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NONINVASIVE ASSESSMENT OF CARDIAC OUTPUT: A VALIDATION STUDY COMPARING PULSE CONTOUR ANALYSIS WITH IMPEDANCE CARDIOGRAPHY

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ABSTRACT

Accurate assessment of cardiovascular risk is imperative in both clinical and research settings to manage care and analyze research findings. The present study assessed the accuracy of pulse contour analysis from fingertip plethysmography (Nexfin formally known as Finapress) against thoracic impedance cardiography (ICG) in measuring both absolute and changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiac output (CO), stroke volume (SV), and total peripheral resistance (TPR). Validation studies comparing ICG and more invasive methods have shown that it is a reliable method for estimating change in CO. ICG requires patients to undress and/or undergo hair removal. Some studies have suggested that the Nexfin device can accurately index changes in CO without this inconvenience. To our knowledge this is the first study to compare hemodynamic measurements from Nexfin to those obtained with ICG.
On average, the Nexfin SBP value was 12.2 ± 4.1 mmHg higher than the same measurement collected via ICG. For DBP, the discrepancy was 2.7 ± 1.7 mmHg on average. As expected, we observed robust correlations for resting SBP (r = 0.67, P = 0.01) and DBP (r = 0.59, P = 0.03) measured between the two systems. There were no significant correlations for resting TPR, CO, and SV between the two methods. Correlation values ranged from -0.19 to +0.09 (all P's > 0.54). Between-method measurements of SBP and DBP during stress were significantly correlated, while measures of TPR, CO, and SV were uncorrelated. We found a robust correlation between CO change scores collected with the two methods (r = 0.57, P = 0.05). This correlation was not evident for change in TPR and SV. Change in SBP and DBP during stress were

correlated between the two methods (r = 0.85, *P* = 0.0002; r = 0.73, *P* = 0.005 respectively). Our study shows Nexfin is a reliable method of measuring both absolute and change in SBP and DBP. Results confirm previous findings of the accuracy of fingertip plethysmography in measuring changes in CO. However, the systematic variability between methods observed does not make the Nexfin device conducive to critical clinical use.

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Chapter 1

Review of Present Literature

Introduction

Accurate assessment of cardiovascular risk is imperative in both clinical and research settings. Clinicians and researchers alike must be able to rely on devices to give accurate and reliable readings in order to appropriately manage patient care and analyze research findings. With this in mind, the purpose of this paper is to assess the accuracy of the continuous and noninvasive Nexfin device (pulse contour analysis from fingertip plethysmography formally known as Finapress) against thoracic impedance cardiography (ICG) in measuring both absolute and changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiac output (CO), stroke volume (SV), and total peripheral resistance (TPR).

Overview of Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of death in the United States for both males and females ("Heart Disease Facts," 2012). This amounts to approximately 600,000 deaths every year. CVD encompasses many diseases and disorders including coronary artery disease, atherosclerosis, angina, stroke, congestive heart failure, and heart or valve infection ("Heart disease: Definition ", 2011).

Traditional CVD Risk Factors

There are many risk factors for CVD, some that can be modified and some that cannot. Family history, age, and ethnicity cannot be altered; however, tobacco use,

hypertension, high cholesterol, obesity, physical inactivity, diabetes, unhealthy diets, and alcohol abuse can all be addressed for a positive change (World Heart Federation, 2014). In order to measure an individual's risk of CVD, these variables must be considered. The measurements also provide information on the etiology and progression of some independent predictors for CVD. Specifically hypertension, having a BP reading higher than 140/90 mmHg, is an independent risk factor for CVD making it an important and easily measureable parameter for CVD risk assessment ("JNC 7 Express: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,"). Moreover, high BP is directly correlated to negative cardiovascular events in a continuous fashion—the higher one's BP, the more CVD risk. For these reasons, the measurement, understanding, and treatment of hypertension is vital to the prevention and treatment of CVD.

Blood Pressure Measurement and Implications in CVD

In order to appropriately diagnose and treat hypertension, accurate and reliable measurement of BP must occur. The gold standard in noninvasive BP measurement continues to be the auscultatory method that uses the Korotkoff sound technique. It is frequently used in both clinical and research settings. The technique requires occlusion of the brachial artery via an inflatable cuff. As the cuff is slowly deflated, blood flow is reestablished and the sound of pulsating blood against the arterial wall can be heard through a stethoscope held on the location of the artery. At the first sound of pulsating blood, the SBP is recorded from a sphygmomanometer by a trained clinician followed by the DBP when the sound disappears (T. G. Pickering, Hall, J.E., Appel, L.J., Falkner, B.E., Graves, J., Hill, M.N., Jones, D.W., Kurtz, T., Sheps, S.G., Roccella, E.J., 2005).

Unfortunately, the Korotkoff sound method requires a trained technician making its utilization difficult for public health programs and research labs without access to trained individuals. This measurement method tends to underestimate SBP and overestimate DBP when compared to intra-arterial measurement (the gold standard in BP measurement). However, as direct intra-arterial measurement is invasive and requires placement of a catheter, it is not appropriate for those patients outside of the hospital or for routine and public health screenings (Perloff, 1993).

Automated oscillometric techniques have been validated against both the Korotkoff method as well as intra-arterial measurement of BP (Myers, McInnis, Fodor, & Leenen, 2008; Ni et al., 2006; T. G. Pickering, 2002). Unlike the Korotkoff sound technique, this method does not require a trained clinician, as cuff placement is not critical (Ni et al., 2006). The ease of use and automation of the device proves its clinical and research significance, as trained professionals are not always available. It also allows for 24 hour ambulatory monitoring. The oscillometric technique works by measuring the oscillations of pressure in a sphygmomanometer cuff during deflation. The point at which the oscillations have reached their peak corresponds to the mean intra-arterial pressure (T. G. Pickering, Hall, J.E., Appel, L.J., Falkner, B.E., Graves, J., Hill, M.N., Jones, D.W., Kurtz, T., Sheps, S.G., Roccella, E.J., 2005). SBP and DBP are then estimated through an empirically derived algorithm.

The clinical significance of accurate BP measurement is paramount in the diagnosis and monitoring of hypertension. A simple, user-friendly, accurate, and reliable method of BP measurement is a necessity for both clinical evaluation and research purposes.

Hemodynamic Indices and Associated CVD Risk

CO, SV, and TPR are all principal hemodynamic indices for assessing cardiovascular health. CO describes the volume of blood pumped by the heart in one minute of time and is measured in liters (L). It can be calculated indirectly by multiplying SV by heart rate (HR). SV is the volume of blood ejected from the left ventricle in one heartbeat and is measured in milliliters (mL) per heartbeat. TPR measures the amount of resistance the blood experiences while circulating through the body once ejected from the heart. It is measured in peripheral resistance units (PRUs), which are derived from perfusion pressure divided by blood flow per second. TPR can also be calculated indirectly by taking the difference between the mean arterial pressure (MAP) and the ventral venous pressure then dividing by CO. CO, SV, and TPR all contribute to paint the picture of an individual's current cardiovascular health.

Applications of Hemodynamics in the Treatment of Hypertension

Both the volume (reflected by CO and SV) and the resistance to flow of blood (reflected by TPR) affect arterial BP. These hemodynamic indices provide insight into the underlying causes of hypertension and can therefore be analyzed for more effective treatment (Ferrario, Flack, Strobeck, Smits, & Peters, 2010). Typically, patient medication plans are tailored through trial and error. However, if the physician has access to the patient's hemodynamic measurements, a more educated diagnostic approach can be used. For example, if an individual presents with high TPR and normal CO, a medication to promote vasodilatation and disrupt the rennin-angiotensin system such as enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), or calcium channel blockers (CCBs) may be considered for treatment. A beta-blocker (BB) would therefore be

discouraged from use as it would lower HR and the force of the heart's contractions—an ineffective route of BP treatment for this particular case (Smith, Levy, Ferrario, & Group, 2006). Prior knowledge of CO, TPR, and SV could allow physicians to improve patient treatment. However, this individualized approach to BP management requires accurate measurement of underlying hemodynamic indices—testing typically not performed in the average doctor's office. A quick, easy, and accurate measurement technique would provide physicians with valuable information allowing for more effective treatment of hypertension.

Application of Hemodynamics in Left Ventricular Hypertrophy (LVH)

Another important application of hemodynamic indices is in the prevention and treatment of left ventricular hypertrophy (LVH). With increasing TPR, the left ventricle of the heart must work harder to pump blood through the body. The increase in workload eventually leads to muscular hypertrophy and an eventual decrease in effective pumping of the heart. The epidemiological Atherosclerosis Risk in Communities (ARIC) Study found that after a fifteen year follow-up, both men and women with ECG-LVH were more likely to have a CVD event independently of other measured CVD risk factors (Desai, Ning, & Lloyd-Jones, 2012). Prior knowledge of a patient's increase in TPR could initiate more aggressive prophylactic care in order to prevent the development of LVH and potential CVD. A meta-analysis of 50 studies has shown that the medications that lower TPR are those most effective at reversing LVH (Schmieder, Schlaich, Klingbeil, & Martus, 1998). Moreover, regression of LVH has been seen to decrease the likelihood of new-onset heart failure and mortality in hypertensive patients (Larstorp et al., 2012). If high TPR can be identified, monitored, and treated easily through

hemodynamic measurement, LVH can potentially be reversed greatly reducing risk for CVD associated death.

Measurement of Hemodynamic Indices

The usefulness of hemodynamic indices is clear. However for application to patient care, accurate and noninvasive measurement methods are needed. Pulmonary artery catheter (PAC) CO assessment is one of the more accurate hemodynamic measurement methods, but this technique is extremely invasive (Porhomayon, Zadeii, Congello, & Nader, 2012). Trained physicians must insert a pulmonary catheter into the patient; therefore, this method is only warranted for the hospital setting. Other less invasive CO devices frequently used include pulse wave analysis devices, Esophageal Dopplers, and echocardiography. All of these devices have been validated for clinical use, but each one has disadvantages regarding the invasiveness of the device is and the amount of technical expertise required.

Thoracic Impedance Cardiography (ICG)

The accuracy and noninvasiveness of a device that measures hemodynamic indices is imperative for better CVD risk assessment and treatment. ICG measures hemodynamic variables including TPR, CO, and SV, is minimally invasive, and provides continuous measurement. Data gathered from noninvasive ICG can explain blood pressure changes and responses allowing a deeper understanding of cardiovascular reactivity (A. Sherwood, 1993). The use of patients' ICG results in the medicinal management of hypertension has been shown to more effectively reduce BP to normal levels in patients than when ICG results were not consulted by physicians (Ferrario et al.,

2010; Krzesinski, Gielerak, Kowal, & Piotrowicz, 2012; Smith et al., 2006; Ventura, Taler, & Strobeck, 2005).

ICG uses four band electrodes to record changes in electrical impedance across the upper thorax, which allows for calculation of various hemodynamic measures from three main electrical signals: electrocardiogram (ECG), the first derivative of delta Z_o (dZ/dt), and the basal thoracic impedance (Z_o) (see Figure 1 for a visual representation). The ECG and dZ/dt signals present as waveforms and are used to calculate SV, systolic time intervals, and measures of contractility (McFetridge & Sherwood, 1999). The most widely accepted and used equation to calculate SV was developed by Kubicek et. al. in 1966:

$$SV = \rho \times (L/Z_o)^2 \times dZ/dt_{(max)} \times LVET$$

where ρ is blood resistivity; L is the average distance (cm) between the voltage recording electrodes; Z_o is the basal thoracic impedance (Ω); dZ/dt is the highest rate of Z_o decrease in systole, which corresponds to the velocity of the blood being ejected from the left ventricle of the heart; and LVET is the left ventricular ejection time in seconds (McFetridge & Sherwood, 1999).

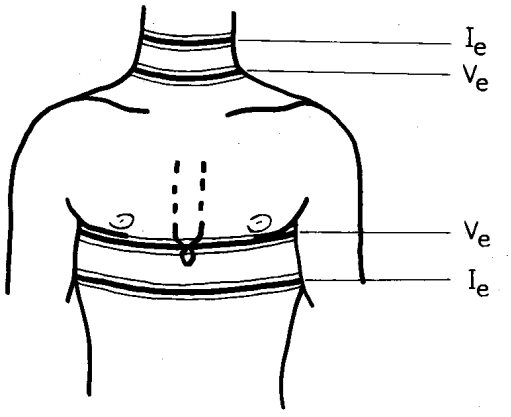

Figure 1: Electrode band placement for thoracic impedance cardiography (A. Sherwood, et. al. , 1990)

ICG has been validated against invasive thermodilution techniques and can be used as an alternative to invasive PACs (Bayram & Yancy, 2009; Parry & McFetridge-Durdle, 2006). It has also been validated against Doppler echocardiography in measuring both CO and SV in patients with suspected coronary artery disease (Scherhag, Kaden, Kentschke, Sueselbeck, & Borggrefe, 2005). A meta-analysis of 112 studies testing the validity of ICG in measuring CO, SV, and other hemodynamic parameters found a reasonable correlation with ICG and standard measurements (Raaijmakers, Faes, Scholten, Goovaerts, & Heethaar, 1999). Studies continue to show that ICG is a reliable method for measuring hemodynamic indices in the research and clinical setting.

ICG has many positive attributes that make it an attractive alternative for more invasive techniques or those that require extensively trained technicians. However, ICG requires an involved setup due to the specificity of the band electrode placement. For some men, hair removal is necessary to ensure proper electrode connectivity, and for all individuals, the patient must undress for the device's application and endure the removal of sticker-like electrodes at the termination of testing. The band electrodes are very sensitive to patient movement, sometimes causing a loss of signal during testing. All of this taken into consideration, a more streamlined and user-friendly device would be useful for hemodynamic measurements. In addition, studies suggest that ICG is not an accurate method for measuring CO and SV in pregnant women, further limiting this method (Moertl, 2012).

Continuous Noninvasive Measurement: The Nexfin Device

New noninvasive finger cuff technology allows for continuous measurement of various cardiovascular indices including BP, CO, SV, and TPR as opposed to traditional

intermittent measurement by other instruments. This new technology is an attractive alternative to ICG as setup simply involves an inflatable finger cuff connected to the device's computer monitor (see Figure 2 for a visual representation). The first generation of continuous noninvasive finger cuff technology appeared in the early 1980s as the Finapres™ device developed by Wesseling et al. (Truijen, van Lieshout, Wesselink, & Westerhof, 2012). This device was later replaced by a new piece of equipment, the Finometer, by Finapres Medical Systems from The Netherlands (Maestri, Pinna, Robbi, Capomolla, & La Rovere, 2005). The most recent generation of finger cuff monitors is the Nexfin developed by BMEYE (Truijen et al., 2012). This technology has been tested against both invasive (Hofhuizen et al., 2010; Lansdorp et al., 2011; Lemson et al., 2009; Martina et al., 2010; Sokolski et al., 2011; Stover et al., 2009) and noninvasive (Akkermans et al., 2009; Bartels et al., 2011; Eeftinck Schattenkerk et al., 2009; Nowak et al., 2011) measures in a variety of populations. Results of studies reveal that noninvasive finger cuff techniques are reliable in identifying relative changes in hemodynamic indices; however, it does not appear to be able to provide reliable absolute values (de Jong, Westerhof, Voors, & van Veldhuisen, 2009). Nevertheless, the simplicity and ease of operation of the Nexfin merit consideration for its use in the research setting when changes in hemodynamic indices (such as stress reactivity) are of specific interest.

The instrument works by measuring the oscillations of pressure in the finger cuff as a result of the arterial pulsation in the finger (T. G. Pickering, 2002). The resulting finger pressure waveform is transformed into a brachial pressure waveform by a transfer function and level correction based off of extensive research ("State-of-the-art

technology," 2013). From the brachial waveform, continuous CO, SV, and TPR values are calculated by a new pulse contour model, Nexfin CO-Trek. Through dividing the area under the systolic portion of the waveform by the aortic input impedance (Z_{in}), beat-to-beat SV can be calculated (Truijen et al., 2012). Z_{in} is estimated through the three-element Windkessel model that consists of peripheral resistance, total arterial compliance, and aortic impedance components (Westerhof, Lankhaar, & Westerhof, 2009). Total arterial compliance is determined primarily from the elasticity of the large arteries. The instrument uses these models to individualize and compute the many hemodynamic indices it measures.

Figure 2: Nexfin finger cuff technology in use ("BMEYE Products: Nexfin ", 2013)

Overview of Present Study

ICG has been used to index changes in cardiac output since the 1960s. Validation studies comparing ICG and more invasive methods have shown that it is a reliable and relatively unobtrusive method for estimating change in CO. However many impedance based systems require patients to remove their shirt so that electrodes can be applied. For men with significant chest hair, ICG cannot be used without shaving. Some studies have suggested that pulse contour analysis from fingertip plethysmography (Nexfin) can

accurately index changes in CO, without the inconvenience of clothing/hair removal. To our knowledge this is the first study to compare hemodynamic measurements from Nexfin to those obtained through impedance cardiography.

Chapter 2

Materials and Methods

Participants

This study included 13 healthy, non-smoking participants with type 2 diabetes. Volunteers were recruited from The Pennsylvania State University campus and surrounding community through fliers, email listservs, radio, newspaper, television advertisements, and information tables at community events.

Participants with self-reported type 2 diabetes, with insulin independence, between 30 and 75 years old (women had to be post-menopausal), and free of all other chronic diseases were recruited. Except for insulin, all type 2 diabetes medications were permitted for use. If medicated, participants were required to be on a stable dose for a minimum of three months before entry into the study. Statins, selective serotonin reuptake inhibitors (SSRIs), and thyroid replacement therapy were also permitted for use. Individuals were excluded from the study if they were taking any oral steroids, hormone replacement therapy, oral contraceptives, or daily aspirin; were on multiple blood pressure lowering medications; had a positive history of CVD or diabetes complications; had any food or latex allergies; or were unwilling to comply to the study requirements. Participants on antihypertensive monotherapy who discontinued use two weeks prior to the study's start under primary care physician approval were allowed to enter the study. Additionally, participants were required to meet the following criteria at in-clinic screening: HbA1c <

7.4%, body mass index (BMI) 18.5 – 45.0, CRP < 10 mg/L, and resting blood pressure < 160/100 mmHg.

Screening

Participants were initially screened for eligibility through telephone interviews, which included questions regarding medical history, medication use, dietary habits, and ability to comply with study procedures. Those who met the initial criteria then completed a clinic visit to confirm eligibility. At this visit, height and weight were obtained to calculate BMI, and a 12-lead ECG and blood draw were completed to evaluate heart health, HbA1c, lipids, and inflammatory status. If the results of any of these tests were found to be outside study guidelines, the participant was excluded from the study and referred for care. Written informed consent was obtained from all participants, and the study was approved by The Pennsylvania State University Institutional Review Board.

Study Design

This study was conducted as part of a larger clinical trial. The larger trial was a randomized, crossover, controlled-feeding protocol with one baseline and two treatment periods. Compliance breaks of 1-4 weeks separated the treatment periods. The data used in this study came from an acute mental stress testing session at baseline (stress visit protocol is described below). Thirty participants completed the overall study; however, only 13 participants underwent testing with the Nexfin device as it was added after the start of the larger clinical trial. Only pre-treatment data is presented here.

Experimental Procedures

The acute mental stress testing session included a 20-minute rest period, two stress tasks, and two 10-minute recovery periods. The participant remained in the seated position and listened to classical music through headphones during both rest and recovery. After 20 minutes of rest, the first stress task performed was the 5-minute Paced Auditory Serial Addition Task (PASAT) where participants were instructed to add together the last two numbers played on an audio recording and state the sum aloud (Gronwall, 1977). Following a 10-minute recovery period, the participants underwent a hand cold pressor task where the right hand was placed in 4°C water for 2.5 minutes. This task was again followed by 10 minutes recovery.

In this testing session, ICG and the Nexfin device were used simultaneously to gather hemodynamic measurements during the PASAT but not the hand cold pressor task due to hand submersion. Also, in 1-4 minute intervals (depending on the task) both systolic (SBP) and diastolic (DBP) blood pressures were measured using an automated oscillometric blood pressure monitor attached to the left arm (Dinamap, Critikon Pro 100, GE Medical Systems). At the same time, ICG using a tetrapolar band configuration with spot ECG electrodes was used to estimate HR and SV (Hutcheson Impedance Cardiograph and the Cardiac Output Program, Bio-Impedance Technology, Inc., Chapel Hill, NC). From this data, CO and TPR were calculated using standard formulae (A. Sherwood, et. al. , 1990). In order to control for the effects of eating on hemodynamic indices, participants ate a standardized meal two hours prior to testing (Sauder, Johnston, Skulas-Ray, Campbell, & West, 2012).

Along with ICG monitoring, the Nexfin finger cuff was placed on the participant's right middle finger in order to measure various beat-to-beat hemodynamic

indices. Resting on an adjustable table, the arm and hand were positioned at heart-level (as according to the device's operating manual) throughout testing (*BMEYE Nexfin HD Operator's Manual,* 2007). Beat to beat measurement by the Nexfin device recorded HR, SV, CO, TPR, SBP, and DBP during the PASAT stress task and during the rest and first recovery period. As the participant's hand was submerged in ice water during the cold pressor stress task, the finger cuff was removed prior to the task and data was not obtained from the Nexfin during this period or the following recovery period.

Statistical Analysis

Analyses were conducted with SAS v. 9.3 (Cary, NC). For the brachial BP measurements obtained by Dinamap, the baseline data are an average of the final 3 readings (one reading per minute) taken during the 20 minute baseline period and the stress data are an average of the 5 readings (one reading per minute) taken during the 5 minute stress period. For the Nexfin data, the baseline data are an average of the final 3 minutes of the 20 minute baseline period and the stress data are an average of the full 5 minutes of the 5 minute stress period.

From this point on, data from the two devices were handled in the same way. Two types of change scores were calculated. The first was the difference (in absolute terms) between the baseline measurements collected by the two systems. Next we calculated reactivity change scores (stress minus resting baseline) for each variable, separately for each device. Distributions were tested for normality and outliers were examined. The following variables required log transformation: baseline TPR, difference in TPR from Nexfin to the standard measurement, and SBP reactivity to stress. We examined Pearson correlations for paired measurements, separately for baseline and

stress. Finally, we tested whether change in hemodynamic parameters during stress were correlated across the two measurement systems. All values are reported as least squares mean ± SEM unless otherwise indicated.

Chapter 3

Results

Correlations between resting measurements collected with Nexfin vs. ICG

On average, the Nexfin SBP value was 12.2 ± 4.1 mmHg higher than the same measurement collected via the Dinamap. For DBP, the discrepancy was 2.7 ± 1.7 mmHg on average. However, Figures 3 and 4 show large variability in the magnitude of this difference in resting BP across individuals. For one participant, the Nexfin recorded a resting SBP that was 55 mmHg higher than the value taken by the Dinamap. When this person's data were removed, the mean discrepancy in SBP (8.8 ± 2.2 mmHg) was reduced by ~30%. Because this study focused on a direct comparison of the two methods, this subject's data were not removed from the correlational analysis. As expected, we observed robust correlations for resting SBP (r = 0.67, P = 0.01) and DBP (r = 0.59, P = 0.03) measured with the two systems. In contrast, there were no significant correlations for resting TPR, CO, and SV collected via the two methods (Table 2). Correlation values ranged from -0.19 to +0.09 (all P's > 0.54).

Baseline Characteristics of Participants		
	Mean	**Range**
Sex (n = 6F, 7M)		
Age (yr)	54.8 ± 6.9	43 – 65
BMI at endpoint of visit	31.5 ± 6.4	22.4 – 42.9

Table 5: Baseline characteristics of participants

Between method correlations for cardiovascular parameters during stress

A similar pattern of correlations was observed during stress measurements as with those at rest. Measurements of SBP and DBP between the two methods were significantly correlated (Table 3), while measures of TPR, CO, and SV were uncorrelated.

Correlation Between Measurements: Resting					
	SBP_N	**DBP_N**	**TPR_N**	**CO_N**	**SV_N**
SBP_ICG	r = 0.67 *P* = 0.0125	---	---	---	---
DBP_ICG	---	r = 0.59 *P* = 0.0345	---	---	---
TPR_ICG	---	---	r = 0.094 *P* = 0.7595	---	---
CO_ICG	---	---	---	r = 0.022 *P* = 0.9442	---
SV_ICG	---	---	---	---	r = -0.19 *P* = 0.5405
Note: SBP=systolic blood pressure, DBP=diastolic blood pressure, TPR=total peripheral resistance, CO=cardiac output, SV=stroke volume _ICG = impedance cardiography; _N = Nexfin					

Table 2: Correlations between resting measurements collected by the two measurement systems

Between-method correlations for change during stress (reactivity)

Because previous studies have shown that the Nexfin is an accurate way to index the change in CO in response to various manipulations, we examined correlations between change scores (stress – baseline) derived from the two systems. We found a robust correlation between CO change scores collected with the two methods (r = 0.57, *P* = 0.05, Table 4). However, this correlation was not evident for change in TPR and SV. Change in SBP and DBP during stress were also correlated between the two methods. The correlation for SBP reactivity was 0.85 (*P* = 0.0002) and for DBP reactivity it was 0.73 (*P* = 0.005).

Correlation Between Measurements: Stress					
	SBP_N	**DBP_N**	**TPR_N**	**CO_N**	**SV_N**
SBP_ICG	r = 0.80 *P* = 0.0011	---	---	---	---
DBP_ICG	---	r = 0.64 *P* = 0.0177	---	---	---
TPR_ICG	---	---	r = 0.14 *P* = 0.6714	---	---
CO_ICG	---	---	---	r = 0.34 *P* = 0.2788	---
SV_ICG	---	---	---	---	r = 0.15 *P* = 0.6324
Note: SBP=systolic blood pressure, DBP=diastolic blood pressure, TPR=total peripheral resistance, CO=cardiac output, SV=stroke volume					

Table 6: Correlations between stress measurements collected by the two measurement systems

Within Subject Change: Reactivity					
	SBP_N	**DBP_N**	**TPR_N**	**CO_N**	**SV_N**
SBP_ICG	r =0.85 *P* = 0.002	---	---	---	---
DBP_ICG	---	r =0.73 *P* = 0.005	---	---	---
TPR_ICG	---	---	r =0.57 *P* = 0.05	---	---
CO_ICG	---	---	---	r =0.04 *P* = 0.90	---
SV_ICG	---	---	---	---	r =0.10 *P* = 0.75
Note: SBP=systolic blood pressure, DBP=diastolic blood pressure, TPR=total peripheral resistance, CO=cardiac output, SV=stroke volume					

Table 7: Correlations between hemodynamic response to stress (reactivity change scores) collected by the two measurement systems

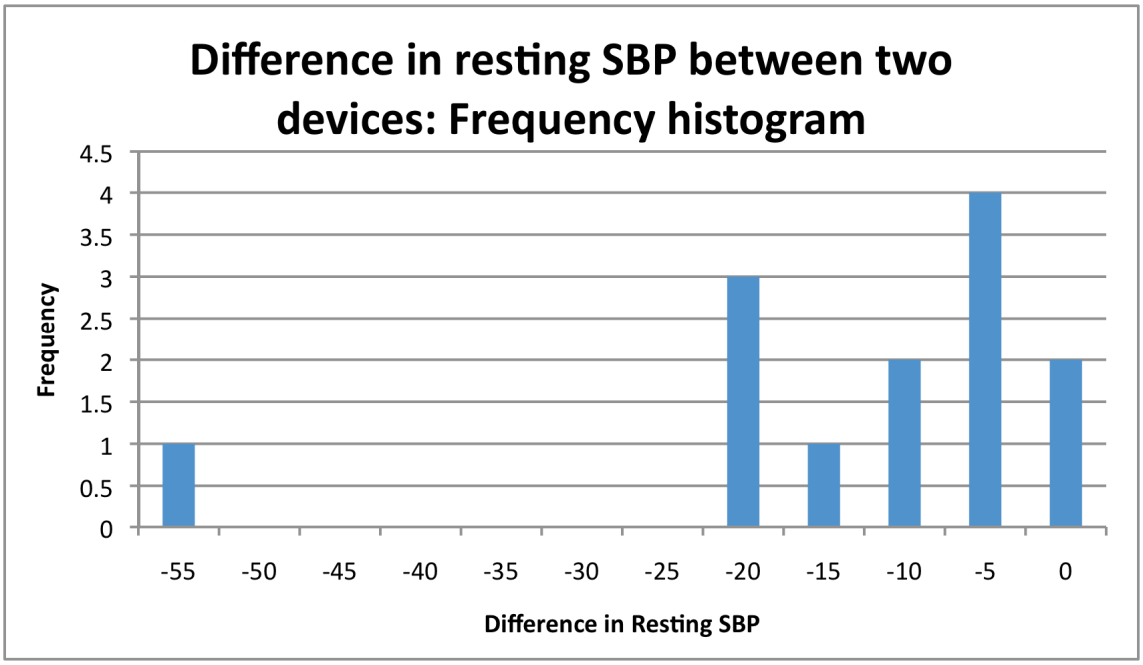

Figure 3: Differences in resting SBP between two devices: Frequency histogram

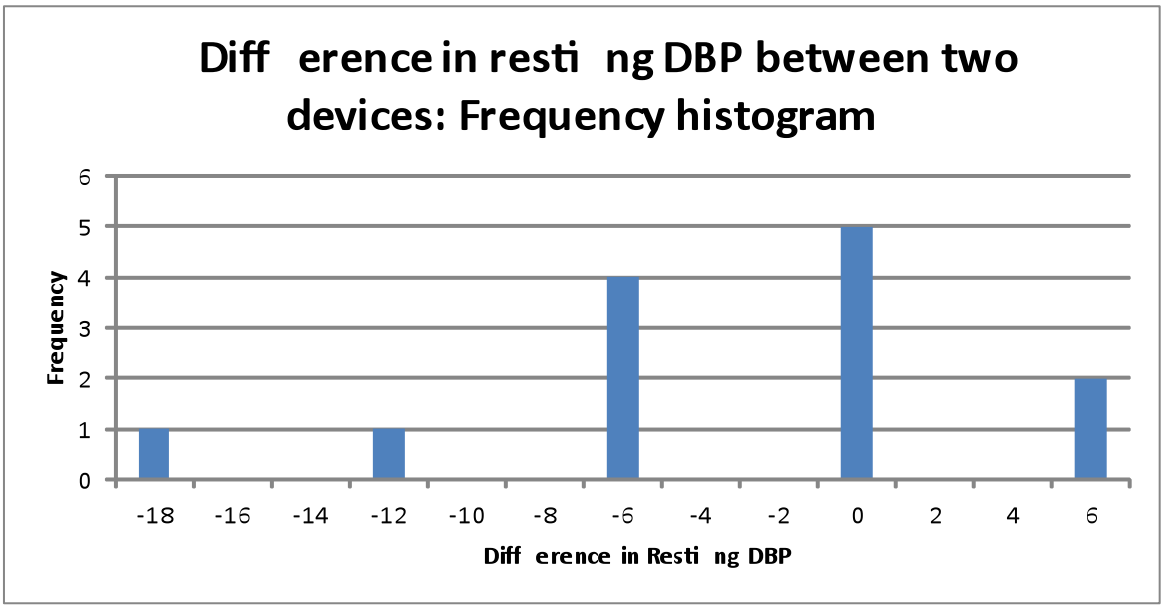

Figure 4: Difference in resting DBP between two devices: Frequency histogram

Chapter 4

Discussion

In this study, data from 13 participants measured at periods of rest and stress illustrate robust correlations between ICG and Nexfin devices in measuring absolute SBP and DBP and changes in SBP, DBP, and CO. Though correlated, there was a high degree of systematic discrepancy between the two forms of BP measurement. Based on this data, the noninvasive and continuous Nexfin device may be a feasible option for measurement of BP and change in CO in future research applications but not for clinical use.

To our knowledge, our study is the first to compare hemodynamic data from ICG and Nexfin. The Nexfin device was validated against inert gas rebreathing, PAC, esophageal Doppler, intra-arterial measurement, and transpulmonary thermodilution for measuring absolute measures of CO (Ameloot et al., 2013; Bartels et al., 2011; Bubenek-Turconi, Craciun, Miclea, & Perel, 2013; Chen et al., 2012; Stover et al., 2009). Our data do not support these findings. However, we documented the validity of the Nexfin in measuring changes in hemodynamic indices including changes in SBP, DBP, and CO replicating findings from past studies on Nexfin validation of hemodynamic change (Bubenek-Turconi et al., 2013; Chen et al., 2012). However, it is important to note that most studies reported high levels of percent error (ratio of the average differences between the Nexfin and the "gold standard" methodology employed in each protocol), ranging from 29-39% (Bubenek-Turconi et al., 2013; Chen et al., 2012; Stover et al., 2009; van der Spoel, Voogel, Folkers, Boer, & Bouwman, 2012). Nevertheless, the

supporting research for accurate monitoring of changes in CO via Nexfin could have implications in methods for monitoring cardiovascular stability and reactivity.

A device that constantly (from heart beat to heart beat) and accurately measures BP in such a noninvasive manner is useful in both the clinical and research setting. The Nexfin is also an attractive option as it is user-friendly and does not require a highly trained technician for its use. However, due to the variability between participants' Nexfin and ICG measurements and the Nexfin's accurate measurement of only a limited number of indices, the device may not be the best investment for clinical care. However, the ease in use and continuous nature make the Nexfin an attractive alternative in the research setting where time, technical expertise, and subject comfort are of top priority. Also, robust correlations between the Nexfin and ICG in absolute and changes in SBP and DBP illustrate the Nexfin's benefits for future studies investigating BP and BP reactivity (defined as within subject change in response to stressors, drugs, and other interventions).

Our study is not without limitations. Only 13 participants taken from the larger study could be monitored by both ICG and Nexfin during testing, leading to a small sample size. Also due to the nature of the Nexfin device, data could not be obtained during the cold hand pressor task, as the task requires the submersion of the participant's hand under water. In addition, the gold standard for CO measurement is not ICG, although ICG has been validated against more invasive measures. For psychophysiologists interested in unobtrusive measurement, the Nexfin may be a good substitute for ICG. More accurate techniques such as pulmonary artery catheterization should be used in future research to investigate and validate the Nexfin device.

Although these findings are useful for future research on hemodynamic monitoring, the amount of variability in the Nexfin data when compared to the Dinamap/ICG measurements cannot be ignored. In fact, for one subject, the SBP measured by Nexfin was 55 mmHg higher than with the Dinamap device. In settings where absolute accuracy is needed for patient assessment (as in the Intensive Care Unit), the Nexfin would not be an appropriate device. However, if the monitoring of hemodynamic shifts in noncritical patients or research participants is needed via a noninvasive manner, the Nexfin's use could be warranted. This is especially true if researchers are interested in changes or stability in SBP, DBP, or CO. Further research is necessary to confirm the Nexfin device's reliability in measuring both absolute and changes in various hemodynamic indices.

Chapter 5

Conclusions

This validation study confirmed earlier work showing that the Nexfin's assessment of change in system hemodynamics is well correlated with changes recorded by other methods. We hasten to offer an additional caveat: one participant exhibited a substantial difference in SBP (55 mmHg) between the automated brachial device and the Nexfin. A calibration procedure may be required to better understand how closely brachial BP tracks with BP recording via Nexfin. Future research should investigate the Nexfin's validity in measuring other indices including heart rate variability. Also, future validation studies should utilize a more diversified subject sample as this study only included Type II insulin-independent diabetics. The validation of the Nexfin device will come with great benefits when other methods such as ICG would not be appropriate such as in pregnant populations.

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