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Construct Validity and Reproducibility of Handheld Ultrasound Devices n Carotid Artery Diameter Measurement.

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) and Philips Lumify (Philips Healthcare, Best, The Netherlands). An *in vitro* set-up was built to evaluate construct validity, compared to high-end US, and intra-observer variability of handheld US. 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 to high-end US. Intraclass agreement with the high-end system as well as intra-observer variability for handheld US devices was classified as excellent with all values above 0.95. Subsequently, interobserver variability of handheld US was investigated in an *in vivo* set-up with 20 healthy volunteers. Interobserver 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. In conclusion, handheld US demonstrated an excellent construct validity and intra-observer variability. Additionally, excellent-to-good interobserver variability for Telemed and Lumify was observed, where Butterfly demonstrated a moderate interobserver agreement. These results indicate that handheld US devices are applicable in measuring carotid arterial diameter.

Keywords 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 (Lerman en Zeiher 2005; Bonetti 2003). 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 1988; van Mil 2017; van Mil 2018; Peace 2018; van Mil 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. Past decades, an increasing number of clinicians started using handheld US. (van den Heuvel 2018; Zieleskiewicz 2021) Important advantages of handheld US include their lower costs in comparison to 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 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 is 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) 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 set-up 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 interobserver variability of the handheld US devices within respectively an *in vitro* and *in vivo* set-up.

Materials and 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 20117) and mechanical (tissue elasticity and viscosity) (Amador 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 the intra-observer 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 2016)

Handheld US devices. The following three commonly used handheld US devices were used to evaluate construct validity and intra- and interobserver reproducibility: 1) Telemed MicrUs EXT-1H (Telemed, Vilnius, Lithuania) with a linear array probe with frequency range 5-12 MHz, 2) Butterfly iQ (Butterfly Network, Inc, Guilford, Connecticut, United States) with single probe emulating a linear and phased array probe by means of microsensors with frequency range 1-10 MHz, and 3) Philips Lumify (Philips Healthcare, Best, The Netherlands) with a linear array probe with frequency range 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 frequency range 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 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 second interval. Hereafter, the flow was increased with 0.1 L/min, corresponding with approximately 1 millimeter diameter increase per minute, and the phantom artery was recorded again. These steps were repeated to a flow of 0.9 L/min. Subsequently, the pressure regulator was set on a pulsatile flow of 0.3 – 0.9 L/min, with 60 pulses per minute, with the phantom artery being recorded for 10 second periods. These procedures were repeated for all devices.

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

I*n vivo*: Interobserver variability

Participants. A total of 20 volunteers were recruited. Inclusion criteria were age between 18 and 65 years and a body mass index of 18-30 kg/m^2. No subjects 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 about gender, age, height, weight, smoking behavior, medical history, and the familial occurrence of cardiovascular diseases were collected. Participants visited the hospital once. During the visit, ultrasound measurements of the common carotid artery were performed. Participants were in supine position with the neck extended and had rested at least 5 minutes 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 (JV, LW), the carotid artery diameter was recorded for 10 seconds. Subsequently, the probe was removed from the participant and handed over to the second experienced examiner without adjusting ultrasound settings. This was followed by the second 10-second recording of the carotid artery diameter. 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, USA) using the original size (resolution 1696 x 1080) and MPEG-4 codec. Additionally, US videos of the Lumify device were converted using MatLab R2018b (Mathworks, Natick, MA, USA) using the VideoWriter function with quality index 90. This resulted in a video resolution varying from 512 x 296 till 512 x 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 x 768. The Telemed ultrasound video was directly saved as AVI file with a resolution of 1556 x 868.

Diameter analysis of the recorded US videos of the phantom and carotid arteries was performed by a single-blinded investigator using BloodFlow Software (Version 4.0; National Instruments LabVIEW, Austin, TX, USA) with 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 (Figure 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 are described previously. (Thijssen 2009) The software is largely independent of investigator bias. (Woodman 2001)

Statistical analysis

Phantom and carotid artery diameters were reported as mean + standard deviation (SD) for each measurement. Baseline characteristics of the participants were reported as median with interquartile range [Q1, Q3] 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 interobserver 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 continuous 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 the intra- and interobserver variability by determining intraclass correlation coefficient (ICC), which was presented for respectively the between-day comparison for the *in vitro set*-up and between-observers comparison for the *in vivo* set-up. ICC were reported according to the guideline of Koo and Li (2016), where a coefficient <0.50, between 0.50 and 0.75, between 0.75 and 0.90 and >0.90 represents respectively a poor, moderate, good and excellent agreement. Additionally, coefficients of variation were calculated per participant, per device, between observers, with the ratio of the standard deviation and the mean absolute differences between observers. After Bonferroni correction, p-values <0.01 were considered as significant. Statistical analysis was performed in IBM 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 high-end US device are shown in Figure 3. Compared to the high-end US device the Telemed demonstrated a significantly larger diameter (0.023±0.030 cm, p<0.001, Table 1),

whilst 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. ICC comparing 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±0.059cm) and Butterfly (-0.012±0.048cm), whilst a small, but significant, difference was found for the Lumify (0.008±0.009cm, p=0.008, Table 1). Bland-Altman plots (Figure 4) reveal comparable limits of agreement across the three handheld US devices. ICC comparing both measurements per handheld US device was 0.986, 0.990 and 1.000 for Telemed, Butterfly and Lumify, respectively.

In vivo: Interobserver variability

Median age of the participants was 21.0 [IQR 20.0, 22.0] years and 40.0% was male. Additionally, median BMI was 21.7 [IQR 20.4, 23.6], 10% was current smoker and 45% had a family history of cardiovascular disease. Bland-Altman plots for *in vivo* measurements comparing the interobserver 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±0.031 cm), Butterfly (0.020±0.050 cm) or Lumify (-0.003±0.033 cm, Table 1, Figure 5). Limits of agreement were smallest for the Lumify, with similar patterns and limits observed for the Telemed and Butterfly. 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%, 3.5% and 5.2% 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. Between-observer reproducibility of the handheld US devices within the *in-vivo* setting revealed an excellent-to-good interobserver 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 analyses 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* set-ups are commonly used to determine validity of US devices, only few studies focused on understanding (construct) validity using an *in vitro* set-up 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 2015), where the other study investigated optic nerve sheath diameters using a pocket-sized US unit compared to a previously validated portable unit (Johnson 2016). Both studies showed an ICC of respectively 0.73 at lowest for the clinical US device against 0.90 at lowest

for the high-frequency US device (Larsson 2015) and 0.75 for between device comparison and 0.83 for interobserver variability of the pocket-sized US device (Johnson 2016), which seems 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 (van den Heuvel 2018; Prekker 2013; Niu 2019) or adopted other imaging modalities (Viadakovic 2007) using patients. A strength of our study is therefore that the handheld US devices were both tested in *in vitro* set-up and afterwards 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 2015), Vscan (Mantella 2019) and Butterfly (Alfuraih 2021)). Importantly, US devices were tested in relation to varying pathological screening areas (e.g. size of liver, spleen and kidneys (Stock 2015), carotid artery plaques (Mantella 2019) and abdominal aorta (Alfuraih 2021)). At least, these studies provide further support that handheld US are feasible and reliable, with an ICC of ~0.8 with high-end systems. (Stock 2015; Mantella 2019; Alfuraih 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 interobserver variability of the Telemed and Lumify, we found a moderate variability of the Butterfly device. This latter observation may, at least in part, be explained by the US transducer specifications of the Butterfly. Whilst Telemed and Lumify utilize a classic linear array probe, the butterfly probe is differently shaped 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. (Beales 2011; Mathiesen 2000; Triboulet 2006) 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 a good interobserver variability in assessing carotid artery plaque assessment (Alfuraih 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 golden standard. Previous studies, however, have shown standard B-mode images to be robust for measuring arterial characteristics with good precision and accuracy. (Steinbuch 2016; Dogan 2009). 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 not standardized between devices or participants, which 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, 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 2001). Woodman et al. described the method of analysis as well as some coefficient of variations for different determined parameters with the software, with the largest conducted 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, since the quality of ultrasound devices have also been improved in the last two decades just as converting software, the impact of this quality, e.g. image resolution and video compression, on the 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 2016). Due to the explorative character of the in-vivo part of this study, no sample size calculation was performed.

Conclusion

In conclusion, all handheld devices showed an excellent construct validity and intra-observer variability *in vitro* and are therefore suitable to analyze carotid artery diameter. Interobserver variability *in vivo* of the handheld devices were excellent-to-good for Telemed and Lumify, where 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 applicable in measuring carotid arterial diameter.

Acknowledgements

None.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

Figures Captions list

Figure 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

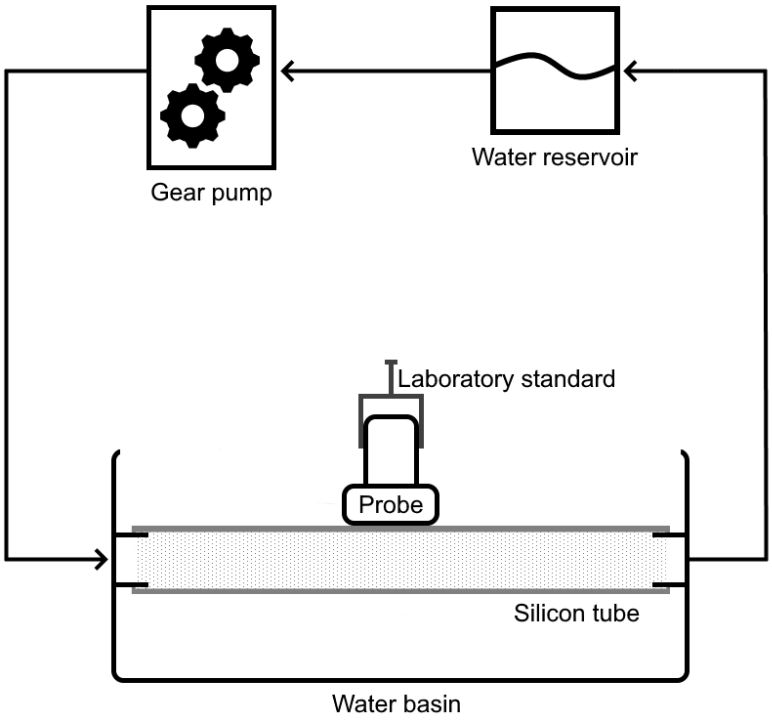
Figure 2. The detected borders of the lumen-arterial wall interface in participants for A) Terason, B) Telemed, C) Butterfly and D) Lumify device, where the yellow square represents the drawn ROI and the yellow lines represent the detected border.

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

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

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

Figures



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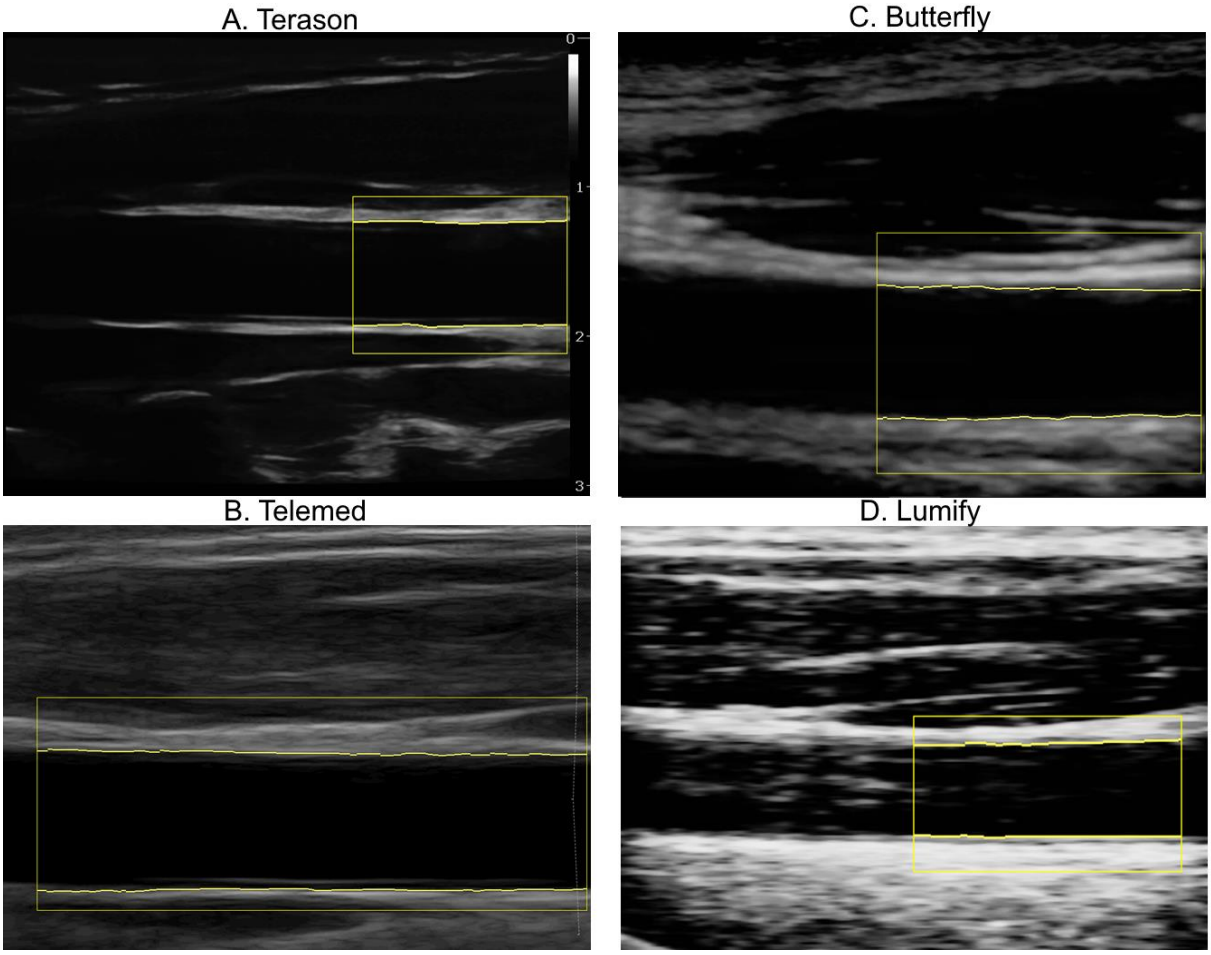

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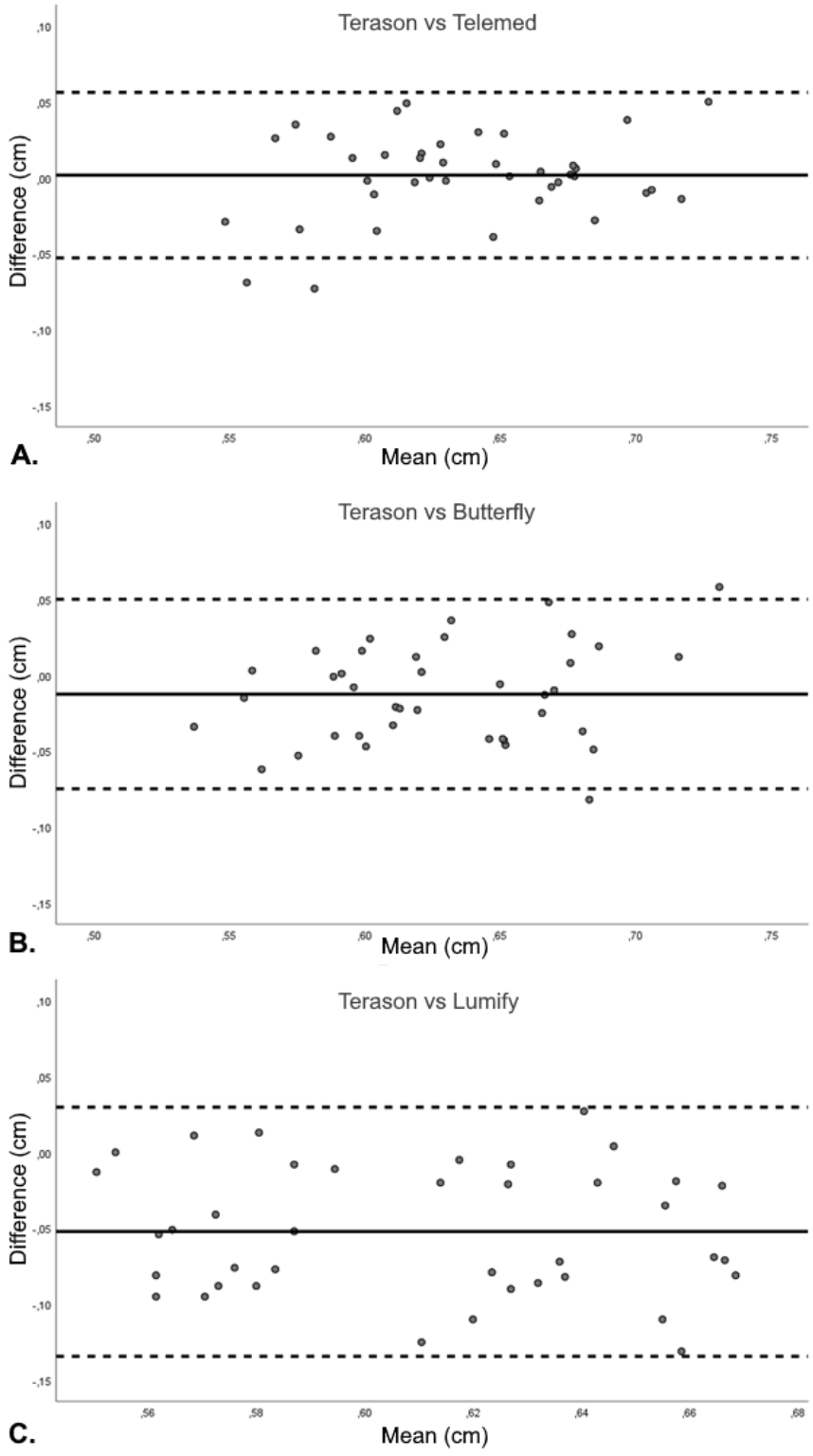

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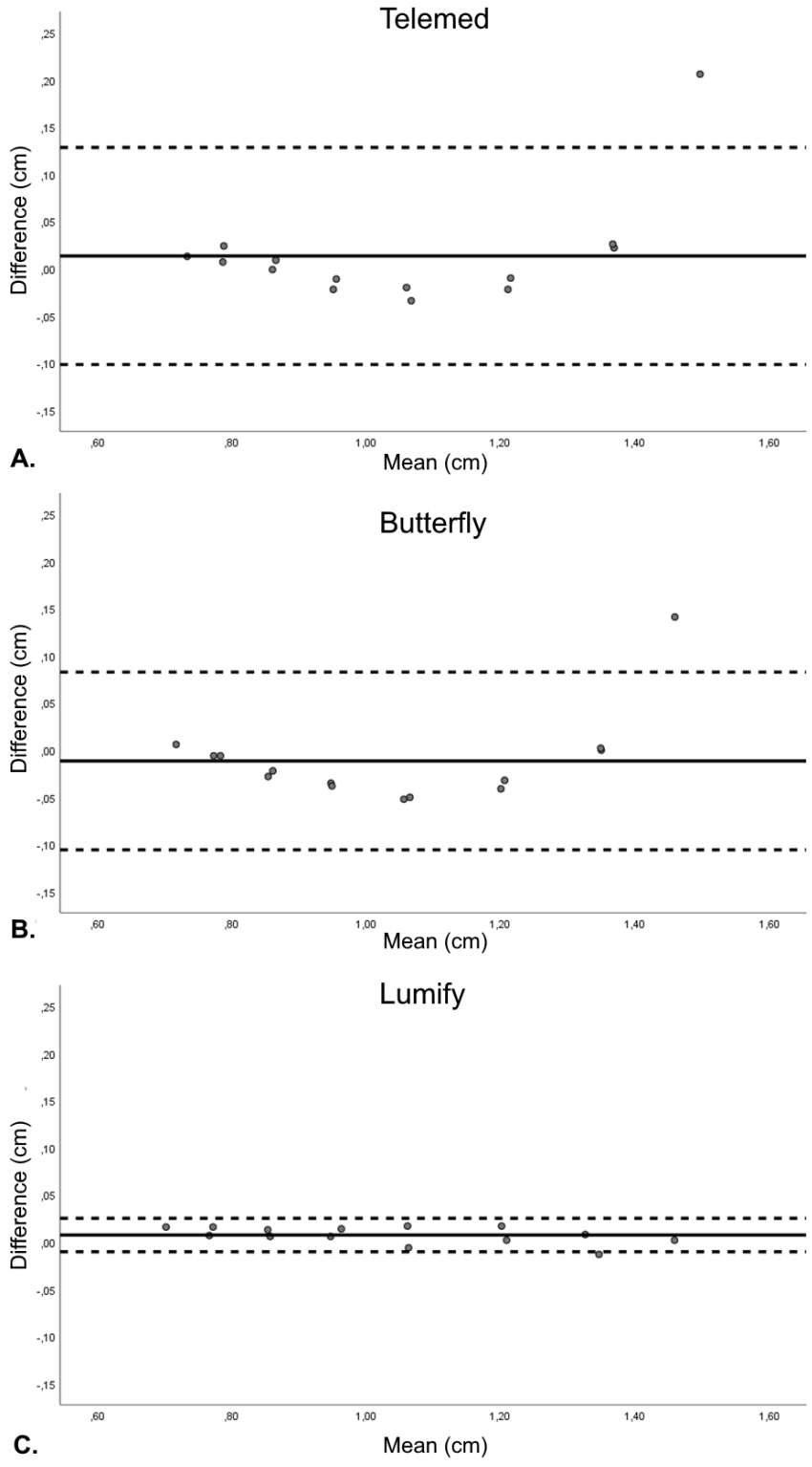

Figure 4. Comparison of the between-day variation of the in-vitro measurement of diameter for A) Telemed, B) Butterfly and C) Lumify device, where the continuous black line represents the mean difference and the dotted black lines represent the limits of agreement per comparison

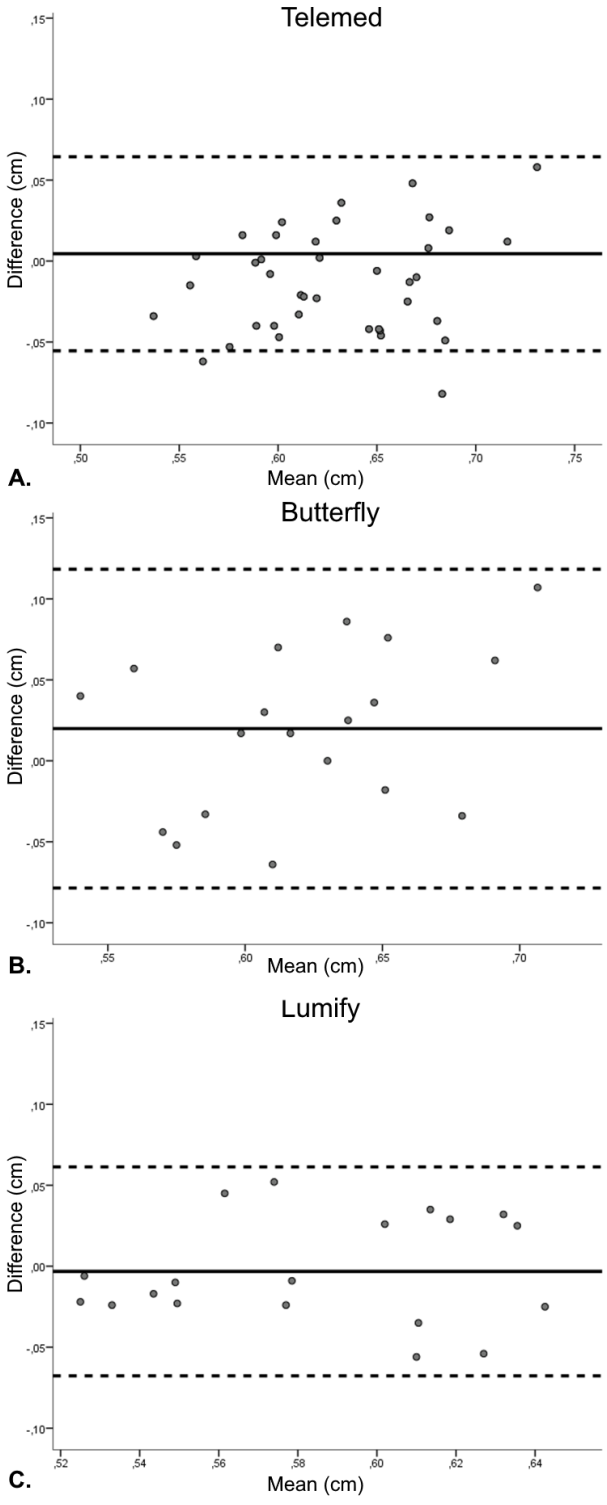

Figure 5. Bland-Altman plots in-vivo measurements of the carotid diameter comparing both operators using the A) Telemed, B) Butterfly and C) Lumify, where the continuous black line

represents the mean difference and the dotted black lines represent the limits of agreement per comparison

Tables

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

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