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ORIGINAL ARTICLE

Technical Validation and Usability of a Portable Ultrasound-Based System for Carotid Assessment of Vascular Ageing: A Pilot Study

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Objective The objective of this work was to investigate technical validation and usability of an innovative, technically simple, easy-to-use, and portable integrated system to assess carotid function and structure by ultrasound.

Methods The studied system integrated a hardware (the Interson SP-L01 embedded ultrasound probe [Interson, Pleasanton, CA, USA]) and a software measuring the instantaneous diameter of the carotid artery in real-time from B-mode ultrasound image sequences (Carotid Studio, by Quipu Srl [Pisa, Italy]). Technical validation was evaluated by intra-operator reproducibility of two measurements acquired by an expert operator, and agreement with state-of-the-art technique (Mylab25 by Esaote SpA [Genova, Italy], Carotid Studio 4.3 by Quipu Srl) was evaluated in laboratory settings in 12 healthy volunteers; usability of the portable integrated system was investigated by administering questionnaires to users and the results were reported with scores based on a five-point scale.

Results Twelve (12) healthy volunteers (five men, mean age 44.5±13.6 years, free of cardiovascular disease or risk factors), were recruited. Agreement with state-of-the-art technique was satisfactory, with no significant bias. Coefficient of variation (intra-operator reproducibility) was 3.2% (2.5% SD) for intima-media thickness, 0.9% (0.7% SD) for diameter, and 2.5% (2.2% SD) for distension. Usability questionnaires showed an overall positive judgement of the integrated system with respect to the traditional one, obtaining an average score greater than 4 (on a five-point scale).

Conclusions A portable, innovative prototype to easily assess ultrasound carotid parameters of vascular ageing was successfully designed, developed, and demonstrated to be comparable with state-of-the art technique. Usability was also satisfactory.

Keywords Carotid IMT • Carotid distensibility • Ultrasound • Portable system

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Introduction

Cardiovascular disease (CVD) represents the leading cause of morbidity and mortality worldwide [1]. However, effective treatments are available and if adopted promptly are able to prevent or minimise the burden of cardiovascular events. Therefore, early detection of individuals predisposed to CVD is of crucial importance to prevent cardiovascular events. A number of prediction scores, based on traditional cardiovascular factors such as age [2], cholesterol [3], smoking [4] and blood pressure [5] are used to predict risk in the general population, but their accuracy in predicting cardiovascular risk in individuals varies considerably across populations [6]. Although most CVD can be explained by traditional risk factors, there is substantial individual variation in the vascular ageing process. Thus, in the past few decades, the use of non-invasive techniques assessing the extent of preclinical vascular damage (atherosclerosis or arteriosclerosis) as a risk modifier to improve risk prediction and decision making, has been extensively investigated.

Since vascular ageing is a systemic process, early detection of arterial disease in apparently healthy individuals has focussed on specific arteries and, in particular, the carotid arteries. The investigation of local stiffness of superficial arteries, such as the carotid, is of interest because it does not require assumptions regarding models of the circulation, at variance with carotid-femoral pulse wave velocity, the reference technique for large artery stiffness assessment [5]. Carotid-femoral pulse wave velocity estimation is based on a propagative model of the arterial system [7]; instead, local stiffness of superficial arteries, such as the carotid, can be determined directly from the change in pressure driving the change in volume [8], and non-invasively at various sites along the arterial tree by ultrasound technique in combination with the local pulse pressure [9]; moreover, the carotid artery is a common site of atherosclerosis development, allowing simultaneous assessment of atherosclerosis and arteriosclerosis [10].

However, current guidelines do not recommend systematic use of carotid ultrasound intima-media thickness (IMT) to improve risk assessment [1] due to its limited added value compared to the Framingham Risk Score in predicting future CVD [11]. Other novel studies contrast this view, demonstrating prognostic values for IMT change over time [12], as do carotid stiffness measurements [13].

Indeed, vascular ageing is not a static picture: increasing evidence supports the concept that repeated measures may be more useful than single measures, in order to show treatment-induced changes over time and highlight trajectories of risk [12,14].

Currently, the methods that allow measurement of local arterial stiffness and IMT require qualified and experienced operators as well as dedicated instruments (i.e., ultrasound equipment and data processing system). The technical challenge is to provide simple, accessible tools still guaranteeing high-quality data performance. Therefore, we propose an innovative integrated device that combines a robust medical device software for carotid parameters assessment with a new generation of low-cost portable ultrasound scanners that can be used in cardiovascular applications. Here, we present a prototype of this portable integrated system, designed to measure carotid IMT, remodelling and stiffness in large screening campaigns, even in non-hospital facilities. The aim of this pilot study was to investigate technical validation and usability of this novel integrated system. A description of the hardware-software integration process is also provided.

Material and Methods

Integrated System

The main components of the integrated system are a software medical device for ultrasound image processing and an USB ultrasound probe.

Software for ultrasound image processing

Carotid Studio (Cardiovascular Suite, Quipu srl, Pisa, Italy) is a software for the estimation of vascular parameters by ultrasound imaging, based on a validated contour tracking algorithm [15,16].

Carotid Studio is a software medical device, compliant with European regulatory requirements and CE marked according to the European Directive 93/42/EEC and subsequent amendments and supplements for medical devices.

The software runs on a computer and measures the diameter (D) and the IMT in B-mode ultrasound image sequences of the longitudinal section of the carotid artery. The measurement is obtained automatically and in real-time, thanks to a well validated method that is based on a contour tracking algorithm [9]. The two borders of the artery are automatically detected, and the diameter is computed as the distance between far and near media-adventitia interfaces. Carotid measurements were previously validated against a gold standard approach based on radiofrequency signal processing [9].

The instantaneous diameter estimation, together with the systolic and diastolic pressure values, can be used to provide stiffness parameters. In particular, carotid distension (ΔD), the stroke change in diameter during the cardiac cycle, is calculated as the difference between the systolic and diastolic diameter values; carotid distensibility is computed as $\Delta A/(A*\Delta P)$, where A represents the diastolic lumen area, evaluated from the diameter values (assuming that the cross-section of the artery is circular), ΔA is the stroke change in lumen area within a complete cardiac cycle, and ΔP the local pulse pressure [17].

USB ultrasound probe

In standard ultrasound imaging, the system generally works with a passive transducer probe, i.e. an analogue coaxial cable directly connects the piezo elements of the probe to an analogue electronic interface located in the main unit of the device. Nowadays, thanks to the miniaturisation in electronic components, the new trend in ultrasound imaging is toward

digital ultrasound probes [18]. These devices embed in the probe itself the analogue front-end and part of the digital processing. This newly developed system no longer needs an expensive and bulky analogue cable, now replaced by a digital standard cable (usually USB) or even by a wireless connection. The cumbersome main unit has been replaced by a smarter and smaller device, such as a smartphone, tablet, or PC, where a dedicated software application is able to control the probe and to display the image. In particular, digital probes connected to a mobile device or laptop can be widely used to build portable systems. Currently, due to limitations in powers, not all scanning features of older ultrasonic devices are implemented [19]. However, these limitations are increasingly being overcome by the newer devices on the market.

In this work we considered one of the digital ultrasound probes available on the market, the SP-L01[2] Array Probe of the SiMPLi™ Series Point-of-Care USB Ultrasound (Interson, Pleasanton, CA, USA). This probe is CE marked and US Food and Drug Administration (FDA) approved for its usage in clinical practice; it has been designed to be directly connected via USB cable to a Windows PC to obtain a portable hand-held ultrasound imaging system. The hardware comes with proprietary software; it is also possible to obtain the complete technical documentation describing the Application Programming Interface (API) used to communicate and control the probe.

Technical Validation

The integrated developed system was compared to the state-of-the-art approach consisting of a standard ultrasound machine with attached transducer, a video converter and a computer console with embedded software.

Study population

Twelve (12) healthy volunteers (five men), aged 44.5±13.6 years, free of CVD or risk factors, were recruited as part of the control group in a larger study protocol aimed at investigating vascular alterations in a wide range of vascular diseases (CCeAD[2], Hypertension, Spontaneous Coronary Artery Dissection [SCAD] and FibroMuscular DysplasIA [FMD] – the FUCHSIA study). The study was approved by the Ethical Committee of the Area Vasta Nord Ovest Toscana (protocol number 1352). Informed consent was obtained from all individual participants included in the study.

Experimental setup

All the acquisitions were performed in a temperature-controlled room with subjects in supine position, according to the guidelines [8]. Brachial blood pressure was taken in the left arm after 5 minutes rest by a trained operator with an automated oscillometric device (Omron 705-IT, Kyoto, Japan). Brachial blood pressure measurement was repeated three times at 2-minute intervals and the average value was used for analysis.

For characterising the population, mean diameter (D), IMT and distension were computed by using the reference technique. In addition, also the distensibility value was computed, combining the measurement of diameters with the brachial blood pressure of the subjects.

Experimental protocol

Technical validation of the portable integrated system, schematised in Figure 1 (a), was assessed for D, IMT and ΔD direct measurement. B-mode longitudinal anterior scans of the left common carotid arteries, 1 cm proximal to the carotid bulb, were obtained by an expert operator; for the 12 healthy volunteers, each scan was acquired and analysed twice with both reference approach and new integrated device in order to evaluate their performance in terms of intra-observer variability.

Reference approach was composed by a standard ultrasound machine (MyLab 25, Esaote, Florence, Italy, 10-MHz linear array probe) linked through a frame-grabber to the Carotid Studio software on an external PC, as schematised in Figure 1 (b).

After each acquisition, the probe was removed and repositioned by an expert operator (experience in the field of vascular ultrasound analysis >3 years) in order to evaluate intra-observer variability as it might occur in real measurement situations.

Statistical Analysis

All statistical analyses were conducted using NCSS Statistical Software (NCSS, LLC. Kaysville, UT, USA, ncss.com/software/ncss). Continuous variables were presented as mean and standard deviation. For each subject two scans were acquired and analysed by an operator with both the reference approach (obtaining two measurements for subject) and the new integrated device (obtaining two measurements for subject); intra-observer variability of reference approach and of the new integrated device for every carotid parameter was calculated by coefficients of variation (CV). CV was expressed as the percentage ratio of the standard deviation to the mean value of the two measurements. Final reproducibility was reported as mean ± standard deviation of individual coefficients of variation.

In addition, for every carotid parameter, the agreement between the mean of the two measurements obtained with the integrated system and the mean of the two measurements obtained with the reference technique was evaluated by Bland-Altman analysis [20]. Finally, intra-class and Pearson correlation coefficients were computed.

Usability Assessment

Usability of the new system was assessed by following the IEC 62366-1:2015 *Medical devices — Part 1: Application of usability engineering to medical devices*, according to which the usability is defined as the "characteristic of the user interface that

[2] https://interson.com/medical/simpli-sp-medical/.

[2] Very high-Frequency Ultrasonography for arterial phenotyping in patients with Cervico-Cerebral Artery Dissection

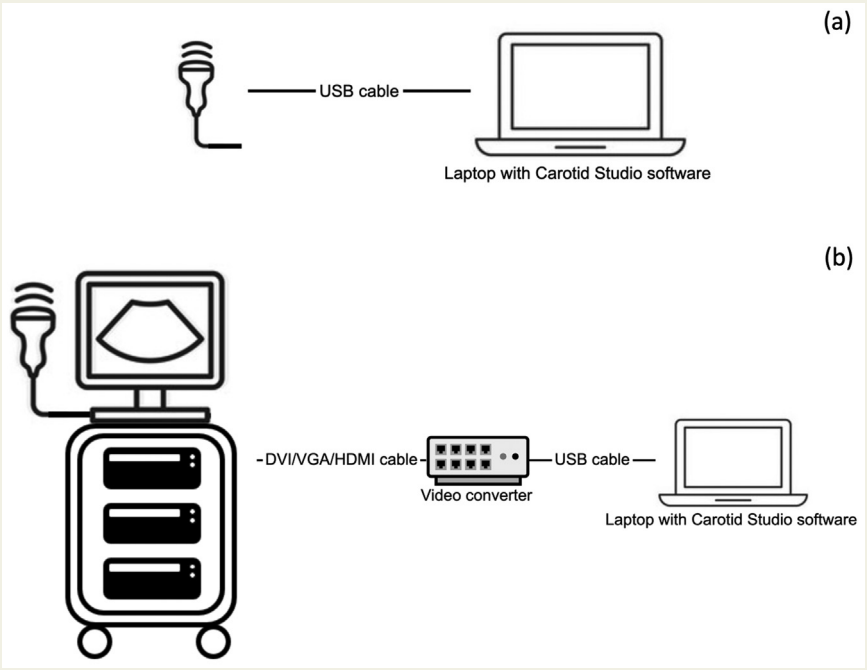

Figure 1 Schemas of the portable integrated system (a) and of the reference configuration system (b).

facilitates use and thereby establishes effectiveness, efficiency and user satisfaction in the intended use environment" [21].

Usability evaluation process can be used to discover the possible use errors that can be avoided before they happen in real clinical practice by re-designing accordingly the system. The analysis of the primary operating functions was performed in order to define the expected tasks of the operator during the system use and consequently to identify some possible use errors. The identified primary operating functions include mainly the Preparation and Configuration Phase and the Examination Execution Phase that can be broken down into a series of user interactions, the so-called "representative tasks".

In particular, the identified primary operating functions and the representative tasks are reported below:

1. Preparation and Configuration Phase
   - 1.1. Run the software
   - 1.2. Plug in the USB probe
   - 1.3. Launch a new study
   - 1.4. Create a new patient
   - 1.5. Choose the USB probe as source
   - 1.6. Create the study
2. Examination Execution Phase
   - 2.1. Calibrate the B-mode image
   - 2.2. Image the carotid artery according to clinical best practice, as recommended by the Mannheim consensus [22] and the expert consensus document [8]
   - 2.3. Draw the B-mode Region-Of-Interest (ROI)
   - 2.4. Start the analysis
   - 2.5. Adjust the B-mode image by using the dedicated controls
   - 2.6. Save one or more documents adjusting the ROI if necessary
   - 2.7. Open the saved document and enter the blood pressure for computing elasticity parameters

Based on the identified tasks, a preliminary evaluation about the usability of the innovative portable integrated system was performed thanks to questionnaires distributed to a small group of physicians testing the system, according to the following protocol.

Usability protocol

A pre-test questionnaire was administered to the physicians who took part in the usability evaluation process. This questionnaire was used to profile the participants (i.e. age, gender, occupation, expertise in vascular biomarkers and previous experience with the system in the traditional configuration) and to verify their experience in the field.

After the pre-test questionnaire, the clinicians underwent a short training phase performed thanks to a multimedia presentation that explained briefly the fundamental steps for the successful execution of the carotid analysis, in order to eliminate potential bias of the study [23]. After the presentation, each participant had a free 15 minute period to become familiar with the integrated system and with its functionalities.

After completing the pre-test questionnaire and the training, each participant was asked to attempt the representative tasks, previously described, using the integrated system.

After each participant attempted all tasks by completing an entire exam, they then filled in a post-test questionnaire.

All the answers of the post-test questionnaire were valued by five-point Likert scale. For each question, it is considered acceptable a score equal or greater than 3.

Both pre-test and post-test questionnaires were developed and delivered by Google Form. Web-based questionnaires with respect to paper-based questionnaires avoid ambiguous hand writing, are in general more graphically appealing and answers can be automatically formatted for being directly used with statistical tools [24]. Both pre-test and post-test questionnaires are available as online supplements.

Results

Integrated System

The development of the integration between the ultrasound probe and the Carotid Studio software application was based on the Software Development Kit (SDK) documentation provided by the manufacturer of the probe. Two (2) different software modules have been developed:

- a video interface module which was able to retrieve the images coming from the ultrasound system and to send them to the software video player for analysis
- a control module that let the probe to intercept commands from the user interface and to automatically adjust its ultrasound parameters (for example image depth, gain, focus depth, etc.).

Both software modules were developed in C++ programming language by integrating the SDK with the Qt platform (https://www.qt.io/) for software development. The SDK contained the description of the Application Programming Interface (API) used to communicate with the probe and it also provided the way to control the probe itself (Figure 2). SDK stands for Software Development Kit which is a collection of tools, libraries, relevant documentation, code samples and processes that guides developers in the creation of software applications on a specific platform. The kit is generally provided into one installable package. The software modules were finally compiled with Microsoft Visual C# 2015/.Net Framework 4.6.1 for Windows operating system environment. An example of the Graphical User Interface (GUI) of the software within the integrated system is shown in Figure 3.

Technical Validation

Reproducibility and agreement with reference approach

Measurements of carotid D, IMT and ΔD were successfully analysed from all 48 sequences of images acquired with both the reference technique and the portable approach in the 12 healthy volunteers. Study population characteristics are shown in Table 1.

Mean CVs of the measurements were: 0.9% (0.7% SD) for D, 3.2% (2.5% SD) for IMT, and 2.5% (2.2% SD) for ΔD with the reference technique and 1.1% (1.1% SD) for D, 3.8% (3.2% SD) for IMT, and 4.5% (3.3% SD) for ΔD with our portable integrated system.

Bland-Altman agreement between the two systems expressed and mean ± 1.96*SD is 0.08±0.210 mm for D (Figure 4), -0.013±0.050 mm for IMT (Figure 5), and 0.018±0.092 mm for ΔD (Figure 6) as shown in the plots below. Bias was not significant for all the three parameters since the 95% confidence interval of the bias includes zero [20].

Intra-class correlation coefficients (ICC) of the portable integrated and the reference system data were ICC equal to 0.950 (CI, 0.835–0.985) for diameter, ICC equal to 0.838 (CI, 0.530–0.950) for distension, and ICC equal to 0.828 (CI, 0.508–0.947) for IMT.

Pearson correlation coefficients were equal to 0.950 (CI, 0.813–0.984) for diameter, 0.840 (CI, 0.496–0.948) for distension, and 0.842 (CI, 0.500–0.948) for IMT.

Usability Assessment

All data obtained from the pre-test questionnaire has been summarised in Table 2.

These data confirm that the physicians were all experts in the field of ultrasound carotid biomarkers and that all clinicians were used to performing carotid biomarker estimation with the reference system configuration, by using a common ultrasound equipment with real-time connection to an external laptop running Carotid Studio software.

All data obtained from the post-test questionnaire are summarised in Table 3 and expressed as mean and standard deviation of the obtained scores (except for the last topic which was an open question and observations were textually reported).

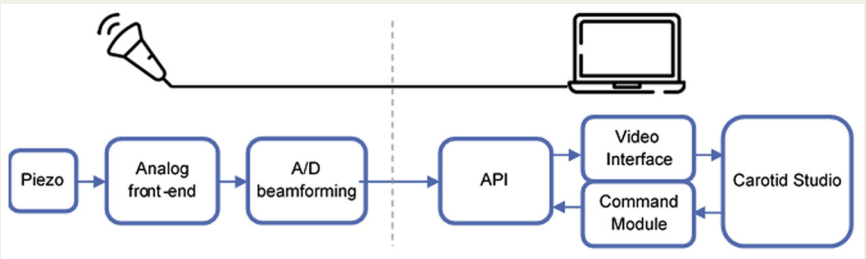

Figure 2 Block diagram of the main modules of the systems integration.

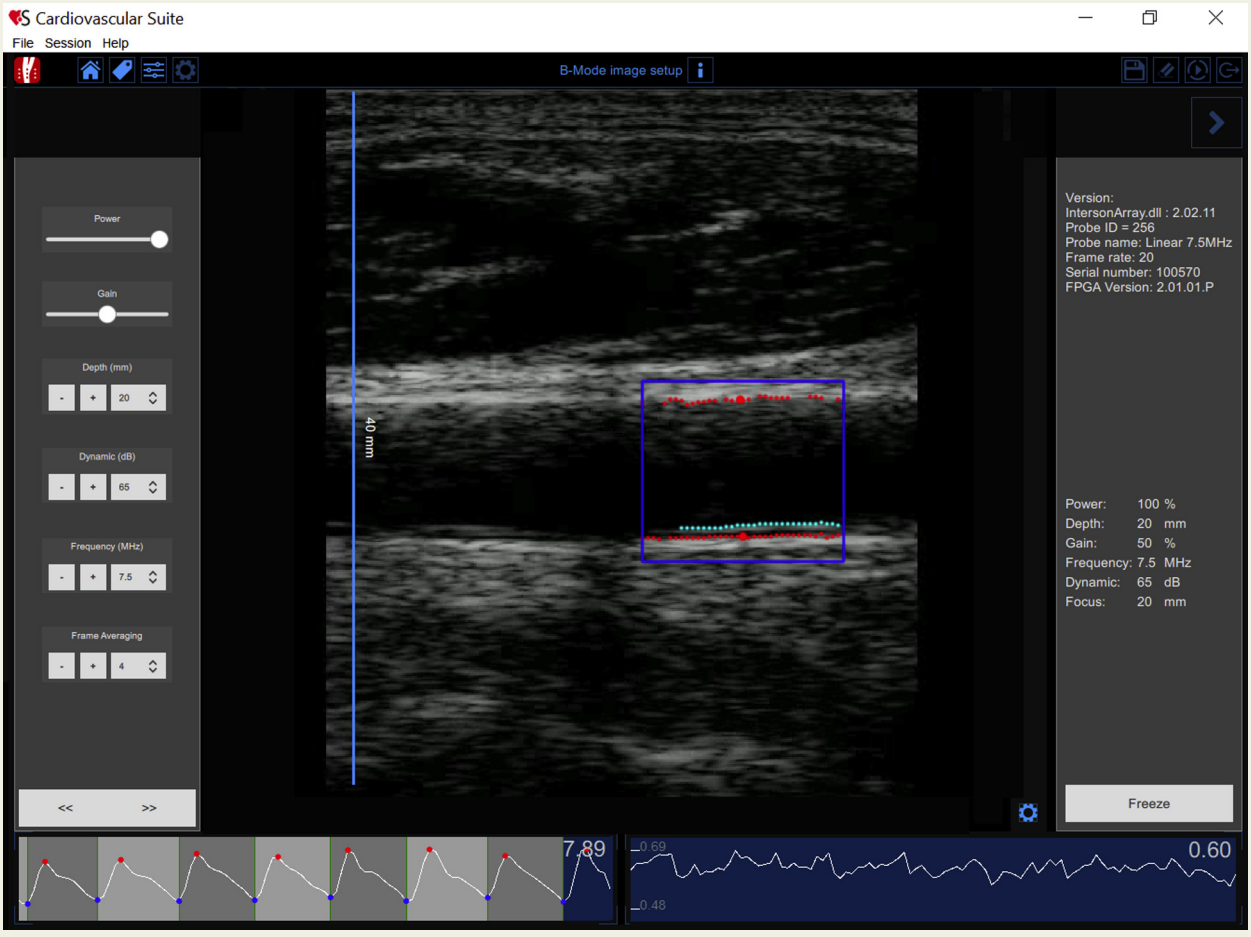

Figure 3 Example of the Graphical User Interface (GUI) of the integrated system.

The data obtained in the post-test questionnaire shows an overall positive judgement regarding the usability of the integrated system with respect to the traditional one. In particular, the first group of questions aiming to investigate the general quality of the integrated system obtained a positive although improvable result (mean group score 4.50±0.62); the second group of topics which aimed to define the likelihood that the user will perform the representative tasks with the final system received a very positive judgement (mean group score 4.88±0.25); and the third part of the questionnaire intending to explore the quality of the potential usage of the integrated system in usual practice again obtained very good results (mean group score 4.65±0.58). In addition, one of the participants reported as a personal consideration the need for a greater degree of automation in probe settings and analysis algorithm and the possibility of using this system with a touch graphical interface.

Discussion

A portable innovative prototype to easily assess ultrasound carotid parameters has been successfully designed, developed, and presented with this first pilot study.

The new ultrasound-based imaging system has been technically validated in a small population by comparison with the reference approach, revealing reproducibility of the measurements and agreement with state-of-the-art technique comparable to values reported in the literature [9,25].

Moreover, the usability of the new integrated system has been evaluated thanks to questionnaires distributed to physicians testing the system and the results show that the new approach is overall very satisfying with regard to its general quality, its ease for the users who performed all the representative tasks, and its potential use in clinical practice. Despite these positive evaluations, the need for improvement of some settings emerged. More specifically, the obtained scores underline the usefulness of reducing the time required to complete the configuration and for improving the suitability of buttons' arrangement for probe control; in particular, the GUI will need to be improved for a greater quality and ease of controlling and adjusting the probe parameters (e.g., gain, depth, etc.) during the examination. In the questionnaire, also the need of a greater degree of automation in probe settings, analysis algorithm, and use of touch interface emerged. The small sample size is a limitation of this paper to be acknowledged: the work aims to be a pilot study for

Table 1 **Study population characteristics.**

Variables	Mean Values ± SD or n (%)
Age (yr)	44.5±13.6
Men, n (%)	5 (42)
Body weight (kg)	69.3±15.6
Body height (cm)	168.7±13.0
BMI (kg/m2)	24.1±3.1
bSBP (mmHg)	122±11
bDBP (mmHg)	77±6
Carotid mean diameter (mm)	6.556±0.768
Carotid distension (mm)	0.521±0.152
Carotid distensibility coefficient (10^{-3} * kPa^{-1})	27.5±9.7
Carotid IMT (mm)	0.519±0.092

Values are mean ± SD or n (%).
Abbreviations: BMI, body mass index; bSBP, brachial systolic blood pressure; bDBP, brachial diastolic blood pressure; IMT, intima media thickness.

sizing the investigated parameters for carotid assessment and results need to be more thoroughly validated in subsequent studies on a larger population.

The new integrated system is able to provide carotid parameters with a simpler approach than the reference method: this low-cost portable integrated system could be well applied in screening campaigns even in non-hospital facilities and in low-resource settings. Risk assessment using carotid ultrasound focusses on the measurement of the IMT, the presence and characteristics of plaques, as well as the assessment of carotid remodelling and stiffness [26]. Carotid IMT is the thickness of the intimal and medial layer of the carotid artery and is considered a marker for the early

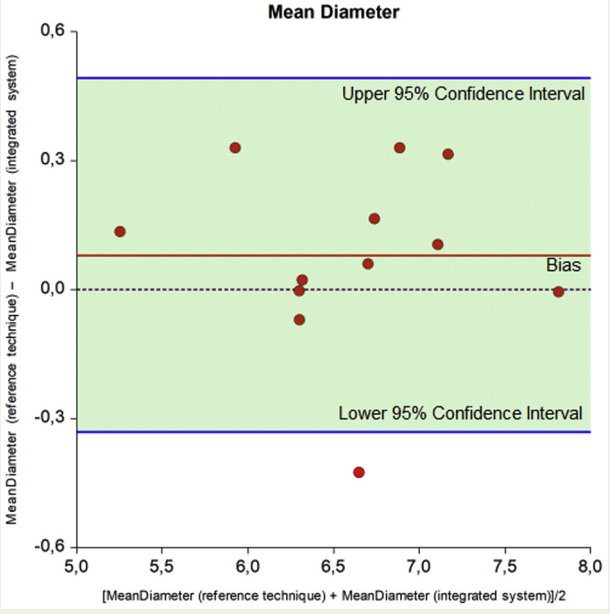

Figure 4 Bland-Altman plot for Mean diameter. The mean difference is the estimated bias, and the standard deviation (SD) of the differences measures the random fluctuations for Mean diameter.

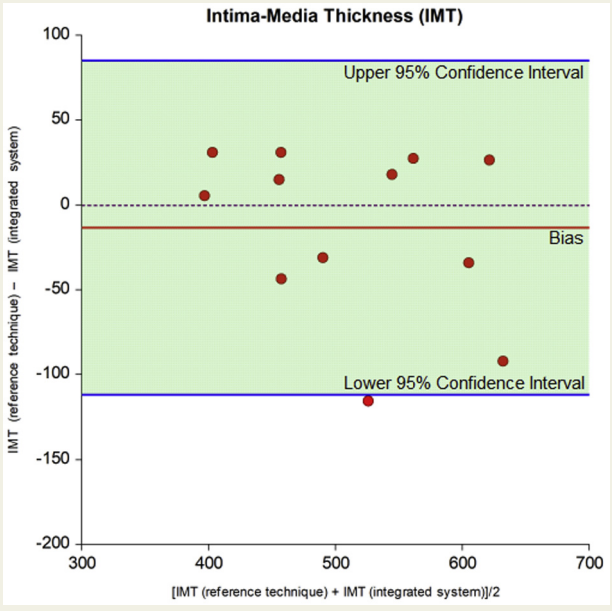

Figure 5 Bland-Altman plot for intima-media thickness (IMT). The mean difference is the estimated bias, and the standard deviation (SD) of the differences measures the random fluctuations for IMT.

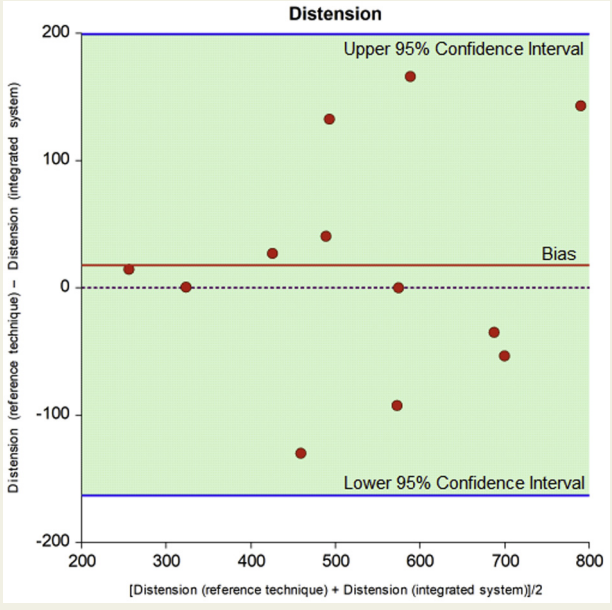

Figure 6 Bland-Altman plot for Distension. The mean difference is the estimated bias, and the standard deviation (SD) of the differences measures the random fluctuations for Distension.

Table 2 Results of the usability pre-test questionnaire.

	Participant_01	Participant_02	Participant_03	Participant_04
Profession	Researcher	Clinician	Clinician	Researcher
Previous knowledge/experience of ultrasound vascular biomarkers	More than 3 yr	More than 3 yr	More than 3 yr	More than 3 yr
Previous usage of Carotid Studio software in real-time analysis with reference ultrasound equipment	More than 3 yr	More than 3 yr	More than 3 yr	More than 3 yr

diagnosis of atherosclerosis [27]. Current guidelines do not recommend systematic use of carotid ultrasound IMT to improve risk assessment [1], due to lack of standardisation regarding its measurement, its high variability and low intra-individual reproducibility, resulting in a limited added value compared to the Framingham Risk Score in predicting future CVD [11]. However, novel studies are contrasting this view. Recently, Willeit et al. reported in a large meta-analysis of 119 clinical trials involving 100,667 patients that carotid IMT reduction under treatment is a reliable predictor of cardiovascular event reduction: reduction of yearly carotid IMT progression results in reduction in CVD event rate, establishing a role for serial IMT assessment as a surrogate marker in clinical trials [12].

Carotid ultrasound allows assessment of arterial stiffness in addition to IMT. Whereas aortic stiffness, evaluated by carotid-femoral pulse wave velocity (PWV) [8], is an established predictor of cardiovascular events [10,16], growing evidence indicates an independent predictive value of carotid stiffness too [13,26]. Furthermore, it is reported that

Table 3 Results of the usability post-test questionnaire, expressed as mean ± standard deviation of the obtained values.

First part aims to investigate the general quality of the integrated system	1. How do you rate the user-friendliness of the graphical interface?	4.50±0.58	Mean group score 4.50±0.62
	2. How do you evaluate the easiness of the hardware-software configuration?	5.00±0.00	
	3. How do you consider the adequacy of time required to complete the configuration?	4.25±0.96	
	4. How do you rate the suitability of buttons' arrangement for probe control for the correct execution of the actions?	4.25±0.96	
Second part aims to define the likelihood that the user will perform the representative tasks with the integrated system	5. Was the operator able to set-up the B-mode image (calibration and region of interest [ROI])?	5.00±0.00	Mean group score 4.88±0.25
	6. Was the operator able to manage (start, pause, cancel, resume), save and successfully conclude the analysis?	5.00±0.00	
	7. Was the operator able to clearly read the results of the analysis in the saved document(s) and export them?	4.75±0.50	
	8. Was the exam/analysis processing time reasonable?	4.75±0.50	
Third part aims to explore the quality of the potential usage of the integrated system in usual practice	9. How do you rate the manageability of the probe in order to find the correct and satisfying scan?	4.75±0.50	Mean group score 4.65±0.58
	10. How do you rate the quality and easiness of controlling and adjusting the probe parameters (e.g., gain, depth, etc.)?	4.00±0.82	
	11. How do you rate the transportability and management of the integrated system?	4.75±0.50	
	12. How the operator is satisfied with the performance of the entire exam session?	4.75±0.50	
	13. Do you agree with the potential usage of the integrated system in screening campaign and/or in non-hospital facility?	5.00±0.00	
	14. Below the operator can report his/her personal considerations	- Need of a greater degree of automation in probe settings and analysis algorithm - Use of touch interface	

aortic and carotid stiffness are differentially associated with target organ damage in hypertensive patients, and carotid stiffness is associated with cardiac organ damage [17]. Furthermore, carotid remodelling may be assessed too by carotid ultrasound. Carotid diameter enlargement is associated with a higher stroke incidence, as well as with a higher risk of any cardiovascular event and mortality [13]. Thus, the availability of simple and portable tools, able to guarantee high-quality data performance, is desirable since it constitutes an opportunity for the implementation of novel risk prediction models.

Our preliminary results pave the way for a faster and simpler evaluation of relevant parameters, describing comprehensively different aspects of the vascular ageing process and allowing multiparametric, reliable, assessment of individual cardiovascular risk. Furthermore, the new smart system will allow tracking through repeated measures the effect of targeted non-pharmacological and pharmacological treatments, thus accelerating the clinical development of new cardiovascular drugs.

Conclusions

A portable, innovative prototype to easily assess ultrasound carotid parameters has been successfully designed, developed, and demonstrated to be comparable with state-of-the art technique. Usability was also satisfactory.

Competing Interests

Elisabetta Bianchini and Vincenzo Gemignani are co-founders of QUIPU s.r.l., Pisa, Italy a spin-off company of the Italian National Research Council and the University of Pisa developing software medical devices.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2021.06.530.

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