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RESEARCH PROJECT:
CCAVB, EXERCISE TESTING & CARDIAC OUTPUT MEASUREMENT

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THESIS/ LITERATURE REVIEW

Cardiac Output measurements during Cardiopulmonary Exercise Testing in Children with Congenital Complete Atrioventricular Block

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Abstract

Congenital Complete Atrioventricular Block (CCAVB) is a rare disease with an estimated incidence of 1 in 15.000 to 20.000 live births. To obtain objective information about the physical capacity of these CCAVB patients, cardiopulmonary exercise tests (CPET) are done. During CPET different parameters are measured using the respiratory gas exchange analysis. CPET is also combined with cardiac output measurement techniques such as, indirect Fick method, electrical bioimpedance and pulse contour analysis. But also new versions of these techniques have been produced. These cardiac output measurement techniques all have their advantages and disadvantages as shown in studies that used these techniques. Therefore, this thesis will review the use of these techniques by making use of electronic databases. The combination of these techniques with CCAVB will also be elucidated and their shortcomings will be discussed. In conclusion, the indirect Fick method and the pulse contour analyses are considered to be the best candidates for cardiac output measurements in pediatric CCAVB patients.
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Introduction

Cardiopulmonary exercise testing (CPET) in pediatric patients with congenital heart disease provides objective information about their exercise capacity [1]. This thesis will focus on the use of cardiac output measurement during CPET in children with congenital complete atrioventricular block (CCAVB). Cardiac function measurement during CPET will be discussed and three noninvasive techniques to measure or calculate the cardiac output (CO) will be reviewed, namely the indirect Fick method, electrical bioimpedance and the arterial pulse contour analysis. A few other techniques that were developed after these will also be discussed.

Congenital Complete Atrioventricular Block

Congenital complete atrioventricular block (CCAVB) is a potentially life threatening disease and is defined as congenital if it is diagnosed *in utero*, at birth or within the neonatal period (0-27 day after birth) [2, 3]. It is estimated that 1 in 15.000 – 20.000 live births may have CCAVB [4, 5]. The mortality rate depends mostly on the type of complications within the first year and is greatest in patients with associated structural cardiac defects [6]. The estimated mortality in children and infants can range from 4 to 40% depending if CCAVB is isolated or accompanied by structural heart disease (Table 1) [5, 6]. The prognosis for patients diagnosed in the neonatal period is better than that of patients that were diagnosed prenatally [6], but morbidity (70%) and mortality (30%) still remains high [4].

Population	Estimated mortality rate (%)
Children with isolated CCAVB	6-8
Infants with isolated CCAVB	4-16
Infants with associated structural heart disease	29-40
Children with associated structural heart disease	10

Table 1: Mortality rates associated with congenital complete atrioventricular block (CCAVB) [5-7]

Etiology & Diagnosis

25-30 percent of the CCAVB cases are caused by structural heart malformations. The remaining cases, about 70-75%, are caused by an autoimmune reaction in a normal heart [4, 5, 8]. Autoimmune-mediated CCAVB correlates strongly with maternal connective tissue disorders (CTDs) especially those involving the Ro/SS-A and/or La/SS-B antibodies. These antibodies have been detected in 98% of CCAVB cases [3, 5]. In the fetal heart these antibodies may have at least three effects; first, they may induce myocarditis; second, they may be arrhythmogenic; and third, they may interfere with apoptosis [2]. The combined effect of the antibodies can lead to three pathologic processes. The first is an interruption of communication between the atrial musculature and the more distal part of the conduction system. Secondly, is a discontinuity of the atrioventricular bundle. Lastly, are pathologic changes within an already aberrant conduction system [6, 9].

Diagnoses of CCAVB can be done *in utero* by the use of echocardiography or at birth by using electrocardiography (ECG) [5, 7].

Treatment

If CCAVB is detected *in utero*, medication can be used to prevent the progression. The medication should pass through the placenta without being metabolized. Examples for such medication are the corticosteroids dexamethasone and betamethasone. These corticosteroids can remain active in the fetal circulation where they can suppress fetal inflammation and decrease cardiac injury [10, 11]. Additionally, in fetuses with a low heart rate of

50-55 bpm or with reduced cardiac contractility sympathicomimetics (i.e. salbutamol) are used to increase the heart rate [4, 11].

After birth most patients need a pacemaker. About 60% of children with CCAVB will undergo pacemaker implantation before they are 20 years old [4]. Table 2 summarizes indications for a pacemaker implantation. In 2002 Breur *et al*. did a retrospective study on 149 patients that were diagnosed with isolated CCAVB in 1972 until 2000 [12]. Their medical records were examined and the patients were divided into two groups, patients with and without PM implantation. The study concluded that most patients with PM therapy develop cardiomegaly or decreases in the normal heart size. Even though pacing has short- and long term risks it still remains one of the safest and most common interventions used for these patients [12].

Indications for pacemaker implantation in children with CCAVB
Bradycardia
Associated congenital heart disease
Exercise intolerance
Pauses > 3 seconds while awake or 5 sec while sleeping
Wide QRS complex
Ventricular ectopy (also with exercise)
Dilatation of the left ventricle
Ventricular arrhythmias
Mitral regurgitation
Cardiac arrest
Syncope

Table 2: Indications for pacemaker implantation in children with CCAVB. [5, 12, 13]

Cardiopulmonary exercise testing

Exercise testing is commonly used to assess the functional capacity of an individual. If exercise testing is combined with direct measurement of the respiratory gas exchange, we call this cardiopulmonary exercise testing (CPET) [14]. Children with congenital heart disease, such as CCAVB, may have impairment in their physical ability [15]. Thus by assessing their exercise capacity and physiological responses (see Figure 1), objective information can be provided about the functional status of the heart, lungs and peripheral muscles (Figure 2) [1, 16]. CPET can also provide objective information about the effect of an intervention such as a pacemaker implantation, therefore the best management decisions can be made for the improvement of their quality of life [15, 17].

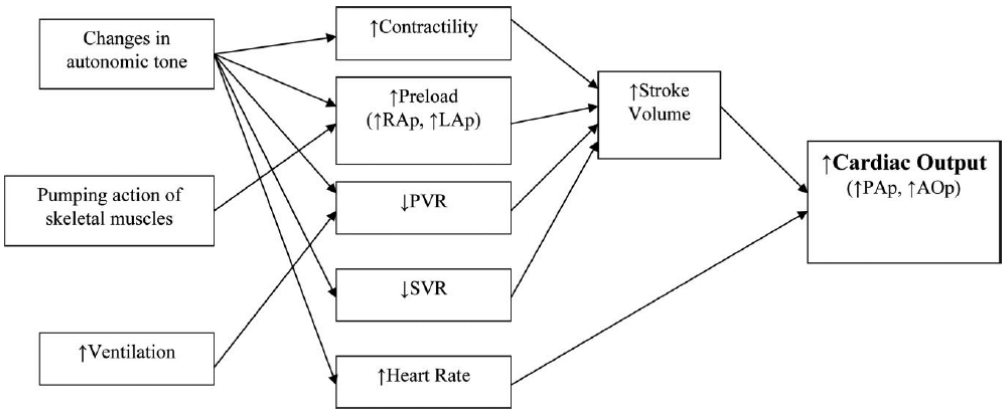

Figure 1: Physiological changes during exercise. Right arterial pressure (RAp), Left arterial pressure (LAp), pulmonary vascular resistance (PVR), Systemic vascular resistance (SVR), Pulmonary artery pressure (PAp) and aortic pressure (AOp) [18].

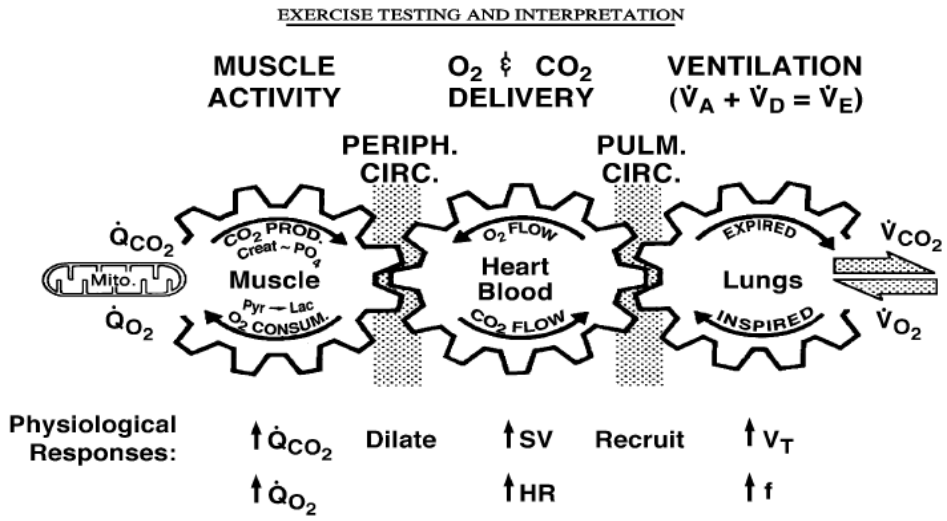

Figure 2: The three organ systems that play a key role in exercise testing and their physiologic responses to exercise testing. HR = heart rate, f = breathing frequency, QCO_2 = muscle carbon dioxide production, QO_2 muscle oxygen uptake, SV = stroke volume, VA = alveolar ventilation, VCO_2 = carbon dioxide excretion of the lungs, VD = physiologic dead space, VE = minute ventilation, VO_2 = oxygen uptake by the lungs and VT = tidal volume [16].

CPET is mostly done on a cycle (Figure 3) or treadmill ergometer. Both ergometers can be used on children depending on their height. The treadmill can be used for a wide range of patients. The measured peak oxygen uptake (VO_{2peak}) on a treadmill is 5 to 10% higher than on a cycle ergometer [1]. The higher VO_{2peak} is due to the recruitment of more muscles. Another difference is that on the treadmill the workload is dependent on the body weight rather than the machine set resistance. With the cycle ergometer, because smaller cycles are not available, patient must be over 125 cm otherwise they may not be able to reach the pedals. The workload on a cycle ergometer can be precisely determined for a patient. On a cycle ergometer the upper body is more stable making ECG and blood pressure measurement more reliable [1].

During CPET different parameters are measured by using additional measurement techniques such as the ECG (cardiac function measurement) and expiratory gas analysis [18]. During this analysis the patient breathes room air through a mouthpiece and the expiratory air are continuously sampled. From the sampled air, volume, oxygen (O_2) and carbon dioxide (CO_2) concentration is calculated. From these measurements breath-by-breath analysis of oxygen uptake (VO_2), carbon dioxide production (VCO_2) and minute ventilation (V_E) can be performed. These parameters can be used to derive clinically useful information about the patient [9].

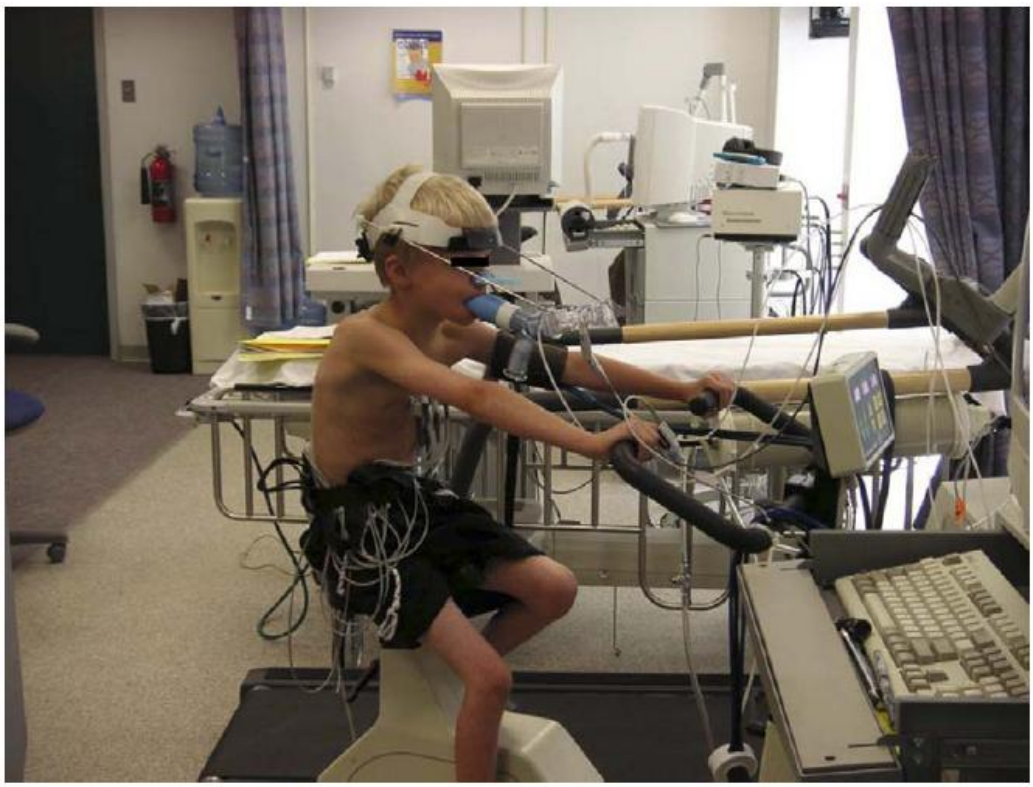

Figure 3: Example of an cardiopulmonary exercise test [16].

The maximum oxygen uptake (VO_{2max}), i.e the highest rate at which an individual can utilize oxygen during exercise, is the clinically most important CPET parameter [19]. Theoretically, this is the value where the oxygen uptake has reached a plateau but this is not always the case during exercise testing. Rowland and Cunningham studied 15 healthy children between the ages of 7 and 10 who underwent treadmill exercise testing and

concluded that most children do not reach a plateau in their VO_{2max} [20]. Therefore instead of using the VO_{2max}, the rate of oxygen uptake at peak exercise (VO_{2peak}) is used [17, 19].

VO_{2peak} can also be used to calculate the cardiac output by using the Fick principle. The Fick principle states that the total uptake or release of a substance by an organ is the product of the blood flow through that organ and the arteriovenous concentration difference of the substance [21, 22]. If we translate ´substance´ into oxygen then the Fick principle states that the oxygen uptake in the lungs is the product of cardiac output and the difference in oxygen concentration in the arterial and venous blood in the lungs [21]. Using the Fick principle we get the following equation:

$$VO_2 = CO \times (C_aO_2 - C_vO_2) \quad (1)$$

in which VO_2 is oxygen uptake, CO is cardiac output, C_aO_2 is the oxygen content in the arterial blood and C_vO_2 is the mixed venous oxygen content [22-25]. By rewriting this equation we can easily calculate the cardiac output (CO):

$$CO = VO_2 / (C_aO_2 - C_vO_2) \quad (2)$$

The above mentioned equation (2) can also be rewritten for carbon dioxide:

$$CO = VCO_2 / (C_vCO_2 - C_aCO_2) \quad (3)$$

in which VCO_2 is the carbon dioxide production, C_vCO_2 is the mixed venous carbon dioxide content and C_aCO_2 is the arterial carbon dioxide content [23, 25]. This equation is mostly used during cardiopulmonary exercise testing. For this type of measurement, called the direct Fick method (abbreviated: direct Fick), a pulmonary artery catheter is needed for the sampling of the venous blood. The direct Fick is very invasive and is very inconvenient for the analysis of the CO during exercise testing especially in children [23]. Thus less invasive techniques are used to measure the cardiac output in children when doing CPET.

Cardiac Output measurements

As stated earlier, the cardiovascular system links the lungs with various other organs where the oxygen consumption and carbon dioxide production takes place (Figure 2). During CPET or any other exercise effort the maximum capacity is reached when the cardiovascular system cannot increase the amount of blood that is being transported to the exercising muscles [23]. Therefore methods to calculate the cardiac output are essential in combination with CPET to understand the effect of a disease upon exercise capacity. Cardiac output is the volume of blood pumped by the heart per minute [21]. The CO can be calculated by using the following formula:

$$CO = HR \times SV \quad (4)$$

The SV from the ventricle is determined by preload, contractility and afterload [26]. By calculating the CO the whole body perfusion, oxygen delivery and ventricular function can be estimated [21]. The cardiac output can be related to body surface area: this is called cardiac index ($L/min/m^2$). This cardiac index can be used to compare values between individuals and with estimated normal values [26]. Different techniques with different levels of invasiveness can be used to measure the cardiac output (Table 3). However, not all these techniques are applicable in children. Some techniques that are mentioned in literature that can be used on children are the Doppler method [23, 26], indirect Fick method [23, 26], electrical bioimpedance [23, 26], bioreactance [26, 27], pulse contour method [26] and inert-gas (acetylene) rebreathing [23]. Not all of these techniques can be used during CPET.

According to Driscoll *et al*. the indirect Fick, inert-gas rebreathing, electrical bioimpedance and the Doppler method can be used during CPET in children [23].

Wiegand *et al*. used inert gas rebreathing during CPET in pediatric patients with ASD [28] and CCAVB [29]. The study on CCAVB patients indicated that inert gas rebreathing is a cost effective and time effective method to determine the patients exercise capacity and for optimizing the pacemaker settings [29].

Another method that was recently used in literature is the pulse contour method in a study by Veijalainen *et al*. during exercise testing in 36 patients' with an age from 6 to 8 years old. The study was done to analyze the reproducibility of the pulse contour method by estimating the arterial stiffness index, reflection index and finger skin temperature that reflects the peripheral circulatory functions [30]. Results indicated that the pulse contour method had better reproducibility after CPET than at rest [30].

The bioreactance method was used during CPET in adults only, e.g in the Myers *et al*. and Elliot *et al*. study [31, 32]. Myers *et al.* studied 23 patients with a mean age of 67 ± 10 with chronic heart failure and 12 patients with a mean age of 51 ± 11 that were considered to be normal/ healthy. These patients underwent CPET and the cardiac output was measured using the bioreactance technique. The estimated CO was compared to results from previous studies done with the direct Fick method. The measured CO correlated with the estimated VO_2 at rest and during exercise and these had a linear association (Figure 4). The estimated CO also correlated with the direct Fick method that was used in both studies. Therefore, the result indicated that bioreactance was a non-invasive CO measurement technique that has validity to be used with chronic heart failure patients to measure their cardiac output [32].

Name (manufacturer)	Technology	Invasiveness	Equipment	Reliability in children	Remarks
PiCCO™ (Pulsion, Munich, Germany)	TPTD + APCCO	+++	Special AC + CVC	+++	Multiple hemodynamic parameters, continuous, gold standard in children
LidCO™ (LidCO, London, UK)	TPLD + APCCO	++	AC + CVC or PVC	+++	Continuous, requires injection of lithium, not for children <40 kg
Dye densitogram 2001 analyzer (Nihon Kohden, Tokyo, Japan)	PDD	+/-	PVC Finger/nose clip	?	Noninvasive, intermittent, no validation in children
COstatus™ (Transonic, NY, USA)	TPUD	+++	AC + CVC	?	Intermittent, no validation in children
FloTrac/Vigileo™ (Edwards Lifesciences, CA, USA)	APCCO	+	AC	?	Continuous, calibration not possible, no validation in children
MostCare® (PRAM method) (Vytech, Padova, Italy)	APCCO	+	AC	+/-	Continuous, calibration not possible
Cardio QP™ (Deltex, Chichester, UK)	Esophageal Doppler	+/-	Esopagus probe	+/-	No intravascular catheters needed Difficult in small children
USCOM (Uscom, Sydney, Australia)	Transcutaneous Doppler	-	External Doppler probe	+/-	Noninvasive, intermittent, operator-dependent
NICO® 2 (Respironics, Paris, France)	CO_2 Fick rebreathing	+/-	Endotracheal tube	?	Noninvasive, only in intubated patients with tidal volume >300 ml
Aesculon® (Osypka medical, Berlin, Germany)	Electrical impedance cardiometry	-	Surface electrodes	+/-	Noninvasive, continuous
NICOM® (Cheetah Medical, Tel Aviv, Israel)	Bioreactance	-	Surface electrodes	?	Noninvasive, continuous
Nexfin™ (BMEYE, Amsterdam, The Netherlands)	APCCO	-	Finger cuff	?	Noninvasive, also measures continuous blood pressure, no calibration incorporated, not for small children

+ and - symbols represent the degree of invasiveness or reliability (e.g., +++: invasive or reliable; -: not invasive or unreliable).
AC: Arterial catheter; APCCO: Arterial pressure based continuous cardiac output; CVC: Central venous catheter; PDD: Pulse dye densitrometry; PRAM: Pressure recording analytical method; PVC: Peripheral venous catheter; TPLD: Transpulmonary lithium dilution; TPTD: Transpulmonary thermodilution; TPUD: Transpulmonary ultrasound dilution.

Table 3: Cardiac output measurement techniques that can be used in children [26].

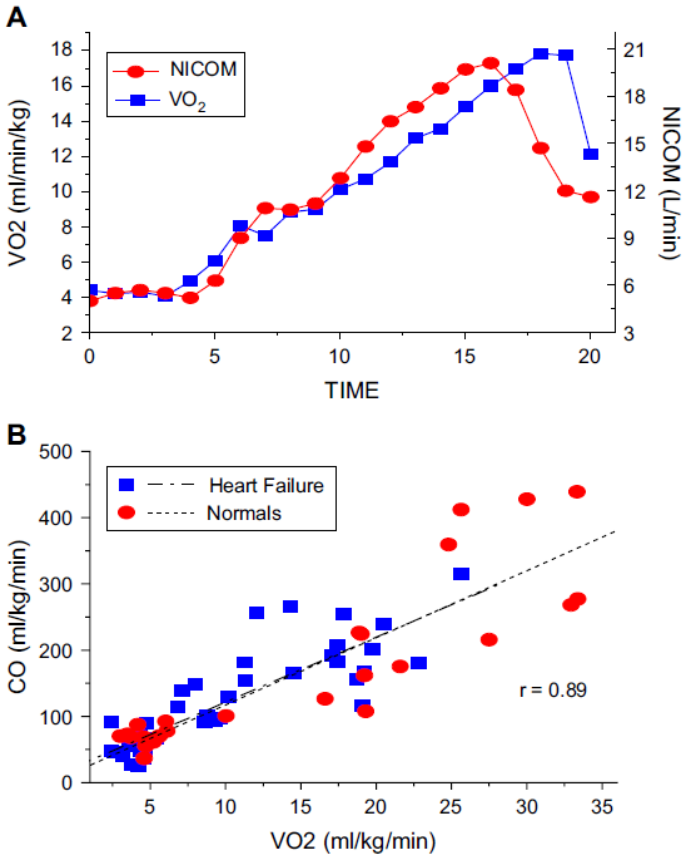

Figure 4: Oxygen uptake (VO_2) and Cardiac output (CO) measurements in patients with chronic heart failure. (A) Mean values for VO_2 during exercise in patients with chronic heart failure. (B) Relation between CO and VO_2 at rest and during peak exercise in healthy and chronic heart failure patients. NICOM = Bioreactance device [32].

Elliot *et al*. analyzed the efficacy of the bioreactance method by evaluating 14 healthy, trained individuals with a mean age of 34 years. These individuals underwent maximal exercise testing. The correlation between bioreactance, VO_2 and inertgas rebreathing (this will be further elaborated in the subheading for indirect Fick method) during exercise testing was estimated. The results indicated that the bioreactance technique had a strong correlation with the VO_2 measurements and that it gave lower values for the CO then the inert gas rebreathing technique (Figures 5, 6 & 7). Elliot *et al*. concluded by saying that more work needs to be done on this method before it is used in exercise testing [31].

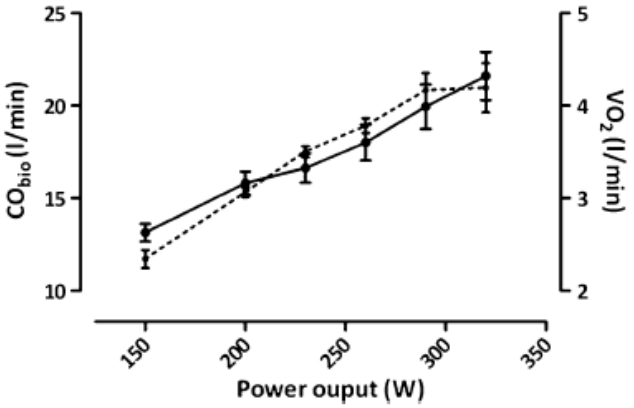

Figure 5: Relationship between power output, VO_2 and CO (n = 14). Dashed line is the VO_2 and continuous line is for the CO [31].

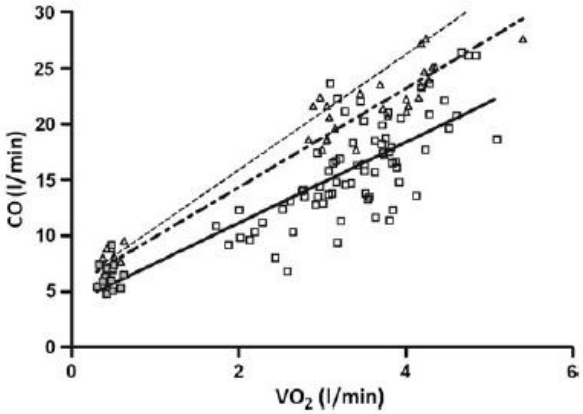

Figure 6: Relationship between CO and VO_2. Filled squares = CO using the bioreactance technique at rest. Open squares = CO using the bioreactance technique during exercise. Filled triagles = CO using the inert gas rev=breathing technique at rest. Filled triangles = CO using the inert gas rebreathing technique during exercise. Regression lines = continuous (bioreactance), dashed dotted (inert gas rebreathing) and dashed line (relashion ship reported by a study by Stringer *et al.* (1997) [31].

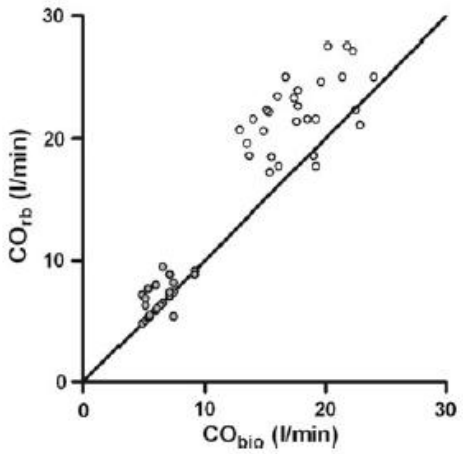

Figure 7: Scatter plot of the Co measurements by bioreactance and the inert gas rebreathing technique. Filled circles are at rest and open circles are during exercise [31].

Ballestero *et al*. published the only study that used bioreactance in pediatric patients [27]. Bioreactance was used in ten children with an age of 1-144 months, admitted at pediatric intensive care units that did not have any hemodynamic disturbances. The results of this study were not compared to other methods because it was not ethically justified to use an invasive reference CO measurement technique on these patients. Ballestero *et al.* concluded that the software and electrodes of the bioreactance method are not suitable for the evaluation of the cardiac index, thus also the CO, in children weighing less than 20 kilograms due to the fact that two patients weighing 10 kilograms could not participate in the study because the autocalibration could not be performed [27]. No literature is found for this method being used in exercise testing with children.

Table 3 summarizes the different CO measurement techniques that are available. Some of these techniques can be used in children and others can only be used for adults. Therefore, a few of these noninvasive methods to measure cardiac output will be further elaborated on especially those that can be used during exercise testing such as the indirect Fick method, inert gas rebreathing, electrical bioimpedance and the pulse contour method. The pros and cons will be evaluated by analyzing different articles that studied these techniques. The literature search was done by using different electronic databases such as, PubMed, Google Scolar and Scopus. Studies that used the different CO measurement techniques were included plus studies that used CCAVB patients and children but also adults.

Indirect Fick method

A derivative of the Fick principle is the indirect Fick in which all measurements are obtained in the gas phase [23]. This method measures the elimination of CO_2 or inert gases instead of uptake therefore, it is also known as the rebreathing indirect Fick method [25] or CO_2 rebreathing technique [33]. This technique uses rebreathing techniques to estimate the arterial and mixed venous carbon dioxide from measurements of end-tidal carbon dioxide (the level of CO_2 in the air exhaled from the body) [25]. For this technique formula (3) is rewritten and becomes the following:

$$CO = \Delta VCO_2 / (S \times \Delta EtCO_2) \quad (5)$$

In which ΔVCO_2 is the change in VCO_2 and $\Delta EtCO_2$ is the end tidal CO_2 between normal breathing and CO_2 rebreathing [33].

The indirect Fick method is also compared with the Inert gas rebreathing method. These techniques such are mostly used as references for other measurement techniques.

The inert gas rebreathing method is a gas exchange technique that determines the cardiac output and other hemodynamic parameters. This is done by using a system that consists of a three-way respiratory valve with a mouthpiece and a rebreathing bag that is connected to an infrared photoacoustic gas analyser (Figure 8) [34]. Two inert gases namely, one blood soluble and one blood insoluble respectively, nitrous oxide (N_2O) and sulfur hexafluoride (SF_6) is used. This mixture of gases including oxygen is respired into the above mentioned closed system that is sampled continuously by photoacoustic analyzers over a period of 4 to 5 breaths. The cardiac output is estimated by measuring the rate of disappearance of the blood soluble gas with the effective pulmonary blood flow. In the absence of intrapulmonary shunt this is than translated into cardiac output [35].

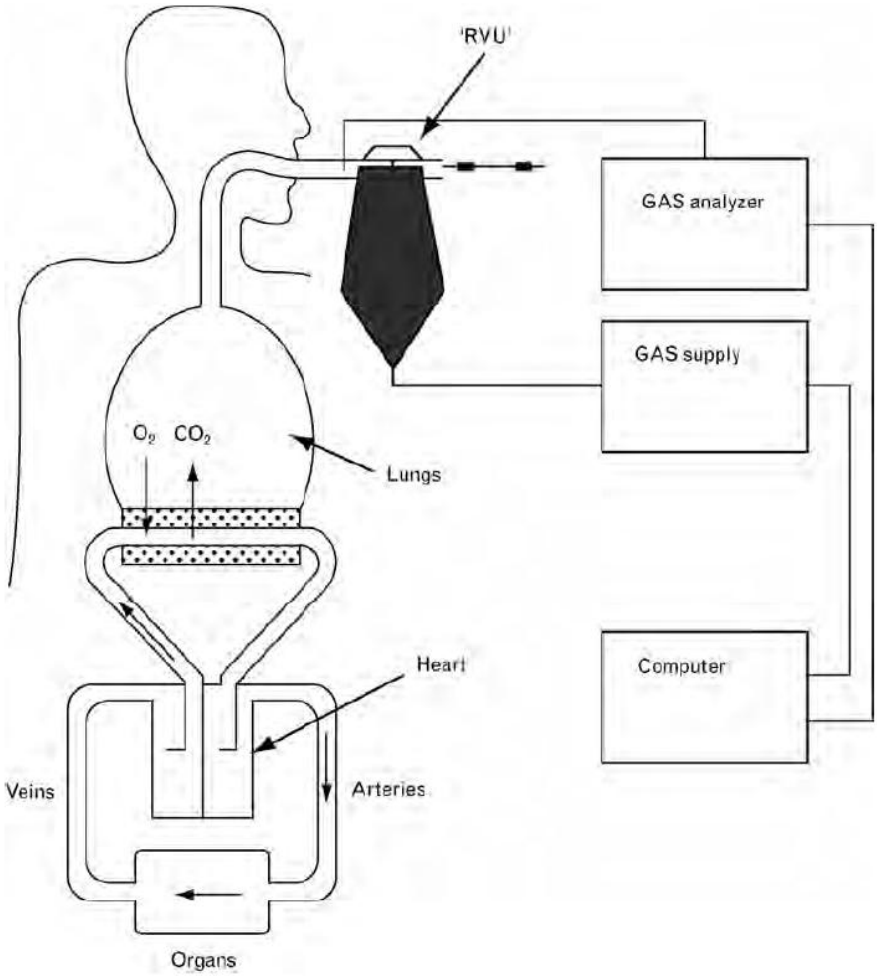

Figure 8: Schematic representation of cardiac output measurement during inert gas rebreathing [36].

The indirect Fick technique was compared to the inert gas rebreathing method by Jakovljevic *et al*. They studied 18 healthy adults (10 males and 8 females) from ages 26 to 58 during incremental exercise testing. The reproducibility and the agreement between the different measurements were assed. They concluded that with the inert gas rebreathing method the estimated cardiac output is more accurate and it showed acceptable levels of of agreement with the indirect Fick method [37]. On the other hand, this study had its limitations due to the absence of a gold standard such as the invasive direct Fick method. Jakovljevic *et al.* suggested that this method should be used in clinical populations but still more studies need to be done to evaluate if this method can also be used on patients with cardio-respiratory disorders [37].

Hauser *et al*. also conducted a study with the inert gas rebreathing method by using the Innocor INN00500 device (Innovision A/S, Odense, Denmark). A prospective observational study was done on 10 patients aging from 6 to 20 years old that were treated with a dual chamber pacemaker due to CCAVB [35]. These patients had a dual chamber pacing mode and then it was switched to single chamber pacing mode where the CO was measured using inert gas rebreathing during exercise. Hauser *et al.* states that due to the fact that this technique can be performed repeatedly in children and adolescents and taking

just 3 to 5 minutes, this is the best technique to use when an estimation of the cardiac output is needed in children [35].

Electrical bioimpedance

(for example: ICON® by Osypka Medical, Berlin, Germany)

Electrical bioimpedance is a non-invasive technique that measures the stroke volume and cardiac output [23, 38]. Electrical bioimpedance makes use of two sets of electrodes (see figure 2). These electrodes uses a constant, low amplitude high frequency alternating current that is passed transversely through the thorax [22]. The pulsatile movement of blood down the aorta alters the thoracic conductivity [39], and this change reflects the cardiac related changes in blood volume [23, 33]. These changes can be monitored and can be translated into cardiac output [39] and stroke volume values.

This method was developed by Kubicek *et al*. who had five assumptions that he translated into a formula. The first is that the thorax acts as a cylinder. Second, this cylinder is homogenously perfused with blood of specific resistivity (ρ) that varies with the hematocrit. Third, this cylinder has a steady state mean base impedance (Z_0). Fourth, the pulsatile variations in thorasic aortic blood flow cause pulsatile decreases in the thorasic impedance (ΔZ). Lastly, ejection blood assumes a square wave pattern [40]. From these assumtions the following equation can be used to determine the stroke volume (there are also other derivatives of this formula that are being used in modern practice):

$$SV = \rho \times (L/Z_0)^2 \times (\Delta Z/\Delta t)_{max} \times LVET \qquad (6)$$

In which ρ is the resistivity of blood, L is the distance between the electrodes, Z_0 is the baseline impedance, $(\Delta Z/\Delta t)_{max}$ is the maximum absolute rate of change in impedance signal for a given heart beat and LVED is the left ventricular ejection time [40].
If the stroke volume is determined, by using equation (3) the cardiac output can be calculated.

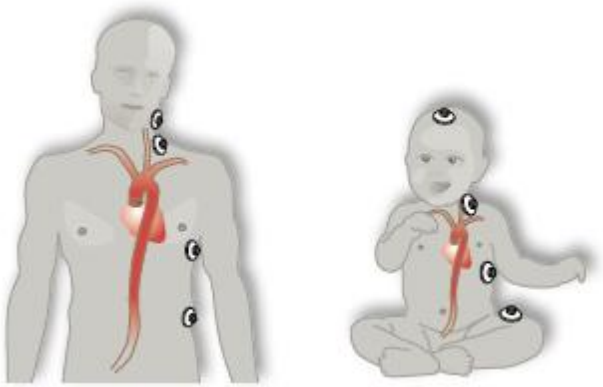

Figure 9: Placement of the 4 ECG sensors for the measurement of electrical bioimpedance. Left: sensor placement for preteens and older. Right: sensor placement for neonates and children.

In the last decade two more techniques for impedance cardiology have been developed, the electrical velocimetry and the bioreactance [26]. The electrical velocimetry is similar to bioimpedance but it calculates the electrical conductivity by using the direction and

changes in the mechanical characteristics of the erythrocytes [41]. According to Schubert *et al*., that studied this technique in children, electrical velocimetry is a reliable technique but it is better used to monitor changes in the heart function rather than to calculate absolute values [41]. On the other hand the study from Tomaske *et al*. on children with congenital heart disease concluded that the results from electrical velocimetry were not reliable when used on patients with changing hemodynamics [42]. In the same year that Tomaske *et al*. published these results, Norozi *et al*. published a paper that also used congenital heart disease patients where electrical velocimetry was compared to the Fick method and these results had an acceptable agreement with each other. Therefore Norozi *et al*. concluded that electrical velocimetry was appropriate for continuous cardiac output measurements and even under abnormal hemodynamics [43].

Recently, Petter *et al*. published a paper that used adult patient with heart failure or heart disease to study the estimations from electrical velocimetry. This study concluded that the electrical velocimetry measurements were affected by increased activity in skeletal muscle, respiratory artifacts and the presence of pulmonary congestion [44]. Petter *et al*. also indicated that the electrical velocimetry overestimates the cardiac output measurement during exercise thus these measurements are not accurate enough to measure changes during exercise [44].

Different studies had different results as can be seen in the above mentioned studies. Therefore more studies need to be done to evaluate the accuracy of this method.

Another impedance cardiology technique that was developed is the bioreactance method. This technique measures the variation in frequency spectra of a delivered oscillating current that occurs when the current traverses the thoracic cavity [26]. Studies suggest that this technique provides accurate results during rest and exercise [45]. The study from Myers *et al*. (mentioned earlier) that was done with adults that had congenital heart disease concluded that the bioreactance technique gave insight into mechanisms that may contribute to limiting exercise such as, interactions between cardiac performance, exercise intolerance and ventilatory efficiency [32]. A recent study with children admitted to a pediatric care unit concluded that this technique is not suitable for patients weighing less than 20 kg due to the fact that it gives an abnormal cardiac index [27]. Therefore more studies are needed to evaluate the utility of this technique in older children with hemodynamic disturbances [27].

The bioreactance method is a relatively new technique therefore more studies need to be done to evaluate its accuracy during CO measurement at rest and during exercise.

Pulse contour method

(for example: Nexfin® by BMEYE, Amsterdam, The Netherlands)

This technique allows non-invasive and continuous beat-to-beat brachial arterial blood pressure monitoring [46, 47]. This incorporates patient specific aortic vascular characteristics and therefore can calculate beat-to-beat stroke volume and cardiac output [48]. This pulse contour method is based on the development of the pulsatile unloading of the finger arterial walls using an inflatable finger cuff (Figure 5) [49]. This then measures the blood pressure and the cardiac output can also be calculated [50].

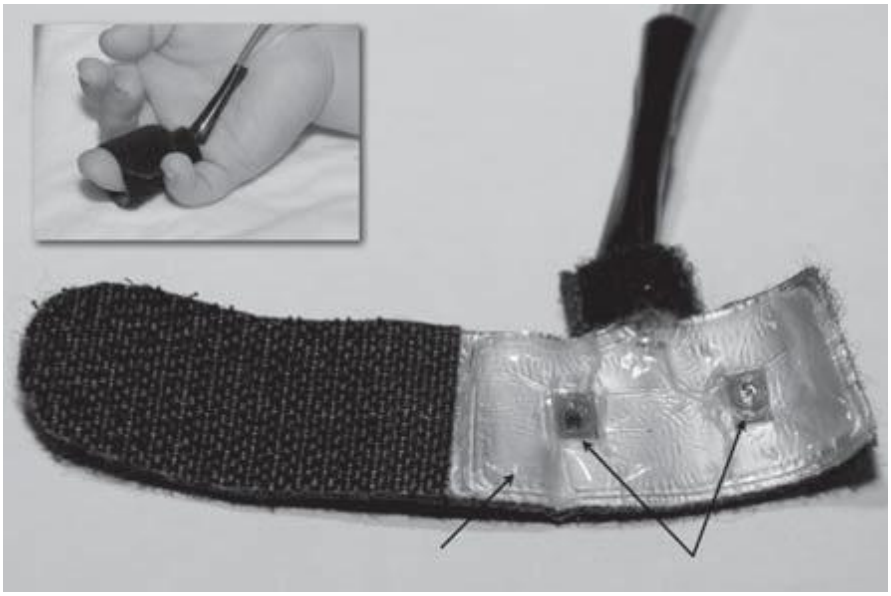

Figure 10: Illustration of a finger cuff and in the upper left corner a child of 2,5 years with a finger cuff [51].

This method is an updated version of the Finapres method (BMEYE 1980) [52] that was originally used in the TNO Finapres model 5 and Ohmeda Finapres 2300 (1986) which the diameter of the artery is kept constant by using a cuff wrapped around the finger; this is also called the set-point [46]. The changes in the diameter of the artery are detected by means of an infrared photo-plethysmograph that is built in to the finger cuff [46]. If an increase in the arterial diameter is detected the finger cuff pressure is also increased to prevent the diameter change [49]. This keeps the artery at its unloaded volume where the transmural pressure is zero [46]. If this is done correctly, the finger cuff pressure equals the finger arterial pressure through the cardiac cycle [46].

The Nexfin technique calculates a reconstructed brachial artery blood pressure. This is done by applying the physiological model and a regression based level correction to obtain this value [46, 49, 53]

Studies have been done to analyze the reliability of this technique. According to Bogert *et al*., if compaired to other cardiac output monitoring techniques, this is an accurate measurement [48]. Stover *et al*. states that this technique cannot be used in critically ill patients because it is less reliable than the invasive techniques [50]. Nexfin was used in a Hofhuizen *et al*. study where they used children undergoing congenital cardiac surgery. In this study he concluded that this technique was useful to determine the blood pressure changes (thus also the cardiac output monitoring) but to obtain a signal was time consuming [51]. This was also the case in the study from Andriessen *et al*. who studied this technique in young children ages 0 to 4 [53]. No studies could be found where Nexfin was used to monitor the cardiac output during exercise in children.

Discussion

In order to choose the optimal non-invasive cardiac output measurement method to be applied during CPET in pediatric CCAVB patients a review of literature was conducted. Indirect Fick method, electrical bioimpedance, pulse contour method, inert gas rebreathing, electrical velocimetry and bioreactance were discussed and the studies using these techniques were evaluated. After critical appraisal of all the literature found by using electronic databases, different methods were identified as suitable: The indirect Fick method and inert gas rebreathing. Other techniques that are considered to be suitable but need further research, are the electrical bioimpedance and the pulse contour method.

The indirect Fick method is commonly used during exercise testing to measure the cardiac output [23] in adults and in children. For example: The technique correlates well with the inert gas rebreathing technique. But this technique still has its disadvantages. First, the rebreathing bag should be chosen very carefully and it has to be accurate otherwise the plateau value for PCO_2 will not be reached [23]. Second, the accuracy of this technique is moderate if the measurements are taken at rest when the mixed-venous-arterial PCO_2 difference is small [23]. Third, this technique measures non-shunted blood instead of total cardiac output therefore a correction for intrapulmonary shunt must be added to this equation [22]. But overall the indirect Fick method forms the golden standard for physiological exercise studies [22].

In conclusion indirect Fick method or inert gas rebreathing is a good candidate for routine non-invasive CO monitoring during CPET in CCAVB patients. Although it takes a while to find the right size for a rebreathing bag, it is a accurate method that is easy to use in children, also during exercise.

Electrical bioimpedance (ICON) is another promising method of non-invasive CO measurement. For example: This technique is validated in adults, as well as in children but still more research is needed to evaluate the accuracy of this technique because studies have shown conflicting results. Electrical bioimpedance is very easy to use but it has its limitations during exercise, due to the fact that respiration and movement can affect the electrical current passing through the chest [23]. Newer impedance measurement techniques as the electrical velocimetry and the bioreactance method have the same limitations as the electrical bioimpedance technique. These techniques perform better during cessation of respiration or body movement and seem therefore less well suited for the use during CPET.

The review of literature concerning impedance measurement techniques revealed conflicting results with regard to accuracy and reproducibility, therefore more research is needed. Finally, it is not clear whether this technique performs well in the presence of a pacemaker, which theoretically can influence the impedance measured by the electrodes. In conclusion, electrical bioimpedance cannot be recommended for the use during CPET in CCAVB patients.

Pulse contour analysis (Nexfin) is another candidate for the use of non-invasive CO monitoring during CPET. But this technique has several disadvantages. To obtain accurate measurements a calibration is always needed against standard values such as the Fick principle [49]. Also, since this technique relies on beat-to-beat monitoring, this forms an important source of error [48]. The literature search did not reveal any study in which this technique was used during exercise testing. Despite of this, there are several reasons which make pulse contour analysis a promising candidate for the use during CPET in CCAVB. It

seems very noninvasive, thus very child friendly. The sensor is placed on the finger therefor the pacing of the CCAVB patients will not interfere with the measurements.

In summary, the most promising non-invasive techniques that can be used to calculate the CO during CPET with pediatric CCAVB patients are the indirect Fick method, inert gas rebreathing and the pulse contour analyses. These techniques are more child friendly and are quite accurate as stated by the different studies. The electrical bioimpedance is also a very good candidate but due to the fact that it uses low frequency electricity to measure the cardiac output, the pacemaker implantation in these patients may lead to false measurements.

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RESEARCH ARTICLE

Congenital Atrioventricular Block and Exercise testing: The comparison between ICON and Nexfin Non-Invasive Cardiac Output Measurement Techniques

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Congenital Complete Atrioventricular Block and Exercise Testing: The Comparison between ICON and Nexfin Non-invasive Cardiac Output Measurement techniques

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Abstract

Congenital complete atrioventricular block (CCAVB) is a rare disease where most of the children undergo pacemaker implantation before they are 20 years old. To assess the fitness capacity of these patients, cardiopulmonary tests are done. Cardiac output measurements are also essential to evaluate the physiological responses of the heart. ICON and Nexfin are two noninvasive techniques that were studied in combination with CPET to evaluate their accuracy. ICON is electrical bioimpedance and Nexfin is pulse contour analysis. SPSS analyses indicated that these techniques did not have a significant difference. In conclusion, Nexfin and ICON did not differ in data, but an effect over time was measured.

Introduction

Congenital Complete Atrioventricular Block (CCAVB) is a rare disease with an estimated incidence of 1 in 15.000-20.000 live born infants [1-3]. CCAVB has a mortality rate of about 6-8% in children with isolated CCAVB and in infants is this 4-8%. This percentage increases in infants and children with structural heart disease reaching a percentage of 29% and 10% [4]. CAVB is considered congenital if it is diagnosed *in utero*, at birth, or within the neonatal period (0–27 days after birth) [5]. The diagnosis is mostly made by echocardiography or electrocardiography [1, 4]. Etiology of CCAVB is not yet elucidated but it is thought to be caused by two mechanisms. In 25-33% of the patients, CCAVB is thought to be caused by structural cardiac abnormalities [2-4]. Secondly CCAVB is caused by the complete or incomplete discontinuity of the AV conduction system; this is also the most common appearing in 70-75% of the patients [3, 6]. Destruction of the conduction system is thought to be caused by a maternal autoimmune disease, connective tissue disorders (CTDs), most commonly the CTDs involving the autoantibodies against SS-A/Ro and/or SS-B/La [2, 4, 6]. Studies have shown that in 98% of the CCAVB cases, autoantibodies anti SS-A/Ro and anti SS-B/La, were present in the maternal sera [4].

Studies have shown that there are three pathological processes in the conduction system of these patients with CCAVB. Firstly, there is a lack of communication between the arterial musculature and the more peripheral part of the conduction system. Secondly, interruption of the atrioventricular (AV) bundle and thirdly,the pathologic changes in an aberrant conduction system [7]. The only effective treatment for these patients to date is permanent cardiac pacing [1].

Children with this type of congenital heart disease have impairment of their functional capacity. Thus measurement of exercise capacity and other physiological responses can provide useful and objective information about the function of the heart, lungs and peripheral muscle [8]. In these patients, increase in the cardiac output can be elucidated by the increase in the heart rate but in other patients, is the increase in the stroke volume the main mechanism. Patients with CCAVB can also be compared to top athletes due to the fact that there stroke volume keeps increasing during exercise and may keep rising until it reaches the maximum VO_2 [9]. If the study from Rowland and Cunningham is taken into consideration, this is also the case under normal circumstances in healthy children [10]. Therefore instead of using the maximum VO_2, the VO_2 peak is used. The VO_2 peak is the highest oxygen uptake at peak workload. The VO_2 peak is easier to estimate than the maximum VO_2 due to the fact that children seldom reach a plateau phase.

After considering the different aspects of CCAVB we focused our research at the analyses of cardiopulmonary exercise testing (CPET) in patients with CCAVB. We combined the CPET with two measurement techniques for cardiac output, namely electrical bioimpedance (ICON) and pulse contour analysis (Nexfin). These two techniques were compared with each other to verify their validity. ICON and Nexfin are used in combination with CPET to measure parameters that the CPET cannot measure such as the stroke volume and most importantly the cardiac output.

Materials and Methods

Patients

Databases of the department of pediatric cardiology in Utrecht and Nijmegen (the Netherlands) were used to find all patients with isolated CCAVB older than 5 years. Isolated CCAVB indicates patients that had no other type of structural cardiac abnormalities [11]. In this study we will be analyzing a subgroup of these patients, namely the patients from Nijmegen who consented to participate in the study. All the medical records of these patients were reviewed and data was collected. These data included age of diagnoses (this was very important to find out if these patients had congenital CAVB or just CAVB), maternal antibody status and age of first pacemaker (PM) implantation [12]. In total 6 patients participated in this study with mean age of 13,7 ± 3,879 (Table 1). All these patients had a pacemaker implanted at the mean age of 1,93 ± 3,879 and had a median PM number of 4. Diagnoses of CCAVB took place at the mean age of 0,23 ± 0,367 years.

Anthropometry

Before starting with the cardiopulmonary exercise testing (CPET) anthropometric measurements were done on each patient. These measurements included body mass (BM in kg; 48,8 ± 19,416) and body height (in cm; 155 ± 19,231). The body mass index (BMI in $kg*m^{-2}$) was calculated by dividing the BM by the square of the body height in meters and to estimate the body surface area (BSA in m^2) the equation of Haycock *et al.* was used [13].

Cardiopulmonary exercise test (CPET)

CPET was done using a electronically braked cycle ergometer [12]. The ECG monitoring was supplemented with expiratory gas analysis using a facemask. The air that flows through this mouthpiece is continually sampled and the concentrations of O_2 and CO_2 are calculated [14].

This breath-by-breath gas exchange analysis, using a calibrated expiratory gas analysis system (Oxycon, CareFusion, the Netherlands), measured the peak values of parameters, such as oxygen consumption (VO_2) and carbon dioxide production (VCO_2), in the expiratory air [14]. Peak values were defined as the highest mean value of any 30-second time interval during exercise. Predicted values were obtained from established values from age- and sex-matched Dutch controls in the Ten Harkel *et al.* study [15]. In addition to these above mentioned parameters the O_2 pulse was also measured, which can be used as an index for stroke volume. The O_2 pulse was calculated by the ratio of VO_2 and heart rate (HR) [16].

ICON

To measure stroke volume (SV), cardiac output (CO) and cardiac index (CI), the ICON (Osypka Medical, Berlin, Germany) was used. ICON (index of contractility) is a non-invasive hemodynamic measurement technique. It uses of electrical bioimpedance by using 4 standard ECG surface adhesive sensors/ electrodes which are placed on the neck and on the side if the thorax area. After attaching these sensors and the measurement starts, the electrical velocimeter determines the value of the above mensioned parameters [17].

Nexfin

Nexfin (BMEYE, Amsterdam, the Netherlands) is a non-invasive measurement that makes use of a finger cuff this is known as pulse contour analysis. This technique utilizes beat to beat monitoring of the heart and calculates the SV, CO, CI and the contractility of the heart (dP/dt) [18-20].

Parameters

Normal values that we need to take into account are the cardiac output and stroke volume. The ideal patient has an increase in their SV and O_2 pulse until about 40 to 50% of the predicted VO_2. The percentage of predicted VO_2 has to be above 80% otherwise these patients have a reduced exercise capacity.

Measurements of ICON and Nexfin will be represented in graphs per patient; a graph for SV and CO. SV is influenced by preload, afterload and contractility. The possible abnormalities in SV may be explained by an anomaly in the contractility. The O_2 pulse can also be used as a surrogate for SV according to Oliveira *et al.* [16].

CO is the product of SV x HR thus further increase in CO after 40-50% of the VO_2% is due to increase in HR. When VO_2% maximum is reached, HR should decrease. But in athletes and patients with CCAVB, the increase in the SV is constant and can keep increasing until the peak of the VO_2 but this is also the case in healthy children as stated by the research of Rowland and Cunningham in 1992.

Thus HR, $VO_{2\%}$ and O_2 pulse will also be included in the graphs.

Statistical analysis

Statistical analysis was done using the SPSS 14.0 for windows. Peak values of SV, CO and CI at peak workload of the 6 patients were used. Other parameters that were included in the statistical analysis are the percentage of the predicted peak workload, percentage of the predicted peak workload corrected by the body mass, percentage of predicted heart rate peak, percentage of predicted VO_2 peak, percentage of predicted O_2 pulse and percentage of predicted VO_2 peak divided by time. These values were analyzed using different tests including the Shapiro-Wilk test, the paired sample T test and correlations (Pearson's and Spearman's correlations). The CV and CO where analyzed using the Repeated

Measurement test to see if there was a difference between the two measurement techniques namely, ICON and Nexfin.

Results

Stroke volume, cardiac output, cardiac index and dP/dt

First of all, each patient will be discussed individually, because some patients have abnormal values, which can cause the discrepancies when the correlation between Nexfin and ICON is determined. Data are represented in table 2.

Patient A (Figure 1 & 2)

With HR of 93 bpm and a percentage of predicted VO_2 of 56% at peak exercise; overall low scores. Peak SV and CO was measured at 59%/93% (ICON/Nexfin) of the peak VO_2. SV and CO increased until after the VO_2 peak. Decrease in the HR also results in increase in the O_2pulse, this results in a peak O_2 pulse right after the peak VO_2. These overall low and aberrant scores may be due to the pacemaker settings (PM blockage) or the low contractility of the heart (801 mmHg/sec). Results may indicate that Nexfin has the most valid results due the fact that the CO kept increasing ad did not decline like the ICON measurements.

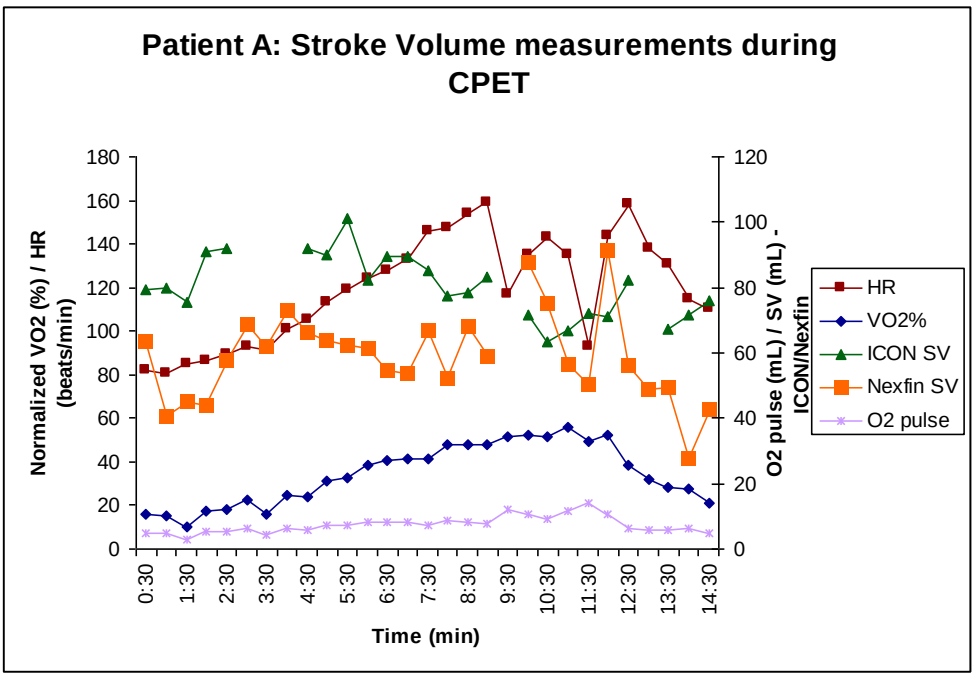

Figure 11: Patient A; Stroke Volume measurements during CPET.
HR at peak exercise was 93 bpm; percentage of predicted VO_2 was 56%; SV and CO increased until 59%/93% (ICON/Nexfin) of the peak VO_2. The peak SV measured by Nexfin was reached after the peak VO_2%. In this case was Nexfin the most accurate measurement because it had the most reliable results. Gaps in the ICON and Nexfin graphs were a result of missing data.

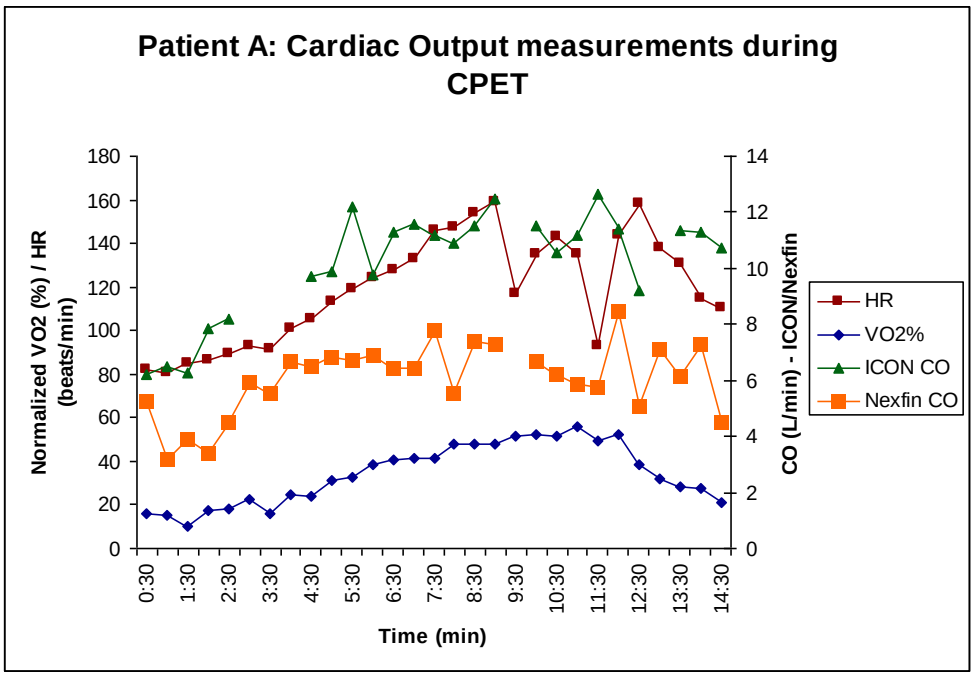

Figure 12: Patient A; Cardiac Output measurements during CPET.
HR and VO_2% are the same as in figure 1. Decrease in the HR leads to decrease in the CO in the ICON measurements but increase in the Nexfin measurements. The Nexfin results were more accurate then the ICON results in this patient. Gaps in the ICON and Nexfin graphs were a result of missing data.

Patient B (Figure 3 & 4)

With a HR of about 143 bpm and a percentage of predicted VO_2 of 98% at peak exercise, this patient had a normal $VO_{2\%}$.. Peak SV was measured at 41%/87% (ICON/Nexfin) and peak CO at 100%/98% (ICON/Nexfin) from the percentage of predicted VO_2. Peak O_2 pulse was reached at peak VO_2. The drastic decrease in HR after the peak VO_2 lead to an decrease in the O_2 pulse and also a decline in the CO using both techniques. SV remains constant with the ICON technique but declines using the Nexfin. When HR declined, CO also decreased, which is normal. But in other aspects of the results, SV increased much more then 40-60% of the peak VO_2, using Nexfin. Only the SV increased until about 41% using ICON and given the fact that the CO increased with the HR we can assume that in this patient that the Nexfin results had more validity.

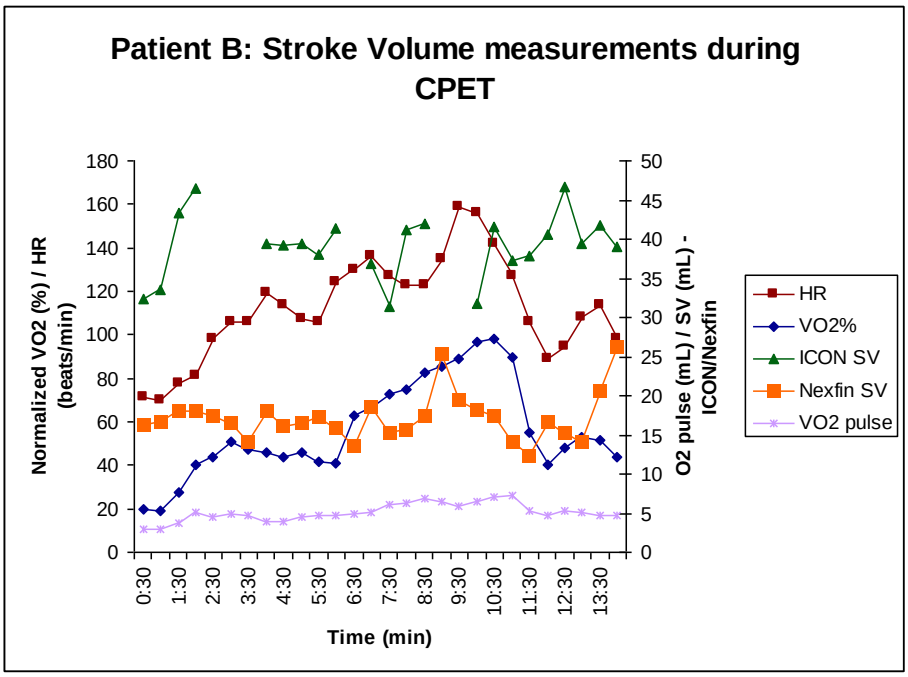

Figure 13: Patient B; Stroke Volume measurements using CPET.
Peak exercise resulted in a peak HR of 143 bpm; percentage predicted VO_2 was 98%; absolute peak SV was reached at 41% of the peak VO_2 using ICON and Nexfin had a value of 87%. Peak O_2 pulse was reached at peak VO_2. Gaps in the ICON and Nexfin graphs are a result of missing data.

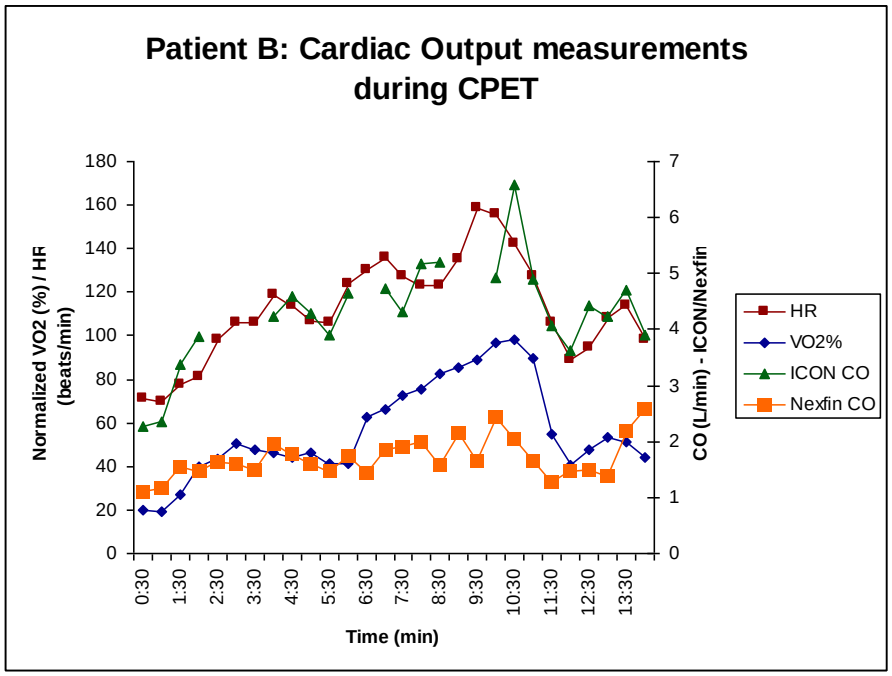

Figure 14: Patient B; Cardiac Output measurements using CPET.
HR and VO_2% are the same as in figure 6. The peak CO is reached at 98% and 100% of the peak VO_2 using Nexfin and ICON. The values of these two measurement techniques were different but reached a peak at about the same time. Gaps in the ICON and Nexfin graphs were a result of missing data.

Patient C (Figure 5 & 6)

With a HR of 155 bpm and a percentage of predicted VO2 of 53% at peak exercise this patient has overal low scores. Patient C was treated with β-blockers and ACE inhibitors, so this may be the reason for the low HR and exercise capacity. Peak SV was measured at 58%/78% (ICON/Nexfin) and peak CO at 50%/78% (ICON/Nexfin) of the percentage of predicted VO_2. The peak O_2 pulse was reached at the same time as the peak SV using Nexfin but overall is the O_2 pulse low and nearly constant during CPET. The SV fluctuated and is low indicating that there was an output problem or the pump function of the heart was not stable. From these measurements we can conclude that the Nexfin measurements had more validity.

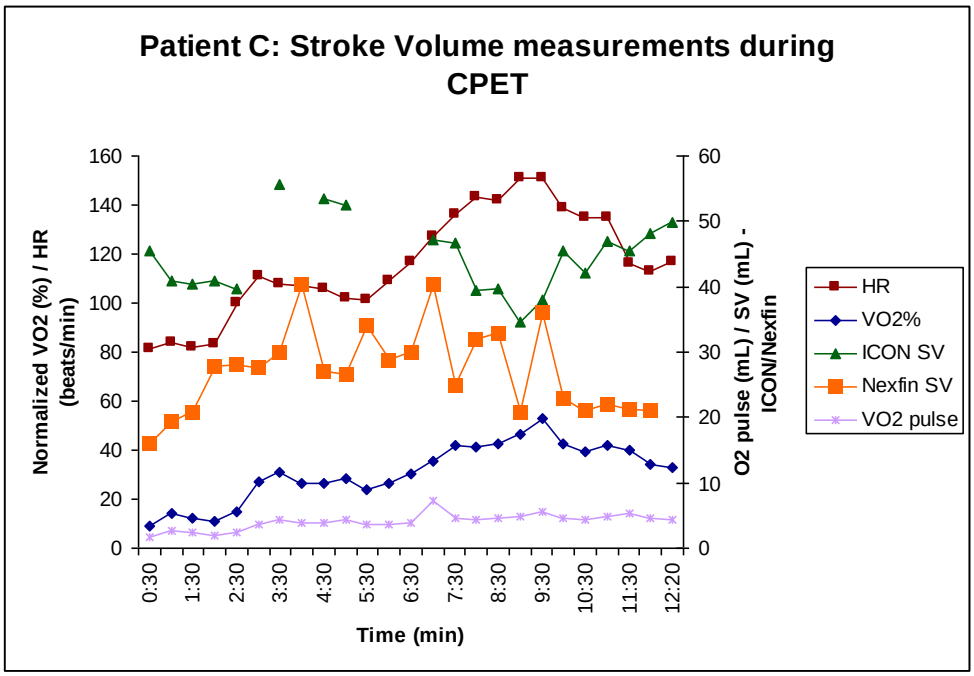

Figure 15: Patient C; stroke volume measurement during CPET
HR at peak exercise is 155 bpm, percentage of predicted VO_2 is 53, increase SV until 58/50% (ICON/Nexfin) of VO_2%. SV was not constant after SV peak. Gaps in ICON-line were the result of missing data, therefore ICON peak was based on an estimation.

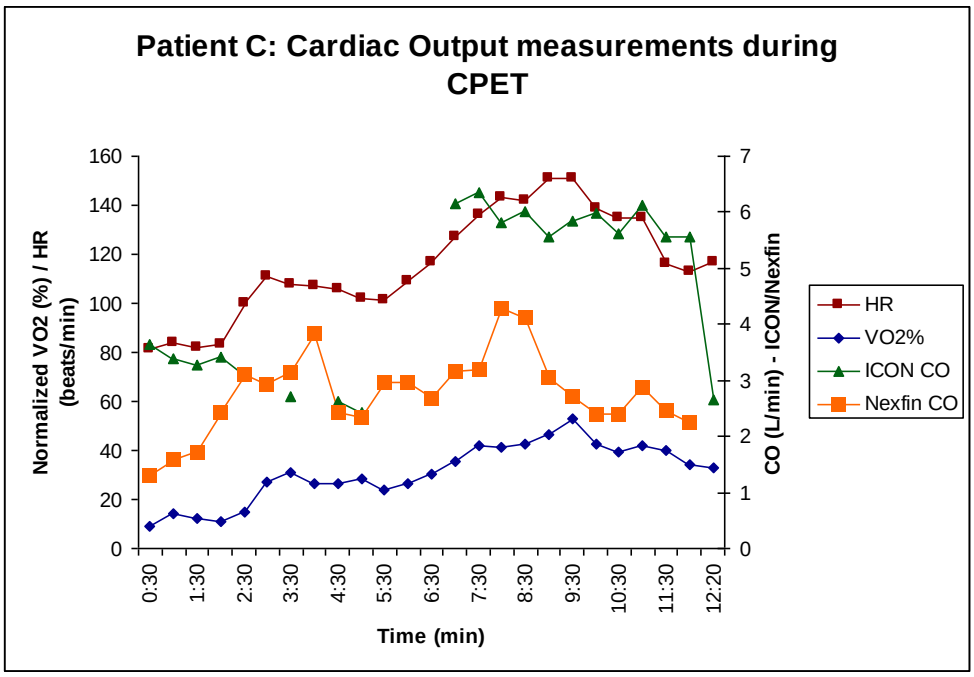

Figure 16: Patient C; cardiac output measurements during CPET
CO fluctuated according to Nexfin. CO, according to ICON, suddenly rose and then remained stable. Gaps in the ICON and Nexfin graphs were the result of missing data

Patient D (Figure 7 & 8)

HR at peak exercise was 95 bpm, percentage of predicted VO_2 was 76; overall a sign of a reduced exercise capacity. The low HR peak could be caused by sub-optimal PM programming. HR suddenly dropped as a cause of PM blockage. SV increased till 100/49% (ICON/Nexfin) of VO_2%,. According to ICON, SV increased till after the VO_2% peak, while according to Nexfin, SV increased until 49% of increase of VO_2%. Nexfin results were normal and therefore had more validity than the ICON results. O_2 pulse slowly increased and peaks at maximum VO_2%. Percentage of predicted VO_2 was 76%. According to Nexfin, when HR fell also CO decreased, which was logical because CO is the product of HR and SV. According to ICON, CO increased while HR decreased; most likely this was an error in the ICON.

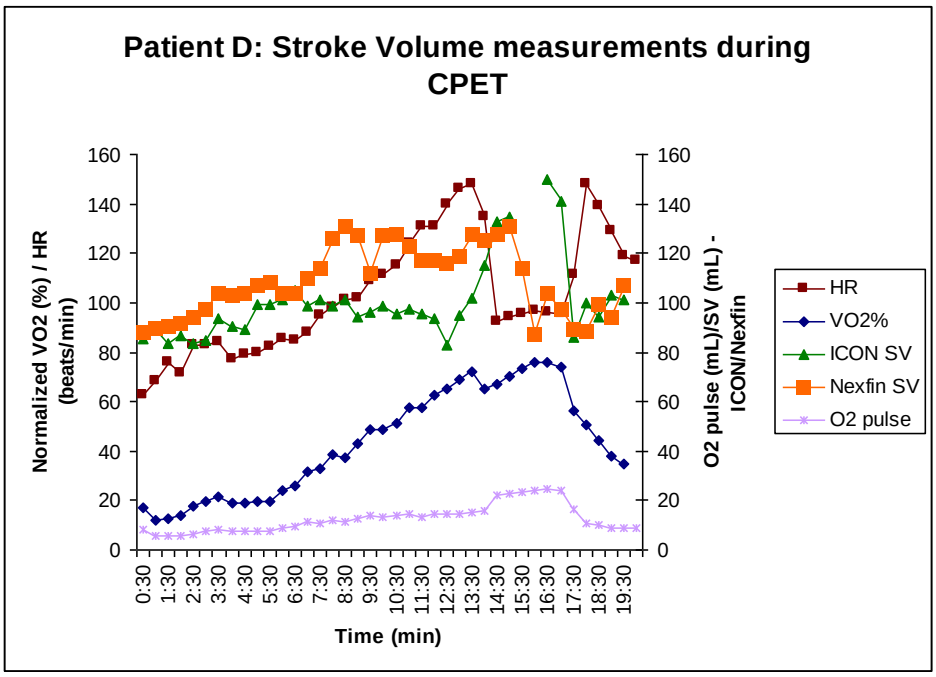

Figure 17: Patient D; stroke volume measurement during CPET
HR at peak exercise was 95 bpm, percentage of predicted VO_2 was 76, increase of SV until 100/49% (ICON/Nexfin) of VO_2%. According to ICON, SV increased till after the VO_2% peak, while according to Nexfin, SV increased until 49% of increase of VO_2%. Nexfin results were normal and therefore more reliable than ICON results. Gaps in ICON-line were the result of missing data, therefore ICON peak was based on the highest results available, which was after VO_2% peak.

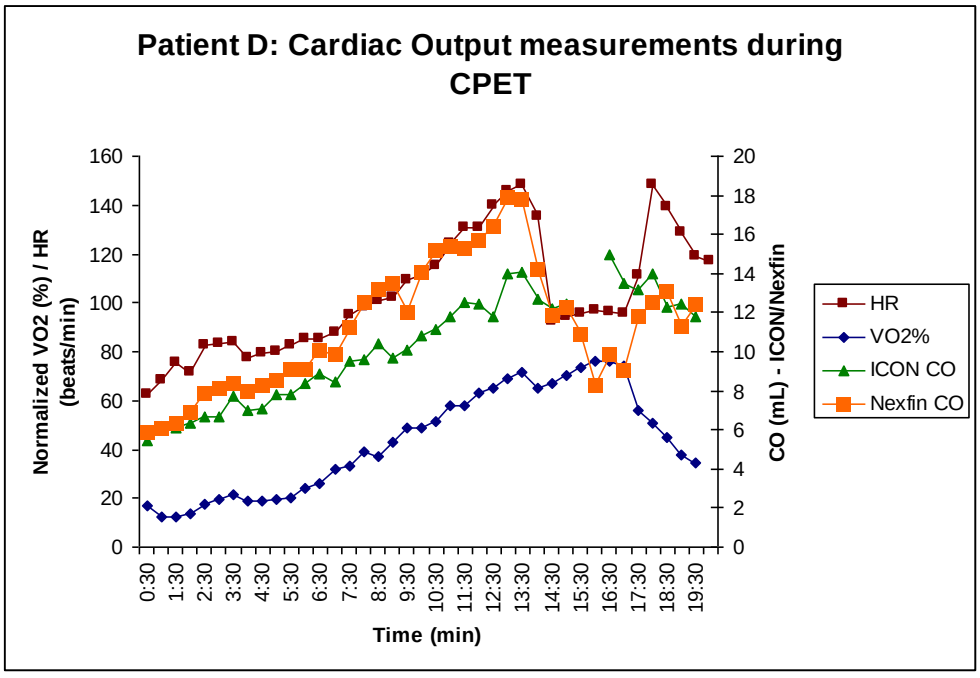

Figure 18: Patient D; cardiac output measurements during CPET
CO decreased according to Nexfin, which was caused by the fall of HR. CO, according to ICON, rose also when HR fell.

Patient E (Figure 9 & 10)

Results of patient E and D were comparable, since they both have a drop in their HR, which caused a decrease in CO. Nexfin gave the most valid results, HR, SV and CO decreased almost simultaneously. According to ICON, SV and CO increased, even when HR fell.

HR at peak exercise was 105 bpm, which was low and caused by the PM block. Highest HR measured during exercise was 164 bpm. Percentage of predicted VO_2 was 64, which is a low score. SV increased until 95/92% (ICON/Nexfin), which was aberrant.

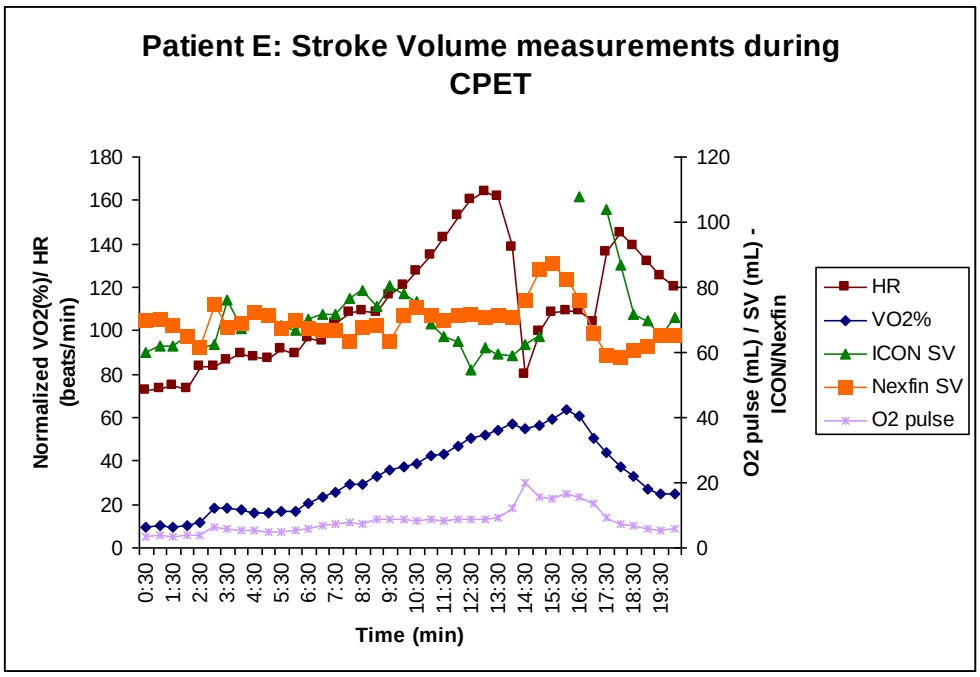

Figure 19: Patient E; stroke volume measurement during CPET

HR at peak exercise was 105 bpm, percentage of predicted VO_2 was 64, increase of SV until 95/92% (ICON/Nexfin) of VO_2%. According to ICON, SV increased till after the VO_2% peak, while according to Nexfin, SV increased until 92% of increase of VO_2%. Both results were aberrant. HR suddenly dropped as a consequence of PM blockage. Gaps in ICON-line were the result of missing data, therefore ICON peak was based on the highest result available, which was just before VO_2% peak.

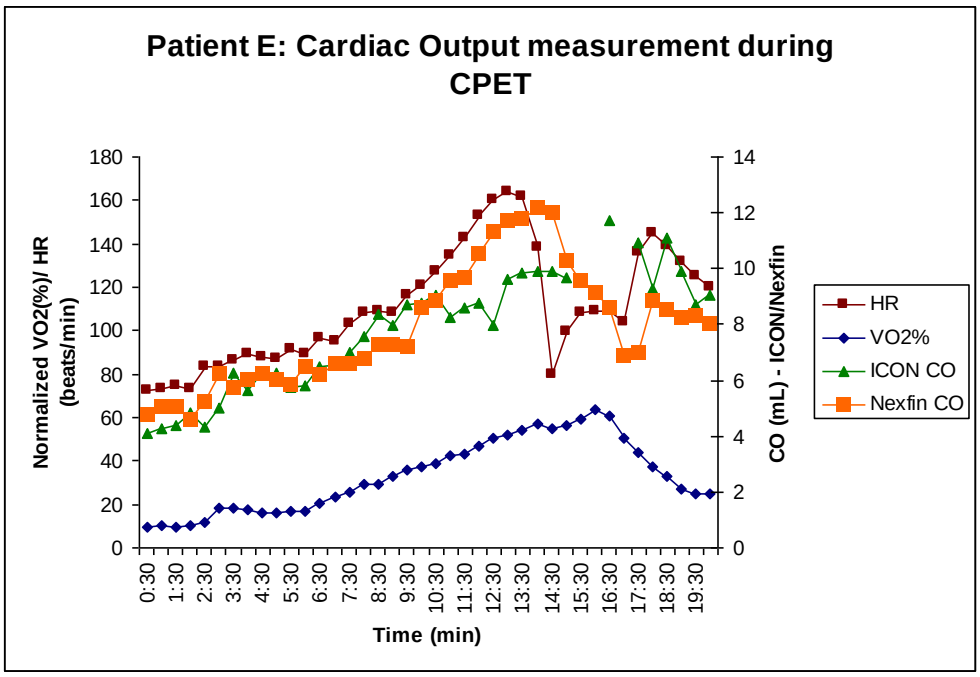

Figure 20: Patient E; cardiac output measurements during CPET
CO decreased according to Nexfin, which was caused by the fall of HR. CO, according to ICON, rose also when HR fell. When HR falls, CO should decrease unless SV increases a lot, which was not the case with this patient. Nexfin results were therefore more reliable.

Patient F (Figure 11 & 12)

HR at peak exercise was 95 bpm, percentage of predicted VO_2 was 29. Both are very low scores. SV increased until 68/83% (ICON/Nexfin), which was longer than normal. HR initially increased, then stayed constant and finally slowly decreased, which was aberrant. The cause of a decrease in HR cannot be explained; since this patient was not treated with any medicine and a PM blockage would have caused sooner a drop in HR. SV course looks normal, both ICON and Nexfin showed an increase in SV, then it stayed constant and after VO_2 peak it decreased.

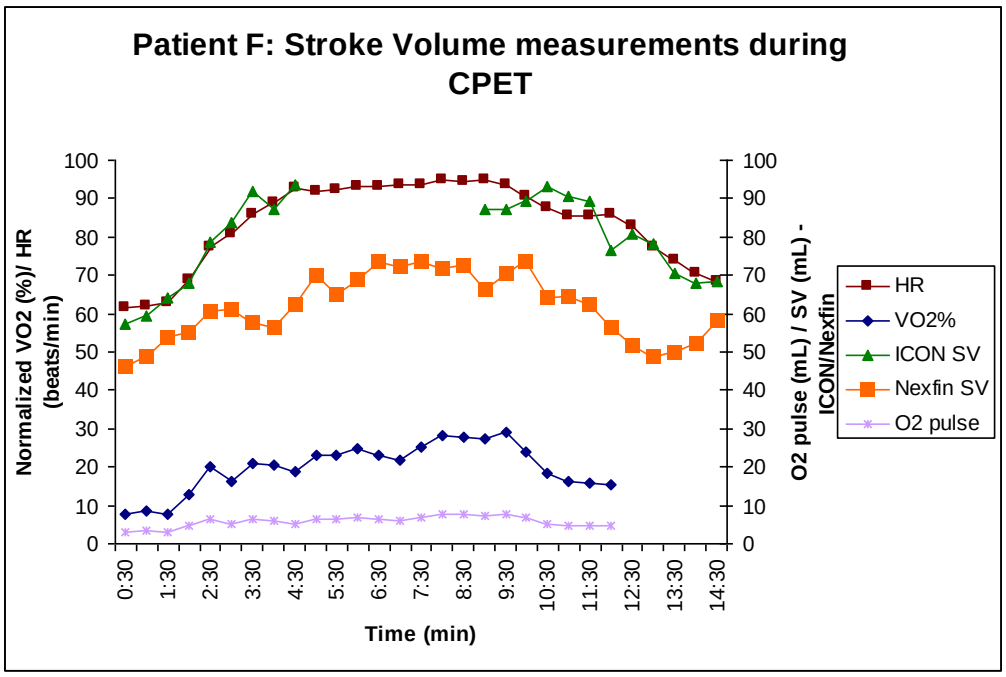

Figure 21: Patient F; stroke volume measurement during CPET
HR at peak exercise was 95 bpm, percentage of predicted VO_2 was 29, increase of SV until 68/83% (ICON/Nexfin) of VO_2%. According to ICON, SV increased till 68% of VO_2% peak, while according to Nexfin, SV increased until 83% of increase of VO_2%. Both results were aberrant. The decrease in HR could not be explained. SV course was normal, both ICON and Nexfin showed an increase in SV, then it stayed constant and after VO_2 peak it decreased. Gaps in ICON-line were the result of missing data, therefore ICON peak was based on the results available.

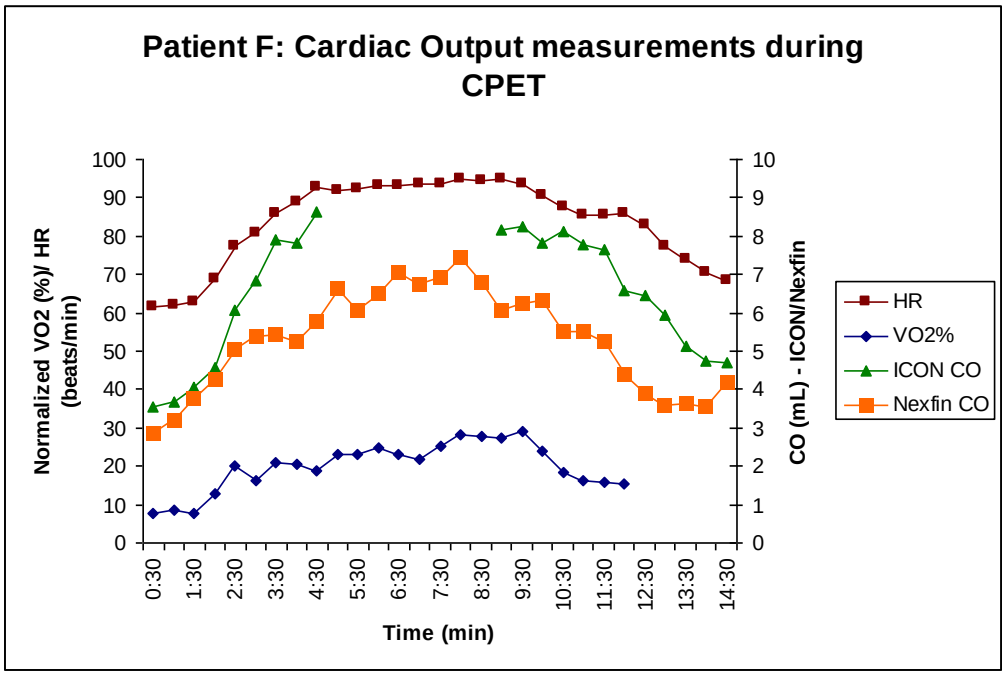

Figure 22: Patient F; cardiac output measurements during CPET
CO decreased according to Nexfin, which was caused by the decrease of HR. CO, according to ICON, increased, then stayed constant and after VO_2 peak it decreased. This course was also aberrant. When HR falls, CO should decrease unless SV increases a lot, which was not the case with this patient. Nexfin results were therefore more reliable. Gaps in ICON-line were the result of missing data, therefore ICON peak was based on the results available.

SPSS: correlations (Pearson and Spearman) – paired sample T test

According to the Shapiro-Wilk test of normality SV, CO and dP/dt were normally distributed. CI was not normally distributed, while the significance was 0,016 (Table 3). This was very unusual, since CI is the product of BSA and CO and CO was normally divided. Therefore, all data were analyzed using Pearson's correlation and Spearman's correlation tests because these where appropriate.

In table 4 results of Pearson's correlation are represented. Measurements of SV, CO, CI and dP/dt were included even as measurements of other parameters, to see whether they correlate with SV, CO, CI and dP/dt. SV of ICON and Nexfin were significantly correlated (R = 0,891, p = 0,017), just as the CO (R = 0,836, p = 0,038). There was no significant correlation between CI of ICON and Nexfin (R = 0,218, p = 0,679) (table 4 or 6). There was also a high, significant correlation between ICON CO and ICON SV (R = 0,895, p = 0,016), between Nexfin CO and Nexfin SV (R = 0,969, p = 0,001), but also between Nexfin CO and ICON SV (R = 0,850, p = 0,032). Significantly high correlation was also found between Nexfin CI and Nexfin SV (R = 0,886, p = 0,019), Nexfin CI and Nexfin CO (R = 0,951, p = 0,004) and Nexfin CI and Nexfin dP/dt (R = 0,847, p = 0,033). This should be the case with values of ICON, but here were some discrepancies.

Considering that CI was not normally divided, also Spearman's correlation was calculated, results are represented in table 5. There was also no significant correlation between CI of ICON and Nexfin.

A significant correlation was found between O_2 pulse and ICON SV (R = 0,943, p = 0,005) and Nexfin SV (R = 886, p =0,019). Which indicates O_2 pulse is indeed a surrogate for stroke volume.

The mean difference between ICON and Nexfin SV was 20,4183 (p = 0,053), so there is, a trend for a difference between the data obtained with ICON and Nexfin. The data gained with ICON and Nexfin differ significantly with measurements for CO and CI (p = 0,004 respectively 0,005) (table 7).

Table 7 represents the results for Spearman's correlation test. ICON CI was not normally distributed, so correlations were calculated with Spearman's correlation test. Except for SV, CO, CI and dP/dt also O_2 pulse was included. These results indicated indeed that there was a correlation between O_2 pulse and SV (R = 0,886, p = 0,019), CO (R = 0,829, p = 0,042) and CI (R = 0,829, p = 0,042) from Nexfin and SV (R = 0,943, p = 0,005), CO (R = 0,943, p = 0,005) from the ICON measurements. However, there was no significant correlation observed between O_2 pulse and ICON CI (p = 0,425). There also was no significant correlation found between ICON and Nexfin CI (p = 0,913). On the whole if we look at the SV and CO from Nexfin and ICON we can conclude that Nexfin correlates for about 87% with the O_2 pulse if we consider that the ICON correlations are the normal values, thus 100%.

Graphics correlation

Even when a correlation is found between two parameters, it could be the case that this correlation is not linear. Ideally, the slope of the graph made from these two parameters is 1. Graphs in which the data gained with ICON and Nexfin for SV, CO or CI are plotted are shown in figures 13, 14 and 15.

Plotted are the data from the six patients with CCAVB with the values of SV, CO or CI at the time of maximal VO_2. There was a high correlation (R = 0,793) found between ICON

and Nexfin SV, but the line indicates ICON gave higher values than Nexfin. The difference was approximately 20 mL, which was also found in the paired T test.

There was a high but not significant correlation (0,698) found between ICON and Nexfin CO, The line indicates ICON gave higher values than Nexfin. The difference was approximately 4 L/min, which was also found in the paired T test.

A low correlation (0,047) between ICON and Nexfin CI was found, which was also the case in the Pearson's and Spearman's correlation tests. ICON gave higher values for CI than Nexfin, the difference is approximately 2,5 L/min/m^2.

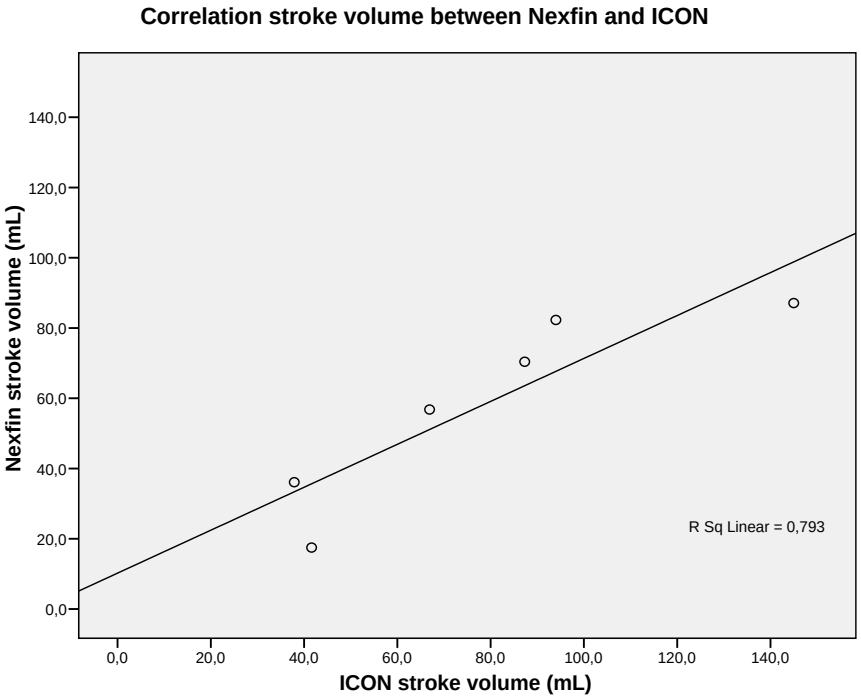

Figure 13: Correlation stroke volume between Nexfin and ICON
Plotted are the data obtained from the six patients with CCAVB with the values of SV at the time of maximal VO_2. There was a high correlation (R = 0,793) found between ICON and Nexfin SV, but the line indicates ICON gave higher values than Nexfin. The difference was approximately 20 mL, which was also found in the paired T test.

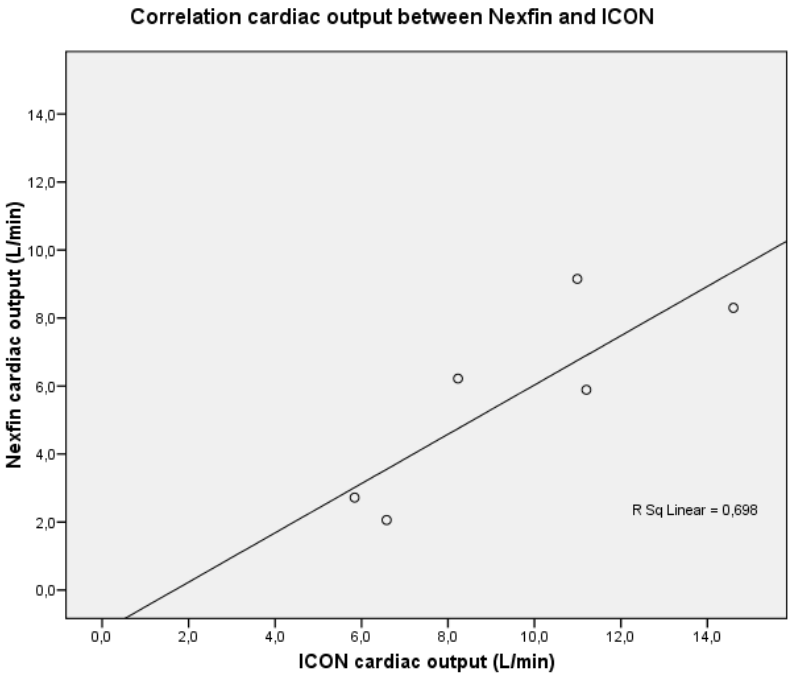

Figure 14: Correlation cardiac output between Nexfin and ICON
Plotted are the data obtained from the six patients with CCAVB with the values of CO at the time of maximal VO_2. There was a high correlation (R = 0,698) found between ICON and Nexfin CO, but the line indicates ICON gave higher values than Nexfin. The difference was approximately 4 L/min, which was also found in the paired T test.

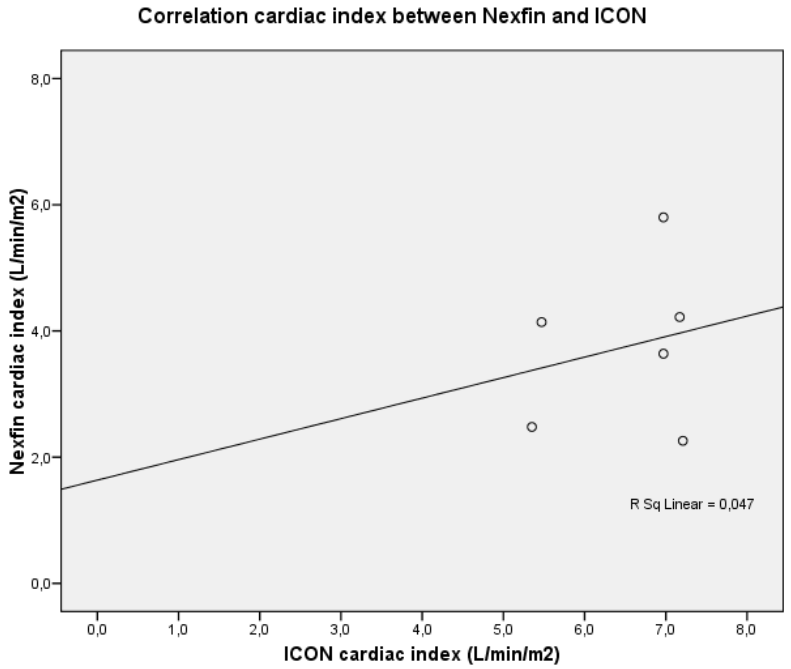

Figure 15: Correlation cardiac index between Nexfin and ICON
Plotted are the data obtained from the six patients with CCAVB with the values of CI at the time of maximal VO_2. There was a low correlation (R = 0,047) found between ICON and Nexfin CI, which was also found in as well as Pearson's correlation test as in Spearman's correlation test. ICON gave higher values for CI than Nexfin, the difference is approximately 2,5 L/min/m^2.

Repeated Measurements

Using the Repeated Measurement analysis a determination was done whether results obtained with ICON and Nexfin for SV and CO were comparable.

First of all, results of SV will be discussed. Represented in table 8 are the results obtained from the tests of within-subject effects for SV when ICON and Nexfin results were compared at time points (levels) 01:00, 04:30 and 10:00. SV data were independent of the method, since significance of M*T and M were bigger than 0,05 (p = 0,257 respectively p = 0,144). However, SV data had an effect over time, since significance of T was p = 0,016. Table 9 represents the results obtained from the tests of within-subjects contrasts for SV when ICON and Nexfin results were compared at the three levels. According to this test, SV data between the three levels were significantly different (p = 0,019 respectively p = 0,029). Represented in table 10 are the results obtained from the pairwise comparisons based on estimated marginal means for SV when ICON and Nexfin results were compared at the three levels. There were no significant differences between data obtained with ICON and Nexfin, since all significances were higher than 0,05. Table 11 represents the results obtained from the tests of within-subject contrasts for SV when ICON and Nexfin results were compared at the three levels, when method and time were polynomial. There was a linear relationship between SV data obtained from ICON and Nexfin (p(quadratic) = 0,100 and p(linear) = 0,029). Although that was not directly visible in the graphic representation (figure 16) Nexfin showed a linear relation, but this was not visible in results of ICON.

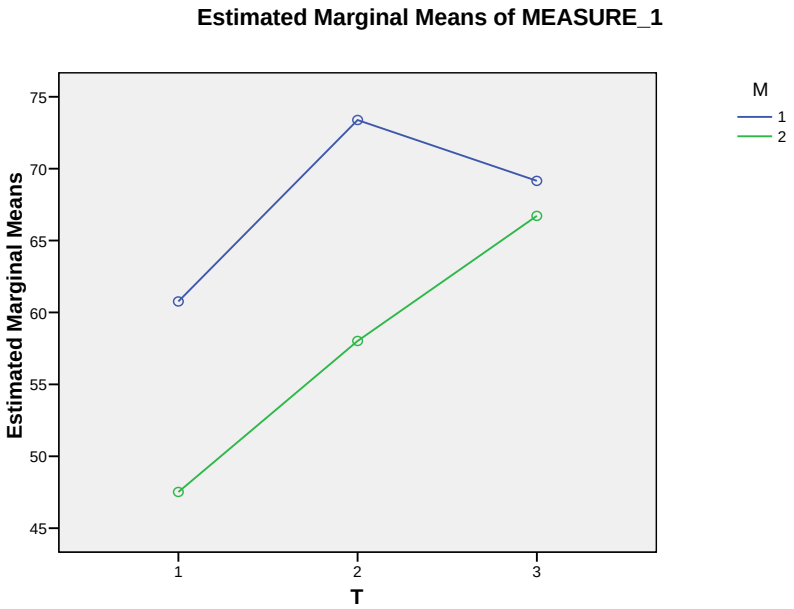

Figure 16: Graphic representation of estimated marginal means of SV for ICON and Nexfin
Method 1 (M1) represents data obtained with ICON, method 2 (M2) represents data obtained with Nexfin. T represents the different time points that were used; 01:00 min (1), 04:30 min (2) and 10:00 min (3). Clearly, there was a linear relation in Nexfin, but this linear relationis not clear in ICON.

Represented in table 12 are the results obtained from the tests of within-subject effects for CO when ICON and Nexfin results were compared at time points (levels) 01:00, 04:30 and 10:00. CO data were independent of the method, since significance of M*T and M were higher than 0,05 (p = 0,775 respectively p = 0,152). However, CO data had an effect over time, since significance of T was p = 0,001. Furthermore, table 13 represents the results obtained from the tests of within-subjects contrasts for CO when ICON and Nexfin results

were compared at the three levels. According to this test, CO data between the three levels were significantly different (p = 0,017 respectively p = 0,003). Represented in table 14 are the results obtained from the pairwise comparisons based on estimated marginal means for CO when ICON and Nexfin results were compared at the three levels. There were some significant difference between data obtained with ICON and Nexfin, since some significances were not bigger than 0,05. There was a difference between level 1 and 3 obtained with ICON and Nexfin (p = 0,010). Table 15 represents the results obtained from the tests of within-subject contrasts for CO when ICON and Nexfin results were compared at the three levels, when as well as method and time were polynomial. There was a linear relationship between CO data obtained from ICON and Nexfin (p(quadratic) = 0,830 and p(linear) = 0,003). This was also directly visible in the graphic representation (figure 17). Both ICON and Nexfin seemed to be linear, although there seemed to be a difference in value obtained for CO between ICON and Nexfin, ICON gave higher values for CO than Nexfin.

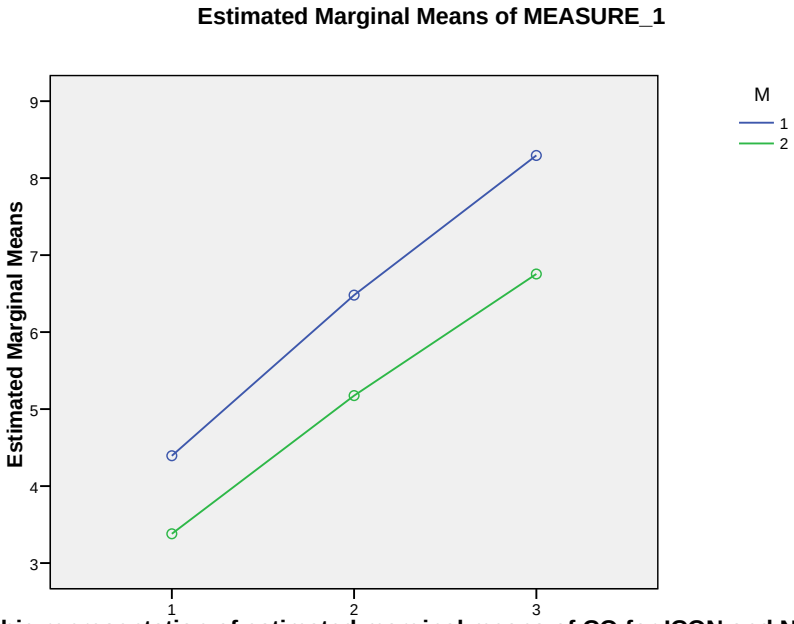

Figure 17: Graphic representation of estimated marginal means of CO for ICON and Nexfin
Method 1 (M1) represents data obtained with ICON, method 2 (M2) represents data obtained with Nexfin. T represents the different time points that were used; 01:00 min (1), 04:30 min (2) and 10:00 min (3). Clearly, there was a linear relation in ICON as well as in Nexfin, although there seemed to be a difference in value obtained for CO. ICON gave higher values for CO than Nexfin.

Discussion

The aim of this study was to compare two noninvasive cardiac output measurement techniques, electrical bioimpedance and pulse contour analysis. These techniques where used during cardiopulmonary exercise testing in 6 patients with CCAVB.

Patient Group

The above mentioned patient group was studied but no control group or reference group was used to compare the results. Therefore we could only base our results on information obtained from the study of Wiegand *et al*. and Hauser *et al*. who measured the CO using inert gas rebreathing technique (Innocor device, Innovision A/S, Odense, Denmark) on patients with CCAVB during exercise [21, 22]. The normal values were obtained by using the information gathered in the study from Ten Harkel *et al*. and Wiegand *et al.* [15, 22].

Data analysis

The program Microsoft Office program Excel was used to calculate the data. The ICON measurements were made every 10 sec, averages per 30 seconds were calculated. The Nexfin measurements were beat-to-beat, therefore estimations per 30 seconds were less accurate. Furthermore, the ICON data skipped a few measurements, which caused gaps in the graphs. For further analyses, the data were estimated, based on the average of surrounding results.

Another difficulty was that no clear notes were made to indicate when the measurements had started. This made it quite difficult to match the CPET, ICON and Nexfin data with each other (matches where made by using the HR). There were no patients where these data were identical, so we had to use the best matched possibilities.

Statistical analysis

The repeated measurement test was used to analyze the agreements between the two measurement techniques. Three time points during the measurement were used. It showed that these two techniques had the same curves, if plotted for time. But each patient had different amount of time that was used to do the CPET and each patient reached their peak VO_2 or other values at different times. Thus the time points used do not mean that each patient was at the same stage of the CPET.

CO and SV measurements (ICON & Nexfin)

ICON measurements gave higher values for SV and CO then Nexfin and according to the paired sample T test the differences were significant. On the other hand no judgment can be made on the basis of the available data, because no gold standard was included. Further investigation should be done with for example indirect Fick as a control test.

In conclusion, more studies need to be done using these techniques to evaluate their accuracy. This was done using only six patients from which no repeated measurements using ICON and Nexfin to compare the results. Our results indicate that these techniques do not differ significantly, but ICON gave in all subjects higher values. In addition, there was an effect over time. Further studies have to be done to analyze the possible differences in the

two techniques to evaluate which technique gives the most accurate results, if there is a difference. These studies should also evaluate the possible effect of CCAVB on the results, especially ICON is sensible for other low frequencies caused by e.g. pacing or other simultaneously used machines due to the fact that electrical bioimpedance monitors low frequency changes in the thorax.

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Tables:

Patient	Gender	Age	BM (kg)	Height (cm)	Age Diagnoses	PM	Age PM	PM System	Medication	Comorbidity	QRS morphology
A	m	14,2	58	163	0	Yes	0	DDDR**	-	-	LBBB*-like
B	f	8,6	23	127	0,6	yes	2,3	VVIR***	-	-	LBBB*-like
C	f	9,9	29	142	0	yes	0	CRT****	ACE + Beta-blokkers	-	indifferent
D	m	17,9	75	183	0	yes	0	DDDR	-	-	LBBB*-like
E	f	17,8	55	162	0	yes	8,3	DDDR	-	-	LBBB*-like
F	f	14	53	155	0,8	yes	1,0	VVIR	-	Lungs	LBBB*-like

Table 1: Data CCAVB patients.
*LBBB = Left Bundle Branch Block
**DDDR = Dual (atrial/ ventricular) paced, Dual (atrial/ ventricular) sensed, Dual (inhibited/ triggered), Rate responsive
***VVIR = Ventricular paced, Ventricular sensed, Inhibited, Rate responsive
****CRT = Cardiac Resynchronization Therapy

Patient	Peak HR (bts/min)	O2 pulse (mL)	Peak VO2/kg/mL	Abs. peak SV reached at % peak VO2 (ICON)	Abs. peak SV reached at % peak VO2 (Nexfin)	Peak pred. VO2** (%)	Abs. peak SV from pred. VO2% (ICON)	Abs. peak SV from pred. VO2% (Nexfin)	Peak SV* (mL) (ICON)	Peak SV* (mL) (Nexfin)	Peak dP/dt* (mmHg/sec) (Nexfin)
A	93	14,7	25,1	58,96	93,23	56	33,02	52,21	66,9	56,8	801
B	143	7	44,1	40,82	86,85	98	40	85,11	41,6	17,5	753
C	155	4,5	28	57,86	50,36	53	30,66	26,69	37,9	36,1	436
D	95	25,3	31,2	100	48,72	76	76	37,03	145	87,1	712
E	105	17	32,7	95,41	92,05	64	61,06	58,91	94	82,3	1426
F	95	7,8	13,9	67,67	83,46	29	18,78	23,16	87	70,4	851

* Value derived from the peak workload

**A percentage lower then 80% of the predicted value is bad

Table 2: Peak ICON en Nexfin measurements during CPET

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
ICON stroke volume	,184	6	,200*	,924	6	,538
Nexfin stroke volume	,171	6	,200*	,935	6	,622
ICON cardiac output	,166	6	,200*	,942	6	,675
Nexfin cardiac output	,190	6	,200*	,922	6	,517
ICON cardiac index	,363	6	,013	,742	6	,016
Nexfin cardiac index	,194	6	,200*	,937	6	,634
Nexfin dP/dt	,307	6	,079	,869	6	,224

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Table 3: Tests of normality

Represented in this table are the results, calculated with SPPS 15.00 for Windows, for the Shapiro-Wilk test. Based on these results, we may conclude that SV, CO and dP/dt are normally divided, both in ICON as Nexfin ($p > 0,05$). ICON CI is not normally divided ($p = 0,016$) and therefore further analyses all parameters will be done with both Pearson's correlation as Spearman's correlation.

Correlations

		Wpeak % of predicted	Wpeak /kg % of predicted	% predicted HRpeak	% predicted Vo2peak	% predicted O2 pulse	VO2peak L/min percentage of predicted	ICON stroke volume	Nexfin stroke volume	ICON cardiac output	Nexfin cardiac output	ICON cardiac index	Nexfin cardiac index	Nexfin dP/dt
Wpeak % of predicted	Pearson Correlation	1	,842*	-,054	,730	,777	,680	,538	,122	,533	,135	,646	-,083	-,165
	Sig. (2-tailed)		,036	,920	,100	,069	,138	,271	,818	,276	,799	,165	,876	,754
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
Wpeak /kg % of predicted	Pearson Correlation	,842*	1	,346	,922*	,635	,902*	,162	-,211	,137	-,126	,623	-,198	-,029
	Sig. (2-tailed)	,036		,501	,009	,175	,014	,760	,688	,796	,813	,187	,708	,957
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
% predicted HRpeak	Pearson Correlation	-,054	,346	1	,355	-,370	,443	-,745	-,817*	-,787	-,819*	-,284	-,718	-,476
	Sig. (2-tailed)	,920	,501		,490	,471	,379	,089	,047	,063	,046	,585	,108	,340
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
% predicted Vo2peak	Pearson Correlation	,730	,922**	,355	1	,693	,981**	-,046	-,379	,090	-,234	,769	-,286	-,001
	Sig. (2-tailed)	,100	,009	,490		,127	,001	,931	,459	,865	,655	,074	,583	,999
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
% predicted O2 pulse	Pearson Correlation	,777	,635	-,370	,693	1	,571	,568	,329	,768	,463	,946*	,312	,324
	Sig. (2-tailed)	,069	,175	,471	,127		,237	,240	,524	,074	,356	,004	,547	,531
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
VO2peak L/min percentage of predicted	Pearson Correlation	,680	,902*	,443	,981*	,571	1	-,165	-,516	-,060	-,388	,678	-,427	-,103
	Sig. (2-tailed)	,138	,014	,379	,001	,237		,754	,294	,910	,447	,139	,398	,847
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
ICON stroke volume	Pearson Correlation	,538	,162	-,745	-,046	,568	-,165	1	,891*	,895*	,850*	,335	,676	,321
	Sig. (2-tailed)	,271	,760	,089	,931	,240	,754		,017	,016	,032	,516	,140	,536
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
Nexfin stroke volume	Pearson Correlation	,122	-,211	-,817*	-,379	,329	-,516	,891*	1	,811	,969**	,118	,886*	,520
	Sig. (2-tailed)	,818	,688	,047	,459	,524	,294	,017		,050	,001	,824	,019	,290
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
ICON cardiac output	Pearson Correlation	,533	,137	-,787	,090	,768	-,060	,895*	,811	1	,836*	,581	,642	,348
	Sig. (2-tailed)	,276	,796	,063	,865	,074	,910	,016	,050		,038	,226	,169	,499
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
Nexfin cardiac output	Pearson Correlation	,135	-,126	-,819*	-,234	,463	-,388	,850*	,969**	,836*	1	,302	,951**	,687
	Sig. (2-tailed)	,799	,813	,046	,655	,356	,447	,032	,001	,038		,561	,004	,132
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
ICON cardiac index	Pearson Correlation	,646	,623	-,284	,769	,946**	,678	,335	,118	,581	,302	1	,218	,398
	Sig. (2-tailed)	,165	,187	,585	,074	,004	,139	,516	,824	,226	,561		,679	,434
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
Nexfin cardiac index	Pearson Correlation	-,083	-,198	-,718	-,286	,312	-,427	,676	,886*	,642	,951**	,218	1	,847*
	Sig. (2-tailed)	,876	,708	,108	,583	,547	,398	,140	,019	,169	,004	,679		,033
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
Nexfin dP/dt	Pearson Correlation	-,165	-,029	-,476	-,001	,324	-,103	,321	,520	,348	,687	,398	,847*	1
	Sig. (2-tailed)	,754	,957	,340	,999	,531	,847	,536	,290	,499	,132	,434	,033	
	N	6	6	6	6	6	6	6	6	6	6	6	6	6

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4: Pearson's correlations between the different parameters that where measured during the CPET

Measurements of SV, CO, CI and dP/dt were included even as measurements of other parameters, to see whether they correlate with SV, CO, CI and dP/dt. SV of ICON and Nexfin were significantly correlated (R = 0,891, p = 0,017), just as the CO (R = 0,836, p = 0,038). There was no significant correlation between CI of ICON and Nexfin (R = 0,218, p = 0,679). There was also a high, significant correlation between ICON CO and ICON SV (R = 0,895, p = 0,016), between Nexfin CO and Nexfin SV (R = 0,969, p = 0,001), but also between Nexfin CO and ICON SV (R = 0,850, p = 0,032). Significantly high correlation was also found between Nexfin CI and Nexfin SV (R = 0,886, p = 0,019), Nexfin CI and Nexfin CO (R = 0,951, p = 0,004) and Nexfin CI and Nexfin dP/dt (R = 0,847, p = 0,033). This should be the case with values of ICON, but here were some discrepancies.

Correlations

			O2PULSE	Nexfin dP/dt	ICON stroke volume	Nexfin stroke volume	ICON cardiac output	Nexfin cardiac output	ICON cardiac index	Nexfin cardiac index
Spearman's rho	O2PULSE	Correlation Coefficient	1,000	,371	,943**	,886*	,943**	,829*	,406	,829*
		Sig. (2-tailed)	.	,468	,005	,019	,005	,042	,425	,042
		N	6	6	6	6	6	6	6	6
	Nexfin dP/dt	Correlation Coefficient	,371	1,000	,429	,314	,257	,543	,029	,543
		Sig. (2-tailed)	,468	.	,397	,544	,623	,266	,957	,266
		N	6	6	6	6	6	6	6	6
	ICON stroke volume	Correlation Coefficient	,943**	,429	1,000	,943**	,829*	,886*	,319	,886*
		Sig. (2-tailed)	,005	,397	.	,005	,042	,019	,538	,019
		N	6	6	6	6	6	6	6	6
	Nexfin stroke volume	Correlation Coefficient	,886*	,314	,943**	1,000	,771	,943**	,029	,943**
		Sig. (2-tailed)	,019	,544	,005	.	,072	,005	,957	,005
		N	6	6	6	6	6	6	6	6
	ICON cardiac output	Correlation Coefficient	,943**	,257	,829*	,771	1,000	,657	,406	,657
		Sig. (2-tailed)	,005	,623	,042	,072	.	,156	,425	,156
		N	6	6	6	6	6	6	6	6
	Nexfin cardiac output	Correlation Coefficient	,829*	,543	,886*	,943**	,657	1,000	-,058	1,000**
		Sig. (2-tailed)	,042	,266	,019	,005	,156	.	,913	.
		N	6	6	6	6	6	6	6	6
	ICON cardiac index	Correlation Coefficient	,406	,029	,319	,029	,406	-,058	1,000	-,058
		Sig. (2-tailed)	,425	,957	,538	,957	,425	,913	.	,913
		N	6	6	6	6	6	6	6	6
	Nexfin cardiac index	Correlation Coefficient	,829*	,543	,886*	,943**	,657	1,000**	-,058	1,000
		Sig. (2-tailed)	,042	,266	,019	,005	,156	.	,913	.
		N	6	6	6	6	6	6	6	6

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 5: Spearman's correlation

Spearman's correlation between the O_2 pulse and the stroke volume, cardiac output, cardiac index and dP/dt of the two techniques. The O_2 pulse indicates the amount of oxygen uptake per heartbeat by the body. This is an indicator for the stroke volume and cardiac output, which is why there is a significant positive correlation between these parameters.

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ICON stroke volume & Nexfin stroke volume	6	,891	,017
Pair 2	ICON cardiac output & Nexfin cardiac output	6	,836	,038
Pair 3	ICON cardiac index & Nexfin cardiac index	6	,218	,679

Table 6: Paired samples correlations

A high correlation is found between ICON and Nexfin stroke volume, 0,891 (p = 0,017) and between ICON and Nexfin cardiac output, 0,836 (p = 0,038). There is no correlation between ICON and Nexfin cardiac index since the significance is 0,679.

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	ICON stroke volume - Nexfin stroke volume	20,4183	19,7990	8,0829	-,3594	41,1961	2,526	5	,053
Pair 2	ICON cardiac output - Nexfin cardiac output	3,8500	1,8189	,7426	1,9412	5,7588	5,185	5	,004
Pair 3	ICON cardiac index - Nexfin cardiac index	2,7667	1,3958	,5699	1,3018	4,2315	4,855	5	,005

Table 7: Paired samples test

To check whether the mean values of the test are approximately the same or differ significantly, a paired T test is done with SPSS 15.0. The mean difference between ICON and Nexfin stroke volume is 20,4183 (p = 0,053), so there is, according to this test, no significantly difference between the data gained with ICON and Nexfin. However, the significance is minimal and the 95% confidence interval is -0,3594; 41,1961. The data gained with ICON and Nexfin differ significantly with measurements for cardiac output and cardiac index (p = 0,004 respectively 0,005).

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power(a)
M	Sphericity Assumed	964,206	1	964,206	2,999	,144	2,999	,291
	Greenhouse-Geisser	964,206	1,000	964,206	2,999	,144	2,999	,291
	Huynh-Feldt	964,206	1,000	964,206	2,999	,144	2,999	,291
	Lower-bound	964,206	1,000	964,206	2,999	,144	2,999	,291
Error(M)	Sphericity Assumed	1607,748	5	321,550				
	Greenhouse-Geisser	1607,748	5,000	321,550				
	Huynh-Feldt	1607,748	5,000	321,550				
	Lower-bound	1607,748	5,000	321,550				
T	Sphericity Assumed	1315,279	2	657,639	7,859	,009	15,717	,866
	Greenhouse-Geisser	1315,279	1,606	818,748	7,859	,016	12,625	,794
	Huynh-Feldt	1315,279	2,000	657,639	7,859	,009	15,717	,866
	Lower-bound	1315,279	1,000	1315,279	7,859	,038	7,859	,615
Error(T)	Sphericity Assumed	836,827	10	83,683				
	Greenhouse-Geisser	836,827	8,032	104,183				
	Huynh-Feldt	836,827	10,000	83,683				
	Lower-bound	836,827	5,000	167,365				
M * T	Sphericity Assumed	288,673	2	144,336	1,556	,258	3,111	,256
	Greenhouse-Geisser	288,673	1,198	240,897	1,556	,267	1,864	,192
	Huynh-Feldt	288,673	1,365	211,454	1,556	,266	2,124	,206
	Lower-bound	288,673	1,000	288,673	1,556	,268	1,556	,175
Error(M*T)	Sphericity Assumed	927,855	10	92,785				
	Greenhouse-Geisser	927,855	5,992	154,858				
	Huynh-Feldt	927,855	6,826	135,932				
	Lower-bound	927,855	5,000	185,571				

a Computed using alpha = ,05

Table 8: Tests of within-subject effects; results of SV

Represented in this table are the results obtained from the tests of within-subject effects for SV when ICON and Nexfin results were compared at time points 01:00, 04:30 and 10:00. SV data were independent of the method, since significance of M*T and M were bigger than 0,05 (p = 0,257 respectively p = 0,144). However, SV data had an effect over time, since significance of T was p = 0,016. Results were obtained from the repeated measurements analyses when methods are polynomial and time is simple first.

Tests of Within-Subjects Contrasts

Measure: MEASURE_1

Source	M	T	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power(a)
M	Linear		321,402	1	321,402	2,999	,144	2,999	,291
Error(M)	Linear		535,916	5	107,183				
T		Level 2 vs. Level 1	1603,141	1	1603,141	11,630	,019	11,630	,777
		Level 3 vs. Level 1	2282,797	1	2282,797	9,162	,029	9,162	,680
Error(T)		Level 2 vs. Level 1	689,234	5	137,847				
		Level 3 vs. Level 1	1245,777	5	249,155				
M * T	Linear	Level 2 vs. Level 1	13,441	1	13,441	,148	,716	,148	,062
		Level 3 vs. Level 1	350,893	1	350,893	1,046	,353	1,046	,134
Error(M*T)	Linear	Level 2 vs. Level 1	453,634	5	90,727				
		Level 3 vs. Level 1	1678,089	5	335,618				

a. Computed using alpha = ,05

Table 9: Tests of within-subjects contrasts: results of SV

Represented in this table are the results obtained from the tests of within-subjects contrasts for SV when ICON and Nexfin results are compared at time points 01:00, 04:30 and 10:00. According to this test, SV data between the three time points (levels) were significantly different (p = 0,019 respectively p = 0,029).

Pairwise Comparisons

Measure: MEASURE_1

(I) T	(J) T	Mean Difference (I-J)	Std. Error	Sig.(a)	95% Confidence Interval for Difference(a)	
					Upper Bound	Lower Bound
1	2	-11,558	3,389	,057	-23,536	,420
	3	-13,793	4,557	,088	-29,896	2,311
2	1	11,558	3,389	,057	-,420	23,536
	3	-2,234	3,097	1,000	-13,179	8,711
3	1	13,793	4,557	,088	-2,311	29,896
	2	2,234	3,097	1,000	-8,711	13,179

Based on estimated marginal means

a. Adjustment for multiple comparisons: Bonferroni.

Table 10: Pairwise comparisons: results of SV

Represented in this table are the results obtained from the pairwise comparisons based on estimated marginal means for SV when ICON and Nexfin results are compared at time points 01:00, 04:30 and 10:00. There were no significant difference between data obtained with ICON and Nexfin, since all significances are bigger than 0,05.

Tests of Within-Subjects Contrasts

Measure: MEASURE_1

Source	M	T	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power(a)
M	Linear		964,206	1	964,206	2,999	,144	2,999	,291
Error(M)	Linear		1607,748	5	321,550				
T		Linear	1141,398	1	1141,398	9,162	,029	9,162	,680
		Quadratic	173,880	1	173,880	4,064	,100	4,064	,373
Error(T)		Linear	622,889	5	124,578				
		Quadratic	213,939	5	42,788				
M * T	Linear	Linear	175,446	1	175,446	1,046	,353	1,046	,134
		Quadratic	113,226	1	113,226	6,375	,053	6,375	,530
Error(M*T)	Linear	Linear	839,045	5	167,809				
		Quadratic	88,810	5	17,762				

a. Computed using alpha = ,05

Table 11: Tests of within-subject contrasts; results of SV (T and M polynomial)

Represented in this table are the results obtained from the tests of within-subject effects for SV when ICON and Nexfin results were compared at time points 01:00, 04:30 and 10:00. Results are obtained from the repeated measurements analyses when methods and time are polynomial. Based on these results we could conclude that there was a linear relation between SV data obtained from ICON and Nexfin (p(quadratic) = 0,100 and p(linear) = 0,029).

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power(a)
M	Sphericity Assumed	14,887	1	14,887	2,852	,152	2,852	,280
	Greenhouse-Geisser	14,887	1,000	14,887	2,852	,152	2,852	,280
	Huynh-Feldt	14,887	1,000	14,887	2,852	,152	2,852	,280
	Lower-bound	14,887	1,000	14,887	2,852	,152	2,852	,280
Error(M)	Sphericity Assumed	26,098	5	5,220				
	Greenhouse-Geisser	26,098	5,000	5,220				
	Huynh-Feldt	26,098	5,000	5,220				
	Lower-bound	26,098	5,000	5,220				
T	Sphericity Assumed	79,543	2	39,772	15,438	,001	30,876	,992
	Greenhouse-Geisser	79,543	1,847	43,055	15,438	,001	28,521	,987
	Huynh-Feldt	79,543	2,000	39,772	15,438	,001	30,876	,992
	Lower-bound	79,543	1,000	79,543	15,438	,011	15,438	,877
Error(T)	Sphericity Assumed	25,762	10	2,576				
	Greenhouse-Geisser	25,762	9,237	2,789				
	Huynh-Feldt	25,762	10,000	2,576				
	Lower-bound	25,762	5,000	5,152				
M * T	Sphericity Assumed	,418	2	,209	,243	,788	,487	,079
	Greenhouse-Geisser	,418	1,875	,223	,243	,775	,456	,078
	Huynh-Feldt	,418	2,000	,209	,243	,788	,487	,079
	Lower-bound	,418	1,000	,418	,243	,643	,243	,069
Error(M*T)	Sphericity Assumed	8,579	10	,858				
	Greenhouse-Geisser	8,579	9,375	,915				
	Huynh-Feldt	8,579	10,000	,858				
	Lower-bound	8,579	5,000	1,716				

a. Computed using alpha = ,05

Table 12: Tests of within-subject effects; results of CO

Represented in this table are the results obtained from the tests of within-subject effects for CO when ICON and Nexfin results were compared at time points 01:00, 04:30 and 10:00. CO data were independent of the method, since significance of M*T and M were bigger than 0,05 (p = 0,775 respectively p = 0,152). However, SV data had an effect over time, since significance of T was p = 0,001. Results were obtained from the repeated measurements analyses when methods are polynomial and time is simple first.

Tests of Within-Subjects Contrasts

Measure: MEASURE_1

Source	M	T	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power(a)
M	Linear		4,962	1	4,962	2,852	,152	2,852	,280
Error(M)	Linear		8,699	5	1,740				
T		Level 2 vs. Level 1	45,202	1	45,202	12,253	,017	12,253	,797
		Level 3 vs. Level 1	158,850	1	158,850	27,913	,003	27,913	,985
Error(T)		Level 2 vs. Level 1	18,445	5	3,689				
		Level 3 vs. Level 1	28,455	5	5,691				
M * T	Linear	Level 2 vs. Level 1	,255	1	,255	,198	,675	,198	,066
		Level 3 vs. Level 1	,832	1	,832	,454	,530	,454	,086
Error(M*T)	Linear	Level 2 vs. Level 1	6,439	5	1,288				
		Level 3 vs. Level 1	9,156	5	1,831				

a. Computed using alpha = ,05

Table 13: Tests of within-subjects contrasts: results of CO

Represented in this table are the results obtained from the tests of within-subjects contrasts for CO when ICON and Nexfin results are compared at time points 01:00, 04:30 and 10:00. According to this test, CO data between level 1 and 2 and between level 1 and 3 were significantly different (p = 0,017 respectively p = 0,003).

Pairwise Comparisons

Measure: MEASURE_1

(I) T	(J) T	Mean Difference (I-J)	Std. Error	Sig.(a)	95% Confidence Interval for Difference(a)	
					Upper Bound	Lower Bound
1	2	-1,941	,554	,052	-3,900	,019
	3	-3,638(*)	,689	,010	-6,072	-1,205
2	1	1,941	,554	,052	-,019	3,900
	3	-1,698	,712	,188	-4,213	,818
3	1	3,638(*)	,689	,010	1,205	6,072
	2	1,698	,712	,188	-,818	4,213

Based on estimated marginal means

*. The mean difference is significant at the ,05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Table 14: Pairwise comparisons: results of CO

Represented in this table are the results obtained from the pairwise comparisons based on estimated marginal means for CO when ICON and Nexfin results are compared at time points 01:00, 04:30 and 10:00. There were significant difference between data obtained with ICON and Nexfin, since some significances are not bigger than 0,05. There is a significant difference between level 1 and 3 (p = 0,010).

Tests of Within-Subjects Contrasts

Measure: MEASURE_1

Source	M	T	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power(a)
M	Linear		14,887	1	14,887	2,852	,152	2,852	,280
Error(M)	Linear		26,098	5	5,220				
T		Linear	79,425	1	79,425	27,913	,003	27,913	,985
		Quadratic	,118	1	,118	,051	,830	,051	,054
Error(T)		Linear	14,227	5	2,845				
		Quadratic	11,535	5	2,307				
M * T	Linear	Linear	,416	1	,416	,454	,530	,454	,086
		Quadratic	,002	1	,002	,002	,966	,002	,050
Error(M*T)	Linear	Linear	4,578	5	,916				
		Quadratic	4,001	5	,800				

a. Computed using alpha = ,05

Table 15: Tests of within-subject contrasts; results of CO (T and M polynomial)

Represented in this table are the results obtained from the tests of within-subject effects for CO when ICON and Nexfin results were compared at time points 01:00, 04:30 and 10:00. Results are obtained from the repeated measurements analyses when methods and time are polynomial. Based on these results we could conclude that there was a linear relation between CO data obtained from ICON and Nexfin (p(quadratic) = 0,830 and p(linear) = 0,003).