CRITICAL INVESTIGATION OF THE PULSE CONTOUR METHOD FOR OBTAINING BEAT-BY-BEAT CARDIAC OUTPUT

by

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A thesis
presented to the University of Waterloo
in fulfillment of the
thesis requirement for the degree of
Master of Science
in
Kinesiology

Waterloo, Ontario, Canada, 2001

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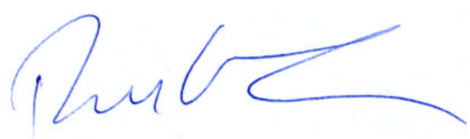

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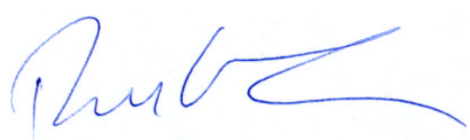

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Abstract

The purpose of this study was to explore the efficacy of two existing pulse contour analysis (PCA) models for estimating cardiac stroke volume from the arterial pressure waveform during kicking ergometer exercise and head-up tilt manoeuvres. Secondly, one of the existing models was modified in an attempt to enhance its performance. In part I, seven healthy young adults repeated two submaximal exercise sessions on a kicking ergometer, each with three different sets of steady-state cardiac output comparisons (pulsed Doppler vs. pulse contour). Across all exercise trials regression results were found to be: PCA = 1.23 × Doppler -1.38 with an $r^2 = 0.51$. In part II, eight young and eight older male healthy subjects participated in a head-up tilt experiment. Cardiac output comparisons were again performed during the supine and tilt conditions using pulsed Doppler and pulse contour cardiac output. Regression results revealed that PCA performed best during supine conditions and preferentially on the older subjects. In all instances, impedance-calibrated pulse contour analysis will provide reasonable beat-by-beat cardiac output within very narrow confines and will result in a progressively more significant bias as cardiovascular dynamics change. In addition, it appears that heart rate variability negatively influences beat-by-beat pulse contour cardiac output results, further limiting application of existing models.

Acknowledgements

As independent as graduate school is, no individual gets through it alone. Many people inevitably contribute to ones success. With this, I am thankful and indebted to those people that have been there for me along the way.

First and foremost, I must extend my deepest thanks for Dr. Richard L. Hughson. Rich, you have provided a perfect balance of encouragement and criticism, support and scrutiny, and independence and guidance to ignite my drive to become a better scientist. You have successfully blurred the line between advisor and friend, thus providing a comfortable platform for me to launch and refine ideas and concepts.

To Dave Northey and the lab. Dave, your persistent meticulousness sets a high standard that I personally strive to emulate. In addition, your knowledge and experience provides all whom work with you unrivalled technical support and assistance. To Debbie O Leary thank you so much for your unyielding assistance and friendship, something that I shall not soon forget. For rest of the crew in the lab and those that have come and gone your cooperation and willingness to assist in whatever capacity made for an enjoyable working environment.

To Bryan McKellar the guy behind the scenes that contributed a great deal of time and effort to help me develop the necessary software. I am forever grateful I owe you one.

Last but not least, I must extend my thanks to my parents, John and Audrey, my brother and sister-in-law, Bev & Beverly, and to my sister and brother-in-law, Bonita and Brett. Your influences have made me who I am today. By growing with you, I cannot help but to take a small part of you with me. You have always been there through all my trials and tribulations, success and summits.

Dedication

To the two people

that have brought me into this world.

My dearest

Mother and Father.

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Chapter 1

LITERATURE REVIEW

1.1 Introduction

When considering the cardiovascular system, the foremost feature is the cardiac output, or the volume of blood the heart pumps in a given unit of time; most commonly expressed in liters per minute $(L \cdot \min^{-1})$. Essentially, it is the *heart* of the system. The significance of cardiac output is appreciated clinically for a plethora of medical conditions and patients. In all cases, circulation is of primary concern in emergent care, only behind airway and breathing concerns. Cardiac output is readily valued as a diagnostic indicator for those patients suspected of an acute myocardial infarction (AMI). The clinical status of a patient suffering from an AMI is directly related to their cardiac output (Forrester *et al.*, 1976, Forrester *et al.*, 1977) in that prognosis deteriorates with a diminishing cardiac output. Fifty percent of AMI patients have an impaired cardiac output and 25% of infarctions are not identifiable by standard clinical criteria (Forrester *et al.*, 1976). Diagnosis of infarction alone is aided with knowledge of real-time cardiac output. Conditions such as cardiogenic shock, hypovolemic shock and pericardial tamponade are also circumstances where cardiac output may be diminished, to name a few. Thus, there is a real clinical demand to have a means readily available to easily determine cardiac output with minimal, if any, invasiveness.

In the realm of sports physiology, assessment of cardiovascular function, particularly cardiac output is imperative when evaluating cardiovascular factors that might otherwise limit oxygen transport. A plethora of techniques, both invasive and non-invasive are available to measure and / or monitor cardiac output during rest and submaximal exercise conditions. However, very few techniques have proven to be accurate and reliable during strenuous, let alone maximal exercise conditions (Warburton *et al.*, 1999a). For exercise physiologists and cardiologists, knowledge of cardiac output during strenuous and maximal conditions is of primary importance. In spite of this, an accurate and reliable process to determine cardiac output under such conditions has remained elusive.

Often times, clinical demands drive the design and motivate the derivation of new equipment that is ultimately used outside of standard clinical practices. In particular, the research field itself will often use clinical techniques to study various phenomena. The pulse contour method for measuring cardiac output is one such example. The pulse contour method as developed by Wesseling *et al.* (1983) was originally designed with a resting, supine subject. From here, others began to use this beat-by-beat technique to acquire cardiac output in situations such as exercise, head-up and head-down tilt and a wide range of patients of differing medical conditions and statuses. As such, it is based on a model with its own inherent assumptions and limitations that may not be applicable to these novel and unique situations. Therefore, the confines to which the technique can be applied with validity and reliability must be ascertained.

1.2 Cardiac Output

Acquiring trustworthy cardiac output is not an easy task. It typically can entail technical expertise, specialized equipment, precise subject cooperation and varying levels of risk. In addition, most measurement techniques are limited to steady-state conditions (see table 1.1). Perhaps most discouraging, all gold-standard measurement techniques are highly invasive, necessitate the finest degree of expertise, require highly specialized equipment, and impose the greatest risk to patients and subjects. These disadvantages are enough to preclude common use. Hence, these techniques are usually restricted to patients who required catheterization for clinical reasons. Complications with such procedures include ventricular arrhythmias and fibrillation, perforation of the pulmonary artery or right ventricle, to name a few (Shaw *et al.*, 1985, Bowdle *et al.*, 1991). Although incidence of complications is low, the risks outweigh the benefit so that exercise physiologists rarely use these highly invasive procedures on healthy participants.

Table 1-1: Existing cardiac output measurement techniques

Type	Cardiac Output Method	Application / Type
Gold Standard Measures	Direct Fick Dye-Dilution Thermodilution	Steady-state
Non-Invasive (Foreign Gas Measures)	N_2O Rebreathe C_2H_2 Rebreathe	Steady-state
Indirect Fick (CO_2 Measures)	Single-breath method Rebreathe method	Steady-state
Other Measures	Doppler echocardiography Impedance cardiography Radionuclide Scintigraphy Pulse contour analysis	Beat-by-beat
New Advances (C_2H_2) (Modified Acetylene Methods)	Single-breath constant exhalation method Double inert foreign gas non-rebreathing method	Steady-state

Rebreathe manoeuvres require precise coordination between the subject and experimenter[1] and experienced judgment when selecting appropriate gas volumes and concentrations. Today, many different gasses and combinations of such are used. Options exist for procedures that utilize either a single-breath of the foreign gas or a period of rebreathing. In all cases, the gas of choice must

[1] Provided that the system is not automated.

rapidly diffuse across the pulmonary membrane, thus being limited only by its removal from the lungs. Furthermore, the rebreathing procedures and the gasses alone can influence cardiovascular status. Therefore, it is necessary to use an average of such variables (i.e. heart rate, end-tidal CO_2, etc.) just prior to the procedure. This further widens the time resolution with which measurement occurs thus further emphasizing the requisite of steady-state conditions.

Beat-by-beat cardiac output essentially improves the time resolution of the measurement procedure to the point that the volume of blood ejected for each beat can be calculated. The two main methods in use are impedance cardiography and Doppler echocardiography. Beat-by-beat measures are advantageous in that they intrinsically do not require steady-state conditions. Subsequently, such methods can be employed when one is interested in a transition between cardiovascular conditions or in patients presenting with an unstable cardiovascular status.

1.3 Vascular Impedance

Whenever fluid flows, we can describe the characteristics in terms of a pressure gradient (ΔP), resistance (R) and flow $(\dot{Q})$. This relationship is commonly described by analogy using Ohm s Law:

$$\dot{Q} = \frac{\Delta P}{R}$$

Equation 1-1: Ohm's law analogy

However, blood flow in the aorta and arteries is inherently pulsatile. Therefore, the term *impedance* instead of resistance is more appropriately used as first suggested by McDonald in 1955. Impedance *is* a resistance term but applies to situations where flow is discontinuous. Additionally, just like resistance, impedance cannot be directly measured but instead is calculated from flow and pressure differences in a blood vessel. Consequently, as it will be discussed in latter sections, determination of impedance for the pulse contour method of cardiac output is the crux of the problem.

Like its electrical analog, impedance exemplifies the importance of a phase difference between pressure and flow (as in the case of alternating electrical current, a phase difference between voltage and current). Impedance, like resistance, is pressure $\left(dyne \cdot cm^{-2}\right)$ divided by flow $\left(cm \cdot s^{-1}\right)$ and therefore has the units of $\left({dyne \cdot s}/{cm^3}\right)$. However, it is more common to report cardiovascular impedance as a function of volume flow giving the units of $\left({dyne \cdot s}/{cm^5}\right)$. When the general term impedance (*Z*) is used, it is usually referring to input impedance[1] or the relationship between pulsatile pressure (*P*) (as opposed to a pressure gradient) and flow $(\dot{Q})$:

$$Z_i = \frac{P}{\dot{Q}}$$

Equation 1-2: Input impedance

Consequently, the phenomenon of reflected arterial waves influences the impedance upstream. Therefore, flow at a particular arterial site not only depends on local features but also on the properties of all vascular beds downstream to the point where all cardiac-generated pulsations have been attenuated. In effect, this corresponds to the arterial-end of capillaries where pressure and flow are nearly continuous without significant pulsations being reflected back to the heart.

1.4 Pulse Contour Analysis

A technique to measure cardiac output was first proposed in 1870 by the German Physiologist, Adolph Fick and although the Fick principle is well over a century old, it is still the common basis of several cardiac output measurement techniques. Nevertheless, a method or device that can easily determine cardiac output non-invasively on a beat-by-beat basis is still being sought. Pulse contour, in theory is just such a method. Specifically, Wesseling *et al.* (1983), identified 3 main advantages for the Pulse Contour Method:

[1] See glossary for definitions

1. It provides beat-by-beat cardiac output. This is especially useful when assessing a changing or unstable cardiovascular status.

2. Output is continuous. Other methods like rebreathing or thermodilution can only provide discontinuous samples of cardiac output.

3. It is simple from an operational perspective. Methods like Doppler echocardiography require the perpetual attention and concentration of a highly skilled technician. Pulse contour method is derived from beat-by-beat blood pressure monitors such as the Finapres (finger photoplethysmography) or the Colin Pilot monitor (radial artery applanation tonometry) in that once they are set, only may require occasional attention.

Similar to Ohm s Law, Wesseling *et al.* (1983) first proposed that stroke volume could be obtained from the area under the systolic blood pressure curve and impedance:

$$SV = \frac{PSA}{Z}$$

Equation 1-3: The basic pulse contour formula

Stroke volume (SV) is calculated in milliliters from the area under the systolic blood pressure curve (Figure 1-1) (PSA) in $(mmHg \cdot s)$ and impedance (Z) in

$(mmHg \cdot s \cdot ml^{-1})$. As simple as this relationship looks, the crux lies in the ability to spontaneously determine the impedance. What's more, as mentioned previously, it cannot be directly measured and must be calculated from pressure and flow.

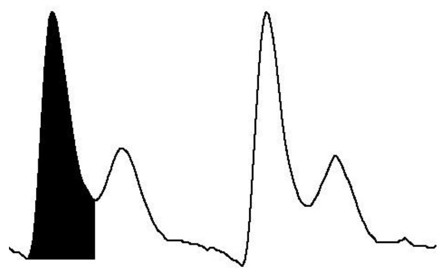

Figure 1-1: Area under the systolic blood pressure curve

To date, several different pulse contour methods have been put forth (Alderman *et al.*, 1972; Starmer *et al.*, 1973; Gratz *et al.*, 1992; Tajimi *et al.*, 1983) but all had serious limitations or narrow confines of applicability, thereby rendering them impractical. However, Wesseling and coworkers (1983) developed a feasible working algorithm (See Figure 1-2 for a pseudo-schematic representation of their approach). It is based on a transmission line model[1] of the circulation from which the concept was first proposed by Kouchoukos *et al.* (1970). Typically, development of algorithms is based on some sort of theoretical model, often using electrical analogs to describe flow behavior.

[1] See glossary for an explanation

From here, specific model parameters are then determined empirically through experimentation. Initial results were encouraging but the solution lacked absolute quantification and only provided values of relative change in stroke volume. Subsequently, a method of resting impedance calibration was implemented as clearly described by Stok *et al.* (1993), thereby increasing the accuracy of the model and adding capability of providing absolute stroke volumes. Nevertheless, this model is most applicable to situations where cardiovascular status is not changing. Such is case where changes in body position are encountered (i.e. various angle of head-up or head-down tilt), thus requiring a re-calibration for the new body position (Stok *et al.*, 1999). Generally speaking, cardiac output as determined by this method of pulse contour analysis and compared to another reference method typically yields correlation coefficients in the range of 0.75 and 0.96 Antonutto *et al.*, (1995).

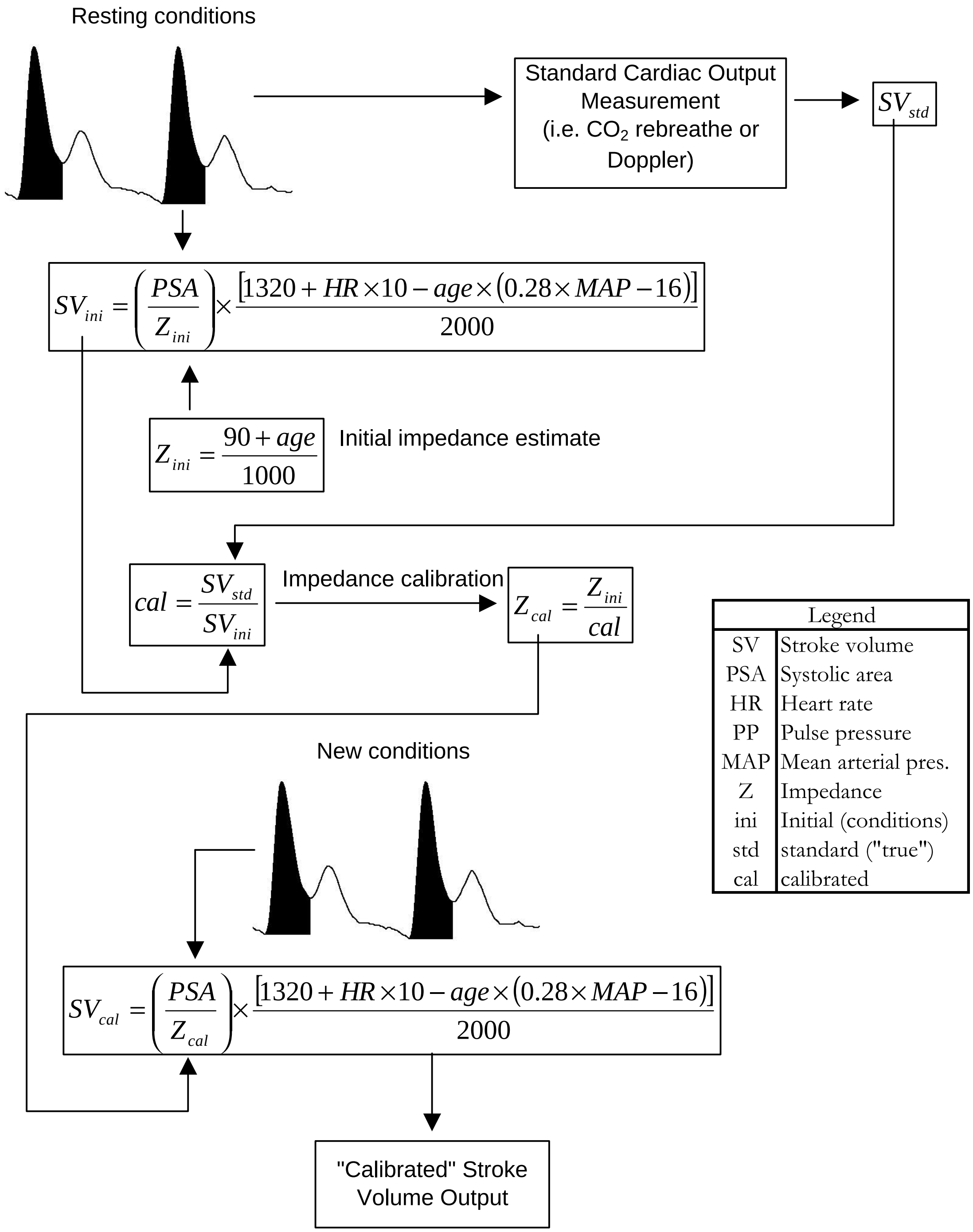

Figure 1-2: Wesseling's approach to pulse contour analysis

Since then, Antonutto *et al.* (1995) presented a series of algorithms with the advantage of providing absolute values for stroke volume integrated into the model. This method utilizes two separate algorithms where the first calculates a resting impedance value from hemodynamic variables without any other correction factor. The second algorithm then adjusts the impedance as hemodynamic variables change. Supposedly, this method is thought to provide more reliable data in exercising conditions or in other states where the hemodynamic status is changing (See Figure 1-3).

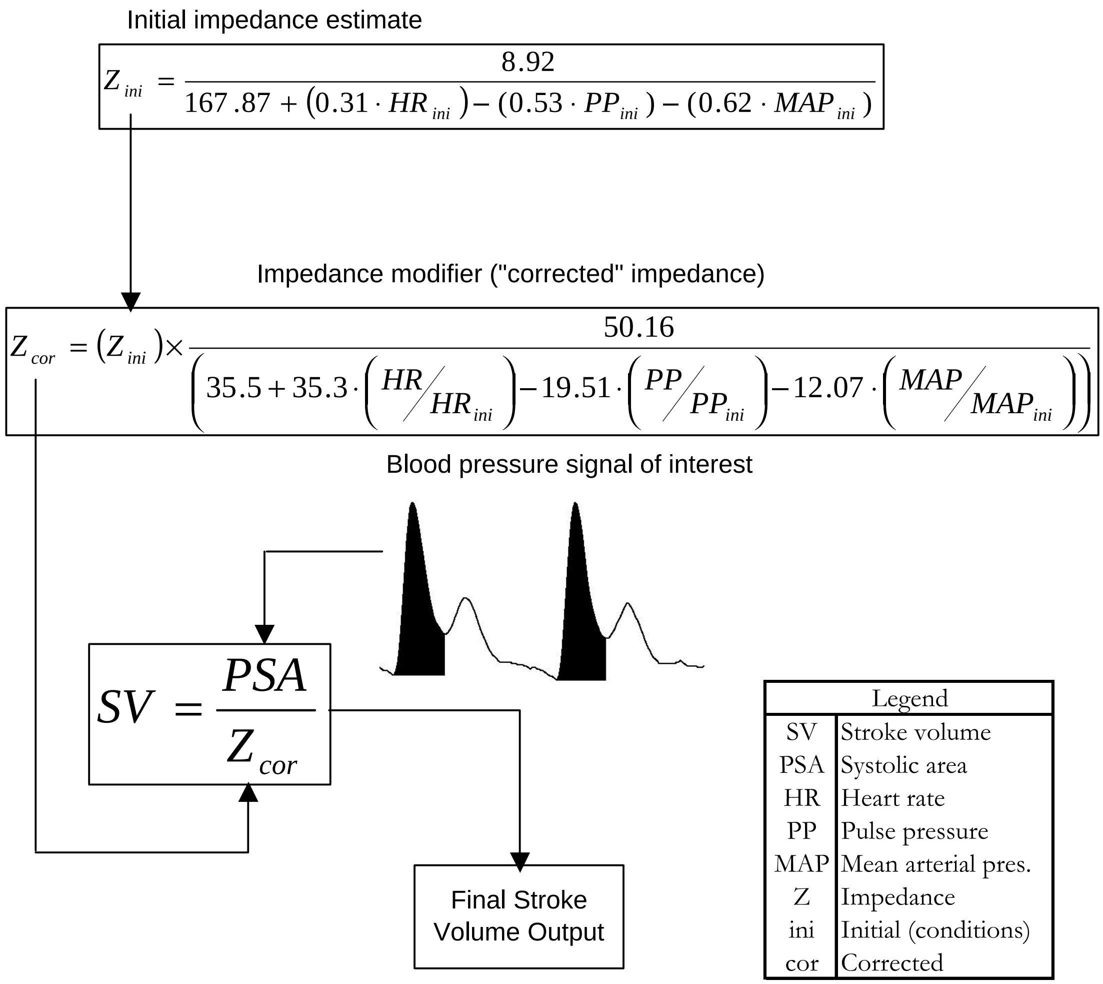

Figure 1-3: Antonutto's approach to pulse contour analysis

In all cases of pulse contour analysis, a mathematical construct is required that adjusts the impedance with associated changes in cardiovascular parameters (heart rate, mean arterial pressure, etc.). Nevertheless the algorithm must accommodate both extensive inter-individual and intra-individual variations in the shape of the pulse contour curve. Part of the problem lies in the fact that the cardiovascular system does not demonstrate complete linearity. Another interesting facet to the problem is how (resting) cardiac output will increase in the progression from childhood to adulthood with nominal change in shape of the pulse contour curve.

Although many attempts have been made to develop a reliable and valid method to obtain cardiac output, the technique that remains most popular is the one by Wesseling and associates. Table 1-1 below lists a history of modern pulse contour analysis studies. Of all the investigations, only the one by Antonutto and coworkers uses a procedure other than that of Wesseling.

Table 1-2: Modern pulse contour analysis studies

Author	Year	Condition(s)	Algorithm	Dye Dil.	Thermo.	Rebrth.	Doppler	Imped.	Subjects	B/P	Cor Coef
Wesseling et al.	1983	Pharmacol.	Wesseling	X					+ 20 (20-30)	F	Yes
Jansen et al.	1990	Crit. Ill	Wesseling		X				+ 8 (?)	IAP	0.94
Gratz et al.	1992	Crit. Ill	Mod. Wesseling		X				+ 27 (44-80)	F	0.75
Tannenbaum et al.[1]	1993	Crit. Ill	Mod. Wesseling		X				+ 29 (43-87)	F	0.64
Stok et al.	1993	HDT/LBNP	Wesseling			C_2H_2			6 (26 ± 5)	F	Yes
Antonutto et al.	1995	Cycle Erg.	Antonutto				PDE		9 (22 ± 2)	F	Yes
Hirschl et al.	1997	Crit. Ill	Wesseling		X				46 (62 ± 12)	F	No
Houtman et al.	1999	Cycle Erg.	Wesseling			CO_2			10 (42 ± 9)	F	No
Stok et al.[1]	1999	HUT / HDT	Wesseling			C_2H_2			+ 12 (31-34)	F	?Yes
Harms et al.	1999	HUT / HDT	Wesseling		X				10 (29 ± 6)	F / IAP	Yes
Nieminen et al.	2000	HUT	Wesseling					X	40 (41 ± 19)	F	No

+ n subjects (age range); all others are: n subjects (mean age ± SD).
Conditions: Pharmacol, Pharmacological interventions; HDT, Head-Down Tilt; HUT, Head-Up Tilt; LBNP, Lower Body Negative Pressure; Crit. Ill, Critically Ill; Cycle Erg, Cycle Ergometer.
B/P F, Finapress; IAP, IntraArterial Pressure.
[1]Conditional success, in that frequent calibrations were implemented

1.5 Summary of Purpose and Hypotheses

The purpose of this study was to evaluate cardiac output as acquired from two different pulse contour algorithms, in addition to a third, modified algorithm during kicking ergometer exercise, using the carbon dioxide rebreathe procedure and pulsed Doppler ultrasound as reference measures of cardiac output. To serve as the platform of comparison, a diverse range of cardiovascular states will be generated. In addition, the same two pulse contour algorithms will be tested against pulsed Doppler ultrasound throughout a supine to head-up tilt regime. Trends will be noted, particularly if one method proves to be advantageous over the others in certain conditions.

Specifically, the hypotheses are:

1) Beat-by-beat pulse contour cardiac output will track beat-by-beat Doppler cardiac output during tilt procedures for young and old adult subjects.

2) Beat-by-beat pulse contour cardiac output will track beat-by-beat Doppler cardiac output during kicking ergometer exercise for young adult subjects.

Chapter 2

THEORY AND METHODOLOGY

2.1 *Introduction*

This section will describe the equipment, techniques and procedures chosen for this thesis in terms of advantages, limitations (both technical and practical) and applications thereof. It is especially warranted to identify the boundaries of non-invasive techniques as they are inescapably accompanied by limitations and assumptions. As such, it is essential to be prudent with the methodology and protocols so as to avoid erroneous results and misguided conclusions. Lastly, a brief a description of the logistics and rationale behind the protocols shall conclude this chapter.

2.2 *Blood Pressure Acquisition*

The basis of pulse contour analysis is to derive flow from a blood pressure profile curve and technically speaking, an *aortic* blood pressure profile. However, since the whole intention is to have a non-invasive cardiac output measurement, seeking aortic pressure would be illogical. Therefore, part of the strategy in developing a model to achieve this, is the ability to use peripheral blood pressure profile curves. For this thesis, two different non-invasive blood pressure monitors were used: the Finapres and Colin Multi-monitor.

2.2.1 *Finapres Blood Pressure Monitor*

The Finapres works on the principle of dynamic vascular unloading. Likewise, this method is also known as: volume-compensation method, volume-clamp method, servo-plethysmomanometry or photoplethysmography. This method of non-invasive blood pressure is based on the theory that if the external pressure applied is equal to the intra-arterial pressure at all times, then the artery is said to be unloaded and will not change in size. If the artery is successfully unloaded, the transmural pressure across the arterial will remain zero throughout the cardiac cycle and the instantaneous external pressure will equal the arterial pressure. As the name implies, the Finapres is applied usually to a finger, specifically the middle phalanx of the middle finger. The device is a small air-filled cuff instrumented with an infrared light emitter and detector on opposite sides to serve as means to monitor the diameter of the finger.

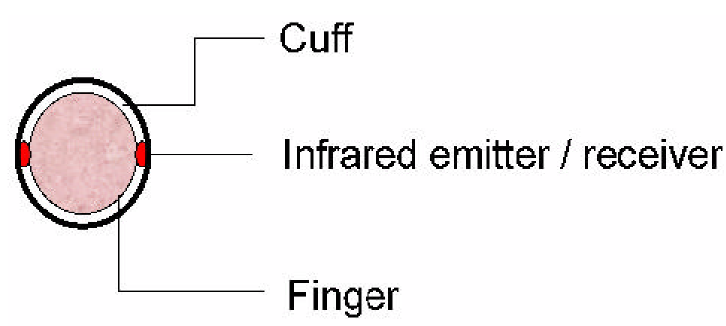

Figure 2-1: Finapres schematic representation

It has been shown that the systolic pressure variation can be as great as 3500 mmHg/sec and as such, the volume-clamp method requires a high-speed servo to keep the arterial size and transmural pressure constant by modulating the finger cuff pressure in parallel with arterial pressure (Langewouters *et al.*, 1998).

Bearing in mind that the Finapres is a peripheral or distal device, inherent fluctuations and deviations from the true arterial pressure will occur as a result of variations of limb position with respect to the gravitational vector. Thus, the position of the hand must be intentional and constant, or else its relative position recorded. One such solution is the Finapres s successor, the Portapres. Besides having the capability to alternate recording from one of two finger cuffs (to alleviate long-term discomfort associated with a finger tourniquet), the Portapres can sense the vertical difference between the hand position and a sensor mounted at heart level.

The Finapres has been used extensively in research and clinical applications and subsequently, has stood the test of time and rigorous investigation in a plethora of situations and conditions. For the purposes of validation, the Finapres has been compared to brachial intra-arterial pressures where blood pressure variations were induced via surgical manoeuvers (Dorlas *et al.*, 1985 and Smith *et al.*, 1985), vasoactive drugs (Imholz *et al.*, 1992), Valsalva manoeuver (Imholz *et al.*, 1988), orthostasis (Imholz *et al.*, 1990) and bicycle exercise to exhaustion (Idema *et al.*, 1989). In summary of this diverse scrutiny (Imholz *et al.*, 1991), it has been shown that the Finapres is usually 5 to 10 mmHg lower than intrabrachial arterial pressure as a result of the pressure differential required to drive fluid flow.

The reliability and validity of the Finapres has been unequivocally demonstrated a number of times in a wide array of situations. Despite its overwhelming popularity the Finapres is not without its limitations. Influential factors are mainly due to the distal nature of the measurement site of the finger where sympathetic innervation is strong (Langewouters *et al.*, 1998) but also includes the following points:

i. The measurement location is inherently distanced from the heart and as a consequence, recorded pressures are lower

ii. Sympathetic stimulation of the finger arterioles may be strong enough to induce a full contraction of the smooth muscle and subsequent collapse. This can occur due to circulatory alterations provoked by psychological stress, severe hemorrhage or pain. Similarly, this can occur in those participants or patients with Raynaud s phenomenon[1].

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[1] See glossary for a description

iii. Cold fingers can create a problem. However, it is the incumbent vasoconstriction leading to the cold fingers that poses the problem rather than the finger temperature itself. External warming of the hand can some times alleviate this problem.

iv. Pressure constantly being applied to the finger reduces distal blood flow to the fingertip, leading to cyanosis and discomfort.

Furthermore, one must bear in mind that the Finapres operates distally at one s finger when in reality it is aortic pressure fluctuations that is desired. Secondly, the pulse travels from the aorta to the periphery as a transverse wave along arterial walls and as such, establishes a phenomenon of reflected waves. Analogously, consider a wave traveling down a taut wire and being reflected back and forth from each end. This occurs within the vascular system, obeying the same principles of wave physics (i.e. a wave velocity is proportional to the tension in the wire). Biologically, harder or tighter blood vessels (i.e. increasing arteriosclerosis with age) will spawn a greater pulse wave velocity. This pulse wave reflection phenomenon is a primary factor behind intra-individual differences in blood pressure profiles that can also trended with corresponding age changes (London & Guerin, 1999). As an aside, the rapid return of pulse-wave from the periphery, back to the aorta occurs early enough (late systole) to augment systolic outflow from the aorta, thus compensating for the age-related loss of aortic elasticity (Karamanoglu & Feneley, 1999).

Despite these potential problems, the Finapres is an indispensable tool in cardiovascular research. For each experimental protocol, an accompanying description is provided, detailing how this device was utilized while minimizing the impact of inherent limitations.

2.2.2 Colin Blood Pressure Monitor

The Colin blood pressure monitor works on the principle of arterial tonometry (Figure 2-2).

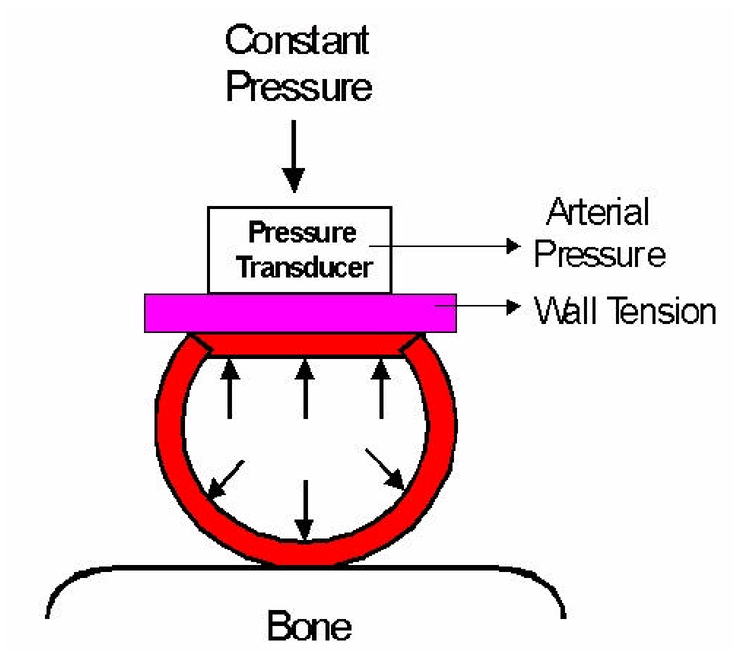


Figure 2-2: Arterial tonometry schematic

The principle is that if a superficial artery, supported by an underlying bone, is maintained in a partially flattened or *applanated* state with a rigid, flat surface, then the force exerted on the surface is nearly proportional to the intra-arterial pressure (Drzewiecki *et al.*, 1983). This arrangement can provide continuous absolute pressures once it is calibrated against a reference method. In the case of the Colin s monitor, the unit initiates continuous blood pressure monitoring with a preliminary sphygmomanometric determination of blood pressure to serve as the calibration. Optionally, the calibration procedure is repeated at various intervals.

Blood pressure monitors taking advantage of arterial tonometry consist of three components (Ng & Small, 1994):

i. Pressure transducer composed or an array of piezoresistive sensors

ii. Electropneumatic system to press against the artery

iii. Electromechanical positioning system to adjust the transducer system transversely to the artery of interest. This is an important component to the system as it eliminates the necessity to manually position the sensor array precisely over the artery.

Conveniently, absolute blood pressure is generally independent of relative arm position provided it does not change because the resultant signal from the applanated artery is calibrated against the prior sphygmomanometer measurement.

The tonometer is positioned over the radial artery with the hand and wrist in a brace-like support that helps maintain a slight degree of wrist extension. Contralaterally, the blood pressure cuff is applied to the upper arm. This arrangement is favored because periodic sphygmomanometric calibrations will not obstruct continuous blood pressure monitoring since cuff inflation will occlude blood flow distally. Once the tonometer is activated, the monitor will search for the radial artery by moving the sensor array transverse to the artery and through algorithms, will select best position and identify the sensor closest to the center of the artery. Subsequently the optimum or hold down pressure will be determined and applied to the artery.

Although not as common as Finapres-type systems, early applanation tonometry systems suffered disfavor because of calibration technical difficulties. In addition, obscurities such as the lack of a standard design, sensitivity to position / movement and transducer technology hindered clinical acceptance. However, technology has since overcome these obstacles to a satisfactory degree and tonometry has proven to be a reliable and valid means to obtain continuous non-invasive blood pressure measurements. One such study verifying this (Siegel *et al*., 1994), evaluated arterial tonometry against radial artery catheterization measurements, resulting in a discrepancy of only 1 ± 5.6 mmHg (mean ± SD).

The most significant drawback to tonometry measurements of blood pressure is the fact that it is especially sensitive to tangential or radial movement relative to the artery of interest. This inconvenience further adds to the justification for using the kicking ergometer as an exercise model. As described previously, the subject is capable of maintaining a fairly relaxed upper body free from extraneous movement and tension.

2.3 Carbon Dioxide Rebreathing

The carbon dioxide rebreathing technique is based on the [indirect] Fick principle as shown below:

$$\textit{Direct Fick} \qquad\qquad \textit{Indirect Fick}$$

$$\dot{Q} = \frac{\dot{V}O_2}{CaO_2 - C\bar{v}O_2} \qquad\qquad \dot{Q} = \frac{\dot{V}CO_2}{C\bar{v}CO_2 - CaCO_2}$$

Equation 2-1: Direct and indirect Fick equations

The advantage to using the carbon dioxide method over the oxygen method is the ease of measurement of carbon dioxide in blood and expired air. Furthermore, all of the variables for carbon dioxide rebreathing can be determined non-invasively and without the need for central-line catheters thereby minimizing the risk.

The variation of the carbon dioxide rebreathing procedure used for this thesis is known as the Collier or equilibrium method, as eloquently described by Jones, (1997). After a normal expiration, the subject rebreathes from a bag of gas that has a higher concentration of CO_2 than that of the $P\bar{v}CO_2$. The gas in the bag will mix with alveolar air and if the appropriate gas volume and CO_2 concentration are used, PCO_2 will fall and equilibrium will occur between the lung-bag system and $P\bar{v}CO_2$. If the gas volume is too great, mixing between the bag and lungs will be incomplete; too low a volume and the subject will experience significant dyspnea, forcing premature termination of the rebreathing manoeuvre. However, selection of CO_2 gas concentration depends greatly on experience and to a certain extent, trial and error. Therefore, to facilitate correct selection of CO_2 gas concentration (balanced O_2), a series of algorithms were developed for this thesis project and graphed accordingly for ease of use during experimentation (Figure 2-3).

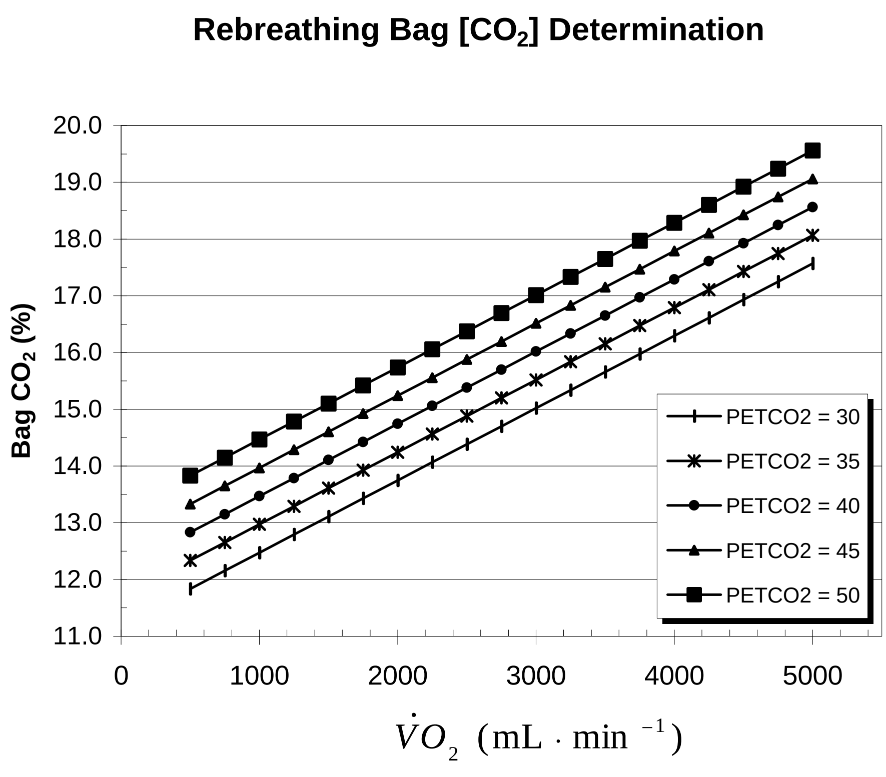


Figure 2-3: Determination of gas concentration for CO_2 rebreathing

The carbon dioxide rebreathing procedure is only valid during steady-state conditions. Particularly, $P_{ET}CO_2$ is easily influenced with rapid changes in ventilation whereas $P\bar{v}CO_2$ would not be affected for about 45 seconds (Heigenhauser & Jones, 1989). A transient increase in ventilation would induce a mismatch between $P_{ET}CO_2$ and $PaCO_2$, with an ostensible widening of the veno-arterial CO_2 difference and subsequent low calculated cardiac output $(\dot{Q})$. The capriciousness of the carbon dioxide rebreathing technique does not invalidate the procedure but rather, simply emphasizes the need for steady-state conditions (Guyton et al., 1973).

The overall validity and reliability of this cardiac output procedure depends on a series of assumptions and empirically derived corrections. Perhaps the two most significant hurdles are the estimate of $P\bar{v}CO_2$ and subsequent determination of CO_2 content. Particularly, assessment of the $P\bar{v}CO_2$ requires a correction factor for anything more than resting conditions. This correction factor was resolved empirically to circumvent the phenomenon of downstream effect[1] . Likewise, the estimate of carbon dioxide content depends on a CO_2 dissociation curve construct. Consideration of the data does suggest however, that the assumptions are less problematic during exercise than rest (Marks *et al.*, 1985). Nevertheless, despite the assumptions and corrections, the Collier carbon

[1] Arterial PCO_2 downstream from the lungs is lower than the lung-bag PCO_2

dioxide rebreathing procedure has been shown to be an accurate technique to ascertain cardiac output during submaximal exercise. Several studies and reviews provide unequivocal verification of the reliability and validity of the carbon dioxide rebreathing procedure during a plethora of conditions and a variety of subjects (Marks *et al*., 1985; Heigenhauser & Jones, 1989; Warburton *et al*., 1999a).

2.4 Doppler Ultrasound

Doppler ultrasound is a valuable tool for researchers and clinicians alike, capable of providing noninvasive measurements of blood flow in addition to imaging of soft tissue. It is based on the principle that a moving object, when insonnated with a sonic pulse will distort or *shift* the frequency of a returning sound wave, relative to the source. With a stationary sound source, an object moving toward the source will induce an increase in the frequency of the reflected wave and the reverse for an object moving away from the sound source. Objects moving perpendicular to the sound source impose no effect on the reflected wave. When insonnating stationary objects (such as the case for some imaging purposes), ultrasound images are derived from wave reflections at tissue-tissue interfaces where there is a disparity in density.

For the measurement of blood flow velocity, Doppler ultrasound penetrates tissue and into a blood vessel where the ultrasound waves are reflected back off moving erythrocytes with an obligatory *shift* from the original transmitted frequency. This *frequency shift* then, is proportional to the velocity of the object(s) insonnated, in this case, erythrocytes. The Doppler formula is given below:

$$V = \frac{\Delta f \times c}{2f \times \cos q}$$

Equation 2-2: Doppler equation

Where V= the velocity magnitude of the object(s) of interest; Δf = Doppler frequency shift; f = the original transmitted frequency; c = velocity of ultrasound through tissue which has been reported to be 1538 m/s (Harrigan & Lee, 1985), 1540 m/s (Nishimura *et al.*, 1984), and 1570 m/s (Huntsman *et al.*, 1983) and q is the angle of insonnation (angle formed between the direction of flow and the ultrasound beam. Interestingly, for measurement of blood velocity in the ascending aorta from a suprasternal approach, the standard practice is to use *either* zero or twenty degrees (Huntsman *et al.*, 1983, Nishimura *et al.*, 1984, Dobb & Donovan, 1987). For this, thesis, it was assumed that the angle of insonnation was 20 degrees in all cases. It is reasonable to presume that aortic insonnation occurs within this range. However, this seemingly arbitrary angle selection is inconsequential because blood flow velocity ultimately depends on the cosine of the angle and the difference between 0 and 20 degrees would result in only a 6% variation.

The particulate nature of blood and inherent discontinuous flow within the aorta necessitates a Fast Fourier Transform (FFT) over individual cardiac cycles. In short, this creates weighted mean frequency shift (see Equation 2-2), which can then be used to solve for a similar weighted mean velocity profile over the cardiac cycle. Subsequent integration of the velocity-time curve provides stroke distance (linear units):

$$stroke\ distance = \int v(t)dt$$

Equation 2-3: Stoke distance

Which when multiplied by cross sectional area, gives stroke volume:

$$SV = CSA \times \int v(t)dt$$

Equation 2-4: Doppler stroke volume

Like all other non-invasive techniques, there are certain assumptions that accompany the practice. The first has been briefly mentioned above, in that the exact angle of insonnation is somewhat of an ambiguity. Secondly, the cross sectional area of the aorta is assumed to be constant over the cardiac cycle. The impact of this assumption does however; depend on the intended point of insonnation. Measurements are usually taken at one of three different levels of the aortic root: (i) aortic annulus, (ii) sinuses of Valsalva and (iii) ascending aorta 1 to 2 cm. above the sinuses of Valsalva (Driscoll *et al.*, 1989; Warburton *et al.*, 1999b). Of these, the aortic ring annulus is generally reported to provide the most accurate determination of cardiac output (Driscoll *et al.*, 1989; Huntsman *et* *al*., 1983). This measurement can be accomplished with pulsed-wave Doppler, as the aortic valves are audibly distinguishable to the operator and pulsed-Doppler allows for control of depth. Contrarily, the ascending aorta dimensions are a function of pressure and can vary over the cardiac cycle ± 3% to ± 12% (Huntsman *et al*., 1983). Although changes in aortic diameter are considered to be small (Goldberg, 1971), the resulting square of the diameter for cross sectional area calculation would magnify the overall error. The third assumption is that the velocity profile through the cross section of the aorta is flat - or is said to mimic plug-flow . Although aortic flow closely resembles plug-flow, there are regional disparities (Figure 2-4).

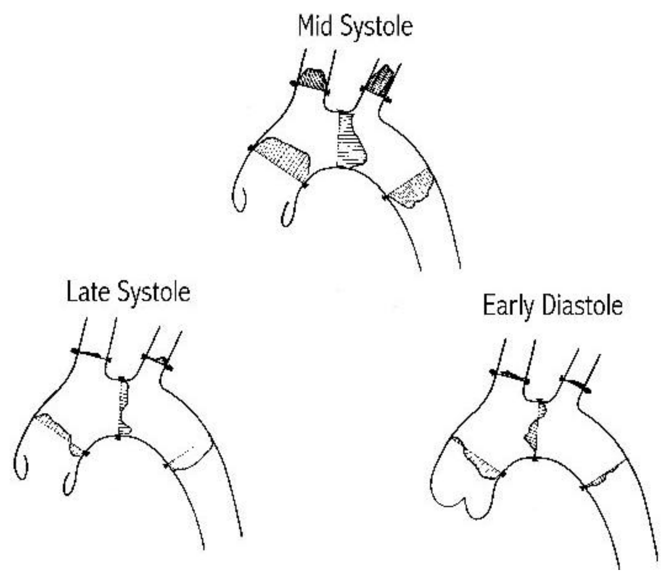


Figure 2-4: Aortic blood flow profiles
(from Nicholas *et al*., 1990)

It is evident plug-flow is fairly well established in mid-systole but tapers towards late systole. Nevertheless, it has been shown that measurement through the center-line should approximate the mean velocity of the entire blood flow (Nishimura *et al.*, 1984). Despite these apparently cumbersome assumptions, an experienced ultrasonnographer can accommodate these problems by systematically and methodically adjusting transducer position and settings until obtaining the strongest possible signal. If the aortic diameter is taken at the annulus and the maximum blood velocity is measured (presumably this occurs at the aortic annulus), then the exact point where velocity measurement occurs is of little consequence (Dobb & Donovan, 1987).

Interestingly, it has been shown that satisfactory cardiac output measurements can only be obtained in approximately 70% of patients (Nishimura *et al.*, 1984). Furthermore, an estimate of $\dot{Q}$ is thought to be difficult to obtain during exercise (Driscoll *et al.*, 1989) with subject movement being one of the main confounding factors (Shaw *et al.*, 1985). Thus further justifying the selection the kicking ergometer as an exercise model. However, during upright cycling, Driscoll *et al* (1989) reported a correlation coefficient of 0.93 compared to C_2H_2 rebreathe. In an involved study by Christie *et al* (1987), correlation coefficients between Doppler and thermodilution ranged from r=0.75 to r=0.96 with a mean of 0.86 and even obtained adequate measures of $\dot{Q}$ during maximal exercise.

With these same data, it was reported that Doppler consistently underestimated $\dot{Q}$ at rest (9%), submaximal exercise stages (20%) and during maximal exercise (15%) (Warburton *et al*., 1999) when compared to thermodilution. During systole, the aortic root moves inferiorly with a peak-to-peak displacement of about 9 mm. If blood velocity is measured relative to fixed point on the body surface (i.e. suprasternal notch), then this 9 mm downward displacement translates into an underestimate of stroke volume of about 5 ml for a 25mm diameter aortic annulus (Eriksen & Walloøe, 1990).

2.4.1 Nyquist Limit

The Nyquist limit is often addressed as an absolute barrier to blood velocity measurements. The Nyquist limit is a theoretical boundary due to the physics of sound propagation and the time it takes to travel there and back . Earlier instruments were not equipped with quadrature circuits and as such, strictly obeyed the Nyquist limit without exception. The pulse repetition frequency (PRF) limits the velocity that can be measured because most instruments must wait for the previous ultrasound burst to return before initiating another burst. As such, the Nyquist limit is defined as half of the PRF. With today s instruments, the Nyquist limit still applies, but can be overcome through technical and mathematical manipulations. Modern algorithms incorporate real and imaginary parts to the Fast Fourier Transform (FFT). The high frequency shifts that would normally appear as low frequency shifts undergo a mathematical process of convolution where these erroneous low frequencies are wrapped around and reconstructed as true higher frequencies. With this approach, modern Doppler units are capable of measuring flow velocities of almost double the Nyquist limit.

2.5 Exercise Model

The kicking ergometer was developed by Andersen and coworkers (1985) and is a dynamic mode of exercise where the subject is in a seated position and is able to elicit the quadriceps and / or hamstrings. The advantage to this form of exercise is that it permits the subject to keep a comparatively relaxed upper body, which improves Doppler data. A tensed, hunched or otherwise mobile upper body greatly diminishes the quality of the Doppler signal. Extraneous subject movement negatively affects Doppler data

2.6 Head-Up Tilt Model

The Head-Up Tilt (HUT) model provides an excellent and controlled means to alter one s hemodynamic state. The key to the HUT model is the ability to passively change the orientation of a subject from a supine position, to some degree of head-up tilt, thereby allowing gravitational stress to exert its toll. The passive nature of the tilt protocol practically abolishes the contribution of the skeletal muscle pump for venous return, thereby amplifying the cardiovascular response to the orthostatic stress. Cardiovascular changes for such procedures and manoeuvres are well documented (Ten *et al.*, 1994 and Wieling *et al.*, 1998).

Chapter 3

EXPERIMENT #1

3.1 Introduction

The superiority of a (working) pulse contour analysis algorithm as a method for obtaining beat-by-beat cardiac output has been clearly demonstrated to be inexpensive, simple to use, low risk and non-invasive. What s more, the concept of pulse contour analysis is not challenged but rather the reliability and validity of the impedance algorithms over vast range of conditions and situations is where the uncertainty lies. The two most significant problems to pulse contour analysis cardiac output are, an unknown vascular impedance and the presence of wave reflections (Gratz *et al.* 1992). Subsequently, most existing pulse contour methods are unreliable under varying hemodynamic conditions (Jansen *et al.* 1990). With confidence in the fact that stroke volume can be derived by dividing the pulsatile systolic area by impedance (Equation 1-3), it is only a matter of time before an adequate aortic impedance model and corresponding algorithms are developed. Until such time, all pulse contour methods must undergo the rigors of diligent scrutiny to identify weaknesses or inadequacies, thus facilitating the advancement of this technology.

The desire to evaluate pulse contour cardiac output necessitates careful design and execution of the experimental protocol. Since pulse contour is intended to provide beat-by-beat cardiac output, it stands to reason to use another beat-by-beat method as the reference. The reference method of choice was Doppler ultrasound. The only other non-invasive beat-by-beat method available to us is impedance cardiography but it is subject to significant breathing-related artifact and it is often recommended to employ this method during breath-hold manoeuvres (Warburton *et al.*, 1999a) highly inappropriate for exercise conditions. Nevertheless, efficacy of Doppler is vulnerable to subject movement or if the subject is positioned in a less than optimal posture such as being hunched over (i.e. as would be the case on a cycle ergometer). These considerations served as the primary impetus behind selecting the kicking ergometer as the choice exercise model. The kicking ergometer allows the subject to maintain a fairly immobile and relaxed upper body while leaning back slightly. This position opens a window to the suprasternal notch, thus facilitating the use of Doppler ultrasound for cardiac output.

The hypothesis for this experiment is that pulse contour cardiac output will accurately track corresponding changes in Doppler cardiac output during rest and kicking ergometer exercise in young healthy adults.

3.2 Methods

3.2.1 Participants

Seven healthy participants with the following characteristics completed the study with the following (mean ± S.E.); age= 22 ± 0.8 years, height= 178.3 ± 4.2 cm., weight= 85.8 ± 6.8 kg. All participants expressed their written, informed consent after explanation of the experimental protocol. Completion of a standardized medical form did not reveal any contraindications to rigorous or maximal exercise nor to the experimental procedures. The Office of Research Ethics at the University of Waterloo previously approved all procedures and manoeuvres. A total of nine participants had started the study with seven participants completing all tests and trials. One participant was discontinued from the experiment during the first set of submaximal trials due to an inability, despite persistent efforts, to obtain a reasonable blood pressure signal. Upon manual examination and palpation, it was noted that the participant had an unusually deep radial artery, sufficiently deep to prohibit use of the Colin blood pressure monitor. A second participant was taken out of the study after the maximal kicking ergometer test due to failure to reach a sufficiently high workload. Such a low maximal workload (50W) would prohibit the participant from maintaining three, sufficiently distributed workloads in steady-state conditions for the purposes of this study. All participants were asked to avoid rigorous exercise 24 hours prior to all sessions and to ensure that no large meals were consumed in the few hours preceding a testing session. Refer to table 3-1 for an outline of the participants physical characteristics.

Table 3-1: Participant characteristics and associated work rates

Subject	Age	Height (cm)	Weight (kg)	Maximum Workload (W)	Submaximal Workloads (W)
1	19	185.0	86.5	195	45, 60, 75
2	22	165.0	65.0	90	15, 30, 45
3	23	188.0	91.0	180	15, 45, 75
4	17	172.5	79.8	165	15, 45, 75
5	22	181.0	106.5	195	15, 45, 75
6	22	172.5	67.5	135	10, 30, 50
7	22	179.0	76.0	225	20, 50, 80
Mean	20.6	178.3	85.8	165	
Std. Error	1.1	4.2	6.8	20	

3.2.2 Protocol

A total of three sessions were required of each participant. During the first session, the participant s height and weight were recorded with the participant wearing only a t-shirt, shorts, and socks. The participant was then seated on the kicking ergometer in a semi-recumbent position. ECG electrodes were applied in the standard 3-lead configuration and aortic diameter was measured using 2-dimensional and M-mode echocardiography with either a 3.5 or 2.75 MHz probe (Toshiba, Sonolayer SSH-140A, Toshiba Inc. Tochigi-Ken, Japan). The left parasternal view was acquired in the 2-dimensional view with concurrent M-mode in a split screen. The M-mode cursor was arranged perpendicular to the point where diameter measurement was to be considered and cine images of both views were simultaneously recorded on a standard VHS tape for subsequent offline measurements. For each measurement, a series of three ECG-synchronized (lead II) diameters were averaged and cross sectional area computed based on the assumption of a circular valve orifice.

All participants completed a progressive, maximal exercise test on a magnetically braked, two-legged kicking ergometer (dynamic knee flexion extension). The test began with 4 minutes of warm-up at zero watts and subsequently increased at 15 $W \cdot \min^{-1}$ until volitional fatigue or the participant began recruiting significant accessory muscles to continue. This point is easily recognized by the fact the participant will have a much less stationary upper body. From the participant s individual performance, three submaximal work rates were determined for the submaximal trials (Refer to Table 3-1).

The second and third sessions started with the recording of the participant s height and weight (as previously described) and required the participant to complete a 3-step exercise protocol. The only difference between the second and third sessions is that the participant s aortic diameter was once again measured using the same protocol on the third and final session. The events occurring during exercise sessions are graphically illustrated below:

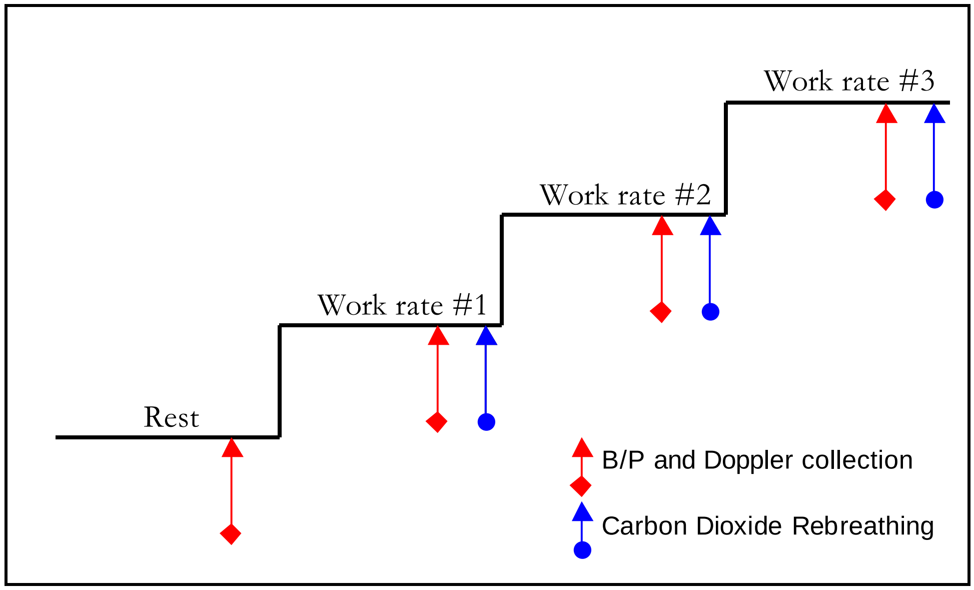


Figure 3-1: Submaximal exercise protocol.

During each of the work rates, Doppler and blood pressure collection did not occur until at least three minutes had elapsed since the start of that workload and steady-state conditions were being observed (i.e. heart rate, $\dot{V}O_2, \dot{V}E,$ etc.). Aortic Doppler (pulsed wave) velocity was obtained via the suprasternal view with a 2 MHz probe (Multigon 500M, Multigon Industries). Doppler settings were systematically adjusted until the cleanest, maximal signal was achieved as verified visually (colour spectral display) and acoustically. Continuous blood pressure and Doppler recordings were made simultaneously for 2 or 3 minutes. By this time, a rebreathing bag was already filled to the desired volume and concentration of CO_2. Shortly after the Doppler and blood pressure recordings were made, the rebreathing procedure was executed and verified. If successful, the participant was taken to the next progressive work rate and the pattern repeated until all three submaximal trials were completed. If the rebreathing manoeuvre proved to be inadequate, another series of measurements was repeated (blood pressure and Doppler) with any necessary adjustments.

It is important to note that the carbon dioxide rebreathing procedure for cardiac output served as a standard to verify the proficiency of the collected Doppler data, in addition to providing the calibration cardiac output for the pulse contour impedance calibrations.

3.2.3 Data collection

Breath-by-breath cardiorespiratory data were obtained and recorded with a PC computer system and designated software (First Breath, St. Agatha, Ontario). Fractional O_2, CO_2 and N_2 concentrations were measured with a mass spectrometer (MGA-1100, Marquette Electronics Inc., Milwaukee, WI) in conjunction with inspired and expired volumes as determined with a volume turbine (VMM-110, Alpha Technologies, Laguna Beach, CA) connected in series to a 2-way valve and mouth-piece (with nose clips applied during testing). All systems and equipment were calibrated immediately prior to each participant. Specifically, the mass spectrometer was calibrated against two different gas mixtures of known concentrations and the volume turbine was calibrated manually with a 3000 ml syringe using flow rates representative of submaximal exercise.

Continuous blood pressure was obtained using radial artery tonometry (Colin Pilot 9200, Colin Medical Instruments Corp., San Antonio, TX.). The tonometer was applied, in all cases to the right arm of the participant with the arm supported using a padded-platform beside the kicking ergometer. The contralateral arm was positioned on the lap of the participant in a relaxed manner and fitted with an appropriately sized blood pressure cuff that is connected to the Colin monitor for automatic and recurring tonometer calibration. This multi-monitor was also utilized for ECG monitoring using lead II of the standard 3-lead configuration.

Aortic blood velocity was obtained using pulsed Doppler (Multigon), with the transducer probe placed in the suprasternal notch of the participant with ample ultrasound gel. Signal feedback was provided in real time via stereo audio (flow towards and away are provided in separate left/right audio channels) in addition to a coloured spectral display. Doppler settings and transducer position were methodically adjusted so as to obtain a maximal signal.

Signal collection (B/P, aortic Doppler velocity, and ECG) was accomplished with an analog-to-digital converter and a PC computer. Intermittent, discrete files were collected at 100 Hz. and stored for subsequent, off-line analysis. Once steady state has been established, a collection of approximately 2 to 3 minutes was obtained, followed immediately by the CO_2 rebreathing procedure.

The nature of pulse contour analysis requires customized software. In this case, software written in Visual Basic v6.0 was used. The author of this thesis played a direct role in the development of the software. The program ultimately reads a text file of continuous blood pressure data and then identifies the points of interest along the blood pressure curve (diastolic, systolic and notch pressure[1]) for each complex. Subsequent calculations were made within the program and outputted into a Microsoft Excel sheet for analysis. In addition, a graphical output for each sample was generated to ensure that the program was indeed choosing the correct points along the blood pressure curve.

3.3 Results

3.3.1 Overall

A total of seven participants had completed all the exercise trials with an average peak kicking work rate of 165 ± 20 Watts (mean ± S.E.). For the submaximal exercise trials, participants completed three different work rates and for this study, these work rates ranged from 10 Watts to 80 Watts. In all cases the utmost work rate during the submaximal rides was at or below 50% of the

[1] Notch pressure refers to the pressure where the aortic valve closes.

participant s own peak work rate. (Refer to Table 3-1 for a detailed listing of work rates). As previously stated, it was intended to induce a range of cardiovascular states through exercise. During these trials across all participants, heart ranged from 55 to 158 beats per minutes and Mean Arterial Pressure (MAP) ranged from 67 to 147 mmHg. This range proved to challenge the limits of existing pulse contour methods of cardiac output derivation.

3.3.2 Trial by Trial

Participants completed two identical trials of the submaximal work rates. Although small intra-individual differences between heart rates and mean arterial pressures, etc. between trials are to be expected, there are a few instances where there was a substantial difference from one trial to the next. However, these cases where significant differences seem to exist are likely due to measurement artifact owing to the precariousness of non-invasive blood pressure measurement or extraneous participant effort (i.e. internal bracing-type activities). Refer to Figures 3-1 and 3-2 (below). Nevertheless, participants had at least two days between successful sessions and therefore it is not reasonable to believe that there is an inherent trial influence on the pulse contour method. Thusly, trials will be appropriately collapsed together for each participant.

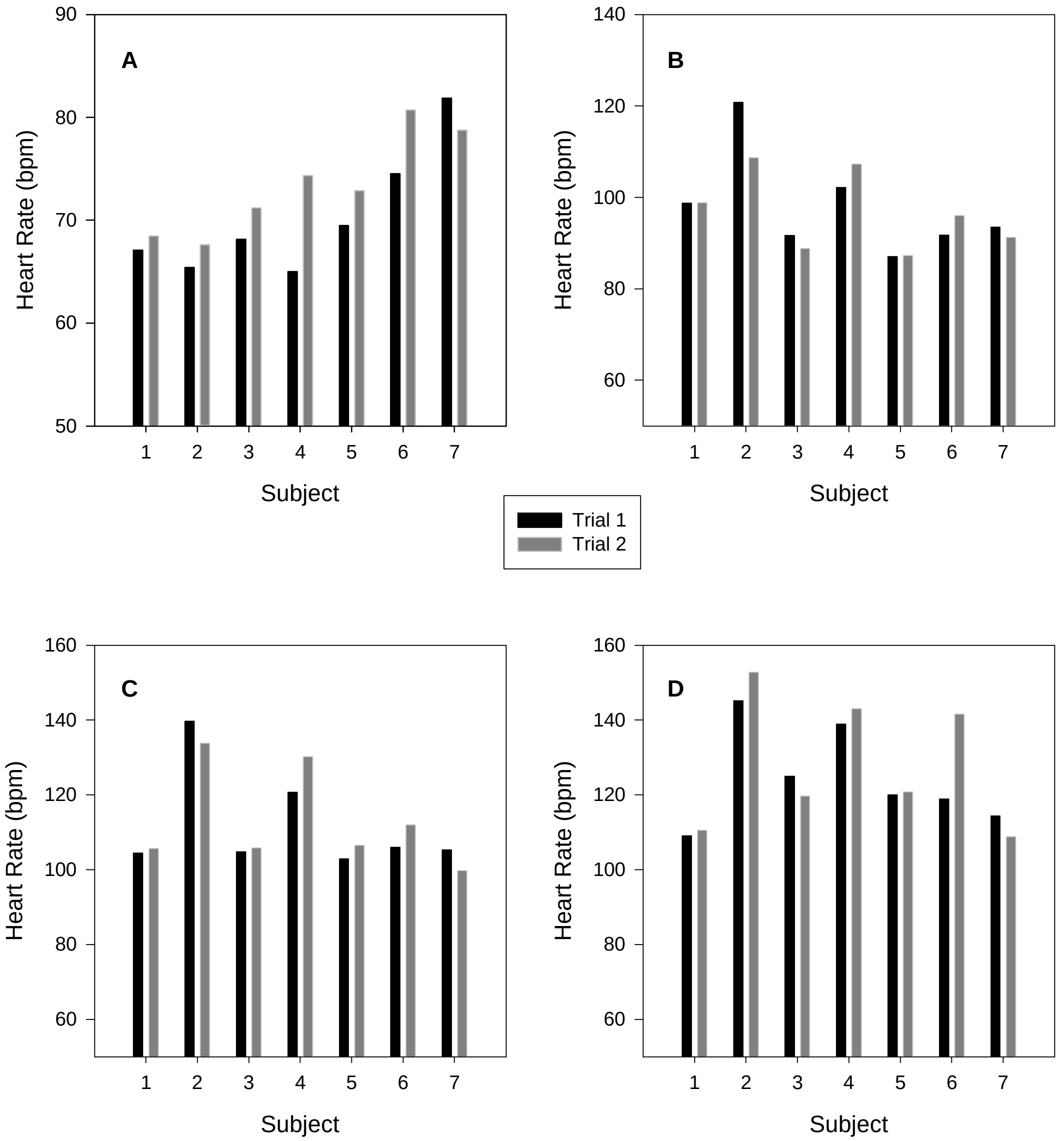


Figure 3-2: Average heart rates by trial for each participant

A=Rest, B,C,D = progressive work rates 1,2, and 3 respectively.

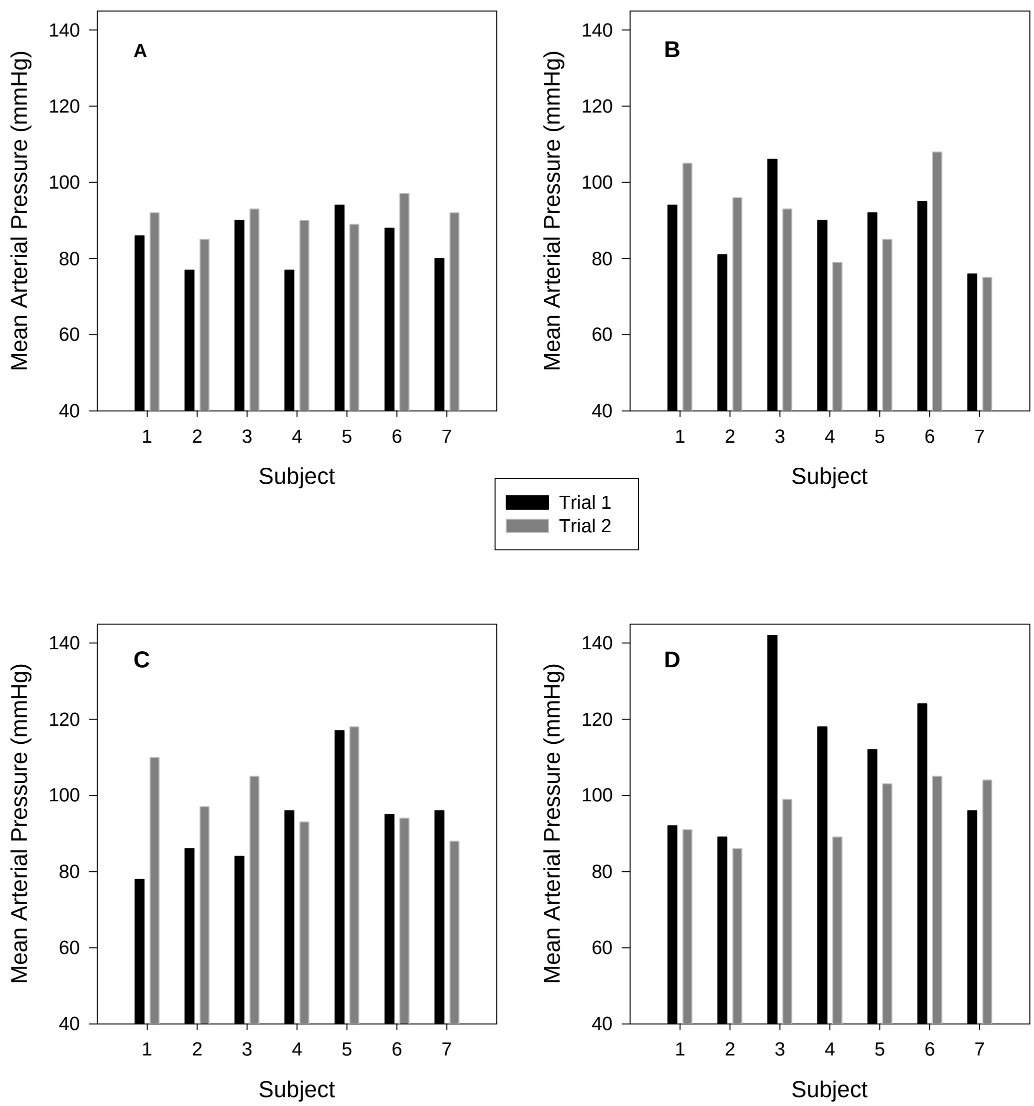


Figure 3-3: Average mean arterial pressure by trial for each participant

A=Rest, B,C,D = progressive work rates 1,2, and 3 respectively.

3.3.3 Pulse Contour Preliminaries

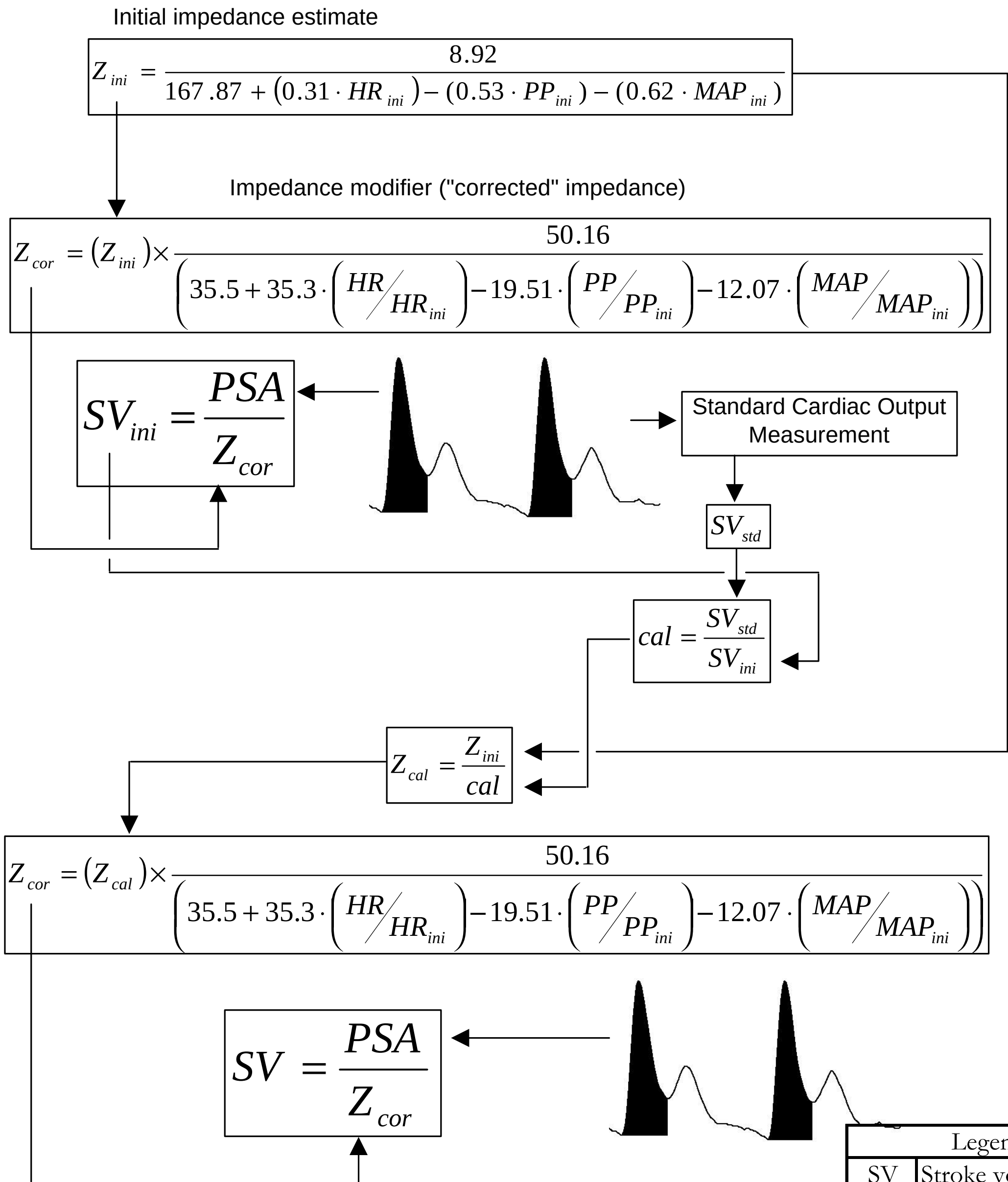
Current research favors the pulse contour method by Wesseling as suggested by its popularity. This method employs the simple strategy of calibrating an individual s impedance with a reference cardiac output measurement[1], which ultimately results in a constant being multiplied to the main algorithm that adjusts impedance as heart rate and mean arterial pressure change. The downfall is that this method tends to have a narrow range of applicability, requiring re-calibration with a new cardiac output measurement if cardiovascular parameters stray too far from initial calibration conditions (Stok *et al*., 1999). Moreover, since the calibration is simply multiplying the resulting impedance by a correction factor (to match existing cardiac output), then this minimally depends on an algorithm to predict impedance changes with a shifting cardiovascular status. Ultimately, the more frequently you must calibrate indicates that the model (algorithm) is less adept at predicting changes in impedance and hence, cardiac output. In fact, calibrating each work rate against itself would yield essentially perfect results as you eventually end up multiplying the predicted impedance by a constant that corrects for the shortcomings of the model. This is not only inconvenient, but also unreliable if a pulse contour method is to be used for something like intensive care monitoring where cardiovascular and hemodynamic status can (and does) vary considerably amongst and within

[1] Carbon dioxide rebreathing procedure was used for the impedance calibration

patients (Goedje *et al.* 1999). Conversely, the method by Antonutto has its merits. Antonutto s method commendably approaches pulse contour analysis without relying on any sort of impedance calibration. As indicated, a more elaborate algorithm is used to estimate initial impedance and a second algorithm adjusts the impedance as cardiovascular parameters change (heart rate, pulse pressure and mean arterial pressure). As successful as either of these methods has been, they still leave much to be desired. Therefore, a third hybrid-model implementing the strengths of each approach has been proposed and evaluated as a part of this thesis. Table 3-2 below compares and contrasts these two main models and the derived hybrid model (modified Antonutto). See Figure 3-4 for a schematic representation of the modified Antonutto approach.

Table 3-2: Pulse Contour Models

Wesseling	Modified Antonutto	Antonutto
• [Too] simple initial impedance estimate • Uses a resting impedance calibration • Depends on MAP, Age and HR • Does not consider resting cardiovascular values	• Elaborate initial impedance estimate • Uses a calibration • Depends on MAP, PP and HR • Incorporates resting cardiovascular values	• Elaborate initial impedance estimate • Fully contained model (no calibration required) • Depends on MAP, PP and HR • Incorporates resting cardiovascular values



Legend	
SV	Stroke volume
PSA	Systolic area
HR	Heart rate
PP	Pulse pressure
MAP	Mean arterial pres.
Z	Impedance
ini	Initial (conditions)
cor	Corrected
cal	Calibrated

Figure 3-4: Modified Antonutto approach to pulse contour analysis.

Initial pulse contour cardiac output results yielded generally poor agreement with Doppler. In short, the main reasons for the overall poor performance of the pulse contour methods may have been the fact that participants had non-representative resting measures and were as such, artificially elevated in anticipation of exercise. This can negatively affect all of the pulse contour models but more so in the Antonutto method because it utilizes resting cardiovascular measures to derive a resting impedance estimate in addition to preserving the resting values as part of a ratio in the subsequent impedance calculations. Figures 3-4 and 3-5 illustrate trials 1 and 2 by participant for mean cardiac output values for each work rate (Participant #6 is not shown because of the meager Doppler data quality as a result of technical difficulty in obtaining a satisfactory data signal, despite persistent efforts.

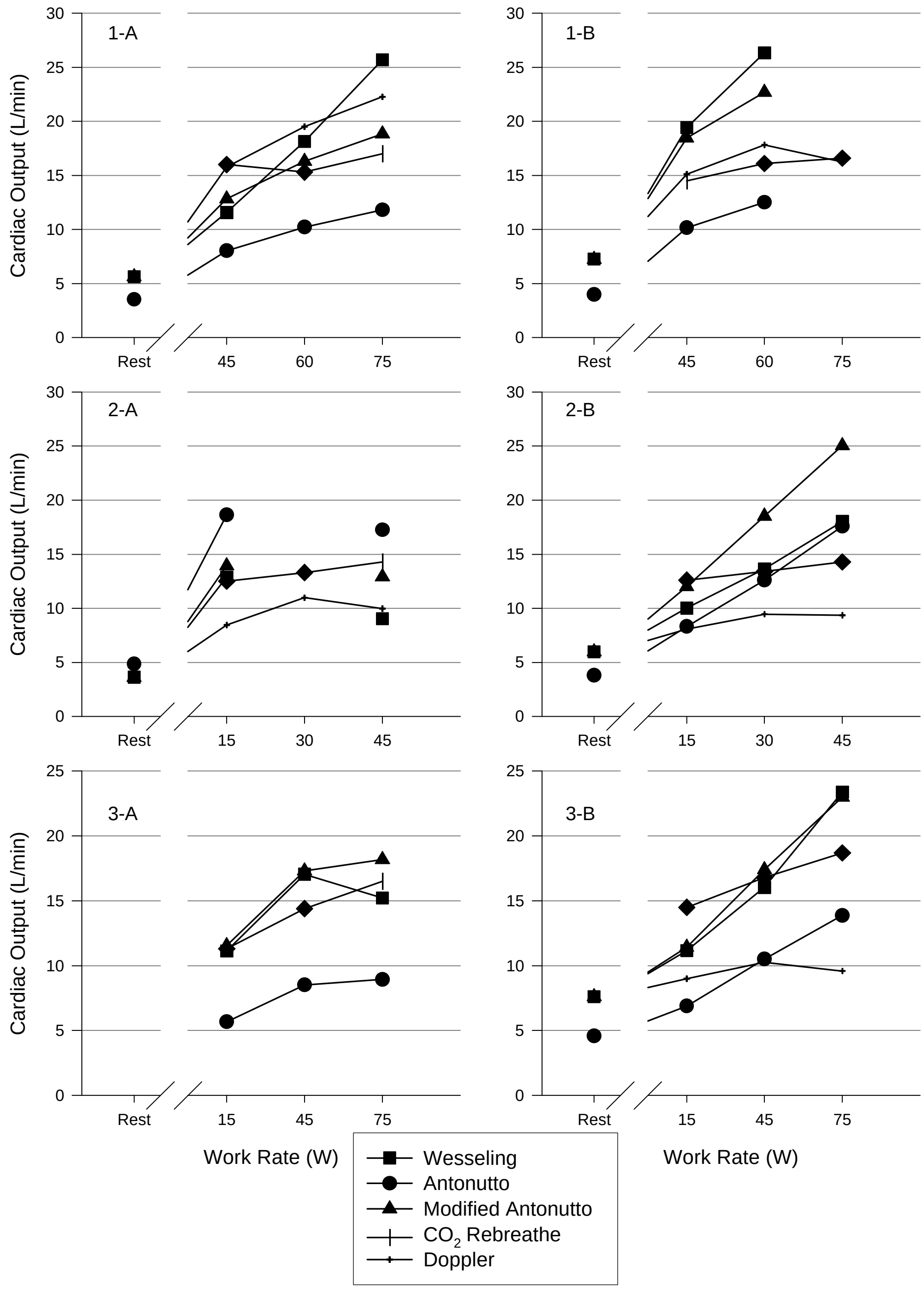


Figure 3-5: Preliminary pulse contour results, part I.

Using resting conditions to calibrate the Wesseling and Modified Antonutto methods. Listed by subject number and trial (A or B).

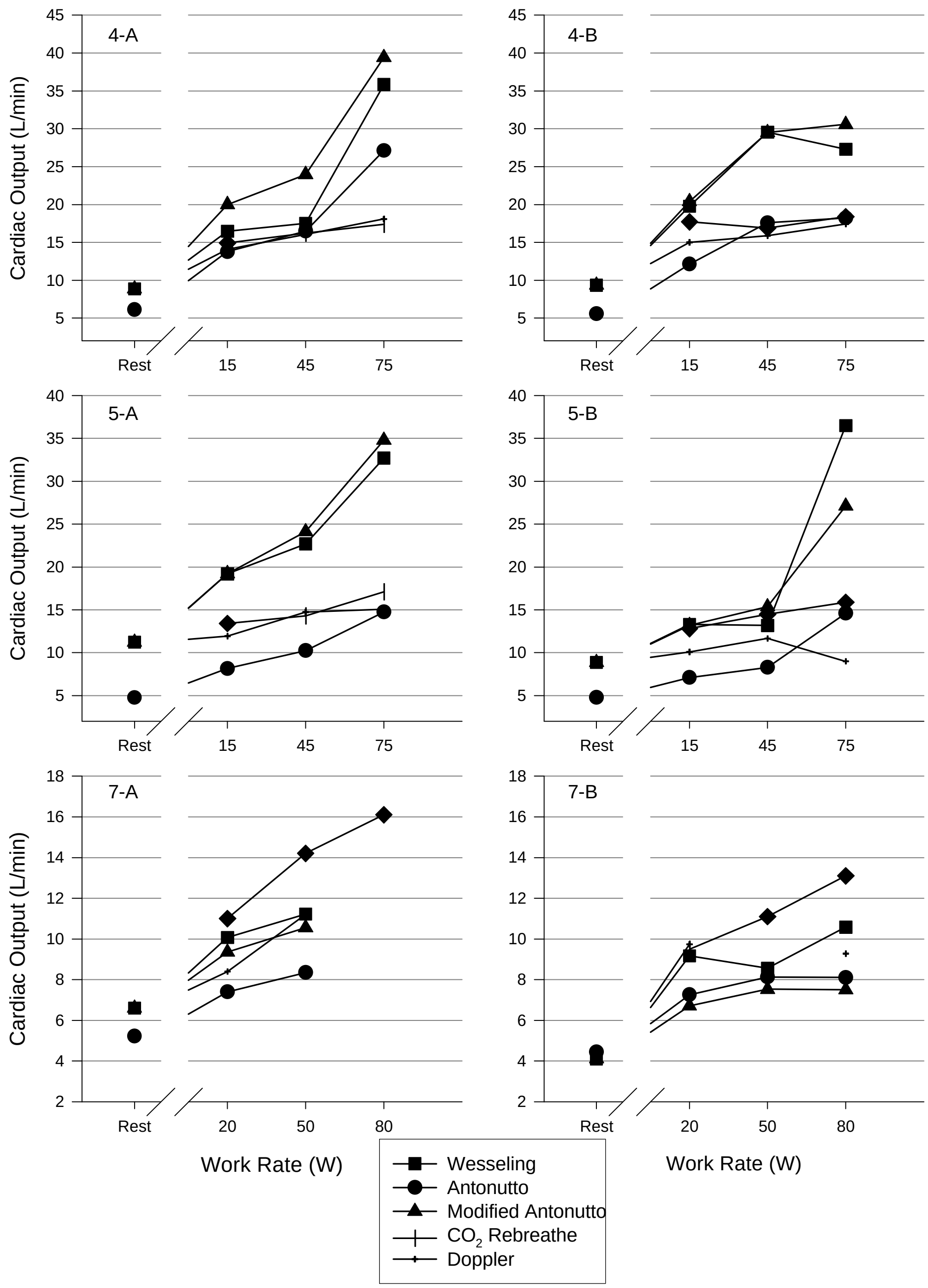


Figure 3-6: Preliminary pulse contour results, part II.
Using resting conditions to calibrate the Wesseling and Modified Antonutto methods.

In light of this problem of an elevated resting state, it was then attempted to use the first work rate as the calibrator for the Wesseling and Modified Anonutto methods (acquired resting measures were retained for the Antonutto method for initial impedance estimates). Encouragingly, an improvement was readily evident as depicted in Figure 3.6 and 3.7 (each graph depicts the mean cardiac output for each participant (numbered) / trial (A or B) as indicated in the top let hand corner of each illustration).

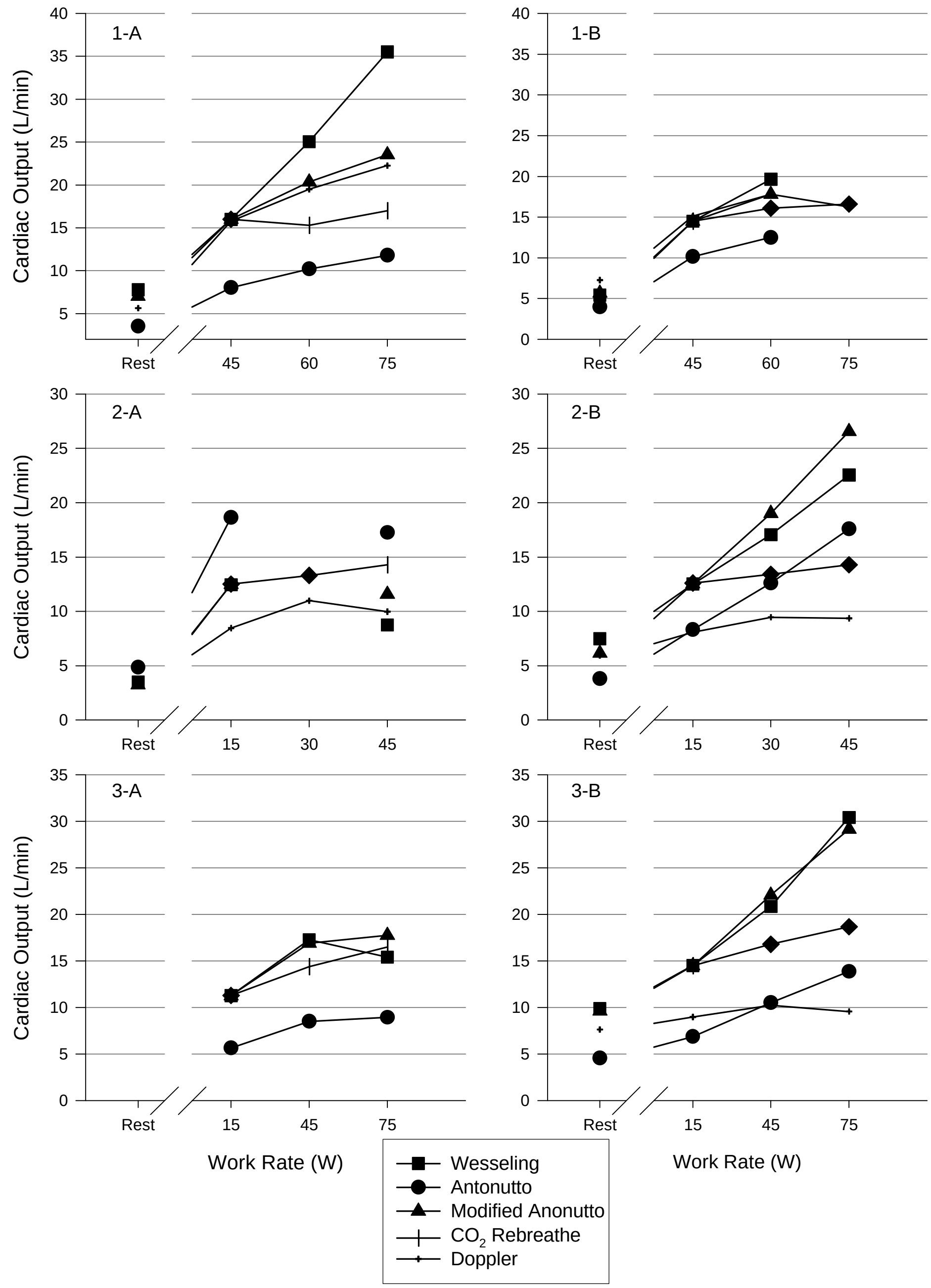


Figure 3-7: Adjusted pulse contour results, part I.

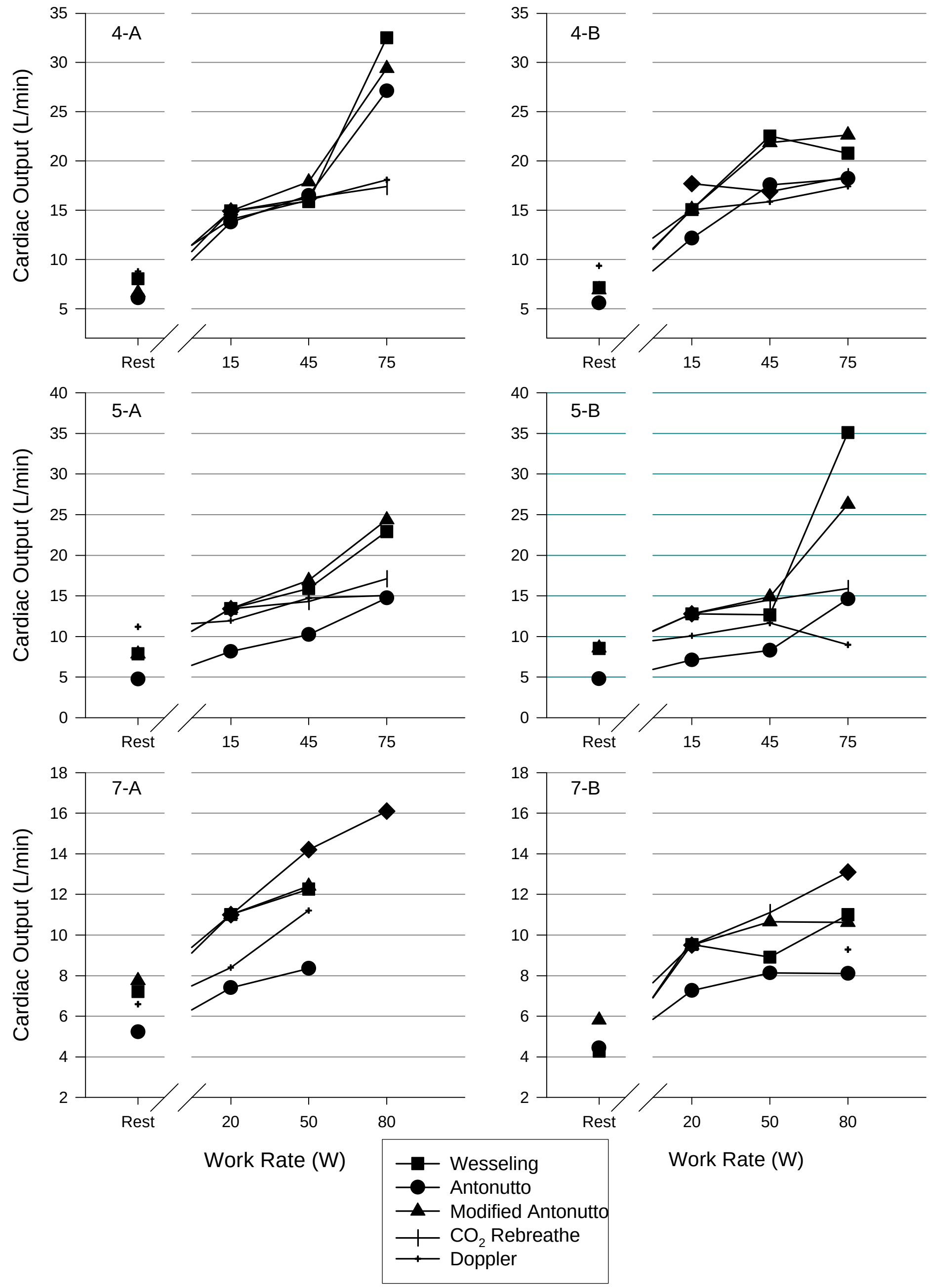


Figure 3-8: Adjusted pulse contour results, part II

Pulse contour results were improved when using the first work rate as the calibrator rather than rest

In using the first work rate as the calibrator for pulse contour cardiac output effected two main changes or enhancements: 1) Accuracy of the models seem to be expanded to a wider range of conditions, as evidenced by a closer fit of reference cardiac outputs (Doppler and CO_2 rebreathing) and 2) the divergence of cardiac output values is less severe at the highest work rate. Furthermore, of the three pulse contour methods (Wesseling, Antonutto and Modified Antonutto), the Modified Antoutto method demonstrated the most consistent results. Therefore, this approach shall be the method of choice and undergo further extensive analysis and evaluation.

3.3.4 Macro Results

Preliminary data organization and general calculations were accomplished using Microsoft Excel 2000. Statistical analysis and graphing was achieved with the software packages SPSS v9.0 and Sigma Plot 2000, respectively. In terms of the detailed analysis to follow, only those trials where Doppler data agreed well with the CO_2 rebreathing cardiac output were included in the analysis. All things considered, it is not unreasonable for there to be a 1-3 L/minute discrepancy (depending on the absolute cardiac output) between the CO_2 rebreathing and Doppler. In light of this tolerance, if a trial failed, it was usually the trial of the highest work rate, owing to the technical difficulty in obtaining valid and consistent cardiac output with Doppler during exercise. Furthermore, inter-individual variations will make Doppler very difficult, if not impossible to obtain in some participants despite expert skill and extensive experience of the ultrasonographer. However, the same proficiency and experience inevitably serves as a solid basis by which to judge the adequacy of a Doppler signal through audio and visual evaluation.

The next series of graphs by participant provide a means to quickly gauge the agreement between Doppler and Modified Antonutto pulse contour analysis on a beat-by-beat basis. Included in each plot, is the corresponding line of equality on which all data points would lie if both methods perfectly agreed with each other (Figure 3-8).

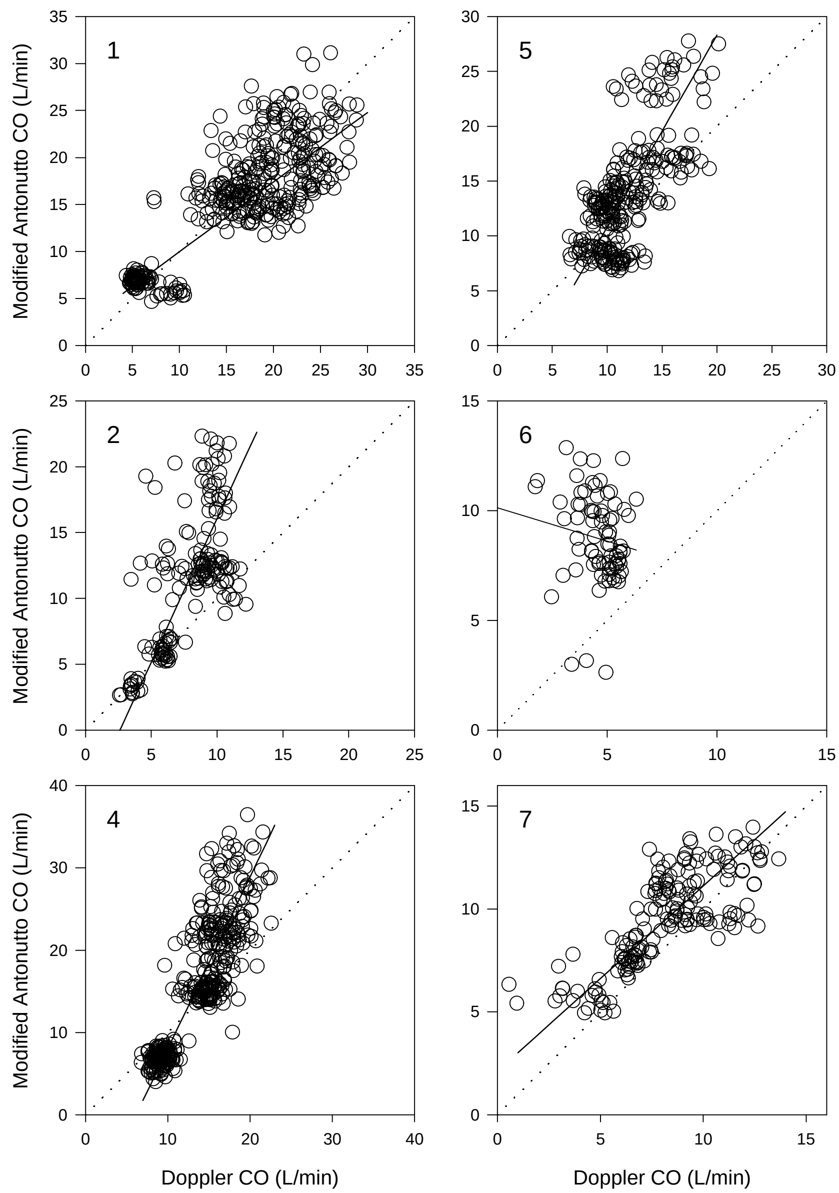


Figure 3-9: Doppler vs. Modified Antonutto Cardiac Output (L/min)

Plots by subject with line of equality (dotted) and regression lines (solid)

However, a better approach to illustrate discrepancies is to plot the scatter of the mean of both measurements (Doppler and Modified Antonutto) against the difference (Doppler   Modified Antonutto) (Figure 3-9). Such a plot also provides the advantage of providing an opportunity to identify some sort of pattern to the disagreement in hopes of making future improvements to the model of interest.

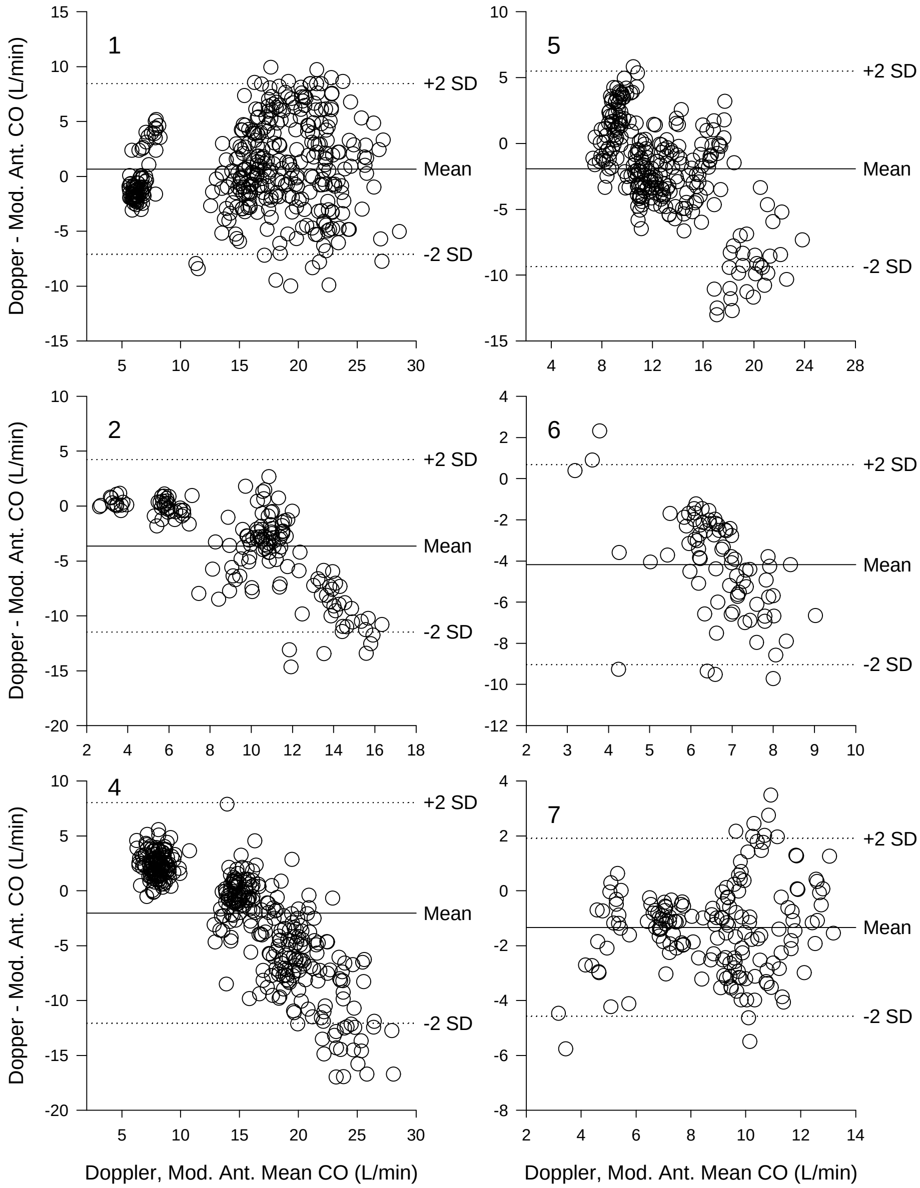


Figure 3-10: Mean vs. Difference CO (L/min)

To objectively evaluate a comparison between these two measures of cardiac output, linear regression analysis is the method of choice. However, there are 5 assumptions that must be satisfied:

1) There is a linear relationship between x and y.
2) Observations are independent.
3) Residuals are normally distributed.
4) Residuals have the same variability
5) The x variable can be measured without error.

All assumptions are satisfied with the exception the last one, in that there is an inherent error to the Doppler measurement. This issue is addressed with the approach as described by Anderson *et al.* (1986). Since the Doppler measurement is not free from error, regression slope and intercept are adjusted or corrected as shown in Figure 3-8 (above) and listed in Table 3-3 (below).

Doppler, although providing beat-to-beat velocity, which allows for beat-to-beat calculation of stroke volume and subsequent cardiac output, is not a perfect system. As such, there is a certain amount of inherent error in all procedures employed here. To thoroughly evaluate such a comparison, when the *true* cardiac output is not known is best approached by the method as described by Bland and Altman (1986). This method emphasizes the difference between correlation and agreement and stresses the erroneous dependence on correlation alone.

Table 3-3: Regression analysis results for PCA vs. Doppler cardiac output during kicking ergometer exercise

				95% Confidence Interval			
Subject	**Parameter**	**Coefficient**	**Std Error**	**Lower**	**Upper**	**r^2**	**SEE**
1	*Slope	0.74	0.01	0.72	0.76	0.73	2.48
	*Intercept	2.59	0.40	1.80	3.38		
2	*Slope	2.18	0.99	0.24	4.12	0.43	3.80
	*Intercept	-5.72	1.09	-7.85	-3.59		
4	*Slope	2.09	0.40	1.31	2.87	0.74	4.05
	*Intercept	-12.89	0.77	-14.41	-11.37		
5	*Slope	1.75	0.37	1.02	2.48	0.43	3.57
	*Intercept	-6.71	0.90	-8.48	-4.94		
6	Slope	-0.30	2.55	-5.30	4.69	0.20	0.52
	*Intercept	10.13	0.77	8.63	11.63		
7	*Slope	0.90	0.14	0.63	1.17	0.61	1.42
	*Intercept	2.12	0.38	1.38	2.86		
All	*Slope	1.23	0.20	0.84	1.62	0.51	4.21
	*Intercept	-1.38	0.31	-1.99	-0.77		

* $p < 0.01$

Parameters listed have been adjusted as described above to accommodate the inherent measurement error of Doppler cardiac output.
Significance ($p < 0.01$) tests for slope and intercepts that are significantly different from 1 and 0, respectively.

Below in Figure 3-10, all the data were grouped together to provide an overall representation of how well the Modified Antonutto Pulse Contour method performs across a range of exercise intensities. Clearly, the pulse contour method performs progressively worse at the higher intensities, or more specifically, the further cardiovascular parameters change from those at which the impedance calibration took place.

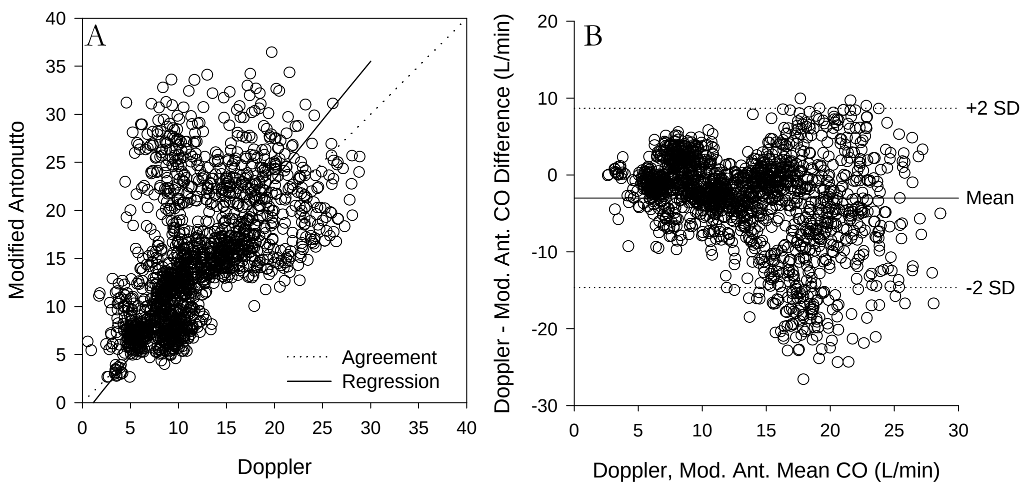


Figure 3-11: Combined regression and scatter plots

Plots with data from all subjects collapsed. A) Line of Agreement and regression line (adjusted) for all data. (PCA = 1.23 · Doppler 1.38 with an $r^2 = 0.51$)
B) Doppler, Modified Antonutto CO vs. Doppler Modified Antonutto CO difference (L/min) with ± 2 Standard Deviations (SD) limits

3.3.5 Micro Results

On a global level, the pulse contour method did not fare too well. The next logical step would be to take a closer look into the inner workings of the model in hopes of elucidating the nature of its pitfalls. Figure 3-11 (below) contains a grid of 16 different plots, each containing beat-by-beat comparisons of cardiac output as obtained with Modified Antonutto pulse contour analysis and Doppler. Each column represents a fixed calibration, applied to all the different intensities (rest, 15, 45 and 75 Watts). Notice that calibrating an individual intensity against itself yields the best results, which is not surprising because the calibration routine ultimately multiplies the impedance term by a constant to correct the deviation. However, it is interesting to note that calibrating with low cardiac outputs (i.e. rest), results in an over-prediction of cardiac output at higher intensities while the converse is true for calibrating at higher cardiac outputs (75 Watts), ending up with an under-prediction of cardiac output at the lower intensities.

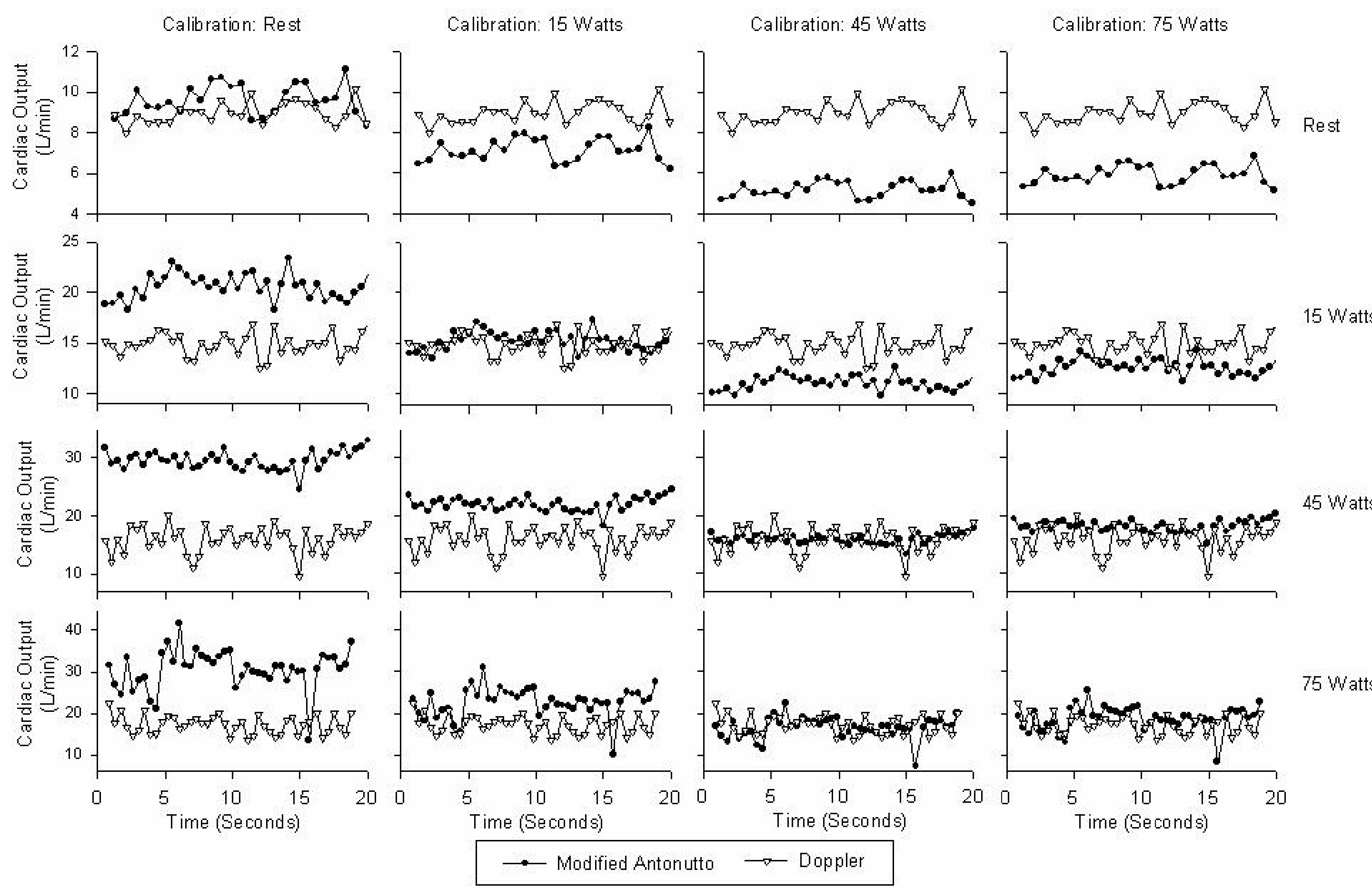


Figure 3 -12 Modified Antonutto with different calibrations in rest and 3 different exercise intensities. Columns and rows represent different calibrations and exercise intensities, respectively.

It is clear that a calibration at a particular cardiac output will not apply across all ranges of cardiac output; in fact the range is disappointingly restricted. Although it appears that the pulse contour method will potentially emulate beat-by-beat cardiac output as obtained via Doppler, a closer examination is warranted. Figure 3-12 is a typical sample taken from a participant exercising at 75 Watts with Doppler, Modified Antonutto Pulse Contour plotted in the top portion and continuous blood pressure in the bottom plot. Notice that the Pulse Contour method tends to follow the Doppler cardiac output (e.g. ~ 2-3 and 6-9 seconds) however; there are frequent occurrences where Doppler and Pulse Contour are moving in opposite directions (examples pointed out with the arrows). Ideally, a pulse contour model would not require subsequent impedance calibrations once initially calibrated as imposing the need for further calibrations reduces the practicality of the pulse contour concept.

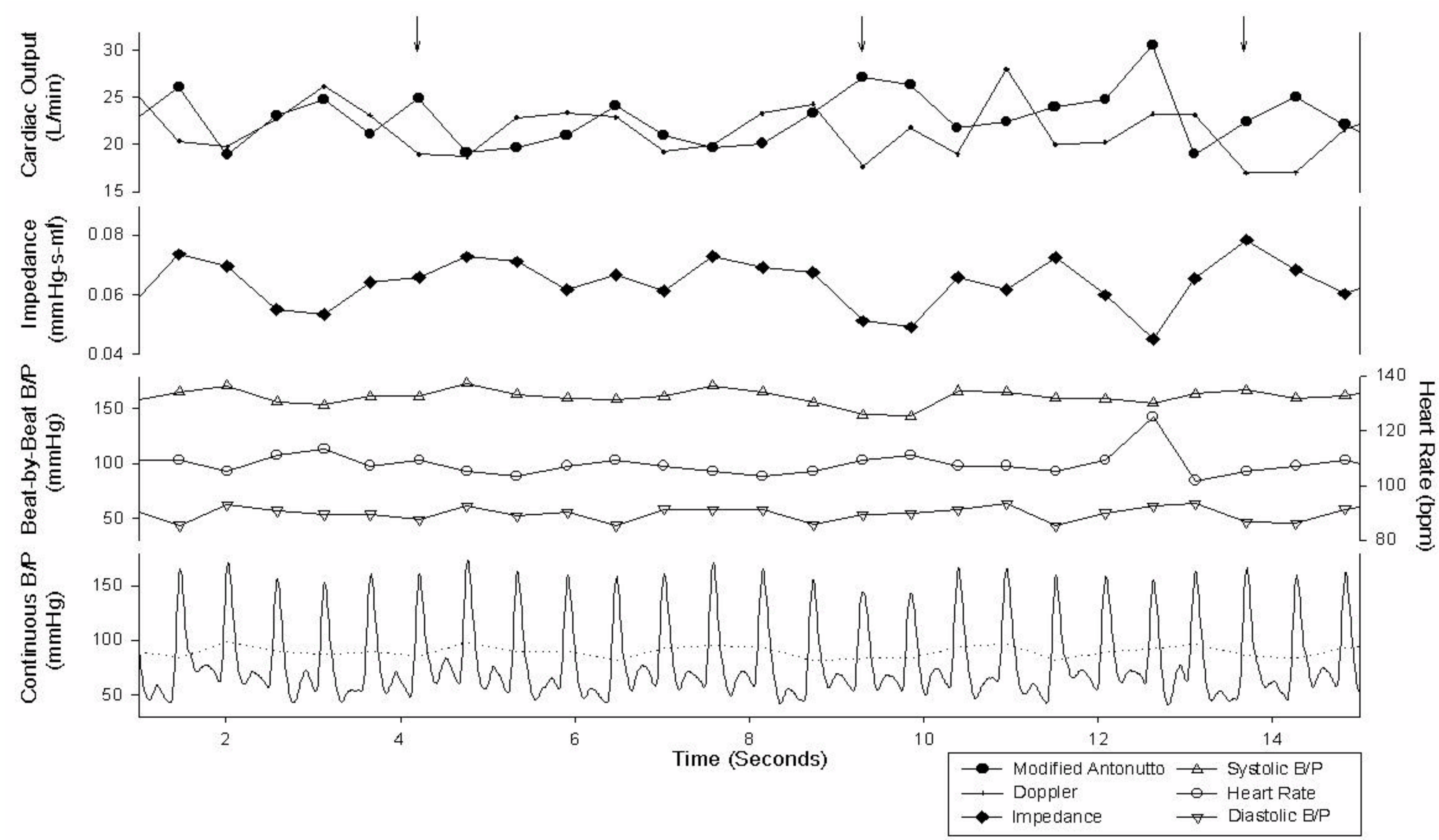


Figure 3-13: Beat-by-beat Pulse Contour analysis (Modified Antonurro) and Doppler cardiac output (top). Remaining plots are (second)) impedance, (third) beat -by-beat B/P values, heart rate and (fourth) continuous blood pressure tracing with beat-specific mean pressure superimposed (dotted line). The pulse contour method, although does tend to follow cardiac output, there are frequent instances where the cardiac output from Doppler and Pulse Contour Analysis are moving in opposite directions (examples indicated by the arrows).

3.4 *Discussion*

The major finding of this study was that existing pulse contour analysis (PCA) algorithms do not adequately track impedance changes during exercise and hence are unable to compute adequate beat-by-beat cardiac output. Failure of PCA occurs as a result of two phenomena: 1) impedance calibrations are not applicable outside the exercise intensity at which a calibration was made. Subsequent calibrations would be necessary for even minimal changes in exercise intensity. 2) PCA algorithms are especially susceptible to radical, spontaneous fluctuations in heart rate (Figure 3-12). Heartbeats that occur slightly early result in an erroneously elevated calculated stroke volume and cardiac output. Conversely, a slight delay of a single heartbeat under-predicts the stroke volume and cardiac output.

From the beat-by-beat comparisons, PCA does tend to follow Doppler cardiac output. Even if exercising well above the calibrated intensity, PCA continues to emulate the shape of the Doppler cardiac output data, except with a significant bias (see Figure 3-11). This suggests that PCA should not be abandoned and simply requires further development. Despite these limitations, PCA is gaining clinical popularity as evidenced by the availability of thermodilution cardiac output equipment integrated with PCA monitoring[1]. In particular, the PiCCO system uses an enhanced version of the algorithm

[1] PiCCO monitoring kit by Pulsion Medical Systems is one such example

developed by Wesseling *et al* (1983) and according to the manufacturer, the algorithm has been refined to reduce to the effects of a changing mean arterial pressure on the calculated impedance. However, this monitor will only produce a running 30-second average cardiac output, perhaps to address the problem of a poor beat-to-beat performance of PCA.

Previous research where favourable results have been demonstrated (Wesseling *et al.*, 1983; Jansen *et al.*, 1990; Gratz *et al.*, 1992; Stok *et al.*, 1993; Antonutto *et al.*, 1995; Harms *et al.*, 1999; Stok *et al.*, 1999) had all used steady-state comparisons of cardiac output (i.e. thermodilution, rebreathing, etc.) and was based on Wesseling s algorithms. The only exception, in both cases, is the study by Antonutto *et al,* which used original PCA algorithms and pulsed Doppler as the reference cardiac output. Antonutto compiled mean data for the regression analysis and obtained coefficients of: (PCA = 0.94 $\cdot$ DOP + 0.24, r^2 = 0.88). However, it neglected to make a legitimate *beat-by-beat* comparison such as is the case with this study. The lack of studies making a true beat-by-beat evaluation of PCA during exercise reaffirms the need to continue progress in this area. Hence, results presented here are novel and cannot be compared with previous research.

3.4.1 Different Pulse Contour Algorithms

Surprisingly, pulse contour methods requiring *frequent* calibrations are being impulsively employed; perhaps owing to the intense desire for a simple, inexpensive and non-invasive method of obtaining beat-by-beat cardiac output. Main differences between the Wesseling and Antonutto models are summarized in Table 3-2. However, the most significant difference is that the Wesseling model *depends* on a calibration whereas the Antonutto model is intended to operate without such a calibration. The calibration routine in Wesseling s is a straightforward approach that ultimately multiplies the model-calculated impedance by a correction factor so that it matches the true impedance as calculated from the area under the systolic blood pressure curve divided by the stroke volume as obtained from an independent measure of cardiac output (see Equation 1-3). Once calibrated for the existing cardiovascular state, the Wesseling model will always produce better *mean* results than the stand-alone Antonutto model. However, once cardiovascular parameters began to deviate from those values present during the calibration, then that mean bias increased substantially. These results suggest that the Wesseling model performs quite poorly at tracking impedance changes with a varying cardiovascular dynamics. However, as previously mentioned, Pulsion Medical systems is currently using a modification of Wesseling s model that lessens the impact of a changing mean arterial pressure.

Antonutto s model is slightly more sophisticated and performs remarkably well despite the lack of an external calibration. Distinctively, this model uses the participant s *resting* values (HR, PP, MAP) in the initial estimate of impedance. However, this can prove to be problematic if the investigator or clinician is unable to acquire true resting conditions. Resting conditions would be unobtainable if a patient was sick or injured and certainly proved to be the case in this study where participants were inevitably anticipating exercise, subsequently resulting in misleadingly elevated values. The Antonutto method utilizes baseline (resting) values to establish initial impedance. Erroneous resting values may be detrimental to Antonutto s model, but in actuality, representative baseline values would be almost impossible to obtain in a clinical setting and certainly can be problematic in a laboratory setting (i.e. anticipation of exercise). As such, results from Antonutto s model showed a greater mean bias, but with a *smaller* standard deviation. Therefore, this suggests that Antonutto s model may be more proficient at emulating beat-by-beat data, but the considerable bias results in a statistically significant mean difference in cardiac output when compared to Doppler. Nevertheless, slightly better results might be expected if true resting values are obtained.

Considering the strengths and pitfalls of these two pulse contour models, it seemed only logical to somehow combine them. Therefore, the *modified* Antonutto method maintains the original algorithms, but incorporates a *resting* impedance calibration like Wesseling. However, as previously mentioned, the Antonutto method utilizes resting cardiovascular parameters in its estimation of initial impedance and as intuitively expected, actual resting conditions are not as critical since the resting impedance is calibrated. This much is true but Antonutto s algorithm contains ratios of current cardiovascular variables with the resting values (HR, PP, MAP). Therefore, the issue of elevated resting values continues (to a lesser degree) to be detrimental.

The second modification implemented is that instead of using the rest condition as the impedance calibration, the first work rate was alternatively used (but still using the acquired resting values in the ratios of the algorithm). This was done to minimize the impact of inflated resting values as the impedance calibration is intended to correct for unaccounted influences that modify a specific person s impedance. This adjustment made discernable improvements in the mean cardiac output values as shown in Figures 3.4 to 3.7. With these modifications, Antonutto s method out-performed the original two models with an overall smaller bias across rest and all work rates (see Figures 3-6 and 3-7).

3.4.2 Overall

To gain an overall perspective of model performance, scatter plots such as those of Figure 3-10 are most informative (Bland & Altman, 1986). The first plot (left) contains the line of agreement and the regression line for all participants, trials and work rates grouped together. What is initially apparent is that the results become progressively worse at the higher cardiac outputs. Scatter increases over a broader range in the y-direction as you progress along the x-axis, demonstrating that at higher cardiac outputs, PCA will generate greater min-tomax fluctuations of cardiac output in steady state conditions. A second contributing factor is the practical limitation at acquiring accurate cardiac output with Doppler where underestimation of stroke volume and cardiac output is common (Shaw *et al.*, 1985). This trend is also readily observable in Figure 3-11 where at 75 Watts, a range of 20 $L \cdot min^{-1}$ was observed when using rest as a calibration and 15 $L \cdot min^{-1}$ when using 15 Watts as the calibrator. With these two trends (elevated and wide range of PCA cardiac output at higher intensities and underestimation of stroke volume by Doppler), regression results will become particularly eroded. Regression analysis performed on beat-by-beat data will be negatively affected with the opposing directions of these two trends. The second contributing tendency is that at higher workloads[1], PCA does tend to over-predict cardiac output. This is nicely depicted in Figure 3-11 where this drift is readily perceptible in the first and second columns where impedance calibration was performed at rest and 15 Watts, respectively.

In conclusion, PCA still requires a calibration if cardiovascular parameters stray from initial conditions. The algorithms are unable to adequately track the impedance changes through different exercise conditions. In spite of this, calibrated (for that specific exercise intensity) PCA does produce replicable means of cardiac output that are not different from Doppler.

[1] Provided that impedance calibration occurred during rest or at low intensity exercise

3.4.3 Beat-by-Beat

The next logical step (and usually neglected) in evaluating PCA methods of obtaining beat-by-beat cardiac output is to assess its ability to track or parallel beat-by-beat cardiac output (disregarding mean performance). Figure 3-12 is a sample of beat-by-beat data, depicting Doppler and PCA cardiac output, impedance, systolic and diastolic blood pressure, heart rate, mean arterial pressure and continuous-wave blood pressure. Examination reveals that PCA in the initial 8 or 9 seconds generally parallels Doppler cardiac output. However, there are a few beats in the plot that are of particular interest as indicated by the arrows. For these beats, Doppler and PCA are moving in *opposite* directions with fairly steep slopes. To explain, notice that this tends to happen with Doppler moving in a downward direction to a low-point and as such, the simplest explanation is that this is not so much a problem with PCA, but a problem with inherent inadequacies of the Doppler data. Interpolating these below-mean Doppler values would tremendously improve the matching of the two cardiac output signals. Doppler inadequacies are not unforeseen despite skilled and experienced ultrasonographers as the method is highly sensitive to participant movement. This problem has led researchers to implement some sort of participant-restraining device when highly accurate measurements are required (Shaw *et al.*, 1985). In light of these issues (inadvertent participant movement) and others like muscle tensioning around the chest/neck region and thoracic anatomical differences has led to poor matching of Doppler cardiac output to that obtained via carbon dioxide rebreathing in some instances. Thus, poor matching forced discontinuance of these data sets from subsequent analysis.

A second problem is revealed in the same plot at approximately 12.5 seconds (where the heart rate spikes up suddenly). Notice that for this beat, the impedance drops and causes an ensuing sudden increase in cardiac output. The problem arises when a beat occurs slightly sooner than normal. In this example, the instantaneous heart rate immediately before the spike is 109 beats· min^{-1} and jumps to 125 beats· min^{-1} and back down to 101 beats· min^{-1}. This corresponds to an RR-interval sequence of 550 480 594 milliseconds. Therefore, a beat occurring 70 milliseconds premature resulted in peak-to-min cardiac output fluctuation spanning approximately 12 L· min^{-1} as the cardiac output jumped to about 30 L· min^{-1} and dropped to 18 L· min^{-1}. The explanation is two-fold. First, heart rate is in the algorithm that calculates impedance and increases in heart rate will decrease the calculated impedance, thus increasing stroke volume. However a single-beat change in heart rate is not enough to dramatically alter impedance. The second problem with this is that, obviously, stroke volume is multiplied by heart rate to calculate cardiac output. As a result, you have an exaggerated stroke volume, being multiplied by an instantaneously elevated heart rate. Likewise, the converse is true when there is a delayed beat; producing exceedingly low PCA cardiac output results. Therefore, it stands to reason that people with especially irregular heart rates would have an elevated standard deviation of steady-state

PCA cardiac output as rapid spontaneous changes in heart rate alone will induce considerable fluctuations of cardiac output. Perhaps the simplest solution to this problem is to implement a moving average into PCA cardiac output. For example, averaging the results over a set number of beats or absolute time frame.

When comparing PCA and Doppler cardiac output, an inter-weaving pattern is often produced which will result in an apparent dissonance in the results; mean cardiac outputs are not significantly different, but there is a considerable residual error on a beat-by-beat level (Figure 3-10). With the interweaving pattern, individual beats can have a considerable difference in the two cardiac output values but over several beats, produce the same mean. These results suggest that PCA does not produce *true* beat-by-beat cardiac output and therefore should rely on a moving average of several beats, thus attenuating this problem if PCA is to be used.

Chapter 4

EXPERIMENT #2

4.1 Introduction

Head-up tilt is a standard method of instigating hemodynamic challenges that are not only graded, but also highly reproducible. The postural or gravitational challenge occurs as a result of a reduced venous return and hence, diminished right atrial filling and subsequent decrease in cardiac output. These said challenges are normally met with a compensatory cardioacceleratory response (increase in heart rate) and a vasopressor response (increase in total peripheral resistance).

Although a completely different experiment from the previous one, the goals, objectives and hypotheses are unchanged. As already evident, the previous experiment utilized exercise as a means to alter hemodynamic status. As an alternative, this experiment employed head-up-tilt manoeuvers to induce changes in hemodynamic status. One particular advantage of such an approach is that it permits consistent evaluation of pulse contour analysis in a much more diverse range of participants. For example, the kicking ergometer exercise used in the previous experiment would be contraindicated in a certain part of the elderly population, whereas, the head-up tilt model will far less frequently disqualify elderly participants from partaking in the experiment. In addition, a pulse contour method that is reliable and valid in elderly patients is appreciably sought after for clinical applications. Therefore, it would be desirable to include such a population in experimentation. Secondly, the present pulse contour algorithms may more aptly predict impedance changes (and hence cardiac output) in certain age groups and noting any discrepancies amongst age-trends would facilitate future modification of the algorithms.

4.2 Methods

4.2.1 Participants

Eight young male (mean ± SE: age= 24 ± 0.8; height= 176.6 ± 1.7 cm; weight= 79.2 ± 3.9 kg) and eight older male (age= 58 ± 3.3; height= 176.9 ± 1.9 cm; weight= 83.8 ± 3.4 kg) participants completed this study after providing written, informed consent and completing a standardized medical screening questionnaire. The older male participants had undergone a medical assessment by a physician prior to testing to rule out any potentially unsafe medical conditions that might otherwise be exacerbated by the experimental protocol. At the physician s discretion, prospective participants were either cleared for the experiment or in some cases, recommended that a physician be present as a precautionary measure during testing. All participants completed the experimental protocol without incident. Table (below) outlines individual characteristics.

Table 4-1: Head-up Tilt participant characteristics

Subject	Age	Height (cm)	Weight (kg)	Resting Conditions HR	SBP	DBP
Y1	23	178.0	88.9	73	138	68
Y2	24	176.5	77.8	52	100	60
Y3	23	180.0	77.0	50	112	68
Y4	28	174.0	65.5	52	122	72
Y5	22	171.0	76.3	68	124	58
Y6	22	185.0	101.0	51	112	68
Y7	23	170.5	73.9	50	124	74
Y8	27	178.0	73.0	51	112	64
Mean	24	176.6	79.2	56	118	67
Std. Error	0.8	1.7	3.9	3.2	4.1	2.0
O1	53	181.0	87.3	48	114	70
O2	51	177.0	67.2	32	102	64
O3	75	171.0	76.0	54	122	70
O4	69	167.0	83.7	57	122	80
O5	51	178.0	79.6	53	120	78
O6	53	180.0	89.9	50	124	80
O7	51	178.0	99.0	58	115	80
O8	57	183.0	87.5	55	124	82
Mean	58	176.9	83.8	51	118	76
Std. Error	3.3	1.9	3.4	2.9	2.6	2.3

Subjects were in a supine position for several minutes for resting conditions
HR = Heart rate, SBP = Systolic blood pressure and DBP = Diastolic blood pressure, and were averaged over approximately one minute of beat-by-beat data.

4.2.2 Protocol

A single laboratory session was required of each participant participating in this experiment and started with standard anthropometric measurements (height and weight in plain clothes, no shoes). Three standard ECG electrodes were applied the participant in the 3-lead configuration and an echo Doppler measurement of aortic diameter (as described in 3.2.2) was acquired with the participant in a supine position on the tilt table. A Finapres cuff (Ohmeda 2300, Finapres, Lakewood, CO) was applied according to Finapres documentation to the third digit of the right hand[1]. Precision of the Finapres output was verified with a simultaneous blood pressure measurement using a sphygmomanometer and stethoscope on the on the contralateral arm. As our participant pool included an older population, hand / arm position varied somewhat as a greater degree of participant accommodation was required. The hand was either placed along the participant s side, or across their chest / abdominal area, remaining in the original position relative to the body throughout the experiment. The position of the Finapres cuff relative to the heart was measured and later used to manually correct the Finapres data for hydrostatic deviation. As previously described, the aortic Doppler (pulsed wave) velocity was obtained using the 500M Multigon unit via a 2 MHz. probe placed at the suprasternal notch.

[1] On occasion, the third digit proved unacceptable in those subjects with significant arthritis and an alternate digit of the same hand was used.

With the participant in a supine position on the tilt table and fully instrumented, several minutes were allowed to pass to ensure steady, baseline physiological conditions. The tilt protocol involved 3 phases: 1) supine rest, 2) 45° Head Up Tilt (HUT) and 3) supine recovery. The first two stages typically lasted 5 to 6 minutes each while the recovery phase was in general 2 minutes in duration. All physiological measurements were recorded continuously through all stages. Data analysis was performed on segments of approximately one minute in duration that were taken from the beginning of the supine phase and again, roughly one minute into the tilt condition.

4.2.3 Data Collection

Continuous data collection was obtained with a magnetic tape unit (Teac RD-111T PCM Data Recorder, Montebello, CA) and configured such that real-time output from the various pieces of equipment was displayed on a monitor. The participant and incoming data were monitored continuously throughout the procedure to prevent complications such as syncope from occurring. Data from the magnetic tapes were later uploaded to a computer for storage and analysis.

4.3 Results

4.3.1 Overall

As in the previous study, the pulse contour method of choice is the modified Antonutto version. Practicality of this method increases as the number of calibrations decrease until ultimately, a model is developed that is independent of calibration procedures. Therefore, it is most appropriate to calibrate the participant s impedance during resting, supine conditions and investigate how well the pulse contour model tracks impedance changes and subsequently, cardiac output adjustments into the Head-Up Tilt (HUT) condition.

A total of eight young male and eight older male participants completed this Head-Up Tilt (HUT) study. All of the young participants were medication free but three of the older male participants were on prescription medications as follows: #O2: Cloxicillin (nose infection), #O3: Norfloxacin (ophthalmic solution) and #O7: nasal corticosteroids and allergy shots. Suitably, these medications are not known to have any serious impact on the cardiovascular system.

For the young participants, heart rates and Doppler cardiac outputs ranged from 35 to 93 beats$\cdot$ min^{-1} and 3.25 and 12.81 L$\cdot$ min^{-1}, respectively. Likewise, the older participants ranged from 28 to 71 beats$\cdot$ min^{-1} and 2.17 and 12.49 L$\cdot$ min^{-1}, respectively. Figure 4-1 (below) summarizes the mean changes in cardiac output for Doppler and modified Antonutto pulse contour cardiac output. Although not as diverse of a range as the exercise conditions, this provides yet another stage to test pulse contour cardiac output in a range of cardiovascular dynamics.

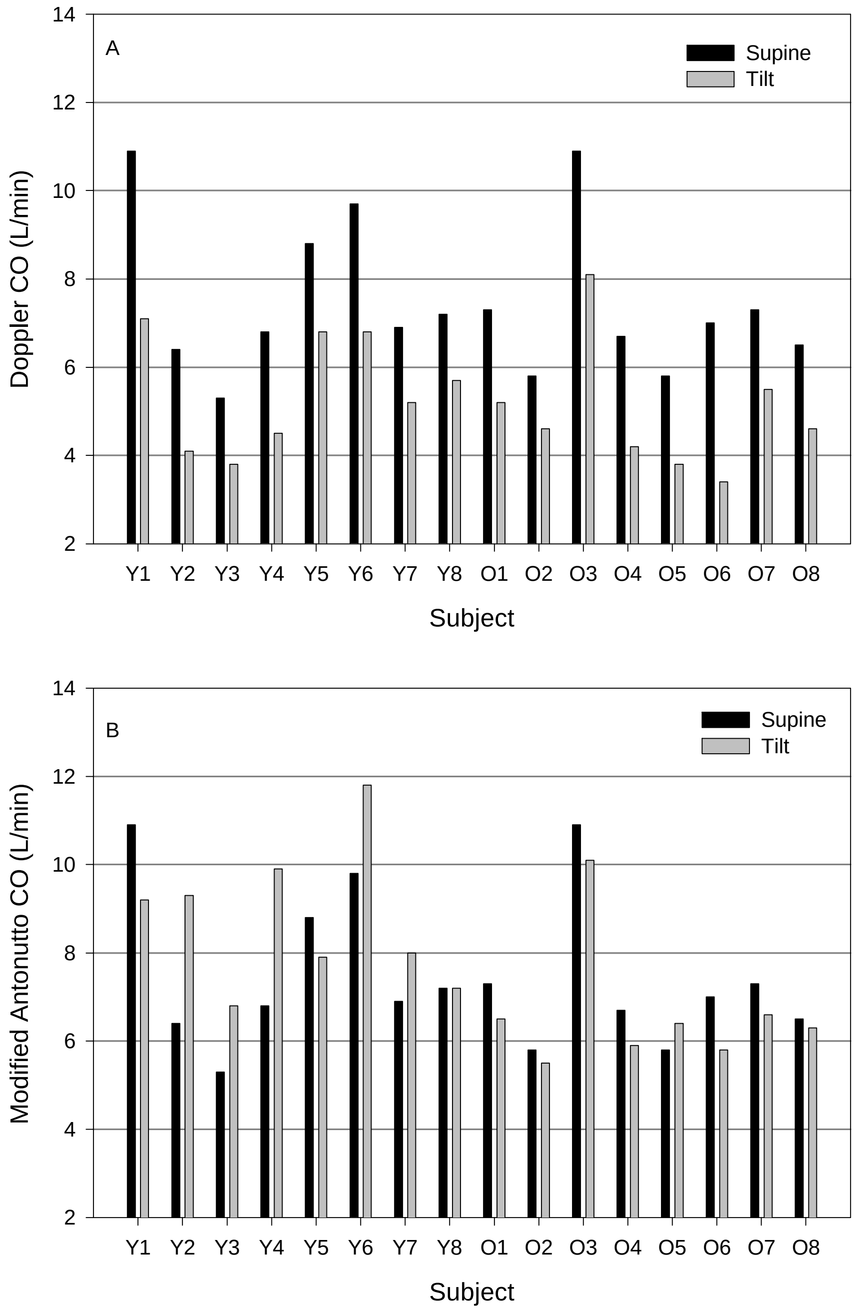


Figure 4-1: Mean cardiac output during supine and HUT

Doppler cardiac output in top panel (A) and modified Antonutto pulse contour (PC) cardiac output in bottom panel (B). As expected, Doppler CO decreases in HUT, but PC fails to produce this trend for some, especially the young subjects.

4.3.2 Macro Results

As previously mentioned, data analysis was performed on one-minute segments of data taken during the supine and tilt conditions. In terms of the pulse contour model, impedance calibration was performed using only the resting, supine data and not subsequently performed for the tilt condition. Expectedly, the mean bias and the limits of agreement (± 2 Standard Deviations) for the supine condition were consistently smaller than that of the tilt condition (Table 4-2).

Table 4-2: Mean bias by group and condition

Subjects - Position	Observations	Bias (L/min)	2 SD (L/min)
Young - Supine	410	0.00	2.57
Young - Tilt	529	-3.36	4.19
Old - Supine	376	0.01	1.33
Old - Tilt	460	-1.59	2.21

The essentially zero bias[1] in the supine conditions is again attributed to its impedance calibration. The second trend that is discernible is that the pulse contour model performs better on the older participants. This is especially evident in the tilt condition where the young participants had a considerably greater bias (more than double) and standard deviation than their older

[1] Bias was calculated using (Doppler Pulse Contour)

counterparts. However, the common tendency of pulse contour in this study is to over-predict cardiac output in the tilt condition, as indicated by the negative bias in both instances.

The following plots provide a better perspective on the performance of the pulse contour model during head-up tilt manoeuvres. In each case, plots are separated by the age-category of the participants (young vs. old) and by condition (supine vs. tilt). The plots further illustrate that the pulse contour model works best in the older participants and preferentially in the supine (calibrated) condition.

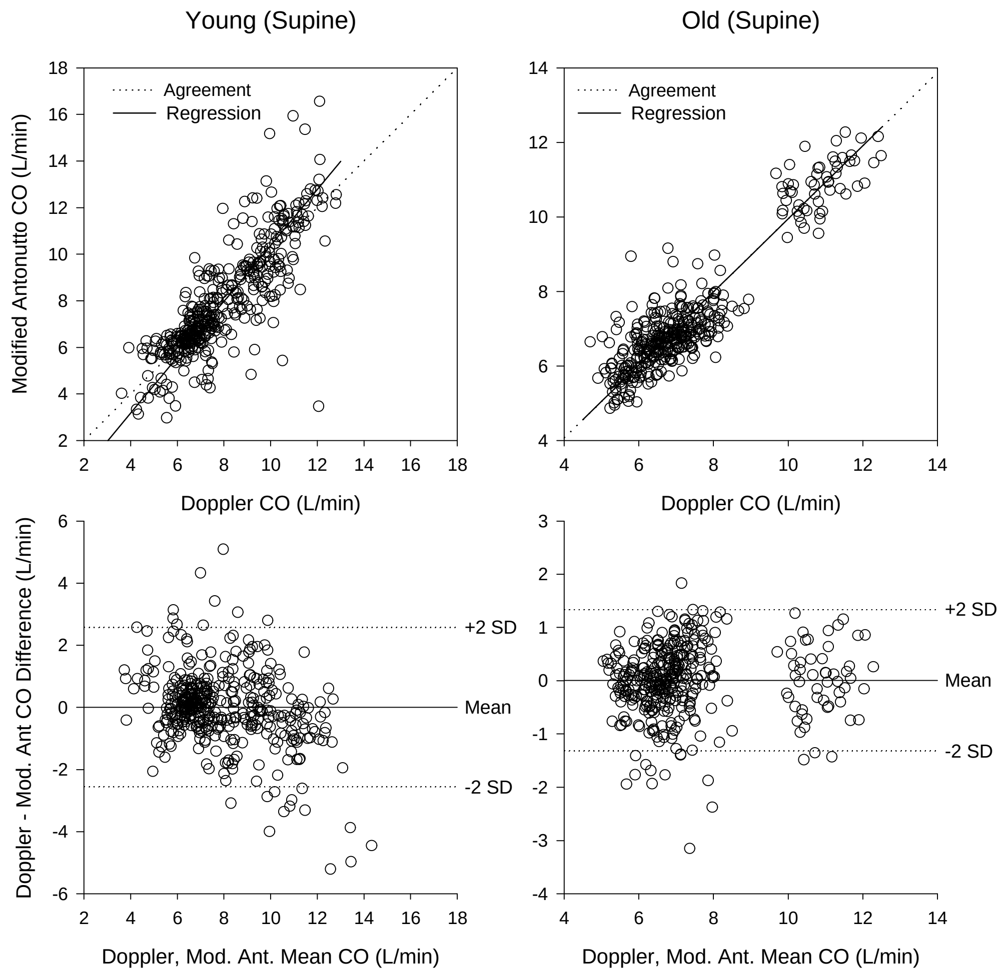


Figure 4-2: Scatter plots (supine) of young and old participants

Top panels display Doppler vs. Modified Antonutto pulse contour cardiac output with the regression line and line of agreement.
Bottom panel contains mean vs. difference plots of the two cardiac output measures along with the mean difference (solid line) and limits of agreement (dotted line).
(Table 4-3 contains the regression summaries.)

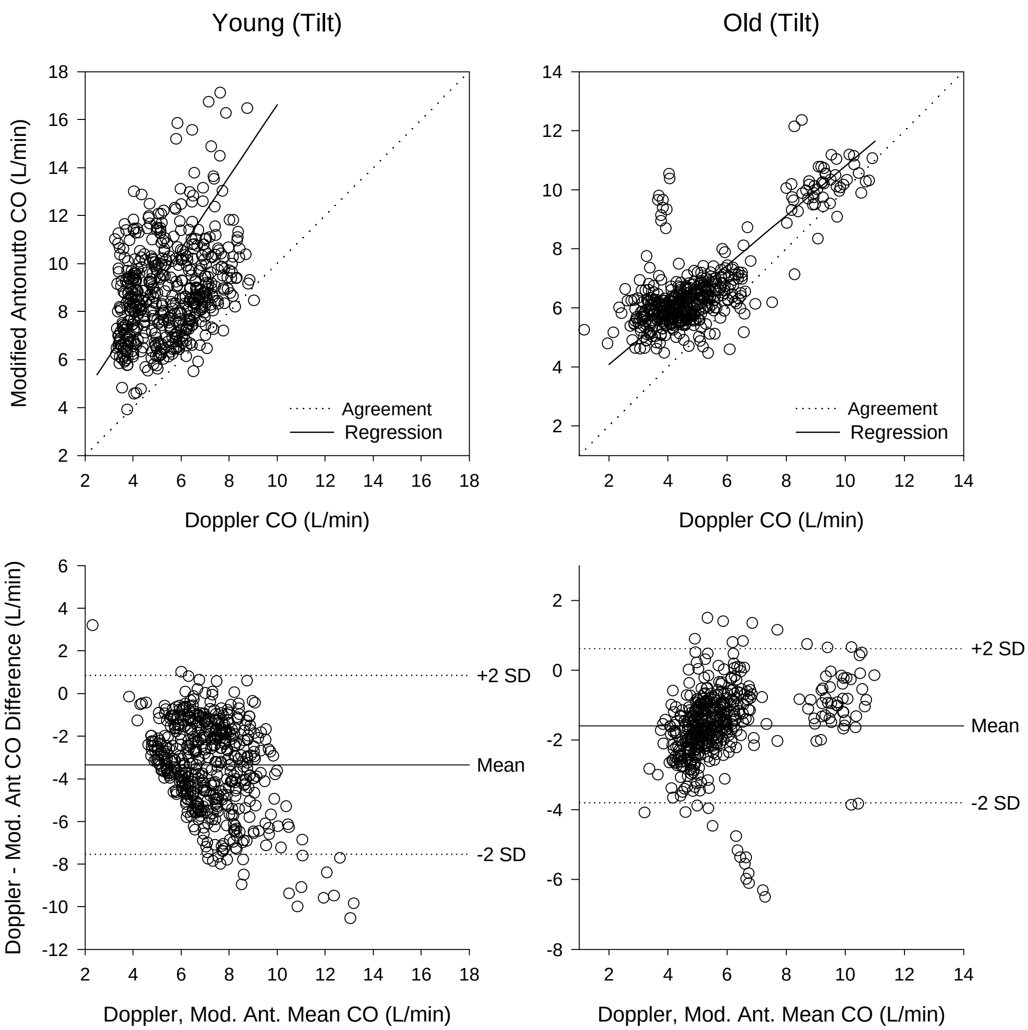


Figure 4-3: Scatter plots (tilt) of young and old participants

Similar to the above plots. Notice that the negative bias is more pronounced in the younger subjects versus the older counterparts.
(Table 4-3 contains the regression summaries.)

-3: HUT Regression Summaries

					95% Confid. Int.			
Subjects - Position	**n**	**Parameter**	**Coefficient**	**Std. Error**	**Lower**	**Upper**	**r^2**	**SEE**
Young - Supine	410	*Slope	1.20	0.03	1.14	1.26	0.69	1.28
		*Intercept	-1.62	0.27	-2.15	-1.09		
Young - Tilt	529	*Slope	1.50	0.06	1.38	1.62	0.11	1.98
		Intercept	0.62	0.35	-0.06	1.30		
Old - Supine	376	*Slope	0.98	0.02	0.94	1.02	0.84	0.65
		Intercept	0.15	0.15	-0.14	0.44		
Old - Tilt	460	*Slope	0.84	0.02	0.79	0.89	0.62	0.92
		*Intercept	2.40	0.13	2.15	2.65		

* $p < 0.01$

Head-up tilt results suggest that impedance calibration performed during supine conditions is not suitable for 45° HUT conditions. In addition, the pulse contourmodel performs better in the older subjects, with regression slopes closer to the line of agreement (slope = and a lower standard error in both the supine and tilt conditions.

These mean results are in agreement with previous studies using similar orthostatic interventions. Perhaps the closest parallel study is the recent investigation by Nieminem *et al.* (2000), which used Wesseling s approach to pulse contour cardiac output and head-up tilt as the model with older participants (age = 41 ± 19 years). However, unlike most studies, this one did use a beat-by-beat reference cardiac output (impedance cardiography) for comparison. Likewise, pulse contour yielded cardiac outputs significantly greater than impedance cardiography with a mean bias of -1.55 ± 1.14 L· min^{-1} whereas this study reports a bias of 1.59 ± 2.21 L· min^{-1} for the older participants during tilt.

4.3.3 Micro Results

In parallel with the exercise trials, it is warranted to evaluate how well the pulse contour model performs on a *beat-by-beat* basis (i.e. without averaging cardiac output over several beats). Linear regression of the beat-by-beat data gives a much better indication of how well the model is performing. Therefore it is not surprising that the regression results (Table 4-3) can sometimes appear disappointing after considering the mean bias (Table 4-2).

The next two series of figures are similar to those of Figure 3-12, providing a beat-by-beat perspective of how the pulse contour model performs against Doppler cardiac output measurements along with the main cardiovascular parameters. The first one is from participant #Y3 (23 year-old male) and the second is from participant #O3 (53 year-old male). In both examples, the first portion of the plots is from supine data while the second half (after the break) is a sample of tilt data (time scale is different for tilt condition in both figures, altered to preserve adequate resolution for detailed visual inspection).

In both instances, Doppler cardiac output decreases in tilt (as expected) while PCA did not follow the same trend. Pulse contour cardiac output in tilt is in fact slightly elevated in the young participant and about the same in the older participant (compared to the supine condition). In addition, the younger participants tend to have a greater absolute impedance and overall range than the older participants. Lastly, it is clear that of the cardiovascular parameters implemented into the pulse contour model (MAP, PP and HR), HR appears to have the greatest influence on the calculated impedance (and hence stroke volume and cardiac output). Heart rate and impedance tend to mirror one another, in that as HR increases, impedance decreases and vice versa.

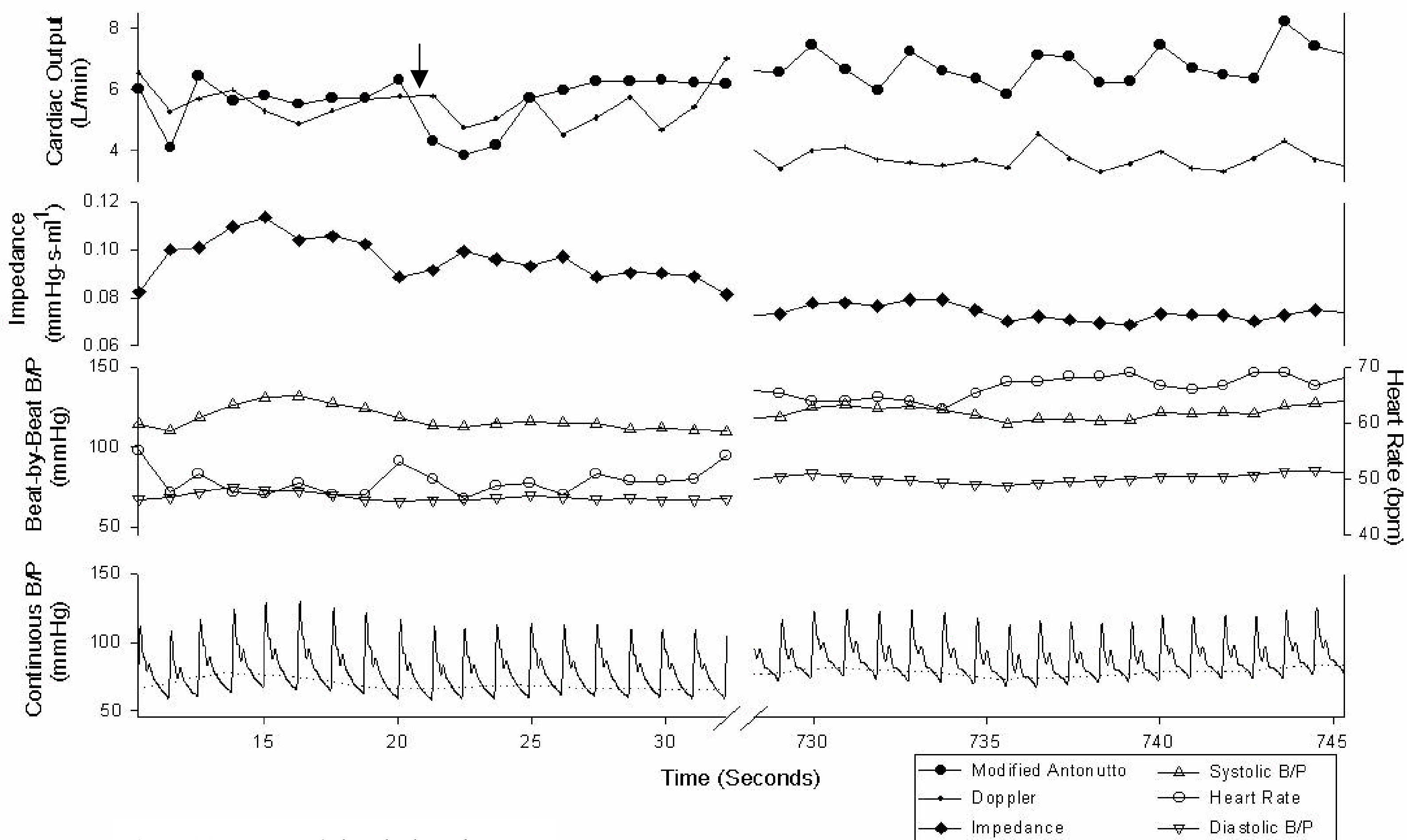


Figure 4-4: Young-male beat-by-beat data

First part of plots is a sample o f supine data while the portion after the break is a sample of 45 ° HUT data. Notice the inter-weaving pattern of pulse contour and Doppler cardiac output. Secondly, notice that sudden, spontaneous jumps in heart rate (for a single beat) will result in a sudden drop in calculated impedance and subsequent increase in cardiac output (indicated by arrow). (Dotted line in bottom plot is the mean arterial pressure). Note the different time scale used for each condition to preserve adequate resolution of be by-beat data for visual inspection.

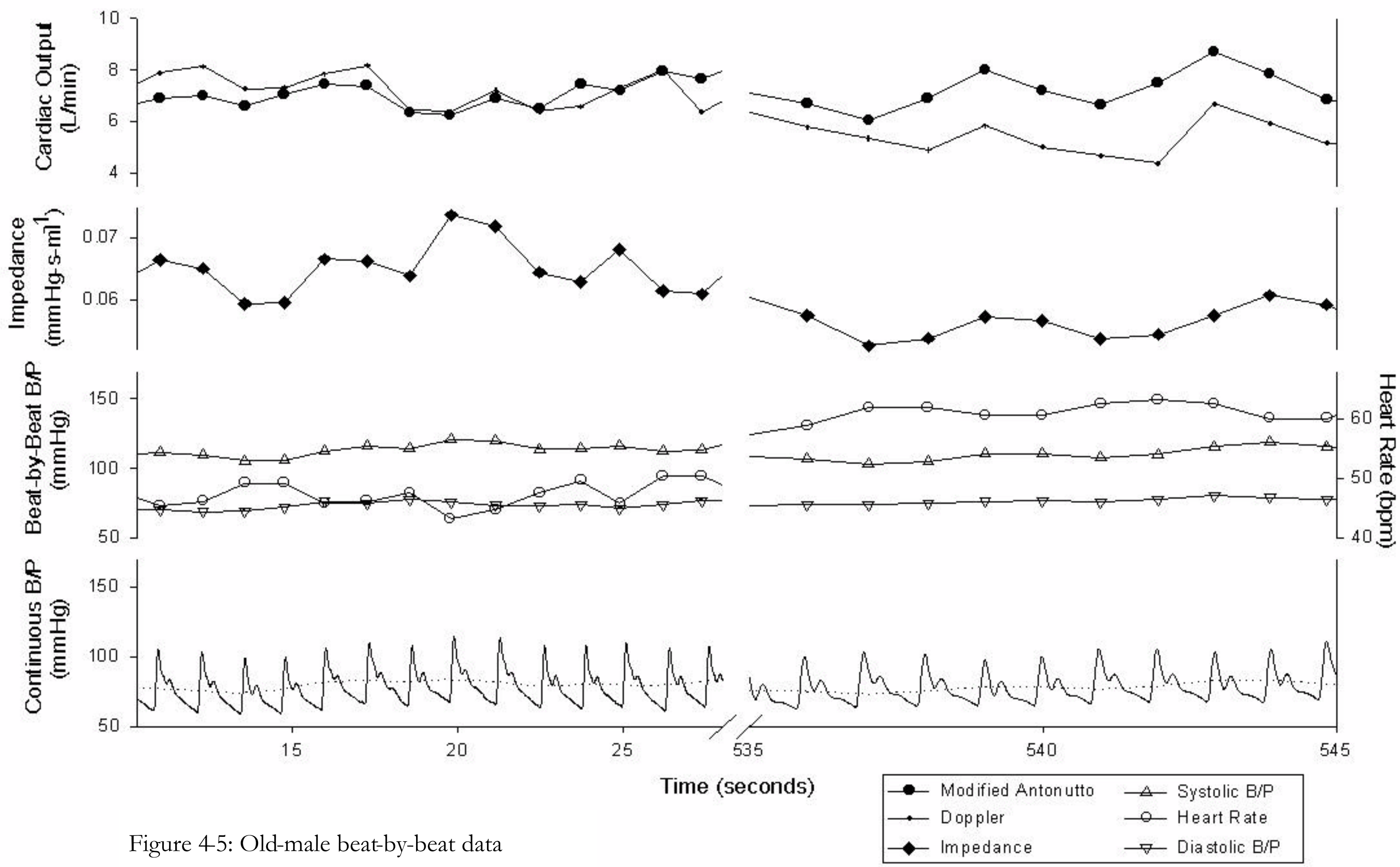


Figure 4-5: Old-male beat-by-beat data

First part of plots is a sample of supine data while the portion after the break is a sample of 45° HUT data. Notice the less-severe inter-weaving pattern of pulse contour and Doppler cardiac output. Secondly, sudden jumps in heart rate and cardiac output appear to be attenuated. (Dotted line in bottom plot is the mean arterial pressure). Note the different time scale used for each condition to preserve adequate resolution of beat-by-beat data for visual inspection.

4.4 *Discussion*

4.4.1 *Overall*

Predictably, supine results are exceptional with a mean bias ± SD of 0.00 ± 2.57 and 0.01 ± 1.33 L· min^{-1} for young and old male participants, respectively. This remarkable accuracy occurs since the pulse contour results are ultimately multiplied by a constant (individual impedance calibration) that sets the cardiac output equal to the reference cardiac output (Doppler). With this, the participant is in a steady state and as such, cardiovascular parameter are not fluctuating a great deal which results in a fairly steady pulse contour cardiac output. As previously mentioned, many studies report admirable results with this approach in models that employ orthostatic manoeuvres to modify cardiovascular dynamics (Stok *et al.*, 1993; Stok *et al.*, 1999; Harms *et al.*, 1999). Nevertheless, most of these studies report a necessity to re-calibrate the individual s impedance upon deviation from the current level of orthostatic stress (Stok *et al.*, 1999).

Previous research generated mixed pulse contour cardiac output results, through varying participant characteristics, situations and interventions. In this study however, the participant pool was divided into young and older male participants (mean age difference 33.5 years). Considering these two groups of participants, there is an apparent trend in the pulse contour model. Starting with the supine condition, mean biases were essentially zero. However, the younger participants had a much wider limit of agreement as compared to the older participants, with 2.57 and 1.33 respectively, during supine conditions. This suggests greater variability in the difference between pulse contour and the reference cardiac output. This may be perhaps a little surprising as the pulse contour model used in this case is that of the one developed by Antonutto and colleagues (1995) who used a young participant pool (22 ± 2 years). The only modification that this study made was to individually calibrate the participant s impedance as it is done in Wesseling s model (1983). Such results are attractive enough to encourage implementation of pulse contour analysis for beat-by-beat cardiac output monitoring, but as the next section describes, this does nothing more than to provide a false sense of security in the model.

In the tilt condition, the biases are both negative (indicating that the pulse contour is over-predicting the cardiac output, or in other words, under-predicting the aortic impedance). Simply put, individual impedance calibration occurred at a relatively higher cardiac output and resulted in an over-prediction at lower cardiac outputs. Interestingly, the reverse trend was noted during exercise in that, calibrating at a higher intensity results in an under-prediction at the lower cardiac outputs (see Figure 3-11). In continuing with the trend established above, once again it is evident that the pulse contour model performs more accurately on the older participants than that of the younger participants, with biases of -1.59 and 3.36, respectively (Table 4-2). Furthermore, there is also a great deal more variation of pulse contour cardiac output amongst the young participants as indicated by the limits of agreement for the two groups. Reportedly, the young participants had limits of agreement of ±4.19 L· min^{-1} whereas the older participants retained a limit of only ± 2.21 L· min^{-1}.

4.4.2 Beat-by-Beat

True beat-by-beat analysis is achieved through linear regression and the approach used by Bland and Altman (1986). Figures 4-2 and 4-3 (above) contain a series of plots for each subset of participants (young vs. old) and for each condition (supine vs. tilt). Starting with the supine plots, both young and old show good results, with the older males having slightly better results. The young males had a regression slope slightly greater than the line of agreement at 1.20 while the older males had a regression slope of 0.98. However, there was one older male participant (#O3) who had unusually high cardiac outputs at rest and during tilt conditions, resulting in a displaced group of points along the regression line, contributing to a levering effect on the data (thus stabilizing the regression slope). Omission of these data would result in a slightly lower slope, but there is no reason to disqualify data from this participant and as such, his results remained in the analysis. In looking at the correlation coefficient (r^2) and standard error of the estimate (SEE), it revealed that the data from the younger participants have a much poorer fit along the regression line in contrast to the older participants who had a larger r^2 and smaller SEE. This trend is continued and exaggerated in the tilt condition: young participants with an elevated regression slope (1.50) and older participants with a depressed regression slope (0.84). Interestingly, although pulse contour is over-predicting cardiac output in both cases, the trends are moving in opposite directions for these two groups of participants.

In considering the mean vs. difference plots (bottom parts of Figures 4-2 and 4-3), we see that in the supine condition, the data are fairly randomized in terms of differences in cardiac output, or that there are positive and negative biases on a beat-by-beat basis. However, in tilt conditions, there is a considerable and consistent negative bias (pulse contour over-predicting cardiac output) and pulse contour quite rarely matches Doppler cardiac output. This drift is readily observable in the sample plots in figures 4-4 and 4-5 (above) where the pulse contour cardiac output is above the Doppler tracing during the tilt condition.

Nevertheless, research continues to pursue an ideal pulse contour model but has so far only resulted in models that only appeared to work within narrow confines in terms of cardiovascular dynamics. The most attractive feature of pulse contour analysis is the capability to non-invasively determine beat-by-beat cardiac output, quickly and easily. The intention is to track *changes* in cardiac output and such changes are inevitably accompanied by general adjustments of cardiovascular dynamics. Therefore, it is unreasonable to depend on a new impedance calibration every time dynamics changes, as the calibration requires a measurement of cardiac output through some other means. Therefore, monitoring of cardiac output via pulse contour analysis appears to only hold accuracy as long as the cardiac output (dynamics) does not drift from the original calibrated state, thereby defeating the purpose. With this, one must consider possible reasons for failure of the cardiac output model in hopes of making constructive future modifications.

Pulse contour model parameters are ultimately derived empirically from a certain subset of participants and conditions. Wesseling s model was developed on an older population during supine, resting conditions whereas Antonutto s model was developed on younger adults exercising on a cycle ergometer. There are two main identifiable deficits in the pulse contour model assessed here. The first is that the model simply does not adequately account for cardiovascular dynamics as they change. In other words, the model s parameters (mathematical coefficients) are not appropriate for the participant and or conditions, or else the model is not including a particular variable that needs to be in the model. This is based on the fact that the model dramatically under predicts the aortic impedance on progressing from supine to a tilt condition. Furthermore, the model consistently performs more poorly on the young participants than on the older participants, indicating that perhaps chronological age as a feature in the model is warranted (Wesseling s model contains age as a variable).

The second major fault in the model has to do with heart rate. The phenomenon revealed itself during the exercise trials and has exposed itself here again. The problem stems from the participant s intrinsic heart rate variability. Heart rate is a variable in the pulse contour model equations and as such, results in susceptibility to radical beat-by-beat changes in heart rate. Pulse contour analysis is performed on a beat-by-beat basis and as such, sudden, spontaneous beats that occur a little sooner or later than expected result in dramatic changes in impedance. A beat that occurs a little sooner results in a sharp drop in the calculated impedance and conversely, a steep up-rise in impedance for beats that occur a little later. The problem is further inflated since the instantaneous heart rate is also modified. For example, a suddenly quicker beat results in a decreased aortic impedance calculation, therefore stroke volume increases for that beat. Additionally, the inflated stroke volume is now multiplied by an increased heart rate (even though it is for a single beat), thereby creating a false-high cardiac output for that beat. This type of artifact is recognizable in Figures 4-4 and 4-5, where every abrupt change in heart rate change from the previous beat, is accompanied by a fairly significant change in cardiac output that is not emulated in the Doppler data.

Lipsitz *et al.* (1990) reported that in passive head up tilt from a supine position, heart rate variability does not change in the older participants, whereas the younger participants had an increase in heart rate variability. Similar results have since been confirmed (Tulppo *et al*., 1998; Akatsu *et al*., 1999). This conclusion parallels the results obtained in this study in that the pulse contour model performed best in the older participants during the supine phase of the experimental protocol. Nevertheless, the pulse contour model did perform more poorly in the tilt condition than in the supine condition for both the young and older participants; but the issue of heart rate variability is not reflected in the mean bias per se, but rather it is an issue of the overall variability. The bias would certainly be corrected if the impedance for the tilt condition were re-calibrated but the heart rate variability would still be manifested as greater statistical variability as represented by the Pearson coefficient and standard error of the estimate. For example, even though the supine biases are essentially zero for the young and older participants, the Pearson coefficient of 0.69 for the young participants is appreciably inferior compared to the supine condition of the older participants, 0.84. Secondly, in the tilt condition, the Pearson coefficient drops by 0.58 to 0.11 for the young and similarly, declines by 0.22 to 0.62 for the older participants. Conversely, a good portion of this error is simply the failure of the model as it stands but given a linear trend, the Standard Error of the Estimate (SEE) scores do represent an overall variance.

Chapter 5

SUMMARY AND RECOMMENDATIONS

5.1 *Summary*

- Modifying Antonutto s pulse contour model improved its performance above all previous models.

- Pulse contour analysis can provide reasonable beat-by-beat cardiac output provided the current cardiovascular state does not deviate from the original impedance-calibration cardiovascular dynamics.

- Performing an individual impedance calibration will result in successful pulse contour model performance for any condition, but for that condition only.

- Pulse contour cardiac output was shown to progressively drift once cardiovascular dynamics change, but tends to parallel Doppler cardiac output with a bias.

- Pulse contour cardiac output is considerably more problematic during exercise due to the impact rhythmic and/or random muscle contractions impose on cardiovascular dynamics

- Heart rate variability appears to negatively affect beat-by-beat pulse contour cardiac output models.

- Pulse contour cardiac output models have been found to perform better on older males compared to young males.

5.2 Recommendations

- A larger number of participants with clean data would be beneficial to elucidating the exact pulse contour model performance characteristics during kicking ergometer exercise.

- Despite the considerable biases between Doppler and pulse contour cardiac output at times, the two still tend to mirror one another, thereby reinforcing the need to continue development of a better pulse contour model rather than abandoning efforts.

- Future model development will need to more aptly accommodate changes in cardiovascular dynamics over a greater range.

- Current models would perform statistically better if taken as a moving mean of at least 3-5 beats to help reduce the impact of heart rate variability

- Develop working algorithms for the 4-element model as developed by Stergiopulos *et al*. (1999).

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Glossary

Acute myocardial infarction (AMI): is the death of part of the heart muscle due to its sudden loss of blood supply. Typically, the loss of blood supply is caused by a complete blockage of a coronary artery by a blood clot.

Cardiac index: Cardiac output in liters per minute divided by body surface area in square meters. Normally about 3 $L \cdot min^{-1} \cdot m^2$ during rest.

Cardiac output: The amount of blood that is pumped by the heart per minute.

Cardiogenic shock: Shock caused by heart failure. The heart fails to pump blood effectively. For example, a heart attack (a myocardial infarction) can cause an abnormal ineffectual heart beat (an arrhythmia) with very slow, rapid, or irregular contractions of the heart, impairing the heart s ability to pump blood, lowering the volume of blood going to vital organs. Cardiogenic shock can also be due to drugs that reduce heart function or abnormally low level oxygen in the blood (hypoxemia) caused, for instance, by lung disease

Downstream effect: The phenomenon where arterial PCO_2 is unexpectedly lower than that of the rebreathe bag PCO_2. There are two hypotheses for this arterial reduction in PCO_2:

i. A disequilibrium is present between the plasma and erythrocytes as blood passes through the pulmonary circulation caused by a slower reaction time for CO_2 equilibrium in plasma due to a lack of carbonic anhydrase.

ii. The PCO_2 difference between the alveolar gas phase and the capillary occurs as a result of a negative charge on the capillary epithelium attracting H^+ and leading to a high PCO_2 in the boundary layer of plasma in contact with endothelium. The end result is a slight inhibition of CO_2 diffusion from alveoli to capillaries.

Hypovolemic shock: Shock due to a decrease in blood volume. This is the #1 cause of shock. It can be due to loss of blood from bleeding, loss of blood plasma through severe burns, and dehydration.

Impedance: Resistance to discontinuous or pulsatile flow *characteristic impedance*: characteristic impedance is the relationship between pressure and flow in an artery (much like input impedance), except without the influence of reflected waves. Wave reflection phenomenon occurs as a result of the natural variation of the vascular bed along it length, its branching patterns and especially at the level of the arterioles (a large increase in fluid resistance). Hence, there are no circumstances where such a situation exists. However, input impedance approaches the characteristic impedance during maximal vasodilation (O'Rourke & Taylor, 1966).

*input impedance***:** similar to the longitudinal impedance, input impedance is the ratio of pressure (as opposed to a pressure gradient) to flow. Consequently, flow at a particular arterial site not only depends on local features but also on the properties of all vascular beds downstream to the point where all cardiac-generated pulsations have been attenuated. In effect, this corresponds to the arterial end of capillaries where pressure and flow are practically continuous without significant pulsations being reflected back to the heart.

longitudinal impedance: this form of impedance is interchangeable with resistance in that it distinguishes the relationship between mean pressure (pressure gradient) and flow along a length of artery. In essence, flow only depends on the local properties of the vessel wall and the blood contained within it. Thus, downstream arterial properties do not influence the upstream flow.

terminal impedance: this is the opposition to flow immediately upstream the termination of the vascular bed and represents the high-resistance arterioles. Although arterioles are vasoactive, their low-frequency response make them essentially purely resistive without influence on blood inertia and vessel distensibility. Terminal impedance is similar to peripheral resistance except that: (1) there is a pressure drop from the point of pressure measurement and (2) the mean pressure beyond the capillary is not zero (even though the transmission of pulsations is extremely small). The difference between terminal impedance and peripheral resistance would become significant in such conditions where the venous pressure is high as is often the case with heart failure.

Model: a simplified, ideal version of a real system, designed for a specific purpose.

analog: model based on an analogy, such as between electrical current and flow, voltage and pressure, or a rubber tube and the aorta.

mathematical: model based on mathematical equations that describe the behaviour or phenomenon of interest

statistical: model based on statistical relationships such as a regression

Pericardial tamponade: A life-threatening situation in which there is such a large amount of fluid (usually blood) inside the pericardial sac around the heart that it interferes with the performance of the heart. The end result, if untreated, is low blood pressure, shock and death.

PSA: Pulsatile Systolic Area. The area under the blood pressure curve from diastole to the dicrotic notch**.**

Raynaud s phenomenon: Intermittent attacks of pallor followed by cyanosis, then redness of digits before return to normal. Initiated by exposure to cold or emotional disturbance. Numbness, tingling and burning may occur during the attacks. Secondary to such conditions as occlusive arterial disease, systemic scleroderma, thoracic outlet syndrome, pulmonary hypertension, myxedema or trauma.

Transmission line model: (for pulse contour): A conceptual model of the arterial system where it is viewed as a uniform distensible tube with constant cross-sectional area, wall thickness and modulus of elasticity along its entire length, driven at its proximal end by a generator. This tube has a finite length and is terminated distally with a peripheral resistance. (From Wesseling *et al*. 1983).

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