Aus der Klinik für Kardiologie Campus Virchow Klinikum

der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Clinical Relevance of the Severity of Left Ventricular Longitudinal Diastolic Strain Rate in Patients with Reduced Ejection Fraction

zur Erlangung des akademischen Grades

Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät

Charité – Universitätsmedizin Berlin

von

Yoanna Savova

aus Sofia, Bulgarien

Datum der Promotion: 25.06.2023

Table of Contents

List of abbreviations

ACE-I – Angiotensin-converting enzyme inhibitors

ACS – Acute coronary syndrome

AHF – Acute heart failure

AF – Atrial fibrillation

CAD – Coronary artery disease

CHF – Chronic heart failure

CI – Confidence interval

ESC – European Society of Cardiology

HF – Heart failure

HFpEF – Heart failure with preserved ejection fraction

HFmrEF – Heart failure with mid-range ejection fraction

HFrEF – Heart failure with reduced ejection fraction

LVDD – Left ventricular diastolic dysfunction

LVSRe – Left ventricular longitudinal early diastolic strain rate

NYHA – New York Health Association

STE – Speckle tracking echocardiography

TDI – Tissue Doppler imaging

TTE – Transthoracic echocardiography

List of tables

List of figures

Abstract English

Introduction: The clinical usefulness of non-angle dependent and global left ventricular (LV) diastolic parameters such as left ventricular early diastolic strain rate (LVSRe) or early mitral inflow velocity to early diastolic strain rate (E/LVSRe) is increasingly becoming recognized in the detection and prediction of the outcomes of LV diastolic dysfunction (LVDD). Nevertheless, these LV diastolic strain parameters are not yet completely established as diagnostic markers for LVDD.

Aim: The aim of the present study was to analyse the potential usefulness and clinical relevance of LVSRe and E/LVSRe in patients with reduced left ventricular ejection fraction (LVEF).

Methods and results: A total of 497 adult patients with LVEF <50% underwent a two-dimensional speckle tracking echocardiographic (2D-STE) analysis of the LV. Alterations in LVSRe and E/LVSRe were significantly associated with elevated LV filling pressures (as estimated by pulmonary capillary wedge pressure [PCWP]). In line with these findings, alterations in LVSRe and E/LVSRe were significantly linked to worse symptomatic status and heart failure (HF) hospitalization within 2 years. In effect, patients with LVSRe values $<0.5 s^{-1}$ or E/LVSRe >71.5 had the highest risk for HF hospitalization within 2 years (OR 3.046, 95% CI 1.51–6.11 for LVSRe, and OR 3.614, 95% CI 1.26–10.36 for E/LVSRe, all adjusted by age and gender). Additionally, when adding LVSRe as a LV diastolic parameter, the probability to detect LVDD raised significantly from 41.1% to 63.7% (p <0.01).

Conclusion: The findings of this study suggest that new diastolic parameters such as LVSRe and E/LVSRe could have significant usefulness and clinical relevance in patients with reduced LVEF.

Abstract German

Einleitung: Die klinische Nützlichkeit winkelunabhängiger und globaler linksventrikulärer (LV) diastolischer Parameter wie die linksventrikuläre frühdiastolische Deformationsrate (Strain rate, LVSRe) oder das Verhältnis der frühdiastolischen Einflussgeschwindigkeit durch die Mitralklappe zur linksventrikulären frühdiastolischen Deformationsrate (E/LVSRe) findet zunehmend Anerkennung bei der Erfassung und Risikostratifizierug der linksventrikulären diastolischen Dysfunktion (LVDD). Dennoch sind die LV-diastolischen Deformationsparameter immer noch nicht vollständig in der Diagnosestellung von LVDD etabliert.

Zielsetzung: Das Ziel des aktuellen Forschungsprojekts ist sowohl die Bedeutung als auch die Wirksamkeit von LVSRe und E/LVSRe zu validieren, indem deren klinische, diagnostische und prognostische Relevanz für die Entwicklung von LVDD bei Patienten mit linksventrikulärer Ejektionsfraktion (LVEF) <50% erforscht wird.

Methodik und Ergebnisse: Bei insgesamt 497 erwachsenen Patienten mit LVEF <50% wurde eine bidimensionale Speckle-Tracking-Echokardiographie (2D-STE) durchgeführt. Negative Veränderungen in den LVSRe- und E/LVSRe-Werten waren signifikant mit erhöhten LV-Füllungsdrücken (geschätzt durch den pulmonalen kapillaren Wedge-Druck [PCWP]) assoziiert. In Übereinstimmung mit diesen Ergebnissen waren Verschlechterungen von den LV-diastolischen Deformationsparameter LVSRe und E/LVSRe signifikant mit einer schlechteren Symptomatik (NYHA Stadien III-IV) und einer Hospitalisierung wegen Herzinsuffizienz (HF) innerhalb von 2 Jahren verbunden. In der Tat hatten Patienten mit LVSRe-Werten $<0.5 s^{-1}$ oder E/LVSRe >71.5 das höchste Risiko für eine HF-Hospitalisierung innerhalb von 2 Jahren (OR 3.046, 95% KI 1.51–6.11 für LVSRe, und OR 3.614, 95% KI 1.26–10.36 für E/LVSRe, beide nach Alter und Geschlecht adjustiert). Wenn zusätzlich LVSRe als diastolischer LV-Parameter hinzugefügt wurde, erhöhte sich die Wahrscheinlichkeit, eine LVDD zu erkennen, signifikant von 41.1% auf 63.7% (p <0.01).

Schlussfolgerung: Die Ergebnisse dieser Studie deuten darauf hin, dass die neuen diastolischen Parameter LVSRe und E/LVSRe einen signifikanten Nutzen und eine erhebliche klinische Relevanz bei Patienten mit reduzierter LVEF haben könnten.

Introduction

Heart failure (HF) is a common and progressive disease which is mainly linked to elevated LV filling pressures because of both systolic and diastolic LV alterations. (1; 2) Due to the disease's seriousness and poor survival rates, it is considered a global health issue as over 25 million people are affected worldwide. (1; 2) Because of the constant deterioration involved, it also imposes an enormous burden for patients, medical professionals and healthcare systems. Therefore, early recognition, adequate monitoring and effective treatment of the main and final mechanism of HF (i.e., elevated LV filling pressures linked to systolic and diastolic LV alterations) are crucial to improving patients' lifestyle and outcomes. (1; 2)

Definition

By definition, heart failure is a structural and/or functional cardiac abnormality which leads to elevated LV filling pressures because of systolic and diastolic alterations. (2) Initially, both the heart and our body develop compensating mechanisms in an attempt to assure the essential levels of oxygen and blood flow. (2) According to different criteria, HF could be classified as the following: HF with preserved, mid-range or reduced ejection fraction – HFpEF, HFmrEF or HFrEF, respectively. (2) Nonetheless, cardiac structural or functional abnormalities such as systolic and/or diastolic left ventricular (LV) dysfunction could be long present even in, as yet, asymptomatic patients. (2) Early recognition of this preclinical stage is crucial for improving patients' outcomes and mortality rates. (2)

Aetiology

Often, it is impossible to identify only one single primary cause of heart failure, as the origin of this condition is commonly a rather multifactorial set of combinations. Nevertheless, coronary artery disease, with or without hypertension, is associated most frequently to the development of HF. (2) The pathophysiology behind this mechanism is that arteries become narrower and eventually get blocked, which reduces cardiac preload, ventricular stretch, myocardial contractility, and consequently cardiac output and the blood pressure. (2)

More precursors of HF are cardiomyopathies (dilated or hypertrophic), valve dysfunctions (aortic or mitral), cardiac arrhythmias (heart block or atrial fibrillation, AF), pericardial diseases (constrictive pericarditis) or infections (rheumatic fever, Chagas disease, viral myocarditis, HIV). (2; 3) Another important indicator of elevated risk for HF is genetics, as in family history. (2) Obesity, because of its close correlation to hypertension, is also believed to play an extensive role. (2) The greater the volume of tissue and fat that requests blood supply, the longer the blood vessels become, which increases distal resistance and requires higher blood pressures and stroke volumes. (4) Furthermore, the presence of diabetes mellitus favours the development of atherosclerosis and subsequently of HF. (2)

Acute heart failure (AHF) refers to a sudden and progressive deterioration of the patient's condition, which could manifest at first occurrence (*de novo*), or commonly as a result of acute decompensation of chronic HF. (2) Generally, it is induced by primary cardiac dysfunction – i.e., acute myocardial dysfunction (ischaemic, inflammatory or toxic), acute valve insufficiency or pericardial tamponade, or it can be accelerated by external triggers such as acute coronary syndrome (ACS), uncontrolled hypertension, rhythm or conduction disturbances, infections, toxic substances or surgeries. (2) Conversely, chronic heart failure (CHF) is the steady permanence of HF, a condition in which patients usually stay stable (their symptoms/signs remain unmodified for at least 1 month). (2)

Epidemiology and Prognosis

According to the European Society of Cardiology (ESC), around 1-2% of the adult population in developed countries is affected by HF, with prevalence rates rising up to 10% among people over 70 years of age. (2) At the age of 55 years, the lifetime risk of HF is assessed to be 33% for men and 28% for women. The hospitalization rate of stable HF patients is known to be around 32%. (2) For hospitalized and ambulatory HF patients, the 12-month all-cause mortality is estimated at 17% and 7%, respectively. (2) Most deaths are caused by cardiovascular events, such as sudden death or worsening HF condition, and mortality rates are on average higher in HFrEF than HFpEF. (2) On a general basis, older age, male gender, tachycardia, hypotension, fluid overload (pulmonary congestion or peripheral oedema), COPD, diabetes, anaemia, high

inflammatory and organ dysfunction markers, renal failure, poor physical state and long HF duration are considered indicators of worse HF prognosis. (2)

Diastolic Dysfunction and Heart Failure

Diastolic dysfunction occurs when the heart's relaxation is impaired, which leads to a decreased cardiac output, increased intraventricular pressure and eventually to fluid congestion in the pulmonary circulatory system. (2)

Aging, as a natural process accompanied by the loss of elastic tissue, inevitably affects the cardiovascular system and damages the normal functioning of the heart muscle, causing it to become stiffer. (5) As a consequence, the early diastolic relaxation happens more slowly and creates higher filling resistance in the late diastole, which results in elevated diastolic pressures. (5) Nonetheless, more key components are believed to play a major role in the development of left ventricular diastolic dysfunction (LVDD). (2) The most frequent one is chronic arterial hypertension, as it induces and advances left ventricular hypertrophy and consequently worsens the cardiac compliance. (2) Furthermore, coronary artery disease, diabetes mellitus, obesity and inactivity, as in the metabolic syndrome, contribute notably to the process. Additional risk factors are aortic stenosis, hypertrophic or restrictive cardiomyopathy, constrictive pericarditis and pericardial disease or tamponade. (2; 5)

Diagnosis

Besides evaluation of patient's clinical history, physical examination, plasma concentration of natriuretic peptides (NPs) and abnormal electrocardiogram (ECG), echocardiography has been the standard for establishing the diagnosis of HF. (2) The information it provides immediately on chamber volumes, ventricular systolic and diastolic function, wall thickness and valve function is indispensable for the introduction of a further correct treatment. (2)

Echocardiography

The first step in characterizing HF with echocardiography (i.e., using transthoracic echocardiography) is by measuring the left ventricular ejection fraction (LVEF). The cutoff is set at EF ≥50%, EF 40-49% and EF <40% for HFpEF, HFmrEF and HFrEF, respectively. (2) Another diagnostic milestone is LV filling pressure, which correlates well with the ratio of transmitral early filling velocity (E) to the early diastolic tissue velocity (e′) measured by pulsed TDI. (2; 6) A further recommended LV diastolic parameter is maximal left atrial volume index (LAVI). (2; 7) Nevertheless, due to several limitations such as angle dependency and high sensitivity to sample location and transverse motion, none of the previously mentioned variables are sufficiently accurate to be considered separate parameters for the diagnosis of HF as they exclusively depict the displacement of a single LV segment (the annular parameters), as well as indirectly the consequences on the LA volume (the volumetric parameters). (6) Recent research has introduced a non-angle dependent and global diastolic parameter – left ventricular early diastolic strain rate (LVSRe), using new echocardiographic techniques such as speckle-tracking echocardiography, which proposes strong correlation with LV filling pressure, reflects global LV relaxation better than E/e′, and avoids the limitations of E/e′. (6; 7) Additionally, early mitral inflow velocity to early diastolic strain rate (E/LVSRe) was recognized as a novel predictor of elevated LV filling pressure. (8; 9; 10) Beyond that, E/LVSRe was identified as a promising indicator of LV diastolic function. (11; 12)

Speckle tracking echocardiography

Speckle tracking echocardiography (STE) is an ultrasound imaging technique that analyses myocardial mechanics and motion. It records the random and naturally occurring speckle patterns – a combination of interference patterns and natural acoustic reflections – which are particular for every myocardial region, and can therefore be traced from frame to frame. When processing them, creating a two-dimensional (2D) or three-dimensional (3D) strain-based sequence is possible. (6-12)

Strain is defined as the fractional or percentage change between the myocardial contraction and relaxation. (6-12) LV deformation is characterized by three normal strains (longitudinal, radial and circumferential) and three shear strains (longitudinal-radial, circumferential-longitudinal and circumferential-radial). (6-12) Additionally, global (average of all segments) and regional (in each segment) strain can be calculated. Strain rate is the speed at which this deformation occurs and is determined by the difference in

velocity between two measurement points, divided by the distance between them. Strain and strain rate are expected to be equal in all myocardial parts. (13)

LV myocardial diastolic parameters

Previous academic work discovered that LV myocardial diastolic dysfunction is a major component of the HF pathophysiology in HFrEF patients. (14) Likewise, LV myocardial diastolic dysfunction in HFpEF patients is greater than in hypertensive patients without HF. (15) Also, plasma brain natriuretic peptide (BNP) is determined extensively by myocardial diastolic dysfunction and stiffness. (16) Recent studies, mainly in patients with preserved LVEF, have suggested that the quantifying of LV myocardial diastolic dysfunction could be measured by new parameters such as LVERe. Various research groups have demonstrated myocardial diastolic parameters as an emerging and useful clinical marker for LV myocardial diastolic function and stiffness, which is directly associated with patients' prognosis. (6-20) Moreover, LV systolic strain parameters have been also suggested to be linked to worse cardiovascular outcomes. (21-25) Consequently, the clinical applicability of LV diastolic strain parameters is increasingly emerging and warrants further investigation.

Background and Aim of the Present Study

As stated above, new myocardial, global, non-angle dependent parameters of LV diastolic function such as LVSRe and E/LVSRe could have significant usefulness and clinical relevance in patients with cardiovascular disease or HF. (6-12; 26-29)

However, the clinical evidence for using these parameters in patients with reduced LVEF is lacking. Hence, the aim of this study was to determine the potential usefulness and clinical relevance of new myocardial, global, non-angle dependent parameters of LV diastolic function such as LVSRe and E/LVSRe in patients with reduced LVEF.

Methods

Study population

The study population of the present study consists of 497 adult individuals with reduced LVEF (defined as LVEF <50%, as determined by transthoracic echocardiography using the Simpson biplane method). These patients were included at the outpatient department of cardiology at the Charité University Hospital Berlin, Campus Virchow in the period from October 2011 until November 2015. Both male and female subjects were enrolled, and adult was defined as over the age of 18 years. Further inclusion criteria were the presence of cardiovascular risk factors, such as arterial hypertension (systolic and diastolic blood pressure levels ≥140/90mmHg), history of coronary disease (i.e., history of (i) ST elevation myocardial infarction STEMI, (ii) non-ST elevation myocardial infarction NSTEMI, and (iii) unstable angina, stable angina or coronary revascularization), diabetes mellitus (fasting plasma glucose ≥126mg/dl or ≥7mmol/l), obesity (body mass index ≥30kg/m^2) or hypercholesterolemia (fasting plasma LDL cholesterol ≥160mg/dl), as the above-mentioned factors are also considered favourable for the development of LVDD.

Exclusion criteria were defined conforming to the recommendations for LV diastolic measurements of the European Association of Cardiovascular Imaging (EACVI). (11) Hence, patients with the following were not included: valvular heart disease, such as at least mild valvular heart stenosis, more than moderate mitral or aortic regurgitation (MR and AR, respectively), severe pulmonary or tricuspid regurgitation (PR and TR, respectively), moderate to severe mitral annular calcification (MAC; ≥5mm), premature closure of the mitral valve, valvular heart surgery repair or replacement, as well as patients with hypertrophic cardiomyopathy (HCM) or constrictive pericarditis. Furthermore, for the purpose of most accurately measuring the LVSRe values, subjects with poor two-dimensional (2D) image quality of >2 LV segments in each apical view, or presenting with atrial fibrillation (AF) or supraventricular arrhythmias were excluded. Additionally, to remove any possibility of enrolling patients with dyspnoea caused by non-cardiac conditions, further excluded patients were: individuals with severe pulmonary diseases, such as those which require oxygen therapy or glucocorticoid treatment; individuals with severe kidney diseases, such as those which require dialysis or have an indication for renal transplantation; and individuals with severe liver diseases who were assigned Class B or C in the Child-Pugh score or have an indication for liver transplantation.

The Charité University Hospital's Ethics Committee approved the implementation of this project, and all patients were informed and gave their consent to participate in this study.

Echocardiographic examination

All patients underwent a conventional transthoracic echocardiography (TTE) at rest. The examination was performed using a Vivid 7 or E9 (GE Healthcare) ultrasound system. All measurements were estimated as the average of three measurements. Moreover, all patients were respiratorily (<20 breaths/min), haemodynamically (RR_{sys} 90-160mmHg) and electrically (51-99 beats/min) stable at the moment of the examination.

As suggested by the EACVI, measurements were carried out in both 2D and Doppler modes. (11) Following the EACVI criteria for establishing LV diastolic function, the following four parameters with their abnormal cutoff values were taken into consideration: **(1)** average E/e′ ratio >14, **(2)** annular e′ velocity – septal e′ <7cm/s and lateral e′ <10cm/s, **(3)** LAVI >34ml/m^2, and **(4)** TR peak velocity >2.8m/s. (11) Consecutively, LVDD is defined when more than half of the recommended variables meet the cutoff points and are thereby classified as positive. And vice versa, LV diastolic function is only considered normal if less than half of the parameters appear positive. In addition, an intermediate LV diastolic function category is presented when exactly half of the values are positive. Further graduation of the LVDD was introduced in line with the EACVI recommendations:

- Grade I – E/A ratio ≤0.8 and E ≤50cm/s or (a) E/A ratio ≤0.8 and E >50cm/s or (b) E/A ratio >0.8 but <2, both (a) and (b) plus ≥2 negative criteria (average E/e′ ratio >14, LAVI >34ml/m^2 and TR peak velocity >2.8m/s);
- Grade II – E/A ratio ≤0.8 and E >50cm/s or E/A ratio >0.8 but <2, both plus ≥2 positive criteria (average E/e′ ratio >14, LAVI >34ml/m^2 and TR peak velocity >2.8m/s);
- Grade III – E/A ratio ≥2 (Supplementary data online, Figure S1). (30)

Furthermore, a parallel analysis of the LVDD was carried out with the purpose of comparing LVSRe with the average mitral E/e′ ratio (abnormal when >14) and the septal and lateral annular mitral e′ velocity (abnormal when septal e′ <7cm/s and lateral e′ <10cm/s), as those two parameters explicitly describe the LV. LV diastolic abnormalities were defined as the following: mild when abnormal septal or lateral e′ plus average E/e′

ratio is <10, moderate when abnormal septal or lateral e′ plus average E/e′ ratio is ≥10 but ≤14, and severe when abnormal septal or lateral e′ plus average E/e′ ratio is >14. Additionally, the possible correlation between the pulmonary capillary wedge pressure (PCWP) and LVSRe was also investigated, using the estimating equation of PCWP=2+1.3xE/e′. (31) In terms of the severity of PCWP, the following graduation was introduced for this study: group 1 = PCWP ≤12mmHg, group 2 = PCWP 13-15mmHg, and group 3 = PCWP ≥15mmHg.

Speckle tracking analysis

A 2D speckle tracking echocardiographic (2D-STE) analysis of the LV was performed offline and blinded to the patients' clinical history, using the ultrasound software package Echo-Pac version 113.0 from GE.

The LVSRe value was defined as the average of the longitudinal early diastolic strain rate peak from all LV segments in the apical four-chamber, two-chamber and long-axis view. The frame rate of the measurements was set at 50 to 80 frames/s and the final outcome was the average of three measurements.

The lower limit of normality of LVSRe was defined at $1s^{-1}$, based on the revelations made by Morris et al. 2017. (7) Hence, the study population was divided into four groups according to the severity of their LVSRe values: group 0 LVSRe $\geq 1s^{-1}$; group 1 LVSRe $0.99\text{-}0.75s^{-1}$; group 2 LVSRe $0.74\text{-}0.5s^{-1}$, and group 3 LVSRe $<0.5s^{-1}$.

The E/LVSRe ratio was also used for evaluation and detection of LVDD. Parameter values >71.5 were considered abnormal. (7)

Data organisation

After the first stage of patient recruitment and echocardiographic data collection, the obtained values were transferred into a static database for further analysis. By searching through the patients' medical files in the database of the Charité's SAP software, further patient information was gathered and added to the study's database. With the purpose of simplification and coherency, it was then grouped by sections. The following main characteristics were recorded: height, weight, body mass index (BMI), body surface, obesity, diabetes mellitus, heart rate, systolic blood pressure (RR_{sys}), diastolic blood

pressure (RR_{dia}), hypertension, history of CAD, NYHA functional class, symptomatic status (dyspnoea), glomerular filtration rate (GFR), serum creatinine levels, and haemoglobin levels (Hb). Echocardiographic parameters were likewise collected: LVSRe, E/LVSRe, global longitudinal strain (GLS), LVEF, LVEF group (group 1 49-40%, group 2 39-30%, group 3 <30%), mitral early diastolic peak velocity E, septal and lateral mitral annular velocities e′, average mitral, septal and lateral E/e' ratios, mitral late diastolic peak velocity A, peak E/A ratio, LAVI, TR peak velocity, existence and grade of LVDD, PCWP, pulmonary artery systolic pressure (PASP), posterior wall thickness at end diastole (PWd), septal thickness at end diastole (IVSd), LV end-diastolic and end-systolic internal dimensions (LVEDD and LVESD), LV mass, and presence of elevated LV filling pressure and LV hypertrophy (more details in Figure 1). The raw material of the population sample was thereby created.

At the second stage of the project, and with the intention of proving a definite correlation between the echocardiographic measurements and the clinical presentation and outcomes of the study population, a retrospective analysis was performed. A *de novo* search was conducted in the SAP database, and information was added to the study's database on the following: re-hospitalization due to HF, appearance of ventricular tachycardia (VT) or ventricular fibrillation (VF) or atrial fibrillation (AF), existence of a cardiac transplant, death due to HF, death by all causes, serum creatinine levels in 2 years, GFR in 2 years, and echocardiography after 11-13 months and after 23-25 months. The obtained information was thoroughly reviewed by the supervisor of the project, and missing or incoherent data was amended.

Statistical data analysis

For the data presentation, the following formats were selected: continuous data as mean ± standard deviation (SD, ±σ) and standard error (SE) or odds ratio (OR) with 95% confidence interval (CI), and dichotomous data in percentage. In order to examine the association between LVSRe or E/LVSRe (continuous variables) and the development of LVDD (measured by categorical variables), one-way analysis of variance (ANOVA) for dichotomous variables as well as one-way ANOVA on ranks (Kruskal-Wallis test) for ordinal variables were undertaken. Subsequently, a Fisher's protected least significant difference (PLSD) test was performed in order to compare and further explore correlations

between the groups. Additionally, a logistic regression analysis was performed, defining the odds ratio for dichotomous variables in association with LVSRe or E/LVSRe. With the purpose of evaluating the relation between an abnormal LVSRe and higher NYHA functional class or risk of HF hospitalization at 2 years, logistic regression analyses were completed unadjusted and adjusted by age and gender. Additionally, the potential usefulness of LVSRe as an early diagnostic parameter of LVDD was examined by Chi-square (χ^2) test of independence. Finally, a receiver operating characteristic (ROC) curve was constructed, testing the predictive performance of LVSRe and E/LVSRe for LVDD and symptomatic status. Statistical analyses were completed with SPSS 22.0 (IBM) and Statview 5.0 (SASInstitute). Statistically significant differences were stated when $p<0.05$.

After consulting a certified member of Charité's Institute of Biometry and Clinical Epidemiology, it was verified that the statistic model of this thesis was sufficient and accurate, and that its implementation was precise, extensive and correct.

Basic clinical and echocardiographic parameters

Name	Date of examination	Date of birth	Age	Height	Weight	BMI	Body surface
Female gender	Hypertension	Diabetes mellitus	History of CAD	Obesity	Heart rate	RR_{sys}	RR_{dia}
E	A	E/A	Septal e′	Lateral e′	E/e’	Septal E/e′	Lateral E/e′
LVEF	LVEF group	GLS	Global LVSRe	LVSRe grade	E/LVSRe	LAVI	TR
PWd	IVSd	LVEDD	LVESD	Elevated LV filling pressure	LV mass	PASP	PCWP Nagueh
NYHA Class	Symptomatic/ Asymptomatic	LV hypertrophy	LVDD	LVDD grade	GFR	Serum creatinine	Hb

Extended

HF re-hospitalization	Death due to HF	VT or VF or AF	Death (all causes)	Cardiac transplant	Creatinine in 2 years	GFR in 2 years	Echocardiography after 11-13 months	Echocardiography after 23-25 months

Current medication	HF re-hospitalization within 2 years	Date of first HF re-hospitalization	HF death within 2 years	Date of HF death
AF at moment of echocardiography	VT or VF or death within 2 years	Date of first VT or VF	CRT implantation	Date of CRT implantation

Figure 1 Overview of the data collection

Describes the process of patient recruitment and echocardiographic data collection. The obtained information is then transferred into a Microsoft Excel 2013 table.

Results

Characteristics of study population

Baseline characteristics

A total of 497 patients were enrolled in the present study, from whom 122 were female (24.5%) and 375 male (75.5%). The mean age throughout the sample was 65.3 years (SD ±14.38) and 290 of the subjects were older than 65 years (58.3%). In this study population, 385 of the patients suffered from arterial hypertension (77.4%). The mean RR_{sys} of the sample was measured at 125.1 ±17.42 mmHg and the mean heart rate was 72.3 ±9.01 bpm. The average body mass index (BMI) was 26.4 ±4.8 kg/m^2 and altogether 96 patients were obese (19.3%). Additionally, 135 had diabetes mellitus (27.1%).

LVDD was diagnosed in 486 subjects (97.7%) - 241 of them were classified with grade III (48.4%), 56 with grade II (11.2%) and 32 with grade I (6.4%). 426 symptomatic cases (85.7%) were recorded. Left ventricular hypertrophy (LVH) was detected in 378 of the test persons (76.05%). The mean PCWP of 311 of the study participants was ≥15mmHg (62.5%). A history of coronary artery disease was found in 305 patients (61.3%). Exactly 244 cases manifested an elevated LV filling pressure (49.1%). Furthermore, 148 men (29.7%) and 70 women (14.1%) presented severely abnormal LV mass values (>148g/m^2 and >121g/m^2, respectively). As a whole, 193 of the participants were assigned to NYHA functional classes III and IV (38.8%).

Within 2 years upon first presentation in the outpatient department, 124 (24.9%) of the enrolled subjects were re-hospitalized due to HF and 65 (13.1%) had suffered a ventricular tachycardia (VT) or a ventricular fibrillation (VF). Atrial fibrillation (AF) or atrial flutter (AFL) was documented in 139 cases (27.9%). Furthermore, 66 participants possessed an implanted CRT device (13.2%). Finally, in the period of 2 years after the first echocardiography, 16 deaths due to HF were registered (3.2%) and a further 21 all-cause deaths occurred (4.22%), so the overall mortality in the study was 7.44% (37 persons).

The demographic and clinical characteristics of the study population are organized in Table 1.

Table 1 Baseline characteristics of the study population

Demographic aspects	
Patients, n	497
Age, years	65.3 ±14.3
Female gender, n (%)	122 (24.5%)
BMI, kg/m^2	26.4 ±4.8
RR_{sys}, mmHg	125.1 ±17.4
RR_{dia}, mmHg	75.5 ±11.8
Heart rate, bpm	72.3 ±9.01
Clinical data	
Arterial hypertension, n (%)	385 (77.4%)
Obesity, n (%)	96 (19.3%)
Diabetes mellitus, n (%)	135 (27.1%)
Symptomatic cases	426 (85.7%)
NYHA III – IV, n (%)	193 (38.8%)
Elevated LV filling pressure, n (%)	244 (49.1%)
LVH, n (%)	378 (76.05%)
LVDD, n (%)	486 (97.7%)
History of coronary artery disease, n (%)	305 (61.3%)
AF or AFL within 2 years, n (%)	139 (27.9%)
Implanted CRT device, n (%)	66 (13.2%)
HF re-hospitalization within 2 years, n (%)	124 (24.9%)
VT or VF within 2 years, n (%)	65 (13.1%)
Mortality due to HF within 2 years, n (%)	16 (3.2%)

Data are expressed as mean ± SD or percentages.

Echocardiography characteristics

The present study population consists of patients with LVEF <50%. The arithmetic mean of all LVEF values was 35.994% (SD ±9.79 and SE 0.43). The highest LVEF value was 49% (34 patients, 68.41%) and the lowest was measured at 10% (3 patients, 0.6%). When measuring the mean mitral inflow velocities, the following results were obtained: mitral early diastolic peak velocity E=75.96cm/s ±25.50, septal mitral annular velocity e′=4.25cm/s ±1.55, lateral mitral annular velocity e′=6.15cm/s ±2.52, and late diastolic peak velocity A=66.786cm/s ±26.55. The corresponding average mitral, septal and lateral E/e′ as well as peak E/A ratios were also determined: 16.11 ±7.24, 20.05 ±9.63, 14.28 ±7.13 and 1.376 ±0.83, respectively. The end-diastolic posterior wall and septal thicknesses were assessed together with LV end-diastolic and end-systolic internal dimensions – IVSd=11.71mm ±1.88, PWd=11.24mm ±1.82, LVEDD=56.12mm ±9.38 and LVESD=45.39mm ±10.54. The mean LAVI was 73.11ml/m^2 ±28.95, the mean TR peak velocity was 2.37m/s ±0.67 and the mean LV mass was 269.01g/m^2 ±82.67. PCWP and PASP of the patients were also averaged and measured as 20.57mmHg ±9.26 and 34.32mmHg ±13.71, respectively. Table 2 below offers an overview of the results.

Table 2 Echocardiographic characteristics of the study population

Echocardiographic parameters	
LVEF, mean %	35.9 ±9.7
Mitral early diastolic peak velocity E, cm/s	75.9 ±25.5
Septal mitral annular velocity e′, cm/s	4.2 ±1.5
Lateral mitral annular velocity e′, cm/s	6.1 ±2.5
Average mitral E/e′ ratio	16.1 ±7.2
Septal mitral E/e′ ratio	20.0 ±9.6
Lateral mitral E/e′ ratio	14.2 ±7.1
Mitral late diastolic peak velocity A, cm/s	66.7 ±26.5
Peak E/A ratio	1.3 ±0.8
IVSd, mm	11.7 ±1.8
PWd, mm	11.2 ±1.8
LVEDD, mm	56.1 ±9.3
LVESD, mm	45.3 ±10.5
LAVI, ml/m^2	73.1 ±28.9
TR peak velocity, m/s	2.3 ±0.6
LV mass, g/m^2	269.0 ±82.6
PCWP, mmHg	20.5 ±9.2
PASP, mmHg	34.3 ±13.7
GLS, %	9.6 ±3.4

Data are expressed as mean ± SD or percentages. IVSd – Interventricular septal end diastole, PWd – Left ventricular posterior wall end diastole, LVEDD – Left ventricular end-diastolic diameter, LVESD – Left ventricular end-systolic diameter, LAVI – Left atrial volume index, TR – tricuspid regurgitation, PCWP – Pulmonary capillary wedge pressure, PASP – Pulmonary artery systolic pressure, GLS – Global longitudinal strain.

LVSRe baseline characteristics

A closer look was taken at the characteristics of the LVSRe parameter. As previously mentioned, the measured LVSRe value is the average of the longitudinal early diastolic strain rate peak in the LV apical four-chamber, two-chamber and long-axis views. Figure 2 presents the single LVSRe values of all enrolled patients in a chart and in a box plot, which graphically depicts the distribution.

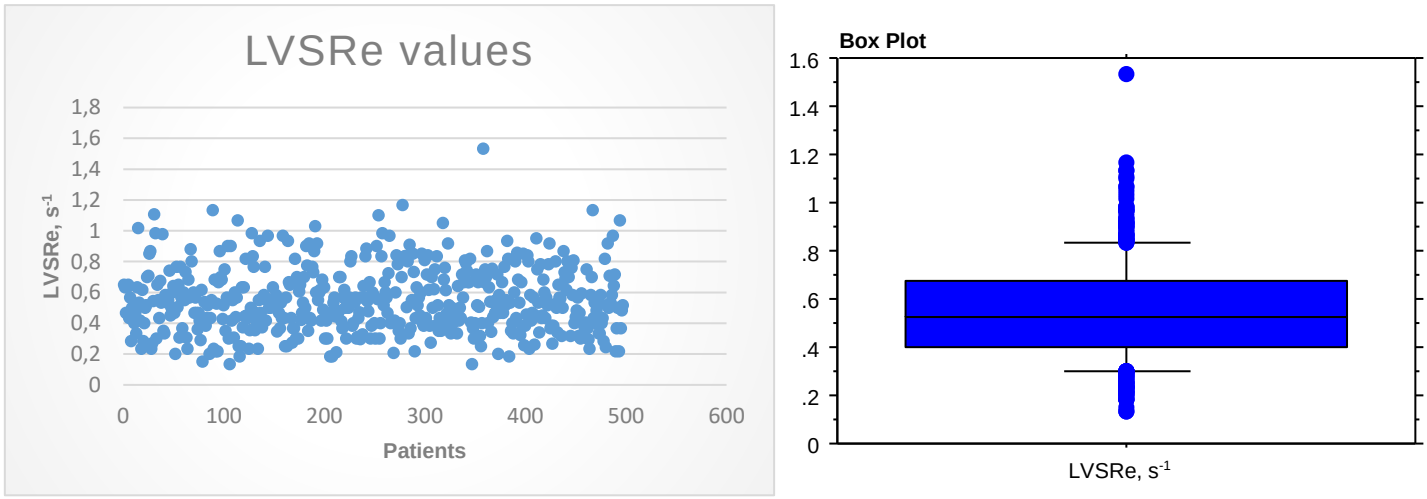

Figure 2 Graphic distribution of LVSRe values

LVSRe is measured in s^{-1}. Left side: chart. Right side: box plot. In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th–75th percentile), and the bars indicate the 10th and 90th percentile of LVSRe.

The arithmetic mean of the LVSRe values was calculated at 0.546s^{-1} with SD of ±0.21 and standard error (SE) of 0.009. The lowest LVSRe value in this patient sample was measured at 0.133s^{-1} and the highest at 1.533s^{-1}. The latter value (1.533s^{-1}) could be observed as an outlier in all LVSRe graphic representations. All in all, 97.7% (486 persons) had abnormal LVSRe values (<1s^{-1}). Specifically, 11 study participants presented with LVSRe ≥1s^{-1} (2.2%), 80 with values 0.99-0.75s^{-1} (16.1%), 192 with values 0.74-0.5s^{-1} (38.6%) and 214 with LVSRe <0.5s^{-1} (43.1%). The mean LVSRe value for the 11 participants with normal LVSRe was 1.127s^{-1} (SD ±0.14). Exactly 6 of them were diagnosed with LVDD (54.5%). Their mean LVSRe was 1.163s^{-1} (SD ±0.18).

A more detailed qualification of the LVSRe mean values ± SD of the study population, as well as for the E/LVSRe ratio, is presented in Table 3. In general, men had a higher LVSRe value – 0.547s^{-1}(SD ±0.21), whereas the mean LVSRe for women was 0.543s^{-1} (SD ±0.20). Study participants above the age of 65 years presented an even lower mean

LVSRe of 0.506s^{-1} and SD ±0.18. The same categorization was also implemented for the E/LVSRe ratio, whose mean value and SD was measured at 163.801 ±98.53. The corresponding values for men, women and >65-year-olds were 165.758 ±102.33, 157.783 ±85.52 and 174.017 ±105.11, respectively.

Table 3 Mean LVSRe values

	All	Men	Women	>65 years
LVSRe, s^{-1}	0.54 ±0.21	0.54 ±0.21	0.54 ±0.20	0.50 ±0.18
Mitral E/LVSRe ratio	163.8 ±98.5	165.7 ±102.3	157.7 ±85.5	174.0 ±105.1

Data are expressed as mean ± SD.

The frequency of occurrence of the parameter's values was examined and sorted in a percentiles plot. According to the LVSRe distribution in our data set, the 10th percentile measures 0.3s^{-1}, the 50th – 0.523s^{-1} and the 90th – 0.833s^{-1} (Figure 3).

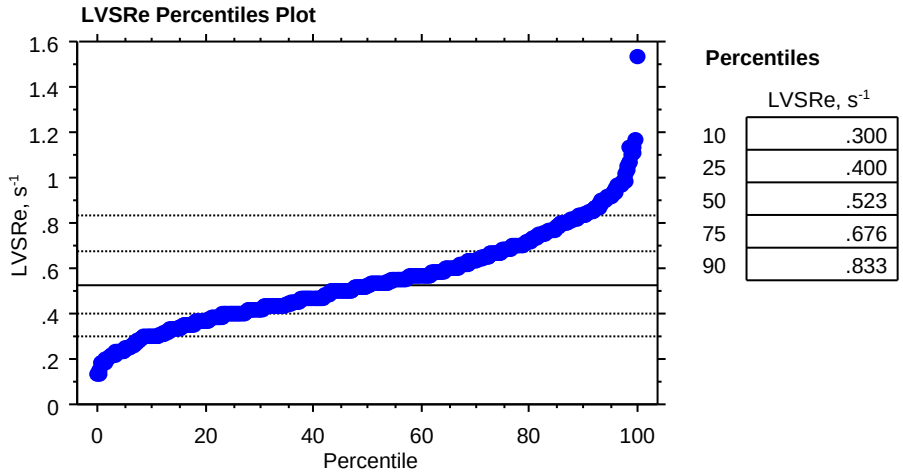

Figure 3 LVSRe percentiles

LVSRe is measured in s^{-1}. Left side: percentiles plot. Right side: table with LVSRe values at the 10th, 25th, 50th, 75th and 90th percentile.

An additional histogram displays the frequencies of the LVSRe values among the study population. The graph represents a characteristic unimodal symmetric Laplace-Gauss distribution (normal distribution, one that follows a bell curve) with the majority of the values dispersed between 0.3s^{-1} and 0.7s^{-1} (Figure 4).

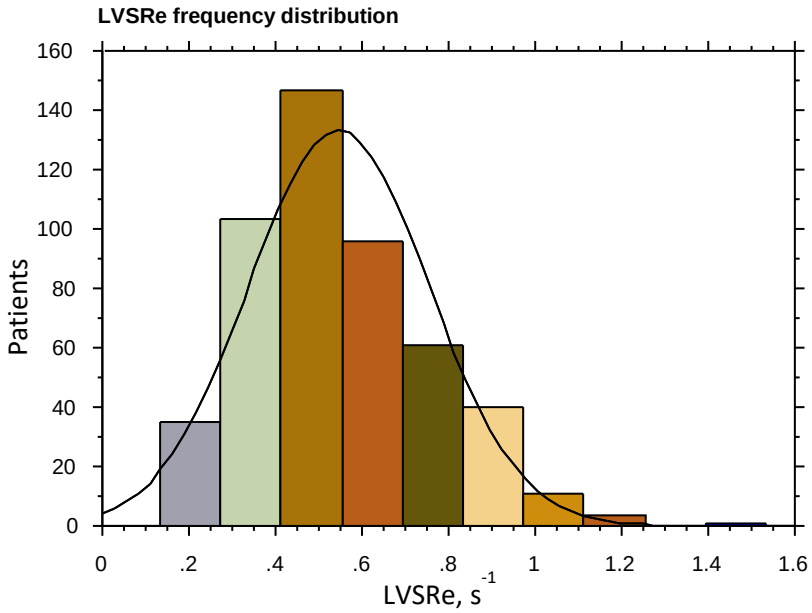

Figure 4 LVSRe frequency distribution

The distribution of the LVSRe values as a characteristic unimodal symmetric Laplace-Gauss (normal) distribution. The number of patients is displayed. LVSRe is measured in s^{-1}.

The distribution of the LVSRe values was further investigated for the variables NYHA functional classes III-IV and HF related re-hospitalization within 2 years.

In total, 193 patients reported symptoms corresponding to NYHA classes III-IV. None of them presented LVSRe values ≥1s^{-1} (0%), 10 had LVSRe values 0.99-0.75s^{-1} (5.18%), 49 had LVSRe 0.74-0.5s^{-1} (25.39%) and 134 were with LVSRe values <0.5s^{-1} (69.43%). The distribution of the NYHA III-IV patients according to their LVSRe value can be seen in the bar chart (Figure 5). Furthermore, the following observations were made:

- of all 11 participants with LVSRe values ≥1s^{-1}, 0 had been allocated to NYHA classes III-IV (0%);
- of the 80 study subjects with LVSRe values 0.99-0.75s^{-1}, 10 were assigned to NYHA classes III-IV (12.5%);
- of the 192 patients with LVSRe 0.74-0.5s^{-1}, 49 had NYHA classes III-IV (25.5%);
- of the 214 test persons with LVSRe <0.5s^{-1}, 134 had NYHA classes III-IV (62.6%).

The Kruskal-Wallis analysis carried out on the distribution of the LVSRe values, divided into 4 sections, as previously mentioned, offered a significant correlation between worsening LVSRe and NYHA classes III and IV ($p<0.0001$).

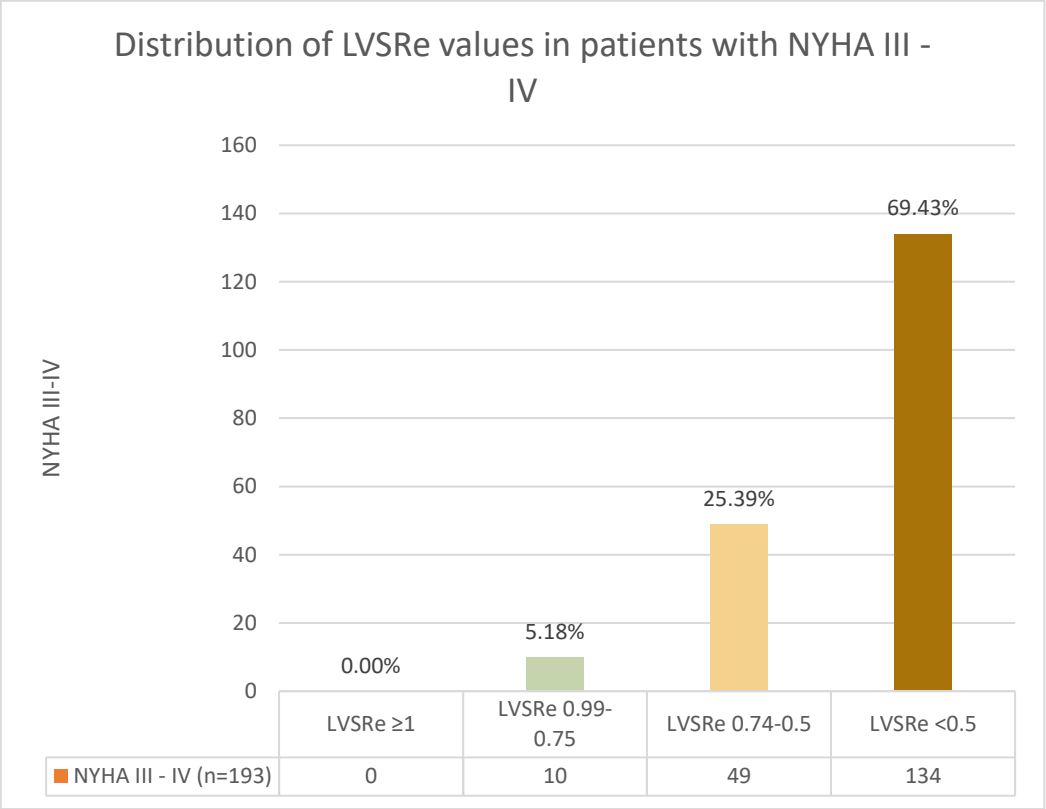

Figure 5 LVSRe distribution in NYHA III-IV patients

Data are expressed as percentages. LVSRe is measured in s^{-1} and divided into 4 groups: ≥1s^{-1}, 0.99-0.75s^{-1}, 0.74-0.5s^{-1} and <0.5s^{-1}.

Altogether, 124 patients were re-hospitalized due to HF within a period of 2 years after their first echocardiographic examination. None of them had LVSRe values ≥1s^{-1} (0%), 12 offered LVSRe values 0.99-0.75s^{-1} (9.68%), 44 had LVSRe values 0.74-0.5s^{-1} (35.48%) and 68 had LVSRe values 0.5s^{-1} (54.84%). The bar chart (Figure 6) demonstrates the distribution of re-hospitalized participants in accordance with their LVSRe value.

Additionally, none of the 11 participants with LVSRe values ≥1s^{-1} had been re-hospitalized due to HF within 2 years of the first echocardiographic examination (0%), while conversely 12 of the 80 patients with LVSRe values 0.99-0.75s^{-1} (15%), 44 of the 192 study subjects with LVSRe 0.74-0.5s^{-1} (22.9%) and 68 of the 214 test persons with LVSRe <0.5s^{-1} (31.7%), were re-hospitalized, respectively.

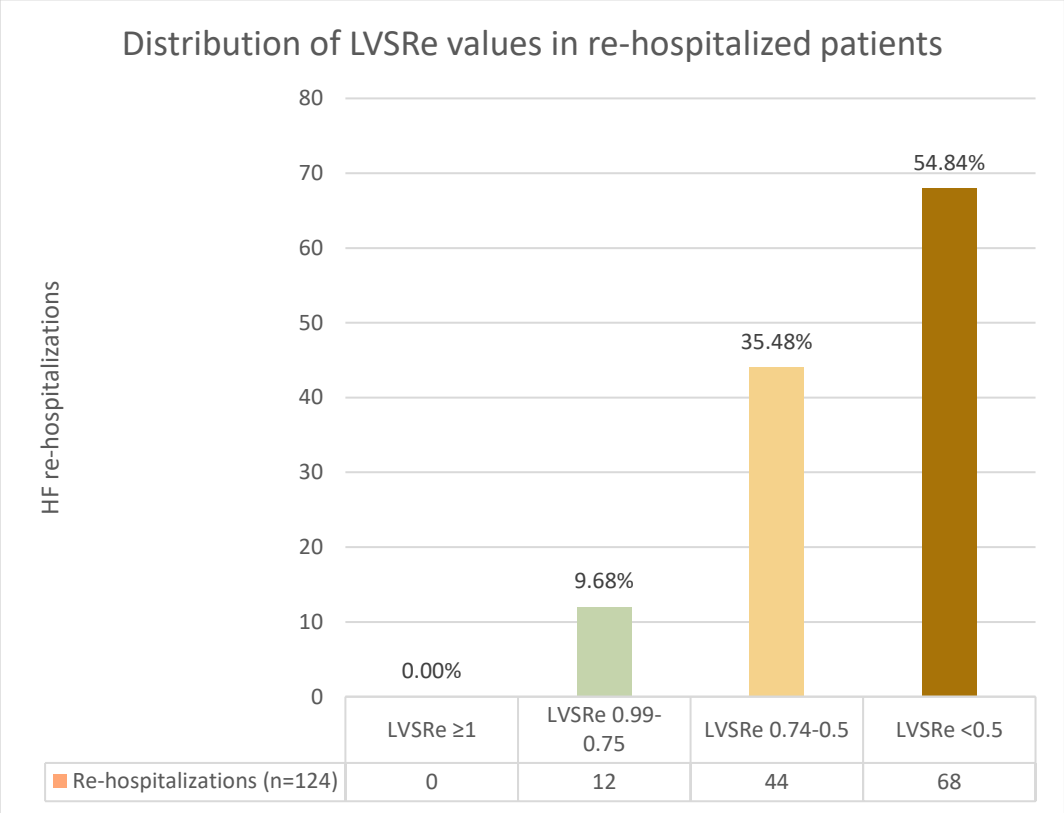

Figure 6 LVSRe distribution in re-hospitalized patients

Data are expressed as percentages. LVSRe is measured in s^{-1} and divided into 4 groups: $\geq 1s^{-1}$, $0.99\text{-}0.75s^{-1}$, $0.74\text{-}0.5s^{-1}$ and $<0.5s^{-1}$.

Additionally, a Kruskal-Wallis analysis was carried out to test the correlation between worsening LVSRe values and re-hospitalization rates between patients. The outcome was significant (p=0.0035).

Relevance of LVSRe and E/LVSRe ratio

In order to evaluate the relevance of LVSRe for the detection of HF, the interaction between LVSRe or E/LVSRe and the following three main variables was examined: worsening NYHA functional class, existence of symptoms and HF re-hospitalization within 2 years. The behaviour of the PCWP and LVEF values in relation to LVSRe and E/LVSRe was also analysed. The findings are presented graphically in box plots and detailed versions of the results of the statistical tests are displayed in the corresponding tables underneath.

NYHA functional class

The mean LVSRe of the patients who were assigned to NYHA class I was 0.740s^{-1}, with a SD of ±0.18 and SE of 0.02. For NYHA class II, the mean LVSRe was 0.582s^{-1} (SD ±0.19 and SE 0.01). In the group with NYHA class III and IV, the mean LVSRe was 0.433s^{-1}, with a SD of ±0.15 and SE of 0.01. The executed ANOVA analysis of the correlation between a worsening LVSRe and a higher NYHA functional class showed significant results ($p<0.0001$). Consequently, to further verify the significance of the hypothesis, a Fisher's PLSD test between the separate groups was carried out. The p-value of all three combinations (NYHA classes I with II, I with III-IV and II with III-IV) was likewise significant ($p<0.0001$). Figure 7 presents these results graphically in a box plot.

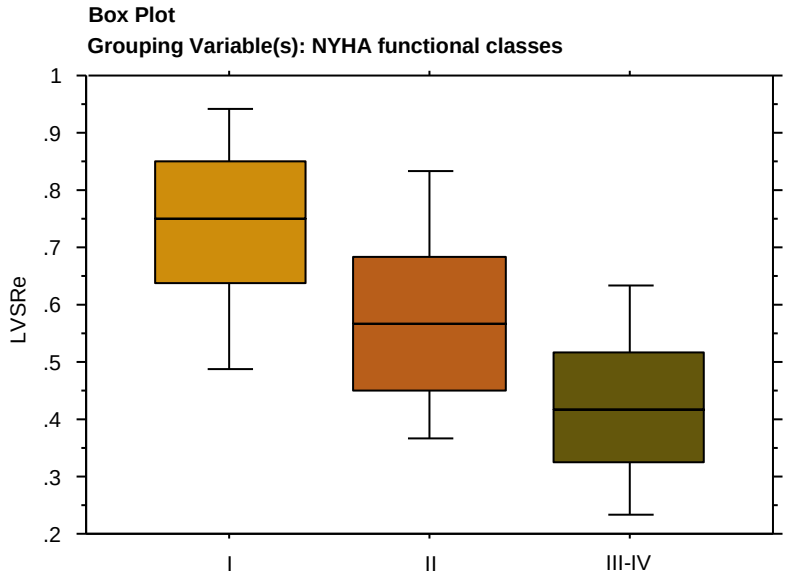

Figure 7 Correlation between LVSRe and NYHA class

LVSRe is measured in s^{-1}. Data are expressed as mean ± SD. NYHA is divided according to the functional classes: I, II and III-IV. In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th–75th percentile), and the bars indicate the 10th and 90th percentile of LVSRe.

The mean mitral E/LVSRe ratio of the patients with functional class NYHA I was measured at 103.529 with SD of ±49.20 and SE 5.83. The study participants with functional class NYHA II had a mean mitral E/LVSRe ratio of 137.402 (SD ±68.63 and SE 4.49) and the ones with NYHA classes III and IV presented a mean mitral E/LVSRe ratio of 217.842 (SD ±115.89 and SE 8.34). The association of a higher mitral E/LVSRe ratio with worsening NYHA functional class produced a significant relationship (ANOVA,

p<0.0001). Furthermore, the inter-group analysis carried out confirmed the significance of the results (Fisher's PLSD test, class I with II p=0.0048, class I with III-IV p<0.0001, classes II with III-IV p<0.0001). Those findings can be seen in Figure 8.

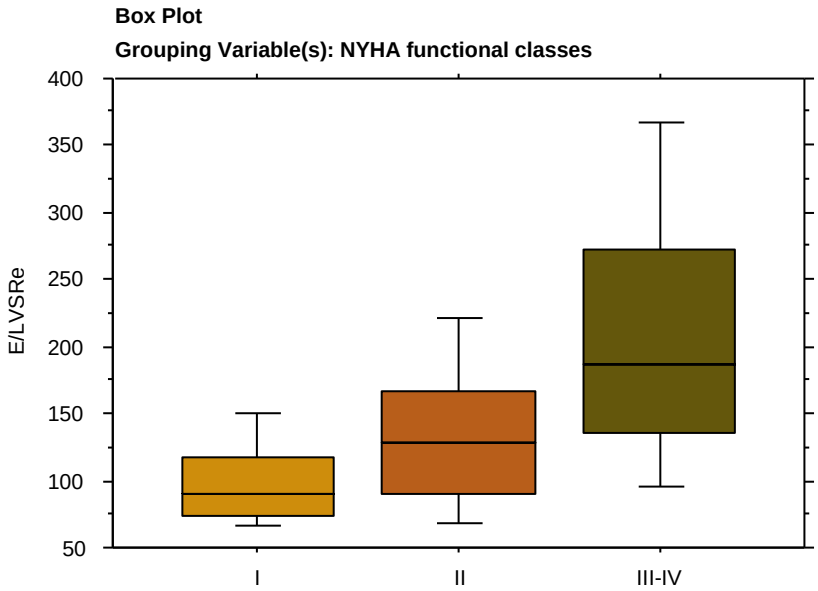

Figure 8 Correlation between E/LVSRe and NYHA class

The E/LVSRe ratio is measured as mean ± SD and NYHA is divided according to the functional classes: I, II and III-IV. In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th–75th percentile), and the bars indicate the 10th and 90th percentile of the mitral E/LVSRe ratio.

All in all, 193 patients presented with NYHA classes III and IV. The mean values of LVSRe and E/LVSRe for this part of the study population were 0.433s^{-1} (SD ±0.15, SE=0.01) and 217.842 (SD ±115.89, SE=8.34), respectively. As those were the groups with the lowest LVSRe and highest E/LVSRe values, a positive, significant association with worse NYHA functional class was proven for both parameters (ANOVA, p<0.0001; Table 4).

Table 4 LVSRe and E/LVSRe mean values according to NYHA class

	NYHA I (n=71)	NYHA II (n=233)	NYHA III-IV (n=193)	P-value
LVSRe, s^{-1}	0.74 ±0.18	0.58 ±0.19	0.43 ±0.15	<0.0001
E/LVSRe	103.5 ±49.20	137.4 ±68.6	217.8 ±115.8	<0.0001

LVSRe is measured in s^{-1}. Data are expressed as mean ± SD. NYHA is divided according to the functional classes: I, II and III-IV. P-value is calculated for both parameters.

Symptomatic vs. asymptomatic

In a subsequent analysis, aiming to investigate the effect of the LVSRe value size on the existence of symptoms, another statistically significant association was proven (ANOVA, $p<0.0001$). The mean LVSRe of the symptomatic patients was $0.514s^{-1}$ (SD ±0.19, SE 0.01), while for asymptomatic ones it was $0.740s^{-1}$ (SD ±0.18, SE 0.02; Figure 9).

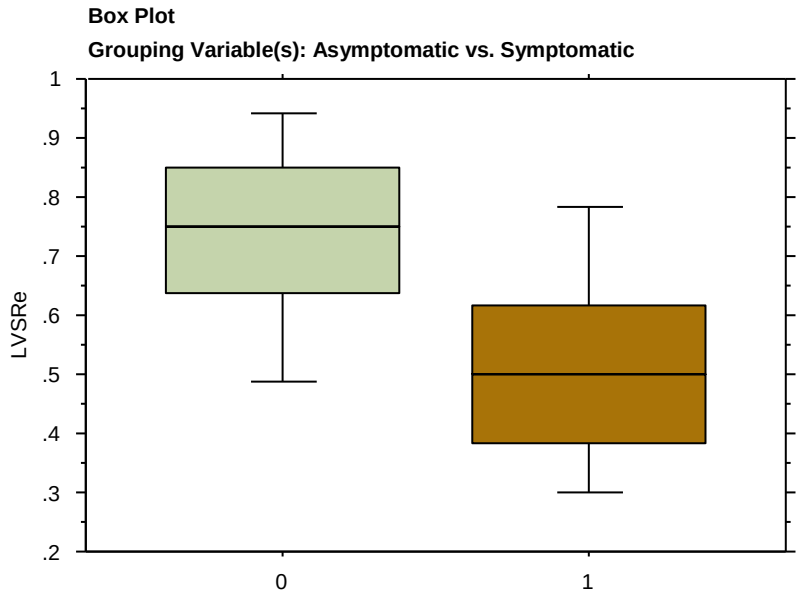

Figure 9 Correlation between LVSRe and symptoms

LVSRe is measured in s^{-1}. Data are expressed as mean ± SD. The grouping variables are defined as follows: asymptomatic =0, symptomatic =1. In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th–75th percentile), and the bars indicate the 10th and 90th percentile of LVSRe.

The comparison of the mean E/LVSRe values of the symptomatic and asymptomatic patients also revealed a significant relation (ANOVA, $p<0.0001$). The mean E/LVSRe was 173.846 (SD ±101.22 and SE 4.90) for the symptomatic and 103.529 (SD ±49.20 and SE 5.83) for the asymptomatic patients. Figure 10 presents the above described data.

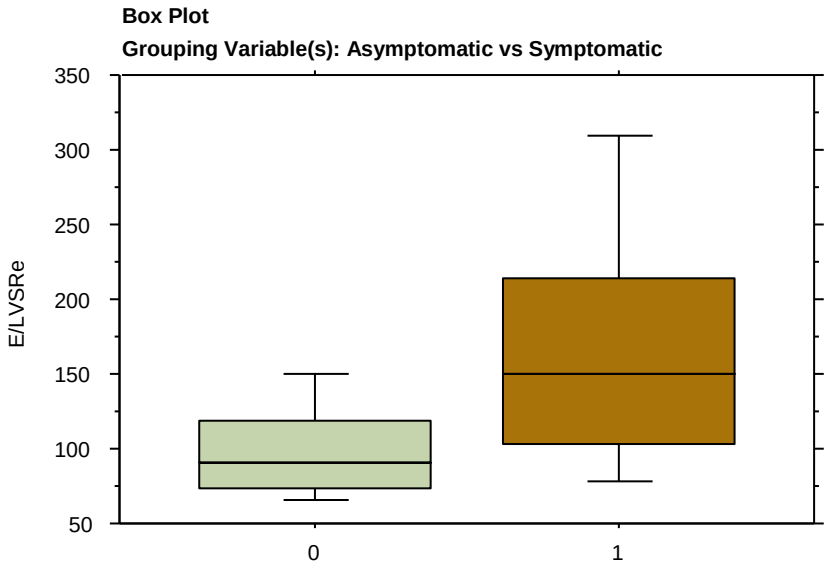

Figure 10 Correlation between E/LVSRe and symptoms

The E/LVSRe ratio is measured as mean ± SD and the grouping variables are defined as follows: asymptomatic =0, symptomatic =1. In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th–75th percentile), and the bars indicate the 10th and 90th percentile of the mitral E/LVSRe ratio.

In the present data set, 426 adults confirmed experiencing symptoms. The mean LVSRe and E/LVSRe values for those patients were 0.514s^{-1} (SD ±0.19, SE=0.01) and 173.846 (SD ±101.22, SE=4.90), respectively. The results of the performed ANOVA analysis suggest that there is a significant correlation between having symptoms and a low LVSRe and high E/LVSRe ratio ($p<0.0001$; Table 5).

Table 5 LVSRe and E/LVSRe mean values according to symptoms

	Asymptomatic (n=71)	**Symptomatic (n=426)**	**P-value**
LVSRe, s^{-1}	0.740 ±0.18	0.51 ±0.19	<0.0001
E/LVSRe	103.5 ±49.2	173.8 ±101.2	<0.0001

LVSRe is measured in s^{-1}. Data are expressed as mean ± SD. P-value is calculated for both parameters.

HF re-hospitalization within 2 years

A positive dependence was also demonstrated when closely inspecting the relevance of LVSRe for the prediction of a HF related re-hospitalization within the following 2 years (ANOVA, p=0.0014). The mean LVSRe of the re-hospitalized cases was 0.495s^{-1} (SD ±0.17, SE 0.01), in contrast to 0.564s^{-1} (SD ±0.21, SE 0.01) for the rest of the study population. Figure 11 visualises these findings.

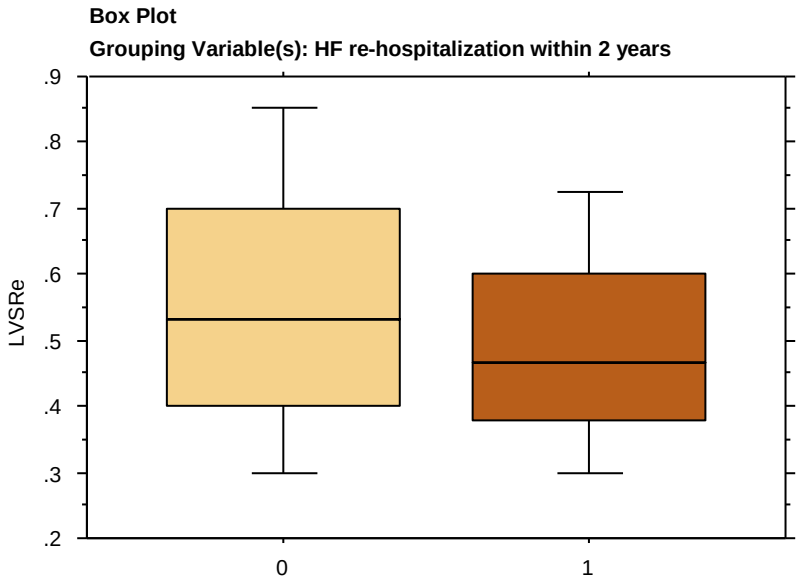

Figure 11 Correlation between LVSRe and re-hospitalization

LVSRe is measured in s^{-1}. Data are expressed as mean ± SD. The grouping variables are defined as follows: no re-hospitalization within 2 years =0, re-hospitalization within 2 years =1. In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th–75th percentile), and the bars indicate the 10th and 90th percentile of LVSRe.

The role of the E/LVSRe ratio for the prediction of an HF related re-hospitalization within the following 2 years was likewise investigated. This association offered another significant result (ANOVA, p=0.0005). The re-hospitalized cases showed a mean E/LVSRe ratio of 190.556 (SD ±109.23, SE 9.81), while the rest of the enrolled participants had a mean E/LVSRe ratio of 154.906 (SD ±93.31, SE 4.83). A box plot was used to visualise this (Figure 12).

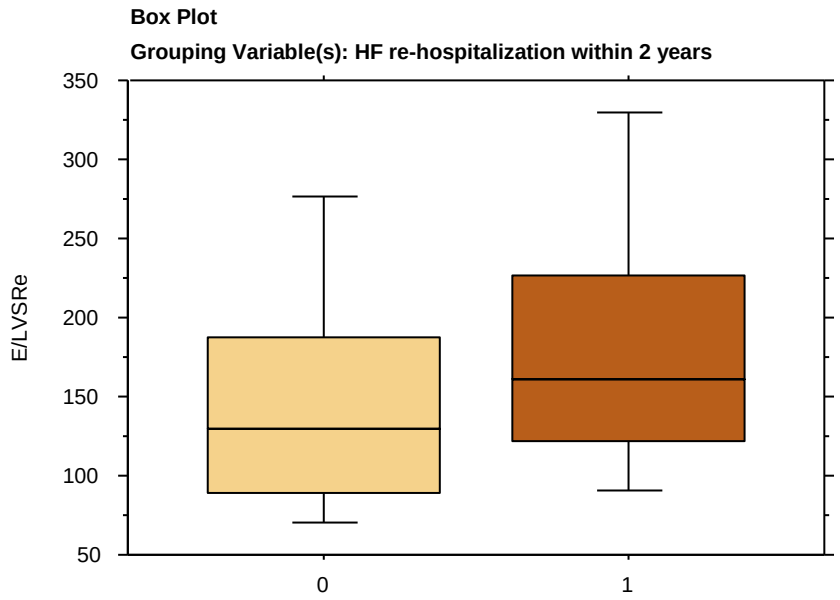

Figure 12 Correlation between E/LVSRe and re-hospitalization

The E/LVSRe ratio is measured as mean ± SD and the grouping variables are defined as follows: no re-hospitalization within 2 years =0, re-hospitalization within 2 years =1. In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th–75th percentile), and the bars indicate the 10th and 90th percentile of the mitral E/LVSRe ratio.

Within 2 years after the first echocardiographic examination, 124 patients were re-hospitalized due to HF. The mean LVSRe and E/LVSRe values of the re-hospitalized group were 0.495s^{-1} (SD ±0.17, SE=0.01) and 190.556 (SD ±109.23, SE=9.81), respectively. The completed ANOVA analysis revealed a significant connection between HF re-hospitalization and both lower LVSRe (p=0.0014; Table 6) and high E/LVSRe (p=0.0005; Table 6).

Table 6 LVSRe and E/LVSRe mean values according to re-hospitalizations

	Non re-hospitalized (n=373)	**Re-hospitalized (n=124)**	**P-value**
LVSRe, s^{-1}	0.56 ±0.21	0.49 ±0.17	0.0014
E/LVSRe	154.9 ±93.3	190.5 ±109.2	0.0005

LVSRe is measured in s^{-1}. Data are expressed as mean ± SD. P-value is calculated for both parameters.

PCWP

The interaction was examined between LVSRe and PCWP, another important echocardiographic parameter. The study population was divided into 4 groups according to the value of their LVSRe. Next, the mean PCWP of each group was calculated. Patients that had LVSRe value ≥1s^{-1} showed a mean PCWP of 11.367mmHg (SD ±2.45 and SE 0.74); those with LVSRe 0.99-0.75s^{-1} had a mean PCWP of 15.881mmHg (SD ±5.44 and SE 0.61). Study subjects assigned to the group with LVSRe values 0.74-0.5s^{-1} presented with mean PCWP of 19.321mmHg (SD ±8.56 and SE 0.61), while for those with LVSRe <0.5s^{-1} the estimated mean PCWP was 23.925mmHg (SD ±9.88 and SE 0.67). Consequently, a significant correlation between a higher PCWP value and the severity of the LVSRe was demonstrated (ANOVA, p<0.0001). Those findings are visualised in Figure 13. The performed inter-group analysis (Fisher's PLSD test) further confirmed the significance of the hypothesis. The following p-values were computed: group 0 with 1 p=0.1069, group 0 with 2 p=0.0033, group 0 with 3 p<0.0001, group 1 with 2 p=0.0031, group 1 with 3 p<0.0001, group 2 with 3 p<0.0001.

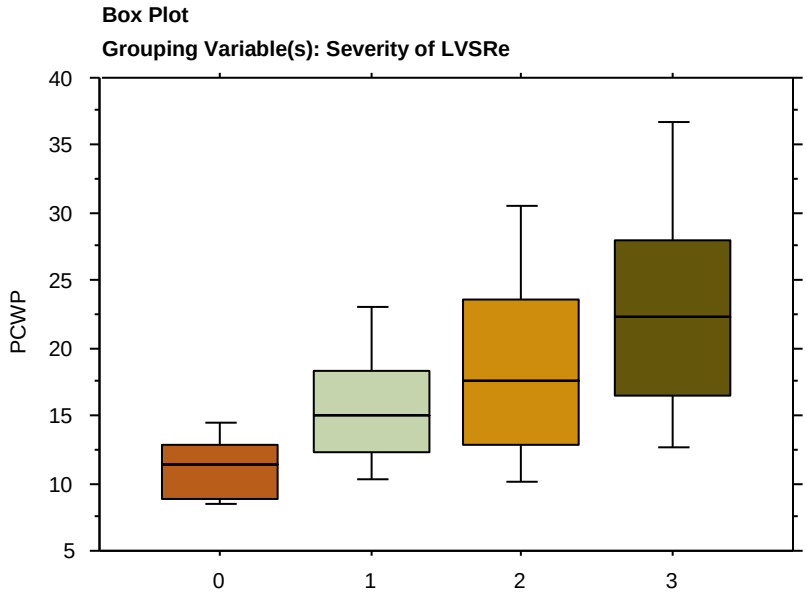

Figure 13 Correlation between LVSRe and PCWP

Association of the estimated pulmonary capillary wedge pressure (PCWP) with the severity of LVSRe. PCWP was estimated in mmHg using the Nagueh formula (i.e., estimated PCWP = 2 + 1.3 × mitral E/lateral e' ratio). Data are expressed as mean ± SD, SE. The grouping variables are defined as follows: group 0 LVSRe ≥1s^{-1}, group 1 LVSRe 0.99-0.75s^{-1}, group 2 LVSRe 0.74-0.5 s^{-1}, and group 3 LVSRe <0.5s^{-1}. In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th–75th percentile), and the bars indicate the 10th and 90th percentile of PCWP.

The interaction between the E/LVSRe ratio and the PCWP value was examined as well. For patients with PCWP ≤12mmHg, the mean mitral E/LVSRe ratio was measured at 97.630, with SD ±40.70 and SE 3.76. Study participants with PCWP 12-15mmHg had a mean mitral E/LVSRe ratio of 135.031 (SD ±83.50 and SE 10.05) and those with PCWP >15mmHg offered a mean mitral E/LVSRe ratio of 195.077 (SD ±102.94 and SE 5.83). Conclusively, a high E/LVSRe corresponded to a high PCWP (ANOVA, p<0.0001), as displayed in Figure 14 below. Additionally, the significance of this result was assessed by performing an inter-group analysis, which confirmed the above-mentioned assumption (Fisher's PLSD test, group 0 with 1 p=0.0061, group 0 with 2 p<0.0001, group 1 with 2 p<0.0001).

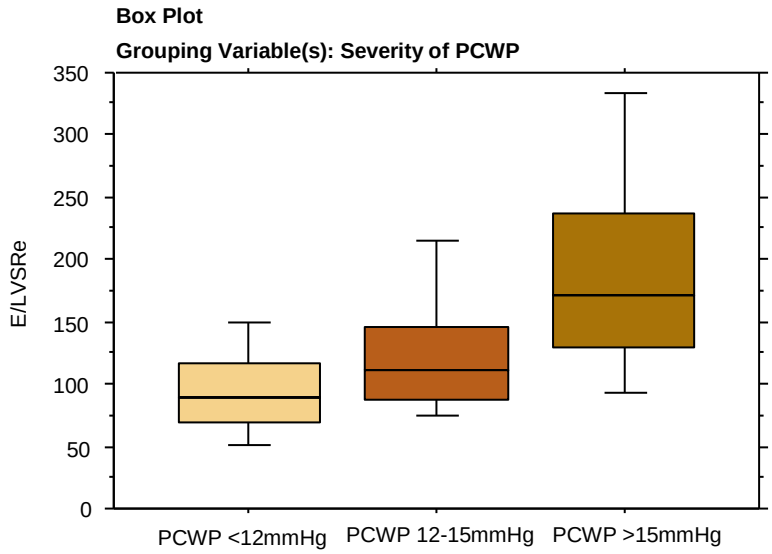

Figure 14 Correlation between E/LVSRe and PCWP

Association of the mitral E/LVSRe ratio with the severity of the estimated pulmonary capillary wedge pressure (PCWP). PCWP was estimated in mmHg using the Nagueh formula (i.e., estimated PCWP = 2 + 1.3 × mitral E/lateral e' ratio). Data are expressed as mean ± SD, SE. The grouping variables are defined as follows: group 0 PCWP <12mmHg, group 1 PCWP 12-15mmHg, and group 2 PCWP >15mmHg. In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th–75th percentile), and the bars indicate the 10th and 90th percentile of the mitral E/LVSRe ratio.

LVEF

The study population was divided into three sections according to the measured LVEF – group 1 with LVEF 49-40%, group 2 with LVEF 39-30% and group 3 with LVEF <30%.

The mean LVSRe value for group 1 was 0.688s^{-1} (SD ±0.19, SE=0.01), for group 2 it was 0.517 s^{-1} (SD ±0.14, SE=0.01) and for group 3 it was 0.360 s^{-1} (SD ±0.12, SE=0.01). The performed ANOVA analysis showed a significant correlation between worsening LVSRe values and lower LVEF ($p<0.0001$). The Fisher's PLSD test further emphasized the significance of the results, when examining the inter-group variances. All three combinations (group 1 with 2, group 1 with 3, and group 2 with 3) delivered p-values <0.0001. Figure 15 represents those results graphically.

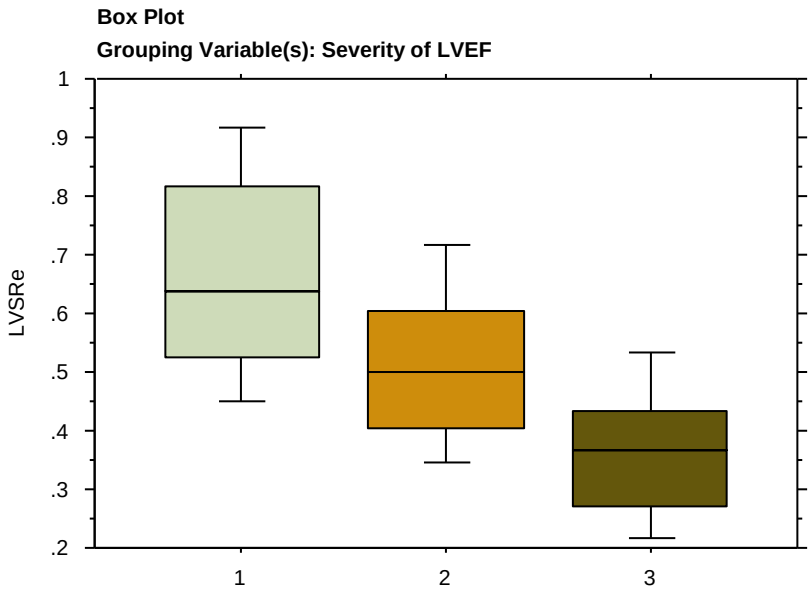

Figure 15 Correlation between LVSRe and LVEF

Association of LVSRe with the severity of LVEF. LVSRe is measured in s^{-1}. Data are expressed as mean ± SD, SE. The grouping variables are defined as follows: group 1 LVEF 49-40%, group 2 LVEF 39-30% and group 3 LVEF <30%. In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th–75th percentile), and the bars indicate the 10th and 90th percentile of LVSRe.

The mean mitral E/LVSRe ratio was also calculated for the different groups. As follows, it was 116.242 (SD ±54.78, SE=3.64) for group 1, 156.992 (SD ±73.82, SE=6.06) for group 2 and 259.376 (SD ±118.29, SE=10.66) for group 3. A high E/LVSRe ratio was significantly associated with worsening LVEF (ANOVA, $p<0.0001$). The inter-group analysis presented a significant interaction as well (Fisher's PLSD test, group 1 with 2, group 1 with 3, and group 2 with 3; $p<0.0001$). Figure 16 displays those findings.

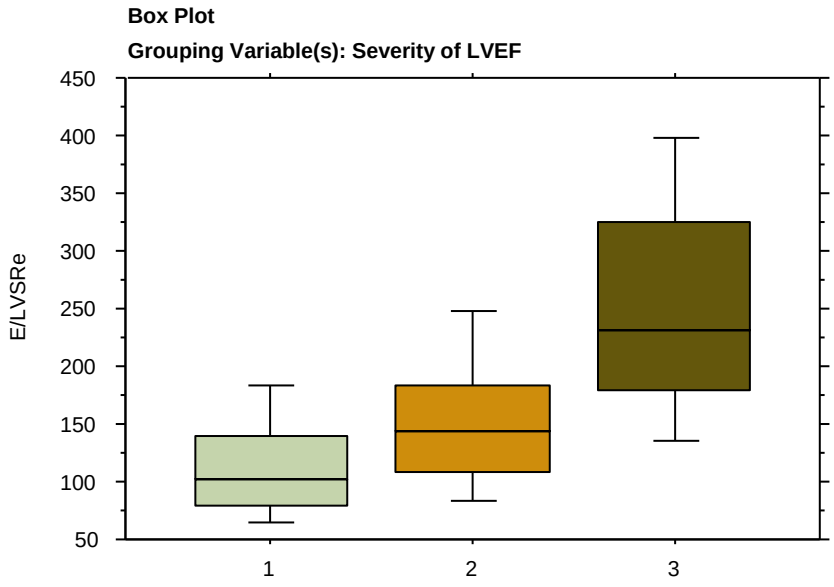

Figure 16 Correlation between E/LVSRe and LVEF

Association of the mitral E/LVSRe ratio with the severity of LVEF. Data are expressed as mean ± SD, SE. The grouping variables are defined as follows: group 1 LVEF 49-40%, group 2 LVEF 39-30%, and group 3 LVEF <30%. In the box plots, the central line represents the median, the length of the box represents the interquartile range (25th–75th percentile), and the bars indicate the 10th and 90th percentile of the mitral E/LVSRe ratio.

In total, 123 test persons appeared with LVEF <30%. Between all participants, their mean LVSRe was the lowest and their mean E/LVSRe ratio was the highest, which proved a significant association between worsening values of both parameters and low LVEF (ANOVA, p<0.0001). All results are summarized in Table 7 below.

Table 7 LVSRe and E/LVSRe mean values according to LVEF values

	LVEF 49-40% (n=226)	**LVEF 39-30% (n=148)**	**LVEF <30% (n=123)**	**P-value**
LVSRe, s^{-1}	0.68 ±0.19	0.51 ±0.14	0.36 ±0.12	<0.0001
E/LVSRe	116.2 ±54.7	156.9 ±73.8	259.3 ±118.2	<0.0001

LVSRe is measured in s^{-1}. Data are expressed as mean ± SD. P-value is calculated for both parameters.

Prevalence rates

The distribution of the study data was closely examined. Patients were split into three groups based on their LVSRe values – >0.75s^{-1}, 0.74-0.5s^{-1} and <0.5s^{-1}. Subsequently, the prevalence of specific factors such as symptomatic status, worse NYHA functional class, elevated PCWP and re-hospitalization within 2 years due to HF as well as mean PCWP and LVEF values were calculated. The corresponding p-values for each section were registered and are presented in Table 8. A significant association between LVSRe grouping and the tested variables was recorded, proving that a worsening state for any of them corresponds to a lower LVSRe (ANOVA, p<0.0001).

Subsequently, a more specific observation of the correlations was made. LVSRe values of the study population were allocated to four sections and filtered. Patients with the following three LVSRe ranges (<0.75s^{-1}, 0.5-0.74s^{-1} and <0.5s^{-1}) were each compared to the ones with LVSRe >0.75s^{-1}. P-values were then examined for the above-mentioned factors. Significant results were found for all but one variable (HF re-hospitalization in the LVSRe 0.5-0.74s^{-1} vs. >0.75s^{-1} section), which confirmed that even a closer and narrower distinction of the LVSRe values correlates to the tested factors (ANOVA, p<0.0001).

Table 8 Prevalence of various variables according to the severity of LVSRe

	LVSRe >0.75s^{-1} (n=91)	**LVSRe 0.74-0.5s^{-1} (n=192)**	**LVSRe <0.5s^{-1} (n=214)**	**P-value**
Dyspnea	59.3% (54)	85.9% (165)	96.7% (207)	<0.0001
NYHA III-IV	10.9% (10)	25.5% (49)	62.6% (134)	<0.0001
Re-hospitalized	13.1% (12)	22.9% (44)	31.7% (68)	0.0019
PCWP, mmHg	15.335 ±5.37	19.321 ±8.56	23.925 ±9.88	<0.0001
PCWP >12mmHg	56.1% (51)	71.8% (138)	89.2% (191)	<0.0001
PCWP >15mmHg	40.6% (37)	57.8% (111)	76.1% (163)	<0.0001

Data are expressed as mean ± SD or percentages. LVSRe is measured in s^{-1}. The number of patients (n) is in brackets. P-value is calculated for all variables.

A similar procedure was completed for the E/LVSRe ratio. This time, the study population was divided in two, with normal values when <71.5 and abnormal ones when >71.5. Prevalence and p-values were calculated and are arranged in Table 9. All results were significant, associating a worsening in the tested variables with a higher E/LVSRe ratio.

Table 9 Prevalence of various variables according to the severity of E/LVSRe

	E/LVSRe <71.5 (n=45)	**E/LVSRe >71.5 (n=452)**	**P-value**
Dyspnea	66.6% (30)	87.6% (396)	0.0001
NYHA III-IV	4.4% (2)	42.2% (191)	<0.0001
Re-hospitalized	8.8% (4)	26.5% (120)	0.009
PCWP, mmHg	11.7 ±3.4	21.4 ±9.2	<0.0001
PCWP >12mmHg	24.4% (11)	81.6% (369)	<0.0001
PCWP >15mmHg	13.3% (6)	67.4% (305)	<0.0001

Data are expressed as mean ± SD or percentages. The number of patients (n) is in brackets. P-value is calculated for all variables.

Another observation of the distribution of the patients' values was made. Table 10 shows the rates of abnormal LVSRe, E/LVSRe and PCWP according to the LVEF. When taking a closer look at the group of participants with LVEF <30%, 100% of them presented with abnormal LVSRe values, 99.1% with abnormal E/LVSRe values, 95.1% with PCWP >12mmHg and 84.5% with PCWP >15mmHg. However, as our population consists of people with mrEF and rEF, high rates of abnormal LVSRe and E/LVSRe were discovered in all LVEF groups. Nevertheless, the prevalence of abnormal values for LVSRe, E/LVSRe and PCWP was the highest in the group with the lowest LVEF. Additionally, 97.7% of all patients presented with abnormal LVSRe values, 90.9% with abnormal E/LVSRe ratio, 76.4% with PCWP >12mmHg and 62.5% with PCWP >15mmHg.

Table 10 Prevalence of various variables according to the severity of LVEF

	LVEF 49-40% (n=226)	LVEF 39-30% (n=148)	LVEF <30% (n=123)	All (n=497)
Abnormal LVSRe (<1s^{-1})	95.1% (215)	100% (148)	100% (123)	97.7% (486)
Abnormal E/LVSRe (>71.5)	83.1% (188)	95.9% (142)	99.1% (122)	90.9% (452)

Data are expressed as percentages. The number of patients (n) is in brackets.

Usefulness of LVSRe

Risk prediction

The realised logistic regression analysis revealed the probabilities of having a NYHA functional class III-IV or getting re-hospitalized due to HF within 2 years. An odds ratio (OR) was calculated for several variables as unadjusted and adjusted by age and gender. All results are listed in Tables 11 and 12.

The following ORs for NYHA III-IV and HF re-hospitalization were computed when comparing participants with LVSRe values <0.75s^{-1} to those with >0.75s^{-1}: for the unadjusted analysis 6.647 (95% CI 3.34–13.19) and 2.508 (95% CI 1.31–4.78), together with 6.362 (95% CI 3.17–12.73) and 2.455 (95% CI 1.27–4.74) for the adjusted one, respectively. Test persons with LVSRe <0.5s^{-1} compared to ones with >0.75s^{-1} showed corresponding unadjusted ORs for NYHA III-IV and HF re-hospitalization of 13.567 (95% CI 6.65–27.67) and 3.066 (95% CI 1.56–6.00), along with adjusted ORs of 12.696 (95% CI 6.13–26.27) and 3.046 (95% CI 1.51–6.11), respectively. Patients with E/LVSRe values >71.5 presented unadjusted OR of 15.734 (95% CI 3.765–65.755) and adjusted OR of 14.771 (95% CI 3.52–61.88) for NYHA III-IV, as well as unadjusted OR of 3.705 (95% CI 1.299–10.564) and adjusted OR of 3.614 (95% CI 1.26–10.36) for HF re-hospitalization. The highest probabilities for both NYHA III-IV and HF re-hospitalization were measured for the variables LVSRe <0.5s^{-1} vs. >0.75s^{-1} and E/LVSRe >71.5. This suggests a strong correlation between low LVSRe or high E/LVSRe and patients developing NYHA functional class III-IV and getting re-hospitalized in the next 2 years due to HF (adjusted logistic regression, p<0.0001 and p=0.002 for LVSRe, p<0.0001 and p=0.017 for E/LVSRe).

Table 11 Risk prediction for NYHA III-IV

	Risk of NYHA III-IV					
	Unadjusted			Adjusted by age and gender		
	OR	95% CI	P-value	OR	95% CI	P-value
LVSRe <0.75s^{-1} vs. >0.75s^{-1}	6.6	3.34–13.19	<0.0001	6.362	3.17–12.73	<0.0001
LVSRe <0.5s^{-1} vs. >0.75s^{-1}	13.5	6.65–27.67	<0.0001	12.696	6.13–26.27	<0.0001
E/LVSRe ratio >71.5	15.7	3.76–65.75	0.0002	14.771	3.52–61.88	<0.0001
Septal e′ velocity <7cm/s	3.5	1.60–7.65	0.0017	3.156	1.42–7.01	0.005
Lateral e′ velocity <10cm/s	4.7	2.27–9.77	<0.0001	4.461	2.14–9.27	<0.0001
Mitral E/e′ ratio >14	3.0	2.11–4.48	<0.0001	2.966	2.02–4.33	<0.0001
LAVI >34mL/m^2	2.3	1.63–3.44	<0.0001	2.368	1.62–3.45	<0.0001
TR >2.8m/s	3.5	2.33–5.49	<0.0001	3.483	2.25–5.38	<0.0001

Adjusted by age and gender indicates adjusted by > 65 years and women. OR – Odds ratio; CI – Confidence interval. P-value is calculated for all variables.

Table 12 Risk prediction for re-hospitalization due to HF

	Risk of re-hospitalization due to heart failure within 2 years					
	Unadjusted			Adjusted by age and gender		
	OR	95% CI	P-value	OR	95% CI	P-value
LVSRe <0.75s^{-1} vs. >0.75s^{-1}	2.5	1.31–4.78	0.0052	2.455	1.27–4.74	0.007
LVSRe <0.5s^{-1} vs. >0.75s^{-1}	3.0	1.56–6.00	0.0011	3.046	1.51–6.11	0.002
E/LVSRe ratio >71.5	3.7	1.29–10.56	0.0143	3.614	1.26–10.36	0.017
Septal e′ velocity <7cm/s	1.2	0.62–2.67	0.489	1.180	0.55–2.51	0.667
Lateral e′ velocity <10cm/s	1.2	0.67–2.38	0.452	1.236	0.65–2.33	0.514
Mitral E/e′ ratio >14	2.1	1.39–3.21	0.0004	2.148	1.41–3.28	<0.0001
LAVI >34mL/m^2	1.7	1.13–2.59	0.0107	1.649	1.08–2.51	0.019
TR >2.8m/s	1.7	1.12–2.78	0.0129	1.699	1.07–2.68	0.024

Adjusted by age and gender indicates adjusted by > 65 years and women. OR – Odds ratio; CI – Confidence interval. P-value is calculated for all variables.

Usefulness of adding LVSRe as a LVDD diagnostic parameter

A Chi-square test of independence was performed to examine the potential usefulness of LVSRe when included as a parameter for the evaluation of LVDD. The relation between the two variables was significant: χ^2=51.5 (1 degree of freedom, N=497), p<0.00001. When adding LVSRe as a LVDD early diagnostic parameter, the likeliness of detecting LVDD was raised from 41.1% to 63.7% (Figure 17).

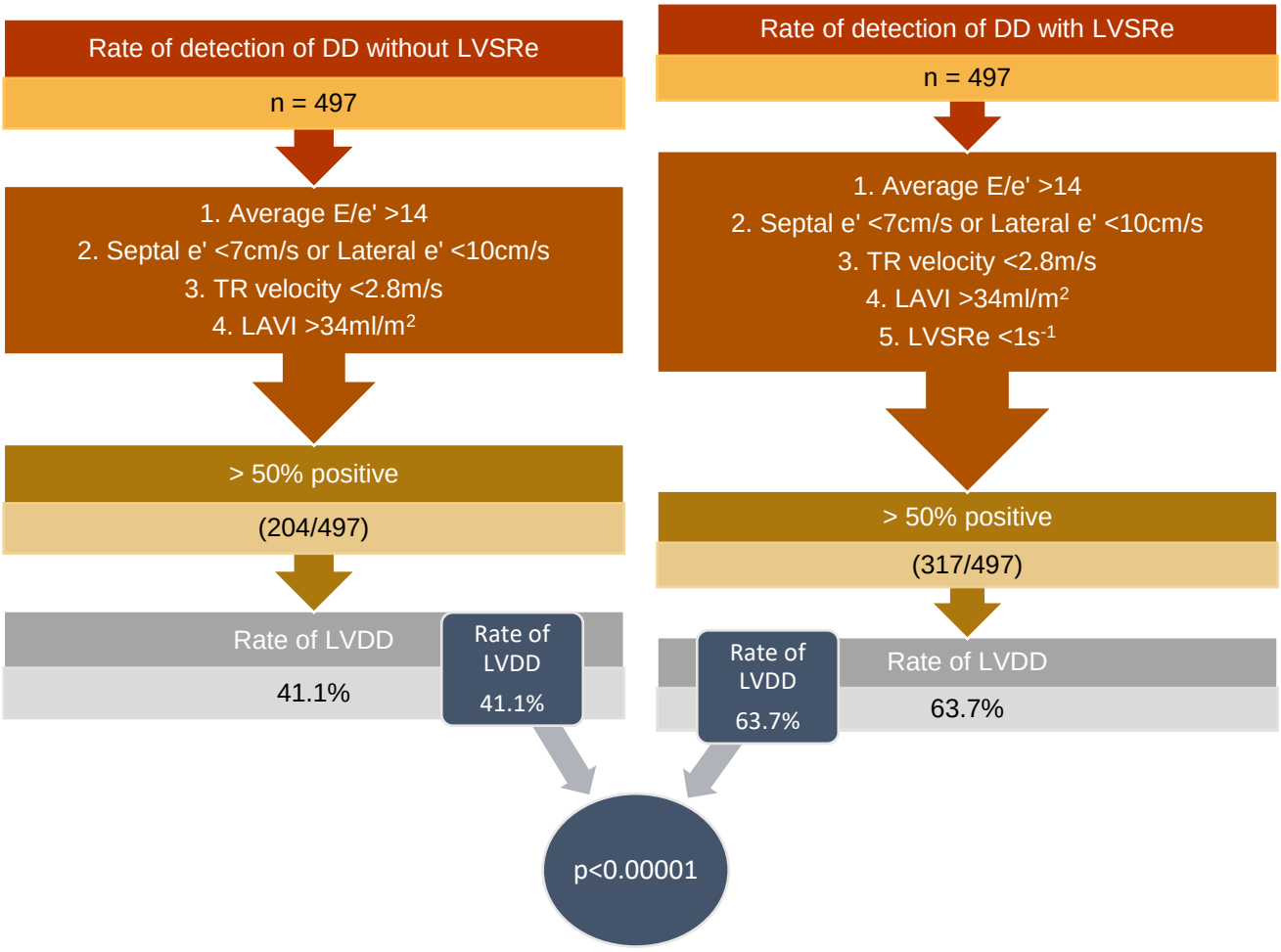

Figure 17 Usefulness of LVSRe as a LVDD diagnostic parameter

The figure displays the potential usefulness of adding LVSRe to the current evaluation of LV diastolic dysfunction. When adding LVSRe the rate of LVDD detection increases significantly (p<0.00001).

Predictive performance

The predictive importance of LVSRe and E/LVSRe for the development of LVDD was evaluated and demonstrated by ROC curves (Figures 18 and 19). The results suggest high overall accuracy for both parameters. The calculated areas under the ROC curve (AUC) were 0.924 (95% CI 0.850–0.997) for LVSRe and 0.864 (95% CI 0.790–0.937) for E/LVSRe. The following cutoffs were chosen: LVSRe=0.76s^{-1} (sensitivity 85%, specificity 90.1%) and E/LVSRe=88.7 (sensitivity 80.5%, specificity 72.7%).

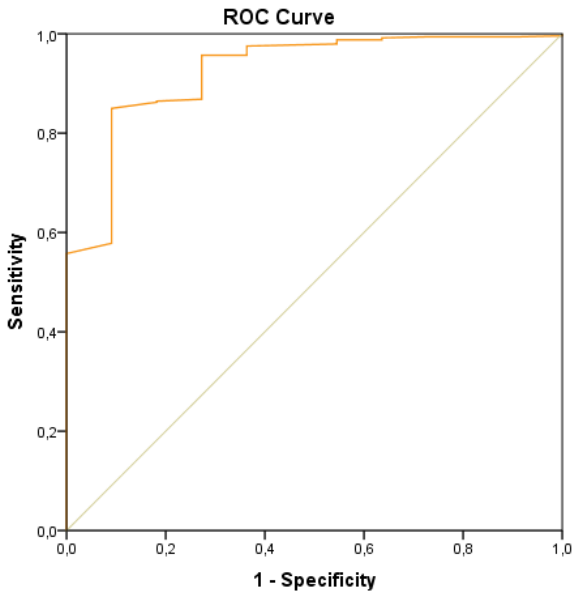

Figure 18 Predictive power of LVSRe for the development of LVDD

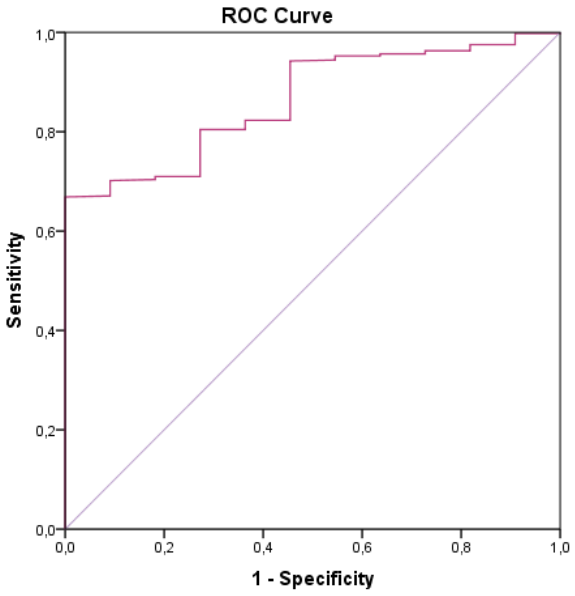

Figure 19 Predictive power of E/LVSRe for the development of LVDD

The same examination model was performed for further and more specific arguments.

The performance of E/LVSRe in the detection of LVDD grades II and III was tested and was classified as holding high predictive accuracy. The computed AUC was 0.830 (95% CI 0.795–0.865) and the following cutoff was selected: E/LVSRe=133, corresponding to 82% sensitivity and 65% specificity (Figure 20).

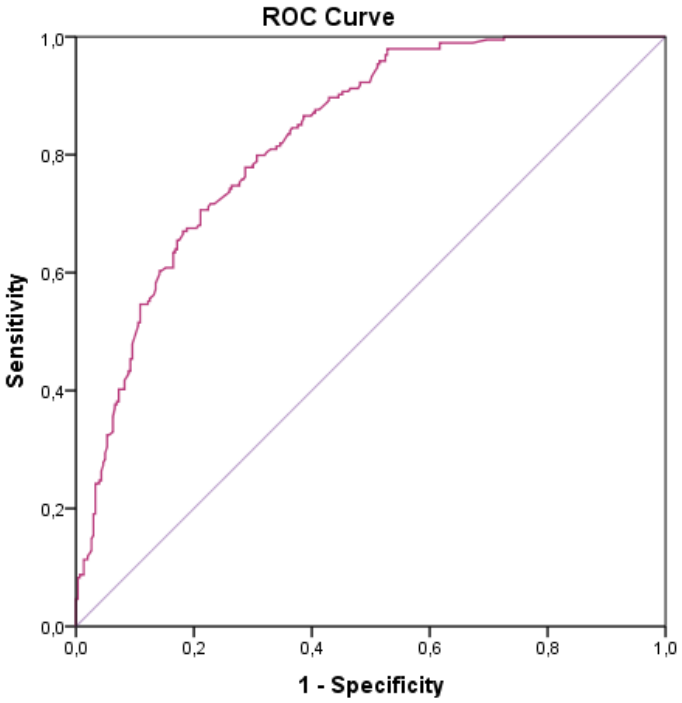

Figure 20 Predictive power of E/LVSRe in the detection of LVDD grades II and III

Subsequently, the predictive power of LVSRe for the symptomatic status of the study participants was investigated. The AUC was 0.811 (95% CI 0.757–0.865), which corresponded to a high prognostic value. The cutoff was set at $0.7s^{-1}$ (sensitivity 84.7%, specificity 67.6%; Figure 21).

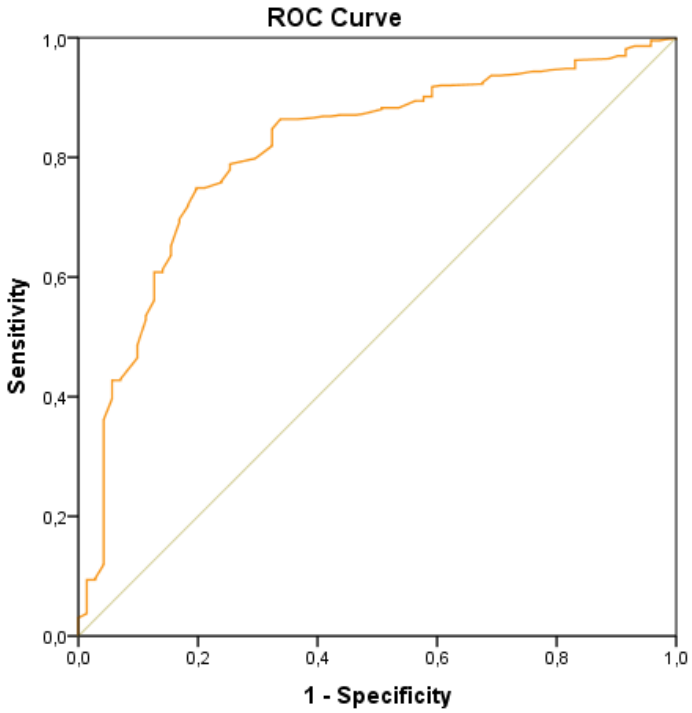

Figure 21 Predictive power of LVSRe on the symptomatic status

The parameter E/LVSRe offered a highly accurate performance as an indicator of elevated LV filling pressure. An AUC of 0.841 (95% CI 0.807–0.876) was estimated. The cutoff point for E/LVSRe ratio was placed at 128.8 (sensitivity 84.8%, specificity 70.4%; Figure 22).

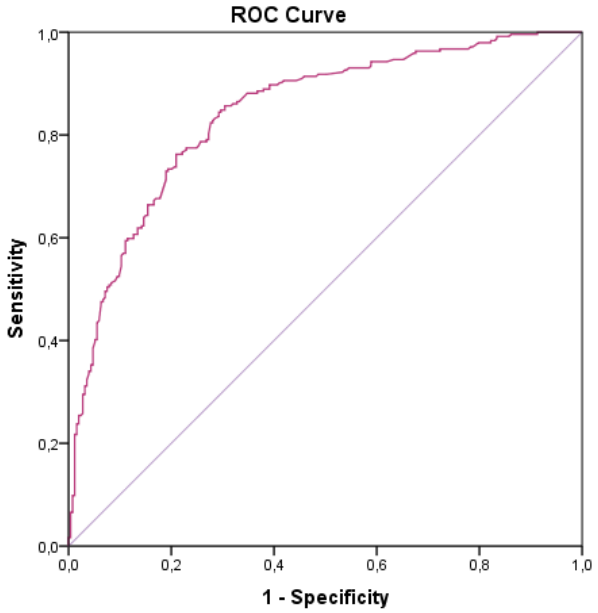

Figure 22 Predictive power of E/LVSRe for the evaluation of elevated LV filling pressure

Lastly, the prognostic value of the E/LVSRe ratio on patients with PCWP >15mmHg was examined. The resulting AUC was 0.808 (95% CI 0.769–0.847) and the determined cutoff point was 117.3 (sensitivity 80.1%, specificity 67.7%; Figure 23).

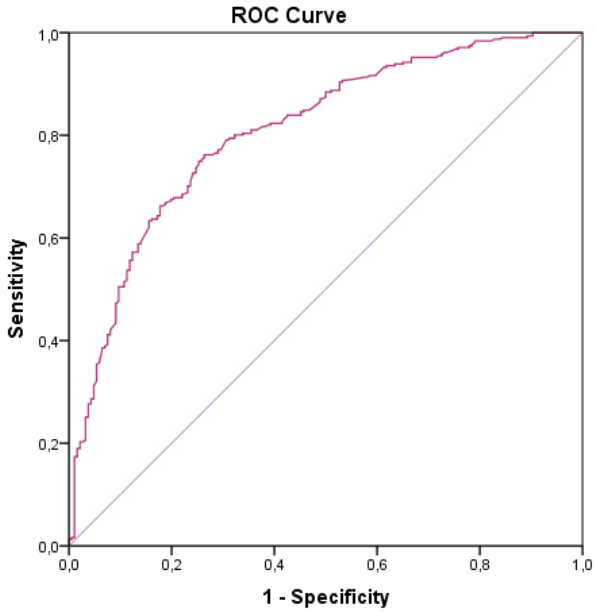

Figure 23 Predictive power of E/LVSRe on patients with PCWP >15mmHg

An overview of the recorded results was made and is presented in Table 13 below.

Table 13 Overview of the predictive performance and the chosen cutoffs

Predictor variable	Outcome parameter	AUC [95% CI]	Cutoff point	Sensitivity, %	Specificity, %
LVSRe	**LVDD**	0.924 [0.850–0.997]	0.76s^{-1}	85%	90.1%
E/LVSRe	**LVDD**	0.864 [0.790–0.937]	88.7	80.5%	72.7%
E/LVSRe	**LVDD grade II and III**	0.830 [0.795–0.865]	133	82%	65%
LVSRe	**Dyspnea**	0.811 [0.757–0.865]	0.70s^{-1}	84.7%	67.6%
E/LVSRe	**Elevated LV filling pressure**	0.841 [0.807–0.876]	128.8	84.8%	70.4%
E/LVSRe	**PCWP >15mmHg**	0.808 [0.769–0.847]	117.3	80.1%	67.7%

Results on the predictive importance of LVSRe and E/LVSRe for the development of LVDD are displayed above. For each couple of predictor and outcome parameter, the selected cutoff point with its according sensitivity and specificity was listed. AUC – Calculated areas under the ROC curve.

Discussion

Conventional echocardiographic LV measurements such as septal and lateral e′ velocity, TR velocity or LAVI are not exact enough to be applied as independent and specific parameters for the diagnosis of HF due to several limitations (e.g. angle dependence and inaccuracy). (6) The indicated restrictions assert the need for further investigation on, and development of the diagnostic echocardiographic tools for the detection of LV diastolic dysfunction. Previous publications raised awareness of a new echocardiographic parameter LVSRe, suggesting its importance for the measurement of the LV diastolic function. (8; 9; 32; 33) Nonetheless, the potential clinical relevance and usefulness of LVSRe as an independent and global LV diastolic parameter for the evaluation of LVDD remains unexplored.

This thesis offers the first insights on the possible benefits of using LVSRe by investigating the parameter's significance and efficacy. The findings from this large cohort of patients highlight the potential diagnostic and clinical importance of this new parameter for the detection and prediction of the outcomes of LV diastolic dysfunction (LVDD) in patients with LVEF <50%.

Relevance of LVSRe and E/LVSRe ratio

While it is assumed that LVSRe and E/LVSRe could facilitate the diagnosis of LVDD, the particular clinical relevance of the examined parameters is still not established. A strong correlation between a worsening LVSRe and a higher NYHA functional class, lower LVEF, higher PCWP, more symptomatic patients and more frequent HF-related re-hospitalization within the next 2 years was found in the present research. Furthermore, the prevalence of the above-mentioned specific factors increased with lower LVSRe values. Previous studies in patients with HF and cardiovascular diseases underline the correlation of LVSRe with patients' symptoms and outcomes. (27; 34; 35) Goebel et al. verified that LVSRe was an independent predictor of combined outcome (death, heart transplantation, HF re-hospitalization and absence of improvement in EF) in comparison with LVEF or LV volume (OR 0.44 (95% CI 0.27-0.70), p=0.001, AUC 0.91). (34) They further suggested that LVSRe could be a prognostic indicator of the response to HF therapy and could therefore contribute importantly to the risk stratification. (34) At the same time LVSRe and E/LVSRe correlated significantly with increased mortality risk in

cardiac amyloidosis patients with HFpEF (HR 7.30, (95% CI 2.08-25.65), p=0.002 and HR 2.98, (95% CI 1.54-5.79), p=0.001, respectively). (27) On top of that, LVSRe values $<0.85 s^{-1}$ were associated with a 4-fold increased mortality. (27) Furthermore, it was observed that HFpEF patients with LV mechanical dyssynchrony present higher LV filling pressures and worse NYHA functional class. (35) Consequently, Morris et al. suggested that a restoration of asynchronous LV contractions could improve the systolic and diastolic dysfunction and the symptomatology of patients. (35) Additionally, LVSRe was proven to be more specific (90.1%) in the detection of LVDD than some conventional diastolic parameters such as LAVI (62%). (36)

A similar investigation was carried out with the E/LVSRe ratio. Again, a worsening in the above-mentioned tested variables correlated with a higher E/LVSRe ratio. Various research groups demonstrated a strong connection between E/LVSRe and invasive measures of LV filling pressure such as PCWP and LVEDP. A recently published systematic review and meta-analysis summarizes E/LVSRe's clinical relevance. (37) Wang et al., Meluzin et al. and Kimura et al. investigated the relationship between E/LVSRe and PCWP and found a significant correlation between the two parameters, which outperformed the results for E/e' (Cohen’s d=3.90 95% CI [2.38–6.39], p <0.001, I^2=0%). (8; 10; 37; 38) Moreover, on the basis of their findings, Kimura et al. suggested that E/LVSRe is the most accurate non-invasive predictor of elevated LV filling pressure. (10) When associating E/LVSRe and LVEDP, another significant relationship was documented (Cohen’s d=5.30 95% CI [2.83–9.96], p<0.001, I^2=0%). (37) Chen et al. found that E/LVSRe correlates strongly with LVEDP in hypertrophic obstructive cardiomyopathy patients and could therefore be a good predictor of elevated LVEDP. (32) Equivalently, patients with coronary artery disease and LVEF >55% demonstrated a significant association between E/LVSRe and LVEDP. (33) What is more, Dokainish et al. verified that E/LVSRe was a superior predictor of LVEDP than E/e' and could better determine the LV filling pressure in HFpEF patients. (9) Besides this, similar results were obtained by Nadorlik and colleagues when examining pediatric biventricular congenital heart patients undergoing cardiac catheterization. (39) The specificity of E/LVSRe as a predictor of the development of LVDD was estimated at 72.7%, also higher than the calculated value for LAVI. (36)

All of the above-mentioned findings highlight the importance of LVSRe and E/LVSRe for the diagnosis of LVDD.

Risk prediction

In a comparison between several variables, the risk for NYHA III-IV and HF re-hospitalization within the next 2 years was calculated. Abnormal LVSRe and E/LVSRe demonstrated a convincingly higher predictive value for developing either of the above-mentioned conditions in comparison to the current echocardiographic parameters. The probability for patients with low LVSRe and high E/LVSRe of having a NYHA functional class III-IV or getting re-hospitalized due to HF within 2 years proved to be significant (adjusted logistic regression, $p<0.0001$ and $p=0.002$ for LVSRe, $p<0.0001$ and $p=0.017$ for E/LVSRe, respectively).

Furthermore, patients with LVSRe $<0.75s^{-1}$ presented with an adjusted by age and gender OR of 6.362 (95% CI 3.17–12.73) for NYHA III-IV, as opposed to OR values of between 2.368 (95% CI 1.62–3.45) and 4.461 (95% CI 2.14–9.27) for the resting conventional echocardiographic parameters (Table 11). Similar results were discovered for the risk of re-hospitalization due to HF within 2 years: adjusted OR of 2.455 (95% CI 1.27–4.74) for LVSRe $<0.75s^{-1}$, and OR values between 1.18 (95% CI 0.55–2.51) and 2.148 (95% CI 1.41–3.28) for the remaining variables (Table 12). The same tendency was also maintained for LVSRe $<0.5s^{-1}$ and E/LVSRe. Finally, patients with LVSRe $<0.5s^{-1}$ are associated with a bigger risk of having a NYHA functional class III-IV or getting re-hospitalized due to HF within 2 years than those with higher LVSRe values (adjusted OR of 12.696 (95% CI 6.13–26.27) and 3.046 (95% CI 1.51–6.11) vs. adjusted OR of 6.362 (95% CI 3.17–12.73) and 2.455 (95% CI 1.27–4.74), respectively). This asserts even more strongly the prognostic value of the examined parameters and is in concordance with previous scientific work.

The systematic review and meta-analysis by Lassen et al. validated that E/LVSRe remains a significant diagnostic tool of adverse outcomes (overall estimated hazard ratio HR 1.58, (95% CI 1.28–1.96), $p<0.001$, per 1m increase). (37) Another scientific project demonstrated E/LVSRe's statistically relevant prognostic value for HF, acute myocardial infarction (AMI) and cardiovascular death in a large cohort in the general population (HR 1.08, (95% CI 1.02–1.13), $p=0.003$, per 0.1m increase). (40) Furthermore, E/LVSRe was found to be a better predictor of composite outcomes such as mortality and HF admissions in patients with AMI than E/e' ($p<0.001$). (28) Along with that, E/LVSRe was indicated to be a reliable prognostic marker for all-cause mortality and heart transplantation in HFrEF patients. (25) Identical results were found for patients with AF in

terms of cardiac mortality and HF hospitalizations or decline in the renal function (eGFR decrease ≥25%). (41; 42) Notably, a deterioration of LVSRe and E/LVSRe was observed in type-2 diabetes mellitus patients who developed new-onset AF. (43) Finally, the survival of amyloidosis patients with cardiac involvement and HFpEF was significantly correlated to LVSRe and E/LVSRe, which were the most significant predictors of the outcome (HR 7.30 (95% CI 2.08–25.65), p=0.002 and HR 2.98 (95% CI 1.54–5.79), p=0.001, respectively). (27) Additionally, the predictive performance of both LVSRe and E/LVSRe for the development of LVDD was evaluated by ROC curves and estimated as highly accurate (Figures 18-20). The following cutoffs were set: $0.75s^{-1}$ for LVSRe and 88.7 for E/LVSRe (Table 13).

Usefulness of LVSRe

Along with examining the possible clinical relevance of LVSRe, the usefulness of adding this new parameter to the current LVDD echocardiographic evaluation was analysed. It was demonstrated that LVSRe can distinguish high rates of diastolic alterations significantly better than the present indirect echocardiographic LV parameters.

Beyond that, when including LVSRe as a LVDD early diagnostic parameter, the LVDD detection rate increased from 41.1% to 63.7%.

All these revelations are congruent with previous studies which indicated that LVSRe could be a promising echocardiographic parameter of LV diastolic function. (8; 9; 32; 33) Conclusively, in conformity with the aforementioned discoveries, this thesis suggests that LVSRe could revolutionize the current detection of LVDD in patients with reduced and mid-range LVEF and should be therefore added to the existing evaluation as a LVDD diagnostic parameter.

Limitations

Regardless of the considerable potential of LVSRe and the significant results that the present study offers, there are some limitations that should be considered.

First of all, the assessment of LVSRe is a method with which doctors are less familiar as it is not part of the standard echocardiographic measurements, and it requires an offline analysis. Moreover, some studies have affirmed that LV longitudinal systolic strain could vary among different ultrasound software packages. (44; 45; 46) Therefore, and as long as there is no verified data displaying a feasibility and offering a variable to calibrate between the single software packages, the estimated cutoffs and assessed measurements in this project should be considered in relation to the software package used. The mentioned inconvenience is intended to provoke and encourage more detailed scientific investigation on the topic.

Additionally, although the inclusion criteria for the research project was kept specific, yet as broad as required for the study population to be considered representative, the potential causal role of alterations of LVSRe and E/LVSRe with worse functional class, symptoms, and hospitalization for HF should be considered merely as an association rather than a direct causal effect, since the present study performed the outcomes analysis retrospectively by analysing digital medical records rather than performing an individualized follow-up of each patient in an outpatient clinic or clinical research unit.

Conclusions

The clinical usefulness of non-angle dependent and global left ventricular (LV) diastolic parameters such as left ventricular early diastolic strain rate (LVSRe) or early mitral inflow velocity to early diastolic strain rate (E/LVSRe) is increasingly gaining recognition in the detection and prediction of the outcomes of LV diastolic dysfunction (LVDD). Nevertheless, these LV diastolic strain parameters are not yet completely established as diagnostic markers for LVDD in patients with reduced LVEF. Hence, the aim of the present study was to analyse the potential usefulness and clinical relevance of LVSRe and E/LVSRe in patients with reduced left ventricular ejection fraction (LVEF).

In the present study, analysing a large cohort of adult patients with LVEF <50%, alterations in LVSRe and E/LVSRe were significantly associated with elevated LV filling pressures (as estimated by pulmonary capillary wedge pressure [PCWP]). In line with these findings, alterations in LVSRe and E/LVSRe were significantly linked to worse symptomatic status and heart failure (HF) hospitalization within 2 years. In effect, patients with LVSRe values $<0.5s^{-1}$ or E/LVSRe >71.5 had the highest risk for HF hospitalization within 2 years, even after adjusting by age and gender. Additionally, when adding LVSRe as a LV diastolic parameter, this approach led to a significant higher rate of detection of LVDD.

Therefore, the findings of this study suggest that new diastolic parameters such as LVSRe and E/LVSRe could have significant usefulness and clinical relevance in patients with reduced LVEF.

Conflicts of interest

None declared.

Funding Sources

None declared.

References

1. *Heart failure: preventing disease and death worldwide.* Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H, Rastogi V, Rohde LE, Samal UC, Shimokawa H, Siswanto BB, Sliwa K, Filippatos G. 2014, ESC.

2. *Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC), Developed with the special contribution of theHFA.* Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, vd Meer P. s.l. : Eur Heart J, 2016.

3. *Epidemiology, aetiology, and prognosis of heart failure.* McMurray John J, Stewart Simon. 5, s.l. : Heart, 2000, Vol. 83.

4. Aetiology and Pathophysiology of Heart Failure. *www.nursinganswers.net.* [Online] November 2018. [Cited: 22 March 2021.] https://nursinganswers.net/essays/aetiology-pathophysiology-heart-1535.php?vref=1.

5. *Diastolic heart failure: a concise review.* Aziz F, Tk LA, Enweluzo C, Dutta S, Zaeem M. 5, s.l. : J Clin Med Res, 2013, Vol. 5.

6. *Ratio of Transmitral Early Filling Velocity to Early Diastolic Strain Rate Predicts All-Cause Mortality in Heart Failure with Reduced Ejection Fraction.* Lassen MH, Sengeløv M, Qasim A, Jørgensen PG, Bruun NE, Olsen FJ, Fritz-Hansen T, Gislason G, Biering-Sørensen T. s.l. : J Card Fail, 2019.

7. *Lower limit of normality and clinical relevance of left ventricular early diastolic strain rate for the detection of left ventricular diastolic dysfunction.* Morris DA, Takeuchi M, Nakatani S, Otsuji Y, Belyavskiy E, Aravind Kumar R, Frydas A, Kropf M, Kraft R, Marquez E, Osmanoglou E, Krisper M, Köhncke C, Boldt LH, Haverkamp W, Tschöpe C, Edelmann F, Pieske B, Pieske-Kraigher E. s.l. : Eur Heart J Cardiovasc Imaging, 2018.

8. *Global diastolic strain rate for the assessment of left ventricular relaxation and filling pressures.* Wang J, Khoury DS, Thohan V, Torre-Amione G, Nagueh SF. s.l. : Circulation, 2007, Vol. 115.

9. *Usefulness of new diastolic strain and strain rate indexes for the estimation of left ventricular filling pressure.* Dokainish H, Sengupta R, Pillai M, Bobek J, Lakkis N. s.l. : Am J Cardiol , 2008, Vol. 101.

10. *Speckle tracking global strain rate E/E' predicts LV filling pressure more accurately than traditional tissue Doppler E/E'.* Kimura K, Takenaka K, Ebihara A, Okano T, Uno K, Fukuda N, Ando J, Fujita H, Morita H, Yatomi Y, Nagai R. 4, s.l. : Echocardiography, Apr 2012, Vol. 29.

11. *Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.* Nagueh SF, Smiseth OA, Appleton CP,

Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD. s.l. : Eur Heart J Cardiovasc Imaging, 2016.

12. *Index-beat assessment of left ventricular systolic and diastolic function during atrial fibrillation using myocardial strain and strain rate.* Kusunose K, Yamada H, Nishio S, Tomita N, Hotchi J, Bando M, Niki T, Yamaguchi K, Taketani Y, Iwase T, Soeki T, Wakatsuki T, Sata M. 9, s.l. : Journal of the American Society of Echocardiography, Sept 2012, Vol. 25.

13. *www.ecgwaves.com.* [Online] [Cited: 03 March 2021.] https://ecgwaves.com/topic/deformation-strain-strain-rate-speckle-tracking-echocardiography/.

14. *Hypophosphorylation of the Stiff N2B titin isoform raises cardiomyocyte resting tension in failing human myocardium.* Borbély A, Falcao-Pires I, van Heerebeek L, Hamdani N, Edes I, Gavina C, Leite-Moreira AF, Bronzwaer JGF, Papp Z, van der Velden J, Stienen GJM, Paulus WJ. s.l. : Circ Res, Mar 2009, Vol. 104.

15. *Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin.* Zile MR, Baicu CF, Ikonomidis JS, Stroud RE, Nietert PJ, Bradshaw AD, Slater R, Palmer BM, Van Buren P, Meyer M, Redfield MM, Bull DA, Granzier HL, LeWinter MM. s.l. : Circulation, Apr 2015, Vol. 131.

16. *Myocardial stiffness is an important determinant of the plasma brain natriuretic peptide concentration in patients with both diastolic and systolic heart failure.* Watanabe S, Shite J, Takaoka H, Shinke T, Imuro Y, Ozawa T, Otake H, Matsumoto D, Ogasawara D, Paredes OL, Yokoyama M. s.l. : Eur Heart J, Apr 2006, Vol. 27.

17. *Noninvasive assessment of wall distensibility with the evaluation of diastolic epicardial movement.* Takeda Y, Sakata Y, Higashimori M, Mano T, Nishio M, Ohtani T, Hori M, Masuyama T, Kaneko M, Yamamoto K. s.l. : J Card Fail, Feb 2009, Vol. 15.

18. *Diastolic stiffness as assessed by diastolic wall strain is associated with adverse remodelling and poor outcomes in heart failure with preserved ejection fraction.* Ohtani T, Mohammed SF, Yamamoto K, Dunlay SM, Weston Sa, Sakata Y, Rodeheffer RJ, Roger VJ, Redfield MM. s.l. : Eur Heart J, Jul 2012, Vol. 15.

19. *Diastolic wall strain is associated with incident heart failure in African Americans: Insights from the atherosclerosis risk in communities study.* Kamimura D, Suzuki T, Hall ME, Wang W, Winniford MD, Shah AM, Rodriguez CJ, Butler KR , Mosley TH. 5, s.l. : J Cardiol, May 2018, Vol. 71.

20. *Prognostic utility of diastolic dysfunction and speckle tracking echocardiography in heart failure with reduced ejection fraction.* Hansen S, Brainin P, Sengeløv M, Jørgensen PG, Bruun NE, Olsen FJ, Fritz-Hansen T, Schou M, Gislason G, Biering-Sørensen T. s.l. : ESC Heart Failure, 2020, Vol. 7.

21. *Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone.* Shah AM, Claggett B, Sweitzer NK,

Shah SJ, Anand IS, Liu L, Pitt B, Pfeffer MA, Solomon SD. s.l. : Circulation, 2015, Vol. 132.

22. *Global 2-dimensional strain as a new prognosticator in patients with heart failure.* Cho GY, Marwick TH, Kim HS, Kim MK, Hong KS, Oh DJ. s.l. : J Am Coll Cardiol, 2009, Vol. 54.

23. *Strain improves risk prediction beyond ejection fraction in chronic systolic heart failure. .* Zhang KW, French B, May Khan A, Plappert T, Fang JC, Sweitzer NK, Borlaug BA, Chirinos JA, St John Sutton M, Cappola TP, Ky B. s.l. : J Am Heart Assoc, 2014, Vol. 3.

24. *Global longitudinal strain is a superior predictor of all-cause mortality in heart failure with reduced ejection fraction.* Sengelov M, Jorgensen PG, Jensen JS, Bruun NE, Olsen FJ, Fritz-Hansen T, Nochioka K, Biering-Sorensen T. s.l. : JACC Cardiovasc Imaging, 2015, Vol. 8.

25. *Ratio of transmitral early filling velocity to early diastolic strain rate predicts outcomes in patients with systolic heart failure.* Chan YH, Lee HF, Wu LS, Wang CL, Wu CT, Yeh YH, Ho YW, Hsu LA, Chu PH, Kuo CT. 1, s.l. : European Heart Journal Cardiovascular Imaging, 2017, Vol. 18.

26. *Left ventricular peak early diastolic strain rate detected by two-dimensional speckle tracking echocardiography and disease severity in pre-capillary pulmonary hypertension.* Liu BY, Wu WC, Zeng QW, Liu ZH, NIU LL, Tian Y, Cheng XL, Luo Q, Zhao ZH, An CH, Huang L, Wang H, He JG, Xiong CM. 3, s.l. : Pilmonary circulation, 2019, Vol. 9.

27. *Predictive value of assessing diastolic strain rate on survival in cardiac amyloidosis patients with preserved ejection fraction.* Liu D, Hu K, Störk S, Herrmann S, Kramer B, Cikes M, Gaudron PD, Knop S, Ertl G, Bijnens B, Weidemann F. s.l. : PLoS One, 2014, Vol. 9.

28. *Early diastolic strain rate in relation to systolic and diastolic function and prognosis in acute myocardial infarction: a two-dimensional speckle-tracking study.* Ersbøll M, Andersen MJ, Valeur N, Mogensen UM, Fakhri, Thune JJ, Møller JE, Hassager C, Søgaard P, Køber L. s.l. : European Heart Journal, 2014, Vol. 35.

29. *Longitudinal, circumferential and radial systolic left ventricular function in patients with heart failure and preserved ejection fraction.* Gregorova Z, Meluzin J, Stepanova R, Sitar J, Podrouzkova H, Spinarova L. 3, s.l. : Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub, 2016, Vol. 160.

30. *Clinical utility of the 2016 ASE/EACVI recommendations for the evaluation of left ventricular diastolic function in the stratification of post-discharge prognosis in patients with acute heart failure.* Tomoko Machino-Ohtsuka, Yoshihiro Seo, Tomoko Ishizu. 10, s.l. : European Heart Journal - Cardiovascular Imaging, 2019, Vol. 20.

31. *Doppler estimation of left ventricular filling pressure in sinus tachycardia. A new application of tissue doppler imaging.* Nagueh SF, Mikati I, Kopelen HA, Middleton KJ, Quinones MA, Zoghbi WA. s.l. : Circulation, 1998, Vol. 98.

32. *Evaluation of left ventricular diastolic function by global strain rate imaging in patients with obstructive hypertrophic cardiomyopathy: a simultaneous speckle tracking echocardiography and cardiac catheterization study.* Chen S, Yuan J, Qiao S, Duan F, Zhang J, Wang H. s.l. : Echocardiography, 2014, Vol. 31.

33. *Correlation of global strain rate and left ventricular filling pressure in patients with coronary artery disease: a 2-D Speckle-Tracking Study.* Ma H, Wu WC, Xie RA, Gao LJ, Wang H. s.l. : Ultrasound Med Biol, 2016, Vol. 42.

34. *Early diastolic strain rate predicts response to heart failure therapy in patients with dilated cardiomyopathy.* Goebel B, Haugaa KH, Meyer K, Otto S, Jung C, Lauten A, Figulla HR, Edvardsen T, Poerner TC. s.l. : Int J Cardiovasc Imaging, 2014, Vol. 30.

35. *Myocardial systolic and diastolic consequences of left ventricular mechanical dyssynchrony in heart failure with normal left ventricular ejection fraction.* Morris DA, Vaz Perez A, Blaschke F, Eichstädt H, Ozcelik C, Haverkamp W. s.l. : Eur Heart J Cardiovasc Imaging, 2012, Vol. 13.

36. *Diastolic dysfunction and left atrial volume: A population-based study.* Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM. 1, s.l. : Journal of the American College of Cardiology, 2005, Vol. 45.

37. *The clinical application of the ratio of transmitral early filling velocity to early diastolic strain rate: a systematic review and meta-analysis.* Lassen MCH, Olsen FJ, Skaarup KG, Tolstrup K, Qasim AN, Gislason G, Biering-Sørensen T. s.l. : Journal of Echocardiography, 2020, Vol. 18.

38. *Estimation of left ventricular filling pressures by speckle tracking echocardiography in patients with idiopathic dilated cardiomyopathy.* Meluzin J, Spinarova L, Hude P, Krejci J, Podrouzkova H, Pesl M, Orban M, Dusek L, Jarkovsky J, Korinek J. s.l. : Eur J Echocardiogr J Work Group Echocardiogr Eur Soc Cardiol, 2011, Vol. 12.

39. *Correlations between echocardiographic systolic and diastolic function with cardiac catheterization in biventricular congenital heart patients.* Nadorlik H, Stiver C, Khan S, Miao Y, Holzer R, Cheatham JP, Cua CL. s.l. : Pediatr Cardiol., 2016, Vol. 37.

40. *Ratio of transmitral early filling velocity to early diastolic strain rate predicts long-term risk of cardiovascular morbidity and mortality in the general population.* Lassen MCH, Biering-Sørensen SR, Olsen FJ, Skaarup KG, Tolstrup K, Qasim AN, Møgelvang R, Jensen JS, Biering-Sørensen T. s.l. : Eur Heart J, 2019, Vol. 40.

41. *The ratio of early mitral inflow velocity to global diastolic strain rate as a useful predictor of cardiac outcomes in patients with atrial fibrillation.* Hsu PC, Lee WH, Chu CY, Lee CS, Yen HW, Su HM, Lin TH, Voon WC, Lai WT, Sheu SH. s.l. : J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr, 2014, Vol. 27.

42. *Association of the ratio of early mitral inflow velocity to the global diastolic strain rate with a rapid renal function decline in atrial fibrillation.* Chen SC, Lee WH, Hsu PC, Lee CS, Lee MK, Yen HW, Lin TH, Voon WC, Lai WT, Sheu SH, Su HM. s.l. : PLoS ONE., 2016, Vol. 11.

43. *Early impairment in left ventricular longitudinal systolic function is associated with an increased risk of incident atrial fibrillation in patients with type 2 diabetes.* Bonapace S, Valbusa F, Bertolini L, Zenari L, Canali G, Molon G, Lanzoni L, Cecchetto A, Rossi A, Mantovani A, Zoppini G, Barbieri E, Targher G. s.l. : J Diabetes Complicat, 2017, Vol. 31.

44. *Comparison of two different speckle tracking software systems: does the method matter?* Biaggi P, Carasso S, Garceau P, Greutmann M, Gruner C, Tsang W, Rakowski H, Agmon Y, Woo A. s.l. : Echocardiography, 2011, Vol. 28.

45. *Variability of global left ventricular deformation analysis using vendor dependent and independent two-dimensional speckle-tracking software in adults.* Risum N, Ali S, Olsen NT, Jons C, Khouri MG, Lauridsen TK, Samad Z, Velazquez EJ, Sogaard P, Kisslo J. s.l. : J Am Soc Echocardiogr, 2012, Vol. 25.

46. *What is the primary source of discordance in strain measurement between vendors: imaging or analysis?* Negishi K, Lucas S, Negishi T, Hamilton J, Marwick TH. s.l. : Ultrasound Med Biol, 2013, Vol. 39.

Eidesstattliche Versicherung

„Ich, Yoanna Savova, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Klinische Relevanz des Schweregrades der linksventrikulären frühdiastolischen Deformationsrate bei Patienten mit reduzierter Ejektionsfraktion“; „Clinical Relevance of the Severity of Left Ventricular Longitudinal Diastolic Strain Rate in Patients with Reduced Ejection Fraction“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher

Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Acknowledgements

Dieser Teil wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.