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Original Contribution

CONSTRUCT VALIDITY AND REPRODUCIBILITY OF HANDHELD ULTRASOUND **DEVICES IN CAROTID ARTERY DIAMETER MEASUREMENT**

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Abstract—The construct validity and reproducibility of three commonly used handheld ultrasound (US) devices in measuring carotid arterial diameter was evaluated: Telemed MicrUs EXT-1H (Telemed, Vilnius, Lithuania), Butterfly iQ (Butterfly Network, Inc., Guilford, CT, USA) and Philips Lumify (Philips Healthcare, Best, The Netherlands). An in vitro setup was built to evaluate construct validity, compared with high-end US, and intraobserver variability of handheld US devices. Handheld devices showed a mean difference of 0.023 ± 0.030 cm, 0.012 ± 0.037 cm and 0.009 ± 0.046 cm for, respectively, Telemed, Butterfly and Lumify in comparison with high-end US devices. Intraclass agreement with the high-end system as well as intra-observer variability for handheld US devices was classified as excellent, with all values greater than 0.95. Subsequently, inter-observer variability of handheld US devices was investigated in an in vivo setup with 20 healthy volunteers. Inter-observer variability was classified as excellent for Telemed (0.901), good for Lumify (0.827) and moderate for Butterfly (0.684) with a difference of, respectively, 0.005 ± 0.031 cm, 0.020 ± 0.050 cm and -0.003 ± 0.033 cm. In conclusion, handheld US devices demonstrated an excellent construct validity and intra-observer variability. Additionally, excellent-to-good inter-observer variability for Telemed and Lumify was observed, and Butterfly demonstrated a moderate inter-observer agreement. These results indicate that handheld US devices are effective for measuring carotid arterial diameter. (E-mail: loes.h.willems@radboudumc.nl) © 2022 The Author(s). Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Key Words: Handheld ultrasound, Ultrasonography, Carotid arteries, Diameter.

INTRODUCTION

Endothelial dysfunction is one of the first signs of systemic atherosclerosis and contributes to its progression by promoting coagulation, vasoconstriction and deficient vascular repair, ultimately leading to thickening of the arterial wall with narrowing of conduit arteries as result (Bonetti 2003; Lerman and Zeiher 2005). Measuring arterial diameter changes in response to physiological stimuli, such as shear stress (e.g., flow-mediated dilation) and sympathetic stimulation (e.g., carotid artery

reactivity), using ultrasound (US) has emerged useful to assess endothelial dysfunction (Nabel et al. 1988; Peace et al. 2018; van Mil et al. 2017, 2018, 2019).

Arterial diameter measurements during endothelial function testing currently depends on high-end US machines. High costs and the static nature of these machines prevent the applicability of these measurements at first- and second-line clinical centers. Over the past decades, an increasing number of clinicians have started using handheld US devices (van den Heuvel et al. 2018; Zieleskiewicz et al. 2021). Important advantages of handheld US devices include their lower costs in comparison with high-end US devices and their simplicity of use, which makes handheld US applicable in outpatient clinics and general practices. Moreover, handheld US may facilitate the implementation of the assessment of

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artery diameters and diameter responses to physiological responses. To date, little is known about the validity and reproducibility of contemporary handheld US to examine arterial diameter.

The purpose of this study was to evaluate the construct validity and reproducibility of three commonly used handheld US devices—Telemed MicrUs EXT-1H (Telemed, Vilnius, Lithuania), Butterfly iQ (Butterfly Network, Inc., Guilford, CT, USA) and Philips Lumify (Philips Healthcare, Best, The Netherlands)—in measuring carotid arterial diameter. For this purpose, first, *in vitro* evaluation of handheld US devices in a phantom setup was performed to evaluate the construct validity of handheld US devices in comparison to a high-end US device. Subsequently, experiments were performed, comparing intra- and inter-observer variability of the handheld US devices within respectively an *in vitro* and *in vivo* setup.

METHODS

Design

In the first part of this study, the construct validity of handheld US devices was evaluated using an in vitro setting to create a controlled environment with fixed parameters like acoustic (speed of sound, acoustic impedance and attenuation, backscattering) (Zell et al. 2007) and mechanical (tissue elasticity and viscosity) (Amador et al. 2011) tissue properties for diameter detection of the US devices. In total, 28 measurements were performed per US device, which were compared against a contemporary high-end US machine. Measurements were repeated on a second day to evaluate intraobserver variability. In the second part of this study, repeated measurements of the carotid artery diameter were performed within twenty healthy individuals. The carotid artery was chosen for diameter assessment because the carotid artery is easily accessible by US and commonly used for the evaluation of atherosclerosis development. (Podgorski et al. 2016)

Handheld US devices

The following three commonly used handheld US devices were used to evaluate construct validity and intra- and inter-observer reproducibility: (i) Telemed MicrUs EXT-1H with a linear array probe with a frequency range of 5-12 MHz; (ii) Butterfly iQ with a single probe emulating a linear and phased array probe by means of microsensors with a frequency range of 1-10 MHz; and (ii) Philips Lumify with a linear array probe with a frequency range of 4-12 MHz. To evaluate construct validity using the *in vitro* setting, handheld US machines were compared against a high-end US system with a linear array probe with a frequency range of

5–14 MHz (Terason 3300; Terason Ultrasound, Burlington, MA, USA).

In vitro: Construct validity and intra-observer variability

Experimental setup. An experimental setup was built to perform US measurements on a custom-made flexible polyvinyl alcohol phantom mimicking an artery; Figure 1 shows a schematic overview. The phantom artery was positioned in an US compatible box (water basin) and connected to an in-house built circulatory system with physiological flow and pressure conditions (Fekkes et al. 2018). Different flow volumes were applied to simulate different phantom diameters.

Measurement protocol. The gear pump, connected to the phantom artery circulation, was set at a continuous flow of 0.3 L/min. The US transducer was longitudinally aligned with the phantom artery and this position was maintained by use of a laboratory standard. Basic carotid ultrasonography pre-sets were used. Gain and depth were adapted when considered necessary. Consensus of the optimal position and settings was reached by two skilled sonographers (JV, LW) and was kept the same for each device. The phantom artery was recorded during a 10-s interval. Thereafter, the flow was increased by 0.1 L/min, corresponding with an approximately 1-mm increase in diameter per minute, and the phantom artery was recorded again. These steps were repeated to a flow of 0.9 L/min. Subsequently, the



Fig. 1. Schematic overview of experimental setup of the *in vitro* experiment, where water from the water reservoir was pumped around by the gear pump through the silicon tube, which was placed in a water basin. The probe of each ultrasound device was mounted in the laboratory standard and positioned above the silicon tube such that a longitudinal plane was visualized.

Measurements were repeated on a second day, which was performed within 30 d, to determine the intra-observer variability. We ensured that all procedures were kept similar, including the order of testing.

In vivo: Inter-observer variability

Participants. A total of 20 volunteers were recruited. Inclusion criteria were age between 18 and 65 y and a body mass index of 18–30 kg/m². No participants with previously diagnosed carotid artery occlusive disease were included. Written informed consent was obtained prior to participation from all volunteers. Approval of the local Medical Ethical Committee (study number: CMO 2020-6700) and the local institutional review board was obtained. This study was conducted in accordance with the latest revision of the Helsinki Declaration of 1964.

Procedures. Data on sex, age, height, weight, smoking behavior, medical history and the familial occurrence of cardiovascular diseases were collected. Participants visited the hospital once. During the visit, US measurements of the common carotid artery were performed. Participants were in supine position with the neck extended and had rested at least 5 min before the start of US measurements. Room temperature was kept constant, and only one type of US gel was used. The left common carotid artery was longitudinally visualized using the three handheld US devices and one high-end US device, which were applied in randomized order. After image optimalisation by the examiner (J.V., L.W.), the carotid artery diameter was recorded for 10 s. Subsequently, the probe was removed from the participant and handed over to the second experienced examiner without adjusting US settings. This was followed by repositioning the transducer at the artery. Subsequently followed the recording of the carotid artery diameter for another 10 s. The order of the two examiners was also randomized.

Diameter analysis

Dependent on US device, data were saved as or converted to an Audio Video Interleave (AVI) file. US videos of the Butterfly device were converted using Movavi Video Converter 20 (Movavi Software, Wildwood, MO, USA) using the original size (resolution 1696×1080) and MPEG-4 codec. Additionally, US videos of the Lumify device were converted using MAT-LAB R2018b (The MathWorks, Natick, MA, USA) using the VideoWriter function with quality index 90. This resulted in a video resolution varying from 512×296 to 512×444 depending on the depth setting during the measurement. For the Terason ultrasound videos, Camtasia (Camtasia Softonic, Barcelona, Spain) was used to record the screen containing ultrasound images. This was saved as an AVI file with a resolution of 1024×768 . The Telemed ultrasound video was directly saved as AVI file with a resolution of 1556×868 . This corresponds to an axial resolution of 28, 68, 39 and 35 microns for the Butterfly, Lumify, Terason and Telemed devices, respectively.

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Diameter analysis of the recorded US videos of the phantom and carotid arteries was performed by a singleblinded investigator using BloodFlow Software (version 4.0; National Instruments LabVIEW, Austin, TX, USA), with a semiautomated edge-detection and wall-tracking algorithm. This software enables the identification of a region of interest (ROI) in the longitudinal plane of an artery. ROIs were identified for each US video. Within the ROI, the lumen-arterial wall interface was detected (Fig. 2). The diameter was determined multiple times per frame depending on the size of the ROI. Subsequently, a median diameter per frame was determined and eventually a median diameter of all frames was determined for the resulting diameter per measurement. For the resulting diameter, full cardiac cycles were included to minimize bias of the average diameter. More details on this technique have been described previously (Thijssen et al. 2009). The software is largely independent of investigator bias (Woodman et al. 2001).

Statistical analysis

Phantom and carotid artery diameters were reported as the mean \pm standard deviation (SD) for each measurement. Baseline characteristics of the participants were reported as the median with interguartile range [O1, O3], and categorical variables are presented as percentages. Bland-Altman plots were created to determine the agreement of measured diameters between the handheld devices and the high-end US device and to determine the intra- and inter-observer variability of the three handheld US devices for in vitro and in vivo measurements. Differences were plotted against the mean per comparison. Bland-Altman plots are visualized with one solid black line representing the mean and two dotted lines representing the limits of agreement (1.96 * standard deviation; Altman and Bland 1983). Variability of measurements was assessed using intra- and interobserver variability by determining the intraclass correlation coefficient (ICC), which is presented for the between-day comparison for the in vitro setup and between-observers comparison for the in vivo setup, respectively. ICC were reported according to the guideline of Koo and Li (2016), in which a coefficient < 0.50,

between 0.50 and 0.75, between 0.75 and 0.90 and >0.90 represents respectively poor, moderate, good and excellent agreement, respectively. Additionally, coefficients of variation were calculated per participant, per device and between observers by using the ratio of the standard deviation and the mean absolute differences between observers. After Bonferroni correction, *p* values <0.01 were considered significant. Statistical analysis was performed using SPSS Statistics, version 25 (IBM Corporation, Armonk, NY, USA).

RESULTS

In vitro: Construct validity and intra-observer variability

The Bland–Altman plots for variability in *in vitro* measurements between handheld devices and the highend US device are shown in Figure 3. Compared with the high-end US device, the Telemed demonstrated a significantly larger diameter (0.023 ± 0.030 cm, p < 0.001; Table 1), while no such difference was reported for the Butterfly (0.012 ± 0.037 cm) or Lumify (0.009 ± 0.046 cm). Visually inspecting the Bland–Altman plots, we found comparable limits of agreement across a large range of diameters between the three handheld US devices. The ICC comparing the handheld US and high-end

US was 0.996, 0.994 and 0.990 for Telemed, Butterfly and Lumify, respectively.

No significant difference was found between measurement days for the Telemed (0.013 \pm 0.059 cm) and Butterfly (-0.012 \pm 0.048 cm), while a small but significant difference was found for the Lumify (0.008 \pm 0.009 cm, p = 0.008; Table 1). Bland-Altman plots (Fig. 4) reveal comparable limits of agreement across the three handheld US devices. The ICC comparing both measurements per handheld US device was 0.986, 0.990 and 1.000 for Telemed, Butterfly and Lumify, respectively.

In vivo: Inter-observer variability

The median age of the participants was 21.0 y [20.0, 22.0] and 40.0% were male. Additionally, the median body mass index was 21.7 [20.4, 23.6], 10% were current smokers and 45% had a family history of cardiovascular disease. Bland–Altman plots for *in vivo* measurements comparing the inter-observer variability of the handheld US devices are shown in Figure 5. No significant difference in carotid artery diameter was found between operators for the Telemed (0.005 \pm 0.031 cm), Butterfly (0.020 \pm 0.050 cm) or Lumify (-0.003 \pm 0.033 cm; Table 1, Fig. 5). Limits of agreement were smallest for the Lumify, with similar patterns



Fig. 2. The detected borders of the lumen-arterial wall interface in participants for the (A) Terason, (B) Telemed, (C) Butterfly and (D) Lumify devices, where the *yellow square* represents the drawn region of interest and the *yellow lines* represent the detected border.



Fig. 3. Bland–Altman plots that compare assessment of the phantom diameters of the (A) Telemed, (B) Butterfly and
(C) Lumify handheld ultrasound (US) devices against the high-end US device (Terason), where the *solid black line* represents the mean difference and the *dotted black lines* represent the limits of agreement per comparison.

and limits observed for the Telemed and Butterfly. The ICC for carotid artery diameter between the operators per device was classified as excellent for the Telemed (0.901), good for Lumify (0.827) and moderate for the Butterfly (0.684). Average coefficients of variation per participant, per device between observers were $2.4\% \pm$

Table 1. p Values for Bland-Altman analysis

	In vitro validation	In vitro variability	In vivo variability
Telemed	<0.001	0.410	0.514
Lumify	0.0303	0.008	0.676
Butterfly	0.089	0.387	0.101

2.5%, 2.2% \pm 2.0% and 5.2% \pm 2.9% for Telemed, Lumify and Butterfly, respectively.

DISCUSSION

This study has demonstrated that the three studied handheld devices show a good construct validity and strong ICC compared with high-end US and excellent between-day intra-observer variability using an *in vitro* setting for measuring arterial diameters. Betweenobserver reproducibility of the handheld US devices within the *in vivo* setting revealed an excellent-to-good



Fig. 4. Comparison of the between-day variation of the *in vitro* measurement of diameter for the (A) Telemed, (B) Butterfly and (C) Lumify devices, where the *solid black line* represents the mean difference and the *dotted black lines* represent the limits of agreement per comparison.

inter-observer variability for the Telemed and Lumify, but a moderate variability for the Butterfly.

Good consistency and excellent reliability were observed between handheld and high-end US devices in an *in vitro* setting, as all ICCs were well above 0.95. Nonetheless, a significant difference between Telemed and the high-end US device was found, which may suggest limited validity of the Telemed. One possible reason for this difference is (not) taking the intima-media thickness into account when analyzing the diameter. Such consistent difference in determining the diameter may result in structural difference between US devices. An example of this can be seen in Figure 2, where the Lumify analysis detects the intima, and the other devices detect the outer wall. Furthermore, it is important to realize that Telemed demonstrated the smallest SD. Taken this together, all three handheld US devices showed excellent construct validity.

Although *in vitro* setups are commonly used to determine validity of US devices, few studies have focused on understanding (construct) validity using an *in vitro* setup for handheld US devices. Two studies were found comparing US devices. One study investigated carotid strain assessment applying US speckle tracking using a clinical and high-end US device (Larsson et al. 2015), whereas the other study investigated optic nerve



Fig. 5. Bland-Altman plots of in vivo measurements of the carotid diameter comparing both operators using the (A) Telemed, (B) Butterfly and (C) Lumify devices, where the solid black line represents the mean difference and the dotted black lines represent the limits of agreement per comparison.

sheath diameters using a pocket-sized US unit compared to a previously validated portable unit (Johnson et al. 2016). The study of Larsson et al showed an ICC of, respectively, 0.73 for the clinical US device and 0.90 for the high-frequency US device (Larsson et al. 2015). Johnson et al demonstrated an ICC of 0.75 for betweendevice comparison (pocket size versus previously validated portable unit) and 0.83 for inter-observer variability of the pocket-sized US device (Johnson et al. 2016). These values seem slightly lower than the results presented in our study. Importantly, these previous studies focused on other outcome measures. Other studies that evaluated the validity of handheld US directly compared handheld US devices with each other (Prekker et al. 2013; van den Heuvel et al. 2018; Niu et al. 2019) or adopted other imaging modalities (Vidakovic et al. 2007) using patients. A strength of our study is therefore that the handheld US devices were both tested in an in vitro setup and afterward evaluated in vivo in volunteers.

In line with our results, other studies reporting on vascular US have positively addressed the use of handheld US devices (*e.g.*, Acuson P10 [Stock et al. 2015], Vscan [Mantella et al. 2019] and Butterfly [Alfuraih et al. 2021]). Importantly, US devices were tested in relation to varying pathological screening areas (*e.g.*, size of liver, spleen and kidneys [Stock et al. 2015], carotid artery plaques [Mantella et al. 2019] and abdominal aorta [Alfuraih et al. 2021]). At the least, these studies provide further support that handheld US devices are feasible and reliable, with an ICC of ~0.8 with high-end systems (Stock et al. 2015; Mantella et al. 2019; Alfuraih et al. 2021). However, the validity and reproducibility must be considered within its specific use, which was related to the carotid artery diameter in our study.

In contrast to the inter-observer variability of the Telemed and Lumify, we found a moderate variability for the Butterfly device. This latter observation may, at least in part, be explained by the US transducer specifications of the Butterfly. While Telemed and Lumify utilize a classic linear array probe, the Butterfly probe is shaped differently and emulates a linear array probe by means of microsensors. The relatively small probe head of the Butterfly device allows for more variability in probe positioning, possibly resulting in some inter-operator variability. Evaluation of arterial diameter is influenced by probe positioning (more proximal or distal), but also artery shape, blood pressure variation and tissue properties (Mathiesen et al. 2000; Triboulet et al. 2006; Beales et al. 2011) Therefore, inter-operator variability in vivo can be multifactorial and does not necessarily indicate lack of quality of the US device. Accordingly, it is important to highlight that the Butterfly device has already proven to have good inter-observer variability in assessing carotid artery plaque assessment (Alfuraih et al. 2021). This highlights the importance of (construct) validity studies for the large range of handheld US devices, as device specifications may importantly determine the potential (clinical) application of a specific US device.

A limitation of this study relates to analyzing standard B-mode images instead of using raw radiofrequency data. The latter has a higher spatial resolution and might be preferred as the gold standard. Previous studies, however, have shown standard B-mode images to be robust for measuring arterial characteristics with good precision and accuracy (Dogan et al. 2009; Steinbuch et al. 2016). Using standard B-mode based analysis made it possible to make the analysis comparable and consistent between the three handheld US devices. However, to optimize the US videos for analysis, ultrasound settings were adjusted between devices or participants, but kept constant between operators. Nevertheless, this could have had an impact on the final results.

B-mode images obtained from the various US machines had differences in format and quality. Some US videos had to be converted to AVI files, which may have caused loss of quality of the US videos (specifically affecting Lumify and Butterfly). The use of a reliable converter software and converting packages effectively minimized loss of quality, which was further supported by visual inspection of the US videos after conversion. Our software has proven to be reliable and largely independent of investigator bias (Woodman et al. 2001). Woodman et al. (2001) described the method of analysis as well as some coefficients of variation for different determined parameters with the software, with the largest coefficient of variation being 6.7%. However, we cannot fully exclude a bias caused by different types of videos obtained with the different US machines. Nevertheless, because the quality of US devices has also improved over the past two decades just as converting software has, the influnce of this quality (e.g., image resolution and video compression) on analysis with this software is expected to be minimized. Importantly, despite this possible bias, all devices showed excellent construct validity compared to the high-end US device and excellent between-day reproducibility. Another limitation could be the small sample size for Bland-Altman analysis (Lu et al. 2016). Due to the explorative character of the *in vivo* part of this study, no sample size calculation was performed.

CONCLUSIONS

All handheld devices showed an excellent construct validity and intra-observer variability *in vitro* and are therefore suitable to analyze carotid artery diameter. Inter-observer variability *in vivo* of the handheld devices was excellent-to-good for Telemed and Lumify, and Butterfly showed a moderate variability. Although analysis software has proven to be reliable, Butterfly and Lumify did not provide compatible US video, which could have caused minor variation between the handheld devices. Nevertheless, this study demonstrated that handheld US devices, especially Telemed and Lumify, are effective for measuring carotid arterial diameter.

CONFLICTS OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

Data availability statement—The data generated during the present study are available from the corresponding author on reasonable request.

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