Developing a Non-Invasive Method to Monitor Cardiovascular Control during Orthostatic Challenge Considering the Limitation of the Finometer™

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, 2009

Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Sensations of dizziness or fainting (pre-syncope or syncope) on standing up from a lying or a seated position are usually associated with impaired blood pressure regulation leading to inadequate perfusion of the brain. The purpose of this project was to develop a simple method to provide scientists and doctors a convenient way to monitor cardiovascular control during orthostatic stress with the non-invasive Finometer™ device. This apparatus provides a continuous estimate of arterial blood pressure (BP) contour from the finger and computes brachial blood pressure contours (systolic (SBP) and diastolic (DBP) blood pressure), heart rate (HR), stroke volume and cardiac output (Q) from the Modelflow equation. In this thesis, a method was implemented to obtain an estimate of central venous pressure (CVP) to provide greater insight into cardiovascular control. The accuracy and potential errors resulting from measurement of finger arterial pressure were also evaluated.

The thesis first examined whether key variables essential to monitor cardiovascular control can be reliably measured by the Finometer™ in comparison to independent methods. HR was accurate and precise at rest and during stress (difference between methods: *0.05± 0.18 beats/min*). According to standards established by the American Association for the Advancement of Medical Instrumentation (AAMI); at rest, DBP was accurate but not precise (*1.6± 8.8 mmHg*) and SBP was not accurate but precise (*14.2± 8.0 mmHg*). These errors could be due to an improper use of our reference method. The post-test correction for individual characteristics proposed by the Finometer™ developers did improve overall Q estimation (*0.255± 0.441 L/min* (*6.9%*) instead of *0.797± 0.441 L/min* (*22.4%*)) when compared with Doppler ultrasound but did not account for the

increasing error with a greater orthostatic stress induced by lower body negative pressure. Using finger BP instead of aortic BP to calculate Q did not explain this error as revealed by a new approach that compared the simultaneous pulse contours from different methods. Indeed, there was no significant difference between the error of the estimation of Q from the finger arterial pulse compared to the estimation of Q from the independent measurement by tonometry on the brachial artery at rest (*-1.13± 14.67%*) and at the maximum orthostatic stress used (*-0.61± 9.33%*) (*p>0.05*). Using brachial BP to calculate Q did not improve the result found with finger BP.

The first hypothesis of this thesis that CVP could be estimated from outputs of the Finometer™ compared to direct venous pressure measurement was supported for the individual (*0.2± 1.7 mmHg*) and test specific (*0.1± 1.2 mmHg*) equations. The general equations derived from group data were accurate but not precise enough (*0.4± 2.8 mmHg*) to be used in clinical and research setting. The success of the individual equations suggests that it might be possible to derive a personal equation that will be useful over a long period for similar tests by using a catheter only once. The second and third hypotheses related to the cause of discrepancy between Q from Finometer™ and Q from Doppler, were not supported by the data. However, a new contour analysis method introduced here in a graphical format might provide an opportunity for systematic analyses of the deviation between methods. It could reveal sources of error allowing future improvements in the accuracy and precision of Q from Finometer™ during orthostatic or physical stress.

Acknowledgements

First of all, I would like to thank my supervisor, Dr Richard Hughson, for giving me the opportunity of doing a Master's degree in Kinesiology. Knowing that I am a mechanical engineer did not stop him to pick me in his lab even though I required a little bit more assistance than a "standard" Kinesiology grad student. He was a great support during the three (3) past years and taught me how to really learn something rather than know where I can find the answer. This experience opened my eyes not only on the world of Kinesiology, but also on the world of Research and provides me with great skills that will be useful for the rest of my life.

I would also like to thank the other members of my examining committee, Dr Joe Quadrilatero and Dr Lora Giangregorio, for taking the time of reading my thesis and giving me very constructive feedbacks.

Danielle Greaves- I really appreciated your help and all the work you have done to answer my non-conventional-grad-student questions. I would like to thank you as well for your technical support during the two experiments needed for this thesis.

Heather Edgell, Anna Grinberg and Keith Beavers- Our 1-year-long project was definitely a big involvement but it could have not happened without the combination of all our efforts. Your presence and support were definitely worth the overnight sleep at school and the very early morning testing.

Andrew Robertson- Your technical help for the second project was much appreciated. This would have not happened within a so short notice without your valuable help.

Myra, Jing, Eric, Sara, Saudia, Michelle, Chantel, Katelyn, Ashley and Ariella- Thanks for your technical support during our many tests. A special thanks to Eric, Jing and Chantel who even came during their time off to help us.

Another special thanks to our subjects who took part of one or two projects and without whom this Master's thesis would have been impossible.

The Lab Crew- Thanks for being such fantastic friends during the three (3) past years. Your friendships, your patience and your support regarding my English skills contributed to make me feel at home and keep my productivity high.

Finally, I would like to express my sincere gratitude to my husband, Eric. His presence and support contributed to keep my sanity. Thanks Eric for your love and support, I will never forget the sacrifices you have made to follow me in this adventure!

Je remercie aussi ma famille (Papa, Maman, Benoit et Jocelyne) pour leurs supports et leurs encouragements tout au long de ces années passées loin d'eux.

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List of Abbreviations

AAMI	American Association for the Advancement of Medical Instrumentation
BP	Blood Pressure
CCC	Cardiovascular Control Centre
CVP	Central Venous Pressure
DBP	Diastolic Blood Pressure
EF	Ejection Fraction
HDBR	Head Down Bed Rest
HR	Heart Rate
LBNP	Lower Body Negative Pressure
LVEDV	Left Ventricular End-Diastolic Volume
LVET	Left Ventricular Ejection Time
MAP	Mean Arterial Pressure
PR	Peripheral resistance
$\dot{Q}$	Cardiac Output *(In the text, the dot is omitted for simplicity but in all cases the Q is intended to be the rate of flow)*
SBP	Systolic Blood Pressure
SV	Stroke Volume
TPR	Total Peripheral Resistance

1. Introduction

Every year, thousands of people faint (syncope) or experience dizziness, light headedness or blurred vision that might be symptoms of pre-syncope after standing from a lying or a seated position. Orthostatic hypotension, defined by a drop >20 mmHg systolic blood pressure or >10 mmHg diastolic blood pressure within 3 minutes of standing [Low, 2008] is often associated with these symptoms. An integrated cardiovascular control response is initiated on moving to a head up posture to counterbalance the footward blood shift induced by the gravity vector and a slow or inappropriate reaction of these mechanisms could lead to an inadequate perfusion of the brain and to a fainting episode. In the elderly population for example, the incidence of orthostatic hypotension might reach as high as 30% with important increased risk of mortality associated with this impaired blood pressure regulation [Low, 2008].

The aim of this project is to develop a simple, non-invasive method that will provide scientists and doctors a way to monitor cardiovascular control during orthostatic stress to enable isolation of the specific factors that might cause fainting in different individuals. This kind of method has a lot of potential to provide a first evaluation of important clinical signs (blood pressure, stroke volume, heart rate, etc.) that might require detailed investigations. This can also be convenient in research setting for situations in which there is a restriction on using more elaborate and specific equipments due to the location (such as on the International Space Station) or the type of research.

The Finometer device for non-invasive estimates of arterial blood pressure is already well known and implemented in clinical and research laboratories. This innovative machine

based on the volume-clamp method [Peñáz et al., 1973] measures continuous non-invasive finger arterial pressure and estimates several variables that can be used in the investigation of the cardiovascular control mechanisms. Although this device has a lot of potential for our purpose, many groups are concerned about its accuracy [Hirschl et al., 1997; Remmen et al., 2002; Azabji Kenfack et al., 2004]. Indeed, a growing body of scientific research shows that the Finometer calibration is quite complex and that it might change depending on the subject and the stress applied [Houtman et al., 1999; Azabji Kenfack et al., 2004; Stok et al., 2006]. This is a concern for us as we are looking for a device that can be applied under conditions of changing postural stress.

In order to cover the first steps of the development of a method, my thesis is separated in two different projects covering three steps. In the first project, we will examine whether key variables essential to monitor cardiovascular control can be reliably measured and calculated by the Finometer in comparison to independent methods. For the second project, we will investigate further what are the causes of the Finometer's limitations and propose solutions to increase its accuracy.

2. Literature Review

2.1- Orthostatic Stress

Every human experiences orthostatic stress in his/her daily life during changes in posture from lying in bed to sitting or standing up. Although these activities seem very simple, changes in the posture will create perturbations of the homeostasis that without appropriate reflex actions of the cardiovascular system would result in fainting.

When a person moves to an upright position 70% to 75% of his/her blood volume is below heart level [Rowell, 1993]. The force of gravity induces this blood downshift and contributes to increase the pressure in the lower limbs (figure 1). The position of the brain above the heart makes it very susceptible to ischemia and challenges the human body to properly perfuse it [Rowell, 1993].

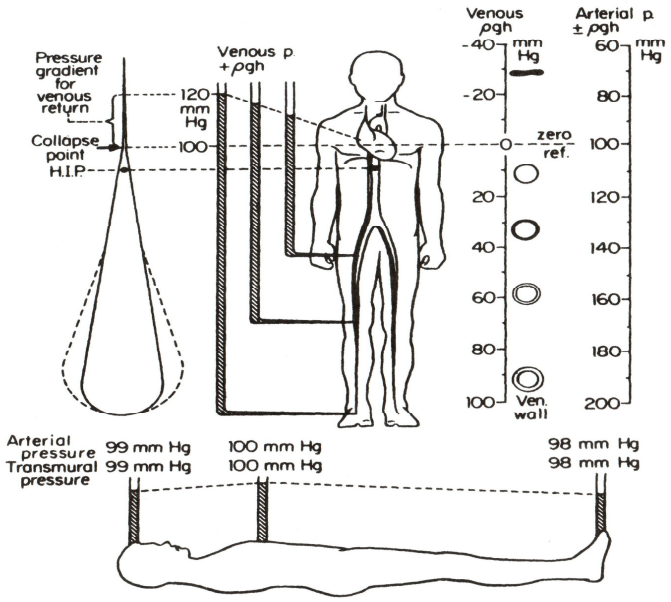

Figure 1: Distribution of vascular pressures in supine and upright human

[from Rowell, 1993]

Although gravity has a big effect on the human blood circulation, individuals are able to move to and keep an upright posture with the help of different regulatory mechanisms that work to maintain sufficient arterial blood pressure to drive blood to the brain.

2.2- Cardiovascular Control in Response to Orthostatic Stress

The cardiovascular control centre (CCC) located in the medulla is responsible for the challenge of maintaining blood pressure to preserve brain blood flow during orthostatic stress. It works in a closed-loop system and controls mechanisms operating on the peripheral resistance and the cardiac output to regulate arterial blood pressure. This relationship is expressed in a form of Ohm's law for the circulation relating the pressure gradient (ΔP) from ejection of blood into the aorta to return to the right atrium as a function of cardiac output and resistance to flow:

$$\Delta P = MAP - CVP = \dot{Q} \times TPR \qquad \text{(Eq 1)}$$

Where *MAP* is mean arterial blood pressure [mmHg], *CVP* is central venous pressure [mmHg], $\dot{Q}$ is cardiac output [L/min] and *TPR* is total peripheral resistance [mmHg/L/min]. The formulation in equation 1 is utilized to represent the whole body reaction to a stress.

The cardiovascular control centre (CCC) receives afferent information about change in pressure from baroreceptors located in the arterial system in the aorta and the carotid sinuses (arterial baroreceptors) and in the low pressure venous side of the heart in the inner wall of the right atrium and the pulmonary arteries (cardiopulmonary baroreceptors). Any record of a change will activate the autonomic nervous system which will send efferent signals to adjust flow and peripheral resistance in order to correct the

situation toward the stability of a steady state. As explained in section 2.1, moving into an upright posture will initiate a downward shift of blood volume and decrease blood pressure above the level of the heart. This situation will decrease the firing rate of the different baroreceptors and send the signal to increase total peripheral resistance (TPR) and Q via the CCC. These changes are made through different pathways. Indeed, TPR will be increased via the sympathetic system releasing more norepinephrine causing primarily arteriolar vasoconstriction. The increase in cardiac output is driven primarily by an initial increase in heart rate (HR) due to parasympathetic nervous system withdrawal, as well as potential increases in sympathetic nervous system activity to further increase HR and cardiac stroke volume (SV) [Silverthorn, 2007].

The clinical relevance to record blood pressure (BP), CVP, TPR, Q, SV and HR is then very significant for doctors and scientists investigating cardiovascular control. Any kind of stress will create variation in these variables and will be unique as the proportion and the amplitude of the reactions will differ.

CVP and arterial blood pressure are key cardiovascular variables that act as inputs to the cardiopulmonary baroreceptors and the arterial baroreceptors respectively. The cardiopulmonary baroreceptors are primarily responsible for regulation of TPR operating in a feed forward manner to reflect changes in venous return. The arterial baroreceptors can affect HR, cardiac contractility and TPR. In this system, a reduction in CVP is a good indicator that blood is pooling in the vascular tree during an upright posture as it will decrease almost instantaneously with the diminution of blood going back to the heart [Rowell, 1993].

The ability to follow changes in TPR provides a valuable indicator of mechanisms working to regulate blood distribution through neural and local mechanisms. The hormonal, myogenic, metabolic and endothelium-mediated vascular control mechanisms are all working locally to change peripheral resistance by amplifying or diminishing the efferent signal sent via the sympathetic nervous system. Although investigation of the specific involvement of these peripheral factors during a stress requires additional techniques such as a blood sample, their general effect is included in TPR.

2.3- Heart Performances in Response to Orthostatic Stress

Standing from a lying or a seated position reduces the quantity of blood coming back to the heart. Since the heart can only pump the blood received, SV will be reduced by approximately 40% in an upright posture [Poliner et al., 1980; Rowell, 1986; Rowell, 1993]

Interestingly, an increase in blood volume coming into the heart will also increase its SV. This is explained by the Frank-Starling mechanism, which refers to the length-tension relationship of the myocardial muscle fibres. Indeed, contraction force increases when sarcomere length increases up to an optimal length. This means that an increase of the left ventricular blood volume will stretch the cardiac wall and increase the SV as shown in figure 2:

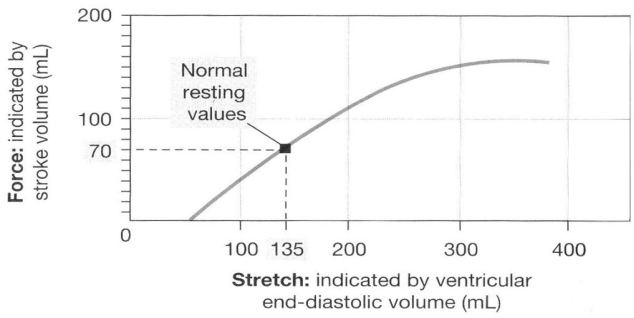

Figure 2: Length-force relationships in the intact heart: a Starling curve

[from Silverthorn, 2007]

In a preliminary study, we demonstrated a linear relationship between CVP and SV using a lower body negative pressure (LBNP) device to simulate gravity in subjects before and after a 4h hour head down tilted bed rest [Gagné et al., 2007]. We reasoned that this relationship followed the Frank-Starling mechanism with CVP as an indicator of the preload of the heart. Further investigations of those preliminary data have shown that this relationship is specific to every subject.

The ejection fraction (EF) is the ratio of blood ejected by the heart relative to the left ventricular end-diastolic volume (LVEDV). EF is very important to take into account when assessing heart performance because it depends mainly on the left ventricular contractility. The Frank-Starling mechanism becomes then very specific to every single heart and is influenced by inotropic agents, aging [Fleg, 1986] and prolonged bed rest [Levine et al., 1997]. The residual pressure in the aorta (DBP) can also influence EF throughout a stress. Indeed, an increase in the afterload of the heart will reduce SV and this will in turn result in an increase in LVEDV [Nevo, 1993].

Although the heart's performance is dependent on its mechanics, it is also influenced by the cardiovascular control of the arterial tree. As explained in section 2.2, to maintain

blood pressure in order to preserve brain blood flow, the CNS is actively controlling the heart rate and cardiac contractility through efferent signals. In addition, blood volume, venous compliance, MAP, Q and TPR are all variables that will influence the quantity of blood available to pump by the heart. For these reasons, it is generally accepted that the performance of the heart is determined primarily by the peripheral circulation [Rowell, 1993].

2.4- Blood Pressure Waveform during Orthostatic Stress

The blood pressure waveform can be described by four elements: the peak of the waveform called systolic blood pressure (SBP), the minimum of the waveform called diastolic blood pressure (DBP), the mean of those two values called mean arterial pressure (MAP) and finally, the difference between SBP and DBP called pulsed pressure (PP). Within the arterial tree, blood pressure is influenced by three different components: the static pressure, the dynamic pressure and the hydrostatic pressure. The first one refers to pressure created by a volume of blood pushing on the arterial wall when there is no flow. The second one refers to the pressure created by a flow pushing in resistance artery. Finally, the third one is caused by the force of gravity on a column of blood [Rowell, 1993]. These three components are in part responsible for the magnitude and the shape of the pressure contour.

The arterial BP waveform is not the same in the aorta as it is in the peripheral arteries. In fact, the transmission of the pressure along the arterial tree is distorted by both pressure gradient and a reflected wave [Bos et al., 1996]. The addition of the forwarded wave and the forepart of a wave returning from a reflecting end of the arterial tree will define the

pressure contour depending of the position of the artery investigated [Remington and Wood, 1956].

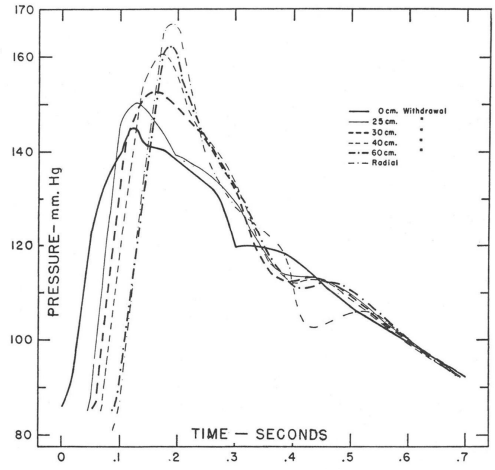

Figure 3: Transformation of pulse starting from aorta and passing in the subclavian-arm system [from Remington and Wood, 1956]

Although MAP is smaller in the peripheral arteries; the pulse pressure increases, the systolic peak pressure is narrowed and progressively delayed to account for the propagation of the wave [Remington and Wood, 1956].

At rest, the pressure waveform difference between central and peripheral arteries will change from person to person due to individual characteristics such as increased arterial wall stiffness as seen with aging [O'Rourke, 2005]. This is indicated by studies showing that an individual transfer function provides better prediction of central BP waveform than a general transfer function developed from a large population [Segers et al., 2000; Karamanoglu et al., 1997]. These transfer functions mathematically represent BP change in the frequency domain between a central and a peripheral artery.

Orthostatic stress will influence the difference between central and peripheral pressure contour. The increased sympathetic activity occurring while moving in an upright posture

will cause greater change in the peripheral vessels than in the aorta [Houtman et al., 1999]. This will affect the pressure waveform by increasing the speed at which the reflected wave will move back [Westerhof and O'Rourke, 1995; Stok et al., 2006] and change the transfer function of central over peripheral pressure. Stok and colleagues (2006) have shown the same idea, but using exercise as a stress.

2.5- Non-Invasive Instrument: the Finometer™

The Finometer is a non-invasive instrument and the successor of the Finapres used in both ambulatory clinics and laboratories all around the world. It is mainly utilized to measure the equivalent of brachial blood pressure (brachial BP) from the finger blood pressure (finger BP) and can also provide estimates of stroke volume (SV) and cardiac output (Q).

The Finometer, as presented in figure 4, monitors hemodynamic events by using three different important steps: monitoring finger BP, estimating brachial BP and finally, estimating Q.

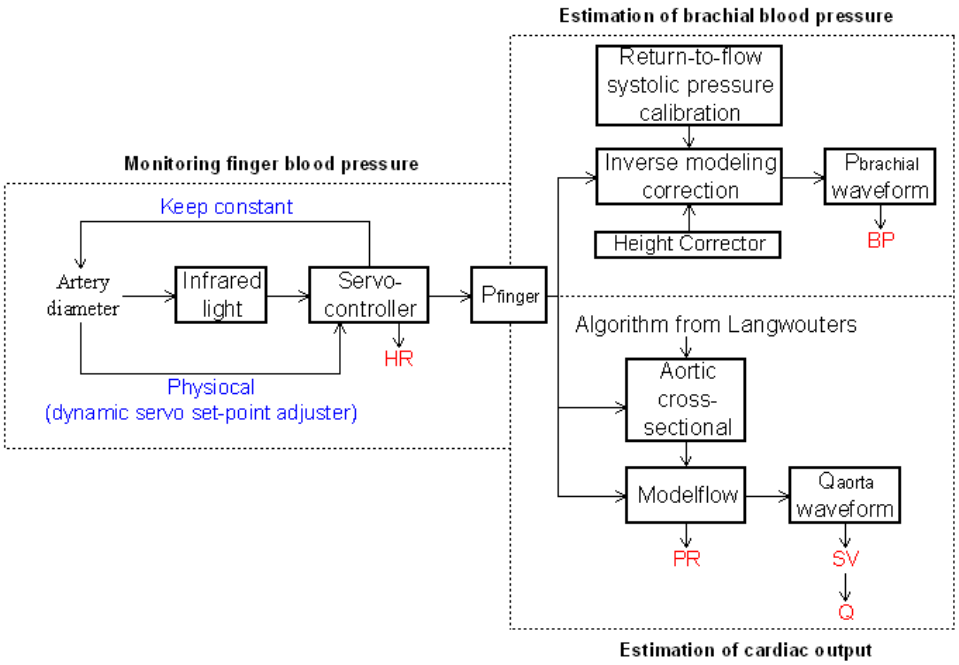

Figure 4: Schematic Representation of the Finometer™ Layout

2.5.1- Monitoring Finger Blood Pressure

Finger blood pressure is measured with a cuff wrapped around the finger (shown in figure 5-A) and following the volume-clamp method developed by Juan Peñáz [Peñáz, 1973]. The principle of this method is to dynamically keep constant the finger arterial diameter at a predefined set-point with the help of a pneumatic servo-system [Wesseling et al., 1995]. The set-point used is defined by an algorithm (Physiocal) that is searching for the "unloaded" diameter [Wesseling et al., 1995]. This particular diameter is established when the transmural pressure of the arterial wall is zero; meaning that the pressure inside is equal to the pressure outside the artery. Therefore, the pressure delivered by the servo-controller to the finger cuff in order to keep constant the artery diameter will also be the finger blood pressure.

Changes in hematocrit, stress and the tone of smooth muscle in the arterial wall will affect the unloaded diameter [FMS website]. The Physiocal algorithm will then recalibrate the unloaded diameter after a set number of heart beats. The changes in diameter are sent to the servo-controller by an infrared photo-plethysmograph placed in the finger cuff [Boehmer et al., 1987].

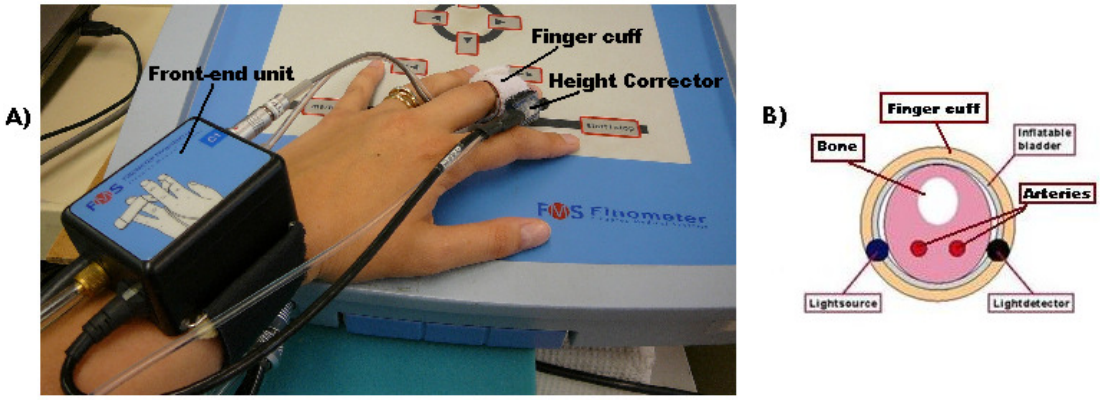

Figure 5: A) Finger Cuff; B) Finger Cross-Section [Modified from FMS website]

From this step, the Finometer can accurately estimate the heart rate (HR) from the servo-controller as a new waveform recorded means a new heart beat.

2.5.2- Estimation of Brachial Blood Pressure

As explained in section 2.4, pressure waveforms change while going from brachial to finger arteries. An inverse modelling correction and a height corrector are then used to reconstruct the brachial blood pressure from the finger blood pressure.

The inverse modelling correction is actually a frequency-dependent transfer function used as a filter [Bos et al., 1996]. The transfer function from brachial to finger blood pressure has been developed by Gizdulich and colleagues and published in 1997. It has been shown to resonate (oscillate at a maximum amplitude) at a frequency ranging from

4.26Hz to 10.58Hz depending of the subject [Gizdulich et al., 1997] and causes a distortion. Since the mean value is approximately 8Hz, the Finometer's designers have used a frequency-dependent filter with an anti-resonance frequency of 8Hz to neutralize this distortion [FMS website].

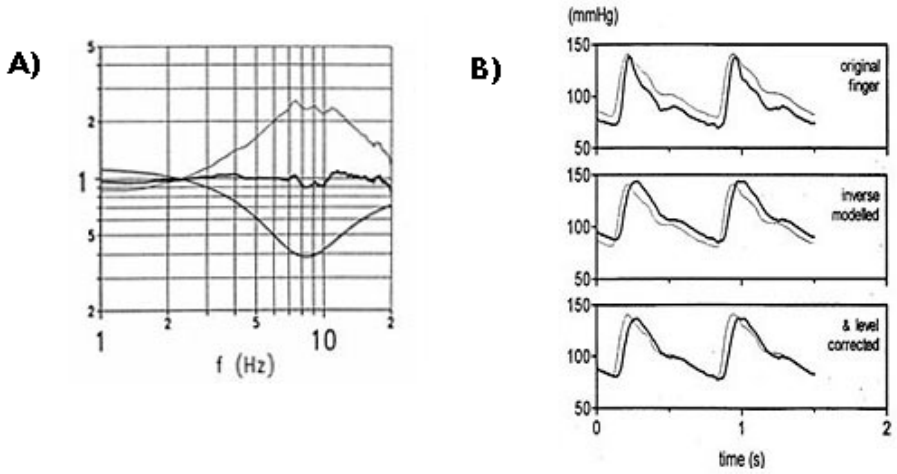

Figure 6: A) Transfer Function Amplitude Comparison; B) Reconstruction of brachial blood pressure (gray line) from the finger blood pressure (black line) [from FMS website]

Figure 6-A, taken from the FMS website, shows the transfer function amplitude (top line), the frequency-dependent filter amplitude (bottom line) and the expected result of the overall transfer function amplitude (middle line) of one subject [FMS website]. It is important that this overall transfer function amplitude stay as close as possible to 1. A deviation from this will give an amplification or an attenuation of the signal at a particular frequency and will be seen as a distortion. The use of a fixed anti-resonance frequency is then good in the case where almost all subjects have their transfer function resonating at around 8Hz, but will create discrepancies in case of subjects having their transfer function resonating at 5 Hz for example.

In the case of an average person, figure 6-A demonstrates that the inverse model will contribute to change a little bit the shape of the brachial blood pressure in the low frequencies but will have a bigger influence in the high frequencies. This means that the shape of the systolic portion will be the most influenced [Bos et al., 1996] as shown in the top and the middle panel of figure 6-B.

A height corrector is also needed to counterbalance the pressure gradient driving the flow from the brachial artery to the finger artery. As explained previously in section 2.1, the hydrostatic pressure will play a role in the pressure gradient and should be taken into account by using two sensors for the finger and the brachial level. The bottom panel of figure 6-B shows its effect.

The return-to-flow calibration is done by an upper-arm cuff following the idea of a standard sphygmomanometer. The upper-arm cuff positioned on the same arm as the finger cuff will completely stop the flow through the brachial artery if its pressure is higher than the systolic blood pressure (SBP). The pressure is then decreased until it reaches the systolic blood pressure and allows the first pulsation that will be sensed and recorded by the finger cuff [FMS website]. This method is used to calibrate the systolic blood pressure and then reach the American Association for the Advancement of Medical Instrumentation (AAMI) standard (bias should be less than ± 5mmHg and precision should be better than ± 8mmHg [Finometer^{TM} User's Guide]).

The estimation of brachial blood pressure waveform allows the Finometer to estimate the mean arterial pressure (MAP), the systolic blood pressure (SBP), the diastolic blood pressure (DBP) and the pulse pressure (PP).

2.5.3- Estimation of Stroke Volume and Cardiac Output

Stroke Volume and Cardiac output are estimated from finger arterial blood pressure with the help of the Langwouters' equation and the Modelflow method. As shown in figure 7-B, the Modelflow method is a non-linear three elements model of the aortic input impedance developed by Wesseling and colleagues in 1993. The model elements represent aortic characteristic impedance (Z_0), Windkessel arterial compliance (C_W) and systemic vascular resistance (R_P) [Wesseling et al., 1993].

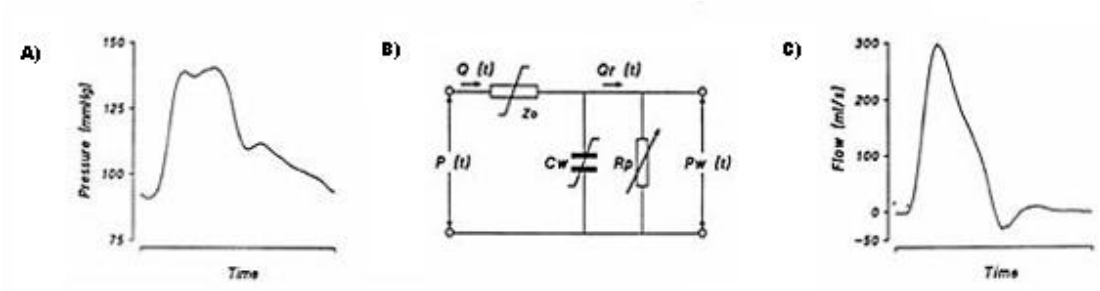

Figure 7: A) Pressure waveform; B) Modelflow model; C) Aortic flow waveform

[from FMS website]

The aortic characteristic impedance element (Z_0) represents the aortic opposition to the pulsatile flow from the contracting left ventricle while the Windkessel arterial compliance element (C_W) refers to the aortic elastic storing property and the opposition to an increase in blood volume [Wesseling et al., 1993; Harms et al., 1999]. Both elements are pressure-dependent because the elastic behaviour of the aorta varies non-linearly with the changing pressure [Langwouters et al., 1985; Bogert et al., 2005]. Their parameter values are then computed with the help of an algorithm to calculate the aortic diameter from the intra-arterial pressure [Langwouters et al., 1984]:

$$A(p) = A_{\max}\left[0.5 + \frac{1}{\pi}\arctan\left(\frac{p - p_0}{p_1}\right)\right] \qquad \text{(Eq 2)}$$

Where A_{max} is a parameter based on the sex of the subject while p_0 and p_1 are parameters based on the age and the sex of the subject.

The systemic vascular resistance element (R_P) refers to the Poiseuille resistance of all vascular beds together. It is a measure of the ease of constant blood drainage from the Windkessel into the peripheral vascular beds [Wesseling et al., 1993] [Harms et al., 1999].

The modelflow method will estimate the aortic flow waveform from the finger arterial blood pressure waveform (see figure 7). Stroke volume (SV) and cardiac output (Q) will then be calculated from the shape of the aortic waveform. Indeed, the integral (area under the curve) of the waveform will give SV, and Q can be determined by the equation 3:

$$\dot{Q} = SV \times HR \qquad \text{(Eq 3)}$$

According to Wesseling and colleagues (1993), the peripheral resistance (PR) at the level of the aorta will be calculated as the sum of the aortic resistance to the pulsatile flow (aortic characteristic impedance - Z_0) and the resistance coming from the vascular beds (systemic vascular resistance - R_P). This is the equivalent of stating that CVP is equal to zero. Although it is not physiologic, removing a small number from the Ohm's equation (Eq1) would not create a big error and it is then often used for quick estimation of TPR.

$$PR = Z_0 + R_P = \frac{MAP}{Q} \qquad \text{(Eq 4)}$$

2.5.4- Concerns about the Accuracy of the Finometer™

Concepts used in the Finometer are the result of a long development process, but it still does not give perfect values. The main problem resides in the non-invasive aspect of the

Finometer. As pointed out in the Finometer™ User's Guide: "non-invasive methods are usually associated with reduced accuracy" given that the variables are not directly measured. Although this innovative device has a lot of potential, the next section reveals a growing body of scientific research that suggests borderline accuracy in regard to the AAMI standard and in comparison with the "gold standard".

Monitoring Finger Blood Pressure

Under normal condition and moderate vasoconstriction, the Finometer is known to give similar finger BP response when compared to other methods of arterial BP measurement [Wesseling et al., 1985; Jagomägi et al., 1996; Raamat et al., 2006]. However, intensive vasoconstriction, as might be observed during cold exposure or activities in which sympathetic neural activity is elevated, decreases the accuracy of the finger BP measurement [Wesseling et al., 1985; Raamat et al., 2000; Jagomägi et al., 2001].

As mentioned in the Finometer™ User's Guide, some situations cannot be accurately monitored by finger volume-clamp method. Indeed, higher BP in an artery would stretch the vessel wall closer to its maximal capacity. An increase in BP in such a vessel would then not change its cross-section as much as an unstressed vessel wall which is more compliant. For the same reason, in vessels that become stiffer due to other factors (aging, hypertension) the cross-section would not change as much as a more compliant one [Langewouters et al., 1986]. The non-linearity of the pressure-diameter relationship can cause the servo-controller to be less accurate in the extreme conditions.

Since finger BP measurements are assumed to be accurate under normal condition, the attention of researchers is turned to the estimation of brachial BP, SV and Q from the finger BP to find the source of the discrepancy problem.

Estimation of Brachial Blood Pressure

According to the Finometer™ User's Guide, the bias and the precision between Finger BP and Brachial BP before and after the full-calibration procedure are as follows:

Table 1: Bias and Precision in Brachial BP [Finometer™ User's Guide]

Level	Pre-Calibration (Finger BP-Brachial BP)	Post-Calibration (Reconstructed Brachial BP-Brachial BP)
SBP	+1 ±11 mmHg	+4 ±7 mmHg
DBP	-8 ±8 mmHg	+1 ±5 mmHg
MAP	-10 ±7 mmHg	+1 ±5 mmHg

Considering that AAMI standard requires bias to be less than ± 5mmHg and precision to be better than ± 8mmHg [Finometer™ User's Guide], the post-calibration data are considered sufficiently accurate and precise.

A recent study from Guelen and colleagues (2008) has shown the importance of the different calibration:

Table 2: Bias and Precision between Finger BP and Brachial BP [Guelen et al., 2008]

Level	Before Calibration	After Waveform Filtering and Level Correction Calibration	After RTF Calibration
SBP	-10 ±13 mmHg	-1 ±11 mmHg	3 ±8 mmHg
DBP	-12 ±8 mmHg	0 ±7 mmHg	4 ±6 mmHg
MAP	-16 ±8 mmHg	-2 ±7 mmHg	3 ±5 mmHg

Many datasets could have been presented here to illustrate the behaviour of the reconstructed brachial BP at rest, but they all conclude the same thing. To estimate brachial BP properly, the finger BP should be calibrated for the pulse shape difference and the pressure gradient between the finger and the brachial artery. Interestingly, it is also possible to see that SBP has a larger error than the two others but still stays within the AAMI standard.

Similar results are observed during stress. DBP and MAP of the finger BP could be good indicator of brachial BP, but SBP is overestimated over the AAMI standard [Idema et al., 1989; Imholz et al., 1990]. The reconstructed brachial BP from finger BP is recommended and proven to account for the bias during orthostatic stress [Bogert et al., 2004].

The distortion of the pulse waveform while passing from compliant to stiffer arteries is the cause of the discrepancy between finger BP and brachial BP. On the other hand, the offset of SBP compared to DBP and MAP after waveform filtering and level correction might be due to the generalised transfer function used in the inverse model. Gizdulich and colleagues (1997) have shown that their transfer function resonates at a frequency ranging from 4.26Hz to 10.58Hz depending of the subject's individual characteristics. Even though this range is quite large, they applied a filter with a fixed anti-resonance frequency of 8Hz. This would lead to a bad neutralisation of the distortion in the high frequency and cause an offset on the estimation of SBP [Bos et al., 1996].

Estimations of Stroke Volume and Cardiac Output

Many studies have shown the inaccuracy of SV and Q Modelflow estimations from finger blood pressure [Hirschl et al., 1997; Remmen et al., 2002; Azabji Kenfack et al., 2004]. Calibrations against a "gold standard" like thermodilution [Jansen et al., 2001] or Fick's equation [van Lieshout et al., 2001(a)] is required in order to get absolute values. These calibrations are done to take into account individual characteristics changing the pressure-area relationship of the aorta [Finometer™ User's Guide]. This relation (Langewouters' algorithm) estimates aorta diameter from a study that investigated the static properties of post-mortem aorta [Langewouters et al., 1984]. The biggest problem comes from the aortic diameter at maximal pressure which is only dependent on gender and may vary up to ±40% from the population average [van Lieshout and Wesseling, 2001].

According to the Finometer™ User's Guide, the bias and the precision of Q before and after the calibration procedure are as follows:

Table 3: Bias and Precision between Finometer™ and Thermodilution Q

[Finometer™ User's Guide, 2003]

	Bias	**Precision**
Pre-Calibration	+0.3 L/min	1.0 L/min (20%)
Post-Calibration	-0.1 L/min	0.5 L/min (8%)

According to table 3, the Modelflow method implemented in the Finometer can accurately measure Q at rest with the same precision as thermodilution. Jellema and colleagues (1999) have shown that once calibrated, the Modelflow model will keep track of Q even after 48h in ICU patient undergoing septic shock. If not calibrated, the values

recorded by the Finometer would then represent only the variations of Q [Harms et al., 1999].

If a stress occurs, the accuracy of the Finometer's estimation of SV and Q is questionable even though it has been previously calibrated. In fact, some researchers have indicated a decrease in accuracy during exercise [Houtman et al., 1999; Azabji Kenfack et al., 2004] and passive head-up tilt [van Lieshout et al., 2003] while others have shown it to be accurate during postural stress [Harms et al., 1999; Matsukawa et al., 2004] and exercise [Matsukawa et al., 2004]. Recently, unpublished research from our lab has shown that the discrepancy in SV increased with an increasing change in TPR [Dyson et al., unpublished]

The causes of the borderline accuracy during a stress are related to the accumulation of error from the three estimations changing finger BP waveform into Q waveform: using finger BP waveform to represent aorta BP waveform, the Langewouters' algorithm and the Modelflow method.

As explained in section 2.4, finger BP differs in shape and magnitude from aortic BP. This difference would become even more significant with a stress because TPR would increase PWV and so, change the shape of the pressure contour in both arteries but not in the same manner. The limitations coming from the Langewouters' algorithm during a stress and after an initial calibration at rest are very small. For example, an increased tonus of the aortic wall smooth muscle will decrease the maximal aortic diameter and decrease compliance for a given pressure [Heerman et al., 2005]. This will create an error in the calculation of SV and Q because these variables are represented by parameters fixed in the model with the age and the gender of the person [Wesseling et al., 1993]. The

Modelflow model can fit experimental data well and can produce realistic Q waveform [Stergiopulos et al., 1999]. But it is still a source of error considering that the three-element model is a representation of vascular properties. To improve this, it has been shown that the addition of the inertia of the whole arterial tree as a fourth element to take into account the very low frequency of the arterial BP may provide more accurate results [Stergiopulos et al., 1999].

Considering this accumulation of error, the easiest way to calibrate the estimation of SV and Q is to create a calibration factor against a "gold standard". This technique could work with well monitored studies but it is not favourable when the Finometer is the only instrument used. It is also challenging because every subject will need a different calibration factor at rest and potentially at every stage of a stress.

3. Hypotheses

To develop a method, several important steps should be taken into account. Figure 8 is a schematic representation of these steps:

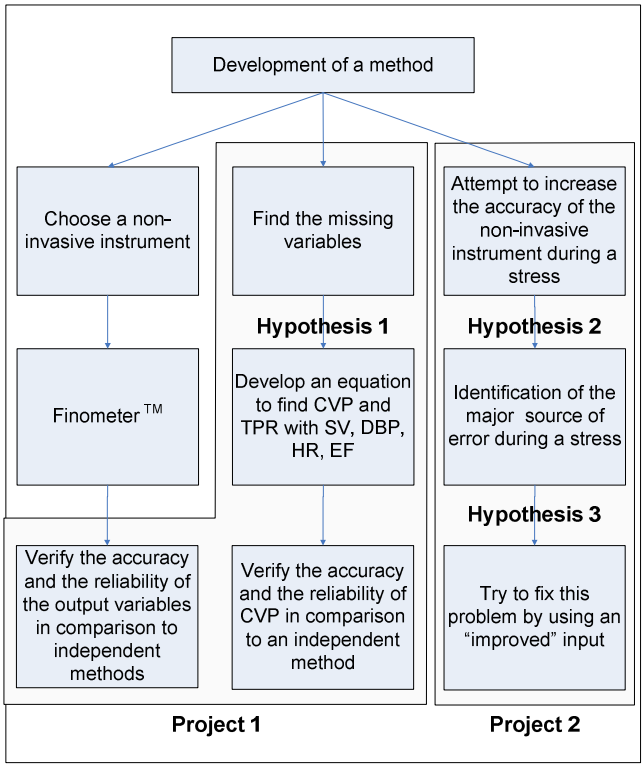

Figure 8: Flow chart of the different steps of the development of the method

The first hypothesis is addressed within Project 1 and the second and the third hypotheses within Project 2.

First of all, we decided to use the Finometer as our non-invasive instrument because it is a well recognised machine used in both research and clinical environments. It also measures and estimates almost all the variables of the cardiovascular control mechanisms.

Second, even though the Finometer is providing almost all the variables essential to monitor the cardiovascular control mechanisms, two of them are missing: TPR and CVP. Our first project is to create a relation providing these variables with the actual setup of the Finometer and all the tools given to us to calibrate it.

Finally, more and more articles are published about the Finometer's "borderline" accuracy of Q in comparison to a "gold standard". The development of a method to get all the information needed from the Finometer would then be more valuable if the machine is reaching higher data quality standard. For our second project, we will be looking at the possible causes of the Finometer's limitations in order to propose solutions to increase its ability to measure Q accurately and precisely.

3.1- Development of the Relation

3.1.1- Initial Calibration of Cardiac Output

As shown in section 2.5.4, the Finometer's designers recognise the need of an initial calibration. They attribute this to an estimation of the aorta diameter made from the Langwouter's algorithm which is using only the age and the gender of the subject. To improve the quality of the measurements they add on the possibility to correct the aorta diameter estimated from the Finometer against another method. This technique has been proven possible on patients with coronary artery bypass graft and/or valve replacement [de Vaal et al., 2005] and so we will be using it for our purpose with the help of an echo ultrasound device.

3.1.2- Relation Between all the Variables

Most of the variables are already estimated by the Finometer. HR is estimated directly by the detection of a new waveform from the servo-controller, BP is estimated from the inverse model and Q is a direct output of the Modelflow method. CVP and TPR have to be found or mathematically extracted.

Our two missing variables are linked together by the physiology version of the Ohm's equation (Eq. 1):

$$TPR = \frac{MAP - CVP}{Q} \qquad \text{(Recall of Eq. 1)}$$

Although CVP can be measured with a catheter, TPR is the only variable of this formula that cannot be recorded with precision. Indeed, as explained in section 2.2, TPR regroups all the mechanisms working to control blood distribution. The only technique to get a good approximation of all their effects together is through this formula. Our search for the two missing variables should then start with CVP.

Looking at the heart as a system is probably the best approach to eliminate TPR from the relation while still including its effect. As explained in section 2.3, TPR per se is not a direct input or output of the heart but does influence its performance by playing on the quantity of blood available to pump [Rowell et al., 1993].

According to the results of Gagné and colleagues (2007) and the further investigations described in section 2.3, **we first hypothesize that estimations of CVP derived from a modified Frank-Starling mechanism relationship would be accurate and reliable compared to CVP measured with a catheter.** To cover the individual characteristics responsible to modify the Frank-Starling mechanism, we will include the EF measured

previously at rest from an echo ultrasound device. DBP will be included in the relation to account for the changes in afterload throughout the test. This will allow a calculation of LVEDV from SV at rest and during different stages of orthostatic stress. Since LVEDV is influenced by the preload (CVP) and the filling time of the heart (HR), a multiple linear regression will be applied.

Creating a relation to find CVP from SV, HR and DBP will be very convenient since they are all outputs of the Finometer. EF measurement, also needed in our relation, is not out of reach since the calibration of the Finometer already requires the use of an echo ultrasound device to fix the aorta diameter. Furthermore, including HR and DBP in the equation is also a manner to take into account the activity of the CNS.

3.2- Investigation of Cardiac Output Measurement

As shown in section 2.5.4, many articles are published about the dubious accuracy of Q and SV estimated by the Finometer in comparison to a "gold standard". The Finometer is very good at tracking variation at rest once calibrated, but when a stress is applied, an error could appear. This error seems to depend on the type of the stress and might vary with TPR [Dyson et al., unpublished], although recent observations of Modelflow estimation of Q during exercise revealed no bias across a wide range of work rates relative to acetylene rebreathing [Faisal et al., In press].

An examination of the process reveals three possible different sources of error in the estimation of Q and SV: using finger BP as a representation of aortic BP, the Langewouters' algorithm and the Modelflow model. Considering that a change in TPR will have a direct effect on the pulse contour of peripheral arteries compared to the main

conduit artery, we thought that the first one will have the greatest impact on the estimation of Q and SV during change in TPR. Our primary objective here was to verify whether or not using finger BP as a representation of aortic BP can lead to an error in the estimation of Q and SV during a stress. In the case that it does play a role in the discrepancy, our second objective was to determine whether or not using finger BP to represent aortic BP is the major source of error. In order to reach these two (2) objectives, **the second hypothesis was that the estimation made by using finger BP to represent aortic BP would account for more than 50% of the error in the estimation of Q and SV during a change in TPR.**

Although we are fully aware that estimations will never give perfect values, the borderline accuracy of Q and SV during a stress may introduce an important error in clinical and research environments. As a follow up to the previous hypothesis and in an effort to reach a precision equivalent to the thermodilution reference technique, **the third hypothesis was that Q and SV error can be reduced to 8% throughout a stress by using the reconstructed brachial BP as an input to the Modelflow model.** Considering that a growing body of research has shown reconstructed brachial BP to be accurate and within the AAMI standard at rest and during exercise, this variable could be a useful tool since it is already calculated by the Finometer^{TM} and would account for different stress.

To achieves all these objectives, it was determined that an alternative approach was required in this study because of a difficulty in solving Modelflow. Thus, the contours of finger BP and the reconstructed brachial BP were compared with a reference brachial BP obtained with the Millar pressure transducer in order to get information about

overestimation and underestimation of Q from the different methods. It is important to note here that this approach only allowed conclusion about the primary objective of hypothesis 2 and the general objective of hypothesis 3. No definitive conclusion can be made about these two hypotheses with the study of pulse wave contours as opposed to direct calculation of Q with Modelflow.

4. Methodology

To investigate the hypotheses above, two protocols were used.

The first protocol was included in a big project serving three Master's theses and one PhD thesis. The experiment design has been constructed by the team to investigate the value of fluid loading procedure given to astronauts before their return to Earth in order to maintain cardiovascular responses with the reapplication of orthostatic stress. Some of the steps in the data collection might seem not related to my own thesis but are very important for others.

The second protocol was a prolongation of the first protocol as it used a similar population and a similar stress. The variables measured are those that were impossible to evaluate on the previous protocol without affecting other variables important to my teammates.

The study was approved by the Office of Human Research Ethics at University of Waterloo.

4.1- Experimental Design

4.1.1- Participants

Twelve healthy young males between the ages of 18 to 33 years old participated in this project. Eight of them took part of the first project. Four of them came back and took part of the second project along with four new subjects.

Prior to the first test in the lab, the subjects signed an informed consent form to confirm that they have read and received explanations of a list of risks related to the test. They

received money for their participation in the study and had the right to withdraw at anytime during the experiment.

4.1.2- First Project

The project required every subject to come five (5) times in the lab for five (5) different tests:

A) 4h seated without fluid loading
B) 4h seated with fluid loading
C) 4h bed rest without fluid loading
D) 28h bed rest without fluid loading
E) 28h bed rest with fluid loading

Contrary to my colleagues, I am not looking at the effect of bed rest and fluid loading on the human body. Consequently, I am only using the dataset from the first LBNP protocol of every test.

Pre-Test Preparation

Subjects were asked to avoid alcohol and caffeine for twenty-four (24) hours prior to the test. They were also asked to keep up to date a food diary starting three days before the test in order to control their sodium intake which should not be more than approximately 2000mg/day. They were also asked to drink 5mL of water per kilogram of body mass the night before the test and the morning of the test to promote proper hydration.

Every subject was asked to come in the lab at 7am after an 8h sleep and a small breakfast taken at 6am. We measured height and weight and a certified lab technician inserted a 22 gauge catheter (*BD Insyte, BD Medical Systems, Sandy, USA*) in the mean cubital vein of the right arm for drawing blood samples and measuring CVP.

Lower Body Negative Pressure (LBNP)

To challenge the cardiovascular control of the human body we simulated orthostatic stress with a lower body negative pressure (LBNP) device. It was a home-made sealed wooden box linked to a vacuum *(Beau•mark 99056).* The level of suction was controlled with a rheostat (*Staco Inc, Dayton, Ohio*) connected to the vacuum and an electronic pressure gauge *(Traceable ®)* hooked directly to the box.

Subject were asked to lie down with their lower body placed in the LBNP box and the area around their waist sealed with a neoprene skirt. They were reminded of the moderate risks to experience dizziness during the suction and were asked to inform the investigators if these symptoms occurred. In such a case, the suction pressure was immediately removed and the symptoms disappeared very quickly since blood was rapidly returned to the heart and the brain. To avoid a fainting episode, the protocol was stopped if the systolic blood pressure (SBP) was less than 80mmHg or the heart rate (HR) or the blood pressure (BP) dropped quickly.

The LBNP protocol as presented in figure 9 occurred at approximately 9am for every test to take into account the circadian cycle. We used a constant decrease of pressure protocol in order to take measurements in both transition (first minute of every stage) and steady state.

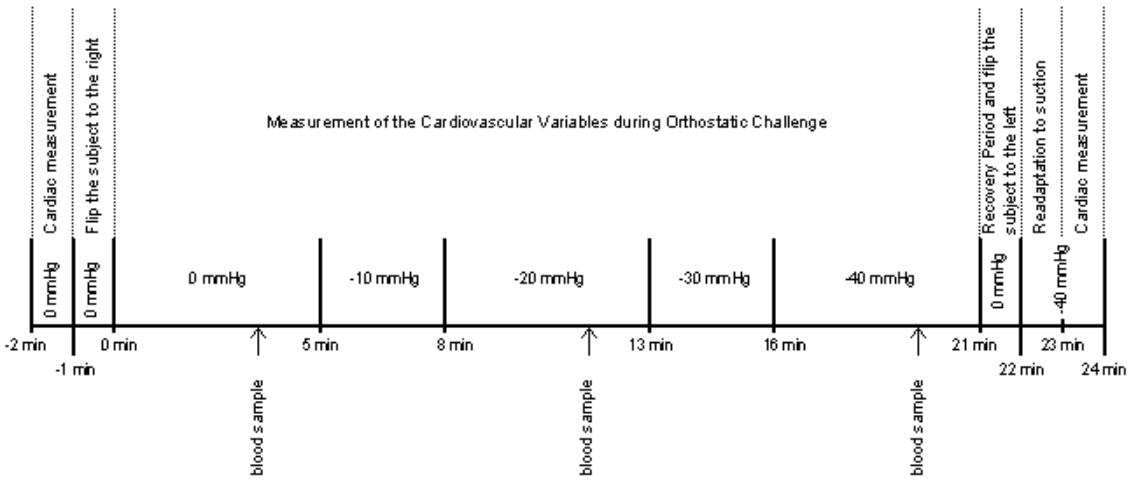

Figure 9: LBNP protocol of the first project

Cardiac Measurement

Cardiac measurements were taken in the baseline period before the start of LBNP and at the end of the LBNP session by first rotating the subject from right-side down (required for CVP measurement) to left-side down (optimizing the ultrasound window to image the heart) then reapplying the -40 mmHg LBNP for an additional 2-minutes with an echo ultrasound device (MicroMaxx, Sonosite Inc, Bothell WA, USA) and a 1-5MHz transducer probe (P17, Sonosite Inc, Bothell WA, USA). The tilt movement was easily accomplished as the entire LBNP box is on three (3) sets of pillow blocks fixed to a table.

The diameter of the aorta was taken at the sino-tubular junction which is the smallest diameter in the root of the ascending aorta. As it will be explained further in the methodology section, the diameter of the aorta will be used to calculate cardiac output with the Doppler aortic velocity (Eq. 5).

Left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV) and ejection fraction (EF) were all calculated from b-mode image of the parasternal long axis view of the left ventricle as shown in figure 10.

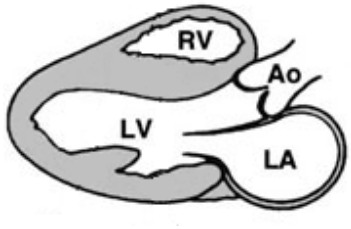

Figure 10: Parasternal long axis view [modified from www.medscape.com]

Where RV is the right ventricle, LV is the left ventricle, LA is the left atria and Ao is the aorta.

Cardiovascular variables

All other cardiovascular variables were recorded while the subject was tilted to the right in order to place the subject's right arm below his heart. According to the method developed by Gauer and Sieker in 1956, this is very important for the measurement of central venous pressure (CVP). We recorded the venous pressure at the level of the junction of the right atrium and the vena cava. Our technique used a saline filled tube connected to the previously inserted venous catheter with a pressure transducer (Medex Inc., CA, USA) set at the level of the right atrium. The pressure transducer was calibrated against a column of water and adjusted to relative pressure by setting the atmospheric pressure at 0 cmH_2O through a three way stopcock located directly beside the transducer.

Heart rate (HR) was measured with a three lead electrocardiograph (Pilot 9200, Colin Medical Instruments, San Antonio, USA).

Blood pressure (BP) was measured continuously from the middle finger of the left hand with a photoplethysmograph cuff in accordance with the volume-clamp method developed by Peñáz in 1973 and integrated in the Finometer (Finapres Medical Systems, Amsterdam, The Netherlands). As described before, the brachial pressure is estimated from the finger pressure with a frequency-dependent filter and a height corrector. BP was also collected manually with a sphygmomanometer and a stethoscope on the left arm at the level of the brachial artery.

Cardiac output (Q) was first of all estimated from the Modelflow method implemented in the Finometer (Finapres Medical Systems, Amsterdam, The Netherlands) [Wesseling et al., 1993]. This method simulates a non-linear three element model of the aortic input impedance to compute the aortic flow waveform from the finger pressure waveform. The estimation of Q from the Modelflow equation incorporates the non-linear elastic behaviour of the aorta by means of the Langewouter's algorithm using the age and sex of the subject [Langewouters et al., 1986]. This algorithm does not take into account all the individual characteristics and can be calibrated either during the test (against either Q values from Doppler ultrasound or aortic diameter taken with an ultrasound device) or post test (against Q values from Doppler ultrasound).

Q has also been computed from the product of the blood flow velocity and the diameter of the ascending aorta (Eq 5). The velocity was collected with a Doppler ultrasound device (Neurovision Doppler Ultrasound Model 500M, Multigon Industries, Mt. Vernon, USA) and a hand-held 2MHz transducer probe pointing at the root of the aorta. The probe was used as a transmitter and a receiver: it sends ultrasonic waves that hit red blood cells then come back at a different frequency that is dependent on the relative speed of the red

blood cells. Only one experienced tester held the probe in place throughout the project to reduce experimental errors as suggested by Rose and colleagues (1984).

$$Qdop = v_{aorta} \cdot \left(\frac{\pi \cdot d_{aorta}^{2}}{4} \right) \qquad \text{(Eq 5)}$$

4.1.3- Second Project

In order to test the hypotheses of the second project we measured the relative effect of orthostatic stress on the finger and brachial BP contour in regard to Q estimated from the Modelflow method of the Finometer.

We asked every participant from the previous project to come back one (1) more time in the lab. Since we were not looking at any circadian cycle outcome and only at the effect of orthostatic stress, one (1) LBNP protocol was performed at the most convenient time of the day for the subject. They were asked to sleep 8h and to not drink alcohol or coffee for 24h prior to the test.

We used a 15 min constant LBNP protocol in order to take measurements in steady state (after 30 sec of each stage). Figure 11 below show the details of the LBNP protocol.

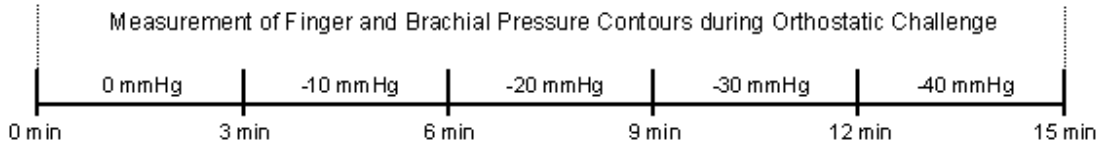

Figure 11: LBNP protocol of the second project

In this second protocol, CVP was not measured so this allowed the subjects to be positioned in a left lateral tilt position throughout to optimize the ultrasound imaging of the heart. The same apparatus was used as in project 1 to collect data for cardiac imaging,

aortic blood flow velocity, heart rate and finger arterial blood pressure following the same steps explained in section 4.1.2. The reconstructed brachial BP contour was also estimated from the Finometer^{TM}. In addition during these experiments, brachial artery blood pressure was measured from the brachial artery of the right arm by applanation tonometry (SPT-301, Millar Instruments, Houston, Texas, USA) as an estimate of aortic BP. In fact, since it is a fairly big artery and it is close to the aorta, doctors usually estimate aortic BP via a sphygmomanometer placed on the brachial artery. The Millar consists of a micromanometer located in the tip of a probe and placed on the vessel wall. It accurately measured the blood pressure profile by flattening the vessel wall under the probe and so measuring directly the circumferential pressure.

Although we are fully aware of the assumption made regarding that both right and left brachial artery are the same and would react the same; we decided to not measure the two pressures on the same arm to avoid any influence of a manipulation on the other signal. In order to remove any hydrostatic difference between the right and the left brachial arteries, the reconstructed brachial BP was corrected with the height corrector of the Finometer and the finger BP was corrected during the data analysis.

4.1.4- Data collection system

Except for the Sonosite, all the instruments were connected to the acquisition hardware Powerlab (Powerlab 16 channel SP unit, ADInstruments, Colorado Springs, CO). The CVP and the Millar signal were amplified (9200, Colin Medical Instruments, San Antonio, USA) before being sent to Powerlab. The Sonosite was connected to a video camera (Sony, Tokyo, Japan) that recorded the image shown on the screen. We also used the analysis software program Chart (Chart V5.5.1 software, ADInstruments, Colorado

Springs, CO) to record the data from the Powerlab at a sample frequency of 1000Hz. The Chart program was used for post-recording data analysis via macros that determined beat to beat values.

4.2- Data Analysis

Different techniques were employed for processing the data in order to investigate the hypotheses. This section presents them briefly.

4.2.1- Development of the Relation

For this project, we used the post-test data from the Beatscope software of the Finometer™. These data accounted for the calibration made to the Langwouter's algorithm.

First of all, to evaluate the potential error introduced by the different outputs of the Finometer™ we compared them to the result obtain from their corresponding independent method. HR from the Finometer™ was compared to HR from the Colin. SBP and DBP from the Finometer™ were compared to SBP and DBP from the sphygmomanometer. The corrected estimation of Q made by the Modelflow model transforming finger BP into Qfin was compared to Q from the Doppler ultrasound (Qdop).

Our recent preliminary study [Gagné et al., 2007] has shown a linear relationship between CVP and SV using a lower body negative pressure (LBNP) device before and after a 4h hour head down tilted bed rest. The equation used is as follow:

$$CVP = a + b \cdot SV \qquad \text{(Eq 6)}$$

Where *a* and *b* are constants of the simple regression equation. We reasoned that it followed the Frank-Starling mechanism with CVP as an indicator of the preload of the heart, but further investigations of those preliminary data have shown that this relationship is specific to every subject.

Secondly, in order to increase the accuracy and reliability of the CVP estimation, we tried to improve this equation with a multiple regression of specific individual variables playing a role in the Frank-Starling mechanism. Knowing that the preload of the heart (CVP) influences the stretch of the left ventricle (represented by LVEDV) and the last one is also influenced by the filling time of the heart (HR), we decided to use these two variables:

$$CVP = a + b \cdot LVEDV + c \cdot HR \qquad \text{(Eq 7)}$$

LVEDV is not an output from the Finometer™ and should be previously calculated from EF and SV following the Frank-Starling mechanism:

$$CVP = a + b \cdot \frac{SV}{EF} + c \cdot HR \qquad \text{(Eq 8)}$$

Since EF might change with a stress, another regression was created to estimate EF with EFrest and DBP. Eq. 9 is the last version of our new equation:

$$CVP = a + b \cdot \frac{SV}{k + l \cdot EFrest + m \cdot DBP} + c \cdot HR \qquad \text{(Eq 9)}$$

Where *a*, *b*, *c*, *k, l* and *m* are constants of the two multiple regressions equations.

Finally, in order to assess if the general equation is representative of every subject and to verify if we increased the accuracy and the precision of the CVP estimations (Eq.9 versus

Eq.6); three types of CVP equations were created with Eqs. 6 and 9. The first one is specific to every test by using the variables of every single test (Test). The second is a little bit more general and represents every single subject (Individual). The last one is even more general and represents our group of subjects (General). The CVP values calculated with both Eq.6 and Eq.9 were compared with CVP measured with the catheter.

Given that no standards have been stated in the literature for the accuracy and the precision of CVP measurements, we a priori decided that a good approximation of CVP measured will have a bias smaller than ± 2mmHg and a precision better than ± 2mmHg. These values are chosen considering the accuracy and precision of the reference method.

4.2.2- Investigation of Cardiac Output Measurement

At the beginning of the test, in order to calibrate for individual variables not taken into account in the Langewouter's algorithm, we corrected Q directly in the display of the Finometer™ with the "Calib-%" function and the aortic diameter taken with the ultrasound device.

The Finometer™ Modelflow method of estimating Q was examined relative to the Doppler method to determine the percent change in the discrepancy of SV with change in TPR during progressive levels of LBNP as conducted previously in the unpublished results from Dyson and colleagues. The initial objective was to determine if increasing distortion of finger BP compared to aortic BP during LBNP contributed to the Modelflow-Doppler differences. An equation was developed (see appendix) allowing for the calculation of SV and Q from the reconstructed brachial BP signal and the Millar BP signal which could have been compared to Doppler ultrasound.

Unfortunately, the program running the equation did not give accurate values of SV and Q. The difficulty of stating the variable tau (τ) in the equation (see appendix) is probably the major source of error. Tau (τ) is a "time-constant" used in the calculation of the resistance offered by the Windkessel arterial compliance element (C_W). The literature about it is very confusing and even sometimes points in different directions.

In order to look at the influence of different BP shape on the estimation of Q and SV, an alternative method was developed. This approach would allow conclusions about the finger versus brachial blood pressure signal as a potential source of deviation of SV from the Doppler method (primary objective of the second hypothesis) and about the possibility of improving the result with reconstructed brachial BP (objective of the third hypothesis). However, this approach would not allow conclusions about the second and third hypotheses per se.

Alternative method

As explained in section 2.5.3, the Modelflow method implemented in the Finometer™ takes into account several physiological characteristics to create a "conversion factor" used to change the systolic part of the finger BP waveform into an aortic flow waveform. SV is then calculated by the integral of the aortic flow waveform and Q is calculated with the following equation:

$$Q = SV \cdot HR \qquad \text{(Recall of Eq 3)}$$

An integral of a function is actually the area underneath its curve. This area can be calculated by adding up rectangles with a height starting at the base and touching the aortic flow contour and a length of our choice. Since we recorded our data with a

sampling frequency of 1000 Hz, we used a length of 0.001s. Figure 12 presents this concept with a typical flow waveform and larger rectangles in order to see them:

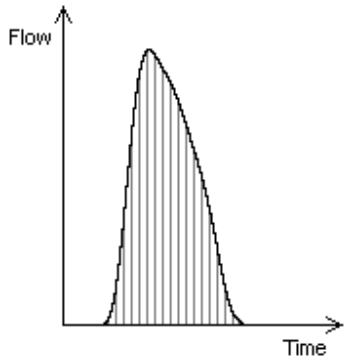

Figure 12: Area underneath the curve of a typical aortic flow waveform

The Modelflow approach can be rewritten in a format consistent with Figure 12:

$$Q = SV \cdot HR = \int_{start\_systole}^{end\_systole} (conversion\_factor \cdot BP)dt \cdot HR$$
$$Q = \sum_{start\_systole}^{end\_systole} (conversion\_factor \cdot BP \cdot 0.001) \cdot HR \qquad \text{(Eq 10)}$$

Where the "*conversion_factor*" is unknown.

The "conversion factor" is very specific to every single beat of one subject because the modelflow model takes into account: age, sex, diastole time of the current beat, MAP of the previous beat and Q of the previous beat. Therefore, if BP is monitored with three different methods for one beat, the "conversion factor" will be the same for these three methods. This allows us to compare the estimation of finger BP and brachial BP with Millar BP, our reference method.

Figure 13-A shows an example of finger BP and Millar BP contours over the course of a heart beat. The methods do not have the same BP contours during systole and we want to see if the difference between them can lead to an error in the calculation of Q. The

computation of the area underneath the curve of BP is adjusted to take into account only the pulse pressure (PP) component like it is shown in Figure 13-B.

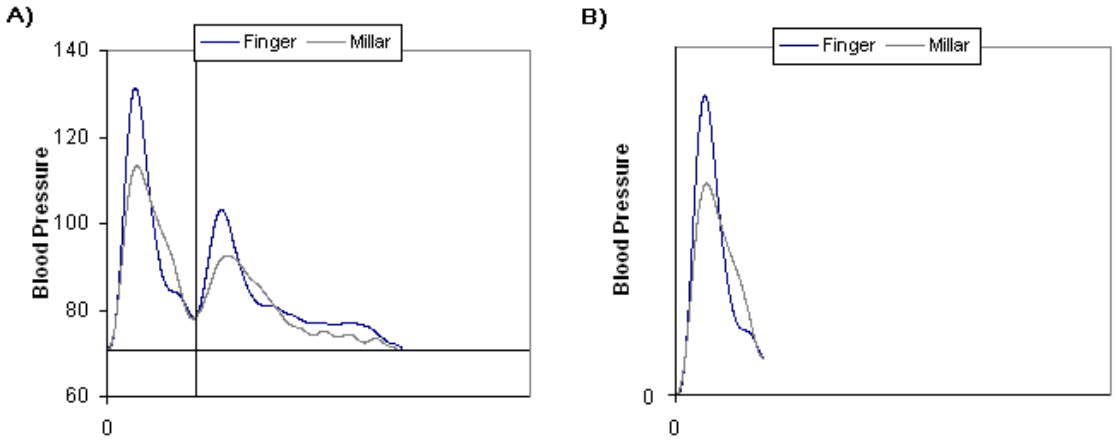

Figure 13: A) Finger BP and Millar BP over the course of a heart beat; B) Finger PP and Millar PP during systole

Since they both have the same "conversion factor", simply comparing the area underneath the curve of both BP contours is sufficient. But in order to visualise their differences, we plotted them against each other (Figure 14-B). The result gives information about the amplitude of the over and underestimation of Millar BP by finger BP. This can potentially explain the reason why brachial BP is better or not than finger BP.

As seen in Figure 14, for a same length of time, finger BP overestimated at first Millar BP and underestimated it at the end of the systole. The addition of both effects can lead to the cancelation of the error.

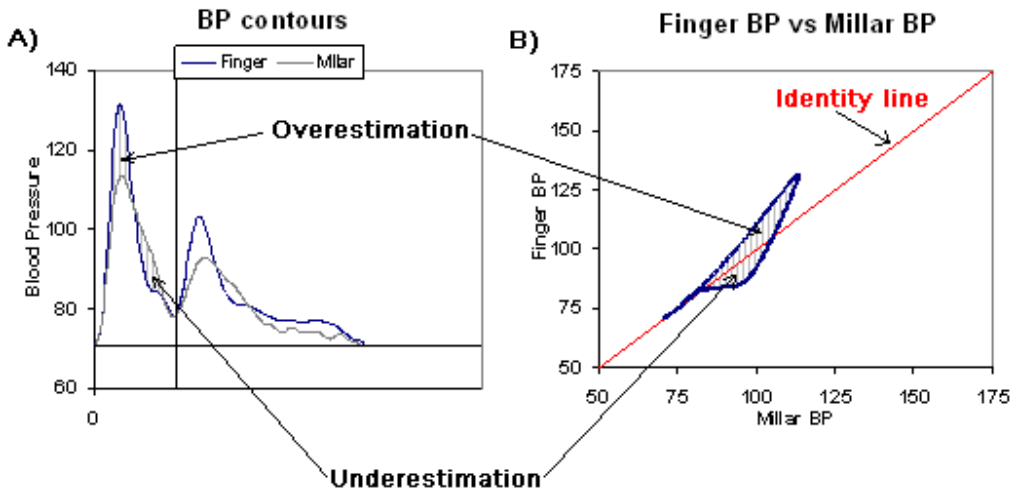

Figure 14: Over and underestimation of Finger BP over Millar BP; A) Finger BP and Millar BP over the course of a heart beat; B) Finger BP vs Millar BP during systole

The "conversion factor" is unknown but it is taken as being the same for each individual beat independent of the method of BP measurement (finger, estimated brachial or Millar). Thus, it is possible to eliminate this factor in the calculation of Q error relative to the reference Qmillar.

For one specific beat the conversion factor is a constant and can be placed outside the summation component of Equation 10. This allows its cancellation in the following equations of error:

$$Qfinger - Qmillar\_error = \frac{0.001 \cdot HR \cdot conversion\_factor\left[\sum_{start\_systole}^{end\_systole}(FingerBP) - \sum_{start\_systole}^{end\_systole}(MillarBP)\right]}{0.001 \cdot HR \cdot conversion\_factor \sum_{start\_systole}^{end\_systole}(MillarBP)} \quad \text{(Eq 11)}$$

$$Qfinger - Qmillar\_error = \frac{\left[\sum_{start\_systole}^{end\_systole}(FingerBP) - \sum_{start\_systole}^{end\_systole}(MillarBP)\right]}{\sum_{start\_systole}^{end\_systole}(MillarBP)}$$

$$Qbrachial - Qmillar\_error = \frac{0.001 \cdot HR \cdot conversion\_factor\left[\sum_{start\_systole}^{end\_systole}(BrachialBP) - \sum_{start\_systole}^{end\_systole}(MillarBP)\right]}{0.001 \cdot HR \cdot conversion\_factor \sum_{start\_systole}^{end\_systole}(MillarBP)} \quad \text{(Eq 12)}$$

$$Qbrachial - Qmillar\_error = \frac{\left[\sum_{start\_systole}^{end\_systole}(BrachialBP) - \sum_{start\_systole}^{end\_systole}(MillarBP)\right]}{\sum_{start\_systole}^{end\_systole}(MillarBP)}$$

In order to asses if BP difference does play a role or not in Qfin-Qdop discrepancy, we completed our analysis by comparing the error of Qfinger and Qbrachial over Qmillar versus change in TPR and the error between Qfin and Qdop.

Validation of the Millar

Even though the Millar device is known to give accurate estimates of the BP contours, it is important to validate that Q calculated from the Millar (Qmillar) will be a reference just like Q measured from the Doppler ultrasound (Qdop).

Knowing that Qfin **is** calculated from the finger BP contours and that Qdop correspond to the "true" aortic BP (estimated by Millar BP), the following ratios were created:

$$\frac{Qfinger}{Qfin}, \frac{Qmillar}{Qdop}$$

Where: $$Qfinger = \sum_{start\_systole}^{end\_systole}(conversion\_factor \cdot FingerBP \cdot 0.001) \cdot HR$$

$$Qmillar = \sum_{start\_systole}^{end\_systole}(conversion\_factor \cdot MillarBP \cdot 0.001) \cdot HR$$

The absolute value of these ratios has absolutely no physiological meaning, but the comparison of them will give information about the validity of using Millar PP.

In order to validate if Q calculated from the Millar is a good reference, we plotted Qfinger/Qfin versus Qmillar/Qdop. If the data follow the identity line, it shows that Qmillar is a good representation of Qdop.

Indeed, Qfinger/Qfin is the "perfect match" as Qfinger **is** a representation of Qfin. If Qmillar/Qdop = Qfinger/Qfin that means that Qmillar/Qdop is also a "perfect match". Thus, if Qmillar/Qdop = Qfinger/Qfin then it means that the Qmillar is a good representation of Qdop.

4.3- Statistical analysis

Statistical analyses were done through SigmaStat version 3.5 (Systat Software, Inc, Chicago, Illinois, USA).

In order to assess the agreement between the different techniques of measurement we performed a Bland-Altman analysis. Since this technique does not quantify statistical differences between methods, we used another technique: One-Way-Repeated-Measures-Analysis-of-Variance (1-way-RM-ANOVA). This approach has been performed to compare every LBNP stage to baseline of each variable measured during both test (Figure 15-B and Figure 22) and every output of the Finometer^{TM} (HR, DBP, SBP, Q) to their corresponding independent method at every LBNP stage. CVP calculated has also been statistically compared to CVP measured at every LBNP stage with this method. We used Tukey's test for all these comparisons. In cases where either the normality test or the equal variance test failed, we executed the non-parametric test Friedman-1-way-RM-ANOVA.

Differences were considered statistically significant when $p<0.05$.

We used a multiple linear regression to create all the CVP relations and a simple linear regression to create the EF relation. The t-test has been used to assess if the independent variables used in the equations significantly contribute to predict CVP and EF.

Variables that contributed to prediction of the independent variable were included when $p<0.05$.

We also used a simple linear regression to examine the relation between Q discrepancies and change in TPR.

Finally, we used the t-test to compare Qfinger discrepancy with Qbrachial discrepancy at both baseline and -40mmHg.

5. Results

5.1 Participant Characteristics

Characteristics of participants in project 1 and project 2 are compared in Table 4. Eight participants have been studied in both projects. Four of the participants in project 1 took part of project 2. Both groups of participants had similar age, height, weight, HR, SBP and DBP.

In project 1, 23 tests out of the 40 tests available were included in the analyses. In project 2; all 8 tests were used. Criteria of test rejection from the pool of test in project 1 are shown in Table 5 along with the number of tests rejected for each reason given.

5.2 Development of the Relation

Physiological Variables during Orthostatic Stress

Figure 15-A illustrates an example of one subject's physiological response during the LBNP protocol of project 1. In order to record other responses relevant to my colleagues, Q, SV, CVP and TPR measurements have been shortly interrupted during the test. The average values for every LBNP stage were calculated and compiled with the other subjects to create Figure 15-B. HR during the first two stages of the LBNP (-10 mmHg and -20 mmHg) was unchanged. HR became significantly elevated from baseline for the two last stages of LBNP (-30 mmHg and -40 mmHg) ($p<0.05$). MAP was unaffected throughout the test. Q, SV and CVP were unchanged from baseline at -10 mmHg, but were significantly reduced at -20 mmHg, -30 mmHg and -40 mmHg ($p<0.05$). TPR was

unchanged for the first LBNP stage and was elevated for the second, third and fourth LBNP stage ($p<0.05$).

Accuracy and Precision of the Different Outputs of the Finometer™

A summary of the accuracy and the precision of the different outputs of the Finometer™ is presented in Table 6.

HR measured from the Finometer™ appeared to be accurate and precise at every stage of the LBNP. As shown in Figure 16, the overall bias was *0.05 beats/min* with an error of *0.18 beats/min*. No particular pattern can be observed in Figure 16, suggesting that the error was not related to the orthostatic stress effect.

DBP from the Finometer™ was within AAMI standard while its error was offset (*8.8 mmHg* compared to *±8 mmHg*). There was no significant difference between DBP measured with the Finometer™ and the sphygmomanometer. On the other hand, SBP measured with the Finometer™ was significantly different from SBP measured with the sphygmomanometer ($p<0.05$) and did not meet the AAMI standard for the accuracy (*14.2 mmHg* compared to *±5 mmHg*) just met it for the precision with a small offset (*8.0 mmHg* compared to *±8 mmHg*). Figure 17 illustrates the accuracy and the precision of both DBP and SBP.

Q measured from the Finometer™ was not significantly different from Q measured with Doppler at baseline, *-10 mmHg* and *-20 mmHg* but became significantly higher at *-30 mmHg* and *-40 mmHg* ($p<0.05$). Throughout the test, Qfin had a smaller precision than it would if measured with the thermodilution technique (*8%*). Qfin post-test-correction with the Beatscope of the Finometer™ brought baseline Qfin data to the same

level of baseline Qdop data (Figure 15). This operation decreased the overall bias and error as shown in Figure 19 (*0.797± 1.122L/min to 0.255± 0.441L/min*) and considerably increased the precision of Qfin for baseline, *-10 mmHg* and *-20 mmHg* relative to that reported for the thermodilution technique. Qfin corrected was not significantly different from Q measured with Doppler at baseline and for the two first LBNP stages but became significantly higher for the two last LBNP stages ($p<0.05$). No particular pattern can be distinguished in the Doppler-vs-Finometer graph of Figure 16, but a negative slope can be observed in the Doppler-vs-Finometer_corrected graph. This shows that the accuracy decreases (bias increases) when Q decreases during orthostatic stress.

Development of the CVP Equation

The equation to determine EF is presented in the Appendix. The constant used in this equation, did not significantly contribute to predict the dependent variable ($p>0.05$), but both EFrest and DBP contributed to predict EF ($p<0.05$). The coefficient of determination was $R^2= 0.964$.

$$EF = 1.471 + 0.881 \cdot EFrest + 0.104 \cdot DBP$$

The details of general, individual and test equations for both relations with either Doppler or Finometer™ are all presented in the Appendix. The general equations for the newly developed relation are:

-With Doppler ($R^2= 0.297$):

$$CVP = -0.35 + 0.0557 \cdot \frac{SV}{1.471 + 0.881 \cdot EFrest + 0.104 \cdot DBP} + 0.004 \cdot HR$$

-With Finometer™ (R^2= *0.259*):

$$CVP = -0.903 + 0.0576 \cdot \frac{SV}{1.471 + 0.881 \cdot EFrest + 0.104 \cdot DBP} + 0.00254 \cdot HR$$

The general equations for the relation developed by Gagné and colleagues (2007) are:

-With Doppler (R^2= *0.242*):

$$CVP = 0.291 + 0.0721 \cdot SV$$

-With Finometer™ (R^2= *0.232*):

$$CVP = -0.795 + 0.0794 \cdot SV$$

According to Table 10, the constants and all the independent variables used in these general equations significantly contribute to predict CVP ($p<0.05$).

Accuracy and Precision of CVP Calculated

The summary of the accuracy and precision of CVP calculated with both relations in comparison of CVP measured with the venous catheter are presented in Table 7. The calculated CVP values were not significantly different from their corresponding CVP measured. CVP calculated from the general equations of the newly developed relation were not significantly different from CVP calculated from the individual or test equations. CVP calculated from the general equations of the relation developed by Gagné and colleagues (2007) were not significantly different from CVP calculated with the individual or test equations with the exception that CVP calculated from the general equation with SVdop was significantly different from CVP calculated from the test equation (at *-40 mmHg* and overall) ($p<0.05$). CVP calculated from the individual equations were not significantly different from CVP calculated with their corresponding

test equations. CVP calculated with SVfin was not significantly different from their corresponding CVP calculated with SVdop. CVP calculated with the newly developed relation was not significantly different from their corresponding CVP calculated with the relation developed by Gagné and colleagues (2007).

Figure 20 depicts the overall accuracy and precision of CVP calculated with the equations of the newly developed relation in comparison to CVP measured with the venous catheter. CVP calculated with general equations using either Doppler or Finometer^{TM} showed a negative but similar slope pattern. CVP calculated with individual equations using either Doppler or Finometer^{TM} showed once again a negative slope, but this time both datasets showed a smaller slope. CVP calculated with test-specific equations using either Doppler or Finometer^{TM} showed an even flatter negative slope. The same observations can be made in Figure 21 which illustrates the overall accuracy and precision of CVP calculated with the equations of the relation developed by Gagné and colleagues (2007) in comparison to CVP measured with the venous catheter. Both relations show very similar corresponding overall results (Figure 20 compared with Figure 21).

Overall, the individual and test equations from both relations (Table 7) were within the standards stated a priori (Accuracy< ±2 mmHg, Precision better than ±2 mmHg). The accuracy (bias) of the general equations met the standard while the precision was not good enough (worse than ±2 mmHg) in all the cases.

5.3 Investigation of Cardiac Output Measurement

Physiological Variables during Orthostatic Stress

Physiological variables during LBNP of project 2 are illustrated in Figure 22. HR during the first two stages of the LBNP (*-10 mmHg* and *-20 mmHg*) was unchanged. HR became significantly elevated from baseline for the two (last stages of the LBNP, -30 mmHg and -40 mmHg) ($p<0.05$). Q and SV were unchanged at -10 mmHg compared to baseline, but were significantly reduced at -20 mmHg, -30 mmHg and -40 mmHg ($p<0.05$). MAP stayed unaffected throughout the test. TPR was unchanged for the first and second LBNP stage and was elevated for the third and fourth LBNP stage ($p<0.05$). TPR calculation does not include CVP ($TPR=MAP/Q$).

Accuracy and Precision of Cardiac Outputs from the Finometer™

As shown in Figure 23, Q measured from the Finometer™ was not significantly different than Q measured with Doppler at baseline, *-10 mmHg*, *-20 mmHg* and *-30 mmHg* but became significantly higher at *-40 mmHg* ($p<0.05$).

Figure 24 illustrates that Qfin-Qdop discrepancy increased when TPR increased. For a change of 10 mmHg/L/min, Qfin-Qdop discrepancy increased in average by 31.6%.

Validation of Cardiac Output estimated from the Millar

Figure 25 presents the validation of Q estimated from Millar. All beats analysed are represented on the graph by comparing two (2) ratios: Qfinger/Qfin with Qmillar/Qdop. A dot on the identity line shows a perfect representation of Qdop by Qmillar. The further the dot is from the identity line, the worse is the representation of Qdop by Qmillar.

The cloud of dots is quite large but does cover both side of the identity line. This suggests a good estimation of Qdop by Qmillar.

Identification of the Major Source of Error

At baseline, Figure 26 presents an example of finger BP and brachial BP versus Millar BP during systole for every subject. In general, brachial BP was closer to the identity line suggesting that it followed very well Millar BP while finger BP had bigger over- and underestimation. In all cases, the initial upstroke of finger BP started by overestimating Millar BP and always peaked over our reference method. During the following down stroke, finger BP passed under the identity line showing an underestimation of Millar BP. This pattern implied a higher but narrower peak of all Finger BP compared to Millar BP during baseline. In subject 1 and 8, brachial BP followed very well Millar BP. Millar BP was overestimated by brachial BP in subject 3, 4, 6 and 7, while it was underestimated in subject 2 and 5. Note that in all cases brachial BP either overestimated or underestimated Millar BP, but never crossed the identity line like finger BP did. Except for subjects 1, 6 and 8, the initial upstroke of all brachial BP moved away from the identity line and came back closer during the down stroke. This suggested that brachial BP of subjects 3, 4 and 7 had a higher but just a little bit narrower peak than Millar BP and brachial BP of subject 2 and 5 had a lower but just a little bit wider peak than Millar BP. In subject 6, brachial BP followed very well Millar BP during the upstroke, but then overestimated it; implying an equal but wider peak than Millar BP.

Figure 27 presents an example of finger BP and brachial BP versus Millar BP during systole for every subject at -40 mmHg. In general, the same observations made for baseline can be made at -40 mmHg. Finger BP overestimated then underestimated Millar

BP. In subject 1 and 2, brachial BP followed very well Millar BP. Millar BP is overestimated by brachial BP in subjects 3, 4, 7 and 8, while it is underestimated in subjects 5 and 6. In contrast to Figure 26 and except for subjects 2 and 5, we can observe in Figure 27 that the end of the down stroke (dicrotic notch BP) went closer to the initial pressure (diastolic BP).

Table 8 presents the error of Qfinger and Qbrachial in comparison to Qmillar. These values represent the normalised difference between areas underneath the curves presented in Figures 26 and 27. At baseline, Qfinger discrepancy (*-1.13 ± 14.67%*) was smaller but not significantly different than Qbrachial discrepancy (*8.80 ± 17.28%*) (*p>0.05*). It was also bigger but not significantly different than Qfinger discrepancy at -40mmHg (*-0.61 ± 9.33%*) (*p>0.05*). During the last stage of the LBNP at -40 mmHg, Qfinger discrepancy was smaller but not significantly different than Qbrachial discrepancy (*9.74 ± 11.95%*) (*p>0.05*). On an individual basis, there was no difference between the ability of Qbrachial (50%) or Qfinger (50%) to provide the best estimate of Qmillar, with no major differences between baseline and -40 mmHg LBNP.

Figure 28 shows no particular pattern between Qfinger discrepancy and Qbrachial discrepancy with change in TPR. Qfinger discrepancy and Qbrachial discrepancy responded in the same direction and almost in the same amount with a change in TPR (*0.42%* in comparison to *0.53%* for a change of *1 mmHg/L/min*).

Figure 29 shows no particular pattern between Qfinger-Qmillar discrepancy and Qbrachial-Qmillar discrepancy with Qfin-Qdop discrepancy. Qfinger-Qmillar discrepancy and Qbrachial-Qmillar discrepancy responded in the same direction and

almost in the same amount with a change in Qfin-Qdop discrepancy (*0.12%* in comparison to *0.11%* for a change of *1%*).

5.4 Figures and Tables

Table 4: Participant characteristics for both projects

	Project 1	Project 2
Number of subjects	8	8
Number of tests used	23	8
Age (years)	24± 5.0	24.4± 4.3
Height (cm)	175.7± 5.9	177.1± 7.7
Weight (kg)	72.2± 6.8	74.6± 6.4
At Rest:		
HR (Beats/min)	52.05± 6.10	56.21± 11.58
SBP (mmHg)	125.4± 11.5	125.5± 13.9
DBP (mmHg)	67.2± 6.5	72.6± 6.1

All values are mean ± SD.

Table 5: Criteria of test rejection from the pool of test in project 1

Nb test rejected	Reason
6	Missing data from the Beatscope of the Finometer™
5	Missing data because of problems encountered with measurement instrument (Doppler or CVP apparatus)
4	Hyperactive subject causing unexpected responses in variables during our passive orthostatic stress
2	Lost file

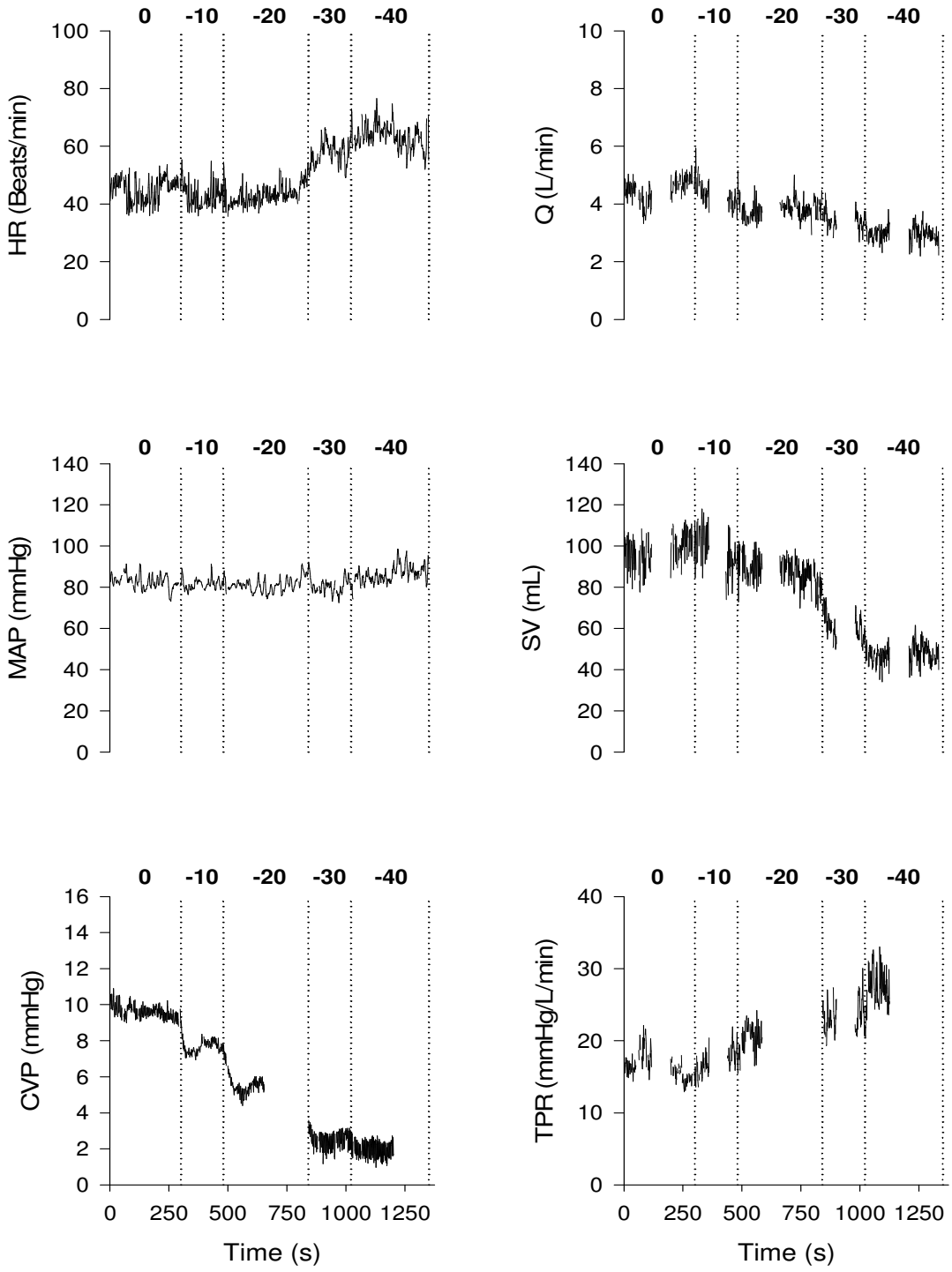

Figure 15-A: Example of physiological variables of one subject during the LBNP protocol of project 1 – Beat-by-Beat representation

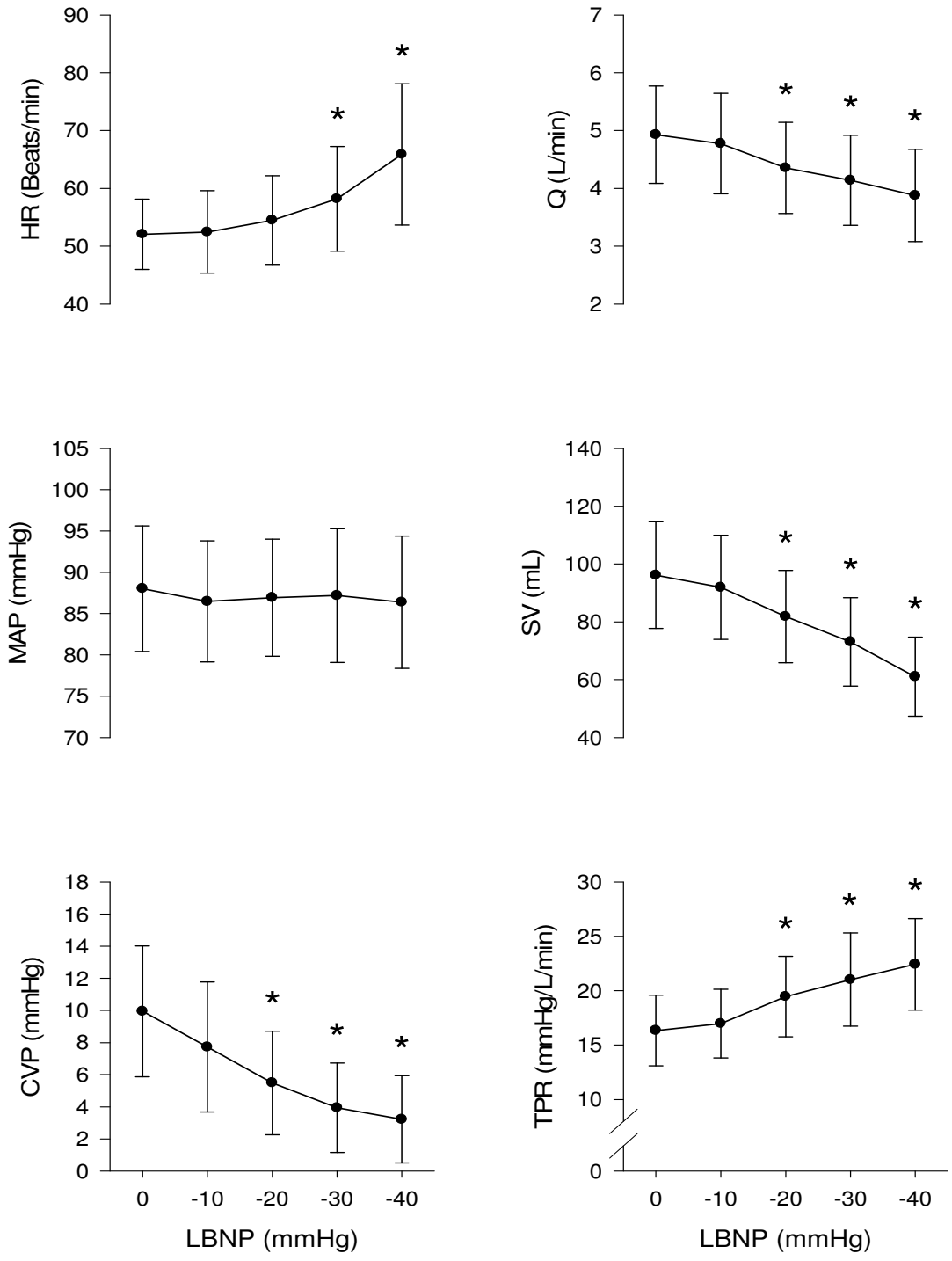

Figure 15-B: Physiological variables during LBNP of project 1

All Values are mean ± SD, n=23. * Significantly different from baseline ($p<0.05$).

Table 6: Summary of the accuracy and precision of the different outputs of the Finometer™ in project 1

	0	-10	-20	-30	-40	Overall
HR	0.04± 0.11	0.02± 0.16	0.07± 0.13	-0.001± 0.23	0.12± 0.21	0.05± 0.18
DBP	1.6± 8.8					
SBP	14.2± 8.0 *					
Qfin	0.511± 1.205 (13.2%)	0.588± 1.240 (15.8%)	0.835± 1.094 (23.1%)	0.928± 0.999 * (26.6%)	1.123± 1.036 * (33.4%)	0.797± 1.122 * (22.4%)
Qfin corrected	-0.056± 0.079 (1.2%)	0.023± 0.271 (0.8%)	0.302± 0.397 (7.5%)	0.406± 0.466 * (10.9%)	0.600± 0.494 * (16.6%)	0.255± 0.441 * (6.9%)

All values are bias ± SD (Accuracy ± Precision), n=23. Values in parenthesis are %error ((Qfin-Qdop)/Qdop). * Variable is significantly different from reference method ($p<0.05$).

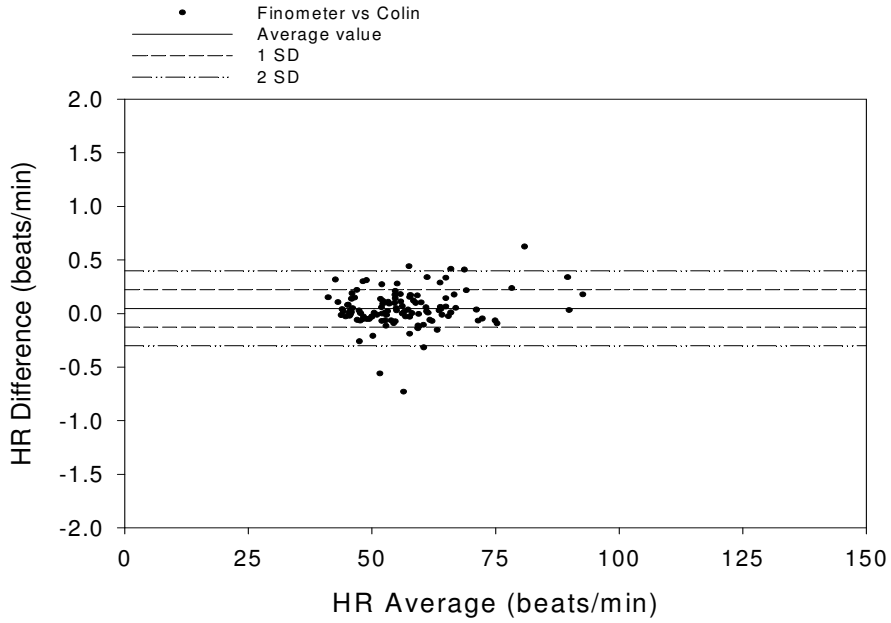

Figure 16: Accuracy and precision of HR measured by the Finometer^{TM} in comparison with HR measured from the electrocardiograph in project 1 – Bland-Altman Analysis

Total of 115 observations in 23 tests

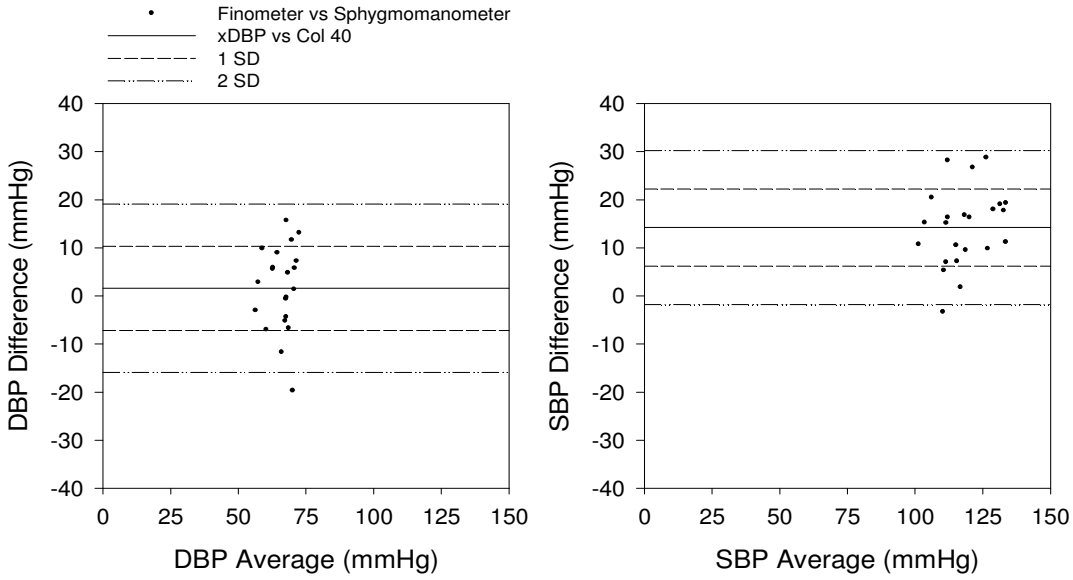

Figure 17: Accuracy and precision of DBP and SBP measured by the FinometerTM in comparison with DBP and SBP measured from the sphygmomanometer in project 1 – Bland-Altman Analysis

Total of 23 observations in 23 tests

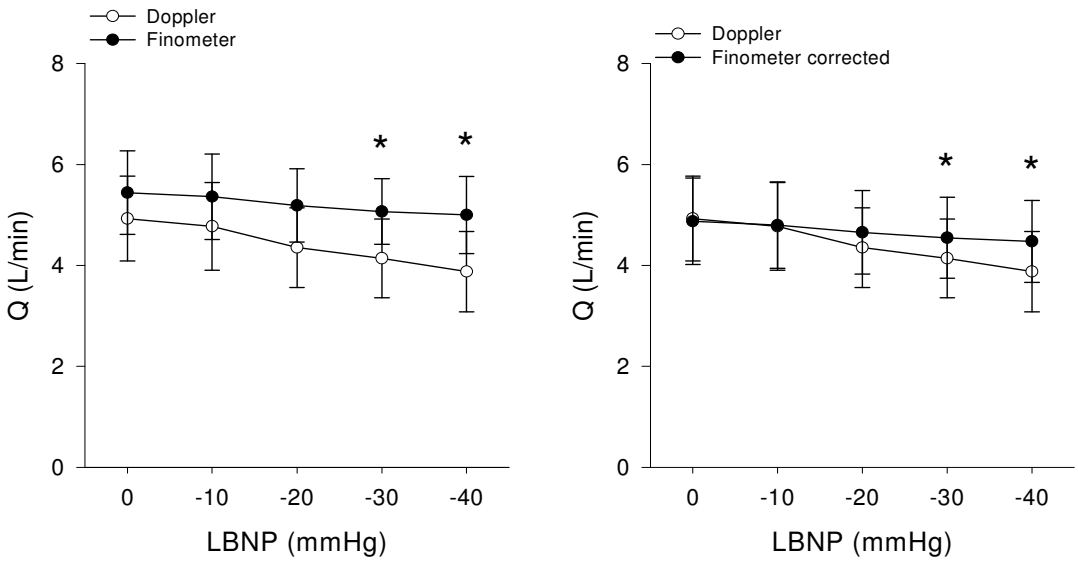

Figure 18: Effect of the correction of Q from the Finometer™ in comparison of Q from the Doppler in project 1

All Values are mean ± SD, n=23. * Finometer is significantly different from Doppler ($p<0.05$).

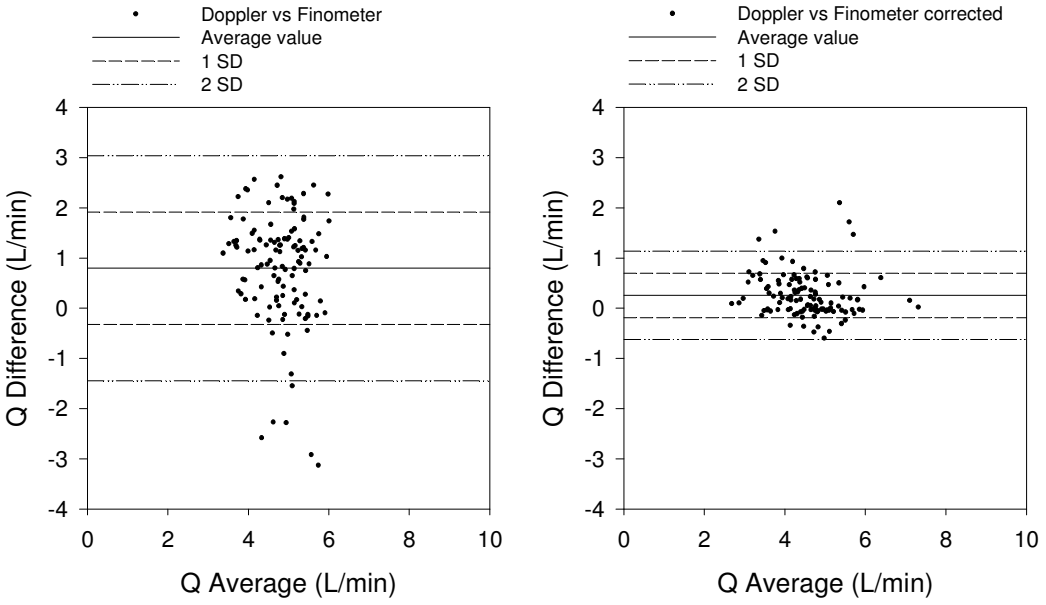

Figure 19: Accuracy and precision of Q from the Doppler and Q from the Finometer™ non-corrected and corrected in project 1 - Bland-Altman analysis

Total of 115 observations in 23 tests

Table 7: Summary of the accuracy and precision of CVP calculated with both the newly developed relation (New relation (Eq. 9)) and the relation developed by Gagné and colleagues (2007) (Old relation (Eq. 6)) in comparison of CVP measured with the venous catheter in project 1

			0	-10	-20	-30	-40	Overall
New relation (Eq. 9)	General	Doppler	-2.0± 2.1	-0.3± 2.6	1.0± 2.7	1.8± 2.4	1.8± 2.1	0.4± 2.8
		Finometer	-2.5± 2.1	-0.5± 2.6	1.1± 2.3	2.0± 1.9	2.1± 1.8	0.4± 2.8
	Individual	Doppler	-1.8± 1.1	-0.2± 1.2	1.0± 0.8	1.2± 0.9	0.8± 1.1	0.2± 1.5
		Finometer	-2.1± 1.1	-0.2± 1.2	1.2± 0.8	1.5± 0.9	0.9± 1.1	0.2± 1.7
	Test	Doppler	-1.4± 0.6	-0.04± 0.7	0.7± 0.5	0.8± 0.3	0.6± 0.7	0.1± 1.0
		Finometer	-1.7± 0.7	0.1± 0.6	1.0± 0.6	0.9± 1.0	0.3± 0.8	0.1± 1.2
Old relation (Eq. 6)	General	Doppler	-2.1± 2.1	-0.4± 2.6	1.0± 2.6	1.8± 2.4	1.9± 2.1$^{\#}$	0.4± 2.8$^{\#}$
		Finometer	-2.5± 2.2	-0.6± 2.6	1.0± 2.3	2.0± 2.0	2.0± 1.8	0.4± 2.8
	Individual	Doppler	-1.7± 1.4	-0.2± 1.5	0.8± 1.4	1.3± 1.4	1.1± 1.1	0.2± 1.8
		Finometer	-2.3± 1.5	-0.4± 1.6	1.0± 1.3	1.7± 1.3	1.4± 1.2	0.3± 2.0
	Test	Doppler	-1.4± 0.6	-0.05± 0.6	0.7± 0.6	0.9± 0.4	0.6± 0.7	0.2± 1.1
		Finometer	-1.7± 0.7	0.01± 0.7	0.9± 0.6	1.1± 0.9	0.5± 0.9	0.2± 1.3

All values are bias ± SD (Accuracy ± Precision), n=23. * CVP calculated is significantly different from CVP measured with the catheter ($p<0.05$). $^{\#}$ General equation is significantly different from corresponding Test equation ($p<0.05$). † General equation is significantly different from corresponding Individual equation ($p<0.05$). $^{\&}$ Individual equation is significantly different from corresponding Test equation ($p<0.05$). $^{\alpha}$ CVP calculated with Finometer's SV is significantly different from CVP calculated with Doppler's SV ($p<0.05$). $^{\beta}$ New relation is significantly different from Old relation ($p<0.05$).

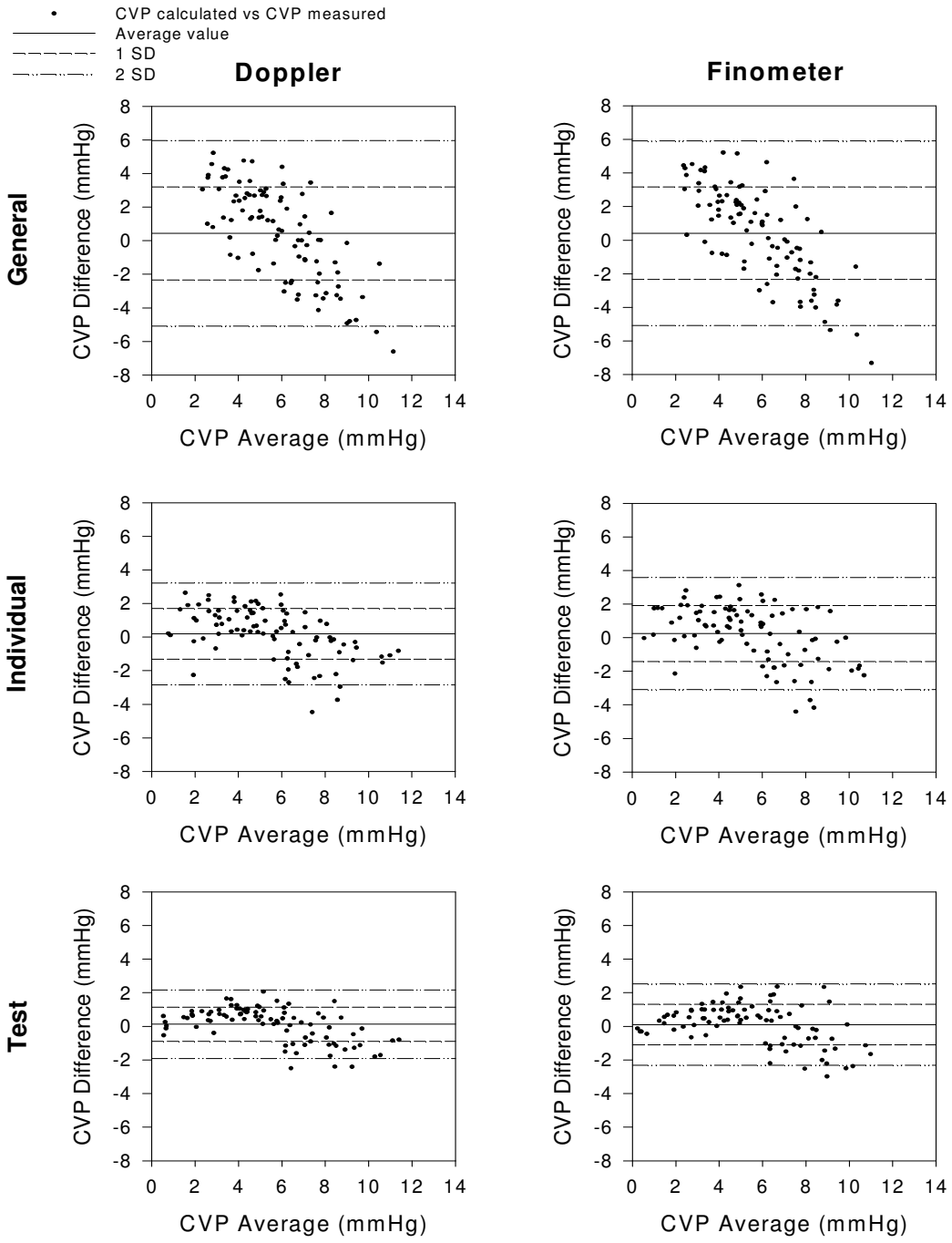

Figure 20: Accuracy and precision of CVP calculated with a general, an individual and a test-specific equation with the newly developed relation (Eq. 9) in comparison of CVP measured with the venous catheter in project 1 – Bland-Altman analysis

Total of 114 observations in 23 tests

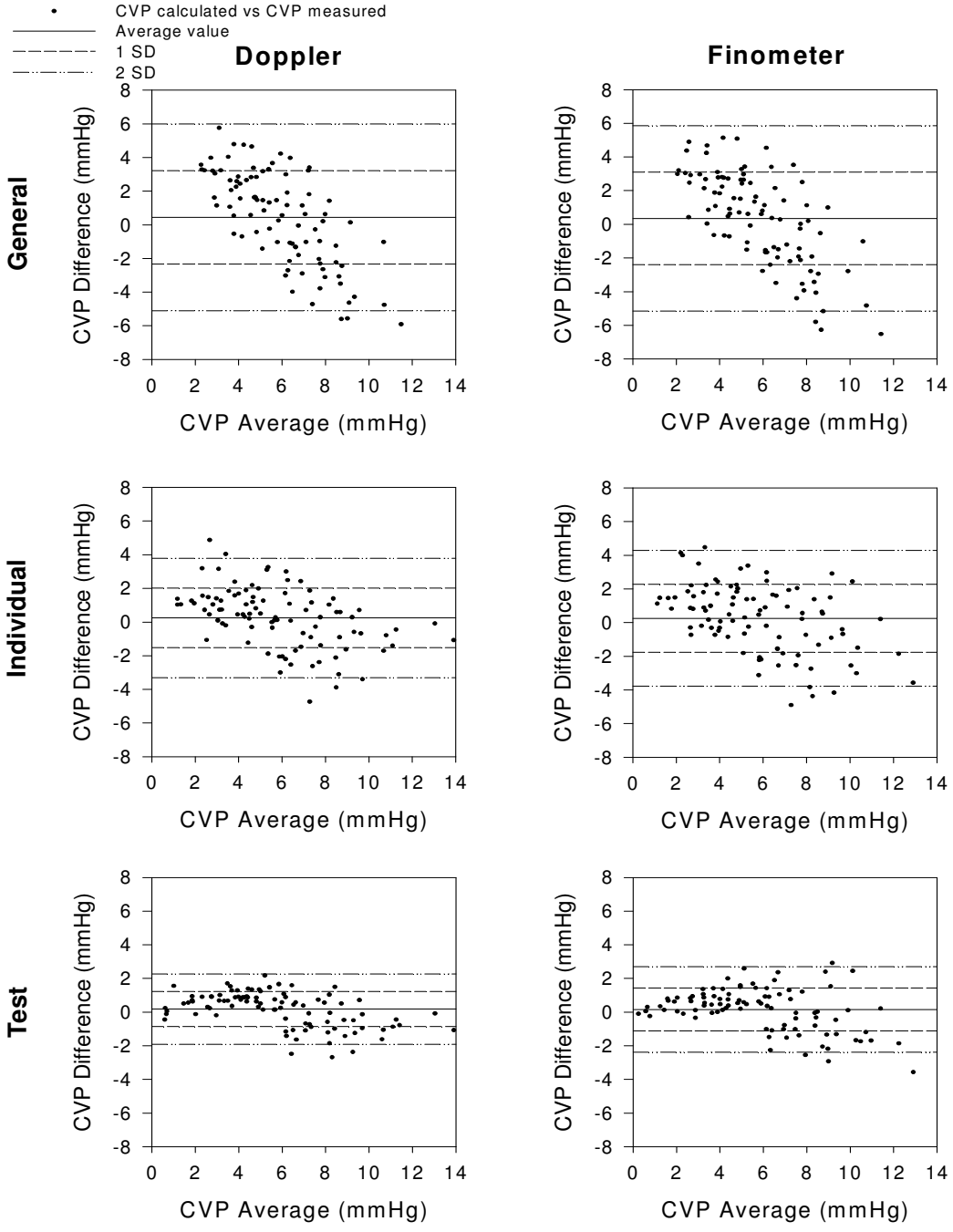

Figure 21: Accuracy and precision of CVP calculated with a general, an individual and a test-specific equation with the relation developed by Gagné and colleagues (2007) (Eq. 6) in comparison of CVP measured with the venous catheter in project 1 – Bland-Altman analysis

Total of 114 observations in 23 tests

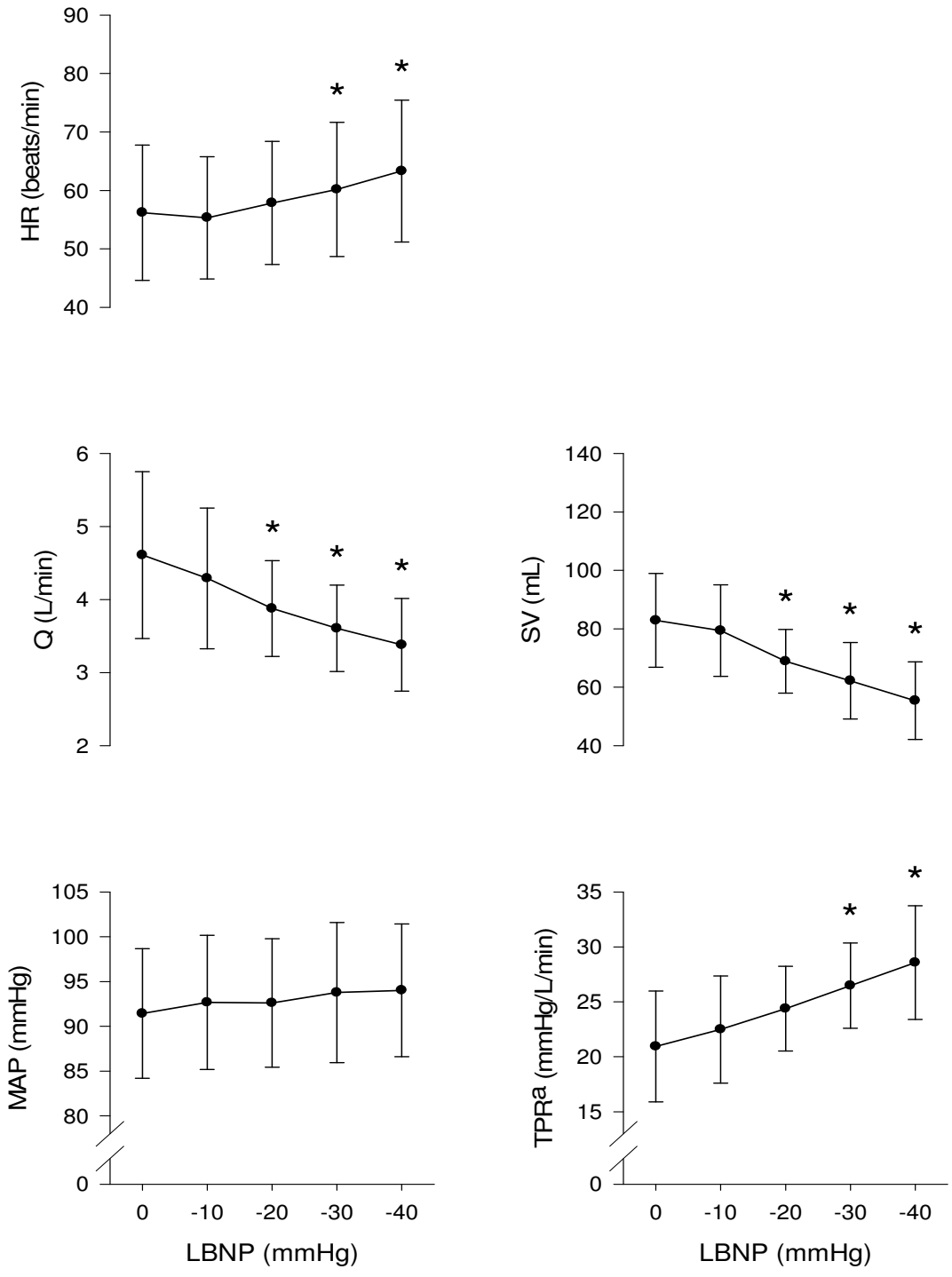

Figure 22: Physiological variables during LBNP of project 2

All Values are mean ± SD, n=8. * Variable is significantly different from baseline ($p<0.05$).
[a] CVP is omitted in the calculation of TPR.

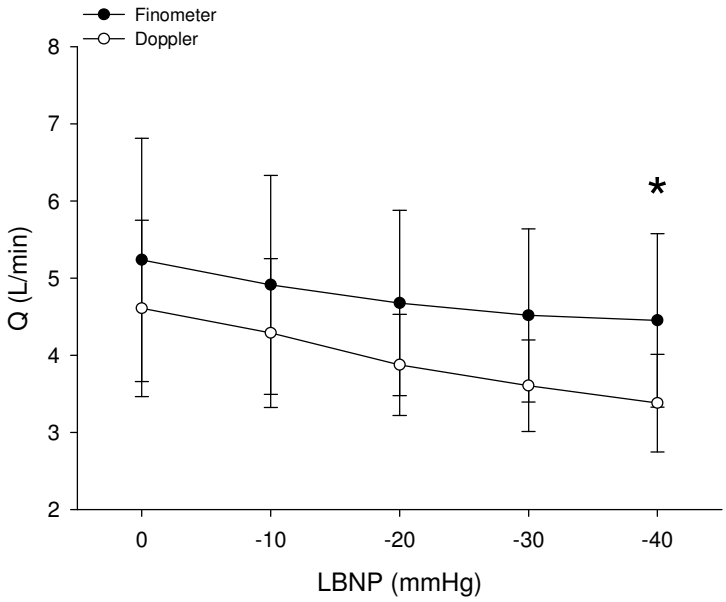

Figure 23: Effect of during-test-correction of Qfin directly in the display of the Finometer™ in comparison of Q from Doppler in project 2

All Values are mean ± SD, n=8. * Finometer is significantly different from Doppler ($p<0.05$).

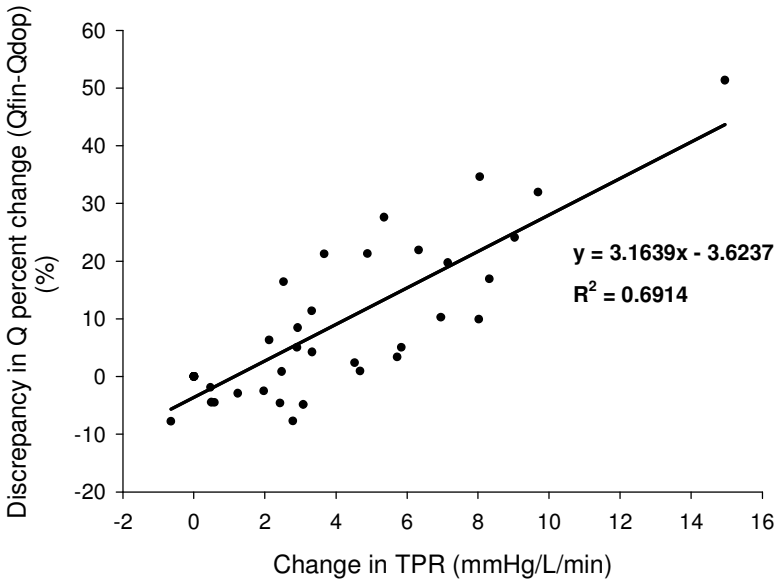

Figure 24: Q discrepancies versus change in TPR

Total of 40 observations in 8 tests

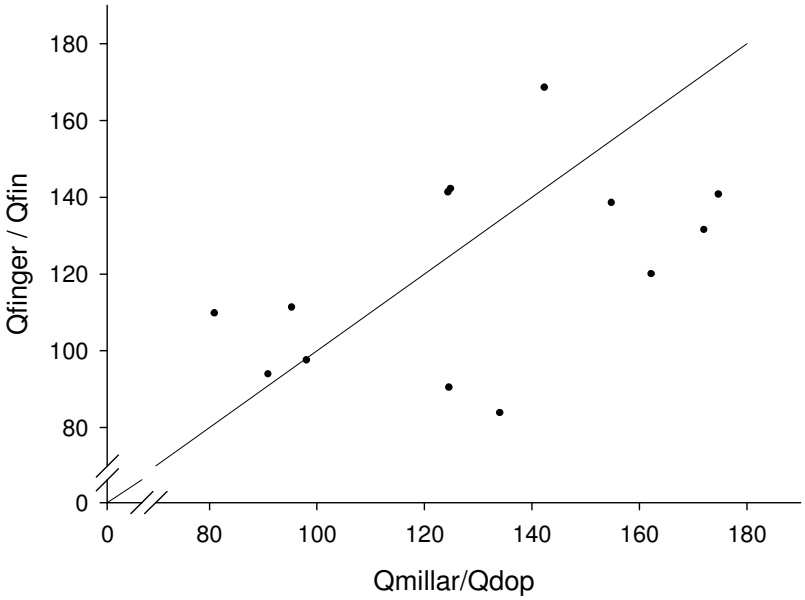

Figure 25: Validation of using Qmillar as a reference for Qdop

Total of 13 observations in 8 tests

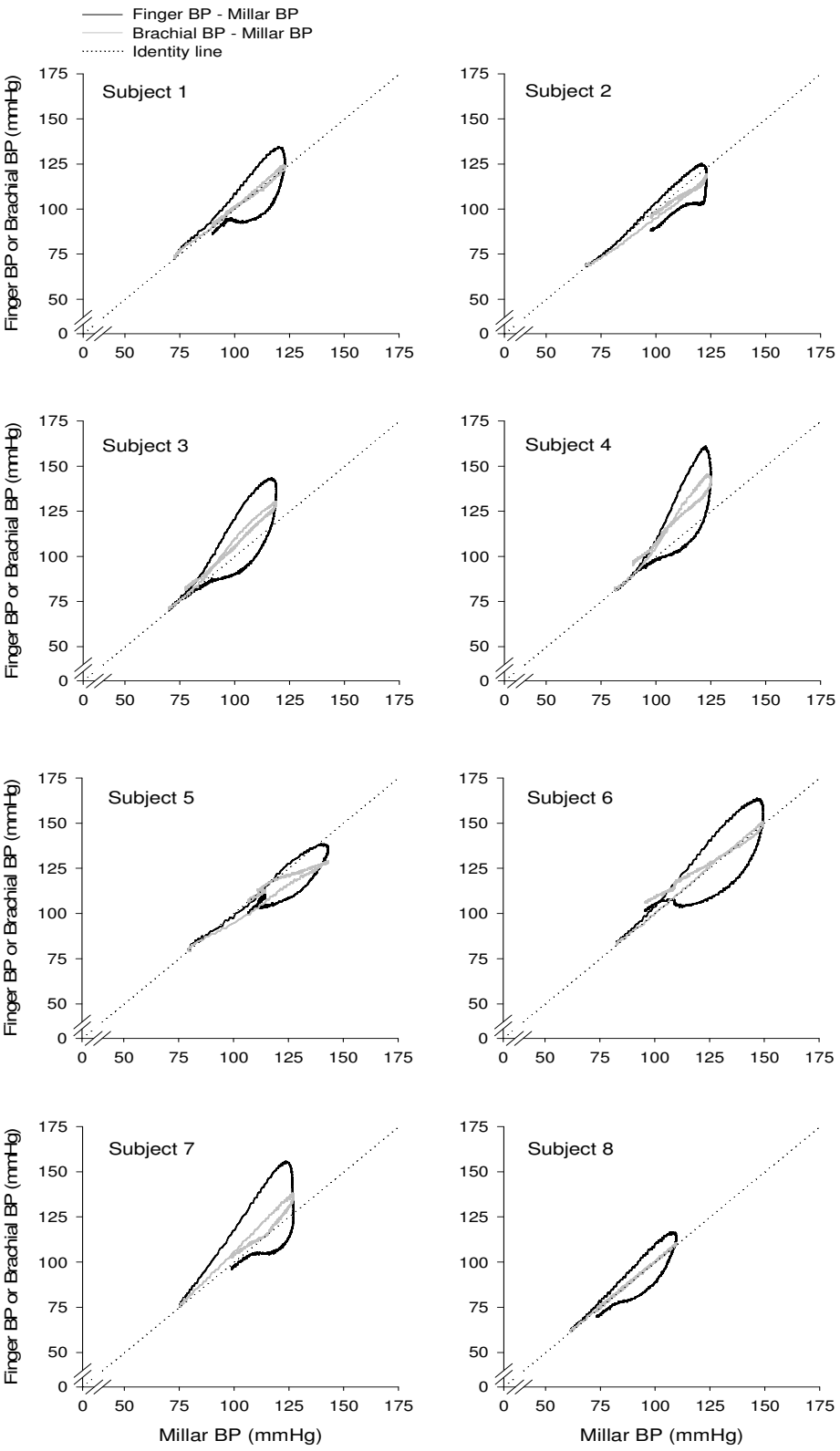

Figure 26: Finger BP and Brachial BP versus Millar BP for every subject during Baseline

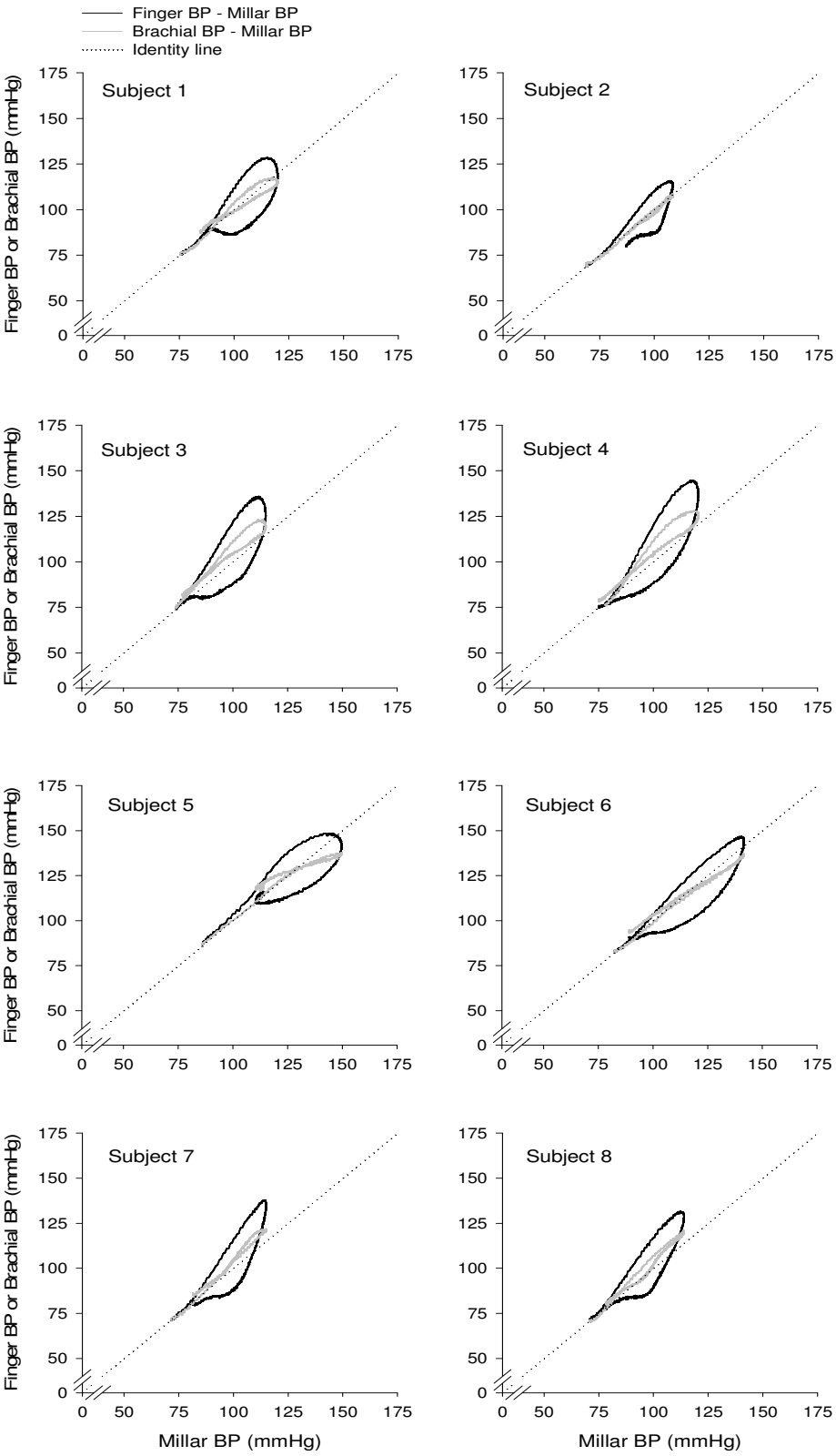

Figure 27: Finger BP and Brachial BP versus Millar BP for every subject at -40mmHg

Table 8: Summary of Qfinger discrepancy and Qbrachial discrepancy

Subject	0 mmHg		-40 mmHg	
	Qfinger discrepancy (%)	Qbrachial discrepancy (%)	Qfinger discrepancy (%)	Qbrachial discrepancy (%)
1	-6.65	2.94	-9.21	0.56
2	-18.93	-11.29	-9.35	-2.34
3	9.01	23.21	11.26	28.34
4	25.23	41.07	7.99	20.42
5	-16.76	-9.34	-6.05	1.31
6	-0.32	7.84	-11.70	-2.68
7	7.26	14.03	5.11	16.90
8	-7.85	1.98	7.08	15.43
Average ± SD	-1.13 ± 14.67	8.80 ± 17.28	-0.61 ± 9.33	9.74 ± 11.95

* Average Qfinger discrepancy during baseline is significantly different from average Qfinger discrepancy at -40mmHg ($p<0.05$). # Average Qbrachial discrepancy during baseline is significantly different from average Qbrachial discrepancy at -40mmHg ($p<0.05$). & Average Qfinger discrepancy is significantly different from average Qbrachial discrepancy at the same LBNP level.

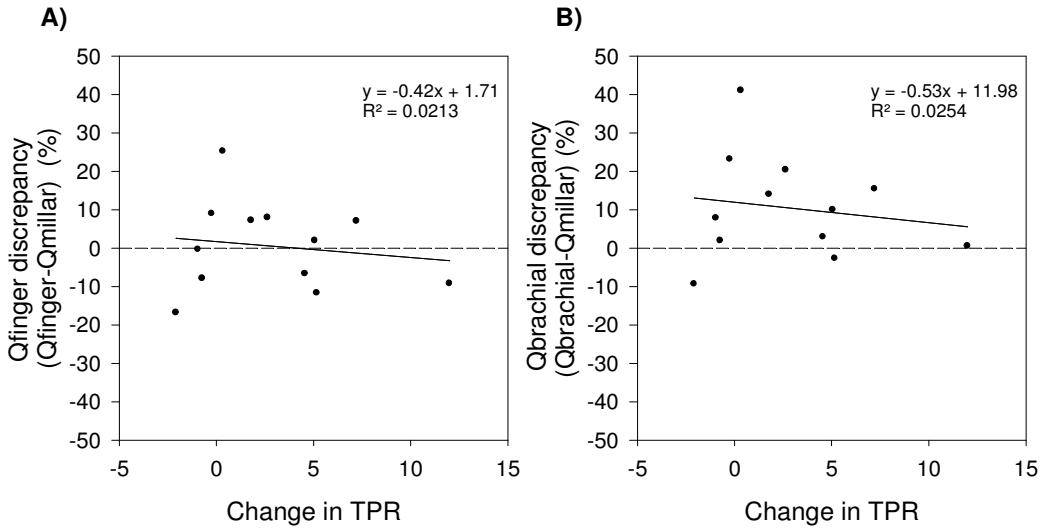

Figure 28: A) Qfinger dicrepancy vs change in TPR; B) Qbrachial discrepancy vs change in TPR

Total of 12 observations in 8 tests

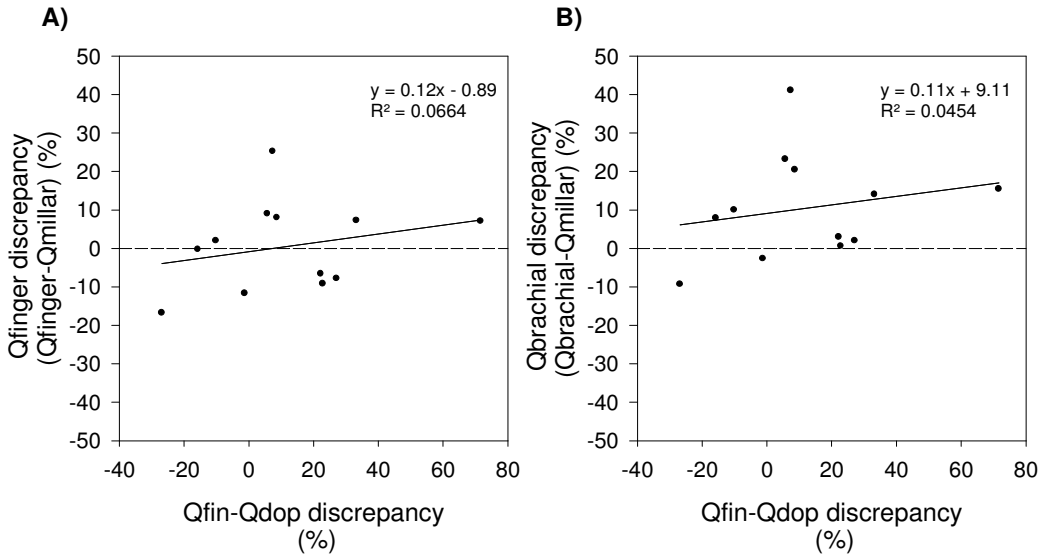

Figure 29: Qfinger-Qmillar discrepancy vs Qfin-Qdop discrepancy; B) Qbrachial-Qmillar discrepancy vs Qfin-Qdop discrepancy

Total of 12 observations in 8 tests

6. Discussion

The aim of this thesis was to develop a non-invasive method to monitor cardiovascular control during orthostatic stress. The first steps of the development of this method have been separated in two different projects covering three hypotheses.

We first found that the Finometer™ had the potential to accurately and precisely be used alone to monitor cardiovascular control during orthostatic stress. It did not give perfect values, but proper use including calibration of the Finometer™ can lead to results for heart rate, SBP and DBP with sufficient accuracy and precision to be valid in most research settings at rest and during mild stress. Secondly, the estimations of CVP made with a general equation are accurate, but contrary to our first hypothesis, not reliable. Individual and test equations gave accurate and precise estimations of CVP, opening opportunities of non-invasive estimations of CVP with a prior test specific adjustment (i.e. correction against CVP directly measured). Moreover, using SV from the Finometer™ to calculate CVP has been shown to be not significantly different than using SV from the Doppler. Finally, the newly developed equation (Eq. 9) did not improve the results of Gagné and colleagues (2007) (Eq. 6).

Hypothesis 2 that using finger BP to represent aortic BP would influence the discrepancy in the estimation of Q by Finometer™ compared to the Doppler estimate of Q when a stress was applied was not supported by the current study. Further investigation of this discrepancy in hypothesis 3 revealed that while brachial BP gave a better estimation of absolute value of Millar BP, the shape of the finger BP was not the source of a discrepancy between Q Finometer™ and Q Doppler. New details concerning the pulse

wave contour obtained by plotting the instantaneous BP during the cardiac ejection phase showed that an over-estimation of BP by the finger BP relative to the Millar BP early in the cardiac cycle was compensated almost perfectly by under-estimation in the latter part of the cardiac ejection phase.

The following sections examine the causes of these results.

6.1 Development of the Relation

Physiological Variables during Orthostatic Stress

The physiological variables recorded during project 1 (Figure 15) are in accordance with the literature covering orthostatic stress. CVP, SV and Q gradually decreased with the increasing orthostatic stress due to the decrease of blood going back to the heart [Rowell, 1993]. In order to maintain sufficient arterial blood pressure (MAP) to drive blood to the brain, reflex responses from the autonomic nervous system were able to increase HR and TPR (vasoconstriction) [Rowell, 1993].

Figure 15 also shows that the first stage of the LBNP (*-10 mmHg*) did not create significant changes in all physiological variables. This concords with the fact that a LBNP stage of -10mmHg is comparable to a head-up tilt of less than 60° [Kitano et al., 2005], which is much milder compared to -40mmHg LBNP representing an upright position [Musgrave et al., 1969; Butler et al., 1993]. In light of these observations, we confirm that the dataset used to create the CVP equations conformed to the expected response during an orthostatic stress.

Accuracy and Precision of the Different Outputs of the Finometer™

According to our results, HR calculated from the working frequency of the finger cuff gives accurate and precise values in comparison of HR measured with an electrocardiograph. Its accuracy and precision are not affected by the stress applied.

DBP and SBP discrepancies are not all in agreement with the literature. The accuracy of DBP (*1.6 mmHg*) is within the AAMI standard, but its precision (*8.8 mmHg*) is a little bit offset. This conflicts with the data of Guelen and colleagues (2008) (*4± 6 mmHg*) and the data presented in the Finometer™ User's Guide (*1± 5 mmHg*), where both studies showed accurate and precise estimation of DBP of the reconstructed brachial BP waveform. SBP accuracy (*12.2 mmHg*) is not within the AAMI standard and does not concord with what has been found in the previous studies [Guelen et al., 2008; Finometer™ User's Guide]. Although SBP precision (*8.0 mmHg*) is considered borderline to the AAMI standard, it is in conformity with what Guelen and colleagues (2008) (*8 mmHg*) and the Finometer™ User's Guide (*7 mmHg*) have shown. The discrepancies seen in our results compared to the two references studies are probably caused by the use of a different reference method. Both studies refer their brachial measurements to intra-arterial pressure instead of manual BP (sphygmomanometer). Considering that the intra-arterial technique is direct; its accuracy is higher then manual BP, which makes the comparison different. According to the AAMI, cuff/stethoscope auscultatory measurements may be used as a reference standard, but trained observers are required [White et al., 1993]. The error seen in our results might come from the fact that different and non-trained observers collected manual BP.

The overall Q, pre and post calibration, are in accordance with the literature. Indeed, Qfin (*0.797± 1.122mmHg*) and Qfin-corrected (*0.255± 0.441mmHg*) concord with the data presented in the Finometer™ User's Guide and shows that a calibration is needed in order to represent absolute value instead of only variations of Q [Harms et al., 1999]. Following the results of van Lieshout and colleagues (2003), we also found that the accuracy of the estimation of Q from the Finometer™ decreased when an orthostatic stress was applied (Figures 18 and 19). This result will be discussed in more detail in section 6.2.

Accuracy and Precision of CVP Calculated

Although EFrest, DBP, SV and HR significantly contributed to predict CVP in the general CVP equations (Table 10), the accuracy and precision of the equations using different techniques and in comparison to the relation Gagné and colleagues (2007) developed are giving some interesting results.

Overall, following the standards we stated a priori (bias< ±2 mmHg and precision better than ±2 mmHg), CVP calculated appears to be accurate in all three types of equations, but is precise only for test and individual equations. The general equations are not precise. This suggests that variability between people is not explained or is not explained solely by the specific and personal value we added in the equation (left ventricular distensibility (EF)). It might also put in evidence the importance of normalising SV data to body surface area in order to take into account other variables touching indirectly the heart function and the Frank-Starling mechanism.

According to Table 7 and Figures 20 and 21, CVP calculated using SV from the Finometer™ is not significantly different from CVP calculated using SV from the

Doppler. At first, this result is surprising considering that the accuracy of the estimation of Qfin (SVfin) has been shown to decrease when a stress occurs (Figures 18 and 19). Even though SV variable (*b*) is small in every equation (Table 10), it will be a mistake to conclude that the SV discrepancy does not influence CVP calculated because it takes a minor place in the equation. Indeed, we should take into account that SV and LVEDV (SV/EF) values are in the hundreds range and should be decreased to the CVP range, around 10. The similar results between CVP calculated using SVfin and CVP calculated using SVdop can be rather explained by the use of two different sets of SV data (Finometer^{TM} and Doppler) to extract the regressions. The regression equation for the CVP calculated with Finometer^{TM} seems to damp the SV problem by taking into account its variation.

Comparing Figure 20 and Figure 21 also shows that the newly developed relation gives similar results as the equation developed by Gagné and colleague (2007). Although our equation failed to improve the accuracy and precision of CVP calculated with our current set of subjects, it will be appropriate to test this equation on a different population before concluding that the added variables are not doing what we expected. For example, it has been shown that performances of healthy and normal hearts are not strongly influenced by after-load (DBP) while performances of old hearts are more sensitive to a change in DBP [Swine, 1992]. Also, EF is influenced by inotropic agents, aging [Fleg, 1986] and prolonged bed rest [Levine et al., 1997]. Furthermore, compared to young subjects during a stress, the maximum HR is reduced in the elderly but SV is increased to maintain Q [Swine, 1992]. Testing our equation on different populations in different situations would give more valuable information about the necessity of using DBP, EF, SV and HR. If

useful, these variables will help providing more accurate and precise results than the equation developed by Gagné and colleagues (2007) for test on other populations.

Overall, general equations are not precise enough to be used in clinical and research setting, but the fact that individual and test equations give good approximations of the actual CVP is promising. Individual equations have proven to be not significantly different than test equations even though subjects have been monitored many times over a long period (reaching a year in one particular case). This suggests the ability to derive a personal equation by using a catheter only once that will be useful over a long period for similar tests. Further tests will be needed to determine how accurately and precisely this equation will estimate CVP in different conditions.

6.2 Investigation of Cardiac Output Measurement

Although the problem of Q (SV) discrepancy with an orthostatic stress did not seem to influence the CVP equation, it is still very important to insure that we get good results out of the Finometer™. This section focuses on the calibration of Q measurement.

Physiological Variables during Orthostatic Stress

Even though project 2 did not use the same timeline as project 1, the physiological variables recorded during project 2 (Figure 22) are in accordance with the literature and are very similar to project 1. SV and Q gradually decreased with the increasing orthostatic stress due to the decrease of blood going back to the heart [Rowell, 1993]. In order to maintain sufficient arterial blood pressure (MAP) to drive blood to the brain, the autonomic nervous system sent efferent signals to increase HR and TPR (vasoconstriction).

Figure 22 also points out that the first stage of the LBNP (*-10mmHg*) did not created significant changes in all physiological variables, just like in project 1.

Accuracy and Precision of Cardiac Outputs from the Finometer™

The differences between Qfin and Qdop illustrated in Figure 23 are in accordance with what we found in project 1 (Figure 18) and follow the results of van Lieshout and colleagues (2003). Indeed, our results showed an increasing discrepancy between the estimation of Q from the Finometer™ and Q from Doppler when an orthostatic stress was applied. Furthermore and in accordance to the unpublished data of Dyson and colleagues, Figure 24 shows that Q discrepancy was correlated to change in TPR.

The correction made in the display of the Finometer™ against aortic diameter at the beginning of the test in order to account for individual characteristics did not increase the accuracy of the measurement (Figure 23 in comparison with Figure 18). Post- test calibration with the Beatscope software against Q values from Doppler ultrasound seems to remain more efficient (Figure 18-B).

Validation of Cardiac Output estimated from the Millar

Figure 25 compares two ratios that, regardless of the absolute value, would give the same result only if Qmillar perfectly represents Qdop. Every dot on Figure 25 corresponds to a beat analysed. The further the dot is from the identity line, the poorer is the representation of Qdop by Qmillar.

The cloud of dots in Figure 25 is quite large but does cover both side of the identity line. Even if this result suggests a reasonably good estimation of Qdop by Qmillar, analysis of more beats would be required in order to firmly validate its use. This is the first time, to

the author's knowledge, that this approach has been taken to examine the relationship between two independent methods of estimating Q.

Identification of the Major Source of Error

When compared to Millar BP during baseline, finger BP showed big overestimations during the initial upstroke and big underestimation during the following down stroke (Figure 26). This behaviour is in accordance with the literature and suggests that finger BP had a bigger pulse pressure, but a narrower systolic peak pressure than aortic BP [Remington and Wood, 1956]. Our results for the comparison of brachial BP and Millar BP are also in accordance with the same literature. Indeed, because of its proximity to the aorta, it was expected to see brachial BP better following Millar BP than finger BP did.

Interestingly, Table 8 reveals that Qfinger discrepancy during baseline was low (*-1.13 ± 14.67 %*) even though finger BP did not follow Millar BP very well. It is important to note here that Qfinger discrepancy is not the average of the bias between finger BP and Millar BP, but rather the normalised difference between the area underneath finger BP contours and Millar BP contours. This suggests that the area underneath the finger BP contours was similar to the area underneath the Millar BP contours, but it was distributed differently. Finger pulse pressure was greater than Millar pulse pressure, but systolic peak pressure was narrowed compared to our reference: the big overestimations of finger BP were then cancelled by big underestimations.

Small visual dissimilarities and minor discrepancies can be distinguished in the estimation of Millar BP by finger BP at baseline and during a stress (Figure 27). Even if we would have expected a more noticeable alteration, this result is in accordance with the

literature and show a different change in the finger artery than in the aorta during an orthostatic stress [Houtman et al., 1999; Westerhof and O'Rourke, 1995; Stok et al., 2006]. Although finger BP is influenced differently than aortic BP during change in TPR, Table 8 shows no significant difference between the average values of Qfinger discrepancy at baseline and -40mmHg (*-1.13 ± 14.67% versus -0.61 ± 9.33%*). This observation is confirmed by Figures 28 and 29 where blood pressure contour differences did not influence Qfinger discrepancy because it is independent of change in TPR and variation in Qfin-Qdop discrepancy. This highlights the fact that using finger BP to represent aortic BP does not influence the discrepancy in the estimation of Q by Finometer™ when a stress is applied.

Even though brachial BP followed Millar BP more accurately than finger BP (Figures 26 and 27), the error of Qbrachial was not smaller than the error of Qfinger (Table 8). There were actually no significant differences between the average Qfinger discrepancy and Qbrachial discrepancy at both baseline and -40mmHg. Moreover, on an individual basis, Table 8 shows that in only 50% of the time the error of Qbrachial was smaller than the error of Qfinger. Figures 28 and 29 also show that Qbrachial discrepancy varied in the same way and almost in the same amount as Qfinger discrepancy during a change in TPR (*0.42%* in comparison to *0.53%* for a change of *1mmHg/L/min*) and during variation in Qfin-Qdop discrepancy (*0.12%* in comparison to *0.11%* for a change of *1%*). This allows us to conclude that using brachial BP instead of finger BP does not help to solve the Qfin-Qdop discrepancy problem.

6.3 Limitations

Here is a list of possible limitations of the project.

- The first project was a shared study. This means that concessions in the specific protocols were made to accommodate the projects of different students.
- We relied on our subjects to follow the rules of no alcohol or caffeine for twenty-four (24) hours prior to the test and concerning the consumption of their breakfast after an 8h sleep.
- The neoprene kayak skirt used to seal the LBNP box might have been too tight on the waist of the subjects causing compression in the splanchnic area influencing fluid distribution. This restriction was not consistent across the different tests.
- Although only one person was in charge of measuring Q with the Doppler ultrasound throughout the project to reduce experimental errors, there was still a possibility that the probe was not *perfectly* oriented toward the root of the aorta at every test. It is unknown whether the orientation of the aorta to the direction of the ultrasound beam might have been altered during LBNP introducing an error in calculation of Q Doppler.
- Although the pulmonary system is known to buffer imbalances between right ventricular and left ventricular output [Rowell, 1993], we assumed that this happened only for the few first beats of a stress. We then assumed that EDV was really representative of the preload of the heart (CVP) and its time of filling (HR).

- Aortic BP is not available in our lab since it required the clinical setting of a hospital. We then chose to use brachial BP because it is a good representation of aortic BP. In fact, since it is a fairly big artery and it is close to the aorta, it is used as the clinical standard for the evaluation of arterial pressure via a sphygmomanometer placed on the brachial artery.
- The applanation tonometry device (Millar) used to monitor aortic BP is not intra-arterial and therefore it is also subject to error and can account for part of the discrepancy between methods.

7. Conclusion

In order to provide scientists and doctors a way to monitor cardiovascular control during orthostatic stress, the aim of this project was to develop a simple method with a non-invasive device: the Finometer^{TM}. This kind of method has a lot of potential to provide a first evaluation of important clinical signs that might require detailed investigation. Its compact design and its non-invasive component are also convenient for research involving restricted situations including studies of astronauts or of elderly participants who might be uncomfortable consenting to more invasive and intrusive technologies. The Finometer^{TM} is already well known and implemented in clinical and research laboratories, but it is criticised regarding its accuracy. The first steps of the development of this method have been separated in two different projects covering the main questions. We first examined whether key variables essential to monitor cardiovascular control can be reliably measured and calculated by the Finometer^{TM} in comparison to independent methods. We then investigated further what are the causes of the Finometer^{TM}'s limitations.

We first found that the Finometer^{TM} does have the potential to accurately and precisely be used alone to monitor components of cardiovascular control during orthostatic stress. Proper use and calibration of the Finometer^{TM} can provide HR, SBP and DBP with sufficient accuracy and precision to be valid in most research settings. The primary concerns revolve around Q that appears to deviate from its reference, even after a calibration, when a stress occurs.

A major objective of the first hypothesis of this thesis was to examine the accuracy and reliability of a non-invasive estimate of CVP. Measurement of CVP requires a catheter

but it might be possible to estimate it on the basis of the link with cardiovascular function. Overall, the general equations created were not precise enough to be used in clinical and research setting, but individual and test equations were more promising. Individual equations have proven to be not significantly different than test equations even though subjects have been monitored many times over a long period of time. This suggests the ability to derive a personal equation that will be useful over a long period for similar tests by using a catheter only once. Furthermore, the individual and test equations did not improve the result of Gagné and colleagues (2007), but we believe that the fact they are using more variables will help to better cover different populations such as studies of the elderly. Further tests will be needed to verify this.

Although a change in TPR induced by LBNP had a direct effect on the pulse contour of peripheral arteries compared to the main conduit artery, using finger BP to represent aortic BP did not appear to influence the discrepancy in the estimation of Qfin compared to Qdop when a stress was applied. Thus, hypotheses 2 and 3 were not supported. It was reported that the Langewouters' estimation causes a small error in the estimation of Q [Heermann et al., 2005], therefore since the change in pulse contour did not seem to contribute, it appears that the Modelflow equation might then account for a bigger part of the error in the estimation of Q and SV during change in TPR than we initially thought. Further investigation of the discrepancy between methods could potentially be explored by the new contour analysis method introduced here in a graphical format that plotted the instantaneous pulse waves by different methods against one another. Systematic analyses of the deviation between methods could reveal sources of error allowing identification of

methods to improve the accuracy and precision of Qfin during orthostatic or physical stress.

Appendix

Calculation of modelflow model

The modelflow model is a lumped parameters model represented as an electric circuit where the tension is the input BP and the courant is Q:

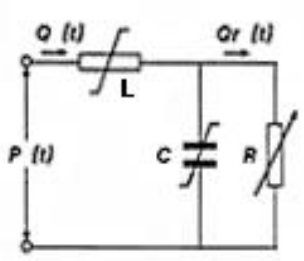

Figure 30: Electric circuit representing the modelflow model [modified from FMS website]

It is possible to get the Q waveform from the BP waveform by using the ohm's equation for an electric circuit: $v = z \cdot i$ where v is the tension, z the impedance (resistance) and i is the courant. Here is the development I have made from electrical physics equations to extract i from v while including all the three elements within the impedance variable (z):

$$i_{eq} = i_L = i_R + i_C = \frac{v_R}{z_R} + \frac{v_C}{z_C}$$

Considering that $v_R = v_C$ we can say that:

$$i_{eq} = \frac{v_R}{z_R} + \frac{v_C}{z_C} = \left(\frac{1}{z_R} + \frac{1}{z_C} \right) v_R = \frac{z_C + z_R}{z_R \cdot z_C} v_R$$

And knowing that: $$v = v_L + v_R$$

and so: $$v_R = v - v_L = v - z_L \cdot i_L = v - z_L \cdot i_{eq}$$

We can say: $$i_{eq} = \frac{z_C + z_R}{z_R \cdot z_C} v_R = \frac{z_C + z_R}{z_R \cdot z_C} \cdot (v - z_L \cdot i_{eq})$$

and so: $$i_{eq} \left(1 + \frac{z_C + z_R}{z_R \cdot z_C} z_L \right) = \frac{z_C + z_R}{z_R \cdot z_C} \cdot v$$

Finally:
$$i_{eq} = \frac{\frac{z_C + z_R}{z_R \cdot z_C} \cdot v}{\left(1 + \frac{z_C + z_R}{z_R \cdot z_C} \cdot z_L\right)} = \frac{z_C + z_R}{z_R \cdot z_C + (z_C + z_R) \cdot z_L} \cdot v$$

Bringing this equation back to cardiovascular variables we can say that:

$$Q = \frac{z_C + z_R}{z_R \cdot z_C + (z_C + z_R) \cdot z_L} \cdot P$$

Wesseling and colleagues (1993) have described z_L and z_R as follows:

$$z_L = \sqrt{\frac{\rho}{A \cdot dA/dP}}, \qquad z_R = R - z_L$$

And presented the conductance component c_w to be: $c_w = l \cdot dA/dP$

Knowing that conductance is inversely proportional to resistance, we can say that:

$$z_C = \frac{\tau}{c_w} = \frac{\tau}{l \cdot dA/dP}$$ Where τ is a time constant.

The calculation of the aortic diameter (A) is dependent on the pressure and is calculated from the Langewouters' algorithm (eq.2). According to Wesseling and colleagues (1993) R is equal to $R = MAP / Q$ and is taken from the previous beat.

z_L, z_C and z_R will then turn into:

$$z_L = \sqrt{\frac{\rho}{A_{\max}\left[0.5 + \frac{1}{\pi}\arctan\left(\frac{P - P_0}{P_1}\right)\right] \cdot \frac{A_{\max}/\pi P_1}{1 + \left(\frac{P - P_0}{P_1}\right)^2}}}$$

$$z_C = \tau \cdot \frac{1 + \left(\frac{P - P_0}{P_1}\right)^2}{l \cdot \left(A_{\max}/\pi P_1\right)} \qquad z_R = \frac{MAP_{x-1}}{Q_{x-1}} - z_L$$

Introducing the Wesseling's equations above into the equation I have made, this is finally giving us the following equation to find Q from arterial BP:

$$Q = \frac{\tau \cdot \frac{1+\left(\frac{P-P_0}{P_1}\right)^2}{l \cdot \left(A_{\max}/\pi P_1\right)} + \frac{MAP_{x-1}}{Q_{x-1}} - z_L}{\left(\frac{MAP_{x-1}}{Q_{x-1}} - z_L\right) \cdot \left(\tau \cdot \frac{1+\left(\frac{P-P_0}{P_1}\right)^2}{l \cdot \left(A_{\max}/\pi P_1\right)}\right) + \left(\tau \cdot \frac{1+\left(\frac{P-P_0}{P_1}\right)^2}{l \cdot \left(A_{\max}/\pi P_1\right)} + \frac{MAP_{x-1}}{Q_{x-1}} - z_L\right) \cdot \sqrt{\frac{\rho}{A_{\max}\left[0.5+\frac{1}{\pi}\arctan\left(\frac{P-P_0}{P_1}\right)\right] \cdot \frac{A_{\max}/\pi P_1}{1+\left(\frac{P-P_0}{P_1}\right)^2}}}} \cdot P$$

$$Q = \frac{\tau \cdot \frac{1+\left(\frac{P-P_0}{P_1}\right)^2}{l \cdot \left(A_{\max}/\pi P_1\right)} + \frac{MAP_{x-1}}{Q_{x-1}} - \sqrt{\frac{\rho}{A_{\max}\left[0.5+\frac{1}{\pi}\arctan\left(\frac{P-P_0}{P_1}\right)\right] \cdot \frac{A_{\max}/\pi P_1}{1+\left(\frac{P-P_0}{P_1}\right)^2}}}}{\frac{MAP_{x-1}}{Q_{x-1}} \sqrt{\frac{\rho}{A_{\max}\left[0.5+\frac{1}{\pi}\arctan\left(\frac{P-P_0}{P_1}\right)\right] \cdot \frac{A_{\max}/\pi P_1}{1+\left(\frac{P-P_0}{P_1}\right)^2}}} + \frac{MAP_{x-1}}{Q_{x-1}} \cdot \tau \cdot \frac{1+\left(\frac{P-P_0}{P_1}\right)^2}{l \cdot \left(A_{\max}/\pi P_1\right)} - \frac{\rho}{A_{\max}\left[0.5+\frac{1}{\pi}\arctan\left(\frac{P-P_0}{P_1}\right)\right] \cdot \frac{A_{\max}/\pi P_1}{1+\left(\frac{P-P_0}{P_1}\right)^2}}} \cdot P$$

Dependent variables of the relations to calculate CVP

-Equation of EF:

$$EF = x + y \cdot EFrest + z \cdot DBP$$

Table 9: Independent variables of EF equation

	x	*y*	*z*	R^2
EF	1.741 *	0.881	0.104	0.964

* Independent variable does not significantly contribute to predict the dependent variable ($p>0.05$).

-Equation to calculate CVP with the newly developed relation:

$$CVP = a + b \cdot \frac{SV}{EF} + c \cdot HR$$

-Equation to calculate CVP with the relation proposed by Gagné and colleagues (2007):

$$CVP = a + b \cdot SV$$

Table 10: Independent variables of both relations to calculate CVP

Subject	Test	New Relation								Old Relation					
		Doppler				Finometer				Doppler			Finometer		
		a	b	c	R^2	a	b	c	R^2	a	b	R^2	a	b	R^2
A															
	1	13.406	0.0146	-0.00639	0.939	15.114	0.00482*	-0.00743	0.925	-1.042	0.126	0.707	1.088*	0.0888	0.056
B		10.381	0.05	-0.174	0.407	5.673	0.0492	-0.1	0.295	-0.318*	0.0782	0.383	-1.019	0.0775	0.286
	1	-17.167	0.146	0.142	0.603	-23.75	0.223	0.0663	0.470	-8.429	0.187	0.592	-19.24	0.29	0.457
	2	-0.999*	0.0774	-0.0645	0.632	-7.69	0.0881	0.0103*	0.634	-5.625	0.115	0.617	-7.291	0.122	0.623
C		2.949	0.0421	-0.0855	0.420	5.621	0.0332	-0.113	0.381	-3.402	0.0769	0.402	-4.649	0.0892	0.365
	1	1.597*	0.0543	-0.0998	0.555	-6.031	0.0799	-0.0392	0.503	-5.718	0.0969	0.506	-9.916	0.128	0.488
	2	0.501*	0.0411	-0.0247	0.311	-5.281	0.0914	-0.021	0.723	-1.18	0.0573	0.308	-6.94	0.123	0.722
D		-2.903	0.0882	-0.00463*	0.647	0.149*	0.0958	-0.0958	0.612	-2.956	0.122	0.533	-9.69	0.192	0.482
	1	-7.161	0.112	0.0439	0.772	-5.735	0.148	-0.0734	0.762	-3.793	0.122	0.772	-14.04	0.233	0.744
	2	-7.65	0.107	0.0446	0.510	-19.06	0.188	0.0649	0.668	-5.332	0.14	0.518	-14.47	0.234	0.662
	3	-1.511*	0.0878	-0.038	0.554	1.782*	0.086	-0.112	0.412	-4.306	0.157	0.558	-13.77	0.266	0.638
E		-3.855	0.0925	-0.024	0.433	-7.986	0.122	-0.0194	0.366	-5.341	0.129	0.412	-8.591	0.162	0.324
	1	-10.371	0.121	0.0558	0.482	-15.23	0.161	0.0476	0.375	-6.769	0.161	0.479	-11.76	0.213	0.375
	2	-1.957	0.0866	-0.0629	0.586	-8.718	0.116	-0.0133*	0.517	-6.595	0.132	0.578	-9.519	0.159	0.500
F		4.142	0.0659	-0.106	0.480	5.127	0.068	-0.125	0.482	-4.443	0.121	0.406	-5.923	0.139	0.354
	1	9.834	0.0526	-0.141	0.790	-4.016	0.142	-0.0724	0.648	-6.173	0.17	0.425	-13.52	0.274	0.622
	2	-3.652	0.111	-0.0524	0.772	-5.965	0.138	-0.0616	0.780	-8.687	0.174	0.769	-12.86	0.227	0.761
	3	-8.57	0.112	-0.0123*	0.749	-2.536	0.108	-0.104	0.736	-9.86	0.203	0.755	-12.25	0.23	0.668
	4	-8.708	0.11	0.00409*	0.679	-6.145	0.122	-0.0523	0.772	-8.564	0.183	0.684	-12.58	0.241	0.757
	5	-0.976*	0.121	-0.138	0.592	-11.84	0.198	-0.11	0.724	-13.587	0.195	0.567	-22.35	0.288	0.706
G		15.015	0.0159	-0.227	0.447	18.032	0.00167*	-0.257	0.465	-0.0791*	0.0651	0.279	1.075	0.0467	0.145
	1	-5.774	0.131	0.012*	0.786	-14.35	0.178	0.1	0.806	-4.99	0.17	0.795	-6.295	0.19	0.781
	2	-3.801	0.0913	-0.0513	0.795	-4.631	0.102	-0.0735	0.773	-7.844	0.138	0.798	-11.29	0.167	0.767
H		6.615	0.0668	-0.0967	0.747	10.509	0.043	-0.139	0.611	-0.893	0.137	0.563	-2.127	0.137	0.400
	1	5.736	0.0611	-0.077	0.656	6.223	0.0622	-0.0979	0.632	-0.417*	0.114	0.615	-3.925	0.153	0.536
	2	4.15	0.053	-0.000738*	0.404	15.504	-0.0219	-0.0571	0.049	4.087	0.0841	0.405	12.79	-0.034	0.032
General		-0.35	0.0557	0.004	0.297	-0.903	0.0576	0.00254	0.259	0.291	0.0721	0.242	-0.795	0.0794	0.232

* Independent variable does not significantly contribute to predict the dependent variable ($p>0.05$).

References

Azabji Kenfack M, Lador F, Licker M, Moia C, Tam E, Capelli C, Morel D, Ferretti G. Cardiac output by Modelflow method from intra-arterial and fingertip pulse pressure profiles. *Clin Sci (Lond). 106:365-369, 2004*

Boehmer RD, Continuous real-time, non-invasive monitor of blood pressure: Peñáz methodology applied to the finger. *J Clin Monit 3: 282-287, 1987*

Bogert LW, Harms MP, Pott F, Secher NH, Wesseling KH, van Lieshout JJ. Reconstruction of brachial pressure from finger arterial pressure during orthostasis. *J Hypertens 22:1873-1880, 2004*

Bogert LWJ, van Lieshout JJ. Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. *Review Article. Exp Physiol 90: 437-446, 2005*

Bos WJW, van Goudoever J, van Montfrans GA, van den Meiracker AH, Wesseling KH. Reconstruction of brachial artery pressure from noninvasive finger pressure measurements. *Circulation 94: 1870-1875, 1996*

Butler GC, Yamamoto Y, Hughson RL. Heart rate variability and fractal dimension during orthostatic challenges. *J Appl Physiol 75:2602-2612, 1993*

de Vaal JB, de Wilde RBP, van den Berg PCM, Schreuder JJ and Jansen JRC. Less invasive determination of cardiac output from the arterial pressure by aortic diameter-calibrated pulse contour. *Br J Anaesth 95: 326–331, 2005*

Dyson KS, Shoemaker JK, Hughson RL. WISE-2005: Bias in Modelflow estimates of cardiac output with vasoactive drugs, static hand grip, tilt and lower body negative pressure can be explained by dynamic changes in vascular resistance. *Unpublished*

Faisal A, Beavers KR, Robertson AD, Hughson RL. Prior moderate and heavy exercise accelerate oxygen uptake and cardiac output kinetics in endurance athletes. *J Appl Physiol: In press, 2009*

Finometer™ User's Guide *FMS, Finapres Medical Systems BV, Version 1.21, 2003*

Fleg JL. Alterations in cardiovascular structure and function with advancing age. *Am J Cardiol 57:33C-44C, 1986*

FMS website. http://www.finapres.com/customers/finometer.php, *Finapres Medical Systems (FMS)*

Gagné N, Fischer D, Greaves DK, Hughson RL. WISE-2005: Developing a non-invasive method to monitor cardiovascular deconditioning. *J Gravit Physiol 14: P137-138, 2007*

Gauer OH and Sieker HO. The continuous recording of central venous pressure changes from an arm vein. *Circ Res 4: 74-78, 1956*

Gizdulich P, Prentza A, Wesseling KH. Models of brachial to finger pulse wave distortion and pressure decrement. *Cardiovasc Res 33: 698-705, 1997*

Guelen I, Westerhof BE, van der Sar GL, van Montfrans GA, Kiemeneij F, Wesseling KH, Bos WJ. Validation of brachial artery pressure reconstruction from finger arterial pressure. *J Hypertens. 26:1321-1327, 2008*

Harms MPM, Wesseling KH, Pott F, Jenstrup M, van Goudoever J, Secher NH, van Lieshout JJ. Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. *Clin Sci 97:291–301, 1999*

Heerman JR, Segers P, Roosens CD, Gasthuys F, Verdonck PR, Poelaert JI. Echocardiographic assessment of aortic elastic properties with automated border detection in an ICU: in vivo application of the arctangent Langewouters model. *Am J Physiol Heart Circ Physiol 288:H2504-H2511, 2005*

Hirschl MM, Binder M, Gwechenberger M, Herkner H, Bur A, Kittler H, Laggner AN. Noninvasive assessment of cardiac output in critically ill patients by analysis of the finger blood pressure waveform. *Crit Care Med. 25:1909-1914, 1997*

Houtman S, Oeseburg B, Hopman MT. Non-invasive cardiac output assessment during moderate exercise: pulse contour compared with CO_2 rebreathing. *Clin Physiol. 19:230-237, 1999*

Idema RN, van den Meiracker AH, Imholz BP, Man in 't Veld AJ, Settels JJ, Ritsema van Eck HJ, Schalekamp MA. Comparison of Finapres non-invasive beat-to-beat finger blood pressure with intrabrachial artery pressure during and after bicycle ergometry. *J Hypertens Suppl. 7:S58-59, 1989*

Imholz BP, Settels JJ, van der Meiracker AH, Wesseling KH, Wieling W. Non-invasive continuous finger blood pressure measurement during orthostatic stress compared to intra-arterial pressure. *Cardiovasc Res. 24:214-221, 1990*

Jagomägi K, Talts J, Raamat R, Länsimies E. Continuous non-invasive measurement of mean blood pressure in fingers by volume-clamp and differential oscillometric method. *Clin Physiol. 16:551-560, 1996*

Jagomägi K, Raamat R, Talts J. Effect of altering vasoactivity on the measurement of finger blood pressure. *Blood Press Monit. 6:33-40, 2001*

Jansen JR., Schreuder JJ, Mulier JP, Smith NT, Settels JJ, Wesseling KH. A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth 87:212–222, 2001*

Jellema WT, Wesseling KH, Groemeveld ABJ, Stouteribeek CP, Thijs LG, van Lieshout JJ. Continuous cardiac output in septic shock by simulating a model of the aortic input impedance. A comparison with bolus injection thermodilution. *Anesthesiology 90:1317-1328, 1999*

Karamanoglu M, Feneley MP. On-line synthesis of the human ascending aortic pressure pulse from the finger pulse. *Hypertension 30:1416-1424, 1997*

Kitano A, Shoemaker JK, Ichinose M, Wada H, Nishiyasu T. Comparison of cardiovascular responses between lower body negative pressure and head-up tilt. *J. Appl Physiol 98: 2081-2086, 2005*

Langwouters GJ, Wesseling KH, Goedhard WJA. The static properties of 45 human thoracic and 20 abdominal aortas in vitro and the parameters of a new model. *J. Biomech 17:425-435, 1984*

Langwouters GJ, Wesseling KH, Goedhard WJA. Age-related changes in visoelasticity of normal and arteriosclerotic human aortas. *In: Biomechanics: Current Interdisciplinary Research, edited by S. M. Perren and E. Schneider. Dordrecht: Nijhoff, 1985*

Langewouters GJ, Zwart A, Busse R, Wesseling KH. Pressure-diameter relationships of segments of human finger arteries. *Clin Phys Physiol Meas 7:43-56, 1986*

Levine BD, Zuckerman JH, Pawelczyk JA. Cardiac atrophy after bed-rest deconditioning: a nonneural mechanism for orthostatic intolerance. *Circulation 15; 96:517-525, 1997*

Low PA. Prevalence of orthostatic hypotension. *Clin Auton Res 18; 8-13, 2008*

Matsukawa K, Kobayashi T, Nakamoto T, Murata J, Komine H, Noso M. Noninvasive evaluation of cardiac output during postural change and exercise in humans: comparison between the modelflow and pulse dye-densitometry. *Jpn J Physiol. 54:153-160, 2004*

Musgrave FS, Zechman FW, and Mainns RC. Change in total leg volume during lower body negative pressure. *Aerospace Med 40:602–606, 1969.*

Nevo E. Constrained optimization of ventricular efficiency in normal and failing hearts. *Am J Physiol 264:H1292-1299, 1993*

O'Rourke MF, Nichols WW. Aortic diameter, aortic stiffness and wave reflection all increase with age and isolated systolic hypertension. *Hypertension 45:652-658, 2005*

Peñáz J. Photoelectric measurement of blood pressure, volume and flow in the finger. *Digest of the international Conference on Medicine and Biological Engineering 104-104, 1973*

Poliner LR, Dehmer GJ, Lewis SE, Parkey RW, Blomqvist CG, Willerson JT. Left ventricular performance in normal subjects: a comparison of the responses to exercise in the upright and supine positions. *Circulation 62:528-534, 1980*

Raamat R, Jagomägi K, Talts J. Different responses of Finapres and the oscillometric finger blood pressure monitor during intensive vasomotion. *J Med Eng Technol. 24:95-101, 2000*

Raamat R, Talts J, Jagomägi K, Kivastik J, Länsimies E, Jurvelin J. Simultaneous application of differential servo-oscillometry and volume-clamp plethysmography for continuous non-invasive recording of the finger blood pressure response to a hand postural change. *J Med Eng Technol 30:139-144, 2006.*

Remington JW, Wood EH. Formation of peripheral pulse contour in man. *J Appl Physiol 9:433-442, 1956*

Remmen JJ, Aengevaeren WR, Verheugt FW, van ver Werf T, Luijten HE, Bos A, Jansen RW. Finapres arterial pulse wave analysis with Modelflow is not a reliable non-invasive method for assessment of cardiac output. *Clin Sci (Lond). 103:143-149, 2002*

Rose JS, Nanna M, Rahimtoola SH, Elkayam U, McKay C, Chandraratna PA. Accuracy of determination of changes in cardiac output by transcutaneous continuous-wave Doppler computer. *Am J Cardiol 54: 1099-1101, 1984*

Rowell LB. Human circulation: regulation during physical stress. *Oxford University Press, New York, USA, 1986*

Rowell LB. Human Cardiovascular Control. *Oxford University Press, New York, USA, 1993*

Segers P, Carlier S, Pasquet A, Rabben SI, Hellevik LR, Remme E, De Backer T, De Sutter J, Thomas JD, Verdonck P. Individualizing the aorto-radial pressure transfer function: feasibility of a model-based approach. *Am J Physiol Heart Circ Physiol. 279: H542-549, 2000*

Silverthorn DU. Human Physiology, an integrated approach, Fourth edition. *Pearson Education Inc, San Francisco, USA, 2007*

Stergiopulos N, Westerhof BE, Westerhof N. Total arterial inertance as the fourth element of the windkessel model. *Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H81–H88, 1999*

Stok WJ, Westerhof BE, Karemaker JM. Changes in finger-aorta pressure transfer function during and after exercise. *J Appl Physiol 101: 1207-1214, 2006*

Swine C. Aging of heart function in man. *Presse Med. 21: 1216-1221, 1992*

van Lieshout JJ, Pott F, Madsen PL, Van Goudoever J, Secher NH. Muscle tensing during standing: effects on cerebral tissue oxygenation and cerebral artery blood velocity. *Stroke 32: 1546–1551, 2001*

van Lieshout JJ, Wesseling KH. Continuous cardiac output by pulse contour analysis? *Br J Anaesth 86:467-469, 2001*

van Lieshout JJ, Toska K, van Lieshout EJ, Eriksen M, Walløe L, Wesseling KH. Beat-to-beat noninvasive stroke volume from arterial pressure and Doppler ultrasound. *Eur J Appl Physiol. 90:131-137, 2003*

Wesseling KH, Settels JJ, van der Hoeven GM, Nijboer JA, Butijn MW, Dorlas JC. Effects of peripheral vasoconstriction on the measurement of blood pressure in a finger. *Cardiovasc Res. 19:139-145, 1985*

Wesseling KH, Jansen JRC, Settels JJ and Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J. Appl. Physiol.* 74*: 2566-2573, 1993*

Wesseling KH, De Wit B, Van derHoeven GMA, Van Goudoever J, Settels JJ. Physiocal, calibrating finger vascular physiology for Finapres. *Homeostasis 36: 67-82, 1995*

Westerhof N, O'Rourke MF. Haemodynamic basis for the development of left ventricular failure in systolic hypertension and for its logical therapy. *J Hypertens 13: 943-952, 1995*

White WB, Berson AS, Robbins C, Jamieson MJ, Prisant LM, Roccella E, Sheps SG. National standard for measurement of resting and ambulatory blood pressures with automated sphygmomanometers. *Hypertension 21:504-509, 1993*