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Reference values for 2D speckle tracking strain analysis of the left atrium : Results of the Hamburg City Health Study

Dissertation

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1 Hypothesis and questions asked

The hypothesis of this work is that there is no difference in Speckle tracking echocardiography (STE) - derived LA global strain between the sexes, addressing an incongruent body of data published. Further the current scientific consensus that LA strain decreases with age and body surface area (BSA), will be tested for a Caucasian population. Standard values for STE LA global strain will be determined and intra- and interobserver variability will be tested.

This thesis raises the following questions:

- What are standard values of 2D speckle tracking derived LA global strain in subjects without classical cardiovascular risk factors or diseases aged 45 to 74 years?

- Do the generated 2D speckle tracking LA global strain values correlate with age in healthy subjects?

- Do the generated 2D speckle tracking LA global strain values correlate with BSA in healthy subjects?

- Are there sex-specific differences in 2D speckle tracking LA global strain standard values?

2 Introduction

This dissertation is concerned with an echocardiographic parameter for myocardial deformation: 2D speckle tracking strain analysis. To date, strain analysis has mainly been used to examine the well-functioning of the ventricles. However, as more and more data are emerging, suggesting its benefits to also use it on the left atrium (LA)[1–3], this work aims at generating reference values for LA strain. Echocardiographic images of the first 10,000 subjects from the population-based Hamburg City Health Study (HCHS), a single-centre, long-term, prospective cohort study in Hamburg, Germany, were analysed. Subjects with major cardiovascular risk factors were excluded from the collected data to obtain reference values for LA global strain from a cohort free of cardiovascular disease.

2.1 Cardiovascular diseases and their impact on humankind

Globally, an estimated 17.9 million people die each year from cardiovascular diseases (CVD). This makes 31% of all deaths worldwide, making cardiovascular diseases the leading cause of death. One-third of these people die under the age of 70.[4] Looking at the European Union alone, CVDs are the leading cause of death as well. With 1.68 million deaths in 2016, CVDs account for an even higher percentage of 37.1% of mortality in this part of the world, far behind the second leading cause of death, malignant neoplasms, which account for 25.8% of deaths.[5] Cardiovascular diseases include diverse pathologies of the heart, ranging from coronary artery disease to various types of heart failure or cardiac arrhythmias, to name a fraction. In all these conditions, early diagnosis is a crucial factor not only for mortality but also for quality of life. This applies to diseases associated with the left atrium as well. For a long time, parameters for assessing left atrial function have primarily focused on volumetric aspects. This thesis is concerned with the newly emerging parameter for LA function: 2D speckle tracking strain analysis.

2.2 Function of the left atrium

The left atrium (LA) has received much less scientific and clinical attention compared to the left ventricle. It has mostly been perceived as a bystander, regulating the filling of the left ventricle (LV). However, the perception of the LA has

changed as recent data suggest that its significance goes beyond that, with LA parameters serving as outcome predictors in a variety of cardiovascular diseases.[1,2]

2.2.1 The LA as a modulator for LV- filling

The LA fulfills a crucial role in the filling of the LV, which can be described in terms of three different phases within the cardiac cycle. In the reservoir phase, oxygenated blood flows through the pulmonary veins to the atrium in the ventricular systole. Atrial compliance and atrial relaxation and contractility are critical for a well-functioning atrium in this phase. In the conduit phase, blood flows from the LA to the LV during early ventricular diastole. The function is determined by LA compliance. The third phase occurs during late systole, when the booster pump function of the LA completes the filling of the LV. This function is influenced by venous return, systolic reserve, and LV end-diastolic pressure.[2]

2.2.2 LA dysfunction as a predictor for cardiac diseases

Filling the LV is not the only important role played by the LA. Studies have shown an association between structural remodeling of the LA and increased cardiovascular events and mortality in asymptomatic subjects recruited from the general population.[2,6] It was shown that a malfunctioning LA leaves asymptomatic probands more at risk for cardiovascular diseases, such as heart failure, atrial fibrillation (AF) and stroke. Therefore, LA dysfunction may be regarded as a harbinger of these diseases.[7]

Next to invasive procedures, LA size, volume and ejection fraction (EF) have been the most commonly used parameters to quantify LA dysfunction, with the promising newer parameter strain entering the field of cardiovascular diagnosis.

Regarding LA size, there are significant differences among healthy individuals. Nevertheless, enlargement of the left atrium is linked to an increased likelihood of cardiovascular events such as stroke, heart failure and AF. A positive association between LA size and mortality rate has also been observed.[8]

Strain analysis of the LA, the parameter this thesis is mainly concerned with (described in detail in Chapter 1.4), has shown to be a viable diagnostic tool for pathologies associated with the LA, e.g. early detection of diastolic dysfunction[9], prediction of cryptogenic stroke risk[10] or prediction of successful treatment of atrial

fibrillation (AF) with pulmonary vein isolation (PVI)[11]. The clinical implications of LA strain will be discussed in more detail later, in Chapter 1.4.3.

2.3 Diagnostic tools for the left atrium

LA function can be assessed either invasively by catheter or by non-invasive tools like cardiac magnetic resonance imaging (CMR), computed tomography (CT), or echocardiography.

2.3.1 Echocardiography as a diagnostic tool for the left atrium

Echocardiography is the most widely used tool for assessing the anatomy and function of the LA. It's major advantages are its availability, simple acquisition, safety, low cost, and a non-invasive procedure. Various parameters can be used to examine the condition of the LA. LA volume, LA volume index (LAVI), LA size, left atrial ejection fraction (LAEF), E/A ratio, E/e' ratio, proper functioning of the mitral valve and strain analysis, the parameter of interest in this work, can all be determined with echocardiography. The limitations of echocardiography are its dependency on the acoustic window as well as errors due to geometric assumptions.[12]

2.4 Strain analysis

Strain and strain rate (SR) analysis is a recognized tool for describing the deformation and velocities of the myocardium. It compares the length of myocardial fibre when under stress L (i.e. at the end of systole) with its length in the relaxed state L_0 (i.e. at the end of diastole). The difference is divided by its relaxed length. Mathematically, it is referred to as "Langrangian strain". It is dimensionless and is commonly expressed as a percentage (%):

$$Strain = \frac{(L - L_0)}{L_0}$$

The strain rate describes the change of strain per time[13]:

$$Strain\ rate = \frac{Strain}{\Delta t}$$

A negative strain value describes thinning or shortening of the myocardium, whereas an elongation or thickening of the myocardium leads to positive strain values.[14] Usually, strain is visualized in shape of a curve (see Figure 6), which can then be interpreted.

Clinically, this translates into the possibility of obtaining relevant information about pathologies of the heart, ranging from valvular disease[15], coronary artery disease[16], systolic and diastolic dysfunction[17], or atrial fibrillation[18], to name just a small fraction. A discussion of the clinical implications of LA strain can be found in Chapter 1.4.

2.4.1 Different types of strain

As an advantage over EF, strain analysis can distinguish between different components of contractile function, depending on the direction of the analyzed vectors.[19] For the ventricular myocardium, three types of strain can be detected, as shown in Figure 1-3:

- Radial strain: describes myocardial thickening/thinning.

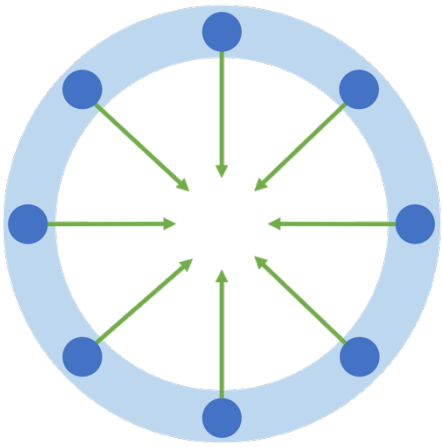

Figure 1: *Radial strain. Own image based on Blessberger and Binder (2010)*

- Circumferential strain: describes the change in the radius of the ventricle and is measured in the short axis.

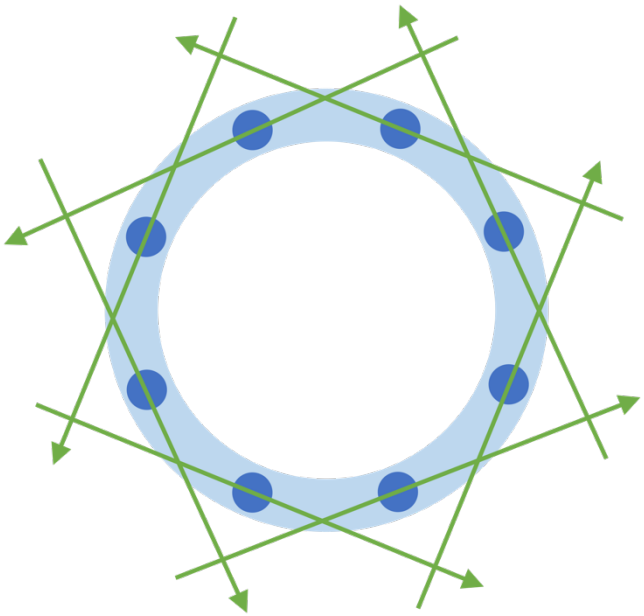

Figure 2: *Circumferential strain. Own image based on Blessberger and Binder (2010)*

- Longitudinal strain: describes the lengthening/shortening of the myocardium from the base to the apex of the heart. As a result, the longitudinal strain of the ventricle is negative, as the myocardium contracts, while the longitudinal strain of the atrium is positive as it fills with blood and expands. [13]

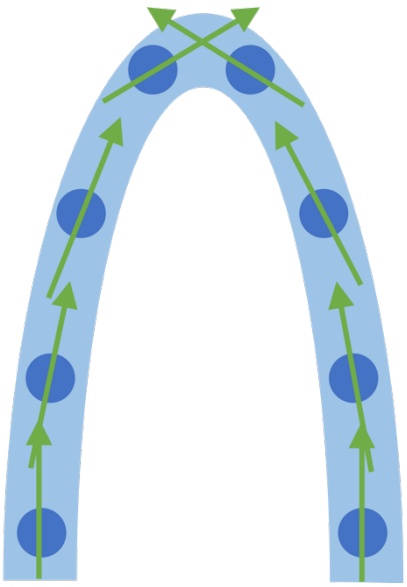

Figure 3: *Longitudinal strain. Own image based on Blessberger and Binder (2010)*

To date, strain analysis has been used mainly to assess the function of the left ventricle, from which the described forms of strain originate.[20,21,22] However, the literature suggests that assessment of atrial function is a promising indication that also needs further exploration. [2,23]

2.4.2 Measuring Strain

Until recently, the only way to determine strain parameters was to use tissue Doppler imaging (TDI). In recent years, however, a new diagnostic tool has sparked enormous interest in the cardiology community, with some going so far as to call it "the next revolution in echocardiography": STE, a non-invasive method for assessing myocardial deformation, strain, and strain rate. It was introduced in 2004 by Leitman et al.[24] and Reisner et al.[25]. Compared with TDI, STE promises to offer many advantages, as shown below.[13]

STE can be performed as an offline analysis of recorded echocardiography DICOM clips using designated software algorithms. When the myocardium is imaged with ultrasound, the echo beams are reflected, scattered, and refracted by the various contours and textures of the myocardium. This interaction produces natural acoustic markers that appear as a speckled pattern. There are some speckles that remain stable during parts of the cardiac cycle. These stable speckles are tracked in the ultrasound image, and by following them from frame to frame, they can be tracked over an entire heart cycle. In this way, myocardial motion can be marked, with each displacement of a speckle representing local tissue motion, as shown in Figure 4. By analyzing this tissue motion using post-processing software, myocardial deformation, the strain, and the strain rate can be calculated.[13,22]

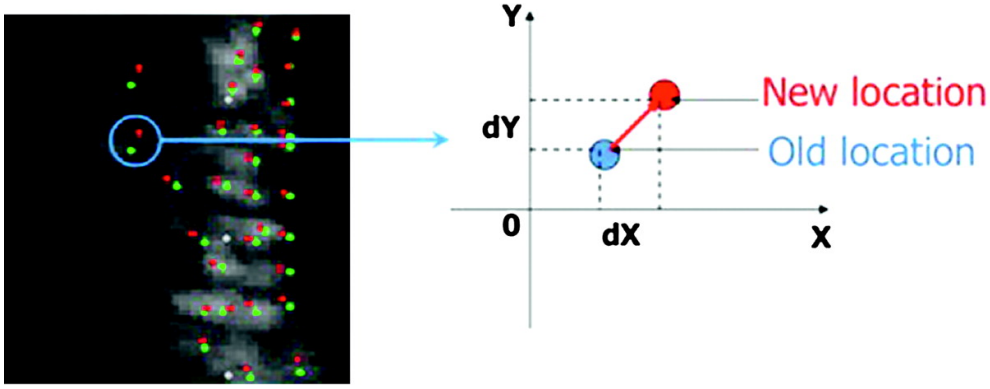

Figure 4: *The principle of speckle tracking. The dots represent acoustic markers. Green dots represent the old position, red dots the new position of the tissue. Figure by Leitman et al.(2004)*

Before speckle-tracking echocardiography was developed, tissue Doppler imaging was the only tool that could measure the above parameters. STE promises many advantages over TDI though, as the latter is angle- and frame-rate-dependent, only moderately robust, and requires a well-trained analyst as it is more complex to interpret.[13] The major disadvantage of tissue Doppler imaging is the angle dependency of all derived data on deformation. For clinical applications, this means that different angles between the transducer and the imaged tissue will result in different values for strain and strain rate.[14] STE, on the other hand, is angle-independent. [22]

Second, the literature suggests that STE is highly reproducible and robust. Several studies have shown that intra- and inter-observer variability is very low, independent of operators experience.[23,26,27]

Another advantage of STE over TDI is that the former is not disturbed by the so-called tethering effect. This describes the phenomenon that scar tissue is passively moved by adjacent vital myocardium and is therefore also incorrectly identified as vital when using TDI, which uses velocities to calculate strain. The strain and strain rate values obtained with STE only reflect active contraction as it compares relaxed fibre length with fibre length when the myocardium is contracting and is independent of velocities.[13]

STE can be performed with 2D and 3D images. Studies suggest that strain imaging with 3D STE offers advantages over 2D STE for certain clinical questions, as some studies suggest that it is less dependent on image quality. However, further studies are needed to verify this trend.[28,29] One challenge of 3D STE is that it is more time-consuming to perform than 2D STE.

2.4.3 LA strain assessment

For STE derived LA strain, it is recommended to use the apical four chamber view as seen in figure 5.[30]

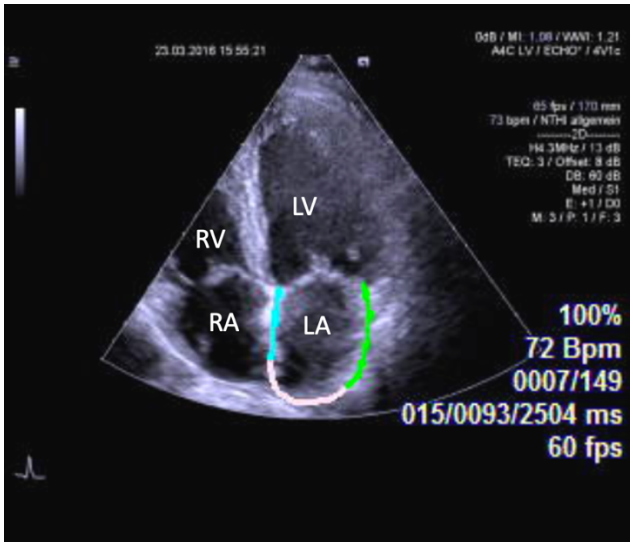

Figure 5: *Apical four chamber view. LV: left ventricle, RV: right ventricle, LA: left atrium, RA: right atrium, own image.*

Global longitudinal strain is internationally recommended for evaluating STE-derived LA strain. It is defined as “strain in the direction tangential to the endocardial atrial border in an apical view”.[30] However, it should be noted that the underlying algorithms are vendor-dependent and not publicly available, making a universal definition difficult.

In principle, global longitudinal strain can be described as the averaged peak atrial longitudinal strain values (global PALS) of all LA segments.[31] Different terms for global PALS are used in the existing literature. Therefore, "global PALS", "LA global strain" and "LA reservoir strain" are used synonymously in this work.[27,28,31,32,33] In Figure 6, the PALS can be found at the highest peak of the yellow dotted line highlighted by the red arrow. This line is the average of the three LA segments, right wall, left wall, and roof represented by the blue, green, and pink curves, respectively.

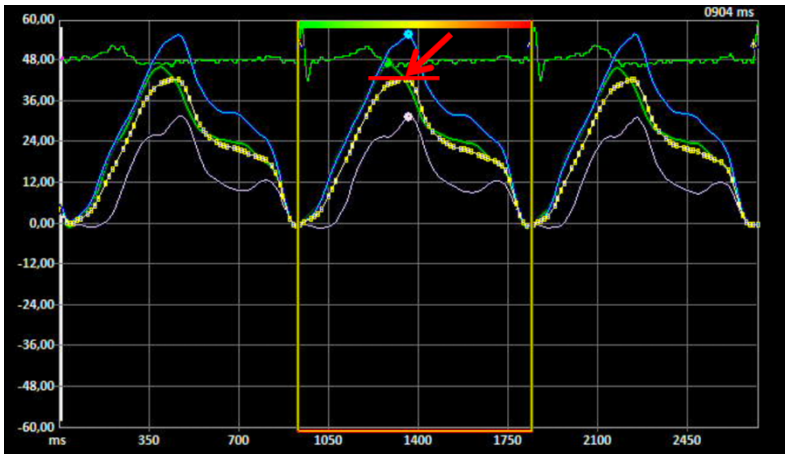

Figure 6: *Typical LA strain curve. The yellow doted line representing the global strain with its peak, the PALS highlighted by the red arrow. Own image.*

To perform a functional analysis of the left atrium, the resulting curve can be differentiated in a reservoir, conduit, and contraction phase, as shown in Figure 7.

During the *reservoir phase*, the atrium is filled with blood. In this phase, the atrium of a healthy individual reaches the greatest volume and thus the greatest value for longitudinal strain. When the global strain or PALS is applied to the atrium, it corresponds to the reservoir strain, since the peak strain in healthy individuals naturally lies in the reservoir phase.

In the *conduit phase*, the atrium loses volume as blood flows passively into the ventricle, following the lower pressure there.

The last phase, the atrial *contraction phase*, describes the end of diastole, when blood is actively pumped into the ventricle.

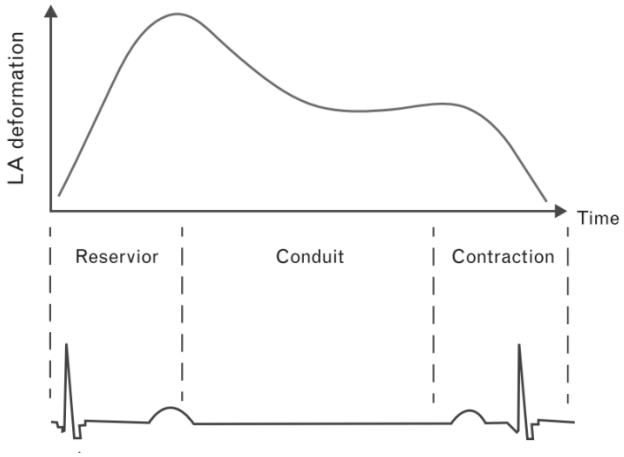

***Figure 7**: The different phases of an LA strain curve. Figure by Inciardi and Rossi (2019)*

As the atrium enlarges and lengthens during systole, the atrial global strain is positive. In contrast, the strain of the ventricle is always negative, as the ventricle contracts and becomes shorter during systole.

The LA strain measurement can be R-tracked or P-tracked, as demonstrated in Figure 8. When it is R-tracked, the cycle begins with the systole of the ventricle. The data presented in this thesis derives from R-gated strain values. Most published data use R-R gating, however there are also publications using P-P gating.[34,35]

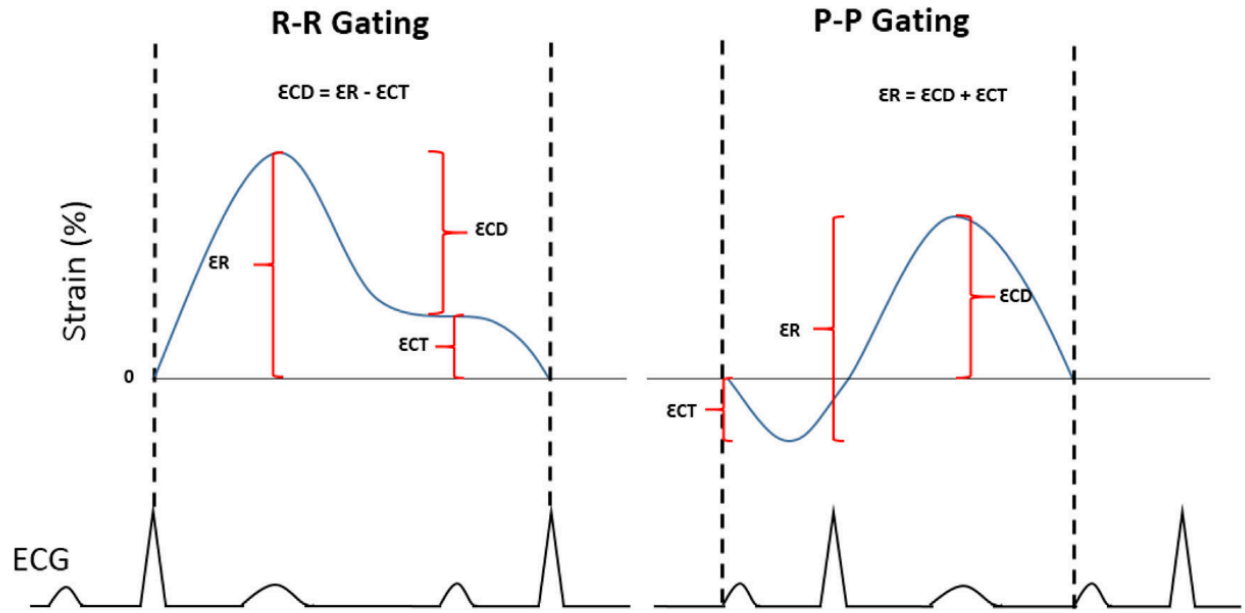

Figure 8: *Two types of zero reference points of an LA strain curve. ER: reservoir strain, ECD: Conduit strain, ECT: Contractile strain, Figure by* Pathan et al. (2017)

2.4.4 Limitations of strain analysis

As a limitation of speckle tracking strain analysis, it must be pointed out that there is no universal definition for global strain as the algorithms are manufacturer dependent and not accessible to the public. However, previous studies have not found significant differences in normal values between different manufacturers, so the clinical implications of the differences appear to be neglectable. Regarding the algorithms, it is worth mentioning that they were primarily developed for LV strain analysis, whereas dedicated tracking algorithms for LA strain have just recently been developed.[34]

One challenge with strain analysis derived from 2D speckle tracking noted in previous studies, is the need for sufficient image quality, which leads to a large number of echocardiographic images that end up being excluded. [13,35]

Strain imaging of the left atrium is more challenging than the ventricle, due to the thin atrial wall, the location of the atrium and the pulmonary veins and appendage making the correct tracing of the LA more time-consuming and difficult.[35]

The correct tracing of the myocardium remains to a certain extent subjective. However, previous research has shown, that strain analysis remains robust among different levels of operator experience.[26,36,37,38]

Lastly, a major limitation of STE derived strain analysis of the LA is the lack of normal reference values from large Caucasian study populations. Most published studies present reference values from exclusively Asian or exclusively black study populations. As a consequence the clinical application of LA strain analysis in a Caucasian population is limited by the lack of well-founded reference values.

2.4.5 Applications of LA Strain in clinical practice

A reduced LA global strain indicates impaired atrial function. Research has shown that LA strain offers several advantages over LAEF or LAVI by assessing the dynamic aspects of the LA:

1) **LA strain and diastolic dysfunction (DD)**

   The 2016 guideline for the detection and grading of DD suggests the use of an algorithm that requires four echocardiographic parameters: LA volume, E/A ratio, E/e' ratio, and peak velocity of the tricuspid regurgitant jet. This is time-consuming in both acquisition and interpretation.[39] A single parameter would hence offer advantages for the clinical practice. Several studies suggest that LA strain measurement is a viable tool to both detect and categorize diastolic dysfunction.[40] Compared with conventional echocardiographic parameters, only peak LA strain was able to show a progression of DD and differed significantly across all DD stages, as shown in Figure 9.[9,41,42] When compared with the invasive gold standard measurement of left ventricular (LV) filling pressure and the current guidelines, LA strain measurement more often reached the same diagnosis as the gold standard (81%) than the current guidelines (72%).[3,9,43] Furthermore, Kurt et al. found that LA global strain can be used to distinguish patients with clinical HFpEF from patients with asymptomatic diastolic dysfunction (DD).[44]

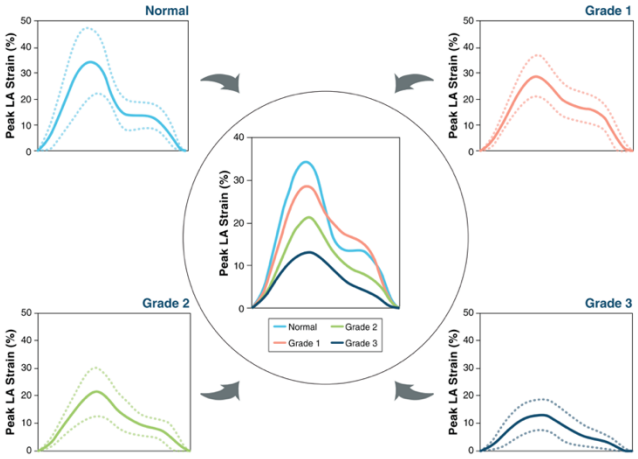

Figure 9: *LA strain in the different stages of DD. At the 4 corners, composite LA strain curves are depicted as mean of each subgroup (solid lines) with standard deviation (dotted lines). Center panel shows all 4 LA strain curves in a single plot to facilitate comparison. Figure by Singh et al. (2017)*

2) LA strain and heart failure

Morris et al. showed that patients with reduced LA strain values (< 23%) and normal LA volume indices had a significantly higher risk of being hospitalized for heart failure in the following two years, independent of sex and age. They also showed that reduced LA strain values are associated with worse NYHA functional class.[45] Freed et al. reached a similar conclusion, showing that LA strain acts as an independent predictor of hospitalization and death from cardiovascular events and that LA strain is associated with LV mass, increased BNP, and reduced exercise capacity.[33] Santos et al. explain the association between impaired LA global strain and higher risk of hospitalization for heart failure in HFpEF patients by a deteriorated LV diastolic and systolic function, which is reflected by LA strain.[46] Furthermore Santos et al. indicate that LA strain functions as an independent parameter for LA dysfunction in patients with HFpEF.[47] Lisi et al. showed that LA strain is the strongest predictor for LA fibrosis in patients with heart failure.[32] In patients with advanced HFrEF LA strain correlates better with pulmonary capillary wedge pressure (PCWP) than E/e'.[48]

3) LA strain and atrial fibrillation (AF)

Yoon et al. found that LA global strain is an independent and the strongest predictor of AF progression. They established a cut-off value of PALS ≤30.9% to be associated with AF progression.[18] Motoki et al. investigated the prognostic significance of baseline LA strain in predicting maintenance of sinus rhythm after PVI in AF patients. It was shown that LA strain serves as an independent predictor and provides higher predictive value than clinical features. The cut-off value for successful catheter ablation was set at a baseline LA global strain ≥ 23.2%.[11] Cameli et al. found that LA strain serves as a predictor for prothrombotic state in non-valvular AF. The included subjects all received transoesophageal echocardiography (TEE) to verify the results. It was shown that STE derived PALS was superior to all other acquired echocardiographic parameters in predicting a thrombus in the left atrial appendix (LAA).[49]

4) LA strain as a predictor of cryptogenic stroke risk

Leong et al. found that reduced LA strain values are associated with a higher risk of cryptogenic stroke (CS), with other cardiovascular risk factors, including atrial fibrillation, being adjusted for in the study design. They demonstrated that LA strain was significantly reduced in patients suffering from CS compared to healthy control subjects (30 ± 7.3% versus 34 ± 6.7%, P < .001). LA strain measurements promise to provide additional information to well-established parameters, such as LA volume index, as a predictor for CS. In their study, the latter was unable to discriminate CS patients from the control group. Furthermore the incremental and independent relation between LA strain and the CS group suggests a stronger relation between LA strain and CS than cardiovascular risk factors alone could account for.[10]

5) LA strain and COVID- 19

ZeinElabdeen et al. found that 2D STE derived PALS was significantly impaired in previously healthy subjects suffering from unexplained persistent symptoms after COVID - 19 infection. They speculate that diastolic dysfunction may cause the impaired LA strain, but acknowledge that further research is needed. In their study of 63 subjects, PALS was a superior parameter for predicting persistent symptoms after infection than conventional diastolic parameters.[50] In addition, Gonzalez et al. found that PALS may be able to identify COVID -19 patients treated in an intensive care unit (ICU) who are at risk for a prolonged inflammatory state by detecting diastolic dysfunction.[51]

2.4.6 Standard values of LA global strain

To implement and interpret strain analysis in the clinic, reliable, reproducible reference values are crucial. Table 1 provides an overview of the data available to date on standard values for LA strain. The large-scale meta-analysis by Pathan et al. with 2542 included healthy subjects in 40 different studies (3 of which were p-p gated) showed standard values for speckle tracking-derived LA strain, yet is based on only modestly sized individual cohorts. The mean global strain for the left atrium they defined was 39.4% (95% CI, 38.0%-40.8%). A subgroup analysis in this meta-analysis showed that large studies (n > 100) yielded larger values for left atrial global strain than small studies (n< 100); 44% and 38%, respectively. They also found that heart rate was significantly associated with PALS.[34] A study by Liao et al. derived standard values for LA strain from an all-Asian study population and found a significantly higher PALS in women than in men.[52] Sun et al. also found a significantly higher PALS in women than in men and a negative correlation with age in both sexes in a Korean study population.[53]

Table 1 Standard values of LA global strain. *Overview over different studies establishing normal reference values for speckle tracking derived LA global strain displayed in mean and standard deviation.*

	n	PALS overall %	PALS women %	PALS men%	p-value
Meel et al. 2017[54]	120	39.0 (8.4)	Not given	Not given	Not given
Pathan et al. 2017[34]	2542	39,4	Not given	Not given	Not given
Liao et al. 2017[52]	2812	38,2	39.26 (8.08)	37.88 (8.11)	<0.001
Sugimoto et al. 2018[55]	371	42.5	Not given	Not given	0.49
Sun et al. 2020[53]	324	35.4 (11.3)	37.0 (11.9)	33.7 (10.3)	0.008
Cameli et al. 2020[38]	309	33.5 (10.9)	Not given	Not given	Not given

2.5 What is the aim of this thesis?

As the largest single centre local prospective health study in the world, the Hamburg City Health Study (HCHS) offers a tremendous opportunity to validate previous research and generate up-to-date reliable standard values for speckle-tracking-derived LA strain in a previously incongruent data situation. Previous research on normal reference values for LA strain was mainly limited to Asia. In this work, normal values for LA strain will be demonstrated for a middle-aged Caucasian population. Furthermore, the aim of this work is to correlate LA strain with other parameters such as sex, age and BSA.

3 Methods

3.1 Study setting

All data analysed in this thesis is based on a sample of the first 10,000 participants from the population-based Hamburg City Health Study (HCHS). The HCHS is a single-centre, long-term, prospective cohort study placed in Hamburg, Germany.[56] It is the largest local cohort study worldwide and will ultimately include 45.000 participants. The HCHS has a special emphasis on imaging to improve early risk stratification and targeted therapy. Enrolled subjects are between the age of 45 and 74 and live in Hamburg. The probands were contacted following a representative statistical procedure on the basis of the local residents registration office and gave written informed consent.

The HCHS is approved by the ethical review committee of the medical association Hamburg ("Ärztekammer Hamburg"). The steering board of the HCHS approved of this study being conducted.

3.2 Exclusion criteria

Of the first 10,000 study participants, 8,245 received transthoracic ultrasound evaluation (TTE). Exclusion criteria were:

- Cardiovascular risk factors: arterial hypertension (defined as blood pressure (BP) >140/90mmHg or use of antihypertensive drugs), smoking (including ex-smokers), BMI >30 kg/m^2, diabetes (defined as fasting blood glucose >126 mg/dl or use of anti-diabetic drugs)
- cardiovascular diseases: coronary artery disease, atrial fibrillation (history or current atrial fibrillation in 12 lead electrocardiogram (ECG))
- Medication: (Betablocker, ACE-inhibitors, MRI (aldosterone-receptor antagonists), platelet inhibitors (ASS, Clopidogrel, Ticagrelor, Prasugrel), Vitamin K antagonists (VKA), loop diuretics (torasemid, furosemide), statins
- Transthoracic echocardiography: insufficient image quality to perform standardised measurements of left atrial strain, left ventricular ejection fraction (LVEF) <50%, any left-sided valvular stenosis, >mild left-sided regurgitation.

3.3 Material

For TTE image acquisition dedicated, state-of-the-art ultrasound machines were used as seen in figure 6 (Acuson SC2000 Prime ultrasound, Siemens Healthineers, Erlangen, Germany)

Figure 10 *Ultrasound device, Siemens*

Figure 11 *Transducer 4V1c, Siemens*

Figure 12 *Transducer 4Z1c, Siemens*

The devices were equipped with a 2-dimensional (4V1c transducer, frequency bandwith 1.25-4.5 MHz) and 3-dimensional (4Z1c transducer, frequency bandwith: 1.5 – 3.5 MHz) piezoelectric ultrasound transducer. The analysis of the collected recordings was performed at off-line workplaces using the Siemens software syngo SC2000 Version 4.0 (Siemens Healthineers, Erlangen, Germany).

3.4 Acquisition and analysis of the data

3.4.1 Acquisition of baseline data

Examinations were performed in the course of a 7-hours lasting baseline visit at the epidemiological study centre at the University Medical Center Hamburg Eppendorf (UKE) in Hamburg, Germany following pre-defined standard-operating procedures. Examiners were trained and internally certified medical professionals who were blinded to the probands clinical information and preconditions.

During this visit, probands underwent validated examinations of different organ systems, including the cardiovascular system with measurements of resting blood pressure and ECG tracings. A vast amount of demographical, anthropometrical and biological data was collected. Furthermore, participants were asked to fill out questionnaires concerning lifestyle, medical history, family history, dietary habits, alcohol consumption and physical activity, to only name a fraction. These questionnaires were completed before, during and after the baseline visit. Basic laboratory analyses under fasting conditions were performed during the baseline visit as well. Variables included relevant to the cardiovascular system were fasting glucose, haemoglobin A1c (HbA1c), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL)/HDL ratio, triglycerides as well as N-terminal pro B-type natriuretic peptide (NT-proBnP). A detailed study protocol has been published.[56]

3.4.2 Acquisition of echocardiographic data

Transthoracic echocardiography was intended to be performed in all participants of the HCHS. All transthoracic echocardiography examinations followed a standard operating procedure, which was based on current guidelines for echocardiography published by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular imaging (EACVI).[57,58] It was conducted and analysed by specially trained and internally certified medical professionals. The certification process included a three-month training period under constant supervision by an ESC TTE certified cardiologist. After this training period, a set of 50 TTE exams was assessed by the trainee and compared to the measurements of the ESC certified cardiologist. Only if the interobserver correlation coefficient was ≥0.9 the internal

certification process was successful. For continuous quality assessment, every 100th TTE exam was analysed twice. Qualitative and quantitative image analyses were performed using an off-line workplace with the commercially available and established Siemens syngo SC2000 software (Siemens syngo SC 2000 Version 4.0, Siemens Healthineers, Erlangen, Germany). The practical TTE assessment was performed with the probands lying in left lateral position. Following views were collected: parasternal long axis view, parasternal short axis view, apical two chamber view, apical three chamber view, apical four chamber view, apical five chamber view, modified apical four chamber view with emphasis on the right ventricle and subxyphoidal long axis. In addition, 3D imaging as well as Doppler velocimetry was used. The probands were asked to hold their breath during each recording. The recordings were ECG-triggered.

3.4.3 Analysis of the data

LA strain was measured by three specially trained study nurses, one physician and one specially trained doctoral candidate. For the analysis of left atrial strain only apical 4-chamber views with sufficient quality were used. Investigators rated each echocardiographic image on a scale from 1 to 4. Images rated a 4 were excluded from LA strain analysis as measurements with insufficient image quality were considered unreliable. The criteria for the evaluation were:

1: No breathing, the endocardium is traceable during all cardiac activity, the image is in a correct angle;

2: No breathing, the endocardium is not completely traceable during all cardiac activity and/or the image is not quite in a correct angle;

3: Respiration and/or poorly traceable endocardium while resulting in a legitimate curve;

4: heavy breathing and/or poorly traceable endocardium with no legitimate curve as a result and/or no full cardiac cycle.

Speckle tracking imaging

LA strain measurement was performed in apical 4-chamber view and rated between 1 and 3 from the aforementioned quality scale. The contour detection of the LA endo-and epicardium was a semi-automatic process. The first and last point, as well as at least 2 points on the lining of the left atrium were manually chosen. For this, the loop was paused at any moment where image quality seemed best, with no regard to the current point of the cardiac cycle. The rest of the endocardium was traced automatically, calculated by the software. The loop was set on play again and the analyst visually checked whether the endocardium was also well framed during movement. When the automatically calculated endo- and epicardial contour did not follow the endo- and epicardium correctly, it was manually adjusted.

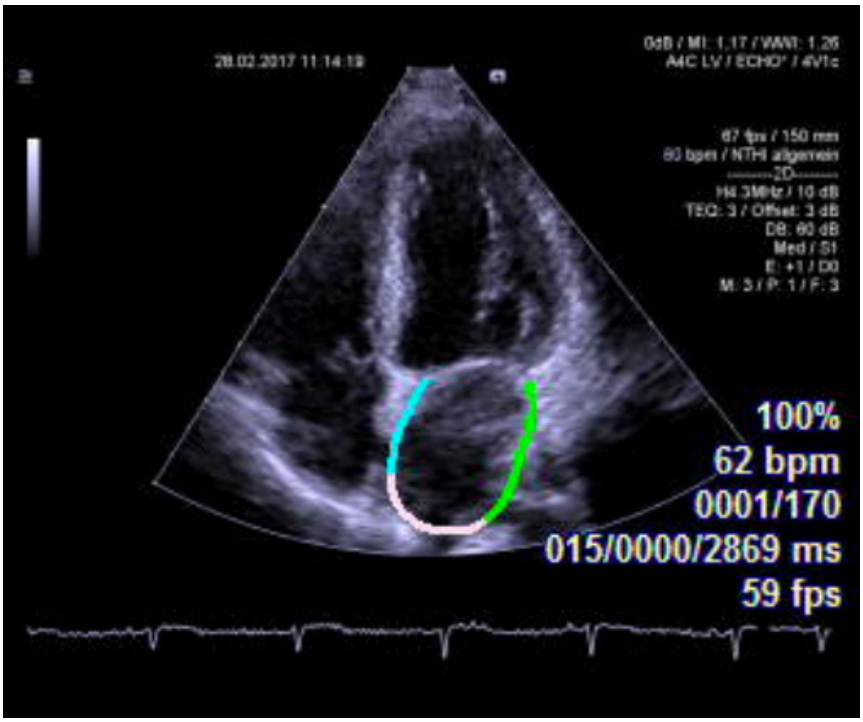

Figure 13: *Framing of the LA, own image*

When the contours correctly moved in line with the blood-tissue-border of the LA, the strain curve was inspected. For the automatically calculated strain and strain curves, the QRS complex was used as a starting and ending point (R-R gated calculation). If it showed a typical LA strain curve, showing a wave with a higher peak followed by a lower plateau shape, the result was considered as appropriate. In that case, the global PALS, LA left wall peak strain, LA right wall peak strain, LA roof peak strain (in %) and the according Time to Peak overalls (in ms) were filed. Figure 15 shows a typical LA strain curve without any pathologies of a healthy

individual. The program shows a separate curve for each region of the left atrium, left wall (green), right wall (blue) and roof (pink). Additionally there is an averaged curve (yellow), overlaying the other three. If no atrial pathologies were present and the tracing process was correctly performed, all lines run close to each other showing the aforementioned typical wave shape:

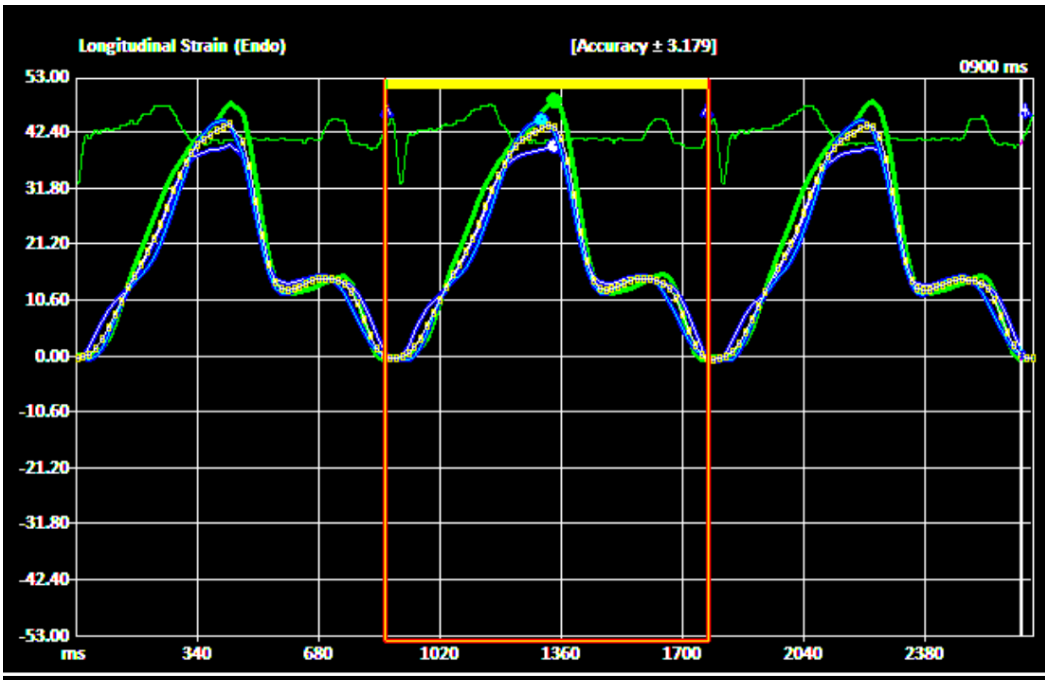

Figure 14: *The typical LA strain wave shape. Own image*

In several cases, the curve did not align with the usual shape of a normal LA strain curve. Then the framing of the endo- and pericardium had to be repeated. Reasons for repeating the framing were as follows:

- None of the four curves align with each other;
- The curve runs a very different shape to the aforementioned typical LA strain curve;
- The yellow curve (average) is negative.

Minor deviations of the aforementioned shape like exemplarily shown in Figure 16 were accepted. They can occur when image quality is mildly impaired in one of the aforementioned segments of the LA. Deviations of the normal shape can also occur due to pathologies of the atrium, such as but not limited to atrial fibrillation, heart failure or amyloidosis. As the differently colored curves describe the different parts of the atrium, it is possible that they do not align when there is a pathology

concentrated either in the left wall, right wall or roof of the atrium. This could result in an impaired deformation of the myocardium and hence in a deviation of a curve. As this thesis aims to produce normal values, the images were excluded when major deviations of a normal LA strain curve occurred.

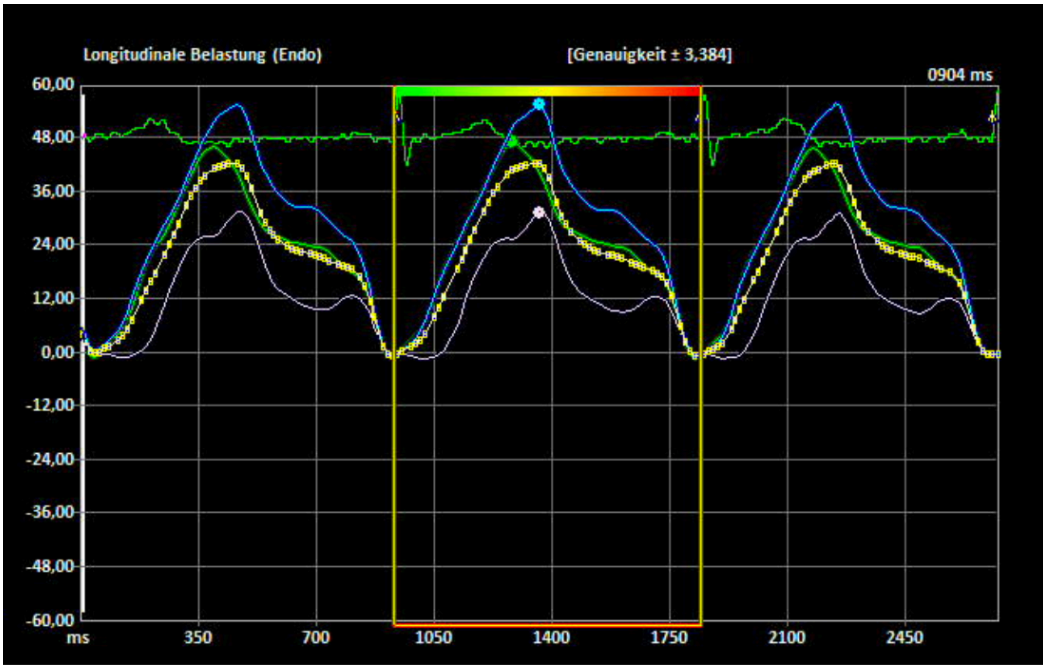

Figure 15: *LA strain curve with deviations of the roof demonstrated by the pink line and right wall demonstrated by the blue line*

3.5 Statistical analysis:

The statistical analysis was conducted with the statisticians of the HCHS Elina Petersen and Alena Haack. In the characteristics of the study population continuous variables are presented as median and interquartile range and categorical variables are presented as absolute numbers and percentages. In the results continuous variables are presented as mean plus standard deviation. Comparisons between groups were performed using Kruskal-Wallis test in the baseline table and one-way analysis of variance in all other tables for continuous variables and Chi-square test for categorical variables. A p-value of <0.05 was considered as statistical significant. All tests were two tailed. For the analysis of intraobserver variability, a subset of 60 images were analysed twice with a time difference of at least 6 months and intraclass correlation coefficient (ICC) estimates and their 95% confident intervals (CI) were calculated based on

a single-rating, agreement, 2-way mixed-effects model.[59] Data analysis was performed using R version 4.1.0.The R- code is attached in the supplements.

4 Results

4.1 Characteristics of the study population

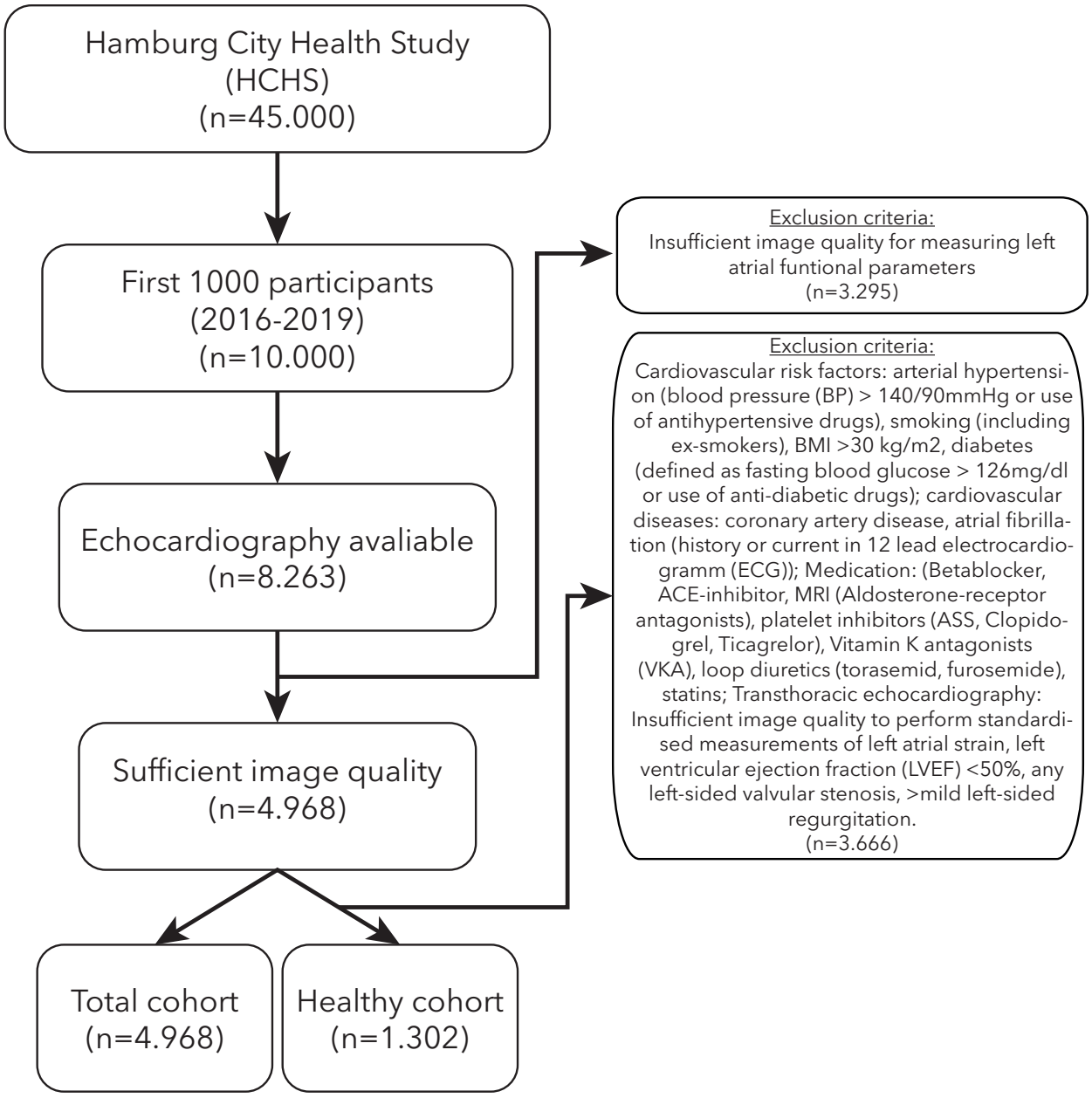

Figure 16: Study Prisma.

Of the first 10.000 HCHS participants 8.263 showed echocardiographic data, 3295 had to be excluded due to insufficient image quality for measuring left atrial functional parameters. 4968 provided sufficient image quality. 3662 probands were excluded according to the following exclusion criteria: cardiovascular risk factors: arterial hypertension (defined as blood pressure (BP) >140/90mmHg or use of antihypertensive drugs), smoking (including ex-smokers), BMI >30 kg/m^2, diabetes (defined as fasting blood glucose >126 mg/dl or use of anti-diabetic drugs), cardiovascular diseases: coronary artery disease, atrial fibrillation (history or current in 12 lead electrocardiogram (ECG)), Medication: (betablockers, ACE-inhibitors, MRA (aldosterone-receptor antagonists), platelet inhibitors (ASA, Clopidogrel, Ticagrelor), Vitamin K antagonists (VKA), loop diuretics (torasemide, furosemide), statins, insufficient TTE image quality to perform standardised measurements of left atrial strain, left ventricular ejection fraction (LVEF) <50%, any left-sided valvular stenosis, >mild left-sided regurgitation. The healthy cohort compromised 1306 individuals.

Of the first 10,000 study participants, 8,245 received transthoracic ultrasound evaluation (TTE). 3295 were excluded due to insufficient image quality. 3666 were excluded because of comorbidities. Our final cohort included 1302 subjects. Figure 17 shows a flowchart on the healthy cohort. The study population showed the characteristics of a middle-aged Western population without major cardiovascular risk factors. Median age was 57.5 [52.0, 64.0], male sex was underrepresented with n=469, median BMI was 24.6 kg/m^2 [22.6,27.0], median heart rate was 68.0 bpm [61.5, 74.0], median systolic and diastolic blood pressure were 127 and 78 mmHg respectively. The laboratories and echocardiographic parameters were within their respective reference ranges.

Table 2: Characteristics of the study population. Continuous variables are presented as median and interquartile range, and categorical variables are presented as absolute numbers and percentages. BMI = body mass index, bp = blood pressure, BSA = body surface area, bp = blood pressure, LVEF = left ventricular ejection fraction, LVEDV= left ventricular end-diastolic volume, LVESV = left ventricular end systolic volume, LVEDD = left ventricular end-diastolic diameter, TAPSE= tricuspid annular plane systolic excursion, TR Vmax= Maximal. tricuspid regurgitation velocity

	Healthy (n = 1,302)
ANTROPHOMETRICS	
Age	57.5 [52.0, 64.0]
Sex = Male n(%)	469 (36.0)
Weight (kg)	71.8 [63.0, 81.7]
Height (cm)	170.3 [164.0, 177.9]
BSA (m2)	1.8 [1.7, 2.0]
BMI (kg/m²)	24.6 [22.6, 27.0]
Waist circumference, cm	88.4 [80.0, 96.5]
Heart rate, bpm	68.0 [61.5, 74.0]
Systolic bp (mmHg)	127.0 [118.5, 134.5]
Diastolic bp (mmHg)	78.0 [72.5, 82.5]
LABORATORIES	*LABORATORIES*
Hemoglobin, g/dl	14.1 [13.4, 14.8]
LDL (mg/dl)	123.0 [100.0, 146.0]

GFR (ml/min)	89.3 [78.6, 96.6]
NT-proBNP (ng/l)	63.0 [38.0, 109.0]
hsCRP, mg/l	0.1 [0.0, 0.2]
Fasting glucose (mg/dl)	89.0 [84.0, 95.0]
ECHOCARDIOGRAPHIC DATA	*ECHOCARDIOGRAPHIC DATA*
LVEF (%)	59.1 [56.5, 62.3]
LVEDV (ml/m2)	111.9 [96.0, 133.1]
LVESV (ml)	45.5 [37.6, 54.7]
LVEDD (mm)	46.9 [43.6, 49.9]
LV mass indexed (g)	76.6 [67.6, 88.0]
LAVI, ml/m2	26.1 [21.8, 30.4]
E/e' ratio	6.8 [5.8, 7.9]
TAPSE	24.6 [22.0, 27.7]
TR Vmax	2.3 [2.2, 2.4]

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4.2 Standard values for global strain of the left atrium

Table 3 shows the results for LA global strain of our healthy study cohort. No significant difference was found between the sexes.

Table 3: Results. Standard values of global strain of the LA. Continuous variables are presented as mean and standard deviation. P-value for intergroup differences.

	Overall n= 1302	Male n=469	Female n= 833	P-value
Global PALS, %	42.21 (15.48)	42.09 (15.85)	42.28 (15.28)	0.828

4.3 Correlation between age and global strain values of the left atrium

Table 4 shows left atrial strain values stratified by age. LA strain decreased with age in both sexes. In women and overall, the decrease was significant ($p < 0.001$).

Table 4: Results. Correlation between age and global strain values of the LA. Continuous variables are presented as mean and standard deviation. P-value for intergroup differences.

	45-49 (n=185)	50-54 (n=308)	55-59 (n=275)	60-64 (n=230)	65-69 (n=178)	70+ (n=126)	P- value
Female (833)	46.90 (15.99)	43.15 (15.01)	43.46 (16.30)	41.97 (14.68)	41.08 (14.44)	33.78 (11.26)	<0.001
Male (469)	41.98 (13.81)	41.82 (14.74)	46.36 (15.66)	40.19 (16.66)	39.38 (17.27)	41.68 (17.60)	0.092
Overall (1302)	44.82 (15.26)	42.69 (14.90)	44.42 (16.12)	41.35 (15.38)	40.45 (15.53)	36.58 (14.29)	<0.001

4.4 Correlation between BSA and left atrial global strain

Table 5 shows that women had significantly higher strain values per BSA than men.

Table 5: Results. Correlation between BSA and LA global strain. Values are presented as mean and standard deviation. P-value for intergroup differences.

	Male	Female	p-value
Global PALS, %	21.05 (8.18)	24.60 (9.42)	<0.001

LAS showed a negative correlation with BSA in women aged above 60. The same trend was shown for males without reaching statistical significance. In subjects younger than 60 years, this trend was also shown in women, but was not significant. For males under 60, the correlation was poled in the other direction, without reaching statistical significance, as shown in Figure 19.

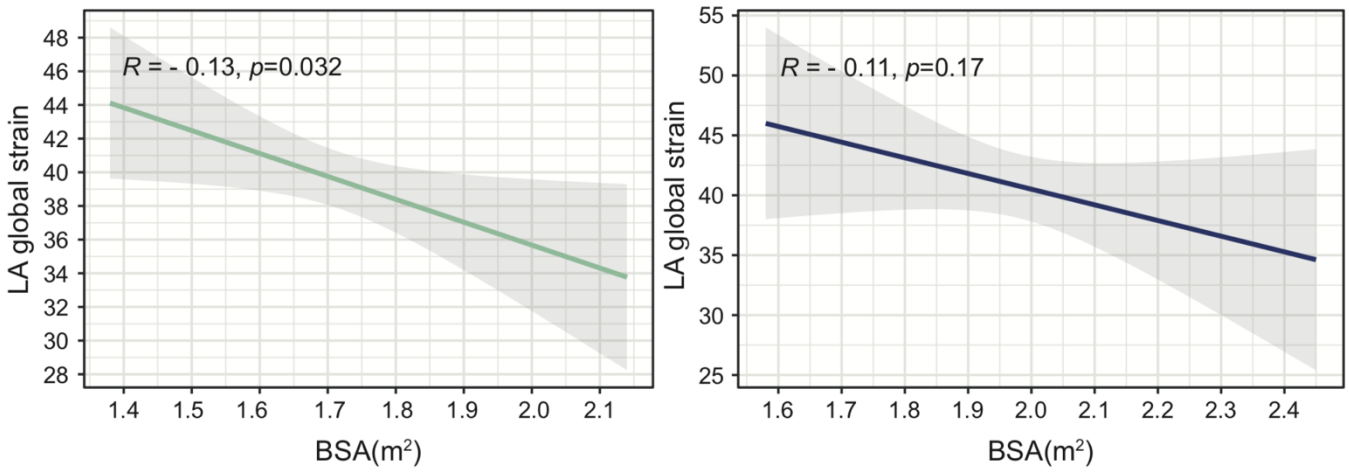

Figure 17: *Correlation between BSA and LA global strain. Probands over the age of 60, women left, men right, HCHS*

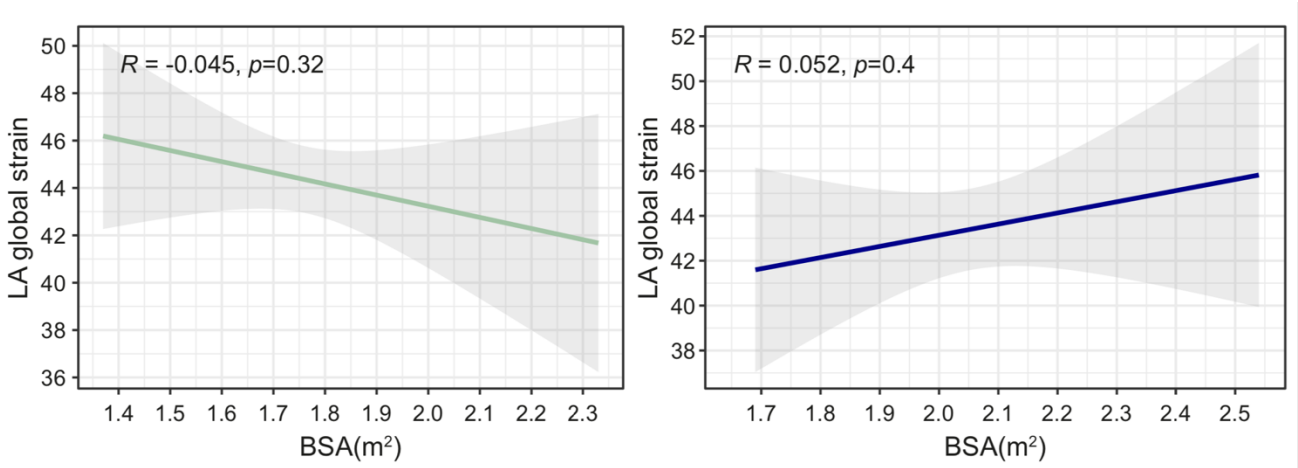

Figure 18: Correlation between BSA and LA global strain. Probands under the age of 60, women left, men right, HCHS

4.5 Intraobserver and interobserver variability

For intraobserver and interobserver variability, 60 random images were examined twice by the same examiner and another examiner respectively, with a time interval of at least 6 months. Interobserver variability was good for LA strain global peak all. Intraobserver variability showed intermediate strength of agreement. The results are shown in Table 6.

***Table 6: Results. Intra- and interobserver variability of strain variables**. Intra-class correlation coefficient (ICC) estimates were calculated based on a single-rating, agreement, 2-way mixed-effects model*

Intraobserver variability of strain variables:	**ICC**
Global PALS	0.57
Interobserver variability of strain variables	**ICC**
Global PALS	0.79

5 Discussion

5.1 Standard values for LA global strain

The aim of this work was to establish standard values for LA global strain, measured with 2D speckle tracking, in subjects without cardiovascular risk factors or diseases between the ages of 45 and 74 years. Up to date, this is the largest single-centre, long-term, prospective cohort study that has established standard values for LA strain derived from 2D speckle tracking. The mean LA global strain of our healthy cohort was 42.21% with a standard deviation of 15.48%. This is higher than the mean strain measured in the largest meta-analysis to date by Pathan et al, who suggested a mean strain of 39.4%.[34] While they also included studies with healthy subjects only, they specified a wider age range from 21 to 80, which makes their results not entirely comparable to the results presented in this thesis. They emphasized the heterogeneity of normal values for LA strain within their included studies and pointed out the significantly higher results in LA global strain in studies with n > 100, which was 44%. With n=1302 and 42.21% (15.48%) LA global strain, this study supports this trend. In contrast to this, Liao et al. published LA global strain standard values of 38.2% with n= 2812, however presenting an exclusively Asian study population.[52] The potential influential factor of rising operator experience in larger studies as a reason for higher LA global strain values was ruled out by previously conducted studies.[37,38] The inconsistent trend suggests that other influential variables are responsible for the heterogeneity of standard values of LA strain.

In comparison with STE- derived standard values of LA strain, CMR, the gold standard of LA imaging, was found to have superior reproducibility of LA strain.[60] However, there is a great heterogeneity between CMR-derived LA strain standard values published so far as well, ranging from 30.7%[61] to 44.7%[62]. The reference standard values for STE-derived LA strain obtained in this work are well within this range. Although all studies are based on a healthy study population, there are differences in age composition, ethnicity and exclusion criteria that could lead to the incongruence of the standard values. Further studies are necessary to determine the extent to which MRI- and speckle tracking-derived LA strain are comparable and

whether there are undetected parameters that influence LA strain and cause the large heterogeneity of the proposed standard values.

5.2 Intraobserver and interobserver variability in 2D speckle tracking LA strain

Interobserver variability was good, reaching an ICC above 0.75. Intraobserver variability showed intermediate reliability, reaching an ICC above 0.5. Both parameters showed lower reliability compared with previous studies.[52,53] A possible reason for the lower reliability is publication bias in favour of more robust results. Furthermore the difference in ICC could be a result of the different software used, as most published studies[34,52,53] used EchoPAC® (GE Medical Systems, Horten, Norway[63]) rather than Siemens syngo SC 2000, which was used in this work. No tangible explanation could be found for the more favourable interobserver variability compared to intraobserver variability. The images used for interobserver variability were from the last 3000 subjects, whereas intraobserver variability was performed with images from the first 6000 subjects. There is a residual chance that the overall image quality has improved over the course of the study, leading to better results. The intraobserver and interobserver variability calculated in this work can lead to the conclusion that the STE-derived LA strain measurement with this particular software used in this work provides moderate to good reliability, in contrast to previous studies that assume excellent reliability.

5.3 LA strain and its influencing variables

The results of this work regarding the effects of sex, age, and BSA on LA strain will be discussed in the following.

5.3.1 Difference in LA global strain between the sexes

While there are sex specific reference values for other echocardiography parameters, they mostly describe the function and anatomy of the ventricles. LV wall thickness, LV volume and LV ejection fraction all have different reference ranges for

women and men.[64] Also concerning strain analysis of the LV, different reference values have been defined for both sexes.[65] For parameters concerning the LA and specifically DD like LAVI, TR velocity, E velocity and e' velocity the same normal ranges have been established for men and women.[64] LA strain is a parameter used to describe the deformation of the atrium and, among other clinical applications, for the early diagnosis and grading of DD. Therefore it is conceivable that there is no difference in reference values for LA strain between women and men in alliance with other parameters describing the functioning of the LA. This fits with our results as in this study, no significant difference in LA global strain was found between the sexes (p= 0.828), which is consistent with most of the previously conducted studies.[34,54,55,66] However, there is no scientific consent on this, as some recent studies also suggest a significant difference in LA strain between the sexes, with female subjects having higher LA strain values.[52,53] Since the latter studies involved all- Asian study populations, further research should be conducted to determine if the sex differences are unique to certain ethnic populations.

5.3.2 Correlation between LA global strain and age

The LA undergoes changes with age, which is reflected by parameters like LA volume, LA expansion index, LA ejection fraction or the E/A ratio all being correlated with age in healthy indviduals.[67] As LA strain depicts the deformation ability of the left atrium it makes sense to assume for LA strain to correlate with age as well. We found that LA strain significantly decreases with age in female subjects and the overall cohort ($p < 0.001$). In male subjects, we found a trend toward significance for the correlation between age and LA strain (p=0.092). LA strain appears to decrease more with age in females than in males. To show the negative relation between age and LA strain in men, this study could be underpowered with n= 469 for men, as compared to n= 833 for women. Liao et al. also showed a stronger decrease of LA global strain in women, however both sexes showed a significant decrease with age.[52] Several other studies showed a negative correlation between LA strain and increasing age, but did not show differences in the decrease of LA strain with age between the sexes. Some of these studies had a much wider age range (e.g., 20-79 years in Sun et al. [53]) than the one in this work though, which might have led to the more significant results.[53,54,55] While this work supports

previous findings that LA strain decreases with age, further research is needed to address the question whether there is a stronger decrease in women than men.

5.3.3 Correlation of LA strain and BSA

Our analysis showed a significant decrease in LA strain with increasing BSA in women over 60 years of age, whereas the decrease was not significant in women under 60 years of age. The decrease with increasing BSA was not significant in men in any age subgroup. A possible reason for this difference is a significantly lower n in men than in women in our study (469 and 833, respectively). Pathan et al. indicated a significant association between BSA and LA global strain.[34] Meel et al. found that BSA was an independent predictor for LA global strain as well, however their study population consisted exclusively of subjects of African descent.[54] This work supports the assumed correlation between BSA and LA strain in women over 60 years of age.

5.3.4 Incongruencies in the proposed influencing factors on LA strain

Regarding the discussed incongruencies, the results of this work support the widely consistent findings that there are no significant differences in LA strain between the sexes. They are also consistent with the assumption that LA strain decreases with age, but more so for women than for men, as stated by some[52] but disputed by other[53,54,55] previously conducted studies. Finally, this thesis challenges the assumption that LA strain is affected by BSA regardless of age and sex, as has been published in the past.[34,54]

5.4 Outlook

In this work, normal reference values for STE-derived LA strain were determined for a Caucasian population of a specific age group without classical cardiovascular risk factors, which can be interpreted in consideration of the limitations below.

Given the heterogeneity of published normal values for LA strain and the incongruities in influencing factors for both, STE-derived values as well as CMR-derived values, the question for influencing factors on LA strain further than sex,

BSA and age arises. While Pathan et al. found that heart rate is an influencing factor for PALS as well, future studies are needed to verify the findings and investigate potential further influential factors on LA strain.[34] There are voices within the scientific community who call for a reconsideration of the method altogether, as they regard it to be too subjective to fluctuation independent of age and sex.[62] Considering the drastic increase of publications in recent years about promising clinical applications of STE-derived LA strain measurements, it seems reasonable though, to conduct further research on the causes of the heterogeneity between published reference values. As a result, this thesis calls for further research into undetected influential parameters on LA strain.

A potential cause of the heterogeneity of reference values are vendor differences. Pathan et al. didn't find vendor differences in their meta- analysis, however most of the included studies used EchoPAC® (GE Medical Systems, Horten, Norway[63]), while none used Siemens syngo SC 2000, the software used in this thesis.[34] Future studies are needed to investigate if there are vendor differences between the Siemens syngo SC 2000 software and the other commercially available software and whether they provide comparable LA strain measurements. Furthermore, LA global strain measurement was shown to be only moderately robust in this study. In contrast to the excellent reproducibility suggested by previously published studies[23,26,27], further research is needed to investigate intra- and interobserver variability for LA global strain measured with Siemens syngo SC 2000 software.

As this thesis presents the results of a single-centre study with a study population entirely from Hamburg, Germany, a multi centric approach should verify our results.

Concerning the limited age range of our study population, future studies are needed to define reference values of LA global strain for a broader age range.

5.5 Limitations

One limitation of the study is a bias in the selection of subjects. All subjects agreed to participate in an elaborate study that spanned several years and included several full-day appointments. All subjects have their primary residence in Hamburg, a city

with above average income and education levels in Europe.[68] Therefore, the study population may not accurately represent the Caucasian population in general.

Another limitation is the limited age range, with subjects between the ages of 45 and 74 being included in the study. The normal values determined in this work do not apply to individuals outside the mentioned age range.

Further, LA global strain measurement was shown to be only moderately robust in this study, in contrast to the excellent reproducibility suggested by previously published studies. The possible reasons for this are discussed in section 4.2.

Also, the standard values proposed in this work apply only to R-R gated LA strain analysis. While this is the case for most published work, there are some studies that use P-P gating with which they consequently cannot be compared.[34]

Lastly, as the algorithms are software-dependent, the normal reference values only apply to the software used in the HCHS between 2016 and 2019 (Siemens syngo SC 2000 version 4.0, Siemens Healthineers, Erlangen, Germany).

6 Summary

This dissertation deals with an echocardiographic parameter for myocardial deformation: 2D speckle tracking strain analysis. Strain and strain rate analysis is a recognized tool for describing the deformation and velocities of the myocardium. Originally the method has been used to examine the functional capacity of the ventricles. However, in recent years, there has been a dramatic increase in publications on clinical applications of strain analysis of the left atrium (LA). Promising results include LA global strain as a parameter for early detection of diastolic dysfunction, as a predictor for progression of atrial fibrillation, as a predictor for cryptogenic stroke risk and as a predictor for a protracted inflammatory state in COVID -19 patients, to name a small fraction.

As there is considerable heterogeneity between published normal values for LA global strain, this work aims to present normal values from the largest Caucasian cohort published so far, while correlating LA global strain with sex, BSA, and age. The data was obtained from the first 10,000 subjects of the population-based Hamburg City Health Study (HCHS), a single-centre, long-term, prospective cohort study in Hamburg, Germany. Subjects with classical cardiovascular risk factors or diseases were excluded from the collected data to obtain reference values for LA global strain from a healthy cohort.

The 1302 included subjects yielded normal values for LA global strain of 42.21% with a standard deviation of 15.48%. The results of this work support the widely consistent findings that there are no significant differences in LA global strain between the sexes. They are also consistent with the assumption that LA global strain decreases with age, but more so for women than for men, as stated by some but disputed by other previously conducted studies. This work challenges the assumption that LA global strain is affected by BSA regardless of age and sex, as has been published in the past. This thesis calls for further research on unknown influencing variables on LA global strain that may be responsible for the heterogeneity of reference values published so far.

7 Zusammenfassung

Diese Dissertation befasst sich mit der 2D-Speckle-Tracking-Strainanalyse. Ursprünglich wurde dieser echokardiographische Parameter zur Beurteilung der Myokarddeformation der Ventrikel entwickelt. In den letzten Jahren zeigte sich jedoch ein rasanter Anstieg an Veröffentlichungen zur Anwendung von Strain am linken Atrium (LA Strain). Zu den vielversprechenden Ergebnissen gehören unter anderem LA Strain als Parameter zur Früherkennung einer diastolischen Dysfunktion, als Prädiktor für das Fortschreiten von Vorhofflimmern oder als Prädiktor für das Risiko eines kryptogenen Schlaganfalls.

Bis dato zeigt sich erhebliche Heterogenität zwischen den veröffentlichten Normwerten für LA Strain, bei zusätzlichem Mangel an kaukasischen Studienpopulationen. Diese Arbeit zielt darauf ab, Normwerte aus der größten bisher veröffentlichten kaukasischen Kohorte zu präsentieren. Zusätzlich soll LA Strain mit Geschlecht, Körperoberfläche und Alter korreliert werden. Die erhobenen Daten stammen von den ersten 10.000 ProbandInnen der bevölkerungsbasierten Hamburg City Health Study, einer prospektiven Kohortenstudie in Hamburg, Deutschland. ProbandInnen mit klassischen kardiovaskulären Risikofaktoren oder Erkrankungen wurden aus der Studienkohorte ausgeschlossen, um Referenzwerte für LA Strain aus einer gesunden Kohorte zu generieren.

Die 1302 eingeschlossenen ProbandInnen ergaben Referenzwerte für LA Strain von 42,21 % mit einer Standardabweichung von 15,48 %. Die Ergebnisse dieser Arbeit untermauern die weitgehend übereinstimmenden Erkenntnisse, dass es keine signifikanten Unterschiede von LA Strain zwischen den Geschlechtern gibt. Sie stimmen auch mit der Annahme überein, dass LA Strain mit dem Alter abnimmt, jedoch bei Frauen stärker als bei Männern was mit einigen Studien übereinstimmt, mit anderen allerdings divergiert. Die Annahme, dass LA Strain unabhängig von Alter und Geschlecht von der Körperoberfläche beeinflusst wird, wie in der Vergangenheit veröffentlicht wurde, wird von dieser Arbeit in Frage gestellt. Um der Heterogenität der bisher veröffentlichten Referenzwerte von LA Strain Rechnung zu tragen fordert diese Dissertation zu weiteren Studien zu bis Dato unbekannten Einflussgrößen auf LA Strain auf.

8 List of abbreviations

A

AF *Atrial fibrillation*
ASA *Acetylsalicylic acid*
ASE *American Society of Echocardiography*

B

BMI *Body mass index*
BNP *B-type natriuretic peptide*
BP *Blood pressure*
BSA *Body surface area*

C

CMRI *Cardiac magnetic resonance imaging*
CS *Cryptogenic stroke*
CVDs *Cardiovascular diseases*

D

DD *Diastolic dysfunction*

E

e.g *exempli gratia*
EACVI *European Association of Cardiovascular Imaging*
ECD *Conduit strain*
ECG *Electrocardiogram*
ECT *Contractile strain*
EF *Ejection fraction*
ER *Reservoir strain*

G

GFR *Glomerular filtration rate*

H

HbA1c *Haemoglobin A1c*
HCHS *Hamburg City Health Study*
HDL *High density lipoprotein*
hsCRP High-Sensitivity C-Reactive Protein

I

ICC *Intraclasscorrelation*
ICU *Intensive care unit*
Ie *id est*

L

LA *Left atrium*
LAA *Left atrial appendage*
LAEF *Left atrial ejection fraction*
LAVI *Left atrial volume index*
LDL *Low density lipoprotein*
LV *Left ventricle*
LVEDD *Left ventricular end-diastolic diameter*
LVEDV *Left ventricular end-diastolic volume*
LVEF *Left ventricular ejection fraction*
LVESV *Left ventricular end systolic volume*

M

MRA *Mineralocorticoid receptor antagonists*

N

NTproBNP *N-terminal pro B-type natriuretic peptide*

O

OR *Odds ratio*

P

PALS *peak atrial longitudinal strain*
PCWP *Pulmonary capillary wedge pressure*
PVI *Pulmonary vein isolation*

R

RA *Right atrium*
RV *Right ventricle*

S

SR *Strain rate*
STE *Speckle tracking echocardiography*

T

TAPSE *Tricuspid annular plane systolic excursion*

TDI *Tissue Doppler imaging*

TEE *Transoesophageal echocardiography*

TR Vmax *Maximal. tricuspid regurgitation velocity*

TTE *Transthoratic ultrasound evaluation*, *Transthoratic echocardiography*

V

VKA *Vitamine K antagonists*

9 List of tables

10 List of figures

11 References

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12 Appendix

12.1 R-Code for the statistical analysis

```
---
title: "Strain Reference"
subtitle: "Auswertungen"
date: "23 Mai 2019"
output:
  pdf_document: default
  word_document: default
---

```{r setup, include=FALSE}
knitr::opts_chunk$set(echo = FALSE)

#N√∂tige Pakete laden
library(readr)
library(readxl)
library(dplyr)
library(tidyr)
library(magrittr)
library(tableone)
library(kableExtra)
library(survival)
library(reshape2)
library(psych)
library(fmsb)
library(ggplot2)
library(extrafont)
library(ggpubr)
library(stringr)
library(irr)
library(gtable)
library(gridExtra)
library(grid)

```

```{r data preparation, include=FALSE, warning=FALSE, echo=FALSE, message=FALSE, error=FALSE}
#Datensatz einlesen
echo <- readRDS("U:/08_Statistik/0805_Analysen_Paper/03_UHZ/Strain Reference/echo.rds")
inter <- readRDS("U:/08_Statistik/0805_Analysen_Paper/03_UHZ/Strain Reference/inter.rds")
intra <- readRDS("U:/08_Statistik/0805_Analysen_Paper/03_UHZ/Strain Reference/intra.rds")

```

```{r table 1}
##Baselinetable erstellen
#Definition der Variablen
vars <- c("Age","Sex", "Weight", "Height", "BSA", "BMI","waist_circ","Heart_rate", "RRsys","RR_dia","Hemoglobin",
"LDL","GFR","NTproBNP","hsCRP","Gluc","Hypertension","Diabetes","Smoking","obesity","CVD","COPD","OSAS","PAD","Af
ib", "LVEF", "LVEDV", "LVESV", "LVEDD", "LVMASS_indexed","LAVI","EE","TAPSE","TR_vmax","AS","AR","MR","TR")

#Erstellen der Tabelle
table1 <- as.data.frame(print(CreateTableOne(data = echo, strata = "healthy", vars = vars),
                              nonnormal = c("Age", "Weight", "Height", "BSA", "BMI","waist_circ","Heart_rate",
"RRsys","RR_dia","Hemoglobin",  "LDL","GFR","NTproBNP","hsCRP","Gluc",
                                            "LVEF", "LVEDV", "LVESV", "LVEDD", "LVMASS_indexed","LAVI","EE","TAPSE","TR_vmax"),
printToggle = F, noSpaces = T, showAllLevels = FALSE,
                              contDigits = 1))
#Speichern der Tabelle
write.csv2(table1, file="table1_03.02.2023.csv", row.names = TRUE)
```

```{r figure1}
###Figure over/under
## Datens√§tze erstellen ------------------------------------------------------------------------------------------------------------------------------------
-------------------------
#Nur healthy cohort
echo <- subset(echo, echo$healthy=="1")
regdata2 <- echo
#Subsets erstellen
```
```

```
regdata2$age_bin <- ifelse(regdata2$Age>60,1,ifelse(regdata2$Age<=60,0,NA))
regdatayoung <- regdata2[regdata2$age_bin==0,]
regdataold <- regdata2[regdata2$age_bin==1,]
regdataoldmale <- regdataold[regdataold$Sex == "Male",]
regdataoldfemale <- regdataold[regdataold$Sex=="Female",]
regdatayoungmale <- regdatayoung[regdatayoung$Sex=="Male",]
regdatayoungfemale <- regdatayoung[regdatayoung$Sex=="Female",]

## Funktion
plot_review<-  function(data,var, name,x,y,col){
  data %>%
  ggplot(aes(x = BSA,
             y = var)) +
  geom_smooth(method = "lm", na.rm = TRUE, alpha = 0.2, colour = col ) +
  labs(y = name, x = "BSA (m¬≤)") +
  theme_bw() +
  #theme(text = element_text(family = "Times New Roman", size = 10), legend.position = "none") +
  theme(text = element_text(size = 10), legend.position = "none") +
  scale_x_continuous(breaks = scales::pretty_breaks(n =10)) +
  scale_y_continuous(breaks = scales::pretty_breaks(n =10))+
  stat_cor(method="pearson",p.digits=2,label.x = x, label.y=y)
}

g_legend <- function(a.gplot){
  tmp <- ggplot_gtable(ggplot_build(p1))
  leg <- which(sapply(tmp$grobs, function(x) x$name) =="guide-box")
  legend <- tmp$grobs[[leg]]
  return(legend)
}

##TN <=60 ----------------------------------------------------------------------------------------------------------------------------------------------------------------
---------------------
p1 <-  regdatayoungfemale %>%
  ggplot(aes(x = BSA,
             y = HCHG_ECHO098_MW)) +
  scale_color_manual(values = "#a1c4a5") +
  geom_smooth(method = "lm", na.rm = TRUE, alpha = 0.2) +
  scale_fill_manual(values=c("#a1c4a5")) +
  labs(y = "LASV 3D", x = "BSA (m¬≤)") +
  theme_bw() +
  #theme(text = element_text(family = "Times New Roman", size = 10), legend.position = "none") +
  theme(text = element_text(size = 10), legend.position = "none") +
  scale_x_continuous(breaks = scales::pretty_breaks(n =10)) +
  scale_y_continuous(breaks = scales::pretty_breaks(n =10))+
  stat_cor(method="pearson",p.digits=2,label.x.npc = 0, label.y.npc=0)
p1

#ED
fig1<- plot_review(regdatayoungfemale,regdatayoungfemale$HCHG_ECHO098_MW, "LASV 3D",1.4,55,"#a1c4a5")
fig2<-plot_review(regdatayoungfemale,regdatayoungfemale$HCHG_ECHO097_MW, "LADV 3D",1.4,28.75,"#a1c4a5")
fig3<-plot_review(regdatayoungfemale,regdatayoungfemale$HCHG_ECHO096_MW, "LAEF 3D",1.4,54.5,"#a1c4a5")
fig4<-plot_review(regdatayoungfemale,regdatayoungfemale$HCHG_ECHO120_MW, "LAS Global Peak
All",1.4,49,"#a1c4a5")


fig5<- plot_review(regdatayoungmale,regdatayoungmale$HCHG_ECHO098_MW, "LASV 3D",1.7,56,"#00008B")
fig6<-plot_review(regdatayoungmale,regdatayoungmale$HCHG_ECHO097_MW, "LADV 3D",1.7,29,"#00008B")
fig7<-plot_review(regdatayoungmale,regdatayoungmale$HCHG_ECHO096_MW, "LAEF 3D",1.7,57,"#00008B")
fig8<-plot_review(regdatayoungmale,regdatayoungmale$HCHG_ECHO120_MW, "LAS Global Peak
All",1.65,51,"#00008B")


plotyoung <- arrangeGrob(arrangeGrob(fig1, top= text_grob(label ="Female",  size = 14), left = "LASV
3D"),arrangeGrob(fig5, top = text_grob("Male",size = 14)),
          arrangeGrob(fig2, left ="LADV 3D" ),fig6,arrangeGrob(fig3, left = "LAEF 3D"),
                    fig7, arrangeGrob(fig4, left = "LAS Global Peak All"),fig8, nrow = 5, ncol = 2,  heights = c(2,2,2,2,0.5))

ggsave(file = "Figure_under_60_03.02.2023.pdf", plotyoung, device = cairo_pdf, height = 297, width = 210, units = "mm")

## Part over60 ----------------------------------------------------------------------------------------------------------------------------------------------------------
-----------------

#ED
fig1<- plot_review(regdataoldfemale,regdataoldfemale$HCHG_ECHO098_MW, "LASV 3D",1.5,49,"#a1c4a5")
fig2<-plot_review(regdataoldfemale,regdataoldfemale$HCHG_ECHO097_MW, "LADV 3D",1.5,27,"#a1c4a5")
fig3<-plot_review(regdataoldfemale,regdataoldfemale$HCHG_ECHO096_MW, "LAEF 3D",1.5,50,"#a1c4a5")
```

```
fig4<-plot_review(regdataoldfemale,regdataoldfemale$HCHG_ECHO120_MW, "LAS Global Peak All",1.4,47,"#a1c4a5")

#MS
fig5<- plot_review(regdataoldmale,regdataoldmale$HCHG_ECHO098_MW, "LASV 3D",1.7,62,"#00008B")
fig6<-plot_review(regdataoldmale,regdataoldmale$HCHG_ECHO097_MW, "LADV 3D",1.7,35,"#00008B")
fig7<-plot_review(regdataoldmale,regdataoldmale$HCHG_ECHO096_MW, "LAEF 3D",1.7,58,"#00008B")
fig8<-plot_review(regdataoldmale,regdataoldmale$HCHG_ECHO120_MW, "LAS Global Peak All",1.6,50.5,"#00008B")

plotold <- arrangeGrob(arrangeGrob(fig1, top= text_grob(label ="Female",  size = 14), left = "LASV 3D"),arrangeGrob(fig5,
top = text_grob("Male",size = 14)),
          arrangeGrob(fig2, left ="LADV 3D" ),fig6,arrangeGrob(fig3, left = "LAEF 3D"),
                  fig7, arrangeGrob(fig4, left = "LAS Global Peak All"),fig8, nrow = 5, ncol = 2,  heights = c(2,2,2,2,0.5))

ggsave(file = "Figure_over_60_03.02.2023.pdf", plotold, device = cairo_pdf, height = 297, width = 210, units = "mm")
```

```{r fig2, warning=FALSE, message=FALSE}
###Figure 4
## Funktion
format_pval <- function(pval){
  pval <- scales::pvalue(pval, accuracy= 0.0001, add_p = TRUE)
  gsub(pattern = "(=|<)", replacement = " \\1 ", x = pval)
}

## Geschlecht Referenz
regdata2$Sex <- relevel(regdata2$Sex, ref = "Female")

##Erstellen der Plots
f31 <- ggplot(data = regdata2, aes(x = agecat, y = HCHG_ECHO098_MW)) +
  geom_boxplot(aes(fill = Sex), alpha = 0.6) +
  scale_fill_manual(values = c("#00008B", "#a1c4a5"), breaks = NULL, labels = NULL) +
  facet_wrap(~Sex)  +
  labs(x = "Age in groups", y = "LASV 3D") +
  stat_compare_means(method = "anova",label.y = 120, size = 5, aes(label = paste(format_pval(..p..)), sep = ", ")) +
  stat_compare_means(label = "p.signif", method = "t.test", ref.group = "45-49", size = 5, label.y = 100) +
  theme_classic() +
  #theme(text = element_text(family = "Arial", size = 18)) + ylim(0,130)
  theme(text = element_text(size = 18)) + ylim(0,130)

f32 <- ggplot(data = regdata2, aes(x = agecat, y = HCHG_ECHO097_MW)) +
  geom_boxplot(aes(fill = Sex), alpha = 0.6) +
  scale_fill_manual(values = c("#00008B", "#a1c4a5"), breaks = NULL, labels = NULL ) +
  facet_wrap(~Sex ) +
  labs(x = "Age in groups", y = "LADV 3D") +
  stat_compare_means(method = "anova",label.y = 90, size = 5, aes(label = paste(format_pval(..p..)), sep = ", ")) +
  stat_compare_means(label = "p.signif", method = "t.test", ref.group = "45-49", size = 5, label.y = 70) +
  theme_classic() +
  #theme(text = element_text(family = "Arial", size = 18)) + ylim(0,100)
  theme(text = element_text(size = 18)) + ylim(0,100)

f33 <- ggplot(data = regdata2, aes(x = agecat, y = HCHG_ECHO096_MW)) +
  geom_boxplot(aes(fill = Sex), alpha = 0.6) +
  scale_fill_manual(values = c("#00008B", "#a1c4a5"), breaks = NULL, labels = NULL ) +
  facet_wrap(~Sex ) +
  labs(x = "Age in groups", y = "LAEF 3D") +
  stat_compare_means(method = "anova",label.y = 120, size = 5, aes(label = paste(format_pval(..p..)), sep = ", ")) +
  stat_compare_means(label = "p.signif", method = "t.test", ref.group = "45-49", size = 5, label.y = 100) +
  theme_classic() +
  #theme(text = element_text(family = "Arial", size = 18)) + ylim(0,130)
  theme(text = element_text(size = 18)) + ylim(0,130)

f34 <- ggplot(data = regdata2, aes(x = agecat, y = HCHG_ECHO120_MW)) +
  geom_boxplot(aes(fill = Sex), alpha = 0.6) +
  scale_fill_manual(values = c("#00008B", "#a1c4a5"), breaks = NULL, labels = NULL ) +
  facet_wrap(~Sex ) +
  labs(x = "Age in groups", y = "Global Peak All") +
  stat_compare_means(method = "anova",label.y = 130, size = 5, aes(label = paste(format_pval(..p..)), sep = ", ")) +
  stat_compare_means(label = "p.signif", method = "t.test", ref.group = "45-49", size = 5, label.y = 110) +
  theme_classic() +
  #theme(text = element_text(family = "Arial", size = 18)) + ylim(0,140)
  theme(text = element_text(size = 18)) + ylim(0,140)

##Zusammenf√ºhren der Plots
fig2 <- grid.arrange(f31, f32,f33,f34, nrow = 4, ncol = 1)
ggsave(file = "Figure4_03.02.2023.pdf", fig2, device = cairo_pdf, height = 297, width = 210, units = "mm")
```

```{r fig2V2, warning=FALSE, message=FALSE}
###Figure 4 V2

f31 <- ggplot(data = regdata2, aes(x = agecat, y = LAVI)) +
  geom_boxplot(aes(fill = Sex), alpha = 0.6) +
  scale_fill_manual(values = c("#00008B", "#a1c4a5"), breaks = NULL, labels = NULL) +
  facet_wrap(~Sex)  +
  labs(x = "Age in groups", y = "LAVI") +
  stat_compare_means(method = "anova",label.y = 120, size = 5, aes(label = paste(format_pval(..p..)), sep = ", ")) +
  stat_compare_means(label = "p.signif", method = "t.test", ref.group = "45-49", size = 5, label.y = 100) +
  theme_classic() +
  #theme(text = element_text(family = "Arial", size = 14)) + ylim(0,140)
  theme(text = element_text(size = 14)) + ylim(0,140)

f32 <- ggplot(data = regdata2, aes(x = agecat, y = HCHG_ECHO055_MW)) +
  geom_boxplot(aes(fill = Sex), alpha = 0.6) +
  scale_fill_manual(values = c("#00008B", "#a1c4a5"), breaks = NULL, labels = NULL ) +
  facet_wrap(~Sex ) +
  labs(x = "Age in groups", y = "LAEF 2D") +
  stat_compare_means(method = "anova",label.y = 105, size = 5, aes(label = paste(format_pval(..p..)), sep = ", ")) +
  stat_compare_means(label = "p.signif", method = "t.test", ref.group = "45-49", size = 5, label.y = 90) +
  theme_classic() +
  #theme(text = element_text(family = "Arial", size = 14)) + ylim(0,120)
  theme(text = element_text(size = 14)) + ylim(0,120)

f33 <- ggplot(data = regdata2, aes(x = agecat, y = HCHG_ECHO120_MW)) +
  geom_boxplot(aes(fill = Sex), alpha = 0.6) +
  scale_fill_manual(values = c("#00008B", "#a1c4a5"), breaks = NULL, labels = NULL ) +
  facet_wrap(~Sex ) +
  labs(x = "Age in groups", y = "LAD Global Peak Strain") +
  stat_compare_means(method = "anova",label.y = 130, size = 5, aes(label = paste(format_pval(..p..)), sep = ", ")) +
  stat_compare_means(label = "p.signif", method = "t.test", ref.group = "45-49", size = 5, label.y = 110) +
  theme_classic() +
  #theme(text = element_text(family = "Arial", size = 14)) + ylim(10,150)
  theme(text = element_text(size = 14)) + ylim(10,150)

f34 <- ggplot(data = regdata2, aes(x = agecat, y = emp_frac_2D)) +
  geom_boxplot(aes(fill = Sex), alpha = 0.6) +
  scale_fill_manual(values = c("#00008B", "#a1c4a5"), breaks = NULL, labels = NULL ) +
  facet_wrap(~Sex ) +
  labs(x = "Age in groups", y = "Total emptying \nfraction 2D") +
  stat_compare_means(method = "anova",label.y = 0.27, size = 5, aes(label = paste(format_pval(..p..)), sep = ", ")) +
  stat_compare_means(label = "p.signif", method = "t.test", ref.group = "45-49", size = 5, label.y = 0.2) +
  theme_classic() +
  #theme(text = element_text(family = "Arial", size = 14)) + ylim(0,0.3)
  theme(text = element_text(size = 14)) + ylim(0,0.3)

f35 <- ggplot(data = regdata2, aes(x = agecat, y = res_exp_2D)) +
  geom_boxplot(aes(fill = Sex), alpha = 0.6) +
  scale_fill_manual(values = c("#00008B", "#a1c4a5"), breaks = NULL, labels = NULL ) +
  facet_wrap(~Sex ) +
  labs(x = "Age in groups", y = "Reservoir expansion \nindex 2D") +
  stat_compare_means(method = "anova",label.y = 0.60, size = 5, aes(label = paste(format_pval(..p..)), sep = ", ")) +
  stat_compare_means(label = "p.signif", method = "t.test", ref.group = "45-49", size = 5, label.y = 0.50) +
  theme_classic() +
  #theme(text = element_text(family = "Arial", size = 14)) + ylim(0,0.65)
  theme(text = element_text(size = 14)) + ylim(0,0.65)

fig2_V2 <- grid.arrange(f31, f32,f33,f34,f35, nrow = 5, ncol = 1)
ggsave(file = "Figure4_V2_03.02.2023.pdf", fig2_V2, device = cairo_pdf, height = 297, width = 210, units = "mm")
```


```{r table 2}
##Table 2
vars = c("HCHG_ECHO053_MW","HCHG_ECHO054_MW","HCHG_ECHO022_MW",
"HCHG_ECHO098_MW","HCHG_ECHO097_MW","HCHG_ECHO088_MW","HCHG_ECHO055_MW",
"HCHG_ECHO096_MW", "emp_frac_2D",
       "res_exp_2D","res_exp_3D", "emp_frac_3D", "HCHG_ECHO120_MW",
"HCHG_ECHO114_MW","HCHG_ECHO118_MW","HCHG_ECHO116_MW", "EE_LAS_GPA",
"EE_LAEF_2D","EE_LAEF_3D")
tmp <- as.data.frame(print(CreateTableOne(data = regdata2, strata = "Sex", vars = vars, addOverall=TRUE), printToggle =
F, noSpaces = T, showAllLevels = TRUE))
```

```
vars = c( "ind053","ind054", "ind022", "ind098","ind097","ind088","ind055","ind096","indemp_frac_2D",
"indres_exp_2D","indemp_frac_3D","indres_exp_3D",
"ind120","ind114","ind118","ind116","indEE_LAS_GPA","indEE_LAEF_2D","indEE_LAEF_3D")
tmp2 <- as.data.frame(print(CreateTableOne(data = regdata2, strata = "Sex", vars = vars, addOverall = TRUE), printToggle
= F, noSpaces = T, showAllLevels = TRUE))

table3 <- cbind(tmp, tmp2)
table3 <- table3[,-c(1,6,7,12)]
table3 <- table3[,c(3,2,1,4,7,6,5,8)]
write.csv2(table3, file="table2_03.02.2023.csv")
```


```{r table4}
##Table 5
data_male <- subset(regdata2, Sex== "Male")
data_female <- subset(regdata2, Sex=="Female")
vars = c("ind098", "ind097", "ind096", "ind120","indemp_frac_2D","indres_exp_2D","indemp_frac_3D","indres_exp_3D")

tmp <- as.data.frame(print(CreateTableOne(data = data_male, strata = "agecat", vars = vars), printToggle = F, noSpaces =
T, showAllLevels = TRUE))
tmp2 <- as.data.frame(print(CreateTableOne(data = data_female, strata = "agecat", vars = vars), printToggle = F, noSpaces
= T, showAllLevels = TRUE))
tmp3 <- as.data.frame(print(CreateTableOne(data = regdata2, strata = "agecat", vars = vars), printToggle = F, noSpaces =
T, showAllLevels = TRUE))
table4 <- rbind(tmp, tmp2, tmp3)

write.csv2(table4, file="table4_03.02.2023.csv")
```

```{r table4b}
##Table 6
vars = c("HCHG_ECHO098_MW", "HCHG_ECHO097_MW", "HCHG_ECHO096_MW",
"HCHG_ECHO120_MW","emp_frac_2D","res_exp_2D","emp_frac_3D","res_exp_3D")

tmp <- as.data.frame(print(CreateTableOne(data = data_male, strata = "agecat", vars = vars), printToggle = F, noSpaces =
T, showAllLevels = TRUE))
tmp2 <- as.data.frame(print(CreateTableOne(data = data_female, strata = "agecat", vars = vars), printToggle = F, noSpaces
= T, showAllLevels = TRUE))
tmp3 <- as.data.frame(print(CreateTableOne(data = regdata2, strata = "agecat", vars = vars), printToggle = F, noSpaces =
T, showAllLevels = TRUE))
table4 <- rbind(tmp, tmp2, tmp3)

write.csv2(table4, file="table4b_03.02.2023.csv")
```


```{r table feasibility}
#Table 7
vars = c("HCHG_ECHO053_MWf","HCHG_ECHO054_MWf","HCHG_ECHO022_MWf",
"HCHG_ECHO098_MWf","HCHG_ECHO097_MWf","HCHG_ECHO088_MWf","HCHG_ECHO055_MWf",
"HCHG_ECHO096_MWf", "emp_frac_2Df",
       "res_exp_2Df","res_exp_3Df", "emp_frac_3Df", "HCHG_ECHO120_MWf",
"HCHG_ECHO114_MWf","HCHG_ECHO118_MWf","HCHG_ECHO116_MWf", "EE_LAS_GPAf",
"EE_LAEF_2Df","EE_LAEF_3Df")


tmp <- as.data.frame(print(CreateTableOne(data = regdata2, strata = "Sex", vars = vars), printToggle = F, noSpaces = T,
showAllLevels = FALSE, contDigits = 1))
 tmp2 <- as.data.frame(print(CreateTableOne(data = regdata2, vars = vars), printToggle = F, noSpaces = T, showAllLevels
= FALSE, contDigits =  1))

tablefeasi <- cbind(tmp, tmp2)
tablefeasi <- tablefeasi[,-c(4)]
tablefeasi <- tablefeasi[,c(2,1,4,3)]
write.csv2(tablefeasi, file="tablefeasi_03.02.2023.csv", row.names = TRUE)
```

```{r IOV}
#Interrater
inter_HCHG_ECHO114<-inter[which(inter$FindingAbbr=="HCHG_ECHO114"),c("Value_12","Value_14")]
inter_HCHG_ECHO116<-inter[which(inter$FindingAbbr=="HCHG_ECHO116"),c("Value_12","Value_14")]
inter_HCHG_ECHO118<-inter[which(inter$FindingAbbr=="HCHG_ECHO118"),c("Value_12","Value_14")]
inter_HCHG_ECHO120<-inter[which(inter$FindingAbbr=="HCHG_ECHO120"),c("Value_12","Value_14")]

ICC_HCHG_ECHO114<-icc(inter_HCHG_ECHO114,model="twoway",type="agreement",unit="single")
```

```
ICC_HCHG_ECHO116<-icc(inter_HCHG_ECHO116,model="twoway",type="agreement",unit="single")
ICC_HCHG_ECHO118<-icc(inter_HCHG_ECHO118,model="twoway",type="agreement",unit="single")
ICC_HCHG_ECHO120<-icc(inter_HCHG_ECHO120,model="twoway",type="agreement",unit="single")

round(ICC_HCHG_ECHO120$value,digits = 2)
round(ICC_HCHG_ECHO114$value,digits = 2)
round(ICC_HCHG_ECHO118$value,digits = 2)
round(ICC_HCHG_ECHO116$value,digits = 2)

#Intrarater
intra_HCHG_ECHO114<-intra[which(intra$FindingAbbr=="HCHG_ECHO114"),c("Value_12","Value_14")]
intra_HCHG_ECHO116<-intra[which(intra$FindingAbbr=="HCHG_ECHO116"),c("Value_12","Value_14")]
intra_HCHG_ECHO118<-intra[which(intra$FindingAbbr=="HCHG_ECHO118"),c("Value_12","Value_14")]
intra_HCHG_ECHO120<-intra[which(intra$FindingAbbr=="HCHG_ECHO120"),c("Value_12","Value_14")]

ICC_HCHG_ECHO114<-icc(intra_HCHG_ECHO114,model="twoway",type="agreement",unit="single")
ICC_HCHG_ECHO116<-icc(intra_HCHG_ECHO116,model="twoway",type="agreement",unit="single")
ICC_HCHG_ECHO118<-icc(intra_HCHG_ECHO118,model="twoway",type="agreement",unit="single")
ICC_HCHG_ECHO120<-icc(intra_HCHG_ECHO120,model="twoway",type="agreement",unit="single")

round(ICC_HCHG_ECHO120$value,digits = 2)
round(ICC_HCHG_ECHO114$value,digits = 2)
round(ICC_HCHG_ECHO118$value,digits = 2)
round(ICC_HCHG_ECHO116$value,digits = 2)
```


```{r tables mri}
##Figure LASV
regdata2$HCHG_CVI42_018 <- as.numeric(regdata2$HCHG_CVI42_018)

tmp <- regdata2
tmp <- subset(tmp, select = c("CollectionID", "HCHG_ECHO053_MW","HCHG_CVI42_018"))
tmp <- pivot_longer(tmp, names_to = "FindingAbbr", values_to ="Value", cols =
c("HCHG_ECHO053_MW","HCHG_CVI42_018"))
tmp$modality[tmp$FindingAbbr=="HCHG_ECHO053_MW"] <- "TTE"
tmp$modality[tmp$FindingAbbr=="HCHG_CVI42_018"] <- "CMR"
tmp <- subset(tmp, !is.na(tmp$Value))

vars <- c("Value")

tmp2 <- as.data.frame(print(CreateTableOne(data = tmp, strata = "modality", vars = vars), printToggle = F, noSpaces = T,
showAllLevels = FALSE, contDigits = 1))
write.csv(tmp2, "table9_healthy.csv", row.names=TRUE)


tmp <- regdata2
tmp$HCHG_ECHO053_MW <- ifelse(tmp$HCHG_ECHO134_MW=="1" | tmp$HCHG_ECHO134_MW=="1.5" |
tmp$HCHG_ECHO134_MW=="2" | is.na(tmp$HCHG_ECHO134_MW),  tmp$HCHG_ECHO053_MW, NA)
tmp <- subset(tmp, select = c("CollectionID", "HCHG_ECHO053_MW","HCHG_CVI42_018"))
tmp <- pivot_longer(tmp, names_to = "FindingAbbr", values_to ="Value", cols =
c("HCHG_ECHO053_MW","HCHG_CVI42_018"))
tmp$modality[tmp$FindingAbbr=="HCHG_ECHO053_MW"] <- "TTE"
tmp$modality[tmp$FindingAbbr=="HCHG_CVI42_018"] <- "CMR"
tmp <- subset(tmp, !is.na(tmp$Value))

vars <- c("Value")

tmp2 <- as.data.frame(print(CreateTableOne(data = tmp, strata = "modality", vars = vars), printToggle = F, noSpaces = T,
showAllLevels = FALSE, contDigits = 1))


#LASV
f1 <- ggplot(data = regdata2, aes(x = HCHG_CVI42_018, y = HCHG_ECHO053_MW)) +
  geom_point(alpha = 0.4, shape = 0) +
  geom_abline() +
  stat_cor(method="pearson", output.type = "text", size = 3, aes(label = paste(..r.label..,format_pval(..p..), sep = ", "))) +
  theme_classic() +
  labs(x = "LASV biplan by CMR (ml)", y = "LASV biplan by TTE (ml)") +
  #theme(text = element_text(family = "Times New Roman", size = 10))
  theme(text = element_text(size = 10))
ggsave(file = "Figure_LASV_03.02.2023.pdf", f1, device = cairo_pdf, height = 150, width = 150, units = "mm")
```

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14 Curriculum vitae

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2003 - 2011	Europagymnasium Baumgartenberg, Österreich

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2011 - 2015	Internationale Entwicklung, Universität Wien
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2016 - 2022	Humanmedizin Universität Hamburg

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Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seiten des benutzten Werkes kenntlich gemacht habe.
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: .....