pulmonary blood flow by three methods (one C₂H₂ and two CO₂) such as omitting CO₂ from the rebreathing bag. As a result the established time of 20s for the determination of the asymptote was too short, and was lengthened to 30s. They reported a rejection of 50% of their data, (a large dead space of their apparatus may have contributed to inadequate mixing, (Dr. Allan Coates, personal communication). Again, the expression of work
rate as watts/m² and according to medians and z-scores allows for an easy comparison between groups within one study, however makes comparison of this group’s data to existing normal values more challenging.

If, as it has been suggested, one can get an increase in Q during the rebreathing manoeuvre (Triebwasser et al., 1977), this would suggest a potential problem with the non-resident techniques, especially at rest, where values of effective pulmonary blood flow would rise instantly with an increase in flow. This would not have an effect in the CO₂ rebreathing technique until after recirculation, however, by which time all measurements would have been completed.

A major advantage of the use of a non-resident gas for a rebreathing technique is that no correction is necessary for a residual level of the inert gas in the body. Nor are there factors in the body that may change the reaction to this gas during exercise, since an inert gas is used in this technique. For example the body’s ability to buffer CO₂ decreases as one approaches maximal exercise (Sun et al., 2001). Perhaps the validity of Q measurements via CO₂ rebreathe at maximal exercise may be affected by the altered dynamics of this gas under maximum exercise conditions, whereas an altered rebreathing due to the manoeuvre may affect Q results at rest with the C₂H₂ method.

Vₐ/Qₐ inequalities and right to left shunting less affect the CO₂ rebreathing technique. Areas with low Vₐ/Qₐ will equilibrate slower, but the PCO₂ in these areas is already very close to the P̄vCO₂, therefore slower areas will not affect equilibrium much (Davis et al., 1978). Therefore the CO₂ rebreathe would be considered the method of choice for patients with lung disease, as areas in the lungs with poor mixing will directly affect the C₂H₂ rebreathe.

There has been increasing interest in the use of non-invasive measurements of cardiac output. Non-resident gas techniques which measure pulmonary blood flow have become automated and have the advantage of allowing multiple measurements during increasing levels of exercise. These techniques are predicated on the rapid uptake of a soluble gas by the pulmonary blood flow with the assumption that all perfused areas of the lung are exposed to the identical concentration of the soluble gas simultaneously.
One limitation of this technique is that rapid intrapulmonary gas mixing must occur which necessitates homogeneity of distribution of ventilation. In virtually all diseases affecting the airways, inhomogeneous distribution is one of the first signs of the abnormality, be it asthma or cystic fibrosis in children (Desmond et al., 1986) chronic obstructive lung disease in adults (Buist and Ross, 1973; Van Muylmen et al., 1995) or even just aging (Anthonisen et al., 1969). The use of resident gas rebreathing to determine mixed venous carbon dioxide tension ($P_v^\text{CO}_2$) has the advantage that poorly ventilated region of the lung have values of PCO$_2$ that approach the $P_v^\text{CO}_2$ so uptake of CO$_2$ by regions of poor ventilation are minimized.

In summary, the rebreathe manoeuvre appears to be more appropriate for children, as spontaneous irregular breaths will not have as direct an impact on these results as on a single breath technique. Either the equilibrium or exponential methods should be suitable, so long as the data have been calculated correctly (end tidal, downstream, collision broadening corrections, where appropriate). A compilation of results of exponential Q data on a large number of children should further clarify our understanding of this method. The acetylene rebreathe method is recommended for patients with healthy lungs and has been well tolerated at high exercise intensity, however its dependence on the use of a mass spectrometer make it a less convenient technique for the average exercise lab. Sequential determinations of cardiac output via the C$_2$H$_2$ or CO$_2$ rebreathe exponential method will allow for the evaluation of stroke volume recruitment enabling us to better understand cardiovascular adaptation to progressive exercise.

2.3.4 Impedance cardiography

Impedance cardiography (ICG) estimates cardiac output noninvasively by measuring the changes in transthoracic electrical impedance in response to the passage of a small alternating current through the chest, which changes inversely to changes in the volume of fluid in the thorax. Assuming that the changes in impedance during systole are representative of SV, Q can then be derived from HR and SV (Warburton et al., 1999b). Several formulae have evolved for the conversion of the signal characteristic to SV, including corrections for body type and size and have been reviewed elsewhere (Jensen et al., 1995; Warburton et al., 1999b; Newman and Callister, 1999).
The Kubicek formula (1966) is the one most often referred to:

\[ SV = \rho \cdot \frac{L}{Z_0}^2 \cdot LVET \cdot \frac{dZ}{dt_{\text{max}}} \]

where,

- \( \rho \) = blood resistivity
- \( L \) = distance between frontal ICG electrodes (cm)
- \( Z_0 \) = baseline impedance displayed on the impedance cardiograph during the recording
- \( LVET \) = left-ventricular ejection time (sec)
- \( \frac{dZ}{dt_{\text{max}}} \) = peak ejection velocity

Pianosi et al. (1996) investigated the use of impedance cardiography (\( Q_{\text{ICG}} \)) in 30 healthy children by comparing \( Q \) at light and moderate workloads (0.5 and 1.5 watts/kg) to \( Q_{\text{RB}} \) and using reference data collected via dye-dilution (Eriksson and Koch, 1971) for comparison. Eighty percent of \( Q_{\text{ICG}} \) results were within ±20% of \( Q_{\text{RB}} \) results. All \( Q_{\text{ICG}} \) results were within ±15% of the hypothetical mean value, derived by Bland and Altman analysis. Advantages of this technique include the ability to measure \( Q \) at rest, and repeatedly throughout exercise. The authors concluded that the technical difficulty of obtaining a good quality phonocardiographic signal, used to verify heart sounds in the ICG technique, was at least as great as that of getting an accurate measure of \( \overline{VCO_2} \) via rebreathing (Pianosi and Garros, 1996). Unfortunately the results of their regression analyses must be viewed in light of the fact that repeated measures data were included. Conclusions are specific to the device and algorithms chosen.

This study was followed a year later by the use of impedance cardiography to evaluate \( Q \) for patients with CF (Pianosi, 1997). Unlike their previous experience in healthy children they experienced greater technical difficulties, either in obtaining signals sufficiently free of artifact or in blood sampling for the rebreathing manoeuvre. This time 83% of the \( Q_{\text{ICG}} \) values were within ±20% of \( Q_{\text{RB}} \) results. The authors recommended that ICG gives accurate \( Q \) measurements in children with CF.

Cardiac output values via ICG are commonly reported as \( L\cdot \text{min}^{-1} \cdot \text{m}^{-2} \). Caution must be exercised when interpreting the results of a correlation between two variables, each of which in this case has been corrected for body size. It is possible that the inclusion of body size in each of the predictor variables may artificially produce a stronger correlation coefficient. An alternative
statistical approach may be to perform a multiple regression analysis with body size included as one of the predictor variables. In this way the relationship between the original two variables would be adjusted for the presence of the body size variable.

It was recently concluded that while the accuracy of ICG may be questionable, its strength lies in monitoring trends in cardiovascular dynamics (Newman and Callister, 1999). Clearly more research is warranted in the use of IC for Q measurements in children and in the meantime, perhaps a ‘healthy skepticism may be warranted for thoracic impedance techniques to measure Q during exercise” (Driscoll et al., 1989). Since this time software algorithms for ICG devices have improved as well as their ability to handle motion artifact. The impact of alterations in cardiac anatomy due to heart disease and surgery on ICG assessment is unknown.

2.3.5 Echocardiography

Various techniques of echocardiography have been used in the determination of Q (Snider et al., 1997). Originally, M-mode echocardiography method was used to measure the size (diameter) of structures within the heart, which was then converted into volume. More recently, two-dimensional (2-D) echocardiography allows for greater visualization of structures and is more commonly used to measure diameter, for example the size of the aorta, for the conversion to volume. Doppler ultrasound technology involves sending a stream of repetitive sound waves to a selected depth. The transducer then measures the ‘Doppler shift’ in sound velocity. This method would be used to measure flow acceleration across an orifice, such as the outflow tract of the heart, or the aorta. In Colour Doppler mode, the moving blood is assigned a colour, depending upon its speed. For example red indicates blood that is moving towards while blue would be assigned to blood moving away. The intensity of the colour is related to the speed or velocity of the blood flow. The use of 2-D guided Doppler is often the method of echocardiography in use.

Rowland et al. have used echocardiography extensively to investigate cardiac responses to progressive exercise in children (Rowland et al., 1998; Rowland et al., 1999; Rowland et al., 2000; Rowland and Whatley Blum, 2000). This group employed 2-dimmensional echocardiography to determine the maximal diameter of the ascending aorta at rest and Doppler
ultrasound at rest and during exercise to measure peak aortic velocity. SV was then derived from the product of the velocity time integral and the cross sectional area measures, assuming that the area of the aorta remained the same during exercise (Christie et al., 1987). Information as to whether the conversion of diameter to volume was based on child-specific algorithms was not provided. They concluded that there was a high degree of reproducibility in their technique (Rowland et al., 1998).

Doppler echocardiography was considered to be a very reliable technique for measuring Q in 14 prepubescent children (Nottin et al., 2000). Repeat measurements were performed and Q values compared to CO₂ rebreathe (equilibrium method at rest or exponential method during submaximal and maximal exercise). The inclusion of resting values for the rebreathe and the use of different methods for rebreathe is unexplained. In addition, gas mixtures in the rebreathing bags contained only 35-40% O₂, although the use of the McHardy’s CO₂ dissociation curve to convert from partial pressure to content necessitates a background of very high O₂ to ensure 100% saturation of all blood in the pulmonary capillary bed (Hornby et al., 1995). No mention was made of a downstream correction applied to the equilibrium data. Together these details make it difficult to use these data for comparison purposes.

While it was previously considered difficult to get an accurate estimate of Q during exercise with Doppler (Driscoll et al., 1989), technological improvements to overcome movement artifact and signal aliasing have been successful. Assuming a high degree of technical expertise, reproducible results have been reported for Doppler (Nottin et al., 2000; Warburton et al., 1999b; Cortes et al., 1994; Espersen et al., 1995), while limitations remain for conditions of obesity and abnormal cardiac anatomy.

2.3.6 Statistical Methods of Comparison

The Jones et al. (1979) study was analyzed with multiple data points per individual included in the regression analysis. This is a common statistical error that continues to be published, resulting in an artificially raised r-value due to multiple measures included for the same individuals in the analysis. It has been suggested that if the number of subjects in the study is large enough (e.g. n≥30), it is possible that the slope and/or intercept may not be too far from
the truth. The strength of the correlation (r-value) should be ignored, however, as the variability will be artificially reduced (Falkner et al., 1977).

Paterson et al. (1982) employed an alternative statistical approach, to bypass the limitation of being able to include only one point per subject into the repeated measures analysis. First they performed the regression analysis including all of the data to derive the inter- and intra-individual variation. Then a regression analysis was performed for each individual’s data alone to get the intra-individual variation. Finally, taking the difference between the two allowed for the calculation of the differences due to inter-individual variation, while taking into account that the design included repeat points per individual.

One of the difficulties in interpreting a comparison of techniques based simply on percent differences, as is generally reported in the literature, is that one is missing a measure of absolute variability of the techniques in question. For example, if the coefficient of variation (standard deviation/mean) were provided for each technique, it would give us an indication of reproducibility. One might question a correlation coefficient between the two techniques if each had a large measurement error (Bohrnstedt and Carter, 1971). Otherwise the use of confidence intervals about the mean would at least provide a practical range for ‘normal’ values instead of simply relying on an r-value. Alternatively, in comparing two techniques, the standardized slope (β) of greater or less than one would indicate over or underestimation of one method by the other respectively.

Yet another approach to the comparison of two techniques is the Bland and Altman (1986) graphical method which is commonly used in studies evaluating two different techniques (VanHees et al., 2001; Espersen et al., 1995; Hoeper et al., 1999). This straightforward procedure plots the mean of the two methods being compared on the x-axis versus the difference of the two on the y-axis. Under or overestimation of one technique is evident when viewing the graph, as is any systematic misrepresentation of the data along the range of values. This would appear as a discernable shape of the data on the graph, instead of an even scatter on either side of the horizontal line drawn through zero. In summary, a measure of absolute variability is recommended as it allows for a more informative and practical comparison.
Critchley et al. (1999) conducted a meta-analysis of studies using bias and precision statistics to compare cardiac output techniques. Their recommendation was that Q, bias (difference of the two methods), limits of agreement (±2SD of bias) and percentage error (2SD of bias /mean), should be reported and that acceptance of a new technique should rely on limits of agreement of the bias, of up to ± 30%.

2.4 Clinical Populations

2.4.1 Congenital Heart Disease (CHD)

Congenital heart disease is often classified into cyanotic (diminished pulmonary blood flow with right to left shunt) and acyanotic (left to right shunts or obstructive lesions) disorders (McManus and Leung, 2000). Exercise testing is essential to assess the child’s functional capacity and in many cases to relieve the overprotection by parents, leading to hypoactivity in these children (Bar-Or, 1993).

The Fontan procedure, performed as palliation for univentricular anatomy (non functional right ventricle), refers to an operation in which systemic venous return is redirected to the pulmonary arteries without passing through a ventricle and the single ventricle is used to propel pulmonary venous return to the aorta (Driscoll and Durongpistikul, 1999). As a result there is a relatively passive pulmonary blood flow and, compared to other types of lesions, this group of patients has a reduced aerobic capacity. Unlike many other subgroups of CHD patients, the slope of Q:VO\textsubscript{2} is reduced in this group, largely due to a decreased SV and subnormal HR and EF response. Arrhythmias are common as is suboptimal blood oxygen saturation. In addition this group tends to overventilate due to ventilation perfusion mismatching (Driscoll and Durongpistikul, 1999). As this operation has become more common, and longer follow-up data has become available, bradyarrhythmias have been increasingly observed, severe enough to impair heart function and require the implantation of a pacemaker (Heinemann et al., 2003).

A pacemaker is an implantable pulse generator, placed subdermally, with a lead wire that connects the pacemaker to the myocardium (Sharp et al., 1998). In clinical practice the first three letters of the pacemaker code are typically used, with an R placed at the end for rate modulation. Position I refers to the chamber paced (atrium, ventricle or dual-chamber), Position II refers to
chamber sensed for intrinsic beats (atrium, ventricle or dual-chamber) and Position III indicates the response to the sensing (inhibited, triggered or dual response) (Sharp et al., 1998).

One of the criteria for pacemaker implantation is AV block, which is defined as impairment of conduction of a cardiac impulse from the atrium to the ventricle (Furman et al., 1989). In simplified terms, the purpose of the pacemaker becomes to coordinate proper filling and ejection of blood and maintain $Q$.

Exercise specific requirements for an individual using a pacemaker include small increments of grade and speed if on a treadmill to allow time to accommodate to the workrate, and choice of exercise mode specific to the type of sensor (QT interval, minute ventilation, activity, acceleromter or acceleration) and to the programmed values in the device.

### 2.4.2 Cystic Fibrosis (CF)

Pulmonary impairment is the most severe manifestation of cystic fibrosis (CF), the most common inherited disease in Caucasians (1 in 2000 live births) (2009). Thickening secretions of mucus in the exocrine glands of the body include pulmonary obstruction, a characteristic of this disease. This obstruction progresses to hyperinflation, and eventually restrictive lung disease, leading to chronic hypoxia, chronic hypercapnea and possible desaturation during exercise.

Progressively impaired exercise tolerance impacts directly on quality of life, and its preservation has been correlated to survival in CF (Nixon et al., 1992). Advanced stage disease is characterized by right heart failure secondary to pulmonary hypertension. Therefore annual measures of cardiorespiratory response to an exercise challenge are a way to chart disease progression and recommend intervention with physical training to potentially delay the crippling effects of disease. (McArdle et al., 2001)

Cardiac output has been investigated in patients with CF by several methods including radionuclide angiography (Zinman et al., 1989; Benson et al., 1984), Doppler echocardiography (Florea et al., 2000), ICG (Pianosi, 1997), impedance cardiography (Pianosi, 1997) and CO$_2$ rebreathe (Pianosi and Hochman, 1996; Lands et al., 1996; Lands et al., 1992a). While more often used to document right ventricular changes in more severe lung disease, Johnson et al. (1991)
concluded that changes in left ventricular patterns of relaxation, as assessed with Doppler echo were detectable early in the course of CF and that these changes were probably progressive. They suggested that perhaps early detection could lead to therapeutic trials designed to improve left ventricular filling and delay the onset of overt cor pulmonale (Johnson et al., 1991; Agostoni et al., 2005). Others were able to show that there was a mechanical element of cardiopulmonary interdependence in patients with CF with a moderately severe degree of expiratory airflow limitation (Hortrop et al., 1988).

2.4.3 Summary

Evaluation of a sick child’s response to exercise necessitates a prior understanding of a “normal” pediatric response to exercise. In treating children with chronic disease it may be of interest to understand how much of an impact structural changes due to surgery or disease and their treatments have on cardiopulmonary function. This is important in the context of the CHD and CF conditions that examined in this dissertation. This dissertation addresses the topics of CHD and CF in the context of evaluating the effects of disease on cardiopulmonary function, and employs measures of cardiac output to aid in the understanding the pathophysiology of disease and the response to pacemaker manipulations.

2.5 Summary of Review of Literature

Children are not small adults and thus require non-invasive methodologies that suit their size and developmental stage. A measure of cardiac output enables us to further our understanding of the cardiovascular response to exercise, which enhances our insight into the pathophysiology of disease.

Although non-resident gas techniques have been used for many years to determine Q, gaps in our knowledge remain in the areas of proper corrections for the calculation of cardiac output in children, and especially children with disease. Inert gas techniques have also been available for many years, however the reliance of these methods on mass spectrometry has limited their use in the general exercise laboratory due to expense and technical difficulties. Improvements in technology in the areas of impedance cardiography, and a device to perform inert gas rebreathe, need to be investigated in their applicability for pediatric use.
2.6 Statement of the Problem

The non-invasive measurement of Q in children requires further methodological studies to enable us to avoid invasive procedures, which are unethical and inappropriate for this age group, unless clinically indicated. Since most of the research on Q has been performed in adults, and since there are well-documented characteristics relating to size and development that are unique to children, we require valid measures of Q in children to provide a measure of cardiovascular response to exercise, to further our understanding of pediatric physiological mechanisms. A measure of Q is a valuable addition to a patient profile, however this measure has thus far not been easy to evaluate.

2.7 Research Questions

Can we improve our ability to accurately and reproducibly measure non-invasive Q in children? Can we use patients with Cystic Fibrosis (with lung disease that will challenge respiratory measurement methods) and congenital heart disease (where the response to exercise will likely be altered) as models to help us to improve and understand the limitations of these methods of cardiac output determination?

2.8 Hypotheses

The primary hypothesis is that we can improve our ability to measure Q non-invasively in children. Each specific hypothesis is listed below, associated with the individual project.

Methods Development

1. Q Corrections
H1: Corrections for collision broadening, end tidal and downstream will all be necessary to derive valid results for Q via the equilibrium method in children with Cystic Fibrosis (CF).

2. PaCO$_2$ estimation
H2: End tidal PCO$_2$ can be used successfully to predict arterial PCO$_2$ in children with CF.
3. CO₂ rebreathe: exponential calculations
H3: The monoexponential curve derived from data fitted to a quadratic function will be more accurate for the determination of $P\bar{\text{v}}\text{CO}_2$ than the standard technique that uses an iterative approach and three unknowns.

Primary Research Projects

4. Innocor™ Validation
H4.1: The Innocor™ will provide reliable measures of Q at rest and during dynamic exercise
H4.2: The nitrous oxide (Innocor™) and SAR (standard acetylene rebreathing) techniques of Q determination will yield similar results at rest and during dynamic exercise for healthy children and adults, and children with CHD.

5. Pacemaker Optimization
H5: AV optimization and atrioventricular synchronized pacing (DDI) will statistically improve Q in Fontan patients at rest and during exercise.
Chapter 3: Research Projects

3.1 Introduction

The non-invasive determination of cardiac output in children requires attention to the details that make children different from adults. Therefore the first part of this dissertation research involved methods development projects employing the CO$_2$ rebreathing methods, both equilibrium and exponential, with the goals of refining these techniques to maximize their validity and accuracy in children. These resident gas respiratory methods are the most accessible to the average laboratory and have been used for many years on both children and adults. Patients with cystic fibrosis (CF) were included as they represented an example of pediatric lung disease, and thus presented a challenge to respiratory gas methods that rely on gas exchange that may be disrupted as a result of their lung disease.

The methods development projects involved the resident gas methods and included: a) an evaluation of the corrections used to calculate cardiac output in healthy children and those with cystic fibrosis, b) a refinement of the estimation of PaCO$_2$ in children with CF and c) a suggested refinement to the calculation of P$_\text{v}$CO$_2$ determined via the exponential CO$_2$ rebreathe technique.

The second part of this dissertation research involved the use of the non-resident gas methods to evaluate Q in a clinical cardiology setting. Patients with congenital heart disease (CHD) were included as they represent a population in which we expect cardiac output to be altered due to the nature of their disease and provided a model to further our understanding of the methodology of cardiac output determination.

Clinical applications project #1 was an evaluation of the suitability of the Innocor$^{\text{TM}}$ device, which employs the non-resident gas technique, for the measurement of cardiac output, at rest and during dynamic exercise, in healthy children and adults, as well as in children with CHD. The objective of the clinical applications project #2 was to assess the importance of atrioventricular (AV) synchronization and pacemaker mode on Q. Optimizing AV synchrony in combination with atrioventricular synchronized pacing (DDI) was hypothesized to maximize the
atrial contribution to ventricular filling in the highly diastolic-dependent circulation of the Fontan patient, and thus enhance Q.

The Hospital for Sick Children and University of Toronto Ethics Boards gave approval for all research and obtained consent was obtained from each participant.

3.2 Methods Development

3.2.1 Cardiac Output Corrections

Calculation of Cardiac Output via CO$_2$ Rebreathe in Children
Research Institute, Hospital for Sick Children, University of Toronto.

ABSTRACT

Objective: To determine the effect of ‘correction factors’ on the calculation of cardiac output (Q) using the CO$_2$ rebreathe technique, in healthy controls (CON) and patients with cystic fibrosis (CF) 9-18 yrs. Methods: Q was measured via CO$_2$ rebreathing in CON (n=104) and MILD (n=51) and moderate/severe (MOD/SEV, n=23) CF. Q was calculated with corrections for collision broadening (cb) to account for sampling CO$_2$ in a background of high O$_2$ concentration, downstream (dm), and Pet-aCO$_2$ difference (j), (Qcbdmj), and compared to Godfrey (1971) (Q$_G$, healthy children). Results: Differences in slopes and intercepts for Q:VO$_2$ (Q$_G$ vs Qcbdmj) for CON, MILD, MOD/SEV were –0.08, -0.5, 0.6 and 0.58, 1.83, 1.33 respectively. ANCOVA of the Q vs VO$_2$ relationship at 50% WRmax revealed that Q$_G$ was significantly different than Qcbdmj in both MILD and MOD/SEV (p<0.001), but not in CON. Conclusion: For CON, the correction factors cancelled out and the Q$_G$ (where PaCO$_2$ was derived from assumed normal dead space) agreed with Qcbdmj (calculated from PetCO$_2$). In disease, Q$_G$ overestimated Q and the correction factors no longer negated each other. Caution should be exercised if using one of the cb, dm or j correction factors on their own, as each exerts a profound effect on Q values.
BACKGROUND

Disagreement remains regarding the use of the downstream correction for the calculation of Q, whether it is appropriate for use in pediatric data, and whether suitable for the equilibrium or exponential CO₂ rebreathe techniques. Due to the number of recommendations for calculating children’s Q results, we reevaluated the various correction factors applied to children’s Q data. Based on our previous experience of measuring Q in children via CO₂ rebreathing we hypothesized that corrections for collision broadening, end tidal and downstream would all be necessary to derive valid results for Q via the equilibrium method in children, using the Q:VO₂ slope as construct validity. In healthy children it may appear that the downstream and collision broadening corrections offset each other, over and under correcting Q respectively. Our preliminary pilot calculations, however, made in 10 previously tested patients with moderately severe CF, suggested this might not be the case in more diseased patients. Hence, we recalculated previously collected Q data (CO₂ rebreathe equilibrium method) from 110 healthy children from the Toronto area, as well as a subset of 65 children with CF to determine the effect of the various corrections on the calculation of Q.

OBJECTIVE

To determine the effect of ‘correction factors’ on the calculation of cardiac output (Q) using the CO₂ rebreathe technique, in healthy children (CON) and those with cystic fibrosis.

HYPOTHESIS

The assumption of normal dead space values in the calculation of cardiac output in healthy children (Q_G) would give significantly different Q values when employed for those with lung disease.

METHODS

To replace the invasive determination of cardiac output we relied on the Indirect Fick principle (Q = VCO₂ / C̄CO₂ - CaCO₂) and the use of the resident gas or CO₂ rebreathe technique to evaluate Q. Carbon dioxide production was determined via respiratory gas analysis
with a mixing chamber based system. Mixed venous CO₂ content (C\text{\textbar}vCO₂) was derived from mixed venous F\text{\textbar}vCO₂ (resident gas technique: CO₂ rebreathe \textit{equilibrium} method, converted to partial pressure), and arterial CO₂ content (CaCO₂) from end tidal FetCO₂, also converted to partial pressure. Both the P\text{\textbar}vCO₂ and PetCO₂ were then converted to content using a standard CO₂ dissociation curve (McHardy, 1967).

Patients cycled on an electrically braked cycle ergometer at 50% of a previously determined WRmax for 5 minutes to achieve a steady state, at which point the CO₂ rebreathe was performed. The patients were switched from room air to rebreathe from a bag containing 11-13% CO₂ in balance O₂. The volume of the bag was approximately 1.5 times their tidal volume and they breathed at a rate of 40 breaths per minute. The maneuver was practiced at rest and then performed again at the 5th minute of steady state exercise. If the CO₂ equilibrium tracing continued to rise or fall at 12 seconds, the Denison extrapolation was applied according to the Jones criteria and the line was extrapolated to 20 seconds to determine the F\text{\textbar}vCO₂ (Denison, 1968). All data represent one Q measurement per subject.

\textit{Correction Factors for P\text{\textbar}vCO₂}

In any indirect calculation of cardiac output researchers employ various ‘correction factors’ to approximate direct measures of arterial and mixed venous CO₂.

\textit{Collision Broadening (‘cb’)}:

CO₂ was sampled via infra red analysis in a background of high [O₂]. Mixed venous PCO₂ was corrected for collision broadening, an often overlooked but well established physical factor. Infrared analysis of CO₂ becomes inaccurate when sampling is performed in a background of high [O₂] (>40%), which is the characteristic of a common mixture used in the CO₂ rebreathe equilibrium technique. The relationship between [CO₂] and the optical density would be altered due to the inelastic collisions between O₂ and CO₂ molecules. A fairly lengthy but simple mathematical correction was used to correct for this problem. Otherwise, a mass spectrometer or a 2-pt calibration with this gas could be used as an alternative gas sampling technique to avoid this problem (Hornby et al., 1995).
Collision broadening correction (provided by Larry Lands, Montreal Children’s Hospital, from work with the manufacturer Physiodyne, unpublished):

\[
P\bar{\text{V}}\text{CO}_2\text{cb} = F_v\text{CO}_2 + (0.07927 \cdot F_v\text{CO}_2 \cdot 0.37) + (0.0005178 \cdot (F_v\text{CO}_2)^2 \cdot 0.37) + (0.04365 \cdot F_v\text{CO}_2 \cdot 0.137) + (0.0004835 \cdot (F_v\text{CO}_2)^2 \cdot 0.137)
\]

**Downstream (‘dm’):**

An apparent difference in \(P\bar{\text{V}}\text{CO}_2\) exists between direct blood measurement and rebreathing (Jones et al., 1967): \(P\bar{\text{V}}\text{CO}_{2\text{dm}} = P\bar{\text{V}}\text{CO}_2 - [(0.24 \cdot P\bar{\text{V}}\text{CO}_2) - 11]\). While the mechanism of the downstream difference remains unclear, there is also a difference of opinion as to whether or not to correct for downstream. Godfrey chose not to correct for downstream as he found that the Q values were too high using it, whereas we applied both the collision broadening and the downstream corrections.

**Correction Factors for PaCO\(_2\)**

**Jones end tidal (‘j’):**

The Jones correction factor was used to correct for an arterial - end tidal difference. \(\text{PaCO}_2 = 5.5 + 0.90 \cdot \text{PetCO}_2 - 0.0021 \cdot V_T\). This factor takes into account tidal volume, which will account for differences in size of patient and respiratory rate.

**Godfrey (1971) (‘G’):**

We solved for \(\text{PaCO}_2\) by assuming normal dead space (usually based on factors such as gender and size) and solving for the Bohr equation: \(V_D = (\text{PaCO}_2 - \text{PeCO}_2) / \text{PaCO}_2 \cdot V_T\).
RESULTS

Table 5. Physical Characteristics of the Subjects

<table>
<thead>
<tr>
<th></th>
<th>CON (n = 104)</th>
<th>MILD CF (n = 43)</th>
<th>MOD-SEV CF (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV₁ (%)</strong></td>
<td>101 (12)</td>
<td>95 (13)</td>
<td>45 (11)</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>14.2 (1.8)</td>
<td>12.2 (3.1)</td>
<td>16.6 (1.8)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>20.0 (2.7)</td>
<td>18.1 (2.2)</td>
<td>18.1 (2.1)</td>
</tr>
</tbody>
</table>

FEV₁ - forced expiratory volume in one sec (% predicted); BMI - body mass index; Mean (standard deviation); CF - cystic fibrosis; CON - healthy control; MILD - mild lung disease; MOD-SEV - moderate to severe lung disease.

As expected, the FEV₁ of the MOD-SEV group are much lower than either of the other two groups. While the MOD-SEV participants are slightly older, their BMI is not larger as one would expect, due to poor nutritional status, as a result of their disease severity.
Figure 2a. Qdm vs Qcb vs Qcbdmj. Cardiac output (Q) versus oxygen consumption (VO₂), with corrections for Q: downstream (dm), collision broadening (cb) and the combination of dm, cb and Jones end tidal corrections (cbdmj).

Figure 2a shows the isolated effects of calculating Q with only either a dm or a cb correction. The correction factors appear to cancel each other out, thus we chose to correct for all three. The fully corrected, or Q calculated with cb, dm and j correction factors (Qcbdmj), lies somewhere between the other two lines.
Next we compared the fully corrected Q (cbdmj) to the Godfrey predicted, derived from healthy children (Q_G), (Fig 2b), and found that in the CON group there was no difference between the two slopes for Q. However in the MILD and MOD-SEV CF groups the fully corrected Q was no longer the same as the Q_G (Figs 2c, 2d).

**Figure 2b. Q_G vs Q_{cbdmj} – Healthy Controls.** Cardiac output (Q) versus oxygen consumption (VO_2), with corrections for Q: Godfrey (1971) compared to the combination of downstream (dm), collision broadening (cb) and Jones end tidal corrections (cbdmj) in healthy controls (CON).
Figure 2c. $Q_G$ vs $Q_{cbdmj}$ – Mild CF. Cardiac output ($Q$) versus oxygen consumption ($VO_2$), with corrections for $Q$: Godfrey (1971) compared to the combination of downstream (dm), collision broadening (cb) and Jones end tidal corrections (cbdmj) in CF patients with mild lung disease (MILD).
Figure 2d. $Q_G$ vs $Q_{cbdmj}$ – Moderate to Severe. CF Cardiac output ($Q$) versus oxygen consumption ($VO_2$), with corrections for $Q$: Godfrey (1971) compared to the combination of downstream (dm), collision broadening (cb) and Jones end tidal corrections (cbdmj) in CF patients with moderate to severe lung disease (MOD-SEV).
Table 6. Differences between \( Q_G \) and \( Q_{cbd mj} \)

<table>
<thead>
<tr>
<th></th>
<th>Slope</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>( Q_G )</td>
<td>6.3</td>
<td>3.3</td>
</tr>
<tr>
<td>( Q_{cbd mj} ):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON (SEM)</td>
<td>6.38 (0.44)</td>
<td>2.74 (0.69)</td>
</tr>
<tr>
<td>MILD (SEM)</td>
<td>7.6 * (0.45)</td>
<td>0.53 * (0.51)</td>
</tr>
<tr>
<td>MOD-SEV (SEM)</td>
<td>5.65 (1.03)</td>
<td>2.11 (1.12)</td>
</tr>
</tbody>
</table>

* \( p <0.01 \)

Cardiac output (Q) versus oxygen consumption, with corrections for Q: Godfrey compared to the combination of downstream (dm), collision broadening (cb) and Jones end tidal corrections. Comparison of slopes and intercepts of Q, according to group (CON healthy control; MILD mild lung disease; MOD-SEV moderate to severe lung disease).

Statistical analysis of the differences in slopes and intercepts between these \( Q:VO_2 \) slopes revealed no difference in the CON group, significant differences in the MILD group, and, possibly due to much smaller numbers and double the error, no significant difference in the MOD-SEV group.

CONCLUSIONS

For CON, \( Q_G \) (where \( PaCO_2 \) was derived from assumed normal dead space) agreed with \( Q_{cbd mj} \) (calculated from PetCO\(_2\)). In patients with lung disease, there was a trend for \( Q_G \) to overestimate Q and therefore the assumption of a normal dead space may not be valid in this group. Caution should be exercised if using one of the ‘cb’, ‘dm’ or ‘j’ correction factors on their own as each exerts a profound effect on Q values. Future research to evaluate a threshold of disease severity in CF for the need for the downstream correction would be a valuable addition to this work.
3.2.2 PaCO₂ Estimation

Non-Invasive Estimation of PaCO₂ in Children with Cystic Fibrosis

Research Institute, Hospital for Sick Children. Graduate Dept. Exercise Science, University of Toronto.

ABSTRACT

Rationale: Prediction equations for arterial CO₂ (PaCO₂) have previously been derived in small numbers of either healthy adult males (Jones et al., 1979) or healthy children (Pianosi and Hochman, 1996). Objective: To develop a prediction equation for PaCO₂ from end-tidal CO₂ (PetCO₂) for use in children with cystic fibrosis (CF) 8-19 yrs. Methods: Arterialized capillary blood was collected from the fingertip for the determination of PaCO₂, followed by the measurement of PetCO₂, during steady state exercise at 50% of a predetermined WRmax (n=51, FEV₁ 28-123% pred). A new equation to predict PaCO₂new was derived via multiple regression analysis in approximately half of the Ss (randomly split according to odd/even study date), then verified in the remaining group. Results: The best model to predict PaCO₂ was PaCO₂new = 0.792 (PetCO₂) – 0.065 (FEV₁ % pred) + 15.23 (SEY = 2.96 R² = 0.66, p<0.001). The overall mean difference between PaCO₂new and PaCO₂ref was −1.52 mmHg, SEM 0.75 (95% CI −3.07, 0.042). Conclusion: Non-invasive estimation of PaCO₂ in children with CF can be performed with similar accuracy to that accomplished in healthy children. This prediction equation will facilitate non-invasive estimation of cardiac output in young patients with CF.

BACKGROUND

Preliminary work in our lab (unpublished work), revealed no significant difference between PCO₂ values derived from the original Jones correction formula (Jones et al., 1979) and the newly derived Pianosi formula (1996), which were derived in healthy adults and children respectively. A non-invasive estimate of PaCO₂ is essential for our work evaluating Q in children with CF. As a result, we compared previously collected data from our lab (Schneiderman-Walker et al., 2000) (measured end tidal PCO₂ values and subsequent PaCO₂ collected from arterialized
capillary blood) from 65 patients with CF in an attempt to clarify the relationship between PetCO$_2$ and PaCO$_2$ in children.

Hand calculations on data in the Coates et al. study (1988) would suggest that the power of their test was 80% to detect a significant difference of 3.2 mmHg between PaCO$_2$ measured via blood sample or estimated via PetCO$_2$. While the actual power of their test was very low to be able to detect the difference (23%), the fact remains that the estimated and directly sampled PaCO$_2$ were similar in this group of patients, and the difference would likely have been within the measurement error of the technique.

At rest, PetCO$_2$ is less than PaCO$_2$ due to dilution of gas from poorly perfused alveoli at top of lungs. In exercise, there is an increase in perfusion of the alveoli, a decrease in alveolar V$_{D}$, and the mean P$_{A}$CO$_2$ is approximately equal to the mean PaCO$_2$. In lung disease, the ‘slow’ alveoli with the highest PCO$_2$ empty last, therefore the increased PetCO$_2$ is greater than the PaCO$_2$. Previous prediction equations have been derived in healthy adults and children.

When using the Indirect Fick equation to calculate non-invasive cardiac output, we made the assumption that PetCO$_2$ $\sim$ P$_{A}$CO$_2$ $\sim$ PaCO$_2$. In fact we know that there are slight differences between these three measures. End tidal CO$_2$ is approximately equal to peak alveolar CO$_2$, and arterial PCO$_2$ is approximately equal to mean alveolar CO$_2$.

At rest, PetCO$_2$ will be less than PaCO$_2$ due to the dilution of gas from poorly perfused alveoli at the top of the lung, in the upright position. With exercise there is an increased recruitment of alveoli, resulting from an increased perfusion of alveoli, thereby reducing alveolar dead space and bringing the mean alveolar CO$_2$ closer to the mean arterial CO$_2$.

In lung disease, however, there is the added issue of ‘slow alveoli’. These areas of the lung have a high PCO$_2$ and empty last, thus making PetCO$_2$ > PaCO$_2$.

*Previous prediction equations:*

*Jones (1979)*

PaCO$_2$ = 5.5 + 0.9 PetCO$_2$ - 0.0021 V$_T$
Jones et al. (1979), formulated a prediction equation for PaCO₂ which has enjoyed widespread acceptance as the correction for PetCO₂. In fact this equation was derived in five healthy male adults, aged 24-34 yrs, during exercise, and verified in 10 others.

Pianosi (1996)

\[ \text{PaCO}_2 = 0.647 \text{PetCO}_2 + 12.4 \]

Later, Pianosi et al. (1996) derived their prediction equation in 23 healthy children during exercise and concluded that this equation should be used with caution in children with CF.

**OBJECTIVE**

To develop a prediction equation for PaCO₂ from end-tidal CO₂ (PetCO₂) for use in patients with cystic fibrosis (CF) 9-19 years.

**METHODS**

We evaluated previously collected data of 51 patients with CF from our lab, 9 - 19 years, with lung function of FEV₁ 28 - 123 % pred. PaCO₂ was determined via an arterialized capillary sample, drawn from the finger during the 5th minute of steady state cycling, at 50% pred WR max. Patients cycled on an electrically braked cycle ergometer with their hand in a warming pad, and had the capillary sample drawn while cycling.

**ANALYSIS**

The subjects were divided into two groups according to their date of study (‘O’- odd, ‘E’- even). We tested the differences between the two groups for age, ht, wt, FEV₁%pred, PetCO₂, PaCO₂. We began our analysis by looking for the variables that were correlated with PaCO₂, which were PetCO₂, Vₜ, and FEV₁. When we tested for differences between the odd and even date groups we found that there were no significant differences between the groups for any variable.
Using the results of correlation analysis, the next step involved deriving a prediction equation for PaCO₂ by performing an ‘all possible regression’ on one half of the sample, the odd group. This analysis involved entering all possible combinations of variables to predict PaCO₂. To evaluate how well the model fit the data we evaluated the $R^2$ (or the amount of variance in the outcome variable accounted for by the predictor variables), the CP Mallow statistic (which should equal the number of parameters in the model), and the Mean Square Error, which should be as small as possible.

RESULTS

Table 7. Physical Characteristics of the Subjects

<table>
<thead>
<tr>
<th></th>
<th>GROUP ‘O’ (n = 30)</th>
<th>GROUP ‘E’ (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (%)</td>
<td>74.3 (27.3)</td>
<td>75.4 (26.5)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>14.9 (3.4)</td>
<td>15.3 (3.1)</td>
</tr>
<tr>
<td>BSA</td>
<td>1.42 (0.24)</td>
<td>1.53 (0.26)</td>
</tr>
</tbody>
</table>

FEV₁ - forced expiratory volume in one second; BSA - body surface area; Mean (SD). ‘O’ - odd study date; ‘E’ - even study date.

Table 7 demonstrates that the physical characteristics of the subjects for the two groups, created according to odd or even patient numbers, were similar for FEV₁ % pred, age and BSA. Initial correlation analysis suggested that the following variables were significantly related to PaCO₂:

\[
\begin{align*}
&\text{PetCO}_2 & r = 0.55 & p<0.0001 \\
&\text{FEV}_1 \% \text{ pred} & r = -0.32 & p<0.02 \\
&P\bar{v}\text{CO}_2 & r = 0.75 & p<0.0001
\end{align*}
\]
Table 8. All Possible Regression Analysis

<table>
<thead>
<tr>
<th>Number of variables in model</th>
<th>R²</th>
<th>C(p)</th>
<th>MSE</th>
<th>Variables in Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.54</td>
<td>9.9</td>
<td>11.7</td>
<td>PetCO₂</td>
</tr>
<tr>
<td>1</td>
<td>0.12</td>
<td>41.9</td>
<td>22.0</td>
<td>FEV₁%</td>
</tr>
<tr>
<td>1</td>
<td>0.01</td>
<td>51.4</td>
<td>25.1</td>
<td>Vₜ</td>
</tr>
<tr>
<td>2</td>
<td>0.66</td>
<td>2.0</td>
<td>8.8</td>
<td>PetCO₂ FEV₁%</td>
</tr>
<tr>
<td>2</td>
<td>0.55</td>
<td>10.9</td>
<td>11.7</td>
<td>PetCO₂ Vₜ</td>
</tr>
<tr>
<td>2</td>
<td>0.14</td>
<td>42.9</td>
<td>22.5</td>
<td>Vₜ FEV₁%</td>
</tr>
<tr>
<td>3</td>
<td>0.66</td>
<td>4.0</td>
<td>9.0</td>
<td>PetCO₂ FEV₁% Vₜ</td>
</tr>
</tbody>
</table>

R² – the percentage of the variance accounted for; C(p) – Mallow’s CP statistic; MSE – mean square error; the bolded results indicate the best model (explanation below).

The results of the All Possible Regression are presented in Table 8. Since adding more variables most often increases the R², the Mallow’s CP statistic was calculated. For the purpose of prediction, if the model has too few variables then it would be biased, and one with too many variables would produce predicted values that are too variable. Therefore, the best model needs to balance bias and variability, or, the model with the highest R², while maintaining the lowest MSE, where the Mallow’s CP statistic is closest or equal to the number of parameters in the model.

**New Prediction Equation:**

\[
\text{PaCO}_2\text{new} = 0.792 \text{ PetCO}_2 - 0.065 \text{ FEV}_1\%\text{pred} + 15.23
\]

(SEY = 2.96, R² = 0.66, p<0.001)
Figure 3. **Bland and Altman Plot.** This plot demonstrates the relationship between the newly derived equation to predict PaCO₂ (PaCO₂new) and the measured value (PaCO₂) in a second group of patients, other than those in whom the equation was derived.

A Bland and Altman plot was used to verify the new equation in the second group (even study date), plotting the average of the new predicted value and PaCO₂, versus the difference between the two. Results of the plot indicate that there was a bias, or mean difference of -1.52 mmHg between the PaCO₂ new and PaCO₂, with a standard error of the mean difference of 0.75 mmHg, and 95% confidence intervals of 0.042 and -3.07 mmHg. While there was no discernible pattern of the data, indicating that the new equation consistently predicted the outcome evenly along the range of x data, there were a fair number of data points which lay outside the CI. The significance of the 95% CI is that 95% of the time the newly predicted PaCO₂ will lie within those lines. Future research, therefore, could investigate additional predictor variables to improve the non-invasive estimate of PaCO₂ in CF, such as a dichotomous variable of rest/exercise, and the degree of ventilation to perfusion mismatch.
CONCLUSION

Non-invasive estimation of PaCO$_2$ in children with CF can be performed with similar accuracy to that accomplished in healthy children. The new prediction equation will facilitate non-invasive estimation of cardiac output in young patients with CF.

3.2.3 CO$_2$ Rebreath: exponential calculations

RATIONALE

One disadvantage of the CO$_2$ rebreathe equilibrium technique is that the effect of rebreathing CO$_2$ during high levels of exercise is quite unpleasant, thereby limiting repeated measurement in all but highly motivated adults. In the past there has been interest in using the “exponential” rebreathing technique to make multiple measurements of cardiac output during a progressive exercise test in children with lung disease (Lands et al., 1992a). In 1958, Defares (1958) demonstrated that rebreathing low concentrations of CO$_2$ would lead to a rise in the partial pressure of CO$_2$ in the lung-rebreathing bag system that can be described as a monoexponential. Later Alves Da Sylva and colleagues (1985) proposed that the end tidal partial pressure of CO$_2$ (Petco$_2$) follows an exponential equation that can be characterized as

$$\text{PetCO}_2(t) = \text{PasymCO}_2 (1 - Ko e^{-\tau t})$$

where PetCO$_2$ is the peak CO$_2$ concentrations during the 15 second rebreathe, PasymCO$_2$ is the asymptote of the rise which has frequently been equated with $\bar{PvCO}_2$, Ko is a positive number less than one where, at time zero, [PasymCO$_2$ (1 – Ko)] is the start of the rise of the monoexponential and $\tau$ is the time constant.

While there have been a number of techniques proposed to solve this equation, especially in the pre personal computer era, Alves da Sylva and colleagues (1985) suggested that a computerized iterative curve fitting technique offered significant advantages. Providing the experimental data is close to the form expected, values for $\tau$ will be in the order of 10-15 seconds and the PasymCO$_2$ will be very close to the $\bar{PvCO}_2$. However, as they observed, this is not always the case and sometimes long time constants and high values for the asymptote are found,
so they defined the $P_v\text{CO}_2$ as the value of the PetCO$_2$ at 20 seconds. There are a number of practical reasons for these difficulties. The first is that the iterative curve fitting techniques use experimental data to derive three unknowns, Pasymco$_2$, Ko and $\tau$. Here, slight errors in either the raw data or the curve fitting technique can give rise to significant errors in each value but really $\tau$ in particular. Furthermore, all logarithmic transforms involved in curve fitting tend to emphasize some values over others in that the difference between data points with larger values is given less weight than differences when the raw data comes from smaller numbers. These inaccuracies are clearly recognized since Alves da Silva and colleagues point out the necessity to take the value at 20 seconds as the $P_v\text{CO}_2$ rather than the PasymCO$_2$ itself, as the theory would suggest the two should be synonymous (Alves da Silva et al., 1985). Our group believed that part of the problem was that any experimental inaccuracies that could be caused by different patterns of breathing throughout the rebreathe or minor equipment problems with the measurement of PCO$_2$, could result in unrealistic values when iterative techniques were used to solve an equation with three unknowns. Hence, Dr. Allan Coates recommended the following alternative approach.

Experimental observation clearly demonstrated that, within a limited time between zero and 15 seconds, the rebreathe curve could be very accurately fit with a quadratic equation with values of “$r$” in excess of 0.97 in virtually all situations. With no logarithmic transform, all data points are valued equally and discrepancies from the expected curve due to irregular breathing and variations in tidal volumes tend to be smoothed by the more valid points. Once the curve was defined, we then sought to use the curve to define the original equation

$$\text{PetCO}_2 = \text{PasymCO}_2 (1 - Ko e^{\gamma t})$$

from the quadratic

$$\text{PetCO}_2 = a + bt + ct^2$$

Since the slope of PetCO$_2(t)$ is completely dependent on $\tau$, the first derivative of the quadratic equation with respect to time can be used to calculate $\tau$. From this, values for Ko and PasymCO$_2$ follow.
HYPOTHESIS

Preliminary work by Coates and co-workers suggested that fitting a quadratic function to the data would be more accurate than using the iterative technique and three unknown variables, as recommended by Alves da Silva et al. (1985). Iterative techniques with three unknowns are very subject to the influence of data errors. The use of a quadratic equation with rigorous statistical curve fitting techniques was hypothesized to be more sensitive to identifying poor quality data (as evidenced by a long time constant; $\tau > 10-12$ seconds) and discrepancies due to irregular breathing, and variations in tidal volumes tend to be smoothed by more valid points. Part of this is because it places mathematical constraints (in keeping with physiological principles) on the equation that minimizes erroneous and clearly non physiological data.

The hypothesis in this study was that the monoexponential curve derived from data fitted to a quadratic function would be more accurate than the standard technique that used an iterative approach and three unknowns. Accuracy would be defined as the sum of the least squares between the differences in the data points and the values calculated from the monoexponential, and the difference between the PasymCO$_2$ and the P$v$CO$_2$ defined as the value of PetCO$_2(t)$ at 20 seconds as defined by Alves da Sylva et al.

METHODS

Data were reviewed from four patients with CF, ages 10-14 years, with mild disease severity, in stable condition. Rebreathe manoeuvres were performed during cycling exercise at four workrates each, below 75% of their previously determined maximum. End tidal CO$_2$ data from 16 rebreathe manoeuvres were examined and P$v$CO$_2$ was calculated by the two different methods described above: a) the iterative technique described by Alves ds Silva et al. and b) the monoexponential curve fitted quadratic function to the data. The residual sums of squares, which represent the deviation of the actual values from the predicted values, were calculated for both techniques and compared via paired $t$ test.

RESULTS
The residual sums of squares of the differences in the data points and the values calculated from the monoexponential curve, were significantly greater than the difference between the data points and the values calculated from the iterative approach (1.405 versus 0.223, \( p=0.034 \)).

**CONCLUSION**

Although this new calculation method was hypothesized to provide a significant improvement in the calculation \( \overline{P\text{CO}_2} \) via the exponential technique, this was a small pilot group with much within and between subject variation in multiple workrates. The monoexponential curve derived from data fitted to a quadratic did not result in a more accurate fit of the data, than the standard technique of using the iterative technique and three unknowns.
3.3 Clinical Applications

3.3.1 Test-retest Reliability and Validity of the Innocor™ Device for the Measurement of Cardiac Output in Children and Adults

Key words: children, adults, cardiac output, reliability, validity, Innocor™, inert gas rebreathing

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADr</td>
<td>Healthy adults, reliability study</td>
</tr>
<tr>
<td>CHDr</td>
<td>Congenital heart disease group, reliability study</td>
</tr>
<tr>
<td>CHDv</td>
<td>Congenital heart disease group, validity study</td>
</tr>
<tr>
<td>CONr</td>
<td>Healthy controls, reliability study</td>
</tr>
<tr>
<td>CONv</td>
<td>Control group, validity study</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>HRmax</td>
<td>Maximum heart rate</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass correlation coefficient</td>
</tr>
<tr>
<td>IGR</td>
<td>Inert gas rebreathing</td>
</tr>
<tr>
<td>LOA</td>
<td>Limits of Agreement</td>
</tr>
<tr>
<td>SaO₂</td>
<td>Oxygen saturation</td>
</tr>
<tr>
<td>QAmis</td>
<td>Cardiac output, Amis mass spectrometer system</td>
</tr>
<tr>
<td>Q</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>Qeff</td>
<td>Effective pulmonary blood flow</td>
</tr>
<tr>
<td>Qinn</td>
<td>Cardiac output, Innocor™</td>
</tr>
</tbody>
</table>
ABSTRACT

**Purpose:** To evaluate the reliability and validity of cardiac output measures with the Innocor™ device (inert gas rebreathing technique) at rest and during exercise in children and adults.

**Methods - Study 1:** Reliability of the Innocor™ device was assessed by measuring cardiac output (Q_{inn}) repeatedly in children (with congenital heart disease CHDr, n=10, ages (±SD, yrs) 12.3 (±2.7); healthy control CONr, n=10, ages 13.0 (±2.7)), and in healthy adults ADr, n=10, ages 27.0 (±3.9). Q_{inn} measurements were made at rest, during cycling at 25 watts, and at workrates eliciting 60% and 70% of predicted maximum heart rate (HRmax; 70% ADr and CONr only). Within day (CHDr, CONr) and the addition of between-day (ADr) reliability was determined using the intra-class correlation coefficient (ICC). **Results - Study 1:** Mean values of Q_{inn} (l.min^{-1}) at rest, 25w, 60% and 70% pred HRmax over the two tests were (±SEM) CHDr: 5.4 (±0.3), 9.1 (±0.4), 10.1 (±0.3); CONr: 5.1 (±0.1), 9.04 (±0.2), 10.1 (±0.3), 11.5 (±0.2); and ADr: 6.0 (±0.3), 9.6 (±0.3), 12.9 (±0.1) 14.4 (±0.2) respectively. Regression analysis revealed mean slopes for Q_{inn}:VO_{2} (±SEM) of CHDr: 6.8 (±1.2), 6.8 (±0.9) CONr: 7.3 (±1.6), 7.1 (±1.4) and ADr: 5.9 (±0.8), 6.2 (±1.0), for Tests 1 and 2 respectively. Repeat Q_{inn} measurements were significantly reproducible with the highest ICC values attained during exercise (0.7 – 0.98).

**Methods - Study 2:** Criterion validity of the device was assessed by comparing cardiac output measured with the Innocor™ (Q_{inn}) to that measured by the AMIS 2000 mass spectrometer (Q_{Amis}). Children with CHD (CHDv, n=11 ages 15.1 (±1.4) yrs) and healthy controls (CONv, n=9 ages 13.1 (±2.6) yrs) were evaluated. **Results – Study 2:** The bias (Q_{inn} - Q_{Amis}) and limits of agreement (±2SD) between the two methods were 0.45 ± 1.9 L.min^{-1} and 0.27 ± 2.1 for CHDv and CONv respectively, with no systematic differences between the two methods. **Conclusion:** The Innocor™ device allows for the reliable and valid non-invasive measurement of cardiac output at rest and during exercise in healthy children and adults, and in children with congenital heart disease.
INTRODUCTION

Non-invasive methods of cardiac output (Q) determination based on respiratory gas analysis have been developed for use in children and adults, enabling us to further understand cardiopulmonary physiology and pathophysiology in various patient populations. Typically, non-resident or inert gas rebreathing techniques (nitrous oxide (Zeidifard et al., 1976) and acetylene (Grollman, 1929; Triebwasser et al., 1977)) are most appropriate for individuals with well-ventilated lungs, as the effective pulmonary blood flow (Q_{eff}) measured by these methods is determined by the rate of disappearance of the inert gas into the bloodstream. The addition of an insoluble tracer gas to the rebreathe mixture is commonly used to assess the adequacy of lung ventilation.

The Innocor™ device (Innovision, Odense, Denmark) employs the nitrous oxide technique to determine Q and has distinct advantages of portability, lower cost, and ease of use over previously available mass spectrometer-based measurement systems. While the latter are highly precise and sensitive, they are also expensive and bulky and require ongoing expert calibration, operation and maintenance. As a result, the clinical application of Q measurement, especially in the ambulatory pediatric age group, has previously been significantly limited. The addition of a reliable technique to conveniently track changes in cardiovascular function would enhance our ability to monitor patients under a variety of conditions such as chronic heart failure, drug therapy, cardiac rehabilitation, exercise stress testing and pacemaker programming.

Reproducibility measures of various non-invasive Q techniques differ markedly between rest and exercise conditions. For example, it is well accepted that the CO_{2} rebreathe technique is less precise at rest, owing to the small veno-arterial PCO_{2} difference which may act to magnify analytical error in the measurement of either PaCO_{2} or P\text{̄}CO_{2} (Godfrey and Davies, 1970). Alternatively, measures of Q via echocardiography and impedance cardiography are less frequently reported during exercise due to the challenge of overcoming movement artifact. Cardiac output is routinely measured at rest and immediately post exercise (Rowland, 2008). Lastly, while maximal exercise alters the CO_{2} dissociation curve characteristics and the corresponding conversion of partial pressure of CO_{2} (PCO_{2}) into content (CCO_{2}) (Sun et al., 2001), factors required for calculations of Q with the resident gas technique, the inert gas
rebreathing technique has been reported to be the most accurate and reliable technique for the determination of maximal Q (Warburton et al., 1999a).

Preliminary results employing the Innocor™ device in adult heart failure patients indicate that the Innocor™ measure of Q is at least as reliable as that derived from invasive measures such as thermodilution, (Gabrielsen et al., 2002; Dong et al., 2005) and direct Fick (Agostoni et al., 2005), potentially offering a valuable asset to research and clinical medicine (Dong et al., 2007). Recently the Innocor™ has been further evaluated during standard graded exercise testing and found to be suitable for moderate to high submaximal power outputs (Fontana et al., 2009a) as well as peak exercise (Fontana et al., 2009b; Jakovljevic et al., 2008; Jakovljevic et al., 2008; Lang et al., 2007) in adults, and feasible for rest and during treadmill exercise in children with third degree and complete atrioventricular block treated with pacemakers. (Hauser et al., 2011; Wiegand et al., 2010). To the best of our knowledge no study has evaluated the reliability and validity of the device in healthy children and children with congenital heart disease.

Validation of noninvasive cardiac output measurement has typically involved a comparison to invasive measures such as the Direct Fick or thermodilution (Warburton et al., 1999a), neither of which is appropriate for a pediatric population. Owing to its sensitivity and accuracy (Triebwasser et al., 1977) the respiratory mass spectrometer has been employed in clinical (Rosenthal and Bush, 1998) and research settings (Narang et al., 2007) and has been validated against dye dilution for the measurement of Q via inert gas rebreathing. (Smyth et al., 1984)

Thus our aim was to evaluate the reliability and validity of the Innocor™ device for the measurement of cardiac output at rest and during exercise in pediatric patients with cardiac disease and in healthy children and adult volunteers with normal respiratory and cardiac physiology.

**STUDY 1: RELIABILITY**

The purpose of the first study was to evaluate the test-retest reliability of the Innocor™ device for the measurement of cardiac output, within the same day of testing in children and between two days in adults.
METHODS

Subjects

Ten children with stabilized congenital heart disease (CHDr), 10 healthy children (CONr), and 10 healthy adults (ADr) participated in the reliability study. Criteria for exclusion for the cardiac patients were, diagnosis of Fontan, aortic regurgitation or presence of shunt (either right to left, or left to right), or having been previously excluded from a routine progressive exercise test by a Cardiologist. For the healthy individuals exclusion criteria included smoking, or any history of respiratory or cardiovascular disease. No participants were involved in competitive level sport participation. The Hospital for Sick Children and University of Toronto research ethics boards gave approval for this study and informed consent was obtained from each participant.

Testing Procedures

Participants arrived at the lab at least one hour post prandial and were measured for height, weight (SR Scales, SR Instruments, Tonawanda, NY) and pulmonary function (Vmax system, SensorMedics, Yorba Linda, CA). Spirometry measurements were performed according to standard spirometric techniques and included forced vital capacity (FVC) and forced expiratory volume in one second (FEV\textsubscript{1}) (Miller et al., 2005). Values were expressed as a percent of predicted value for height and gender based on previously developed standards (Stanojevic et al., 2008). An online calculator was used (Quanjer, 2011), incorporating these norms, using standard deviation scores (z-scores) to classify spirometric tests as normal or abnormal (obstructed or restricted patterns) in all participants.

Oxygen saturation was measured on the right index finger with the probe that accompanied the Innocor\textsuperscript{TM} device (since the blood pressure was being monitored on the left arm), as well as with a reflectance probe placed on the forehead as a comparison measure (Radical, Massimo Corp, Irvine, CA). Since the Innocor\textsuperscript{TM} device requires a measure of saturation from the index finger, and we have experienced variable results in children from this site while cycling, we used the forehead probe as a quality control comparison. Heart rate was monitored via the saturation
probe (pulse) for ADr and CONr, and via a four-lead ECG system for the CDHr (Case-12, Marquette Electronics Inc.) for arrhythmia detection in the cardiac patients.

**Innocor**

Participants were familiarized with the rebreathing technique in the demonstration mode (room air in the bag) of the Innocor™ device (Innovision, Odense, DK). The subject began breathing room air through a mouthpiece while wearing noseclips. The mouthpiece was attached to the flow sensor of the Innocor™, with a filter placed in line. They were then switched into a 3-litre anaesthetic bag at end expiration, from which they rebreathed a mixture of 0.5% nitrous oxide (N₂O, soluble inert gas), 0.1% sulphur hexafluoride (SF₆, insoluble tracer gas), 28% oxygen (O₂) in balance nitrogen (N₂) for 15-20 seconds. They breathed at a rate of approximately 20 breaths per minute, with a gas volume of 40% of their previously measured FVC. In this method, the rate of disappearance of the soluble inert gas is proportional to the blood flowing by the lungs, or the effective pulmonary blood flow (Qₑₑ). Given that total cardiac output (Q) equals Qₑₑ plus any shunted blood, in the absence of such a shunt, Qₑₑ is representative of Q. The tracer gas, SF₆ is used to calculate total systemic volume and is used to correct the soluble gas prior to any calculations, to compensate for incomplete mixing, or a loss of gas into poorly ventilated areas of the lung.

**Testing Protocol**

The participants performed rebreath maneuvers for the measurement of cardiac output using the Innocor™ device at rest and at three (ADr, CONr) or two (CHDr) exercise levels (25 watts (w), 60 and 70% predicted maximum heart rate (maxHR)). The levels were selected such that all participants could be expected to accomplish the 25watts, many would be able to complete the 60% maxHR and the healthy controls were anticipated to be able to finish the 70% maxHR. All individuals repeated the protocol twice in one day (Tests 1, 2) separated by approximately 15 minutes, while the adults returned on a second day within one week, at the same time of the day, to repeat the entire testing protocol (Tests 3, 4). The research design is illustrated in Figure 4.
**Figure 4. Research Design – Reliability Study.** Day 1, 2: testing days; a: Adults (ADr) only; b: 15 minutes rest between Tests 1,2 or 3,4; c: Ex 3 no CHDr.

**Data Collection**

All details are applicable to both the Reliability and Validity studies. Demographic data were collected on all participants including age, sex, weight, height and body surface area. Maximum heart rate was obtained for CHDr patients from their previously performed maximal exercise test within the last year, to determine the appropriate level of exercise for the test protocol (60%, 70%). Otherwise, predicted maximum heart rate was assumed for ADr (220 - age) (McArdle et al., 1981) and CONr (210) (Rowland, 1996) as the basis for calculating their 60% and 70% exercise levels. Heart rate and oxygen saturation were measured at each level. Exercise testing took place in the Cardiopulmonary Exercise Laboratory of the Hospital for Sick Children.

**Statistical Analysis**

Physical characteristics of the subjects were analyzed via descriptive statistics of means and standard deviations and differences between the groups via Student’s t-test. The test-retest reliability of the Innocor™ device was evaluated using Intraclass Correlation Coefficient (ICC model 2,1) to compare within-day agreement for children as well as between-day measures for adults who returned for a second testing day. ICC results of 0.6-0.80 were considered substantial and above 0.8 excellent (Landis and Koch, 1977). Reliability was further evaluated with the coefficient of variation (SD/mean) and the limits of agreement (twice the standard deviation of the paired differences) for Tests 1 and 2 (Critchley and Critchley, 1999).
Paired t-tests and one-way ANOVA were used to identify whether a systematic trial effect was observed between Tests 1 and 2 (CONr, CHDr) and Tests 1-4 (ADr) respectively. A Bonferroni adjustment was made for multiple comparison t-tests. The relationship between Q and oxygen consumption (VO\textsubscript{2}) was determined with simple linear regression at each workrate, for each group. The data were analyzed using SAS 9.1 (SAS Institute, Cary, NC) and SPSS 12.0 (SPSS Inc, Chicago, IL). Statistical significance was considered to be p<0.05.

Based on a reported standard deviation in Q measurement (nitrous oxide technique) of approximately 0.7-1.0 l/min at all levels of work (Zeidifard et al., 1976), alpha level of 0.5, power of 80%, and a meaningful difference of at least 10% (or 1.5 standard deviations), approximately 8 subjects were required for each arm of this study (Machin et al., 1997). The data were gathered from this methodological study to evaluate the measurement properties of the Innocor\textsuperscript{TM} cardiac output system for future studies of healthy children and those with cardiac disease.

RESULTS

Ten children with congenital heart disease, CHDr, were recruited from the Cardiology clinic at the Hospital for Sick Children. Diagnoses included Tetralogy of Fallot (2), repaired ventricular septal defect (1), transposition of great arteries (2), Ebstein’s anomaly with Wolff-Parkinson White syndrome (1), isolated right pulmonary artery (1) and coarctation (2). Ten healthy age matched controls, CONr, were recruited via an advertisement in the Hospital for Sick Children weekly newspaper and ten healthy adult hospital staff, ADr, volunteered to participate.

Characteristics of the study participants are presented in Table 9. There were no significant differences between the CONr and CHDr for any measure of size or pulmonary function variable. None of the CHDr group had evidence of intracardiac shunt as determined by previous echocardiographic evaluation. The spirometry results of one participant in ADr was classified as mild obstruction, and one in CONr and two in CHDr were classified as restriction.
### Table 9. Characteristics of Participants

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Reproducibility</th>
<th>Study 2</th>
<th>Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHDr</td>
<td>CONr</td>
<td>ADr</td>
<td>CHDv</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Height, cm</td>
<td>12.3 (2.7)</td>
<td>13.0 (2.7)</td>
<td>27.0 (3.9)</td>
<td>15.1 (1.4)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>57.1 (19.6)</td>
<td>57.3 (22.5)</td>
<td>75.4 (12.9)</td>
<td>60.1 (14.4)</td>
</tr>
<tr>
<td>Body surface area</td>
<td>1.58 (0.32)</td>
<td>1.55 (0.36)</td>
<td>1.91 (0.20)</td>
<td>1.66 (0.19)</td>
</tr>
<tr>
<td>Body mass index,</td>
<td>21.8 (4.5)</td>
<td>22.6 (5.2)</td>
<td>24.5 (3.5)</td>
<td>21.7 (4.9)</td>
</tr>
<tr>
<td>kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC, % pred</td>
<td>90.3 (10.1)</td>
<td>94.4 (9.9)</td>
<td>97.2 (7.9)</td>
<td>77.9 (11.6)</td>
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<tr>
<td>FEV₁, % pred</td>
<td>92.0 (10.9)</td>
<td>94.5 (10.1)</td>
<td>97.7 (9.0)</td>
<td>77.8 (12.3)</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>87.6 (6.3)</td>
<td>86.6 (7.1)</td>
<td>83.6 (8.8)</td>
<td>87.2 (6.7)</td>
</tr>
<tr>
<td>MVV sprint, % pred</td>
<td>85.2 (20.0)</td>
<td>88.5 (12.4)</td>
<td>120 (16.3)</td>
<td>91.7 (12.0)</td>
</tr>
</tbody>
</table>

Mean (SD); CHD, congenital heart disease; CON, healthy child; AD, healthy adult; FVC, forced vital capacity; FEV₁, forced expiratory volume 1 second; MVV, maximum voluntary ventilation; r = reliability study, v = validity study; a: CHDv<CONv, p=0.002; b: CHDv<CONv, p=0.001.

Test-retest reliability results are presented in Table 10. All ICC results exceeded 0.6, were highest at the top two levels of exercise for ADr and CONr, and were similar across all levels for CHDr. Coefficients of variation were ≤ 6%, except for CONr (rest, 6.8%) and ADr (rest, 10%).
Table 10. Reliability Analysis Results of Cardiac Output Measures

<table>
<thead>
<tr>
<th>Group</th>
<th>Rest</th>
<th>25 watts</th>
<th>60% HR max</th>
<th>70% HR max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHDr</td>
<td>CONr</td>
<td>ADr</td>
<td>CHDr</td>
</tr>
<tr>
<td>ICC</td>
<td>0.98</td>
<td>0.67</td>
<td>0.85</td>
<td>0.98</td>
</tr>
<tr>
<td>LOA</td>
<td>0.5</td>
<td>1.2</td>
<td>1.8</td>
<td>0.6</td>
</tr>
<tr>
<td>CV</td>
<td>3.4</td>
<td>6.8</td>
<td>10.0</td>
<td>3.1</td>
</tr>
</tbody>
</table>

CHD, congenital heart disease, CON, healthy child, AD, healthy adult; n=10 each; r=reliability study; ICC: Intraclass correlation coefficient; a: n=9; b: n=8; ADr reflects Tests 1-4, CHDr and CONr reflect Tests 1-2; LOA: Limits of agreement (twice the standard deviation of the paired differences between Tests 1 and 2, 1.min\(^{-1}\)); CV: Coefficient of variation calculated for Tests 1-2, (SD/mean).

There was no evidence of systematic bias at any workrate for CONr, or ADr. There were small absolute significant differences between Tests 1 and 2 for CHDr for 25w level (p<0.008, mean difference 0.33 L.min\(^{-1}\)), and 60% (p<0.04, mean difference 0.51 L.min\(^{-1}\)). Correlation coefficients for the CHDr Tests 1 and 2 for 25w and 60% levels were 0.99 and 0.98 respectively.

Mean oxygen consumption and cardiac output values for Tests 1 and 2 for children and Tests 1-4 for adults are presented in Table 11, each variable gradually increased with increasing workrates.

The relationship between averaged oxygen consumption and cardiac output values is presented graphically in Figure 5, demonstrating a similar relationship between these two variables for the all three groups (CHDr, CONr, ADr). Tests 1 and 2 were averaged for children and Tests 1-4 averaged for adults for this analysis.
Table 11. Cardiac Output and Oxygen Consumption Results: Reliability

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>25 watts</th>
<th>60% HR max</th>
<th>70% HR max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHDr</td>
<td>CONr</td>
<td>ADr</td>
<td>CHDr</td>
</tr>
<tr>
<td>VO₂ (L/min)</td>
<td>0.22 (0.11)</td>
<td>0.18 (0.06)</td>
<td>0.33 (0.13)</td>
<td>0.71 (0.19)</td>
</tr>
<tr>
<td>Q (L/min)</td>
<td>5.4 (1.4)</td>
<td>4.9 (0.7)</td>
<td>6.0 (1.4)</td>
<td>8.9 (2.0)</td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

Mean (SD), values represent mean of Tests 1-2 for CHDr and CONr, Tests 1-4 for ADr.
Figure 5. Relationship between Cardiac Output and Oxygen Consumption. ADr: $y = 5.98x + 4.21$, $R^2 = 0.99$, T1-4; CHDr: $y = 6.42x + 4.07$, $R^2 = 0.99$, T1, 2; CONr: $y = 6.9302x + 3.8367$, $R^2 = 0.9881$, T1,2 (based on average of multiple trials).

**STUDY 2: VALIDITY**

The purpose of this study was to evaluate the validity of the Innocor™ device for the measurement of $Q_c$, by comparing results obtained by the Innocor™ to standard acetylene rebreathing (SAR).

**METHODS**

*Subjects*

Ten children with stabilized congenital heart disease (CHDv) and 10 healthy children (CONv) participated in the validity study. Criteria for exclusion for the CHD group were the same as those for the reliability study, as were those for healthy individuals. The Hospital for
Sick Children and University of Toronto Research Ethics Boards gave approval for this study and informed consent was obtained from each participant.

Testing Procedures and Data Collection of Innocor™ were the same as for the Reliability Study.

Standard acetylene rebreathing (SAR)

The AMIS 2000 mass spectrometer (Innovision, Denmark) calculates effective pulmonary blood flow (Q_{eff}) from the rate of disappearance of the soluble gas in the rebreathing manoeuvre. Since we confirmed all subjects to be free of any measurable intracardiac shunt, as determined by previous echocardiographic evaluation, the Q_{eff} was accepted as the total cardiac output (Q) with this instrument. Since the AMIS measures Q_{eff} and the Innocor™ corrects for any measurable shunt, we mathematically adjusted all Innocor™ values to ensure they were comparable. Therefore all Innocor™ rebreathe trials were mathematically adjusted to a SaO$_2$ of 98%, (indicating no evidence for shunt) if they were measured otherwise, and recalculated, which would allow us to compare Q_{eff} for both instruments.

Participants were familiarized with the rebreathing manoeuvre for the SAR device. They began by breathing room air through a mouthpiece attached to a one-way non-rebreathing valve, while wearing nose clips. They were then switched into a 3-litre anaesthetic bag from which they rebreathed a mixture of 0.3% acetylene (soluble inert gas), 5% sulfur hexafluoride (insoluble tracer gas), 35% oxygen (O$_2$), balance nitrogen (N$_2$) for approximately 20 seconds, at a rate of 20 breaths per minute, with a gas volume of 40% of their previously measured FVC. Similar to the Innocor™ device, the rate of disappearance of the inert, blood soluble gas is proportional to the blood flowing by the lungs, or the Q_{eff} and a visual display of equilibrium of the tracer gas was used to indicate adequacy of lung ventilation. A two-point calibration of the mass spectrometer was performed immediately prior to each rebreathing manoeuvre.

Testing Protocol

Up to two cardiac output measurements on each system were made at rest, depending on acceptability of technique, each separated by a 5-minute washout period (Figure 6). Participants
then completed three constant power output levels of exercise on an electrically braked cycle ergometer. At each level the participant exercised for 4-5 minutes, which was assumed to be a steady state. Cardiac output was then measured by the two systems in random order, separated by two minutes of continued cycling (washout period). Work rates were the same as those used in the reliability study.

<table>
<thead>
<tr>
<th>Level</th>
<th>Comparison of Innovor™ and SAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>Innovor™ - SAR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ex 1</td>
<td>Innovor™ - SAR&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ex 2</td>
<td>Innovor™ - SAR&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ex 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Innovor™ - SAR&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Figure 6. Research Design – Validity Study.** a: 5-minute rest between measures; b: 5-minutes active recovery between levels; c: no CHDv; SAR – standard acetylene rebreathing.

**Data Cleaning**

All AMIS tracings were evaluated carefully after rebreathing. First, tracings for SF6 were carefully inspected to confirm equilibrium of the insoluble gas with the lungs. Next, the analysis time for manoeuvres at rest and exercise were limited to 15 and 10 seconds respectively. Lastly, a portion of the tracings were collected with a message of ‘high background soluble gas’ and the data were reviewed to see if there was any systematic effect of this reading on the variability of the data.

**Statistical Analysis**

Validity of the Innovor™ device was evaluated by comparing paired differences of cardiac output measurements between the devices plotted against the average of the two devices according to the Bland Altman plot (and the associated limits of agreement) (Bland and Altman, 1986). As well, a Pearson product moment correlation was used to evaluate the agreement between the Innovor™ and SAR measures, and paired t-tests were used to assess any systematic
bias. Sample size determination was the same as used for the Reliability study. Statistical significance was set at $p \leq 0.05$.

RESULTS

A separate group of subjects were recruited for the validity study; children with congenital heart disease (CHDv) and age and size matched controls CONv (Table 9). Original diagnoses for CHDv included corrected VSD (2), Tetralogy of Fallot (5), dilated cardiomyopathy (1) and TGA (3). In the CHDv group the spirometry of one participant was classified as moderate obstruction and four as restriction due to previous cardiac surgery. The FVC $%\text{pred}$ ($p<0.01$) and FEV$_1$ $%\text{pred}$ ($p<0.02$) were significantly smaller for the CHDv compared to the CONv group.

Bland and Altman plots comparing cardiac output values measured via Innocor$^\text{TM}$ to SAR mass spectrometer for children with congenital heart disease (CHDv) and healthy controls (CONv) are presented in Figure 7. There was consistent agreement between the two techniques for the two groups, with a mean bias ($Q_{\text{Inn}} - Q_{\text{Amis}}$) and limits of agreement ($\pm 2$ SD) between the two methods of $0.45 \pm 1.9 \text{L.min}^{-1}$ and $0.27 \pm 2.1$ for CHDv and CONv respectively, for all data combined. There were no systematic differences across rest to exercise between the Innocor$^\text{TM}$ and AMIS measures of $Q$, and all but one data point in each group fell within the limits of agreement.

The validity data are further broken down in Table 12, which outlines the limits of agreement and percentage error for each level. In most cases both bias and LOA during exercise are larger than at rest, for both CHDv and CONv. All percentage errors are less than 30% for CHDv, and are decreasing for CONv with increasing ex levels.

All comparisons of $Q$ between Innocor$^\text{TM}$ and SAR were significantly correlated with correlation coefficients ranging from 0.73 – 0.98 (Table 13).
Figure 7. Bland and Altman plots comparing cardiac output values measured via Innocor™ to AMIS mass spectrometer for children with congenital heart disease (CHDv) and healthy controls (CONv). The average of Innocor™ and mass spectrometer is plotted on the horizontal axis, while the difference between the two is plotted on the vertical axis. The solid line represents the overall average and the broken lines represent 2 SDs above and below the overall average, or the limits of agreement.
Table 12. Agreement between Innocor™ and SAR for cardiac output: Validity Study

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Bias</th>
<th>SD</th>
<th>min</th>
<th>max</th>
<th>LOA</th>
<th>Average Q</th>
<th>SD</th>
<th>min</th>
<th>max</th>
<th>% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHDv</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>11</td>
<td>0.22</td>
<td>0.60</td>
<td>-0.77</td>
<td>1.13</td>
<td>1.2</td>
<td>4.74</td>
<td>0.76</td>
<td>3.29</td>
<td>5.84</td>
<td>25.3</td>
</tr>
<tr>
<td>Ex 25</td>
<td>10</td>
<td>0.34</td>
<td>0.96</td>
<td>-1.07</td>
<td>1.71</td>
<td>1.92</td>
<td>8.12</td>
<td>1.19</td>
<td>6.04</td>
<td>9.64</td>
<td>23.6</td>
</tr>
<tr>
<td>Ex 60</td>
<td>9</td>
<td>0.84</td>
<td>1.21</td>
<td>-0.99</td>
<td>3.41</td>
<td>2.42</td>
<td>8.87</td>
<td>1.68</td>
<td>6.35</td>
<td>11.2</td>
<td>27.3</td>
</tr>
<tr>
<td>All Ex</td>
<td>19</td>
<td>0.58</td>
<td>1.09</td>
<td>-1.07</td>
<td>3.41</td>
<td>2.18</td>
<td>8.47</td>
<td>1.45</td>
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<td>11.2</td>
<td>25.7</td>
</tr>
<tr>
<td>All Levels</td>
<td>30</td>
<td>0.45</td>
<td>0.94</td>
<td>-1.07</td>
<td>3.41</td>
<td>1.88</td>
<td>7.10</td>
<td>2.20</td>
<td>3.29</td>
<td>11.2</td>
<td>26.5</td>
</tr>
<tr>
<td><strong>CONv</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rest</td>
<td>8</td>
<td>-0.01</td>
<td>0.83</td>
<td>-1.75</td>
<td>0.65</td>
<td>1.66</td>
<td>4.75</td>
<td>1.61</td>
<td>3.11</td>
<td>7.98</td>
<td>35.0</td>
</tr>
<tr>
<td>Ex 25</td>
<td>9</td>
<td>0.18</td>
<td>1.63</td>
<td>-3.25</td>
<td>2.12</td>
<td>3.26</td>
<td>8.45</td>
<td>2.22</td>
<td>5.74</td>
<td>12.84</td>
<td>38.6</td>
</tr>
<tr>
<td>Ex 60</td>
<td>8</td>
<td>0.37</td>
<td>0.72</td>
<td>-0.65</td>
<td>1.70</td>
<td>1.44</td>
<td>10.8</td>
<td>3.19</td>
<td>6.02</td>
<td>16.15</td>
<td>13.3</td>
</tr>
<tr>
<td>Ex 70</td>
<td>6</td>
<td>0.67</td>
<td>0.79</td>
<td>-0.68</td>
<td>1.30</td>
<td>1.58</td>
<td>13.41</td>
<td>4.20</td>
<td>8.18</td>
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<tr>
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<td>20.64</td>
<td>21.8</td>
</tr>
<tr>
<td>All Levels</td>
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<td>0.27</td>
<td>1.07</td>
<td>-3.23</td>
<td>2.12</td>
<td>2.14</td>
<td>9.06</td>
<td>4.11</td>
<td>3.11</td>
<td>20.64</td>
<td>23.6</td>
</tr>
</tbody>
</table>

CHDv - congenital heart disease validity study; CONv - healthy controls validity study; min - minimum, max - maximum; L/min; SAR standard acetylene rebreathing; Average of Innocor™ and SAR cardiac output; Bias - difference of paired measurements; LOA - limits of agreement (2 x SD of paired difference); % Error - LOA/Average Q.
Table 13. Agreement between Cardiac Output Measures: SAR versus Innocor™

<table>
<thead>
<tr>
<th></th>
<th>CHDv</th>
<th>CONv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>r = 0.73</td>
<td>r = 0.95</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>11</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>25w</td>
<td>r = 0.73</td>
<td>r = 0.78</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.02</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td>r = 0.77</td>
<td>r = 0.98</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>70%</td>
<td>r = 0.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>.</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>All levels</td>
<td>r = 0.91</td>
<td>r = 0.97</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>30</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

SAR: standard acetylene rebreathing; CHDv: congenital heart disease validity study; CONv: healthy controls validity study.

DISCUSSION

The findings of this study indicate that the Innocor™ device is a reliable and valid device for the measurement of cardiac output in healthy children and adults and in children with congenital heart disease. It is the first known study to provide reliability and validity results for inert gas rebreathing measurements via the Innocor™ device in the pediatric age group at rest and during cycle exercise.

A noninvasive measure of cardiac output is an important addition to a cardiopulmonary assessment. Through the use of the Fick equation, \( Q = \frac{VO_2}{CaO_2 - CvO_2} \) one can derive stroke volume and peripheral oxygen extraction, allowing for a more complete understanding of the adaptation to the increasing demand of exercise, and thus of pathophysiology and mechanisms of disease.
Typically, cardiac output has been measured invasively or indirectly with the latter measures validated primarily in adults. Clarifying the reliability of a measure of cardiac output in children is important, since children typically display more variation in physiological measurements than adults, especially at rest (Godfrey, 1974a). The success of Q measurements in children beginning at 9 years in this study, (and at 8 years previously (Wiegand et al., 2010)), suggests sufficient maturity and ability of this age group and older, to be able to perform the rebreathe technique required for the Innocor™ device in a reliable manner.

To evaluate the success of an intervention, one must account for the inherent error or variability of the measurements involved. Analysis of the reliability, or the consistency of a measurement, is recommended to be performed with a series of different tests, and reported in both absolute units of measurements and a dimensionless ratio, rather than simply statistical significance alone (Critchley and Critchley, 1999).

Reliability in this study was tested in three different groups of subjects, using a test-retest design, both at rest and during exercise. Measures included the intraclass correlation coefficient (ICC: takes into account both within- and between-subject variance, Tests 1 and 2 for children and Tests1-4 for adults ), limits of agreement (LOA: twice the standard deviation of the paired differences between Tests 1 and 2, provides an absolute context for comparison) and coefficient of variation (CV: SD/mean, expressed as a percentage, has the advantage of being dimensionless and has been used widely to report on the reliability of a variety of cardiac output measurement techniques).

Reliability: Children

Children with congenital heart disease (CHDr) were matched with healthy controls (CONr) for age, size and lung function. The within session reliability of measurements of cardiac output using the Innocor™ device was assessed in these two groups by repeating the protocol a second time, following a 15-minute rest. The CHDr Q measures showed excellent reliability (all ICCs over 0.94), for rest and two levels of exercise, with the lowest limits of agreement for rest and 25watts. While the CONr measures displayed more variability than CHDr, all coefficients of variation were <10%, indicating that 68% of the differences in repeat measurements were within 10% of the mean (Atkinson and Nevill, 1998). CHDr were less variable than CONr at rest and two levels of exercise, perhaps explained by the fact that children with chronic disease may perform annual pulmonary function testing as a part of their clinical follow-up and had previous experience with rebreathing manoeuvres.
Two other groups have evaluated the Innocor™ device for the measurement of cardiac output in children, however none have reported specifically on the reliability of the technique. Wiegand et al. (2010) reported that the use of the Innocor™ device was feasible for measuring Q in children with complete congenital atrioventricular block (CCAVB) compared to healthy controls, during standard treadmill exercise at rest and two levels of exercise. Cardiac output measures were successfully determined for all participants, similar to the current study. These investigators reported that there were issues in attention span and concluded a minimum age of 8.5 years and proper technique was required.

Hauser et al. (2011) used the Innocor™ device to evaluate the atrial contribution to cardiac output in 10 pediatric patients with congenital complete atrioventricular (AV) block in two different modes of pacemaker (single-chamber pacing mode (VVIR) and dual-chamber pacing mode (DDD/VDD)), at rest, with optimized AV delay. They reported improvements of Q of up to 30% in DDD/VDD, assuming previous validation reports of adults (Agostoni et al., 2005; Sobanski et al., 2008; Peyton and Thompson, 2004; Saur et al., 2009).

Our range of coefficients of variation (CV) of 3-7% for the Innocor™ device compare favourably to reliability values of other rebreathing techniques in children, such as the day to day variability for the CO₂ rebreathe equilibrium method (7-8%) (Paterson et al., 1982), and are significantly lower than those reported for CO₂ exponential rebreathing method (Nottin et al., 2001) (16.8% at rest and 11.7% at maximal effort).

Reliability: Adults

Unlike children, the reliability of the Innocor™ device has been extensively evaluated both at rest and during exercise, in adults. In the current study the CV for ADr ranged from 2.8% at 70%HRmax to 10% at rest and reflects the variation on Day 1 of testing. These reliability results are comparable to others employing the Innocor™ in adults with heart failure (10.8%) (Agostoni et al., 2005), healthy adults at rest (8.6%) and during exercise (4.3%) (Fontana et al., 2009b), and in patients with fibrotic lung disease (6.6%) (Corte et al., 2010). They are similar to average reports for the acetylene rebreathe manoeuvre of 15% at rest and 5% during exercise (Warburton et al., 1998) and higher than those measured in 18 healthy adults at rest (Jakovljevic et al., 2008) (4.8%). It has been suggested that the practical implication of the CV is that 1.5-2 times the CV represents a real change in Q (Fontana et al., 2009b).
We also assessed the reliability of the Innocor™ device with the intraclass correlation coefficient which explains the measurement error relative to the total variance. We found that the Q measurements for adults in this study (ADr) were highly reliable (ICC between 0.84 and 0.98), similar to the CHDr and greater than CONr. Our results were stronger than those reported by one group who demonstrated repeatability ICC results of 0.64 in heart patients and 0.77 in healthy volunteers (Peyton et al., 2009) and recommended that the average of repeat samples be used for a given individual. The current results are in line with other values reported in healthy adults (0.72-0.9, rest to peak exercise) (Fontana et al., 2009b).

The third measure of reliability used to evaluate the Innocor™ was the limits of agreement (LOA, twice the SD of the difference). In this study the LOA ranged from 1.4-1.8 (L.min⁻¹) for adults. Our LOA results are similar to those of Peyton et al. (2009) who reported values for standard deviation of the difference between repeat measures of 0.85 and 1.25 L.min⁻¹ in cardiac surgery and control groups respectively, which would correspond to half our values, since we reported twice the SD of the difference. Jakovljevic et al. (2008) evaluated the agreement and reliability of cardiac output measured by three techniques including the Innocor™ device and CO₂ rebreathe (equilibrium and exponential) at rest and peak exercise, and reported small limits of agreement of repeat measures compared to ours, -0.49 to 0.79 L.min⁻¹.

Similar to previous work comparing IGR to CO₂ rebreathing methods for cardiac output determination in general (Dibski et al., 2005), and CO₂ rebreathing equilibrium method in particular (Zeidifard et al., 1972), we found a trend for variability to decrease from rest to exercise in both the CONr and ADr groups. Dibski et al. (2005) reported a similar finding (decreasing CV as exercise level increased), and postulated a higher variability in Q at rest due to pre-exercise anxiety.

Both the CONr and ADr groups completed a third exercise level (70% HRmax) that the CHDr participants were unable to complete. Given that all three groups had the same 15 minutes rest between Tests 1 and 2, this might explain the added variability at rest for CONr and ADr.

**Technical Issues**

There are several discrepancies in the reported use of the Innocor™, the first being the length of the rebreathing manoeuvres. Recirculation times for inert gas rebreathing have been documented for adults to be 15s at rest, 8.5s at high levels of exercise (Zeidifard et al., 1976;Warburton et al., 1999a),
and slightly longer in children (Zeidifard et al., 1976). Furthermore, the time required to attain equilibrium with the inert gas in this technique has been documented to be approximately 3 seconds in exercise (Fontana et al., 2009b), and stated in manufacturer guidelines to be attained within approximately 5 breaths, or 15 seconds, at rest (Innocor, 2007). Rebreathing past the point at which recirculation occurs should be avoided (Driscoll et al., 1989) as it would decrease the absorption of the soluble gas and underestimate cardiac output. Furthermore, a left-to-right shunt would compound this technical error since the recirculation time would be reduced dramatically to less than a second or so. There have been reports describing durations of rebreathing of up to or more than 30 seconds (Wiegand et al., 2010), however our experience was that equilibrium was attained within 2-3 breaths or less than 15 seconds.

The second issue involves the use of the Innocor™ with patients with lung disease. Given that the rate of disappearance of the soluble gas determines cardiac output, it has long been accepted that well ventilated lungs are required for complete mixing of gases to occur and therefore, for this technique to be valid (Zeidifard et al., 1976). The current study included one ADr with mild obstruction and one CHDv with moderate obstruction, but in both cases an acceptable equilibrium of the insoluble tracer SF₆ was confirmed prior to recirculation, and therefore did not invalidate the technique (Zeidifard et al., 1976; Saur et al., 2010). Three investigations have recently validated the Innocor™ device for use in patients with respiratory disease (Saur et al., 2009; Saur et al., 2010; Corte et al., 2010). In one case (Saur et al., 2009) the conclusions were that the measurements compared favourably against the gold standard cardiovascular magnetic resonance (CMRI) in the physiological ranges and were easy to perform, however the recommended error levels were exceeded. They also reported that 13% of those recruited were either unable to perform the manoeuvre or had incomplete mixing of the test gases and therefore the data could not be included. In another report (Corte et al., 2010), patients with a restrictive lung pattern participated, which would present less of a problem with actual mixing of gases, more so of emptying the rebreathing bag and inhaling a sufficient amount of the test gas. Saur et al. repeated their work one year later (Saur et al., 2010) including patients with both obstructive and restrictive lung diseases and reduced diffusing lung capacity (DLCO) and concluded that none of these impairments influenced the accuracy of the IGR method, based on a non significant influence of pulmonary function parameters in a regression analysis, on the mean bias of Q measurements. Caution should be exerted when considering the use of the Innocor™ in patients with respiratory limitations however, as incomplete mixing of the test gases will invalidate the inert gas rebreathing technique. Even with these publications, however, the Innocor™ has not yet been
expressly indicated for use in patients with lung disease at this time (personal communication with manufacturer).

The third discrepancy issue is the requirements for calculating shunt with the Innocor™. Effective pulmonary blood flow will equal total cardiac output in the absence of a shunt. In patients with lung disease this shunt will be characterized by a right-to-left-shunt, indicating that a portion of the blood does not participate fully in gas exchange. For this study, patients with a left-to-right, or intracardiac shunt were excluded. The Innocor™ device and software incorporate an insoluble gas, SF\textsubscript{6} which provides feedback about incomplete mixing of gases within the alveoli (Gabrielsen et al., 2002). In order to determine shunt, a valid measure of SaO\textsubscript{2} is required for calculations. A common site for the measurement of SaO\textsubscript{2} at rest is the index finger. However it is not uncommon to experience technical problems with a measurement of SaO\textsubscript{2} when using the finger site while riding a cycle ergometer, due to reduced blood flow to the periphery and excessive squeezing of the handle bars. To avoid this we used the forehead site as it offers a reliable, constant blood supply, with little chance of loss of signal (personal experience). Although there are recommended corrections for shunt, all these patients had been cleared by previous echocardiographic evaluation. Therefore the quality of the saturation reading is critical, for precise calculations of a shunt and correction of cardiac output.

Failing the availability of a direct measure of Q for the purpose of validity, the Q:VO\textsubscript{2} relationship is commonly used as an alternative, as a measure of construct validity. In this case it was used to provide a physiological context for the reliability study. Cardiac output increased linearly with increasing VO\textsubscript{2} for adults and children (Fig 2). Our regressions of Q on VO\textsubscript{2} (ADr Q=5.98VO\textsubscript{2} + 4.21; CHDr Q=6.42 VO\textsubscript{2} + 4.07; CONr Q=6.93VO\textsubscript{2} + 3.84) were similar to a previous report by Zeidifard et al. (1976) (Q=5.82 VO\textsubscript{2} + 3.04), who also reported an overlap of slope and intercept for adults and children. Our values were also similar to a combination of nine previous studies of Q measured by direct methods, reported by Rowell (1969) of Q=6.01VO\textsubscript{2} + 3.07. Zeidifard et al. (1976) reported Q:VO\textsubscript{2} for children by both the N\textsubscript{2}O and CO\textsubscript{2} rebreathing methods: QN\textsubscript{2}O = 3.62 + 5.07 VO\textsubscript{2}, r = 0.92, and QCO\textsubscript{2}= 2.63 + 6.49 VO\textsubscript{2}, r = 0.90. These values were in the expected range for healthy children (Eriksson et al., 1971; Godfrey, 1974a).

Our slopes and intercepts for Q:VO\textsubscript{2} are similar to those reported by Pianosi et al (2004) (Q=5.16 (VO\textsubscript{2}) + 4.25), and Diibski et al (2005), (similar to Figure 2) and Warburton et al (1998) Q (L·min\textsuperscript{-1}) = 5.39 (VO\textsubscript{2}) + 4.6.
In conclusion, we found good reliability in children (both healthy and with CHD) and adults for the use of the Innocor™ device at rest and during exercise.

Validity

Children who participated in the validation study were similar to those in the reliability study, however the CHDv (4 restrictive, 1 moderate obstruction) had lower lung function than the CONv. While the two groups were matched for age and size, the CHDv had significantly smaller FVC and FEV₁ % predicted values. All tracings were carefully checked for equilibrium of the inert gas, to ensure adequate mixing of the soluble gas, otherwise the data were removed.

Agreement

Barring the feasibility of a comparison of the Innocor™ device to a direct measure of cardiac output, we compared the device to a highly sensitive, accurate device, the mass spectrometer. This model of mass spectrometer is manufactured by the same company, thus it employs the same considerations for software and assumptions in calculations, albeit with a different soluble rebreathing gas (N₂O versus C₂H₂).

The AMIS mass spectrometer system has been shown to be accurate and reliable for the use of metabolic testing in adults (Narang et al., 2007) and has been used to measure Q_{eff} in children with CHD (Rosenthal et al., 1995; Rosenthal and Bush, 1997; Rosenthal and Bush, 1998; Rosenthal et al., 2009). It is a sensitive instrument, requiring dedicated service and maintenance, which limits its popular use for this purpose. The photoacoustic analyzer used in the Innocor™ was first validated with the mass spectrometer (Clemensen et al., 1994) in an attempt to replace the bulky mass spectrometer. Simultaneous measurements of mass spec and photoacoustic analyzer were performed in adults, rest and submaximal exercise and small differences between the analyzer and the mass spectrometer were reported (-0.006 ± 0.030 l/min). Coefficients of variation for repeat measurements were 4.4%, and it was recommended that it would be suitable to replace the mass spectrometer. Our method of consecutive trials and the use of children would likely explain the larger differences between repeat measurements. The foreign gas rebreathing technique (employing the mass spectrometer) has also been compared to the Direct Fick and dye-dilution methods of Q determination and has been accepted as an adequate alternative (Warburton et al., 1999a).
Bland and Altman analysis has been widely used to assess the validity of a new technique. Our findings of a small bias (mean difference) between the two methods 0.45 L/min\(^{-1}\) (CHD\(_v\)) and 0.27 (CON\(_v\)) is similar to others evaluating this device. Our overall limits of agreement (\(\pm 2SD\)) 1.88 L/min\(^{-1}\) (CHD), 2.14 (CON\(_v\)) are further broken down in Table 5, showing that the LOA are lower in exercise overall than at rest. Our standard deviations are in line with those reported by Zeidefard (1976) using the nitrous oxide technique, who reported SD of 0.7-1.0 and limits of agreement as twice the SD.

The Innocor\(^{\text{TM}}\) (Q\(_{\text{eff}}\)) has been compared to the Direct Fick Q (Q\(_{\text{FICK}}\)) by Corte et al. (2010) who measured 28 patients with lung fibrosis referred for right heart catheterization. They found good agreement between Q\(_{\text{FICK}}\) and Q\(_{\text{eff}}\), with no evidence of systematic bias. Bland Altman analysis revealed a mean difference of -0.32 and limits of agreement of -2.10 to +1.45.

Following the criteria of Critchley et al (1999) for the acceptance of a new Q technique, Table 12 demonstrates that the percentage error (LOA/average Q) is less than 30% with all data combined, therefore the Innocor\(^{\text{TM}}\) device would be considered acceptable for Q measurements in children. The higher variability at rest could have reflected higher anxiety which disappears in exercise. In summary, while the mean bias and LOA are reported in absolute units and provide a context within which to evaluate the measure, an additional measure of percentage error is important for comparison of measures from different methods. As the Q values increase from rest to exercise, one would expect a larger bias and often larger LOA, but with the larger Q, the percentage error could remain the same or even decrease.

**Limitations**

While work rates were kept constant, we did not use HR to equalize relative work performed between groups and sessions. This could have further minimized any variability in VO\(_2\) and Q at each level, and further reduced any confounding effect of actual differences in Q (Warburton et al., 1998). Nor was it feasible to measure the two techniques in series, due to the required washout period for each of the different gas mixtures.

In conclusion, the Innocor\(^{\text{TM}}\) device allows for the reliable and valid non-invasive measurement of cardiac output at rest and during exercise in healthy children and adults, and in children with congenital heart disease.
3.3.2 Pacemaker Optimization in Patients with Fontan Repair: A Pilot Study

ABSTRACT

Background: With the high success rate of Fontan surgery for univentricular anatomy, emphasis for this group has shifted from survival to long-term cardiac function. Given that Fontan patients are characterized by diastolic dysfunction, atrioventricular (AV) synchronization and the resultant atrial contribution to ventricular filling may have important effects on cardiac function. Objectives: To assess the effect of individualized AV delay on cardiac function at rest and to assess the effect of atrioventricular synchronized pacing (DDI) versus ventricular pacing (VVI) on cardiac function at rest and during exercise in Fontan patients with dual chamber pacemakers. Methods: Eight (4 male, 6 children) Fontan patients aged 18.6 ± 4.6 yrs with dual chamber pacemakers participated in this study. Patients were clinically stable at the time of the study. At rest, AV delay was sequentially increased in increments of 50 msec, from 50-300msec, and the optimal delay was determined from measures of cardiac output based on impedance cardiography (QICG). The optimal AV delay was set and cardiac output via inert gas rebreathing (QIGR) and aortic VTI (aVTI, echocardiography) were then determined, at rest, and at two levels of submaximal exercise, controlling for constant paced heart rate (25w at 125HR and 50w at 150HR). Measurements were made in each of atrioventricular synchronized pacing (DDI) and ventricular pacing (VVI) modes, in random order, on a recumbent cycle ergometer. Results: At rest, QICG (L/min) was significantly higher in the optimal (2.79±0.80) compared to the nominal (150ms) (2.29±0.96) AV interval setting (p=0.04). The optimal AV delay varied among the patients, including 50 (n=2), 100 (n=3), 150 (n=1) or 250ms (n=2). Aortic velocity time integral (aVTI) for both pulse wave and continuous wave Doppler, used as a surrogate of stroke volume, were significantly greater in DDI vs VVI mode, at sub-maximal exercise of 25w at 125HR level (p<0.04 and p<0.02 respectively). There were no significant differences found at rest or at the 50w at 150 HR level. Trends of both a lower systemic vascular resistance (SVR) in exercise compared to rest, and an association of lower SVR with greater differences in aVTI between pacing modes were found. Conclusions:
Individualized AV delay settings may be more appropriate than nominal device settings for Fontan patients with dual chamber pacemakers. A small, significant improvement in heart function observed with atrioventricular synchronized pacing in this group warrants further study with a larger sample of Fontan patients.

Abbreviations

aVTI | aortic velocity time integral
DDI | atrioventricular synchronized pacing
MAP | mean arterial blood pressure
QICG | cardiac output via impedance cardiography
QIGR | cardiac output via inert gas rebreathing
SVR | systemic vascular resistance
VVI | ventricular pacing
INTRODUCTION

Congenital heart disease repair resulting in a normal series circulation through the lungs and body can now be achieved with low mortality in most children through staged surgical repairs at young age. However, significant residual limitations frequently persist or develop during later childhood and early adulthood, whether recognized as symptomatic or not (Driscoll and Durongpistikul, 1999). The focus of pediatric and congenital cardiology has shifted to assess factors that influence long-term ability, rather than survival, but techniques to measure and compare such outcomes have not been studied in depth in this population.

Fontan surgery is used for congenital heart disease repair of univentricular hearts such as in tricuspid atresia. Fontan patients improve clinically, but are often prone to diastolic dysfunction (Vitarelli et al., 2005); therefore atrioventricular (AV) synchronization and atrial contribution to ventricular filling may be of increased importance. This is in contrast to other conditions associated with pacemaker therapy, where AV synchrony has not been consistently demonstrated to have benefit (Horenstein et al., 2003; Connolly et al., 2000).

Traditional clinical practice has been to program a nominal device AV delay setting of 150ms at implant (Medtronics default), in most but not all pacemakers. This value has been empirically derived from adult practice rather than congenital heart disease. An individualized approach to optimizing the AV setting might enhance diastolic filling time for each patient, thus enabling a greater cardiac output. This strategy has proven successful at rest, in a group of 19 adults, with implanted dual chamber pacemakers due to AV block but otherwise normal hearts (Crystal and Ovsyshcher, 1999).

In addition, it is unclear if the VVIR pacemaker setting, where ventricular pacing is dissociated from the patient’s intrinsic atrial rhythm, is sufficient to maximize cardiac function. Karpawich et al. (1991) found that in spite of an improved chronotropic response to exercise in VVIR compared to VVI pacing in six children with univentricle hearts, these benefits were negated by altered hemodynamics following Fontan repair. They reasoned that the VVIR induced tachycardia, combined with the lack of atrial contribution to ventricular filling, decreased diastolic filling time and volume. This combination decreased ventricular end-diastolic filling pressure and volume, which diminished stroke volume and myocardial coronary flow and resulted in decreased performance.

Alternatively, there are results to suggest that DDD mode, which provides AV synchrony between the atria and the ventricles, improves single ventricle hemodynamics and can help
decompensated pediatric Fontan patients (Dodge-Khatami et al., 2005). Recommendations have been made for implantation of a dual chamber pacemaker system in children after Fontan-type operations, to avoid repeat sternotomy and enhance clinical improvement in these patients (Heinemann et al., 2003). Both VVIR and DDD modes are equally safe and acceptable, however it is inconclusive as to a hemodynamic benefit of one mode over the other.

Previous studies have compared low rate pacing, VVI, to atrioventricular synchronized pacing DDD (Chabernaud et al., 1993) or low rate pacing, VVI, to rate-responsive pacing VVIR (Karpawich et al., 1991). Another group attempted to compare rate-responsive atrioventricular synchronized pacing, DDD, with rate-responsive ventricular pacing VVIR, however only two subjects had devices that could be crossed over to both of these modes (Paridon et al., 1993). While they reported no benefit of the dual chamber pacemaker they concluded that further study with DDD,R was needed.

Although retrospective studies in adults have suggested that physiologic (atrioventricular synchronized) pacing is associated with reduced morbidity and mortality (Charles, 2000), a prospective randomized Canadian study of adults (the Canadian Trial of Physiologic Pacing, CTOPP (Connolly et al., 2000)) demonstrated only a benefit of decreased atrial fibrillation.

Therefore the objectives of this study were to assess the effect of individualized AV delay on cardiac function at rest and to assess the effect of atrioventricular synchronized (DDI) versus ventricular (VVI) pacing on cardiac function at rest and during exercise in Fontan patients with dual chamber pacemakers. We hypothesized that there would be a benefit from atrioventricular synchronized pacing, in light of the impaired diastolic function but relatively preserved systolic function, in which case the contribution from atrial kick may play a greater role.

METHODS

Research Design

This was a randomized single-blind crossover pilot study of the effect of pacing mode (atrioventricular synchronized pacing versus ventricular pacing) on cardiac output. Fontan patients with a dual-chamber pacemaker were enrolled. The mode (DDI versus VVI) was randomly selected, and rate-response and AV interval (in atrioventricular synchronized pacing patients) were assessed and optimized at rest.
Participants

Study patients were recruited from the Sickkids Congenital Heart Disease population and the Toronto Congenital Cardiac Centre for Adults. Inclusion criteria were ages \( \geq 8 \) years, Fontan repair, implanted with a dual chamber pacemaker, in stable condition and able to perform pulmonary function testing and pedal a recumbent cycle ergometer.

Data Collection

Patients were randomized (and blinded) for the order of pacemaker testing mode (VVI, DDI) for the exercise testing (SAS randomization procedure). They arrived to the lab at least one hour post prandial and were measured for height (standard Stadiometer with heel plate), weight (SR Instruments, Model 555, Tonawanda, NY).

Blood Pressure, Systemic Vascular Resistance (SVR)

Blood pressure was assessed via manual oscillation (sphygmomanometer) on the right arm at rest and at the 3rd minute of each exercise level. Mean arterial pressure (\( \text{MAP} = \frac{\text{diastolic pressure} + \frac{1}{3}(\text{systolic pressure} - \text{diastolic pressure})}{1} \)) and systemic vascular resistance (\( \text{SVR} = \frac{\text{MAP}}{Q}; \text{mmHg} \cdot \text{L}^{-1} \cdot \text{min}^{-1} \)) were determined. \( Q \) for SVR was measured by the inert gas rebreathing method.

Spirometry

Spirometry measurements (Sensormedics Vmax system, SensorMedics, Yorba Linda, CA) included forced vital capacity (FVC) and forced expiratory volume in one second (FEV\(_1\)) and were performed according to standard spirometric techniques (Miller et al., 2005). Values were expressed as a percent of predicted value for height and gender based on previously developed standards (Stanojevic et al., 2008). An online calculator was used incorporating these norms and z-scores to classify spirometric tests as normal, obstruction or restriction patterns in all participants (Quanjer, 2011).
Echocardiography

The echocardiographer met with the patient, determined the best available window for echo measurement and marked the spot for future reference. The patient's chest was then prepared and stickers applied for 12-lead ECG and impedance cardiography measurement.

The aortic velocity time integral (aVTI) was measured by echocardiography from a modified apical 5 chamber view, with the larger the volume (area under the curve) indicating better ventricular systolic function and was used as a surrogate for stroke volume and cardiac output (Barold et al., 2008).

All echocardiographic images were acquired using a general Electric Vivid 7 using an M4S phased array transducer. Images were analyzed off-line on a GE EchoPac workstation. The average of three consecutive beats (whenever possible) was recorded.

Impedance Cardiography (ICG)

Four electrodes were placed according to manufacturer recommendations and the measurement added, of the distance between the base of the neck and the xiphoid process, to enhance accuracy of readings (Sorba Medical Systems, CIC-1000). Impedance cardiography estimates stroke volume non-invasively by detecting the voltage changes in transthoracic electrical impedance, which change inversely to the volume of fluid in the thorax, and has been used in the Fontan population (Weipert et al., 1997). Cardiac output was determined as the average of 2-4 readings.

AV Optimization

While in DDI mode, with the patient seated on the recumbent bike at rest, HR paced at 10 b/min above baseline, the AV interval was sequentially raised in increments of 50msec, from 50-300msec by the Pacemaker Technologist. One minute was allowed to lapse after changing the setting and prior to measurements of cardiac output via ICG. The optimal AV setting was chosen as that setting in which the highest cardiac output was observed, as measured by ICG, and was used at rest and during the exercise trials. Baseline pacemaker settings were restored at the completion of the study.
Exercise Protocol

HR and WR Selection

Prior to the study we reviewed the heart rate response to incremental cycle exercise, in a group of eligible Fontan patients, 5/6 of who were subsequently recruited for the study. Work rates of 25 and 50 watts were selected to maximize the possible data collection. Heart rates were then set at approximately 10 beats higher than previously recorded, at 125 and 150 b/min, to ensure that all patients would be paced above their intrinsic rate throughout their exercise bouts, since not all patients had complete AV block.

Cardiac function measurements were made at rest, and during the 5th minute of each of two levels, 25w/125HR, 50w/150HR, in each of the two pacemaker modes, VVI and DDI. The patient rested for 15 minutes in between the two modes.

Innocor™ Measurements

Participants were familiarized with the inert-gas rebreathing technique in the demonstration mode (room air in the bag) of the Innocor™ device (Innovision, Odense, DK). The patient began breathing room air through a mouthpiece (while wearing noseclips) attached to the flow sensor of the Innocor, with a filter placed in line. They were then switched into a 3-litre anaesthetic bag at end expiration, from which they then rebreathed a mixture of 0.5% nitrous oxide (N$_2$O, soluble inert gas), 0.1% sulphur hexafluoride (SF$_6$, insoluble tracer gas), 28% oxygen (O$_2$) in balance nitrogen (N$_2$) for 15-20 seconds. They breathed at a rate of approximately 20 breaths per minute, with a gas volume of 40% of their previously measured forced vital capacity. In this method, the rate of disappearance of the soluble inert gas is proportional to the blood flowing by the lungs, or the effective pulmonary blood flow ($Q_{\text{eff}}$). In the case where there is no shunt, $Q_{\text{eff}}$ is representative of cardiac output or $Q_{\text{tot}}$, or $Q_{\text{IGR}}$ as will be referred to in this document. The insoluble tracer gas is used to measure total systemic volume which is the combination of the lung volume at end expiration, the dead space volume of the rebreathing valve, the residual volume of the bag when empty and the volume of the rebreathing bag. The total systemic volume is used to correct the soluble gas prior to any calculations, to compensate for incomplete mixing. As well, a display of the insoluble gas during rebreathing provides evidence of adequate mixing, the absence of which will indicate a loss of gas into poorly ventilated areas of the lung (Innocor, 2007).
Oxygen consumption was measured via the Innocor™ device, based on the assumption that the slope of the disappearance of O$_2$ was proportional to the O$_2$ uptake during the rebreathe manoeuvre.

Oxygen saturation readings were measured via a reflectance probe placed on the forehead (Massimo Radical-7, Irvine, CA). The pulse rate obtained via the forehead probe was compared to the ECG heart rate, to provide a quality assurance of the forehead oxygenation signal. The paced heart rate was used to calculate stroke volume, and the saturation reading was recorded from the forehead site, if it differed from the reading on the finger probe. Q$_{ICR}$ values from the VVI and DDI modes were then compared.

Data Analysis

The primary outcome variables were cardiac output, as measured by the inert gas rebreathing (Q$_{ICG}$) and aortic velocity time integral (aVTI) (echocardiography) techniques, in each of the two pacemaker modes (VVI, DDI), at rest and during each of the two levels of exercise. For AV optimization, univariate analysis (paired t-test) was used to detect any difference between Q$_{ICG}$ at the nominal (150ms) and optimal settings, as well as between aVTI at the two modes, at each level, with Bonferroni correction applied for multiple comparisons (SAS, Vers 9.1). VO$_2$ was compared to ACSM predicted values at each WR with unpaired t-test, due to insufficient numbers for ANOVA.

Sample Size

As this was a pilot study we recruited as many eligible patients as possible from the two institutions. This allowed us to assess both the feasibility of this protocol and the sensitivity of measurements of various heart function measurements at rest and during exercise.

We hypothesized that in the highly diastolic-dependent circulation of the Fontan patient, atrioventricular synchronized pacing programming (DDI), with optimization of the AV delay, would enhance cardiac function both at rest and during exercise.
RESULTS

Participant Characteristics

Of 11 children who were identified from the pediatric database as post-operative Fontan repair with dual chamber pacemaker, 4 declined and 7 agreed to participate, however one had a broken pacemaker lead on the study date and became ineligible. Of 19 patients identified by the adult database, 3 were deceased, 4 did not respond to the study invitation, 4 had moved away, 1 was on the transplant list, 1 had recently transitioned to adult clinic and was already in the study, 1 declined participation, 1 was awaiting an ablation procedure and became ineligible, and 2 agreed to participate. Reasons for subsequent missing data were limitations of pacemaker settings below protocol target HR (n=1), difficulty performing the second level of exercise (n=2), intolerance to changes of AV setting precluding change to VVI mode (n=1), and inadequate compliance (n=1). Cardiac descriptions of the study patients are presented in Appendix 4 indicating the reasons for pacemaker implantation, and baseline characteristics in Table 14, indicating 5 patients with restrictive and one with moderate-severe obstructive pattern of spirometry.

Table 14. Baseline Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Ht (cm)</th>
<th>Wt (kg)</th>
<th>HR rest</th>
<th>FVC (%pred)</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; (%pred)</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>16.5</td>
<td>171</td>
<td>48.1</td>
<td>80</td>
<td>76</td>
<td>82</td>
<td>91&lt;sup&gt;r&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>m</td>
<td>17.7</td>
<td>177</td>
<td>60</td>
<td>98</td>
<td>78</td>
<td>76</td>
<td>82&lt;sup&gt;r&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td>16.9</td>
<td>175</td>
<td>51.3</td>
<td>83</td>
<td>65</td>
<td>73</td>
<td>95&lt;sup&gt;r&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>f</td>
<td>17.6</td>
<td>168</td>
<td>71.5</td>
<td>98</td>
<td>81</td>
<td>80</td>
<td>86&lt;sup&gt;r&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>f</td>
<td>16.5</td>
<td>172</td>
<td>55.7</td>
<td>79</td>
<td>79</td>
<td>82</td>
<td>91&lt;sup&gt;r&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>12.6</td>
<td>158</td>
<td>53.8</td>
<td>97</td>
<td>87</td>
<td>92</td>
<td>93&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>28.9</td>
<td>162</td>
<td>66.2</td>
<td>75</td>
<td>67</td>
<td>58</td>
<td>74&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>m</td>
<td>21.9</td>
<td>162</td>
<td>58.4</td>
<td>70</td>
<td>88</td>
<td>86</td>
<td>86&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>18.6</td>
<td>168.1</td>
<td>58.1</td>
<td>85.0</td>
<td>77.6</td>
<td>78.6</td>
<td>87.3</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>4.6</td>
<td>6.4</td>
<td>7.2</td>
<td>3.5</td>
<td>7.8</td>
<td>9.5</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Ht = height; Wt = weight, FVC = forced vital capacity; FEV<sub>1</sub> = forced expiratory volume in one second r = restriction, o = obstruction, n = normal, based on SpirXP interpretation software (Quanjer, 2011), using predictions for adults and children (Stanojevic et al., 2008)
**AV Optimization Results/ICG**

Individual results of AV optimization using impedance cardiography and comparison to the nominal device setting of 150ms are presented in Table 15, indicating all optimal settings were different from the nominal setting. Of the 8 pts, #3’s intrinsic rate fused with the pacemaker setting at 150 (therefore no further adjustments could be made), and #4 had a technical problem at 150 and the Q could not be determined.

Impedance cardiography-measured resting cardiac output ($Q_{ICG}$) was optimal at different AV delays, depending on the patient: 50ms (n=1), 100ms (n=3), or 250ms (n=2). $Q_{ICG}$ (mean ± SD, L/min) was significantly higher in the optimal (2.70 ± 0.84) compared to the nominal (150ms) (2.12 ± 0.93) AV interval setting, or an increase of 34% (p=0.04).

Table 15. Individual Results of AV Interval Optimization

<table>
<thead>
<tr>
<th>ID</th>
<th>Optimal AV Interval (ms)</th>
<th>Difference From Nominal Setting (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>-50</td>
</tr>
<tr>
<td>2</td>
<td>250</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>150</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>-100</td>
</tr>
<tr>
<td>5</td>
<td>250</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>-100</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>-50</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>-50</td>
</tr>
<tr>
<td>Mean</td>
<td>131.3</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>79.9</td>
<td></td>
</tr>
</tbody>
</table>

AV = atrioventricular; Nominal Device Setting = 150ms; ID # 3 fused at 150 so could not test higher, #4 technical problem - no Q at 150 ms.
**Exercise Protocol**

Five of the eight study patients tolerated the complete exercise testing protocol, two exercised at 40 instead of 50w for their second work rate, one had extreme sensitivity and intolerance to the change to the VVI pacemaker mode and six patients’ pacemakers were able to be paced at the 150HR for the second exercise level.

**Comparison of Pacemaker Mode**

Results for the comparison of aVTI, $Q_{\text{IGR}}$ and VO$_2$ between DDI and VVI modes are shown in Table 16 and Figure 8. Aortic VTI for both pulse wave and continuous wave Doppler were significantly greater in DDI vs VVI mode at 125HR ($p<0.04$ and $p<0.02$ respectively). There were no significant differences for aVTI, between the modes, at rest or at the 150HR level. There were no differences for $Q_{\text{IGR}}$, or VO$_2$ at any of the levels.

Table 16. Comparison of Pacemaker Modes (DDI vs VVI)

<table>
<thead>
<tr>
<th></th>
<th>VVI</th>
<th>DDI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>aVTI pw (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest$^a$</td>
<td>11.4 (2.7)</td>
<td>12.3 (2.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>125HR$^a$</td>
<td>12.2 (2.1)</td>
<td>13.6 (2.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>150H$^b$</td>
<td>9.9 (1.9)</td>
<td>11.0 (1.4)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>aVTI cw (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest$^a$</td>
<td>13.0 (2.2)</td>
<td>13.0 (3.0)</td>
<td>0.97</td>
</tr>
<tr>
<td>125HR$^a$</td>
<td>12.4 (2.3)</td>
<td>13.9 (3.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>150H$^b$</td>
<td>11.3 (2.5)</td>
<td>12.2 (1.7)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>$Q_{\text{IGR}}$ (l.min$^{-1}$)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest$^b$</td>
<td>3.90 (0.75)</td>
<td>4.37 (1.24)</td>
<td>0.30</td>
</tr>
<tr>
<td>125HR$^c$</td>
<td>5.18 (1.11)</td>
<td>5.64 (0.72)</td>
<td>0.20</td>
</tr>
<tr>
<td>150HR$^b$</td>
<td>5.77 (0.77)</td>
<td>5.65 (0.68)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Mean (SD); a: n=7; b: n=5; c: n=6; aVTI$^{pw}$ – aortic velocity time integral, pulse wave; aVTI$^{cw}$ – aortic velocity time integral, continuous wave; $Q_{\text{IGR}}$ = cardiac output via inert gas rebreathe. DDI: atrioventricular synchronized physiologic pacing; VVI: ventricular pacing.
Figure 8. Aortic VTI: Pacemaker Mode Comparison. Aortic velocity time integral, according to level (rest or exercise), and pacemaker mode (DDI: atrioventricular synchronized physiologic pacing; VVI: ventricular pacing).

Oxygen Consumption

The VO$_2$ values in VVI and DDI modes were compared to ACSM predicted values and are presented in Table 17. There were no significant differences in VO$_2$ between modes at any level, however VO$_2$ values for Fontan patients were significantly lower than those for healthy adults (ACSM pred) at both exercise levels (p<0.05).
Table 17. VO$_2$ (VVI and DDI modes) compared to ACSM predicted values.

<table>
<thead>
<tr>
<th></th>
<th>VVI</th>
<th>DDI</th>
<th>ACSM pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest$^a$</td>
<td>3.41 (1.61)</td>
<td>3.14 (1.03)</td>
<td>3.5 (0)</td>
</tr>
<tr>
<td>125HR$^b$</td>
<td>9.75 (1.17)$^*$</td>
<td>10.23 (2.05)$^*$</td>
<td>11.95 (0.64)</td>
</tr>
<tr>
<td>150HR$^a$</td>
<td>11.38 (1.79)$^*$</td>
<td>11.15 (2.59)$^*$</td>
<td>16.04 (1.18)</td>
</tr>
</tbody>
</table>

Mean (SD); $^a$ n= 5; $^b$ n= 6; ACSMpred: American College of Sports Medicine predicted oxygen consumption for leg ergometry (Whaley et al., 2006); $^*$ = significantly lower than ACSM predicted at that level; DDI : atrioventricular synchronized physiologic pacing; VVI: ventricular pacing. (p<0.05)

**Cardiac Output : Oxygen Consumption Relationship**

The average slopes and intercepts for the group in VVI are represented by $Q_{IGR} (l.min^{-1}) = 4.41 (VO_2) + 3.07$, and in DDI by $Q_{IGR} (l.min^{-1}) = 3.54 (VO_2) + 3.77$ (in both modes n=5, and there are a minimum of two points per subject including rest and exercise data).

**Systemic Vascular resistance**

Results for systemic vascular resistance are presented in Table 18 and Figure 9. There are trends to suggest that SVR was lower in exercise than at rest (Table 18) and that a lower SVR is associated with a greater the difference in aVTI, between the two modes (Figure 9).
Table 18. Systemic Vascular Resistance as a Function of Level and Mode

<table>
<thead>
<tr>
<th></th>
<th>VVI</th>
<th>DDI</th>
<th>p-value(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest (^a)</td>
<td>22.6 (3.7)</td>
<td>20.1 (4.5)</td>
<td>0.26</td>
</tr>
<tr>
<td>125HR (^b)</td>
<td>15.5 (1.34) (^*)</td>
<td>15.3 (1.5) (^*)</td>
<td>0.84</td>
</tr>
<tr>
<td>150HR (^b)</td>
<td>15.3 (1.5) (^*)</td>
<td>14.8 (1.5)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Mean (SD); a: n=5, b: n=4; c: comparison of modes; \(^*\) = significantly lower than rest, n=4, (p<0.05). DDI : atrioventricular synchronized physiologic pacing; VVI: ventricular pacing.

Figure 9. Aortic VTI Difference Between Pacemaker Mode as a Function of Systemic Vascular Resistance. SVR: Systemic vascular resistance; DDI: atrioventricular synchronized physiologic pacing; VVI: ventricular pacing; aVTI: aortic velocity time integral. 125: 125 HR; 150: 150 HR; There is a trend to suggest that a lower SVR is associated with a greater the difference in aVTI, between the two pacemaker modes.
DISCUSSION

The findings of this pilot study suggest that Fontan patients with dual chamber pacemakers require unique optimal AV delay settings, with a corresponding cardiac output significantly higher than the nominal setting, suggesting the benefit of individualized adjustments according to individual physiological profiling. The second purpose of this study was to identify the optimal pacing mode in this group, by measuring cardiac output at rest and during sub-maximal exercise in both atrioventricular synchronized pacing (DDI) and ventricular (VVI) pacing modes. We found modest improvements in aortic velocity time integral (aVTI), a surrogate of stroke volume, attributed to atrioventricular synchronized pacing in this pilot group, which warrants further study with a larger sample of Fontan patients. The significance of both these findings is that they could potentially result in changes in standard practice of care of patients with dual chamber pacemakers.

The Fontan heart has been described as an aged heart, and is characterized by diastolic dysfunction with a preserved left ventricular systolic function (Vitarelli et al., 2005). While the younger heart is able to take advantage of the suction effect, to aid in diastolic filling, as the heart ages it becomes stiffer, however, and relies more on the atrial kick, or atrial systole, to aid in ventricular filling in diastole (Groban, 2009). Therefore our hypothesis was that with an optimized AV delay and synchrony of the atrium and ventricle, one could harness the benefit of the atrial kick, or atrial contribution to ventricular filling.

AV Optimization

The goals of AV optimization in general are to identify the AV delay that leads to the best atrial contribution to left ventricular filling, the maximum stroke volume and the longest diastolic filling time (Barold et al., 2008). We confirmed the optimal AV interval for each patient at rest by identifying the largest cardiac output as assessed with ICG, or QICG. The large range of optimized AV intervals in the eight patients (50-250ms) would suggest a need for individualized, rather than nominal device settings. One of the reasons for the differences in AV optimization is due to the individualized placement of the leads at the time of surgery, which would in turn individualize the electrical conduction for each patient.

Impedance cardiography was employed for AV optimization due to its abilities to measure stroke volume independently (Secher et al., 1977) and to assess the instantaneous effect of pacemaker
programming changes, allowing for repeat evaluations of change in cardiac output (Ovsyshcher et al., 1993b). Previous reports indicate that changes of cardiac output of greater than 4% in DDI and more than 6% in VVI represent true hemodynamic changes within 95% confidence (Ovsyshcher et al., 1993a). ICG has been used during exercise in Fontan patients (Weipert et al., 1997) and repeatedly to track changes in cardiac output (Newman and Callister, 1999; Bogaard et al., 1997).

Both impedance cardiography (Crystal and Ovsyshcher, 1999) and aortic VTI derived from continuous-wave Doppler (Kerlan et al., 2006) have been used successfully to optimize AV delay for cardiac resynchronization therapy in adults. In a small group of older adults, these techniques were found to be well correlated (Tse et al., 2003). Unlike Tse et al., who studied 6 older adults with sick sinus syndrome, we did not find significant correlation between ICG and echo measurements for AV interval optimization (data not presented). The degree of missing data due to pacemaker limitations in several patients, coupled with the heterogeneity of the native defect leading to Fontan correction (Takken et al., 2007b) contributed to enhanced variability within our small group of patients.

The 34% improvement in cardiac output in the optimal AV setting for our Fontan patients was similar to the 30% reported by others (Ovsyshcher et al., 1993b) in pacemaker patients in supine position, and substantially higher than the 12% increase reported by Crystal et al, (1999) in patients with AV block and otherwise normal hearts. The large gain in this group of Fontan might be explained by the fact that the Fontan circulation was specifically chosen for its known diastolic function and preserved left ventricle function, and they may have had the most to gain from the optimization procedure.

Non optimized delays, or even ‘disrupted AV concordance caused by VVIR’, can lead to a group of symptoms known as pacemaker syndrome, including dizziness, shortness of breath and hypotension’ (Hauser et al., 2011). Moreover, the use of nominally selected AV delays can “significantly impair not only cardiac function but even the clinical condition of the patient” (Ovsyshcher, 1997). Thus the importance of AV optimization has been previously well established by others.

Comparison of Pacemaker Mode

We found no significant difference in $Q_{\text{INN}}$ between the two pacemaker modes at any level. The Innocor™ device employs the inert gas rebreathing method to determine $Q_{\text{eff}}$, which has yet to be
validated in Fontan. While the software corrects the soluble gas to account for any incomplete mixing of the gas in the determination of \( Q_{eff} \), there is no documentation to deal with a limitation of the technique for an intracardiac shunt, such as possible fenestration (right to left shunt) in a Fontan patient. While the creation of a fenestration may be a temporary strategy to reduce pulmonary vascular resistance in the Fontan patient, the effect of a fenestration can be retrograde flow during ventricular systole, a reduction of arterial saturation to approximately 80-85% and a reduction in \( Q \) (Hasselman et al., 2005). Thus future use of the Innocor\textsuperscript{TM} in this group should likely include a description of the presence of a fenestration or not.

Others have shown an improvement in \( Q_{INN} \) at rest in DDD versus VVIR using the same device, however they were evaluating 10 adolescents with complete heart block but otherwise excellent cardiac function (Hauser et al., 2011), unlike our group of Fontan patients with hemodynamically significant cardiac defects. They waited 20 minutes in between changes in pacemaker mode and all measurements were made at rest, while ours were made after a waiting period of one minute, which still exceeded the recommendation used by others (Jansen et al., 2006) of \( \geq 20 \) seconds to allow for hemodynamic stabilization.

The echocardiographic measurement of aortic VTI, has been used as a surrogate for stroke volume to evaluate AV optimization in severe heart failure (Barold et al., 2008), and has been measured in a broad range of age groups (Evangelista et al., 1996). We found a significant increase in aVTI in the DDI mode, at the 125HR workload, however no difference between modes at rest or at the 150HR workload. It is possible that once the stress of exercise is imposed on the heart and the time for diastolic filling has been reduced, benefit of AV synchrony may be more apparent than at rest. Our reduced data available at the 150HR level (due to pacemaker limitations) may have reduced the power to see such a change.

Early work by Karpawich et al. (1991) and later confirmed by Paridon et al. (1993) showed that an increase in heart rate alone, such as the comparison of VVI to VVIR, was insufficient to increase \( Q \), and in fact there were residual problems that contributed to reduced exercise tolerance, such as decreased venous return and diastolic dysfunction. The hypothesized benefit of the DDI mode was that the added benefit of AV synchrony would allow for more efficient atrial filling and improved contribution to ventricular filing, which would help to increase \( Q \). Larger number of subjects and diastolic measurements during exercise, will be needed to evaluate this theory further.
The benefit of maintaining AV synchrony was further highlighted in a group of Fontan patients in junctional rhythm who had a reversal of fenestration flow with restoration of synchrony through DDD pacing (Hasselman et al., 2005). DDD pacing has also been shown to improve quality of life in elderly patients with a pacemaker, in which case they reported that no patient preferred VVI over DDD (Ouali et al., 2010). Interestingly, whereas one of our eight patients was intolerant of the change to VVIR (13%), Hauser et al. reported 50% of their participants (child/adolescent) felt worse in this mode. While every effort is made to blind the participant to the treatment, in many cases it is readily apparent to the patient.

*VO₂ Quality Control*

Oxygen consumption values for a given workload for our Fontan patients were similar to predicted (American College of Sports Medicine, 2009) at rest, however lower than predicted in both pacemaker modes, and at each exercise level. This finding is similar to earlier reports of a reduced VO₂ at a given power output in children with Fontan, both submaximal and maximal exercise (Troutman et al., 1998) and is suggestive of either increased efficiency or increased anaerobic contribution. The mechanisms to explain the decreased VO₂/WL are likely a reduced SV at all levels of exercise, an abnormal linkage of ventilation to VCO₂ and an increased dependence on anaerobic metabolism in skeletal muscle (Troutman et al., 1998).

One point to note is that our patients were paced at artificially selected heart rates to ensure that they would be paced above their intrinsic rates, based on previous exercise testing of a group of Fontan patients. Whereas Troutman et al. (Troutman et al., 1998) found a decreased HR/WR, our HR was artificially fixed due to pacing, therefore the normal Fick equation would have been altered [VO₂ = (HR × SV) × (CaO₂ – C₀₂)]. This could have further led to a compensatory increase in a-DO₂ and reliance on anaerobic metabolism, either of which could be confirmed in future with the use of near infrared spectroscopy (NIRS) and lactate measurement, respectively.

*Q:VO₂ Relationship*

The lower Q:VO₂ slopes we observed have been confirmed by others for Fontan patients (Stromvall and Eriksson, 2003; Driscoll and Durongpistikul, 1999) and suggests a failure to adequately increase cardiac output to meet the metabolic demand and a compensatory increased reliance on arterial mixed venous oxygen content difference.
Systemic vascular resistance, a function of MAP and Q, is a force against which the heart must pump and is higher in Fontan patients compared to healthy controls (Goldstein et al., 2010; Senzaki et al., 2002). Clausen (1977) demonstrated that a decrease in SVR is a requisite change for oxygen consumption and therefore cardiac output to increase (Clausen, 1977). In fact, an elevated SVR has been identified, along with diastolic dysfunction and reduced VO$_2$max (Takken et al., 2007a), as limitations that are characteristic of Fontan patients in exercise.

In this study SVR was similar between pacemaker modes; however there was a trend of a lower SVR in exercise compared to rest, as one would expect. Further investigation of the data revealed a trend of an increasing aVTI difference between DDI and VVI, with exercise, suggesting that the benefits of the DDI over VVI may be seen with increasing reductions of SVR. In fact Szabo et al. (2005) described the contractility-afterload mismatch, which reduces mechanical efficiency after the Fontan operation. This highlights the important relationship between preload (which is altered due to the unique series arrangement of the systemic and pulmonary vascular beds and causes resistance to venous return (Senzaki et al., 2002)), afterload and contractility. They and others (Sundareswaran et al., 2006) have concluded that strategies to reduce afterload may be critical to maximizing the functional aspects of these patients during exercise. This reinforces earlier work by Clausen et al. (1977), illustrating the requirement of a reduction in SVR to increase VO$_2$ and Q. Simply increasing heart rate such as in the change from VVI to VVIR, without an increase in myocardial efficiency, may further compromise this inherent Fontan-specific cardiac function (Paridon et al., 1993). Lastly, simply increasing venous return, such as through supine exercise (Goldstein et al., 2010) would not entirely solve the Fontan reduced cardiac output, without correcting the inherent diastolic dysfunction.

Larger numbers of patients and more precise measurements may be needed to more definitively answer the question of whether physiologic pacing is able to offer a strategy to maximize stroke volume and functional capacity in this group.

**Future Considerations**

This is a useful pilot study that has demonstrated the feasibility and measurement challenges in performing this research in a single institution and has demonstrated the need for a multi centre trial. Notwithstanding the limitations of this study, the goal was to provide pilot data to determine exclusion
criteria for future studies, to discuss the challenges of these techniques and to inform the future sample size necessary to document differences in pacemaker mode. Given the demonstrated individualized optimization needs, it would be interesting to correlate location of surgical lead placement with AV optimization requirements to understand the association between the two.

As cardiac imaging techniques improve and measures of diastolic function in univentricle hearts become more feasible, especially during exercise, this will allow for a more detailed evaluation of the potential benefit of physiological pacing for the Fontan patient.

Limitations of the Study

The small sample size and heterogeneity of Fontan patients limit us to descriptive statistics. These patients have an extensive background of surgeries and procedures and were reluctant to have their pacemaker settings changed for any longer than necessary. They agreed to a short period of testing only with direct supervision from the pacemaker technologist they trusted. Some data were lost due to the limitations of the pacemaker settings, since not all patients had complete AV block and fusion occurred, which limited the data availability.

There were no exclusion criteria for fenestration, which leads to desaturation in exercise, since this intracardiac shunt allows blood from right atrium to flow directly into the left heart, without passing through the lungs. While most fenestrations are used as a temporary strategy after surgery and are subsequently closed, if it were not, the Innocor™ would not be valid for this type of anatomy.

Due to limitations of the ICG technology during exercise, we used the optimal AV interval determined at rest for the entire protocol. The ideal would have been to re-optimize under exercise conditions however this was not feasible. In addition, at the heart rates that we were evaluating (>100 beats per minute), fusion of the E and A waves occurred, thus impeding our ability to measure diastolic function during exercise.

CONCLUSIONS

While teleological evidence exists for its selection, there has been resistance to uniformly implant dual chamber pacemakers in all Fontan patients requiring pacing, due to its greater cost and added potential complications of pneumothorax, hematoma formation, atrial lead dislodgement, or infection (Horenstein et al., 2003).
The results of this study would suggest that individualized AV delay settings may be more appropriate than nominal device settings for Fontan patients with dual chamber pacemakers. A small, significant improvement in heart function observed with atrioventricular synchronized pacing in this group warrants further study with a larger sample of Fontan patients.
Chapter 4: Discussion

Wherever possible the goal is to keep children moving, to enhance their quality of life and to avoid the progression of inactivity in childhood to the development of adult onset illnesses and further inactivity. To equip the child who has a health impairment or disease with the ability to be active requires an understanding of where their limitations lie. While cardiopulmonary exercise testing traditionally concentrates on the VO$_2$max measure as the best indicator of functional capacity, a measure of cardiac output adds valuable information to the profile of a patient and thus can be used to elucidate pathophysiological mechanisms of disease. The measurement of Q provides a valuable addition to the evaluation of patients with a cardiac or respiratory disease and lays the groundwork for building an intervention to provide further options for improvement in future care.

Therefore, the first objective of the research outlined in this dissertation was to provide a comprehensive, systematic evaluation of several non-invasive respiratory gas methods available to determine Q in children. Due to the unethical nature of invasive Q determination in this age group, every attempt was made to find and/or refine valid, feasible, reliable alternatives to invasive procedures. While each non-invasive method has its inherent set of assumptions, the benefit of the non-invasiveness must be weighed against the loss of accuracy, both of which are related to the validity of the Q measurement. Feasibility includes cost of equipment, technical expertise required to perform the measurement, on the parts of both the technician and child, and the breadth of the technique to accommodate various types of populations.

There are a variety of methods available for evaluating cardiac output non-invasively and a different set of limitations, assumptions and degree of difficulty of use associated with each. While the respiratory gas techniques (resident and non-resident gas) have long been popular in evaluating adults, questions have been posed as to the appropriate adaptations for use required in children and in disease. Impedance cardiography presents an alternative technique with attractive features such as ease of use and ability to make many repeat measurements in a short period of time, given the proper equipment and assumptions used for a given patient population. Lastly, the use of echocardiography for cardiac output measurement is a growing field, both for resting and exercise conditions.
In this dissertation research these methods were tested in healthy children and adults, and in children with cardiac and respiratory disease, refinements developed and recommendations made where possible, to improve the accuracy for their use in children. Among these investigations were: Methods Development Project 1: Q corrections for CO$_2$ rebreathe, Methods Development Project 2: PaCO$_2$ estimation, Manuscript 1: Validity and Reliability of the Innocor$^\text{TM}$ device (inert gas rebreathing), and Manuscript 2: Pacemaker Optimization (included use of inert gas rebreathing, ICG and echocardiography techniques).

As defined by Portney et al. (2000) while reliability is a prerequisite of validity, strong reliability does not suggest strong validity. As well, assessing validity is an ongoing process, incorporating multiple evaluations of the method or instrument in question. Therefore several criteria used to assess the usefulness of a non-invasive Q measurement technique were, how well it compared to the original direct measures of Q data in children, or alternatively selected gold standard (criterion-related validity), it’s ability to replace a previous less practical method (concurrent validity) the relationship of Q:VO$_2$ compared to previous reports (construct validity) and its test-retest reliability.

**SUMMARY OF TECHNIQUES EVALUATED**

*Resident Gas: CO$_2$ Rebreath (Equilibrium)*

The advantages of this technique are that the equipment required is fairly standard for many laboratories that perform respiratory gas testing, and, while technician expertise is essential, more automated systems have now been developed recently to make this technique easier to perform. Given the findings of Lands et al. (1996) the CO$_2$ rebreathe method can be used in patients with significant lung disease, since the poorly ventilated areas will contain CO$_2$ at or near the P$v$CO$_2$, so that they will not substantially affect the estimate of P$v$CO$_2$.

This dissertation research has shown evidence to avoid using only one of collision broadening, downstream and end tidal correction factors in determining Q via this method in children (Methods Development Project 1). While Godfrey et al. (1971) did not report a need for the downstream (Dm) correction, they tested only healthy children. However since the magnitude of the Dm correction depends on P$v$CO$_2$ and the latter increases in lung disease, the need for this correction increases with
disease and is therefore recommended in CF patients. In addition this dissertation research has provided evidence to support the use of a disease specific correction for PaCO₂ in children with CF (Methods Development Project 2).

The CO₂ rebreathe (equilibrium) technique continues to be used intermittently for a variety of populations including pediatric patients with CF (Pianosi, 2008), premenopausal obese women (Carroll et al., 2007), patients with sleep apnea with no evidence of heart failure (Alonso-Fernandez et al., 2006), peripheral atherosclerotic disease (Hodges et al., 2008) and post menopausal women (Sun et al., 2001), with a high level of expertise required.

*Resident Gas: CO₂ Rebreathe (Exponential)*

The biggest advantage of this method is the use of lower concentrations of CO₂ (4-5%), compared to the 11-15% required for the equilibrium method, which may give rise to feelings of lightheadedness during exercise. Since it does not require steady state conditions, this method is well suited for repeat determinations during progressive exercise (Trachsel et al., 2006). Discussion remains, however, over the appropriate correction for pH changes above the anaerobic threshold, therefore the validity of this method performed non-invasively at maximal exercise is not uniformly accepted (Sun et al., 2001), though still employed (Hodges et al., 2008; Trachsel et al., 2006). This dissertation research did not support the hypothesis that a monoexponential curve derived from data fitted to a quadratic function would improve the derivation of derive PvCO₂ in the CO₂ exponential technique (Methods Development Project 3).

*Non-Resident Gas: Acetylene or Nitrous Oxide Rebreathing*

This method measures effective pulmonary blood flow, has been used to measure Q at maximal levels of exercise in athletes, requires a mass spectrometer and is used primarily in athletes and research applications (Warburton et al., 1999a). In some laboratories this technique is being supplanted by the Innocor™ device which utilizes the inert gas rebreathe (N₂O), and is being used with cardiac and respiratory patient populations, at rest and during progressive up to maximal exercise. The device has offered a portable, lower maintenance alternative than the mass spectrometer based system and is being used regularly to monitor the clinical status of heart failure patients.
Given that the Innocor™ device employs a non-soluble tracer gas to correct for incomplete mixing, it provides a degree of quality control and is able to correct for shunt, and therefore give a more accurate measure of cardiac output than the C₂H₂ method alone.

As in all non-resident gas techniques, the lungs must be able to ventilate and mix the soluble gas well, to have confidence the disappearance of the soluble gas is proportional to and representative of the effective pulmonary blood flow. This technique would be recommended for cardiac patients, so long as they do not have an obstructive pattern in their lung function, which would delay and possibly impede equilibration of the non soluble tracer gas, used as a quality control measure. This technique requires a period of time to washout the soluble gas (approximately 5 minutes at rest) for repeat determinations at rest and is therefore practiced in a demonstration mode utilizing room air to learn the technique. Control of one’s breathing during intense exercise is difficult as the drive to breathe is strong and ventilatory rates are very high. Therefore any rebreathing method may be limited to a degree by the participant’s technique, at peak exercise.

In the case of a system that calculates shunt, such as the Innocor™, a reliable and valid measure of SaO₂ is essential as this variable is incorporated in the calculations. Generally, it is difficult to obtain a valid measure from a finger probe during exercise, due to reduced blood flow to the area as a result of squeezing a handle bar, or possible reduction in peripheral blood flow. The forehead site and use of the reflectance probe is a stable, reliable source for this measurement. The system has not yet been validated for patients with intracardiac or left-right shunt.

It has been suggested that at rest, one gets an increase in Q during the rebreathing, due to changes in intrathoracic pressures with the breathing maneuver (Triebwasser et al., 1977). This would present a potential problem with for the non-resident techniques at rest, where values of effective pulmonary blood flow would rise instantly with an increase in flow. This would not have an effect in the CO₂ rebreathing technique until after recirculation, however, by which time all measurements would have been completed. Nor should it affect the non resident technique during exercise, due to the already increased rate of ventilation. More recently Damgaard et al. (2005) reported that the inert gas rebreathing maneuver should be performed following a tidal expiration, with a bag volume of approximately 1.5-2.5 L, and that variations of 15-30 breaths/minute would not alter the outcome of the measurement.
All respiratory gas techniques require the full cooperation of the participant to follow instructions for proper technique. A minimum age of eight years old has been required to provide acceptable results for this method (Wiegand et al., 2010). The level of skill required of the child is similar for both resident and non-resident gas rebreathing techniques, and the sources of variability decrease as the level of ventilation increases, moving from rest to increasing levels of exercise.

**Impedance Cardiography**

Advantages of instantaneous results and the ability to make consecutive measurements of Q with little hesitation make this technique attractive for use in a clinical setting, for example for procedures such as pacemaker AV optimization (Ovsyshcher et al., 1993b; Ovsyshcher et al., 1993a). Impedance cardiography has been described as unsuitable for accuracy but acceptable for reporting directional change (Bogaard et al., 1997; Kemps et al., 2008). However others report improved equipment and software development to deal with motion artifact, and successful use of this technique in children with CF during exercise (Pianosi and Garros, 1996; Pianosi, 2004). The recommendation is that ICG is equipment specific and needs to be validated for the individual patient population to be studied.

**Echocardiography**

Rowland et al. have published extensively on the use of echocardiography to measure cardiac output in healthy children during exercise and concluded recently that the utility of this technique is suggested by the consistency of reported findings (Rowland, 2008). However, given the fact that Doppler echocardiography assumes the aortic valve and ascending aorta have a normal orientation, size and shape, this method may have limitations in patients with congenital heart disease, in whom these structures may have differences in orientation, and variations in laminar flow exist (Rowland and Obert, 2002).

Table 9 provides a comparison of various methods of cardiac output measurement in children, including the requirements for each method, assumptions upon which the method is based and limitations for each. In general, high operator expertise is required in all but the ICG method, and the respiratory gas techniques are differentiated by requirement for well ventilated lungs (non resident gas) or not (resident gas).
Critchley et al. (1999) have recommended a number of criteria for evaluation of the acceptability of a technique to measure cardiac output: comparison to direct measure of cardiac output (criterion validity), whether the Q:VO\textsubscript{2} relationship has been evaluated (construct validity), and reliability: percentage error of <30\%, CV, coefficient of variation (assuming that 1.5 – 2 times the CV reflects a \textit{real} change in Q (Fontana et al., 2009b)) and ICC (measurement error relative to total variance, assuming > 0.6 is substantial reliability (Landis and Koch, 1977)). Table 20 provides examples of validity and reliability of non invasive measurements of Q in children, with the limited availability of this type of data in children. While the ICC would be the reliability variable of choice, few early reports made use of this measure, therefore the CV is primarily reported. Lacking a safe, feasible direct validation of cardiac output in children, the use of the Q:VO\textsubscript{2} relationship to confirm a new measure has clearly been the most common strategy.
Table 19. Review of Non Invasive Methods of Cardiac Output Measurement

<table>
<thead>
<tr>
<th>Method of Q Determination</th>
<th>Requirements</th>
<th>Assumptions</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resident Gas: CO₂ rebreathe - equilibrium</td>
<td>Rapid response CO₂ analyzer, steady state, high level of operator expertise</td>
<td>Equilibration of rebreathed CO₂ with PaCO₂</td>
<td>Rest: less accurate due to small a-VO₂</td>
</tr>
<tr>
<td>Resident Gas: CO₂ rebreathe - exponential</td>
<td>Rapid response CO₂ analyzer</td>
<td></td>
<td>Debate remains as to best method to make corrections for pH above anaerobic threshold</td>
</tr>
<tr>
<td>Non resident gas: Inert gas rebreathing (N₂O)</td>
<td>Mass spectrometer or Innocor™ device</td>
<td>Equilibration of inert gas with lungs</td>
<td>Requires well ventilated lungs</td>
</tr>
<tr>
<td>Non resident gas: Inert gas rebreathing (C₂H₂)</td>
<td>Mass spectrometer, expensive device, high level of maintenance and expertise</td>
<td>Equilibration of inert gas with lungs</td>
<td>Requires well ventilated lungs</td>
</tr>
<tr>
<td>Impedance Cardiography</td>
<td>ICG device</td>
<td>Q=cross sectional area of aorta x HR</td>
<td>Shape of thoracic cavity, movement artefact</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Echocardiography machine, high level of expertise of technician</td>
<td>Aortic valve and ascending aorta have normal orientation, size and shape</td>
<td>Systolic and diastolic function, especially with the unique anatomies of congenital heart disease.</td>
</tr>
</tbody>
</table>
Table 20. Validity and Reliability of Non-Invasive Q measurements in Children

<table>
<thead>
<tr>
<th>Method</th>
<th>Validity</th>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>Population</td>
<td>Q:VO₂</td>
</tr>
<tr>
<td>Resident Gas: CO₂ rebreathe (equilibrium)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Godfrey 1971</td>
<td>n=117; 6-16 yr</td>
<td>5.7 (VO₂) + 0.22</td>
</tr>
<tr>
<td>Zeidifard 1972</td>
<td>12-30 yr</td>
<td>5.82 (VO₂) + 3.04</td>
</tr>
<tr>
<td>Zeidifard 1976</td>
<td>n=10 7-16 yr</td>
<td>6.49 (VO₂) + 2.6</td>
</tr>
<tr>
<td>Paterson 1982</td>
<td>n=47 10-14 yr boys</td>
<td></td>
</tr>
<tr>
<td>Resident Gas: CO₂ rebreathe (exponential)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bar-Or 1971</td>
<td>n=56; 10-13 yr</td>
<td>5.7 (VO₂)</td>
</tr>
<tr>
<td>Jacob 1997</td>
<td>n=23 7-14 yrs</td>
<td>5.8 (VO₂) +1.42 + 0.06(wt)</td>
</tr>
<tr>
<td>Nottin 2001</td>
<td>n=14 prepub children</td>
<td>16.8 rest; 11.7 max ex</td>
</tr>
<tr>
<td>Non resident gas: Inert gas rebreathing (N₂O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeidifard 1976</td>
<td>n=10; 7-16 yr</td>
<td>5.07 (VO₂) + 3.6</td>
</tr>
<tr>
<td>Study</td>
<td>Subjects</td>
<td>Data (VO₂) + Error</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Impedance cardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pianosi 1996</td>
<td>n=30 healthy children</td>
<td>4.6 + 3.8</td>
</tr>
<tr>
<td>Pianosi 1996</td>
<td>CF</td>
<td></td>
</tr>
<tr>
<td>Pianosi 2004</td>
<td>n=115 healthy 7-19 years</td>
<td>5.16 + 4.25</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rowland 2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nottin 2001</td>
<td>n=14 prepub children</td>
<td>7.5 rest; 5.2 max ex</td>
</tr>
</tbody>
</table>

80% of Q<sub>ICG</sub> values were within ± 20% of the Q<sub>RB</sub> result.

Accurate tracking of Q<sub>ICG</sub>
The second major objective of this dissertation was to provide an exercise science perspective for understanding pediatric cardiac output measurement. Since exercise allows us the opportunity to view the integration of the body systems under stress, an added measure of heart function allows the relative contributions of the cardiovascular and respiratory systems and their compensatory adjustments in disease to become apparent, both during submaximal and maximal exercise. Several different populations were used as models for this dissertation research, to further our understanding of Q methodology: healthy children and adults, children with CF, and children with Fontan repair, as an example of congenital heart disease.

A number of overarching themes have emerged throughout this research, providing a context within which to apply our findings of the physiology related to cardiac output. For example, Lindstedt et al. (1988) offered the view of the respiratory system as comprised of a cascade of ‘resisters’, such that a change in one area of the system would influence another area, contrasting to other theories of a rate limiting step for VO$_2$. An understanding of the Fick equation then enables us to appreciate the reciprocal relationship between VO$_2$ and a-DO$_2$. In a patient population such as the Fontan group where the Q for a given VO$_2$ is low (Stromvall and Eriksson, 2003), an increased oxygen extraction at the periphery would enable the patient some degree of compensation for their limited heart function. We acknowledge that there are limits to this compensation, however.

Another important theme is that of the heart as receptor and reactor to venous return, in contrast to the more popular emphasis placed on the forceful pumping action of the heart. In the case of the Fontan patient, in whom there is a single functional ventricle, the body must compensate for the limited pumping capacity in order to maintain cardiac output. According to this theory, the emphasis is shifted to the periphery and the effect of arteriolar dilatation, which facilitates blood flow to exercising muscle to accommodate the increasing demand. On the other hand, it was reported that a group of Fontan patients were able to maintain their blood pressure, by an increase in their total peripheral resistance (Stromvall and Eriksson, 2003). While according to Rowland et al. (2008) in the healthy individual, cardiac responses are governed by the quantity of systemic venous return, which are then matched by increases in heart rate to maintain a constant ventricular filling volume, the cardiac patient may not be able to augment HR as much as necessary, and may thus be unable to maintain Q. Finally, evidence from Rowell et al. (2002) supports this emphasis of the periphery in detailing the importance of the combination of the skeletal and respiratory pumps which greatly add to the venous return.
Keeping in mind that the determinants of cardiac output are preload, afterload and myocardial contractility, one cannot assess Q in isolation. In fact the Pacemaker Optimization study offered an interesting application of this idea. First, we confirmed a trend of a decrease in systemic vascular resistance moving from rest to exercise. Second, we found a significant improvement in aortic VTI (an echocardiographic surrogate of cardiac output) in DDI versus VVI mode of pacing, and a trend showing that the lower the SVR, the greater was the benefit of the DDI pacing. This might suggest that, in the face of a decreased afterload (decreased SVR), the heart was able to take advantage of the enhancements to diastole offered to it (by synchronizing the AV interval) by maximizing passive filling and atrial kick and ultimately improving cardiac output (aVTI). Such is an example of an integrated approach to understanding cardiac output within a physiological framework.

If we assume potential similarities of alterations in preload, afterload and contractility between the child with Fontan repair and the child with heart failure, another example of an integrated approach is the compensatory mechanisms utilized by the body to restore homeostasis, in the face of chronic heart failure (CHF). As outlined by Cheitan et al. (1993) in Figure 10 below, a reduced cardiac output stimulates the sympathetic nervous and renin-angiotensin systems, which attempt to alleviate the problem of a reduced cardiac output in the acute phase.
Figure 10. Pathophysiology of heart failure. Decreased cardiac output leads to changes mediated by the renal compensatory and sympathetic nervous systems. Raised venous pressure results in peripheral and pulmonary edema and hepatic and visceral congestion. (Cheitlin et al., 1993)

Over time, however, they will result in structural changes in the heart and skeletal muscle which will compromise their ability to function. For example, the elevated plasma catecholamines commonly reported in CHF due to chronic sympathetic stimulation are correlated with early mortality (Goodman, 1995).

Elevated sympathetic activity, as measured by serial heart rate variability assessments over time, has been reported in 13 Fontan patients who had undergone total cavopulmonary connection, compared to matched controls (Rydberg et al., 2005). Alternatively, a reduced parasympathetic activity has been reported in Fontan patients, which would create a relatively greater sympathetic activity (Ohuchi, 2005). Similarly, Ohuchi et al. (2007) found an increased chemosensitivity associated with sympathetic activation, which had a significant impact on accelerated rest and exercise ventilation in some Fontan patients.
Whether due to physical deconditioning (Chati et al., 1996) or the additional effects of central hemodynamics and medical treatment (Schaufelberger et al., 1997), it is accepted that CHF is characterized by skeletal muscle alterations that impair exercise tolerance. In the earlier efforts to understand exercise intolerance characterized by patients with CHF it was assumed that the main bottleneck was a cardiovascular limitation. Upon restoring Q pharmacologically, however these patients still had symptoms of dyspnea and a high rating of perceived exertion (RPE) with exercise. Subsequently it was accepted that as the body moved beyond its ability to compensate for the symptoms of CHF, a remodeling occurs within the cardiac and skeletal muscles.

A muscle hypothesis has been proposed in CHF as presented by Clark et al. (1996), displayed in Figure 11.

![Figure 11. Muscle Hypothesis in Heart Failure (Clark et al., 1996)](image)

In a chronic state of CHF one could have an overstimulated sympathetic nervous system (placing more stress on a left ventricle that is already compromised) and augmented sympathetic vasoconstriction, when blood supply to the exercising muscle is already insufficient. The consequences of a reduced blood flow to skeletal muscle would be acidosis and would lead to muscle dysfunction if not alleviated. Poor exercise tolerance has been documented in Fontan (Driscoll and Durongpistikul, 1999;Harrison et al., 1995) and it is possible that this negative spiral of compensatory adjustments is evident in the long term-follow up of this population. In addition, poor blood flow to working muscle
in Fontan has been documented (Inai et al., 2004), as has elevated levels of norepinephrine and their relation to increased hypercapnic chemosensitivity in this group (Ohuchi et al., 2007). An exercise training program, under careful supervision may be recommended to positively influence the factors limiting exercise capacity in Fontan (Takken et al., 2007a), including the abnormal muscle function reported in this group (Brassard et al., 2006). Regular exercise reduces sympathetic overactivity in CHF and improves morbidity and mortality in that population, and perhaps some of these same benefits could accrue to the Fontan patient.

In keeping with the integrated systems approach to exercise physiology and understanding disease, it is imperative to view the respiratory and cardiovascular systems as interdependent. It is not surprising therefore to learn of the prevalence of respiratory disease in cardiac patients and vice versa. In the severe lung disease stage of cystic fibrosis, for example, the patient may develop pulmonary hypertension, right sided heart failure, and high end diastolic pressures. The Fontan patient, on the other hand, experiences multiple open thoracic surgeries over a number of years, leading to a restrictive pattern of lung function. What implications does this have for the measurement of cardiac output? These factors may influence the choice of Q measurement methodology for different patient populations.

The specific disease populations were selected as models to develop our understanding of methodology, to evaluate how far we could stretch the limits of the Q methodology. For example, our abilities to employ ICG in Fontan and the respiratory gas rebreathing in CF have allowed us to delineate the limits for the techniques.

Once measurement techniques are clarified and refined, their use to evaluate patients with cardiac and respiratory dysfunction allows us to take advantage of the addition of a measure of cardiac output to further our understanding of the pathophysiology of their disease. This information may contribute to the management and treatment of the child, to help equip them with the ability to remain physically active. Patients with congenital heart disease were chosen as they represented a population in which we expected cardiac output to be altered due to the nature of their disease. Patients with cystic fibrosis were also selected as they represented an example of pediatric lung disease, and thus presented a challenge to non-invasive methods that rely on gas exchange that may be disrupted as a result of their lung disease.
Since completing this research one is able to have a better understanding of integrated aerobic function and have the ability to evaluate cardiac function in the presence of respiratory and cardiac dysfunction in children. The limitations and strengths of measurement of non invasive cardiac output via respiratory gas methods have been delineated and recommendations made for their use.
Chapter 5: Limitations

This dissertation research involved highly technical measurements requiring precise equipment and excellent technical support. A mass spectrometer system, for example, requires ongoing, highly specialized maintenance and expertise both in imaging and interpretation of data. The system used in this research was shared between two groups and as a result had to be moved periodically, which is not ideal for the optimal functioning of this equipment.

Echocardiography is also a highly specialized measurement technique, requiring highly trained expertise. Using echocardiography techniques with the Fontan population presented a challenge, due to the single ventricle anatomy and heterogeneous native diagnoses of the group. This limited our original goal of measuring diastolic function at rest and during exercise in the Fontan group as they were not feasible. While the unforeseen technical challenges limited results of cardiac function in the Fontan group, the work still met the global objective to refine non-invasive cardiac output techniques in children.

Upon review of the databases at both SickKids and Toronto General Hospital, the available number of Fontan patients with dual chamber pacemakers was small and thus we were able to recruit a total of eight patients. Given the heterogeneity of their anatomy and degree of missing data, we were limited to discussing trends in this pilot group.

To ideally investigate the differential effects of atrioventricular sequential (DDI) versus ventricular (VVI) pacing in the Fontan group, we would have had them perform a maximal exercise test in each of the two modes, separated by a month in either of the pacemaker modes, in addition to obtaining a measure of quality of life. These patients were not comfortable with leaving the hospital with their pacemaker settings changed; therefore we were restricted to two submaximal tests on one day, to evaluate the two different pacemaker modes.

We optimized the AV delay at rest and this setting was used both at rest and during exercise as it was not feasible with the ICG device we used, to optimize the AV delay during exercise. On the other hand however, this design would simulate the clinical experience of a patient being optimized at rest in clinic and being sent home with that AV delay setting, which would remain for all activities.
The decision to include patients with CF in research involves a delicate balance of selecting periods of time when their health is in a stable state. This is generally easier in younger patients with CF, as the likelihood of chest exacerbations is less. Thus time allowed for data collection in this group may need to be longer to account for this fact.
Chapter 6: Future Directions

The non invasive measurement of cardiac output in children has evolved over the last 40-50 years, from manual techniques, involving simplistic basic measurements with basic assumptions of physiology, to increasingly complex devices requiring highly specialized expertise, such as the cardiac MRI (CMRI) which has rapidly become a ‘non invasive gold standard’.

Clearly the goal is to develop techniques which are less invasive and more accurate than their predecessor. The challenge for those who work with pediatric populations, however, is to keep up with the rapid advance in technology, without sacrificing adequate validation in children. Most equipment is aimed at measurement in adults, since they represent the bulk of the market for equipment manufacturers.

The resident gas techniques have perhaps been available the longest and thus have had the longest opportunity of development. Commercially prepared systems are now available which have succeeded at automating several of the necessary steps in CO₂ rebreathing, such as the required changes in volume and concentrations of gas used in the rebreathing bag, however the operator must independently develop the background knowledge of the various correction factors (end tidal CO₂, downstream and collision broadening) in order to not to be lulled into ‘black box technology’.

The non resident gas technique has recently been significantly advanced with the availability of the Innocor™ device, which has been validated against direct, invasive measures of cardiac output in adults, and against non invasive methods in children. The long accepted limitation of the inert gas technique to be useful only in well ventilated lungs has recently been challenged by several groups. Further validation work with direct measures of Q is warranted, to carefully outline the limitations of this technique (and therefore of the device) in adult and pediatric patients with lung disease. The basic premise of the disappearance of the soluble gas being proportional to the effective pulmonary blood flow can only be accepted with a measure of quality control, in the form of an insoluble tracer gas, to confirm adequate mixing of the gas in the lungs. Failing that, the results will not be valid. Future groups that would benefit from this measurement technique would be patients with chronic heart failure, those on immunosuppressant medication to evaluate secondary effects on myocardial function, cardiomyopathy and to establish a minimal heart function threshold for cardiac transplant.
The work of this dissertation included preliminary reliability and validation of the Innocor™ device in a small number of children. This needs to be followed up in a larger group, similar to the ICG (Pianosi, 2004), echocardiography (Rowland and Obert, 2002) and inert gas rebreathing via C₂H₂ (Rosenthal and Bush, 1998) reference values that have been published.

Given the ease of use and speed of data acquisition of ICG, further validation is warranted of this method against acceptable standards such as Direct Fick, in children undergoing cardiac catheterization. As well, motion artifact appears to be device specific and users will have to research the purchase of their device carefully to ensure that it is capable of handling the continuous movement of exercising conditions.

Echocardiography is a technique that is evolving rapidly. As recently reviewed by Dragulescu et al. (2010) an area that remains a challenge is imaging systolic and diastolic function in children with heart disease, especially those with aortic or mitral valve regurgitation. New techniques of tissue Doppler, deformation imaging and three-dimentional imaging will have great application in advancing this field. Challenging applications such as congenital heart disease and obesity will need to be developed for this technique, while stabilizing the chest wall during exercise will help to advance these measurements.

Assessments outside the laboratory, in the field, are becoming increasingly possible with portable and wireless technology. Measurement of the cardiac output to oxygen consumption relationship, evaluated accurately in the lab, can be then inferred from portable metabolic monitoring devices during activities of daily living. This allows us to assess quality of life in children who are living longer due to improved surgical techniques, but with residual limitations.

A long standing quest for a non invasive method to determine stroke volume recruitment during exercise is closer to being achieved than ever before, whether with improvements in ICG, echocardiography or inert gas rebreathing techniques. The importance of this measure cannot be understated as it provides valuable quantitative and qualitative information on the strategy employed by the individual to meet the increasing demands of exercise. If the objective is to keep children moving, understanding how those with chronic disease cope with the limitations imposed upon them by their disease process will enable clinicians to improve their treatment strategy.
Appendices

Appendix 1. Abstract: Calculation of Cardiac Output via CO$_2$ Rebreath in Children

Calculation of Cardiac Output via CO$_2$ Rebreath in Children
Research Institute, Hospital for Sick Children, University of Toronto.

Objective: To determine the effect of ‘correction factors’ on the calculation of cardiac output (Q) using the CO$_2$ rebreathe technique, in healthy controls (CON) and patients with cystic fibrosis (CF) 9-18 yrs. Methods: Q was measured in CON (n=104) and MILD (n=51) and moderate/severe (MOD/SEV, n=23) CF. Q was calculated with corrections for collision broadening (cb) to account for sampling CO$_2$ in a background of high O$_2$ concentration, downstream (dm), and Pet-aCO$_2$ difference (j), (Qcbdmj), and compared to Godfrey ’71 (Q$_G$, healthy children). Results: Differences in slopes and intercepts (Q$_G$ – Qcbdmj) for CON, MILD, MOD/SEV were –0.08, -0.5, 0.6 and 0.58, 1.83, 1.33 respectively. ANCOVA of the Q vs VO$_2$ relationship at 50% WRmax revealed that Q$_G$ was significantly different than Qcbdmj in both MILD and MOD/SEV (p<0.001), but not in CON. Conclusion: For CON, the correction factors cancelled out and the Q$_G$ (where PaCO$_2$ was derived from assumed normal dead space) agreed with Qcbdmj (calculated from PetCO$_2$). In disease, Q$_G$ overestimated Q and the correction factors no longer negated each other. Caution should be exercised if using one of the cb, dm or j correction factors on their own, as each exerts a profound effect on Q values.
Appendix 2. Abstract: Non-invasive Estimation of PaCO₂ in Children with Cystic Fibrosis

Non-invasive Estimation of PaCO₂ in Children with Cystic Fibrosis
Research Institute, Hospital for Sick Children. Graduate Dept. Exercise Science, University of Toronto.

Rationale: Prediction equations for arterial CO₂ (PaCO₂) have previously been derived in small numbers of either healthy adult males (Jones ’79) or healthy children (Pianosi ’96). Objective: To develop a prediction equation for PaCO₂ from end-tidal CO₂ (PetCO₂) for use in children with cystic fibrosis (CF) 8-19 yrs. Methods: Arterialized capillary blood was collected from the fingertip for the determination of PaCO₂ref, followed by the measurement of PetCO₂, during steady state exercise at 50% of a predetermined WRmax (n=51, FEV₁ 28-123%pred). A new equation to predict PaCO₂new was derived via multiple regression analysis in approximately half of the Ss (randomly split according to odd/even study date), then verified in the remaining group. Results: The best model to predict PaCO₂ was PaCO₂new = 0.792 (PetCO₂) – 0.065 (FEV₁%pred) + 15.23 (SEY = 2.96 R² = 0.66, p<0.001). The overall mean difference between PaCO₂new and PaCO₂ref was –1.52 mmHg, SEM 0.75 (95% CI –3.07, 0.042). Conclusions: Non-invasive estimation of PaCO₂ in children with CF can be performed with similar accuracy to that accomplished in healthy children. This prediction equation will facilitate non-invasive estimation of cardiac output in young patients with CF.
Suitability of the Innocor™ Device for the Measurement of Cardiac Output

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We evaluated the reproducibility of the Innocor™ device (non-resident, nitrous oxide rebreathe technique) for the measurement of cardiac output (Q) at rest and during exercise in nine healthy adults (females=5; age 27.3 ±4.0; BMI 24.4 ±3.6; FVC, FEV₁ >100% pred). Q measurements were made at rest, during the fourth minute of cycling at 25 watts, and at workrates that elicited 60 and 70% of predicted HRmax. Reproducibility of the Innocor™ was evaluated over a 7-day period and was determined using the intra-class correlation coefficient (ICC₁,₁), which incorporated both the within-day and between-day sources of variation. Mean values of Q at rest, 25w, 60 and 70% pred HRmax over the four testing sessions were (±SEM) 5.9 (±0.3), 9.4 (±0.2), 12.4 (±0.1) and 13.8 (±0.2) l/min respectively. Regression analysis revealed mean slopes for Q:VO₂ (±SEM) of 5.9 (±0.9), 6.1 (±1.0), 6.3 (±1.0) and 6.5 (±0.8) for tests 1-4 respectively. Reproducibility of the Innocor™ for Q was greatest and similar during the two higher levels of exercise (ICC₁,₁ = 0.98, 95% CI 0.94,0.99), somewhat lower at rest (ICC₁,₁ = 0.88, 95% CI 0.72, 0.97) and 25w (ICC₁,₁ = 0.86, 95% CI 0.66, 0.96). We conclude that the Innocor™ device allows for the reproducible, non-invasive, measurement of Q in healthy adults at rest and during exercise.
## Appendix 4. Cardiac Description of Study Patients

<table>
<thead>
<tr>
<th>Pt</th>
<th>Anatomical Diagnosis</th>
<th>Repair Operation</th>
<th>Indication for Pacing</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PA IVS</td>
<td>Thmboexcl RV p/o Fontan</td>
<td>p/o HB</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Levocardia, Situs Solitus, UniLV</td>
<td>p/o Fontan</td>
<td>p/o SSS</td>
<td>Carvedilol, coumadin, enalapril, amiodarone</td>
</tr>
<tr>
<td>3</td>
<td>UniLV subAs</td>
<td>p/o Fontan</td>
<td>p/o HB</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>TGA UniV subAs</td>
<td>p/o Fontan</td>
<td>p/o HB</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>5</td>
<td>DILV TGA PS</td>
<td>p/o lateral tunnel Fontan</td>
<td>Tachy</td>
<td>Digoxin</td>
</tr>
<tr>
<td>6</td>
<td>MS AS CoA hypopl LV</td>
<td>p/o Norwood I/Fontan</td>
<td>p/o HB</td>
<td>Altase, digoxin</td>
</tr>
<tr>
<td>7</td>
<td>Complete AV septal defect DORV Hypoplastic RV SS with levocardia</td>
<td>Classical Glenn Shunt, Modified (L) BT shunt, Surgical creation of (R) subclavian artery to subclavian vein fistula, Fontan operation, Pulmonary artery banding</td>
<td>A Flutter, bradycadia Torsades</td>
<td>Amiodarone, Lasix, Ramipril, Coumadin, K-dur, Birth control pill</td>
</tr>
<tr>
<td>8</td>
<td>DORV DIRV Severe sub valve and pulmonary valve stenosis</td>
<td>Mod (R) BT anastomosis and Blalock-Hanlon atrial septectomy, Subaortic myectomy and anastomosis of LA to PA to complete Fontan procedure</td>
<td>AV Block</td>
<td>Ramipril</td>
</tr>
</tbody>
</table>

**BT shunt** – Blalock-Taussig shunt; **DILV TGA PS**: Double Inlet Left Ventricle, Pulmonary Stenosis; **DORV DIRV** – Double outlet/inlet right ventricle; **SS situs solitus MS AS CoA hypopl LV**: Mitral Stenosis, Aortic Stenosis, Coarctation of the aorta, Hypoplastic left ventricle; **PA IVS**: Pulmonary atresia, intact ventricular septum; p/o HB: post operative heart block; **TGA UniV subAs**: Transposition of the great arteries; Thmboexcl RV p/o Fontan: Thromboexclusion of the right ventricle, post op Fontan; **UniLV subAs**: Univentricular connection, Sub Aortic Stenosis;
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