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Variability and reproducibility of carotid structural and functional parameters assessed with transcutaneous ultrasound – Results from the SAPALDIA Cohort Study

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ABSTRACT

Objective: Carotid intima media thickness (CIMT) and local stiffness are vascular biomarkers of atherosclerotic burden. We investigated the variability and reproducibility of clinically relevant structural (CIMT, lumen diameter) and functional parameters (strain, distensibility, compliance, β-stiffness index, Peterson's elastic modulus and Young's elastic modulus) measured in B-mode ultrasound sequences of the common carotid artery in the second follow up of the **S**wiss Cohort Study on **A**ir **P**ollution **a**nd **L**ung and Heart **D**iseases **I**n **A**dults (SAPALDIA3).

Methods: Ultrasound sequential images were examined twice over a 1 cm segment across at least one heart cycle in 165 SAPALDIA3 participants. To assess variability and reproducibility of structural and functional parameters, individual coefficients of variation (CV), intraclass correlation (ICC), Bland–Altman plots and mixed effect regressions were used.

Results: ICCs of repeated examinations ranged between 0.67 and 0.77 for blood pressure indices, between 0.87 and 0.97 for structural properties and between 0.75 and 0.79 for functional parameters. CV was lowest in structural parameters (1.6–4.6%), followed by blood pressure (5.1–7.9%) and functional indices (11.0–13.1%). Variations in all parameters were predominantly explained by subjects (>74% in functional, >82% in structural properties). Bland–Altman plots for functional indices showed mean and standard deviation of the respective mean value of 4.2(19.6)% for strain, 1.9(24.4)% for distensibility, 2.4(22.2)% for compliance, 3.0(24.4)% for β-stiffness index, 0.9(25.7)% for Peterson's elastic modulus and 1.2(27.9)% for Young's elastic modulus.

Conclusion: The results show that SAPALDIA3 measurements of transcutaneous ultrasound examinations have an excellent reproducibility of structural parameters and a good reproducibility of functional indices.

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1. Introduction

Cardiovascular diseases are a major cause of death [1]. The development and application of validated surrogate endpoints to identify risk and evaluate therapeutic intervention have become increasingly available in the last decades [2–5]. Based on numerous clinical studies non-invasive structural or functional endpoints as carotid intima media thickness (CIMT) and lumen diameter (LD) assessed by B-mode ultrasound or aortic stiffness assessed by pulse wave velocity are now widely accepted as identifiers of the atherosclerotic status and predictors of atherosclerotic events, respectively [6–9]. Carotid functional indices such as distensibility are under discussion regarding their validity and sensitivity to predict cardiovascular events in the general population [9–12].

The widespread availability of non-invasive high resolution ultrasound in combination with advanced automated reading software [13] allow the in-vivo evaluation and modelling of the haemodynamic effects and properties of the arterial wall in humans in cross-sectional and follow-up studies [14]. CIMT and LD describe the anatomic and structural properties of the CCA segment, whereas vascular function can be described by changes in CIMT and LD across the heart cycle.

Accuracy and repeatability of CIMT and carotid LD measurements have a decisive impact on the sample sizes needed for cross-sectional and longitudinal risk identification and assessment of treatment efficacy. This implies that the evaluation of data quality needs a thorough methodical validation of all parameters used for future analyses within the same study setting. We therefore investigated the variability and reproducibility of carotid structural wall parameters (CIMT, LD) and the carotid functional indices strain, distensibility, compliance, β-stiffness index, Peterson's elastic modulus and Young's elastic modulus by means of repeated ultrasound scans. For our purposes a randomly selected sample of participants of the SAPALDIA3 cohort, a general population study (second follow up of the **S**wiss Cohort Study on **A**ir **P**ollution **a**nd **L**ung and Heart **D**iseases **I**n **A**dults), was selected and scanned a second time on top of the study visit. To better understand the significance of our reproducibility study, we additionally compared our results with different population based studies [9,15–22].

2. Methods

2.1. Study design and subjects

The SAPALDIA multicentre cohort study recruited in 1991 is a population-based random sample of adults (18–60 years) from eight areas of Switzerland representing rural and urban environmental conditions (Aarau, Basel, Davos, Genève, Lugano, Montana, Payerne, Wald) [23]. SAPALDIA3 was executed in 2010/2011. It is the second follow-up of the SAPALDIA cohort after the previous survey's in 2001/2002 and 1991 [23,24]. In SAPALDIA3 carotid B-mode ultrasound scans were performed in 3489 participants (49% males, 51% females) turning 50 years within the same year or older, mean age 63.9 (SD 8.1, range 50–81) years. A health screening questionnaire was applied before health examinations and participants were excluded partially or fully if a health risk for a clinical examination existed. Ethical approval had been granted by the respective Swiss cantonal ethical committees. Participants gave written informed consent according to their preferences either globally for all examinations or separately for single assessments.

To assess variability and reproducibility of carotid structural and functional parameters repeated scans were performed in a representative random sample of 165 SAPALDIA3 participants (see Fig. 1). Participants were examined on two different occasions, at least one night in between scans and within a maximum of three months. Sequential image analyses were consecutively performed within SAPALDIA3 and all readers were blinded in terms of the initial and the repeat ultrasound examination date (intersession validation).

2.2. Ultrasound examination

Examinations were performed following a standardised ultrasound scan protocol. Eight standardised ultrasound instruments (Fukuda Denshi UF-870) equipped with an LA38 5–16 MHz linear array transducers. The ultrasound temporal resolution was 10.47 ms per frame. All sonographers were trained, certified prior to study entry and supervised by two collaborating vascular labs: the Department of Vascular Medicine at the Academic Medical Center/Imagelab, University of Amsterdam and Erichem, The Netherlands and the Division Sport and Exercise Medicine at the Institute of Exercise and Health Science, University of Basel, Switzerland. To guide sonographers through the scan procedures, all ultrasound instrumentation was equipped with the SAPALDIA3 application protocol, jointly developed by Vascular Imaging/Imagelab, ISSW and Fukuda Denshi.

Before start of the ultrasound examination, each individual rested in supine position for at least 10 min in a 22–25 °C dimly lit room. During the bilateral carotid scans the head rested comfortably against a 45° foam wedge to standardise the horizontal and ear-to-ear angles of insolation of the four right and left distal CCA locations: In all CCA B-mode ultrasound scans the sonographer aimed to visualise the following standardised and predefined anatomic arterial wall structures: the lumen-intima to media–adventitia layer (CIMT) of the far wall and the media–adventitia interface of the far wall to the media–adventitia interface of the near wall (outer LD) were assessed longitudinally in the CCA along the 1 cm arterial wall segment proximal to the carotid bifurcation for a duration of at least three heart cycles (see Fig. 2) [25].

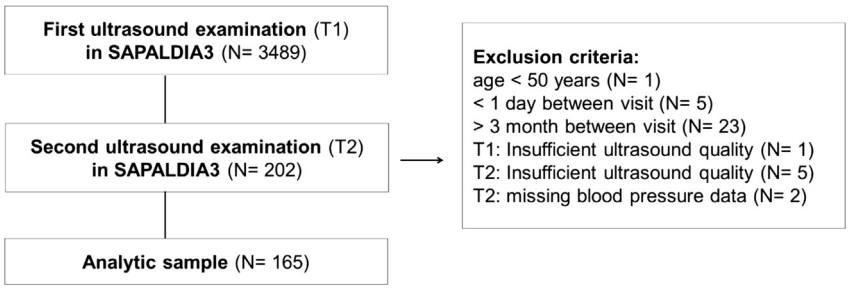

Fig. 1. Participation and feasibility flow chart.