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Intra- and inter-rater reproducibility of the echocardiographic data of the Nigerian UPRIGHT-HTM trial participants

Running title: Echocardiography in UPRIGHT-HTM in Nigeria

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Abstract

BACKGROUND: Echocardiography is the guideline-recommended tool for risk stratification of asymptomatic high-risk patients. This study assessed the intra- and inter-rater repeatability of the risk-carrying echocardiographic traits among 42 patients enrolled in the UPRIGHT-HTM trial at three Nigerian sites.

METHODS: The echocardiographic images (184 and 82 for the intra- and inter-rater agreement) were acquired according to current recommendations and blindly analysed by randomising the order of the digitised images. The study focused on left ventricular mass (LVM) index to body surface area of height$^{2.7}$ and ejection fraction (EF), and left ventricular diastolic dysfunction (LVDD). Repeatability was assessed by the Bland and Altman approach, the coefficient of variation (CV), the intra-class correlation coefficient (ICC) and Cohen's κ statistic. The current findings were compared with a systematic literature review of 27 publications.

RESULTS: LVM showed slight but significant intra-rater bias but no inter-rater bias with CVs around 30%, ICCs ranging from 0.75 to 0.84, and κ statistics for LVH varying from 0.49 to 0.64. For EF, the intra- and inter-rater CVs ranged from 13.0% to 29.8%, the ICCs from 0.60 to 0.69, while the κ statistics were 0.71 and 0.53 in the intra- and inter-rater assessment. For LVDD, the intra- and inter-rater κ values were around 0.50. The current repeatability statistics were in agreement with most of the 27 reviewed publications.

CONCLUSIONS: The risk-carrying echocardiographic traits were obtained with moderate repeatability in three Nigerian tertiary referral centres. As data quality augments with expertise, these findings call for a Nigerian training programme in echocardiography with certification.

Keywords echocardiography, heart, left ventricle, randomised clinical trial, reproducibility, sub-Saharan Africa,

Non-standard abbreviations and acronyms

95% CI	95% confidence interval
95% LA	95% limits of agreement, according to the Bland and Altman approach
AEFUTH	Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria
APPREMED	Non-Profit Research Association Alliance for the Promotion of Preventive Medicine, Mechelen, Belgium (URL: www.appremed.org
BSA	Body surface area
CKD	Chronic kidney disease
CV	Coefficient of variation
HF	Heart failure
HTM	Home blood pressure telemonitoring
ICC	Intra-class correlation coefficient
FTHK	Federal Teaching Hospital, Katsina, Nigeria
LV	Left ventricle or left ventricular
LVH	Left ventricular hypertrophy
LVDD	Left ventricular diastolic dysfunction
RC	Repeatability coefficient according to the Bland and Altman approach
UATH	University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria
UPRIGHT-HTM	Urinary Proteomics Combined with Home Blood Pressure Telemonitoring for Health Care Reform Trial
WIPAM	Wireless Patient Monitoring, RDSM Inc., Hasselt, Belgium (URL: www.rdsm.eu

Abbreviations referring to the echocardiographic measurements are commonly used, self-explanatory in most cases and spelled out in the article text

Introduction

Echocardiography is a commonly used non-invasive imaging technique in cardiology and is valuable for both clinical and research purposes.[1] However, its utility in research is often limited due to challenges in obtaining high-quality images for all individuals and the variability in repeated measurements.[2] In sub-Saharan Africa, where age-related cardiovascular disease is reaching epidemiological proportions,[3] the demand for accurate and reliable echocardiographic imaging is particularly high. However, unlike many other regions of the world, evidence of reproducibility of echocardiographic measurements is virtually non-existent.[4-27] This is mainly due to research infrastructure deficiencies, financial constraints, competing health interests, variability in health care systems, and shortage of trained personnel.[15]

In the ongoing Urinary Proteomics Combined with Home Blood Pressure Telemonitoring for Health Care Reform Trial (UPRIGHT-HTM),[28,29] echocardiography is deployed as instrument to examine target organ damage in high-risk patients randomised to risk profiling by home blood pressure telemonitoring (HTM) alone or HTM combined with urinary peptidomic profiling. Given the critical role of echocardiography and the well-known limitations of its application in sub-Saharan countries,[15] an assessment of the reproducibility of the echocardiographic measurements was an essential step in the UPRIGHT-HTM data management. The current study aimed to determine the intra- and inter-observer reproducibility of the structural and functional echocardiographic measurements obtained by multiple trained observers across the three Nigerian UPRIGHT-HTM recruitment sites. The wider implication of the present study is that its results may potentially reveal a strategy for improving the reliability of echocardiographic risk markers in sub-Saharan Africa and other low- and middle-income countries worldwide.

Methods

Study population

The study population consists of adult Nigerian patients enrolled in UPRIGHT-HTM from July 2021 until November 2023 at three Nigerian centres: the Federal Teaching Hospital, Katsina (FTHK), the University of Abuja Teaching Hospital (UATH), Gwagwalada, Abuja and the Alex Ekwueme Federal University Teaching Hospital (AEFUTH), Abakaliki. All patients selected for this study complied with the entry and exclusion criteria of UPRIGHT-HTM, an investigator-initiated clinical trial, in which patients are being recruited in multiple centres across Europe, Asia, and sub-Saharan Africa.[28,29] Eligible patients are asymptomatic adults of either sex and must in addition to being aged (55-75 years) have five or more guideline-defined risk factors,[30] preferably including hypertension, type-2 diabetes, or both. Furthermore, to qualify, patients must have an email address, internet access via an android smartphone, and be willing to engage in HTM during follow-up. Asymptomatic patients with chronic kidney disease (CKD) stage 3A[31] or left ventricular (LV) diastolic dysfunction (stage-1 heart failure [LVDD])[32] meet the entry criteria on condition that only one of these two disorders is present. On top of the exclusion criteria common to all clinical trials, study-specific exclusion criteria comprise an impracticable echocardiographic window, atrial fibrillation or flutter or frequent extrasystoles, because these conditions interfere with the echocardiographic assessment of LVDD and HTM using oscillometric devices.[30] After a screening visit and a run-in period of variable length (1-5 weeks or longer), patients are stratified by centre and sex and randomised using a fully automated web-based computerised random function.[28,29] UPRIGHT-HTM complies with the Helsinki Declaration for research on humans.[33] The Ethics Committee of University Hospitals Leuven, Belgium (Belgian registration number, B3222020000276), acting as the central Ethics Committee and the Institutional Review Boards of all recruitment sites approved the trial. Patients provide

written informed consent using paper forms translated in the local native languages. These forms are the only paper documents in the trial and allow identification of the patients. However, in line with the European General Data Protection Regulations,[34] these forms have to be filed in each patient's local medical record and are not part of the electronic trial database.

At the time of this analysis, 195 Nigerian patients had been recruited, among whom 42 sequential patients were selected among 181 who had undergone echocardiography after excluding 10 patients with impracticable echocardiographic window. The study patients included 12 from Abakaliki (AEFUTH), 20 from Katsina (FTHK), and 10 from Abuja (UATH). Two cardiologists from each study centre conducted repeat M-mode and 2D-echocardiography and tissue Doppler imaging, blinded to each other's findings. Each patient underwent two serial evaluations separated by approximately 30 minutes to reduce the impact of the physiological variability in cardiac function. The 164 images were digitally stored and analysed offline in random order by the same cardiologist to determine intra-rater repeatability. Next the test and retest values as coded by the same cariologist were averaged to determine inter-rater repeatability from 84 datasets (Fig. 1).

Echocardiography

Following a procedure which has been detailed elsewhere,[28] all centres performed echocardiography using General Electric echocardiographic devices (Horton, Norway, and Jiangsu, China) interfaced with appropriate probes (Table 1)**.** Briefly, imaging included the M-mode assessment of the LV dimensions under two-dimensional guidance, measurements of the early (E) and late (A) peak diastolic velocities of the transmitral blood flow by pulsed Doppler, and the corresponding early (a') and late (e') peak diastolic velocities of the mitral annular movement by tissue Doppler. The cardiologists followed the recommendations of the

American Society of Echocardiography.[35,36] The LV end-diastolic (EDD) and end-systolic (ESD) diameters were determined using M-mode echocardiography from the parasternal view at the distal border of the mitral valve leaflets. The LV end-diastolic (EDV) and end-systolic (ESV) volumes were calculated from the EDD and ESD as follows: EDV= [7/(2.4+EDD)] x $(EDD)^3$; ESV= [7/(2.4+ESD)] x $(ESD)^3$. The LV ejection fraction (EF) was calculated as: [(EDV−ESV)/EDV × 100. The end-diastolic LV dimensions were also used to calculate LV mass (LVM) by an anatomically validated formula.[37] LVM was indexed to body surface area (BSA) or to body height expressed in metre and powered to 2.7.[38] Tissue Doppler imaging was obtained at the lateral and mitral annulus, from an apical four-chamber view, using a sample volume size of 1.5 mm. The average of these two measurements was taken for each patient. The angle of insonation of the ultrasound beam was kept below 20° with respect to the orientation of the LV wall without correction of the angle. LVDD was categorised by applying age-specific thresholds for the transmitral E/A ratio and E/e' of 8.5, as previously described.[32,39]

Other measurements

Blood pressure was measured according to current guidelines[30] by means of validated[40] oscillometric OMRON HEM 9210-T monitors (Omron Healthcare Co., Ltd., Kyoto, Japan). Patients were allowed a 5-minute rest in the sitting position, after which three consecutive blood pressure measurements were taken and averaged. Investigators completed electronic case report forms to summarise information on each patient's medical history, smoking and drinking habits, intake of medications and the clinical, biochemical and echocardiographic data. As described in detail in the published protocol,[28] anonymised data were transferred in real time to the web-based WIPAM platform (Wireless Patient Monitoring), developed by RDSM, Hasselt, Belgium (URL: www.rdsm.eu), from which they were downloaded for

database construction and statistical analysis at the APPREMED (URL: www.appremed.org), Mechelen, Belgium.

Statistical analysis

Data was managed and analysed using SAS software, version 9.4. Means and standard deviations were used as measures of central tendency and spread for all continuous normally distributed variables. Numbers and percentages were adopted for categorical variables. Means were compared by t-test and proportions by Fisher exact or McNemar tests, as appropriate for paired or unpaired data.

Following offline analysis of echocardiographic images, data from across the three study sites were pooled together, and intra-rater and inter-rater agreements were determined using two-way mixed effect models with adjustment for centre effects attributable to differences in observer expertise, equipment models and quality of echocardiographic images (Fig. 1). Intra-rater and inter-rater agreement in continuous measurements were analysed using the repeatability coefficient (RC),[41] the coefficient of variation (CV), and the intra-class correlation coefficient (ICC).[42] Differences between retest minus test values (bias [Δ]) are given with 95% confidence interval (95% CI). The RC is twice the standard deviation of the signed differences between repeat measurements and was expressed as a percentage of the average of test and retest measurements.[41] Lower values in RC and CV indicate better reproducibility. Bland and Altman plots allow the assessment of Δ plotted against the mean of test and retest.[43] Given the distribution of Δ, the 95% limits of agreement (95% LA) are $\Delta \pm (1.96 \times SD)$.[43] In case of significant bias, the contribution of regression-to-the mean was evaluated by excluding the bottom (<10th percentile) and top (>90th percentile) deciles of the first test values and the pairwise associated retest values.[44] ICC values of 0.50-0.69, 0.70-0.80 and >0.80 indicate moderate, strong and nearly perfect reproducibility (>0.80).[42] For

categorical variables, the intra- and inter-rater agreement were evaluated by the Cohen's κ statistic. Values of <0.20, 0.21-40, 041-061, 061-080, and 0.81-1.00, respectively, indicate none or slight, fair, moderate, substantial or almost perfect agreement. The thresholds applied were as follows: for left ventricular hypertrophy (LVH) in women/men, >95/>115 g/m^2 for LV mass indexed to BSA and >47/>51 g/m$^{2.7}$ for LV mass indexed to body height[38]; for LV ejection fraction <50 *vs* ≥50%; for the E/e' ratio >8 *vs* ≥8 and >15 *vs* ≥15, given that <8 is certainly normal and ≥15 is surely abnormal.

Results

Patient characteristics

The characteristics of the 42 patients from the three study centres, including 20 from Katsina, 12 from Abakaliki, and 10 from Abuja are shown in Table 2. In all 24 patients, age averaged 58.4 years, body mass index 28.3 kg/m^2, waist circumference 89.8 cm, the estimated glomerular filtration rate 76.3 mL/min/1.72 m^2, and office systolic/diastolic blood pressure 137.0/81.3 mmHg. Turning to risk factors, 41 patients were hypertensive, of whom 40 (97.6%) were on antihypertensive drug treatment, calcium-channel blockers or inhibitors of the renin-angiotensin system in 27 (67.5%) and 25 (62.5%) patients, with 29 patients (72.5%) requiring combination therapy. Among all patients, 23 (54.8%) had type-2 diabetes and 15 (32.7%) had a body mass index of 30 kg/m^2 or more. The study participants comprised predominantly Igbo (31.0%) and Hausa-Fulani (45.2%), the major ethnicities in Nigeria and reflecting the catchments areas of the recruitment centres.

Significant between-centre differences (P≤0.011) were recorded for obesity and waist circumference, being highest in the Abuja patients and the estimated glomerular filtration rate, being lowest in the Abakaliki patients (Table 2). The 42 analysed and 153 non-analysed patients had largely similar characteristics with exception of body mass index and waist

circumference, which were respectively 2.3 kg/m^2 (95%CI: 0.2 to 4.4 kg/m^2) and 8.5 cm (95% CI: 2.8 to 14.1 cm) greater in non-analysed patients (Table 3).

Intra-rater repeatability

The statistics capturing the intra-rater agreement appear in Table 4 (164 images analysed). With regard to the LV dimensions, only the LVM indexed to BSA or to height$^{2.7}$ showed significant bias with lower values at the retest compared to the test (*P*<0.001). Bias amounted to -4.37 g/m^2 (-8.17 to -0.57 kg/m^2) and -2.00 g/m$^{2.7}$ (-3.89 to -0.11 g/m$^{2.7}$), respectively, while the 95% LAs encompassed -38.7 to 30.0 g/m^2 (Fig. 2, Panel A) and -19.0 to 15.0 g/m$^{2.7}$ and the CVs were 33.6% and 31.8%. The ICCs for LVM, irrespective of indexing, were >0.80. The κ statistics for LVH in the intra-rater analysis were 0.64 (95% CI: 0.45-0.83; *P*<0.001) for LVM indexed to BSA and 0.55 (95% CI: 0.36-0.74; *P*<0.001) for LVM indexed to height$^{2.7}$. For the other LV dimensions, the RCs expressed as a percentage of the mean of the test and retest values ranged from 17.6% for the EDD to 47.0% for relative wall thickness, while the corresponding CVs were 13.8% and 21.9% and the ICCs 0.81 and 0.55, respectively. Notably, after excluding the bottom and top deciles of the LVM values at the initial test and the pairwise associated retest values, bias decreased from -4.37 g/m^2 to -2.90 g/m^2 (95% CI: -9.4 to3.4 g/m^2; *P*=0.37) and -1.30 g/m$^{2.7}$ (95% CI: -4.5 to 1.9 g/m$^{2.7}$; *P*=0.42).

Turning to the intra-rater evaluation of LV systolic function, none of the measurements had a significant bias with RCs expressed as percentage of the mean of the test and retest values ranging from 24.8% for EF to 57.5% for cardiac output with corresponding CVs of 14.5.% and 40.1% and ICCs of 0.69 and 0.77, respectively (Table 4). For the EF, bias was 0.83% (95% CI: -0.98 to 2.64%; *P*=0.36) and the 95% LA encompassed -15.5 to 17.2% (Fig. 2; Panel B). The κ statistic for the EF amounted to 0.71 (95% CI: 0.40-1.00; *P*<0.001).

For none of the diastolic function measurements, there was significant bias. For the E/e' ratio bias was 0.28 (95% CI: -0.27 to 0.83; *P*=0.32) and the 95% LA encompassed -4.7 to 5.3 (Fig. 2; Panel C). The κ statistics for the E/e' ratio amounted to 0.38 (95% CI: 0.17-0.58; *P*=0.0027) and 0.26 (0.00-0.88; *P*=0.26) for the <8 and >15 thresholds, respectively, and for LVDD 0.55 (95% CI: 0.34-0.75; *P*<0.001).

Inter-rater repeatability

The inter-rater repeatability statistics (82 images analysed) are listed in Table 4. None of the measurements describing the LV dimensions or LV systolic or diastolic function showed significant bias. For LV mass indexed to BSA or height$^{2.7}$, bias was -4.39 (95% CI: -11.0 to 2.24 kg/m^2) and -2.28 (-5.36 to 0.79 kg/m$^{2.7}$), while the corresponding 95% LA encompassed -46.1 to 37.3 g/m^2 (Fig. 2; Panel D) and -21.6 to 17.1 g/m$^{2.7}$. The κ statistics for LVH in the inter-rater analysis were 0.49 (95% CI: 0.17-0.81; *P*=0.012) for LVM indexed to BSA and 0.61 (95% CI: 0.33-0.89; *P*<0.001) for LVM indexed to height$^{2.7}$ For the other LV dimensions, the RCs expressed as a percentage of the mean of the test and retest values ranged from 19.5% for the EDV to 62.1% for the width of the interventricular septum, while the corresponding CVs were 13.0% and 19.9%, and the ICCS 0.75 and 0.24, respectively. Considering the inter-rater statistics for EF, bias was -0.36 (95% CI: -3.07 to 2.35) and the 95% LA ranged from -17.4% to 16.7% (Fig. 2, Panel E). The κ statistic for the EF was 0.53 (95% CI: 0.07 to 1.00; *P*=0.025). For the E/e' ratio, the inter-rater statistics were 0.21 (95% CI: -0.50 to 0.92) for bias with the 95% LA ranging from -4.20 to 4.70 (Fig. 2; Panel F). The inter-rater κ statistic for the E/e' ratio was 0.67 (95% CI: 0.44-0.89; *P*<0.001) for the <8 *vs* ≥8 contrast, was 1.00 (P<0.001) for the <15 *vs* ≥15 contrast, while for LVDD the inter-rater κ was 0.48 (95% CI: 0.21-0.76; *P*=0.017).

Literature review

Table 5 list the reviewed studies,[4-27] sorted by year of publication and first author as retrieved from the literature by the strategy shown in Fig.3. The studies published over nearly 30 years from 1994 until 2023 reflect to a large extent the development and progressive sophistication of the examination of cardiac structure and function by ultrasound, moving from two-dimensional to real-time three-dimensional approaches, starting in 2004.[9] The first reproducibility study including the early and late peak diastolic transmitral blood velocities obtained by pulsed Doppler was published in 1995[5] and the first report on the reproducibility of the early and late peak diastolic mitral annular velocities examined by tissue Doppler imaging in 2003.[8] Some studies aimed at validating LV echocardiographic structural or function characteristics versus other imaging modalities, nuclear magnetic resonance in most instances,[13,14,19,24] focused on the added value of contrast imaging,[10,11] compared the transoesophageal with transthoracic window in the assessment of the mitral annular velocities,[26] or assessed commercially available with proprietary ultrasound algorithms.[17]

To place the added value of the current study in the context of the available literature, several considerations merit to be stressed. First, of the 24 reproducibility studies reviewed, only one took place in sub-Saharan Africa (Nigeria).[15] Second, of the 24 reviewed studies (Table 5), some specifically recruited patients with hypertension, whereas other reports included patients with varying cardiac pathologies, ill defined disease or referred patients, or healthy volunteers, in most instances as a minority. Only two studies were population based.[23,24] The current UPRIGHT-HTM patients were all at high cardiovascular risk and enrolled according to the UPRIGHT-HTM selection and exclusion criteria,[28,29] although they were free of major symptoms at the time of their echocardiographic examination. However, 41 (97.6%) had hypertension, but 2 of the 42 UPRIGHT-HTM patients were on antihypertensive drug treatment, while 23 (54.8%) had type-2 diabetes and 15 (35.7%) were

obese (Table 2). Third, as UPRIGHT-HTM, 12 reports were multicentre studies,[4-7,12,14,18,20-22,25,27] of which 4 were embedded in randomised clinical trials.[4,6,7,18] Finally, training[20] and high *vs* lower experience of the echocardiographer[25] substantially improve reproducibility.

Fig.4 shows box plots for the intra- and inter-rater CVs and ICCs as retrieved from the literature review (Table 5) and as obtained in the current study (Table 4). As quantified by the ICC, the current result for LV dimensions and the measurements reflecting systolic and diastolic LV function are in substantial agreement with the literature. For the CV, there were notable differences, because few articles reviewed reported the CV and because this metric is expressed as percentage of the mean and therefore dependent on the characteristics of the study population.

One multicentre study reported κ statistics for the transmitral pulsed Dopler measurements, the atrial filling fraction, the isovolumetric relaxation time and the E-wave propagation time, as indexes of LV diastolic function.[12] The intra-rater κ statistics ranged from 0.40 to 0.92 and showed from moderate to near perfect agreement except for the isovolumetric relaxation time less than 60 ms (κ=0.05). In the STANISLAS population study,[23] the intra- and inter-rater κ statistics for the diagnosis of LVDD were 0.93 and 0.88, respectively and greater than in the present study.

Discussion

According to the comprehensive literature review (Table 5), the current study is the first to examine the intra- and inter-rater repeatability of common risk-carrying echocardiographic characteristics in the multicentre setting of a randomised clinical trial in a sub-Saharan country, using a wide range of statistics. The study was designed in support of the data

quality of the left ventricular structural and functional echocardiographic traits. The only previous study in sub-Saharan Africa dates back to 2006 and was a single-centre report.[15]

The key findings pertain to the prognostically most relevant echocardiographic traits, including LV mass indexed to BSA or height$^{2.7}$, the EF, the E/e' ratio, analysed as continuous or categorical variables. In the continuous analyses, LVM indexed to BSA or height$^{2.7}$ showed slight but significant intra-rater bias with slightly lower values on the retest compared with the first test but no inter-rater bias. The CVs were around 30% and the ICCs ranged from 0.75 to 0.84, indicating substantial agreement. Excluding the bottom and top deciles of the LVM indexes at the initial test and the pairwise associated retest values,[44] decreased bias, thereby suggesting that regression-to-the mean at least contributed to the significant bias of the two LVM indexes. The intra- and inter-rater κ statistics for LVH ranged from 0.49 to 0.64, values compatible with moderate reproducibility. With regard to the EF and the E/e' ratio, the intra- and inter-rater CVs ranged from 13.0% to 29.8% and the ICCs from 0.60 to 0.69, again signifying moderate reproducibility. In the categorical analyses of the EF, the κ statistics were 0.71 and 0.53 in the intra- and inter-rater evaluation, respectively. The intra-rater κ statistics for the E/e' ratio, considering as thresholds <8 *vs* ≥8 and <15 *vs* ≥15, were 0.38 and 0.26, whereas in the inter-rater analysis they were 0.67 up to 1.00. LVDD was moderately reproducible with intra- and inter-rater κ values of around 0.50. By and large, the current intra- and inter-rater repeatability statistics were in line with most of the 27 reviewed publications.

Clinical implications

Dating back over 30 years, the first Framingham reports already demonstrated that common cardiovascular risk factors, in particular high blood pressure, cause echocardiographically determined LVH[45] and symptomatic heart failure (HF).[46] LVH is an independent risk factor

for major cardiovascular complications and mortality.[47,48] In Nigerian Blacks, electrocardiographic LVH is also associated with blood pressure, but the relation was significantly steeper than in White Flemish.[49] HF is commonly[50] subdivided in four stages: the mere presence of risk factors (stage A), discrete LV structural and function changes in asymptomatic individuals (stage B), clinically overt HF (stage C); and end-stage HF (stage D). Over half of HF patients dye within 5 years of the diagnosis.[50] LVDD is initially asymptomatic (stage B),[32,39] represents over half of all HF cases, is a forerunner of major cardiovascular complications,[51] overt HF (stage C)[52] and premature mortality.[53] Timely prevention of LVH and HF by risk factor management is the most powerful instrument in mitigating the dire consequences of these conditions. Echocardiography is currently the imaging modality of choice to detect the early structural and functional changes, which precede LVH progressing to symptomatic HF with reduced or preserved EF. As the cardiac risk of any individual patient should be firmly established in symptom-free patients (stage B), echocardiographer should have developed the skills to detect the minor structural and functional changes at stage-B of HF. Thos clinical necessity underscores the importance of assessing the intra- and inter-rater reproducibility, in particular in multicentre clinical trials.

Strengths and limitations

Strong points of the present study are that at each centre, two observers independently from one another acquired the echocardiographic images and in a blinded manner achieved by randomisation of the order of images re-read the images. Additionally, the images analysed and re-analysed were much larger than in the literature review with 184 sessions re-read for the intra-rater repeatability and 84 for the inter-rater repeatability. However, the current study must also be interpreted within the context of its limitations. First, reproducibility was assessed based on the agreement of multiple raters from three different centres. However,

the mixed models adjusted for the potential biases that may have been introduced by equipment, quality of echocardiographic windows, patient load, and expertise of raters. It is also important to note that the measurements analysed were mostly initial results at the beginning of a learning curve with the echocardiographers at varying levels of experience. Second, the literature review (Table 5) highlighted the vast heterogeneity of the echocardiographic technologies applied and the individuals included in the reproducibility studies. This precluded a formal statistical comparison between the literature data and the present observations. However, this problem was addressed by construction box plots for the distributions of the intra- and inter-rater CVs and ICCs without formal statistical tests but with a visual representation of concordance.

Conclusions

Ogah and coworkers have to be commended for having assessed already in September and November 2005 in a single-centre study, located at Department of Medicine, Federal Medical Centre, Abeokuta, Nigeria, the intra-rater variability of atrial and LV dimensions.[15] The centre was a relatively young tertiary institution, established in 1993 by the Federal Government of Nigeria to cater for the health needs of the people of Ogun State in south-west Nigeria. One cardiologist read the images of 20 of 104 referred patients at an interval of 1 week, resulting in correlations between test and retest measurements ranging from 0.60 to 0.96.[15] The current investigation was conducted mid-way into the deployment of the UPRIGHT-HTM clinical trial in Nigeria, as a proactive step to validate the echocardiographic measurements included in the database and to ensure further standardisation of the echocardiographic data as the trials continues. To our knowledge and in line with the literature review (Table 5), this is the first attempt to comprehensively investigate the intra- and inter-rater repeatability of the echocardiographically determined LV dimensions and systolic and diastolic LV function

among trialist in the sub-Saharan African region. The current multicentre study included tertiary referral centres in the northern, central, and southern regions of Nigeria, hence allowing to generalise the findings to the broader Nigerian context. The risk-carrying echocardiographic traits were obtained with moderate repeatability in three Nigerian tertiary referral centres. As data quality augments with expertise, the present findings call for a Nigerian training programme in echocardiography with certification, which could be organised by the Nigerian Society of Cardiology.

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Conflict of interest

The authors declare no conflict of interest.

Legends to figures

Fig. 1. Protocol of the reproducibility study.

Abbreviations: N°, number of patients; R1, rater 1; R2, rater2; M1, first measurement; M2, repeat measurement; MR1, average of repeated measurements by rater 1; MR2, average of repeated measurements by rater 2. Pooled data refers to the combined data across the three study centres.

Fig. 2. Bland and Altman plots.

Bias computed as retest minus test value is displayed along the vertical axis and plotted against the average of test and retest along the horizontal axis. Given the distribution of bias, the 95% limits of agreement (95% LA) are bias ± (1.96 × SD). The full line indicates bias and the dotted lines correspond with the 95% limits of agreement. P-values denote the significance of the bias. Results are given for left ventricular mass (LVMI) indexed to body surface area (A,D), stroke volume (B,E) and the transmitral E/A ratio (C,F). The intra-rater results appear in panels A-C and the inter-rater results in panels D-F.

Fig. 3. Literature flow diagram.

Fig. 4. Box plots summarising the intra- and inter-rater repeatability for the echocardiographic assessment of LV dimensions as assessed by the coefficient of variation and the intra-class correlation coefficient.

Data from the literature review (Table 5) are presented in green and those generated in UPRIGHT-HTM (Table 4) in orange. The vast heterogeneity of the echocardiographic technologies applied and the individuals included in the reviewed reproducibility studies precluded a formal statistical comparison between the literature data and the present observations. However,

the box plots for the distributions of the intra- and inter-rater CVs and ICCs without formal statistical tests allow a visual comparison of literature and current results for left ventricular dimensions (A) and systolic (B) and diastolic (C) left ventricular function.

Table 1. Echocardiographic equipment by centre

Centre	Echocardiographic device	Probe
Abuja (UATH)	GE, Vivid E95 (Horten, Norway) with 0-5 cm minimum field-of-view range, 0-50 cm maximum field-of-view range, 0-120^{o} width range, M and 2D mode, Doppler imaging (pulsed, continuous and tissue)	4Vc with 1.5-4.0 MHz scanner range, 90^{o} field of view and 30 cm depth of field
	GE, Vivid S70N (Horten, Norway) with 0-2 cm minimum field-of-view range, 0-36 cm maximum field-of-view range, 10-120^{o} width range, M and 2D mode, Doppler imaging (pulsed, continuous and tissue)	M5Sc-D with 1.5-4.5 MHz scanner range, 120^{o} field of view and 30 cm depth of field
Abakaliki (AEFUTH)	GE, Vivid T8 version 203 (Jiangsu China) with 0-5 cm minimum field of view range, 0-50 cm maximum field of view range, 0-120^{o} width range, M and 2D mode, Doppler imaging (pulsed, continuous and tissue)	1-7/3.4 MHz 3Sc-RS scanner, 90^{o} field of view and 16 cm depth of field
Katsina (FTHK)	GE Vivid T9 version 203, by GE Medical System (Jiangsu China). Minimum field of view 1 cm, maximum field of view 33 cm and width range of 10° to 168°. M and 2D mode, Doppler imaging (pulsed, continuous and tissue)	3Sc-RS 30cm depth, 120°field of view, 1.3-4.0 MHZ scanner frequency

GE indicates General Electric with headquarters in Horton, Norway.
Centre identification: University of Abuja Teaching Hospital; AEFUTH, Alex Ekwueme Federal University Teaching Hospital; UATH, Katsina; FTHK, Federal Teaching Hospital Katsina.

Table 2. Characteristics of analysed patients overall and by centre

Characteristic	All	By recruitment centre			
		Abuja	Abakaliki	Katsina	*P* value
Number in group	42	10	12	20	
Number with characteristic (%)					
Ethnicity					
Igbo	13 (31.0)	2 (20.0)	11 (91.7)	0 (0.0)	<0.001
Yoruba	4 (9.5)	4 (40.0)	0 (0.0)	0 (0.0)	
Hausa-Fulani	19 (45.2)	0 (0.0)	0 (0.0)	19 (95.0)	
Other Nigerian ethnicity	6 (14.3)	4 (40.0)	1 (8.3)	1 (5.0)	
Women	23 (54.8)	7 (70.0)	5 (41.7)	11 (55.0)	0.45
Hypertension	41 (97.6)	10 (100)	11 (91.7)	20 (100)	0.52
Treated hypertension	40 (97.6)	10 (100)	11 (100)	19 (95.0)	>0.99
Monotherapy	11 (27.5)	5 (50.0)	2 (18.2)	4 (21.1)	0.23
Combination therapy	29 (72.5)	5 (50.0)	9 (81.8)	15 (78.9)	
Antihypertensive drugs used					
Diuretics	16 (40.0)	4 (40.0)	6 (54.5)	6 (31.6)	0.45
β-blockers	10 (25.0)	2 (20.0)	3 (27.3)	5 (26.3)	>0.99
Calcium-channel blockers	27 (67.5)	7 (70.0)	6 (54.5)	14 (73.7)	0.62
RAAS inhibitors	25 (62.5)	5 (50.0)	8 (72.7)	12 (63.2)	0.58
Type-2 diabetes	23 (54.8)	6 (60.0)	9 (75.0)	8 (40.0)	0.31
Obesity, n (%)	15 (35.7)	7 (70.0)	5 (41.7)	3 (15.0)	0.011
Mean characteristic (± SD)					
Age, y	58.4 (5.5)	60.8 (5.1)	58.8 (4.4)	56.9 (6.0)	0.18
Body mass index, kg/m^2	28.3 (5.8)	31.3 (7.5)	29.7 (5.1)	26.1 (4.4)	0.037
Body surface area, m^2	1.9 (0.2)	1.8 (0.3)	1.9 (0.2)	1.8 (0.2)	0.42
Waist circumference, cm	89.8 (16.0)	101 (17)	103 (10)	76 (6)	<0.001
eGFR, mL/min/1.73 m^2	76.3 (20.0)	79.8 (17.4)	61.1 (24.2)	83.1 (18.2)	0.013
Office blood pressure					
Systolic, mmHg	137.0 (17.0)	135 (16)	132 (16)	141 (18)	0.41
Diastolic, mmHg	81.3 (9.2)	81 (9)	77 (10)	84.1 (8.0)	0.11
Office heart rate, bpm	76.6 (11.0)	73 (11)	78 (12)	78 (11)	0.56

Values are number of patients (%) or mean (SD). Hypertension is an office blood pressure of ≥140 mmHg systolic or ≥90 mmHg diastolic or use of antihypertensive drugs. Diabetes is use of antidiabetic drugs, fasting blood glucose ≥7 mmol/L (126 mg/dL), random blood glucose ≥11.1 mmol/L (200 mg/dL), or diabetes documented in hospital records. Body mass index is weight (kg) divided by height squared (m). Obesity is a body mass index of ≥30 kg/m^2. Body surface area is computed by the Du Bois formula (Arch Intern Med 1916; XVII: 863-71). The estimated glomerular filtration rate (eGFR) is derived from serum creatinine by the Chronic Kidney Disease-Epidemiology Collaboration formula (Ann Intern Med 2009; 150: 604-12). None of the patients reported use of smoking materials or alcoholic beverages. RAAS inhibitors refer to inhibitors of the renin-angiotensin system, including angiotensin I converting-enzyme inhibitors and angiotensin-II type-1 receptor blockers.

Table 3. Characteristics of analysed and non-analysed patients

Characteristic	Analysed	Not analysed	*P* value
Number in group	42	153	
Number with characteristic (%)			
Women, n (%)	23 (54.8)	104 (53.3)	0.86
Hypertension	41 (97.6)	150 (98.0)	0.60
Treated hypertension	40 (97.6)	146 (97.3)	>0.99
Monotherapy	11 (27.5)	38 (26.0)	
Combination therapy	29 (72.5)	108 (74.0)	0.13
Antihypertensive used			
Diuretics	16 (40.0)	64 (43.8)	0.15
β-blockers	10 (25.0)	21 (14.4)	0.84
Calcium-channel blockers	27 (67.5)	97 (66.4)	0.85
RAAS inhibitors	25 (62.5)	110 (75.3)	0.15
Type-2 diabetes	23 (54.8)	97 (49.7)	0.49
Obesity	15 (35.7)	91 (46.7)	0.12
Mean characteristic (± SD)			
Age, y	58.4 (5.5)	60.1 (6.0)	0.038
Body mass index, kg/m^2	28.3 (5.8)	30.6 (6.4)	0.008
Waist circumference, cm	89.8 (16.8)	98.3 (16.7)	<0.001
eGFR, mL/min/1.73 m^2	76.8 (20.6)	75.5 (21.0)	0.64
Office blood pressure			
Systolic, mmHg	136.8 (17.0)	135.0 (15.4)	0.39
Diastolic, mmHg	81.3 (9.2)	82.1 (10.0)	0.58
Office heart rate, bpm	76.6 (11.2)	76.6 (12.7)	>0.99

Values are number of patients (%) or mean (SD). Hypertension is an office blood pressure of ≥140 mmHg systolic or ≥90 mmHg diastolic or use of antihypertensive drugs. Diabetes is use of antidiabetic drugs, fasting blood glucose ≥7 mmol/L (126 mg/dL), random blood glucose ≥11.1 mmol/L (200 mg/dL), or diabetes documented in hospital records. Body mass index is weight (kg) divided by height squared (m). Obesity is a body mass index of ≥30 kg/m^2. Body surface area is computed by the Du Bois formula (Arch Intern Med 1916; XVII: 863-71). The estimated glomerular filtration rate (eGFR) is derived from serum creatinine by the Chronic Kidney Disease-Epidemiology Collaboration formula (Ann Intern Med 2009; 150: 604-12). RAAS inhibitors refer to inhibitors of the renin-angiotensin system, including angiotensin I converting-enzyme inhibitors and angiotensin-II type-1 receptor blockers.

Table 4. Intra-rater and inter-rater repeatability of left ventricular structural and functional echocardiographic measurements

Analysis type Structural or functional trait	Retest minus test value			Repeatability statistics				
	Test	Retest	Δ (95% CI)	Δ (95% LA)	RC	%AVR	CV	ICC (95% CI)
Intra-rater analysis								
LV structure								
LVM indexed to BSA, g/m^2	95.6 (34.9)	89.4 (29.4)	-4.37 (-8.17 to -0.57)*	-38.7 to 30.0	34.2	37.0	33.6	0.84 (0.79 to 0.88)
LVM indexed to height$^{2.7}$ g/m	44.6 (15.8)	42.6 (13.1)	-2.00 (-3.89 to -0.11)*	-19.0 to 15.0	17.4	39.9	31.8	0.81 (0.76 to 0.85)
Relative wall thickness	0.41 (0.10)	0.41 (0.10)	0.00 (-0.02 to 0.02)	-0.18 to 0.19	0.2	47.0	21.9	0.55 (0.47 to 0.62)
Systolic dimensions								
Septum, mm	14.7 (4.1)	14.5 (3.8)	-0.21 (-0.86 to 0.44)	-6.1 to 5.7	6.0	41.1	25.1	0.71 (0.64 to 0.77)
Posterior wall, mm	14.9 (3.1)	15.2 (3.0)	0.31 (-0.19 to 0.81)	-4.2 to 4.8	4.6	30.7	18.8	0.71 (0.64 to 0.76)
Diameter, mm	30.1 (6.9)	29.7 (6.7)	-0.44 (-1.30 to 0.42)	-8.2 to 7.3	7.9	26.5	21.8	0.83 (0.78 to 0.87)
Diastolic dimensions								
Septum, mm	10.2 (3.0)	9.8 (2.6)	-0.39 (-0.84 to 0.07)	-4.5 to 3.7	4.2	42.1	26.0	0.71 (0.64 to 0.77)
Posterior wall, mm	9.5 (1.8)	9.5 (2.0)	0.02 (-0.36 to 0.40)	-3.4 to 3.5	3.5	36.8	18.1	0.59 (0.51 to 0.66)
Diameter, mm	47.8 (7.2)	47.3 (6.6)	-0.45 (-1.36 to 0.46)	-8.7 to 7.8	8.4	17.6	13.8	0.81 (0.76 to 0.85)
LV systolic function								
Fractional shortening, %	37.7 (8.1)	38.2 (8.6)	0.55 (-0.96 to 2.07)	-13.1 to 14.3	14.0	36.8	19.9	0.65 (0.57 to 0.71)
Ejection fraction, %	66.9 (10.6)	67.7 (10.5)	0.83 (-0.98 to 2.64)	-15.5 to 17.2	16.7	24.8	14.5	0.69 (0.61 to 0.74)
Stroke volume, mL	71.6 (25.5)	70.1 (23.2)	-1.47 (-5.74 to 2.81)	-40.1 to 37.1	39.4	55.6	31.5	0.67 (0.60 to 0.73)
Cardiac output, L/min	5.4 (2.4)	5.3 (2.1)	-0.08 (-0.41 to 0.26)	-3.1 to 2.9	3.1	57.4	40.1	0.77 (0.71 to 0.82)
Diastolic function								
Transmitral E/A	1.0 (0.4)	1.0 (0.3)	-0.03 (-0.07 to 0.01)	-0.39 to 0.33	0.4	37.0	35.4	0.87 (0.83 to 0.90)
E/e’	9.2 (3.1)	9.4 (2.9)	0.28 (-0.27 to 0.83)	-4.70 to 5.30	5.1	54.6	29.1	0.64 (0.56 to 0.70)
Inter-rater analysis								
LV structure								
LVM indexed to BSA, g/m^2	94.1 (32.6)	90.8 (29.8)	-4.39 (-11.01 to 2.24)	-46.1 to 37.3	43.3	46.8	31.7	0.75 (0.66 to 0.82)
LVM indexed to height$^{2.7}$	94.1 (32.6)	90.8 (29.8)	-2.28 (-5.36 to 0.79)	-21.6 to 17.1	43.3	46.8	31.7	0.75 (0.66 to 0.82)
Relative wall thickness	44.7 (14.9)	42.4 (12.8)	-0.01 (-0.04 to 0.02)	-0.21 to 0.19	19.7	45.3	29.8	0.74 (0.63 to 0.80)
Systolic dimensions								
Septum, mm	14.5 (3.4)	14.7 (3.9)	0.26 (-1.15 to 1.67)	-8.6 to 9.1	9.1	62.1	19.9	0.24 (0.17 to 0.32)
Posterior wall, mm	15.1 (2.4)	15.0 (3.2)	-0.12 (-0.96 to 0.72)	-5.4 to 5.2	5.4	35.6	16.6	0.55 (0.43 to 0.65)

Table4. Intra-rater and inter-rater repeatability of left ventricular structural and functional echocardiographic measurements (continued)

Analysis type Structural or functional trait	Retest minus test value			Repeatability statistics				
	Test	Retest	Δ (95% CI)	Δ (95% LA)	RC	%AVR	CV	ICC (95% CI)
Diameter, mm	29.9 (6.5)	29.9 (6.6)	0.01 (-1.29 to 1.31)	-8.2 to 8.2	8.3	27.9	20.8	0.80 (0.71 to 0.85)
Diastolic dimensions								
Septum, mm	10.1 (2.6)	9.9 (2.7)	-0.22 (-1.23 to 0.79)	-6.6 to 6.1	6.5	64.5	20.6	0.24 (0.16 to 0.31)
Posterior wall, mm	9.6 (1.7)	9.4 (1.7)	-0.29 (-0.91 to 0.34)	-4.2 to 3.7	4.0	42.4	14.8	0.31 (0.22 to 0.40)
Diameter, mm	47.8 (6.8)	47.3 (6.4)	-0.45 (-1.90 to 1.00)	-9.6 to 8.7	9.3	19.5	13.0	0.75 (0.65 to 0.81)
Systolic function								
Fractional shortening, %	38.2 (7.3)	37.7 (7.8)	-0.56 (-2.80 to 1.67)	-14.6 to 13.5	14.3	37.7	17.7	0.55 (0.43 to 0.65)
Ejection fraction, %	67.5 (9.5)	67.1 (10.0)	-0.36 (-3.07 to 2.35)	-17.4 to 16.7	17.4	25.9	13.0	0.60 (0.49 to 0.69)
Stroke volume, mL	72.2 (22.6)	69.5 (22.2)	-2.76 (-8.80 to 3.28)	-40.7 to 35.2	38.8	54.7	28.5	0.62 (0.5 to 0.71)
Cardiac output, L/min	5.4 (2.1)	5.3 (2.2)	-0.11 (-0.61 to 0.38)	-3.2 to 3.0	3.2	59.0	37.5	0.73 (0.63 to 0.80)
Diastolic function								
Transmitral E/A	1.0 (0.3)	1.0 (0.4)	0.03 (-0.07 to 0.13)	-0.59 to 0.66	0.6	63.7	31.8	0.60 (0.48 to 0.68)
E/e' ratio	9.2 (2.3)	9.4 (3.1)	0.21 (-0.50 to 0.92)	-4.2 to 4.7	4.5	48.7	26.6	0.65 (0.54 to 0.73)

The number of echocardiographic images analysed is 164 for the intra-rater repeatability and 84 for inter-rater repeatability. Values are mean (SD) for test and retest and mean difference (Δ) of the retest minus test value, given with 95% confidence interval (95% CI). An asterisk indicates a significant $P<0.001$ Δ (bias). Given the distribution of Δ, the 95% limits of agreement (95% LA) are Δ ± 1.96 × SD of Δ. The repeatability coefficient (RC) is twice the SD of the signed differences between test and retest measurements and is also expressed as percentage of the average of the test and retest value (%AVR) or as the coefficient of variation (CV), i.e., the SD of the averaged test and retest measurements expressed a percentage of the average. Greater values of RC, %AVR, CV and wider 95% LA indicate worse reproducibility. The readings obtained by each of the two raters are averaged to compute inter-rater repeatability. Mixed models are used to combine data from the three centres, while accounting for clustering within centres. E/A is the ratio of the early (E) and late (A) diastolic peak velocities of the transmitral blood flow obtained by pulsed Doppler. E/e' is the ratio of peak velocity of the early diastolic transmitral blood flow to the peak velocity of the mitral annular movement during early diastole, as obtained by tissue Doppler. E/e' is an index of the left ventricular diastolic filling pressure.

Table 5. Literature review on reproducibility of left ventricular structure and function

Articles	Location	Setting	Features	Main results
Grandits, 1994 (4)	USA (M)	RCT (HT) N=902 (54.8 y) Nim=4987 (4y)	LV dimensions	Intra: r (reader 1) 0.86-0.97 r (reader 2) 0.37-0.97 Inter: ρ 0.64-0.92
Gottdiener, 1995 (5)	USA (M)	HT N=96 (55 y) Nim=148-176 (6±8 d)	LV dimensions	Intra: r 0.72-0.88 ρ 0.72-0.90
			EF and FS	Intra: r 0.53-0.91 ρ 0.53-091
			Transmitral Doppler	Intra: r 0.26-0.65 ρ 0.12-0.65
Lantelme, 1999 (6)	France (S)	RCT (HV) N=48 (28.9 y) Nim=38	LV dimension	Intra: ρ 0.67-0.99 No influence of NO_2 on LVM
Palmieri, 1999 (7)	Sweden, USA, New Zealand (M)	RCT (HT) N=183 (65 y) Nim=366 (45±25 d)	LV dimensions	Intra: ρ 0.83-0.94
			Systolic function	Intra: ρ 0.56-0.68
			Transmitral Doppler	Intra ρ 0.57-0.58
Palmieri, 2003 (8)	Italy (S)	HV and patients N=40 (39 y) Nim=80 (<1 d [patients] to 3±1 mo [13 HV])	Transmitral Doppler, IVRT, AFF	Intra: ρ 0.56-0.94
			MAD (e'/a')	Intra: ρ 0.90
Jenkins, 2004 (9)	Australia (S)	Unselected patients N=50 (64 y) Nim=100 (<24 h) 2D *vs* 3D	LV dimensions 2DE	Intra: r 0.61-0.90 Inter: r 0.61-0.79
			3DE	Intra: r 0.61-0.79 Inter: r 0.88-0.97
			2DE *vs* 3DE	Intra: r 0.66-0.93 (2DE) Intra: r 0.87-0.99 (3DE)
Malm, 2004 (10)	Norway (S)	Consecutive patients N=100 (>18 y) Nim=200 (<24 h)	LV dimension (EDV, ESV and EF) 2D ± contrast (no *vs* yes)	Limits of agreement for EF Intra: -11.1 to 7.8% *vs* -2.8% to 2.4% Inter: -16.6 to 14.2% *vs* -5.9 to 6.9% Limits of agreement for EDV Inter: -33 to 18.1 mL *vs* -18.8 to 22.6 mL Limits of agreement for ESV Inter: -23.5 to 16.5 mL *vs* -15.6 to 14.8 mL

Table 5. Literature review on reproducibility of left ventricular structure and function (continued-1)

Articles	Location	Setting	Features	Main results
Malm, 2005 (11)	Norway (S)	Selected patients N=62 (60±11 y) Nim=248 (<24 h)	Ejection fraction 2-chamber view (2CH) ± contrast *vs* apical long axis view (APLAX) ± contrast	Limits of agreement without contrast 2CH *vs* APLAX Intra: -9.5 to 9.6% *vs* -6.3 to 7.1% Inter: -11.7 to 14.7% *vs* -12.2 to 9.0% Limits of agreement with contrast 2CH *vs* APLAX Intra: -4.7 to 5.2% *vs* -2.7 to 3.4% Inter: -8.3 to 12.2% *vs* -6.2 to 6.0%
Palmieri, 2005 (12)	Italy (M)	HV + patients N=56 Nim=112 (<24 h)	TMD, IVRT, AFF, E-Vp	Intra: ρ 0.76-0.96 κ 0.40-0.92 (except for IVRT < 60 ms [κ=0.05])
Chan, 2006 (13)	Australia (S)	CHD and DCM N=30 (62) Nim=30 (…)	LV dimensions	No reproducibility of echocardiographic images 3DE is accurate compared with TI-201 single-photon CT and MRI
Jacobs, 2006 (14)	Spain, USA (M)	Various cardiac pathologies, N=50 (58±19 y) Nim=84 (…)	EDV, ESV, EF 2DE *vs* RT3DE compared to MRI	2DE *vs* RT3DE EDV Intra: CV 13% *vs* 10% Inter: CV 19% *vs* 10% ESV Intra: CV 24% *vs* 11% Inter: CV 24% *vs* 11% EF Intra: CV 13% *vs* 10% Inter: CV 14% *vs* 5%
Ogah, 2006 (15)	Nigeria (S)	23 randomly selected cases of 104 referred patients (Federal Medical Centre, Abeokuta) 20 analysed (59.8 y) Nim 40 (1 week)	LV and atrial dimensions (see Table 3), AOD and RVOT diameter	Intra: r 0.60-0.96
Jenkins, 2007 (16)	Australia (S)	HV and various cardiac pathologies 20 (60 y) Nim 40 (< 1h)	EDV, ESV, EF 2DE, 3DE *vs* RT3DE	2DE, 3DR *vs* RT3DE EDV Intra: r 0.84 *vs* 0.92 *vs* 0.99 Inter: r 0.91 *vs* 0.89 *vs* 0.99 ESV Intra: r 0.89 *vs* 0.84 *vs* 0.99 Inter: r 0.97 *vs* 0.90 *vs* 0.99 EF Intra: r 0.89 *vs* 0.90 *vs* 0.92 Inter: r 0.87 *vs* 0.85 *vs* 0.96

Table 5. Literature review on reproducibility of left ventricular structure and function (continued/2)

Articles	Location	Setting	Features	Main results
Hansegård, 2009 (17)	Norway (S)	35 of 56 patients included in previous studies N=35 (23-76 y) Nim 70 (>14 d)	EDV, ESV, EF RT3DE (TomTec™ [https://www.tomtec.de/excellence-in-digital-healthcare) *vs* 4DLVQ (General Electric)	TomTec *vs* 4DLVQ EDV Intra: CV 5.5% *vs* 5.8% Inter: CV 11% *vs* 5.9% ESV Intra: CV 6.0% *vs* 8.0% Inter: CV 15% *vs* 5.6% EF Intra: CV 4.9% *vs* 7.1% Inter: CV 8.5% *vs* 5.9%
Douglas, 2013 (18)	USA (M)	RCT (PARTNER I) N=1055 (83 y) Nim=30 (baseline)	EF, mAVG, pAVG, AVA, pvAR, tvAR and MR	
			Pairwise comparisons: 649-1101	Sonographer Intra: ρ 0.70-0.99 (EF) ρ 0.99-1.00 (mAVG) ρ 1.00 (pAVG) ρ 091-1.00 (AVA) Inter: ρ 0.89-089 (EF) ρ 0.97 (mAVG) ρ 0.97 (pAVG) ρ 0.90 (AVA) Physician Intra: ρ 0.56-0.99 (EF) ρ 0.99-1.00 (mAVG) ρ 0.99-1.00 (pAVG) ρ 095-0.97 (AVA) Inter: ρ 0.92-0.99 (EF) ρ 0.99 (mAVG) ρ 0.99 (pAVG) ρ 0.95 (AVA)
			Thresholds for pvAR, tvAR and MR ≤grade 1 Pairwise comparisons: 1360	Sonographer Intra: κ 0.68-1.00 Inter: κ 0.35-0.41 Physician Intra: κ 0.58-0.85 Inter: κ 0.28-0.85
Shibamaya, 2013 (19)	Japan (S)	HV and patients with cardiac pathologies N=41 (63±11 y) Nim=41 (<3 d) 8 randomly selected patients for intra- and inter-rater reproducibility	EDV, ESV, EF determined by 2DE, RT3DE and NMR	Validation *vs* NMR for EDV, ESV and EF 2DE r 080-0.97 sa3DE r 0.88-0.97 fa3DE r 0.54-0.90 Repeatability *vs* MRI for EDV, ESV and EF Intra: 2DE ρ 0.88-0.97 sa3DE ρ 0.84-0.90 fa3DE ρ >0.99 Inter: 2DE ρ 0.89-0.96 sa3DE ρ 0.92-0.98 fa3DE ρ 0.92-0.95

Table 5. Literature review on reproducibility of left ventricular structure and function (continued/3)

Articles	Location	Setting	Features	Main results
Tsang, 2013 (20)	UK, USA (M)	Wide range of LV function Before training N=50 (55±19 y) Nim 50 (…) After training N=23 (…) Nim 23 (…)	Interinstitutional differences in EDV, ESV, SV and EF by RT3DE before and after training One rater in each of two institutions	Between-centre (inter-rater) reproducibility for EDV, ESV and EF Before training ρ 0.69-0.86 CV 6.5-19.5 After training ρ 0.87-0.97 CV 12.1-15.9
Tognon, 2014 (21)	Brazil (M)	ELSA-Brazil cohort N=119 (50.2±7.0 y) Nim=119 (…)	AOD, LAD, and LV dimensions and systolic function (EF), as listed in Table 4	Difference between acquisition and central reading centres (inter-rater) ρ 0.35-0.79
Armstrong, 2015 (22)	USA (M)	CARDIA cohort study year 25 Four acquisition centres and central reading centre N=3475 (50±4 y) Intra-rater CV Nim=46 of 200 (…) Inter-rater CV Nim=42 of 200 (…) Intraclass correlation coefficient for all sonographers Nim=88 of 200 (…)	AOD, LAD, and LV dimensions and systolic function (EF), as listed in Table 4 M-mode and 2DE	Intra: CV 5.1-11.2 Inter: CV 5.1-11.2 All sonographers ρ 0.58-0.91
Frikha, 2015 (23)	France (S)	Stanislas cohort 4th examination (2011-2014) N=60 randomly selected participants in sinus rhythm (50±14 y) Nim=60 (…)	Left ventricular dimensions and diastolic function M-mode, 2DE and TMD and MAD	LAV, EDV, ESV, EF and LVMI (BSA) Intra: ρ 0.89-0.99 Inter: ρ 0.87-0.99 (E, A and DT) Intra: ρ 0.98 Inter: ρ 0.96-0.97 (e', a') Intra: ρ 0.99 Inter: ρ 0.98-0.99 Diastolic dysfunction Intra: κ 0.93 Inter: κ 0.88

Table 5. Literature review on reproducibility of left ventricular structure and function (continued/4)

Articles	Location	Setting	Features	Main results
Nacif, 2017 (24)	USA (S)	MESA (Baltimore / 2000-2002) 102/149 (age 66.2 y) Nim=102 (…) for validation *vs* NMR Nim=20 (…) for repeatability	TMD and MAD by 2DE (two readers) *vs* NMR	Validation vs NMR (n=102) r 0.09-0.71 (TMD) r 0.11-0.24 (MAD) Repeatability (n=20) Intra: r 0.72-0.96 (TMD) r 0.89-0.92 (MAD) Inter: r 0.84-0.95 (TMD) r 0.85-0.89 (MAD)
Coisne, 2020 (25)	France (M)	Patients referred to five tertiary hospitals N=25 (62±18 y) Nim24=400 (NA)	LAV, EDV, ESV, SV, EROA, MRV, E/A Results for 16 senior and 16 junior cardiologists and all	Inter-rater repeatability LAV, EDV, ESV, SV ρ 0.53-0.97 E/A ratio ρ 0.74-0.87 EROA ρ 0.33-0.61 MRV ρ 0.36-0.57
Mauermann, 2021 (26)	Belgium (S)	Anaesthetised patients undergoing cardiac surgery on pump N=25/32 (50-81 y) Nim=NA	MAD as measured by transthoracic *vs* transoesophageal tissue Doppler	r 0.71 (e' transthoracic *vs* transoesophageal measurement) Repeatability (e') for n=24 Intra: ρ 0.97 Inter: ρ 0.87
Lenell, 2023 (27)	Sweden (M)	SWEDEHEART Registry (acute coronary syndrome) N=130/177 randomly selected patients from 3 sites (65 y) Nim=130 (NA)	EF by 2DE and categorised in to <30, 30-39, 40-49 and ≥50%)	EF categorisation registry *vs* re-evaluation by raters: agreement in 86 (66.0%) of patients registry < retest: 33 patients (25.4%) registry > retest: 11 patients (8.5%)

Articles (see Fig. 3) are ordered by year of publication and within publication year alphabetically by the first author's surname. Reference numbers (see References) are given between parentheses. **Location** identifies the countries, in which the studies were conducted, "M" and "S" indicating multicentre and single centre studies. **Settings** refers to the following information: RCT=randomised clinical trial; N=number of participants (age); Nim=number of echocardiographic images analysed or number of analyses per parameter (interval between test and retest); NA=not applicable; HT=hypertensive patients; HV=healthy volunteers; PARNER I=Placement of Aortic Transcatheter Valves (PARTNER) I trial; ELSA-Brazil=Brazilian Longitudinal Study of Adult Health; STANISLAS= single-centre familial longitudinal cohort comprised of 1006 families(4295 subjects) from the Nancy region recruited in 1993–1995; MESA= Multi-Ethnic Study of Atherosclerosis at the Johns Hopkins Hospital. **Features** refers to the echocardiographic variables reflection left ventricular dimensions, systolic and diastolic function as listed Table 4; EDV=end-diastolic volume; ESV=end-systolic volume; EF=ejection fraction; SV=stroke volume; FS=fractional shortening; IVRT=isovolumetric relaxation time; AFF=atrial filling fraction; E-Vp=E wave propagation rate; AOD=aortic diameter; LAD=left atrial diameter; LAC=left atrial volume; RVOT=right ventricular outflow tract; TMD=measurement of the transmitral diastolic blood flow by pulsed Doppler; MAD=measurement of the mitral annular diastolic velocities by tissue Doppler; DT=deceleration time of the transmitral blood flow; mAVG=mean gradient over the aortic valve; pAVG=peak gradient over the aortic valve; AVA-aortic valve area; pvAR=paravalvular aortic regurgitation; tvAR=valvular aortic regurgitation; MR=mitral regurgitation; EROA=effective regurgitant orifice area of the mitral valve; MRV=mitral regurgitant volume. **Main results** do not include the reproducibility of non-echocardiographic imaging techniques, in particular nuclear magnetic resonance imaging. To describe intra-rater (intra) and inter-rater (inter) reproducibility of continuous measurements, if available, precedence was given to the correlation coefficient (r), the intraclass correlation coefficient (ρ) or the

coefficient of variation (CV), because these estimates are less dependent on the characteristics of participants compared to the 95% limits of agreement. ICC values of 0.50-0.69, 0.70-0.80, and >0.80 indicate moderate, strong, or nearly perfect agreement. The κ statistic was extracted to describe agreement between test and retest in categorised variables; values <0.20, 0.21-40, 041-061, 061-080, and 0.81-1.00 respectively indicate none or slight, fair, moderate, substantial or almost perfect agreement. Unless stated otherwise, values of the correlation coefficient, the intraclass correlation coefficient, the coefficient of variability or the κ statistic are ranges of the echocardiographic characteristics examined A single value indicates similar estimates for all echocardiographic characteristics analysed. 2DE=two-dimensional echocardiography; 3DE=three-dimensional echocardiography; RT3DE= real-time three-dimensional echocardiography; 4DLVQ=semi-automated tool for 4D LV volume quantification in RT3DE (EchoPAC version 108.1.0, GE Vingmed Ultrasound, Horten, Norway); fa3DE=fully automated real-time three-dimensional echocardiography; sa3DE=semi-automated real-time three-dimensional echocardiography; CT=computed tomography; MRI=magnetic resonance imaging. An ellipsis indicates that data could not be extracted.

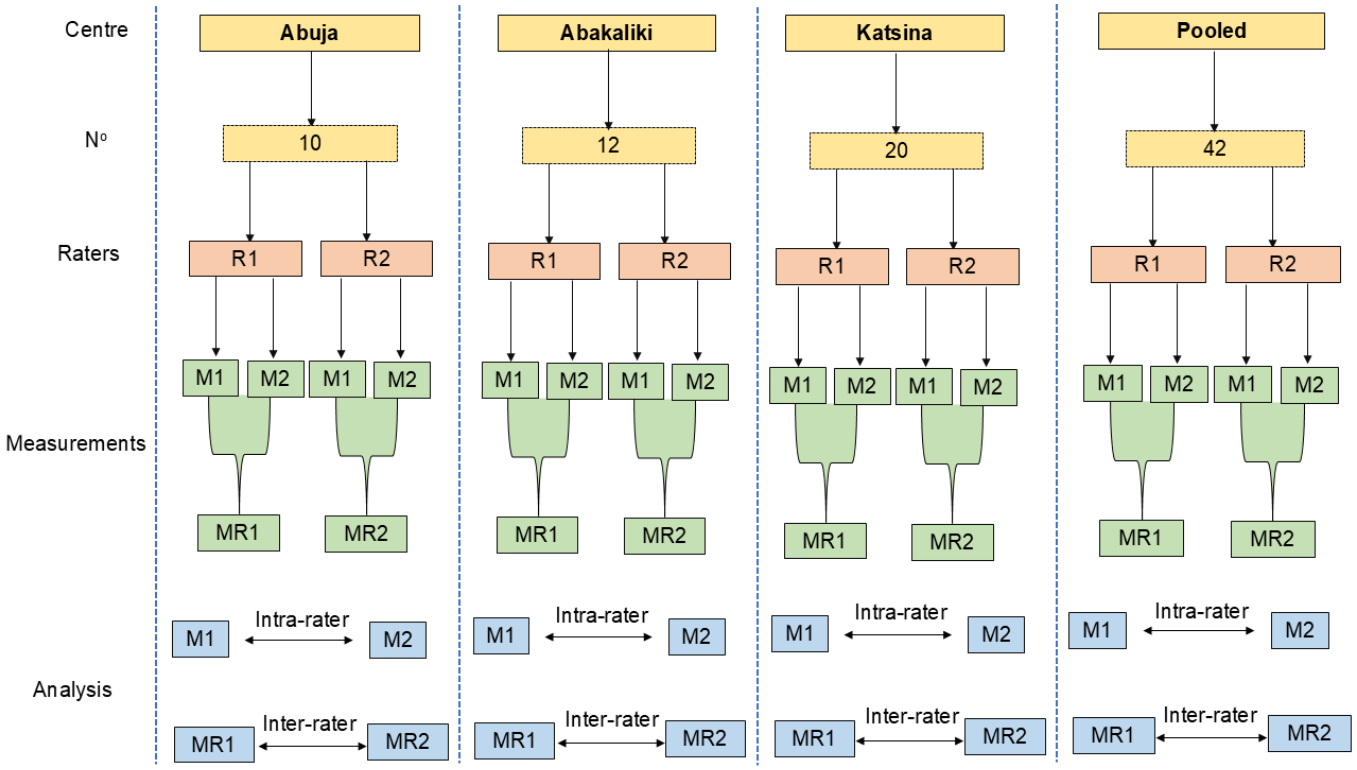

Fig. 1.

Protocol of the reproducibility study.

Abbreviations: N°, number of patients; R1, rater 1; R2, rater2; M1, first measurement; M2, repeat measurement; MR1, average of repeated measurements by rater 1; MR2, average of repeated measurements by rater 2. Pooled data refers to the combined data across the three study centres.

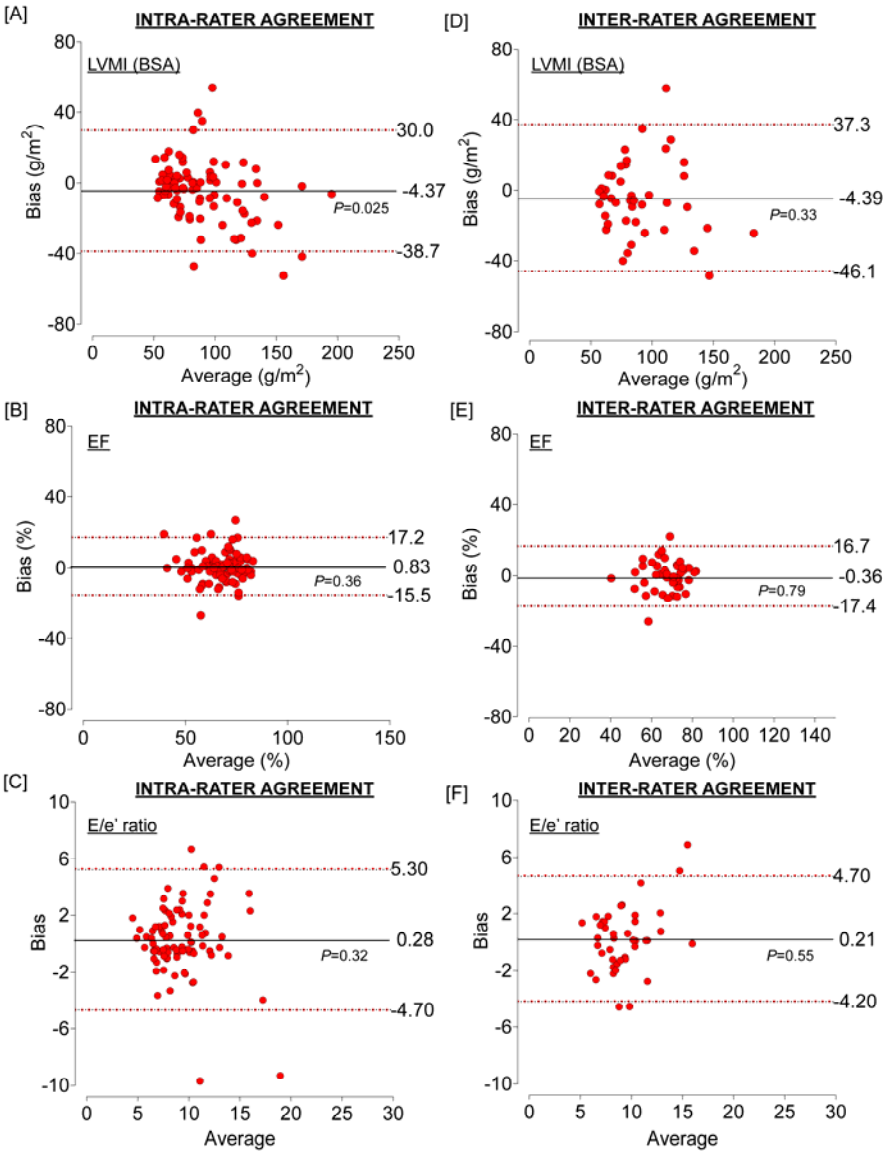

Fig. 2

Bland and Altman plots .

Bias computed as retest minus test value is displayed along the vertical axis and plotted against the average of test and retest along the horizontal axis. Given the distribution of bias, the 95% limits of agreement (95% LA) are bias ± (1.96 × SD). The full line indicates bias and the dotted lines correspond with the 95% limits of agreement. *P*-values denote the significance of the bias. Results are given for left ventricular mass (LVMI) indexed to body surface area (A,D), left ventricular ejection fraction (B,E) and the E/e' ratio (C,F), an index of left ventricular diastolic filling pressure. The intra-rater results appear in panels A-C and the inter-rater results in panels D-F.

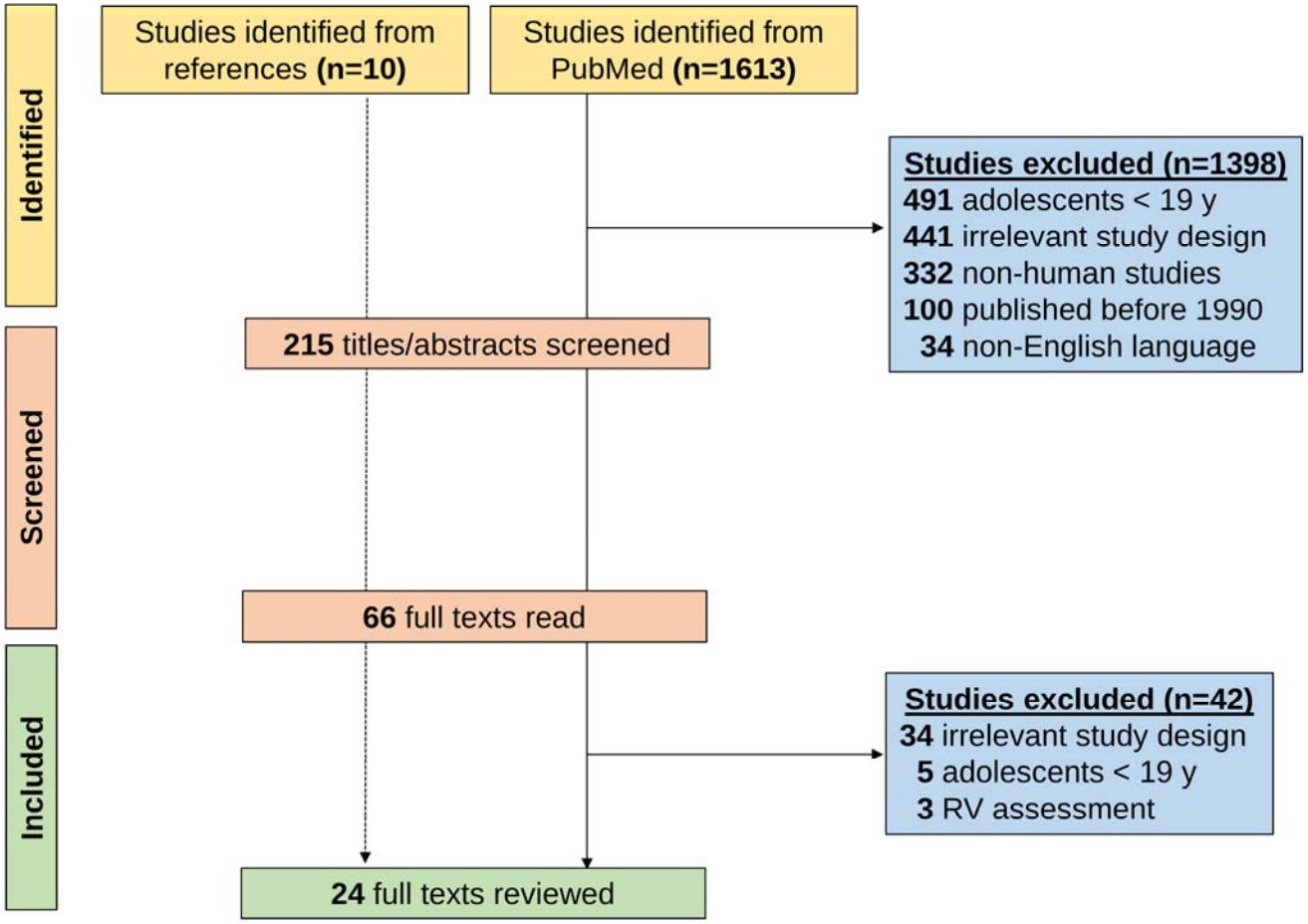

Fig. 3

Literature flow diagram.

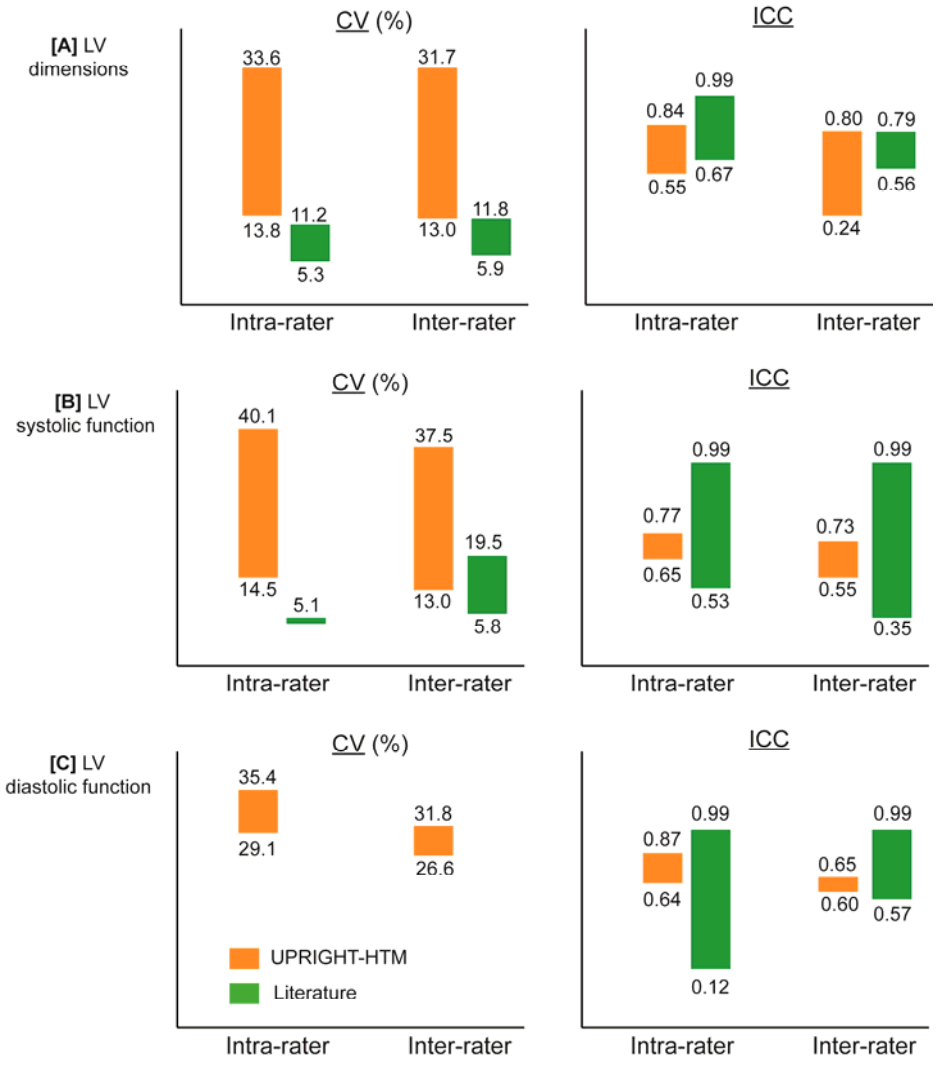

Fig. 4

Box plots summarising the intra- and inter-rater repeatability for the echocardiographic assessment of LV dimensions as assessed by the coefficient of variation and the intra-class correlation coefficient.

Data from the literature review (Table 5) are presented in green and those generated in UPRIGHT-HTM (Table 4) in orange. The vast heterogeneity of the echocardiographic technologies applied and the individuals included in the reviewed reproducibility studies precluded a formal statistical comparison between the literature data and the present observations. However, the box plots for the distributions of the intra- and inter-rater CVs and ICCs without formal statistical tests allow a visual comparison of literature and current results for left ventricular dimensions (A) and systolic (B) and diastolic (C) left ventricular function.