A novel operator-independent noninvasive device for assessing arterial reactivity

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\textbf{ABSTRACT}

Background: Endothelial dysfunction is associated with increased risk of cardiovascular disease (CVD). Currently available noninvasive methods of measuring endothelial function have limitations. We tested a novel device that provides an automated measurement of the difference between baseline and post-ischemic, hyperemia-induced, brachial arterial compliance, a phenomenon known to be endothelium-dependent. The association between the calculated index, Flow-mediated Compliance Response (FCR), and established CVD risk indices was determined.

Methods: Adults with CVD risk factors or known coronary artery disease (CAD) were enrolled. Framingham Risk Score (FRS) was calculated and presence of metabolic syndrome (MetSyn) was assessed. Carotid artery plaques were identified by ultrasound. Cardiorespiratory fitness was assessed by 6-minute walk test (6MWT). FCR was measured using the device.

Results: Among 135 participants, mean age 49.3 +/- 17.9 years, characteristics included: 48% female, 7% smokers, 7% CAD, 10% type 2 diabetes, 34% MetSyn, and 38% with carotid plaque. Those with MetSyn had 24% lower FCR than those without (p < 0.001). Lower FCR was associated with higher FRS percentile (r = -0.29, p < 0.001), more MetSyn factors (r = -0.30, p < 0.001), more carotid plaques (r = -0.32, p = 0.01), and lower 6MWT (r = -0.34, p < 0.0001).

Conclusion: FCR, an index of arterial reactivity obtained automatically using a novel, operator-independent device, was inversely associated with established CVD risk indices, increased number of carotid plaques, and lower cardiorespiratory fitness. Whether measuring FCR could play a role in screening for CVD risk and assessing whether endothelial function changes in response to treatments aimed at CVD risk reduction, warrants further study.

1. Introduction

Endothelial dysfunction is widely considered to be a common pathway by which risk factors lead to atherosclerosis, and is one of the earliest measurable indicators of cardiovascular disease (CVD) [1]. Dysfunction of the endothelium has been shown to be an early marker of future adverse cardiovascular events in patients with and without CVD [2-6]. Hence, there has been much interest in the potential clinical utility of a noninvasive tool that could assess endothelial function. The technique most often used in clinical research to measure endothelial function, flow-mediated dilation (FMD) measures brachial arterial dilation by ultrasound in response to a hyperemic shear stress stimulus...
2. Methods

The Cordex SmartCuff™ (Fig. 1) is a non-invasive and operator-independent device that measures blood pressure and the post-occlusion, hyperemia-induced, time-varying, arterial compliance without requiring disposable and expensive peripheral sensors. The system consists of 1) a standard blood pressure cuff coupled to a pulse oximeter, and main control unit. The device provides arterial compliance measurements at 0, 30, 60, 90, and 180 min. At visit 2, participants completed a six-minute walk test [34] as an objective measure of fitness.

Fig. 1. Cordex SmartCuff™ System which includes a standardized blood pressure cuff, pulse oximeter, and main control unit.

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2.1. Inclusion/Exclusion criteria

Participants were eligible for inclusion in the study if they were at least 18 years of age, not pregnant, and not breastfeeding. Individuals with various CVD risk factors and with known coronary artery disease (CAD) (prior infarction, percutaneous coronary intervention, coronary bypass surgery, or high coronary artery calcium score), were enrolled. Exclusion criteria included: use of long-acting nitrates or insulin, diagnosis of non-ischemic cardiomyopathy, known systemic inflammatory disease such as rheumatoid arthritis, skin sensitivity precluding use of electrocardiogram electrodes, infection in the preceding week or temperature > 38 °C, upper extremity pathology such as arteriovenous fistula or shunt, and participation in any other ongoing device or clinical trial. Participants were also excluded if they were unwilling or unable to: 1) fast for 6 hours prior to each visit, 2) discontinue tobacco use 12 hours prior to each study visit, 3) withhold all over-the-counter medications and supplements the morning of each visit, 4) refrain from exercise for 24 hours before each study visit, or 5) refrain from the use of the following medications for 7 days prior to study visits: vasoactive agents such as decongestants (e.g. pseudoephedrine), recreational drugs (e.g. marijuana, cocaine, amphetamines), or phosphodiesterase-5 inhibitors used in erectile dysfunction (e.g. sildenafil, vardenafil, tadalafil).

2.2. Measuring the flow-mediated compliance response score

The device (SmartCuff™, Cordex Medical Systems) uses the platform of segmental plethysmography and oscillometry through a novel proprietary algorithm to quantify repeated instantaneous measurements of arterial compliance taken at a baseline condition and following a 5-minute reactive hyperemia condition. The device provides arterial compliance measurements over the entire transmural pressure range where the artery diameter spans from complete collapse to fully open. Using fundamentals of segmental plethysmography [31] and oscillometry [32], the blood pressure cuff is converted into a calibrated volume sensor providing accurate arterial compliance values in response to the cumulative shear stimulus [33]. The area between the two curves (Fig. 2) in the positive arterial transmural pressure range is calculated and is displayed as a metric referred to as the FCR.

2.3. Assessment of FCR repeatability

To clinically validate the FCR score reproducibility, a cohort of 20 of the participants underwent a series of SmartCuff™ measurements at 0, 45, and 90 min. Descriptive statistics and the intra-subject, intra-day coefficient of variation was calculated from the three FCR scores. The same guidelines for fasting, avoiding drugs with nitrates, not smoking, and avoiding exercise were used for the repeatability testing. The within-subject standard deviation (SD) was used to estimate the repeatability of the intra-day measurements. To estimate the within-subject SD, we fit a one-way analysis of variance (ANOVA) model to the data containing the repeat measurements made on participants.

2.4. Baseline data and FCR measurements

Eligible participants were invited for two visits separated by 1–7 days. At visit 1, an initial screening was completed. Compliance with pre-visit instructions on diet, medications, smoking, and activity were reviewed. Anthropometric data including height, weight, and waist circumference were obtained and a blood draw was performed to obtain fasting lipids and glucose. Smoking status in the past 12 hours was assessed using a carbon monoxide breath analyzer. Participants then underwent FCR measurements using the SmartCuff™. At visit 2, participants completed a six-minute walk test [34] as an objective measure of fitness.

The SmartCuff™ measurements were performed using a
standardized protocol. Participants were placed in a quiet, temperature-controlled room on a comfortable exam table with the head slightly elevated. The left arm was extended and comfortably immobilized at heart level. A blood pressure cuff attached to the device was placed on the arm and the SpO\textsubscript{2} finger sensor was placed on a finger of the ipsilateral hand. Then baseline and hyperemia measurements were obtained. Baseline measurements were achieved by pressing the start button which automatically inflated the cuff to a suprasystolic pressure. This suprasystolic pressure was confirmed through dissipation of the pulse signal at the finger sensor. Once this suprasystolic pressure was reached, the cuff pressure automatically decreased at an approximate rate of 2–3 mmHg/s as data acquisition took place from the suprasystolic pressure to 20 mmHg to calculate baseline arterial compliance. Once the cuff reached 20 mmHg, it automatically inflated again to a suprasystolic pressure which was maintained for 5 min, following which the cuff pressure automatically decreased at a rate of 2–3 mmHg/s. Data acquisition also took place during the slow constant pressure descent to 20 mmHg cuff pressure to calculate the hyperemic arterial compliance. The data obtained during the 2–3 mmHg/s rate of cuff blood pressure descent of both the baseline and hyperemia tests was used to calculate the FCR.

2.5. Measures of CAD burden and CVD risk factors

Using demographic, anthropometric, behavioral and biological measurements, the Framingham Risk Score [35] was calculated. Metabolic syndrome (MetSyn) was defined as having 3 of the 5 component risk factors: large waist circumference (>40 in. in men, >35 in. in women), elevated triglycerides (≥150 mg/dL), low high-density lipoproteins (<40 mg/dL in men and <50 mg/dL in women), elevated blood pressure (≥130/≥85 mmHg), and elevated fasting blood sugar (≥110 mg/dL) [36]. Cardiorespiratory fitness was assessed by a standard 6-minute walk test (6MWT) [34].

Carotid ultrasound was used to measure carotid artery plaque. A Toshiba Aplio Ultrasound System with a linear array transducer (PL-704) that has a frequency range from 4.8 – 11.0 MHz was used to obtain carotid images. From a supine position, transverse and longitudinal images of both carotid arteries are obtained from anterior, lateral, and posterior angles to assess for plaque (a focal area of wall thickening 50% thicker than the neighboring intima media thickness and/or ≥ 1.5 mm). Additional B-mode ultrasound images of the distal centimeter of the right common carotid artery and the proximal centimeter of the right internal carotid artery segments were recorded digitally as 3–5 cardiac cycle beat loops with emphasis on the far wall for offline measurement. Semi-automatic edge detection software was used with 3 readings averaged for intima media thickness measurement and plaque scoring. An experienced vascular medicine physician confirmed the presence or absence of carotid plaque in all subjects.

2.6. Statistical analysis

Descriptive statistics were used to calculate univariate summary statistics for each variable. Depending on the type of variable, we calculated mean ± SD and summary distributions. Depending on types of variables involved, the associations of the FCR and CVD risk markers were assessed using linear regression models for continuous or categorical responses.

3. Results

Among 135 participants, the mean age was 49.3 ± 17.9 years, 47% were female, 7% were smokers, 7% had known CAD, 10% had type 2 diabetes mellitus, and 34% had MetSyn. Carotid plaque was found in 38% of participants. Table 1 shows the demographics and clinical characteristics of the participants. The test–retest coefficient of variability between FCR values was 15.33% (10.81 to 19.33, 95% CI).

Table 2 shows the correlation between known CVD risk factors and FCR score. Those with MetSyn had a 24% lower FCR score than those without, \( p < 0.001 \). Using bivariate analysis, a lower FCR score was associated with a higher FRS percentile, \( \rho = -0.29, p < 0.001 \) (Fig. 3); a higher number of MetSyn factors, \( \rho = -0.30, p < 0.001 \) (Fig. 4); a higher number of carotid plaques, \( \rho = -0.22, p = 0.01 \) (Fig. 5); and with a lower 6MWT, \( \rho = 0.34, p < 0.0001 \).

4. Discussion

We tested a noninvasive, automated, operator-independent device that measures changes in arterial compliance in response to gradated
increases in post-ischemic flow. The main finding was that the device’s FCR score, was associated with established CVD risk indices. A lower FCR score was associated with a higher number of carotid plaques, the presence of MetSyn, a higher number of MetSyn risk factors, a higher FRS percentile, and a lower 6MWT.

It is well-established that arterial compliance is modulated in part by smooth muscle relaxation in response to endothelial release of nitric oxide [22–26]. Further, it has been shown that compliance increases in the setting of higher flow [22]. A small study by Heron and colleagues demonstrated decreased compliance of the radial arteries in the setting of reactive hyperemia after 5 minutes of brachial artery occlusion in hypertensive patients compared to matched controls [37]. The technique presented in this study offers a non-invasive, operator-independent modality of assessing instantaneous changes in brachial artery compliance during post-ischemic hyperemia. It also incorporates the established property that the arterial response to hyperemia is related to the time-integral of the shear stress stimulus, not just one time point of shear [38]. The observed relationship between the FCR score and known CVD risk factors found in this study suggests that the device may have the potential to identify individuals at increased risk of CVD.

Wide ranges of FMD reproducibility have been reported in the literature, with values as high as 50% in a cohort of healthy patients [13]. While this has been improved upon in subsequent studies, improving reproducibility depends on rigorous, standardized protocols [39,40]. The FCR score has a coefficient of variation of 15.33% which is well within the established goal for clinically applicable medical devices.

Evaluation of endothelium-dependent changes in arterial compliance and its response to treatment in patients at risk for CVD has potential to augment current methods of clinical assessment. As noted by Deanfield and colleagues [41], future work should focus on the predictive value of measures of endothelial function compared to established risk factors, the applicability to the general population, and development of an appropriate testing profile. Much of the current work on endothelial function has focused on evaluation and response in
patients with known CVD. Assessment of subclinical atherosclerosis may be a useful tool to evaluate and mitigate disease progression.

EndoPat™ and Vendys® are two automated devices on the market that assess microvascular arterial reactivity. Past studies indicate that information on clinical risk provided by microvascular function is complementary to information provided by macrovascular function. The EndoPat™ uses pressure sensors at the fingertip to assess pulse wave amplitude (PWA). It calculates the change in PWA that occurs in response to the hyperemia in the fingertip that follows the immediate release of a 5-minute wrist occlusion. Accurate measurements depend on finger-cuff probe placement and thus are impacted by fingernail length and digit deformities. Probes are also single use. The Vendys® uses digital thermal monitoring via temperature sensors at the fingertip, to assess temperature changes in the fingertip that occur with reactive hyperemia after the release of a 5-minute arm occlusion. The temperature changes reflect changes in fingertip blood flow and therefore microvascular dilation. The need to achieve a baseline digit temperature to improve device accuracy is one limitation of this method.

With FMD, measuring brachial artery diameter changes requires ultrasound equipment, is dependent on a highly trained technologist, and is subject to substantial measurement variability.

In comparison, the SmartCuff™ integrates the stepwise changes in brachial artery compliance that follows the graded release of a 5-minute upper arm occlusion. It is the first user-independent, automated device for assessing brachial artery reactivity. The SmartCuff™ fits well into clinical workflow since it also measures vitals (blood pressure, heart rate, and oxygenation).

4.1. Study limitations

Our study has several limitations. The relative importance of the endothelial and non-endothelial factors underlying the observed FCR response is yet to be determined. Knowing whether FCR measures a predominantly endothelial-dependent process will add further clarity and validation of its utility in assessing endothelial function. As such, a comparison to FMD would be a valuable study. We did not compare the SmartCuff™ to other non-invasive, operator-independent devices such as EndoPat™ and Vendys®. Though the mechanism of assessing endothelial function in the microcirculation is different, a comparison of the output in a similar patient population would be another valuable study. Additionally, the cross-sectional nature of our study limits assessment of direct causality. Further study is needed to assess whether the FCR can identify individuals with CVD and those at risk for CVD. A prospective, longitudinal study to observe whether the FCR predicts which individuals will develop disease will be an important step. Further, it will also be useful to determine if the FCR changes in response to interventions that may improve endothelial health such as exercise, diet, weight management, and medical therapy.

4.2. Conclusion

We have shown that an index of arterial reactivity can be obtained with an automated, user-independent system that uses a blood pressure cuff to measure time-varying compliance changes resulting from post-occlusion hyperemic shear stress stimuli. The Flow-mediated Compliance Response is inversely associated with established CVD risk indices. Further study is needed to establish the clinical utility of this technique, particularly for assessing response to preventive measures.

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Disclosures

Dr. Whitt is the inventor of the technology. Dr. Whitt and Dr. Magliato are co-founders of a company formed to commercialize the technology. Harry Silber reports financial support was provided by Cordex. Kerry Stewart reports financial support was provided by Cordex. Michael D. Whitt and Kathy E. Magliato have patent #8708921 issued to Cordex Systems, LLC. The other authors have no additional disclosures or conflicts of interest.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijjcha.2022.100960.

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