INTRODUCTION

Endothelial dysfunction results in reduced vascular reactivity, which fosters gradual, asymptomatic, plaque development within the arterial system. Measures of vascular reactivity are more predictive of cardiovascular disease (CVD) risk compared with traditional risk factor assessments such as the Framingham risk score. Nevertheless, clinical settings often rely solely on risk factors to assess for atherosclerotic risk due to its simplicity and low expense. Consequently, a considerable number of at-risk patients go unidentified on the basis of these conventional risk factors. Thus, discovering an easy-to-use and convenient methodology for vascular reactivity that can be incorporated into the routine clinical setting is of paramount clinical importance.

Abstract

Digital thermal monitoring (DTM) is an alternative, noninvasive, methodology to evaluate endothelial function using temperature change on finger as a surrogate measure of the magnitude of vascular reactivity index (VRI). A most recent modification to the technique includes the application of occlusion cuff at the base of a finger. We evaluated the validity of DTM compared with the standard flow-mediated dilation (FMD) protocol. Thirty-eight (22 males; 38 ± 15 years) participants were studied. Occlusion cuff was placed over the right antecubital fossa or at the base of the right index finger. Temperature monitors were placed on bilateral index fingers to assess change in temperature throughout 5-min occlusion and recovery phases. VRI values obtained with the finger occlusion (1.58 ± 0.29 AU) were not significantly different from VRI measured with the brachial artery occlusion (1.55 ± 0.26 AU; \( p = .47 \)), and the agreement of VRI values was confirmed in the Bland-Altman plot with a mean difference of −0.03 ± 0.34 (95% confidence interval: −0.15 to 0.09). Shear rate_{AUCI} was significantly correlated with VRI obtained from brachial occlusion (\( r = .34 \)) and finger occlusion VRI (\( r = .54 \); all \( p < .05 \)). Moreover, brachial FMD was significantly correlated with brachial occlusion VRI (\( r = .69 \); \( p < .05 \)) and finger occlusion VRI (\( r = .53 \); \( p < .05 \)). Therefore, finger-based VRI may be a valid and novel alternative measure of endothelial function that is more suitable than the standard FMD or hyperemic shear rate for the assessment of endothelial function in the routine clinical setting.
Several methodologies have been utilized to assess vascular reactivity within the research setting, the most popular being brachial artery flow-mediated dilation (FMD). FMD is useful for its ability to provide independent prognostic information for those with CVD or CVD risk. However, for an assessment of pre-clinical disease to be feasible, the assessment must be incrementally predictive over risk factors, responsive to therapy, operator-independent and reproducible, low-cost and widely accessible. Based on this criterion, FMD is impractical for the clinical setting due to its large intra- and inter-tester variability, reliance on expensive equipment, and highly skilled research technicians.

Digital thermal monitoring (DTM) uses temperature change on finger following 5 min of blood flow occlusion as a surrogate measure of tissue perfusion and subsequently vascular reactivity. The underlying assumption is that changes in tissue temperature following blood flow occlusion are a direct function of blood perfusion and are dependent on the arteries ability to dilate. This measure provides instantaneous, operator-independent assessments of vascular reactivity index (VRI). Assessments of VRI following brachial artery occlusion have been shown to be correlated with brachial FMD and reactive hyperemia index assessed by peripheral artery tonometry. Poor VRI has been associated with subclinical atherosclerosis measured by coronary artery calcium score (CAC) and the presence and extent of coronary artery disease (CAD) measured by CT angiography.

The most recent modification to the technique includes the application of an occlusion cuff at the base of the index finger instead of the upper arm, which provides users a more comfortable testing option than the standard full arm brachial artery occlusion. Due to the simplicity, this temperature-based assessment may provide a more feasible technique to assess vascular endothelial function in the clinical setting. However, evidence supporting its validity is lacking. Therefore, the purpose of this study is threefold: (1) to determine whether VRI assessments are associated with changes in shear stress, (2) to compare both finger- and brachial-based VRI to brachial FMD, and (3) to determine the association between VRIs derived from finger occlusion compared to those derived from brachial occlusion.

2 | METHODS

Adults between the ages of 18 and 80 were recruited through flyers and online advertisements posted in Austin, Texas. Emphasis was placed on recruiting participants varying widely in age, health, ethnicity, and socioeconomic status to ensure that the sample was representative of the general population. All participants completed a Health History Questionnaire prior to initiating testing. Participants were excluded from participation if they were pregnant or had undergone a surgical procedure or medical intervention within 48 hours of study participation. The study was in accordance with the Declaration of Helsinki and was approved by the local institutional review committee. All the participants provided written informed consent.

All the vascular assessments were performed in the morning in a quiet, dimmed laboratory room at a controlled ambient temperature between 22.5 and 25.0°C. Studies were conducted after an overnight fast of at least 8 hours and abstinence from alcohol, tobacco, caffeine, vasoactive medications, and exercise. Measurements were obtained after 15 min of supine rest.

Participants underwent two independent DTM assessments, finger occlusion or brachial artery occlusion, with a 30-min resting period between each assessment (Figure 1). The order in which the two assessments were conducted was randomized. While resting, all participants were placed under a heated blanket to ensure they reached the required baseline fingertip temperature (>27°C) needed for accurate DTM measurements. Prior to testing, an automated blood pressure measurement was taken to determine the necessary occlusion pressure. Each assessment followed an operator-independent protocol that was 15 min in duration. There were three stages.
including 5 min of temperature stabilization, 5 min of blood flow occlusion at 50 mmHg above systolic blood pressure, and 5 min of post-occlusion reactive hyperemia. Thermal changes were continuously monitored using VENDYS-II temperature sensors (VENDYS-II, Endothelix Inc) placed bilaterally on pulp of the participants’ index fingers of both the occluded and non-occluded arm. Following test completion, participants’ VRI value was automatically generated by the device. VRI values range from 0.0 to 3.5 and are classified as being indicative of poor (0.0 to <1.0), intermediate (1.0 to <2.0), or good (≥2.0) vascular reactivity as previously described.6

Finger occlusion assessments utilized neonatal blood pressure cuffs (Medline Industries) placed at the base of the right index finger to obtain a blood pressure and administer 5 min of arterial occlusion. Due to the variation in participants’ index finger size, diameter at the base of the index finger was measured to determine the optimal cuff size. If a reliable blood pressure reading was unable to be obtained from the finger site (due to a small finger diameter, etc), an automated blood pressure was obtained from the upper arm and manually entered into the device. Participants remained supine for the assessment, with their hands placed comfortably on an insulated pad located on their lap to ensure body-temperature did not interfere with temperature measures. The measurements of blood flow velocity and shear rate were not feasible as the sensor on the fingertip and the occlusion cuff were occupying the available space in the finger.

Participants’ right arm was abducted to a 90° angle and placed onto an arm support. The occlusion cuff was moved to the ipsilateral forearm distal to the antecubital fossa.7 Tape was placed around the extending right index finger to ensure constant pressure on the temperature sensor. Participants were instructed to hold the remaining fingers on their right hand in a fisted position to limit heat radiation onto the temperature sensor. Participants’ left hand rested comfortably on the insulated pad placed on the participant’s lap.

High-resolution ultrasound (iE 33 Ultrasound System, Philips) was used to measure brachial artery diameters and blood flow velocity. Brachial artery images were obtained in a longitudinal orientation located 5–10 cm proximal to the antecubital fossa.7 Once an acceptable ultrasound image had been obtained, the 15-min DTM protocol commenced. One minute of baseline arterial diameter and blood flow velocity was acquired during the 5-min temperature stabilization period.

Following the release of arterial occlusion, ultrasound-derived blood velocity and diameter data were recorded for the entire 5-min recovery period.

All ultrasound brachial images were analyzed by the same investigator using image analysis software (Vascular Research Tool Brachial Analyzer, Medical Imaging Applications). FMD was expressed as the percent change in brachial artery diameters recorded during the pre- and post-occlusion phases and was calculated using the equation: (maximum diameter – baseline diameter)/baseline diameter × 100.7 Vessel diameter and blood velocity were used to calculate shear rate (s⁻¹) using the following equation: (8 × blood viscosity (assumed to be 0.035 dyn × s/cm²) × peak blood velocity/brachial artery diameter) following the release of cuff occlusion.16 Blood flow was calculated from the following formula: (mean blood velocity) × (circular area).17 Integrated area under the curve (AUCI) for shear rate (Shear rate_{AUCI}) in respect to the increase were calculated.18

Statistical analyses were performed using Prism version 8.3.1 (GraphPad Software). All group data were presented as group means (±SD). Statistical difference between the two assessments was evaluated by using Student’s t tests for paired data. Associations of interest were analyzed by Pearson correlational and regressingional analyses. Statistical procedure proposed by Bland and Altman was used to compare the two different methods;19,20 A p-value < .05 was considered statistically significant.

### RESULTS

Of the forty-one participants recruited for participation, thirty-eight were included in final statistical analyses (Table 1). Rationale for the

| Variable                        | Mean ± SD or n (%) |
|--------------------------------|--------------------|
| Sex (M/F)                      | 22/16              |
| Age (years)                    | 38 ± 15            |
| Height (cm)                    | 175 ± 9            |
| Body weight (kg)               | 82.5 ± 20.9        |
| BMI (kg/m²)                    | 26.7 ± 6.4         |
| Brachial systolic BP (mmHg)    | 112 ± 13           |
| Brachial diastolic BP (mmHg)   | 63 ± 12            |
| Finger systolic BP (mmHg)      | 108 ± 12           |
| Finger diastolic BP (mmHg)     | 57 ± 10            |
| Self-reported health history   |                    |
| Obese (BMI > 30 kg/m²)         | 8 (20%)            |
| Hypertension                   | 7 (18%)            |
| Antihypertensive medication    | 4 (11%)            |
| Family history of hypertension | 16 (42%)           |
| Hypercholesteremia             | 4 (11%)            |
| Smoking                        | 8 (21%)            |
| Sedentary                      | 8 (21%)            |
| Ethnicity                      |                    |
| Caucasian                      | 28 (74%)           |
| African American               | 3 (8%)             |
| Hispanic or Latino             | 2 (5%)             |
| Asian                          | 5 (13%)            |
| Highest level of education     |                    |
| High school diploma or equivalent | 6 (16%)         |
| Associate degree               | 2 (5%)             |
| Bachelor degree                | 14 (37%)           |
| Master degree or higher        | 16 (42%)           |

Abbreviations: BMI, Body mass index; BP, blood pressure.
exclusion of three participants were an inability to obtain a finger temperature >27°C, extreme discomfort expressed by a participant with brachial artery occlusion causing a sympathetic response, and a difference in VRIs greater than three standard deviations from the group mean difference suggestive of statistical outlier. Participants varied widely in age, health history, ethnicity, and educational background. Mean values (± SD) for brachial artery vascular reactivity measures are displayed in Table 2. As depicted in Figure 2, shear rate_AUCI was significantly correlated with VRI obtained from brachial occlusion (r = .34; p < .05), and finger occlusion VRI (r = .54; p < .05). Additionally, Figure 3 depicts significant correlations between brachial FMD and brachial occlusion VRI (r = .69; p < .05), and VRI obtained from the finger (r = .53; p < .05). FMD and shear rate_AUCI were not significantly correlated with each other (p = .08). Mean VRI values obtained from finger (1.58 ± 0.29) and brachial (1.55 ± 0.26) occlusion were not significantly different (p = .47) with a mild (r = .25) correlation between the two. This agreement is consistent with the results of the Bland-Altman plot with a mean difference of −0.03 ± 0.34 (95% confidence interval: −0.15 to 0.09) depicted in Figure 4.

4 | DISCUSSION

The purpose of the present study was to characterize VRI obtained from finger and brachial occlusion. The primary finding of the present study is VRIs determined with finger, brachial occlusion was not significantly different, and the agreement between the two assessments was confirmed with the Bland-Altman plot. Another noteworthy finding is the significant associations between both VRI assessments and brachial FMD. Additionally, the significant correlations between shear rate and both finger- and brachial-based VRI assessments suggest that changes in temperature rebounds reflect blood flow changes in the arteries. Taken together, these results suggest that VRI as determined by the finger occlusion may be a promising technique to assess vascular endothelium-dependent vasodilation.

**TABLE 2** Brachial artery measures

| Variable                        | Mean ± SD   |
|---------------------------------|-------------|
| Brachial Occlusion VRI (AU)     | 1.55 ± 0.26 |
| Finger Occlusion VRI (AU)       | 1.58 ± 0.29 |
| Resting Brachial Diameter (mm) | 4.2 ± 0.6   |
| Brachial artery FMD (%)         | 7.5 ± 2.2   |
| Resting Blood Flow Velocity (cm/s) | 100.5 ± 21.7 |
| Peak Blood Flow Velocity (cm/s) | 208.6 ± 37.5 |
| Reactive hyperemia_AUCI (AU)   | 44 612 ± 16 575 |
| Shear rate<sub>rest</sub> (s<sup>−1</sup>) | 196.1 ± 50.7 |
| Shear rate<sub>peak</sub> (s<sup>−1</sup>) | 428.7 ± 124.9 |
| Shear rate_AUCI (AU)            | 6241 ± 2230 |

Abbreviations: AUCI, integrated area under the curve; AU, area under the curve in respect to the increase; FMD, flow-mediated dilation; VRI, vascular reactivity index.
finger-occlusion VRI in the current study offering an even easier and more comfortable testing option than the standard full arm brachial artery occlusion. Interestingly, brachial shear rate was correlated slightly better with finger VRI than with brachial VRI. The reason for this is not clear but this may be related to the notion that even though shear rate is measured at brachial artery, more prominent vascular changes that result in greater shear rates may originate in microvasculatures and that more distally located finger VRI may capture these changes more effectively. In this context, assessments of microvasculature function may be more indicative of CVD risk than FMD with poor VRIs shown to be significantly associated with subclinical atherosclerosis and the presence and extent of CAD. VRI assessments may also be used to assess the effectiveness of therapeutic interventions, shown to be responsive to a 1-year dietary intervention which improved coronary artery calcium and temperature rebound. All of which suggest that DTM assessments provide a more feasible methodology for assessing vascular reactivity within the clinical setting.

Similarities in the underlying physiological mechanisms mediating FMD and DTM assessments provide useful context for the significant correlations found in the present study. Brachial artery FMD uses noninvasive ultrasound to assess changes in brachial artery diameter and blood flow velocity following 5 min of arterial occlusion. During occlusion, distal ischemia within the microvasculature stimulates a reactive hyperemic response to accelerate local blood flow to deliver oxygen and remove metabolic by-products following occlusion release. A notion supported by the twofold increase in blood flow velocity from rest to post-occlusion peak seen in the present study. The subsequent increase in shear stress along the endothelium caused by augmented local blood flow being the primary stimulus for NO synthase (eNOS) enzymatic activity and NO-mediated vasodilation within the conduit arteries. Comparable, DTM uses temperature, a direct function of blood perfusion within the tissue. During blood flow occlusion, fingertip temperature drops due to reductions in limb perfusion. Once occlusion is released, fingertip temperature rebounds due to a reactive hyperemic influx in blood flow to the previously ischemic tissue. The rate and intensity of the temperature rebound being dependent on the arterioles ability to vasodilate and restore normal circulation. Therefore, by assessing temperature rebound, normalized with baseline, and core temperatures, the endothelial response to changes in blood flow can be identified with good sensitivity. The significant correlations found in the present study between both VRI assessments and Shear rate and brachial FMD are supported by physiological rationale.

Brachial occlusion VRI and finger-based VRI were not significantly different, and the difference between the two assessments for each participant was not greater than two standard deviations based on the Bland-Altman plot. The novel findings of the present study are that both finger- and brachial-based VRI assessments are mediated by changes in shear stress and therefore reflect microvascular function. This finding is consistent with a previous study although there are some conflicting findings reported. These discordant results may be attributable to the use of different generations of DTM technique as newer generations incorporate an algorithm to normalize temperature rebound with baseline and core temperatures. One surprising finding of the study is the significant association between finger occlusion VRI and shear stress induced by brachial cuff occlusion. The implication of this outcome is that either brachial or finger occlusion VRI may be used to assess vascular reactivity. This is of significant clinical importance because of the impractically of using FMD assessments in the clinical setting due to their inherently high cost and reliance on highly trained ultrasound technicians. Additionally, FMD methodologies have been shown to be highly sensitive to even slight changes in protocol or motion artifact. Due to this, reproducibility has been a significant issue plaguing studies which have utilized FMD assessments. In contrast, the coefficient of reproducibility for DTM is 2%-3%. Use of finger cuff is particularly attractive as anecdotally it involves much less pain and discomfort associated with blood flow occlusion.

The current study was conducted with a relatively small sample size. Therefore, a community-based study with a larger sample and repeated measures is necessary to further assess the sensitivity of finger-based VRI assessments. The primary limitation of the DTM device is the required baseline fingertip temperature to be >27°C, which may prevent the use of DTM assessments in places that experience extreme external temperatures or for patients with poor limb perfusion. To ensure all subjects reached the threshold temperature in the current study, a heated blanket was placed over the participants. Despite this, one participant was dropped from analyses for an inability to obtain the required fingertip temperature. Two other participants were dropped for other experimental reasons.

In summary, VRI obtained following finger and brachial occlusion provide similar values and are significantly correlated with standard brachial FMD. Additionally, changes in shear stress appear to mitigate changes in finger temperature. Therefore, due to its operator-independent protocol that is low-cost and easily applied, DTM following finger occlusion may be a promising methodology.

FIGURE 4 Bland-Altman plot with average for individual participants’ finger and brachial vascular reactivity index (VRI) plotted against the difference between the two assessments. Dotted lines indicate ±2 SD from the group mean difference and shaded areas 95% confidence intervals.
for assessment of endothelial dysfunction and atherosclerotic risk in the routine clinical settings.

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CONFLICT OF INTEREST
One of the authors (MN) works for Endothelix that manufactures the device that was evaluated in the present study.

AUTHOR CONTRIBUTIONS
MH, MN, SK, and HT involved in study conception and design. MH and DG involved in acquisition of data. MH, DG, MN, SK, and HT analyzed and interpreted the data. MH and HT drafted manuscript and DG involved in acquisition of data. MH, DG, MN, SK, and HT involved in study conception and design. MH

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ORCID
Hirofumi Tanaka https://orcid.org/0000-0002-1780-7471