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**Habilitationsschrift**

# Clinical Relevance and Lower Limit of Normality of New Left Ventricular, Right Ventricular, and Left Atrial Functional Parameters Using Speckle-Tracking Echocardiography

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## Abbreviations

**LVEF** = left ventricular ejection fraction

**GLS** = left ventricular global longitudinal systolic strain

**LV** = left ventricular or left ventricle

**RV** = right ventricular or right ventricle

**LA** = left atrial or left atrium

**2D** = two-dimensional

**STE** = speckle-tracking echocardiography

**TTE** = transthoracic echocardiography

**TDI** = pulsed tissue Doppler imaging

**LAVI** = maximal left atrial volume indexed by body surface area

**TAPSE** = tricuspid annular plane systolic excursion

**S-TDI** = tricuspid systolic peak velocity using TDI

**FAC** = fractional area change of the RV

# Contents

# Introduction

## Analysis of the Systolic Function of the Left Ventricle using Left Ventricular Ejection Fraction (LVEF)

The analysis of the systolic function of the left ventricle (LV) is of key importance in evaluating the symptomatic status and prognosis of patients with cardiovascular diseases.[1-4] In effect, so far and since more than 50 years, the key functional analysis of the heart is the well-known “left ventricular ejection fraction (LVEF)” (namely, the change between diastole and systole of the volume of the LV in each cardiac cycle and expressed in percentage [i.e., LVEF = (LV end-diastolic volume – LV end-systolic volume / LV end-diastolic volume) x 100).[3] This standard parameter was first introduced by Braunwald and Folse in April of 1962,[5] who using a radioisotope indicator-dilution technic suggested for the first time that the fraction of LV end-diastolic volume ejected per beat (i.e., the “LVEF”) could be used as a parameter of LV systolic function.[5] Nonetheless, it should be mentioned that Holt using a dye dilution technic in 1956 suggested that the LV empties itself in a "fractional" manner (ejecting approximately 46% of its LV end-diastolic volume with each stroke [i.e., the fractional emptying of the LV or the “LVEF”]).[6] Moreover, it should be highlighted the first validation studies in 1966 using biplane angiographic planimetry of the LV to calculate the LVEF

(named by Bartle et al.[7] as “ejected fraction of the LV” and by Kennedy et al.[8] as “the systolic ejection fraction of the LV”). In addition, it is also interesting to mention the two excellent reports in 1968[9,10] using for the first time the term “LV ejection fraction” to define the previously named “fraction of LV end-diastolic volume ejected”,[5] “ejected fraction of the LV”,[7] or “systolic ejection fraction of the LV”[8] (i.e., as had been previously named the LVEF), a term that even today is used (i.e., left ventricular ejection fraction [LVEF]).[3,9,10] After these first angiographic studies analyzing the LVEF, started studies using transthoracic echocardiography (TTE). In this respect, Pombo et al.[11] in April of 1971 demonstrated for the first time the usefulness of analyzing the LVEF with TTE using an M-mode method, which was later validated by Fortuin et al.[12] in 1972 using M-mode TTE and for Teichholz et al.[13] in 1974 using B-can TTE. Nonetheless, it is important to mention that the pioneering study of Feigenbaum et al.[14] in 1967 demonstrated for the first time how to calculate LV volumes or the stroke volume with M-mode TTE, which later helped Pombo et al.[11] to validate for the first time the usefulness of the analysis of LV volumes to calculate the LVEF using TTE. In addition, it is also interesting to mention the first studies validating LVEF with TTE using the Simpson biplane method (i.e., the biplane method of discs or modified Simpson's rule method), such as the studies of Schiller et al.[15] and of Folland et al.[16] in 1979 using the short and long axis views to calculate the

LVEF and the important study of Starling et al.[17] in May of 1981 validating for the first time the current methodology of LVEF (namely, using the apical 4- and 2-chamber views with the Simpson biplane method). The findings of these pioneering first works using TTE served as input to carry out several studies to demonstrate the clinical relevance of LVEF.[18-30] In effect, in the past 20 years several studies demonstrated the usefulness of biplane LVEF using TTE with the modified Simpson's rule method in different cardiovascular diseases.[18-30] However, while so far LVEF still being a pivotal functional cardiac parameter,[1-4] in the last years several studies have highlighted some major limitations of this standard systolic parameter, such as its high dependence on systemic and intracardiac changes in volume and pressure,[31-35] since LVEF is rather a volumetric than a myocardial parameter. Thus, taking into consideration these major limitations of LVEF, technological and clinical studies began to investigate the potential usefulness of new functional systolic parameters among which stands out LV global longitudinal systolic strain, a myocardial rather volumetric cardiac parameter, using new technologies such as two-dimensional speckle-tracking echocardiography.[36-65]

## Analysis of the Systolic Function of the Left Ventricle using Left Ventricular Global Longitudinal Systolic Strain (GLS)

Two-dimensional speckle-tracking echocardiography (2DSTE) is an echocardiographic method destinated to analyze mainly the myocardial rather than the volumetric function of the LV.[36-65] Accordingly, using 2DSTE-derived parameters such as LV global longitudinal systolic strain (GLS) allows to decrease the limitations of LVEF regarding its dependence on systemic and intracardiac changes in volume and pressure.[31-35] In this respect, several studies suggested the potential usefulness of this new myocardial parameter (namely, GLS) to detect subclinical LV systolic dysfunction, despite a normal LVEF.[45,46,48-58,60-65] Notwithstanding this, few studies demonstrated the rate and clinical relevance of subclinical LV systolic dysfunction detected by GLS in common cardiovascular diseases such as arterial hypertension. In addition, the lower limit of normality of GLS, which would provide the right cutoff to determine a subclinical LV systolic dysfunction using GLS, was also poorly studied in large cohorts of healthy subjects. Hence, the purpose of the author and his research group was to study the clinical relevance of GLS in patients with arterial hypertension and to determine the lower limit of normality of this new parameter by analyzing a large cohort of healthy subjects.

## Analysis of the Diastolic Function of the Left Ventricle

LV diastolic dysfunction also plays a pivotal role in the symptomatology, functional capacity, and dyspnea in patients with cardiovascular diseases, mainly in those with preserved LVEF without severe valvular or congenital heart disease.[66-69] In this respect, several studies analyzing the early diastolic velocity of the mitral annulus using tissue Doppler imaging (TDI) and the early diastolic velocity of the mitral inflow by mean of pulsed Doppler demonstrated the usefulness of these measurements to analyze LV diastolic function (namely, the usefulness of the septal and lateral early diastolic peak velocity [e`] by TDI as well as the ratio of the early diastolic mitral inflow peak velocity (E) on the septal or lateral e` [i.e., the mitral E/e` ratio] in patients with preserved LVEF).[70-85] However, despite these interesting previous studies,[70-85] these conventional parameters reflect mainly a mitral-annular functional analysis rather than a global or myocardial LV diastolic analysis (i.e., in all LV segments). Hence, the purpose of the author and his research group was to determine the clinical relevance of new diastolic parameters, which would help analyze the global or myocardial LV diastolic function in patients with preserved LVEF. In effect, the authors studied the usefulness and clinical relevance of LV early diastolic strain rate (LVSRe) and of the ratio of mitral E / LVSRe (both new global LV diastolic parameters) in patients with preserved LVEF. In addition, the authors

conducted a multicenter study to determine the lower and upper limits of normality of these new global LV diastolic parameters by analyzing a large cohort of healthy subjects.

**Analysis of the Systolic Function of the Right Ventricle**

While LV functional analyses have proven to have clinical and prognostic relevance in patients with cardiovascular diseases,[2,3,66,67] in the last years the functional analysis of the right ventricle (RV) and the left atrium (LA) have also become clinically relevant in the assessment of these patients.[86-96] In this respect, concerning the RV systolic function, echocardiographic parameters such as the tricuspid annular plane systolic excursion (TAPSE), the tricuspid systolic peak velocity using TDI (S-TDI), and the fractional area change of the RV (FAC) have demonstrated to have clinical and prognostic relevance in patients with cardiovascular diseases.[3,86,97-101] Nonetheless, recent studies using new myocardial and global RV parameters such as RV global longitudinal systolic strain (RV global strain) and RV free wall longitudinal systolic strain (RV free wall strain) have suggested that these new parameters could be more accurate to analyze the systolic function of the RV than the previous conventional RV parameters (i.e., TAPSE, RV S-TDI, and FAC).[102-111] However, despite these advances, there remained uncertainty about the

potential usefulness of RV global and free wall strain to detect early or subtle RV systolic dysfunction in patients with heart failure with reduced or preserved LVEF. In addition, the lower limit of normality of these new RV parameters was not known, which would be of pivotal importance to determine a normal or abnormal RV strain and thereby, a normal or abnormal RV systolic function. Hence, considering these gaps in evidence on RV global and free wall strain, the purpose of the author and his research group was to study the potential usefulness of RV global and free wall strain to detect subtle RV systolic dysfunction and to determine the lower limit of normality of these new RV parameters by analyzing a large cohort of healthy subjects.

**Analysis of the Function of the Left Atrium**

Left atrial (LA) parameters such as the maximal LA volume indexed by body surface area (LAVI) using TTE has demonstrated to have clinical and prognostic relevance in patients with cardiovascular diseases.[3,66-69] Nonetheless, recent studies using new myocardial and functional parameters such as LA global longitudinal reservoir strain (LA strain) have suggested that this new parameter could be more accurate and sensitive than LAVI to detect functional LA alterations.[112-115] However, despite these advances

regarding new functional LA parameters, there remained uncertainty about the potential clinical relevance of LA strain in patients with preserved LVEF. In addition, the lower limit of normality of this new LA functional parameter was not known, which would be of pivotal importance to determine a normal or abnormal LA strain and thereby, a normal or abnormal LA function. Hence, considering these remaining issues concerning the potential clinical usefulness of LA strain, the purpose of the author and his research group was to analyze the usefulness and clinical relevance of LA strain in patients with preserved LVEF and to determine the lower limit of normality of this new LA parameter by analyzing a large cohort of healthy subjects.

## Rationale for Investigating New Echocardiographic Parameters to Analyze the Function of the LV, RV, and LA

As it has been stated above, the standard parameter and method to analyze the systolic function of the left ventricle (LV) is a volumetric analysis of the LV (namely, left ventricular ejection fraction [LVEF]).[1-4] Nonetheless, new LV systolic parameters focused on myocardial analyses rather than on volumetric analyses could provide early or subclinical detection of functional LV myocardial alterations despite a preserved volumetric function of the LV. Hence, the goal of the author (Dr. Daniel A. Morris) and his research group was to determine first the normal range of new myocardial systolic parameters such as LV global longitudinal systolic strain (GLS) and then to determine the clinical relevance of this new LV myocardial parameter to detect an early or subclinical LV systolic dysfunction despite a preserved LVEF.

Concerning LV diastolic function, standard methods to analyze the diastolic function of the LV are annular and flow analyses of the mitral valve (namely, the septal and lateral annular early diastolic peak velocity [e`] by TDI and the ratio of the early diastolic mitral inflow peak velocity (E) on the septal or lateral e` [i.e., the mitral E/e` ratio]).[67] Nevertheless, new LV diastolic parameters focused on myocardial analyses rather than mitral annular

analyses could provide a global and direct (i.e., in all LV segments) diastolic analysis of the LV instead of an annular and flow analysis of the mitral valve. Hence, the goal of the author (Dr. Daniel A. Morris) and his research group was to determine first the normal range of new myocardial and global diastolic parameters such as LV early diastolic strain rate (LVSRe) and the ratio of mitral E / LVSRe and then to determine the clinical relevance of these new LV myocardial diastolic parameters.

Regarding innovative methods to analyze the systolic function of the RV, novel myocardial and global RV parameters such as RV global longitudinal systolic strain (RV global strain) and RV free wall longitudinal systolic strain (RV free wall strain) have shown to be accurate parameters to analyze the systolic function of the RV.[102-111] However, despite these advances, there remained uncertainty about the normal range and potential usefulness of RV global and free wall strain to detect early or subtle RV systolic dysfunction in patients with heart failure with reduced or preserved LVEF. Hence, the goal of the author (Dr. Daniel A. Morris) and his research group was to determine first the normal range of these new myocardial RV systolic parameters such as RV global and free wall strain, and then to determine the clinical relevance of these new RV systolic parameters to detect an early or subclinical RV systolic dysfunction in patients with heart failure.

Regarding the analysis of the LA, the standard parameter to analyze the LA is a volumetric measurement named LA volume index (LAVI) (namely, the maximal LA volume indexed by BSA).[3,67] However, new LA parameters focused on functional analyses rather than on size could provide important clinical information on functional alterations of the LA. Hence, the goal of the author (Dr. Daniel A. Morris) and his research group was to determine first the normal range of new myocardial and functional parameters of the LA such as LA global reservoir strain (LA strain), and then to determine the clinical relevance of this new functional LA parameter to detect an early or subclinical LA dysfunction despite a preserved size of the LA (i.e., despite a normal LAVI).

## Selected Studies of the Author

### Selected Study 1 – New Parameter to Analyze the Systolic Function of the LV:

**Hypothesis / Goal of the Selected Study:**

The standard parameter to analyze LV systolic function is a volumetric analysis of the LV (namely, left ventricular ejection fraction [LVEF]). New LV systolic parameters focused on myocardial analyses rather than volumetric analyses could provide early or subclinical detection of functional LV systolic alterations despite a preserved LVEF. Hence, the goal of the selected study of the author was to determine first the normal range of new myocardial systolic parameters such as LV global longitudinal systolic strain (GLS) and then to determine the clinical relevance of these new LV myocardial parameters to detect an early or subclinical LV systolic dysfunction despite a preserved LVEF.

**Summary and Results of the Selected Study:**

As previously mentioned, while several studies demonstrated the potential usefulness of GLS to detect subclinical LV systolic dysfunction despite a normal LVEF, [45,46,48-58,60-65] few studies analyzed the rate and clinical relevance of subclinical LV systolic dysfunction as detected by GLS in common cardiovascular diseases such as arterial hypertension. In addition,

the lower limit of normality of GLS, which would provide the right cutoff to determine a subclinical LV systolic dysfunction using GLS, was also poorly studied in large cohorts of healthy subjects. Hence, the purpose of the author and his research group was to study the clinical relevance of GLS in patients with arterial hypertension and to determine the lower limit of normality of this new parameter by analyzing a large cohort of healthy subjects. In this respect, the author and his research group conducted a multicenter study in 10 university hospitals from Japan and Germany to investigate the clinical relevance and usefulness of GLS in patients with arterial hypertension and to determine the lower limit of normality of this new parameter by including a large cohort of healthy subjects. Three hundred twenty-three healthy adult subjects and 310 patients with arterial hypertension were included in this multicenter study. By analyzing the healthy cohort, the lower limit of normality of GLS was 17%, and the mean value of GLS was significantly reduced in patients with arterial hypertension in comparison with healthy subjects (GLS values [mean ± SD; absolute values] = 17.4 ± 3.5% vs. 21.2 ± 2.0%; p value < 0.01). In line with these findings, despite a normal LVEF (i.e., Simpson biplane LVEF ≥ 55%), GLS enabled to detect early or subtle LV systolic function in 46.1% (i.e., 143 out of 310) of patients with arterial hypertension (i.e., GLS < 17%). In addition, by integrating GLS in the global systolic performance of the LV (i.e., by averaging the longitudinal, radial,

and circumferential systolic function/strain [global systolic index]), the functional capacity and symptomatic status were significantly correlated with the systolic performance of the LV including GLS (i.e., with the global systolic index). Thus, this study also demonstrated the potential usefulness and clinical relevance of a new systolic parameter including GLS (i.e., the systolic myocardial performance of the LV or global systolic index), which could also be used together with GLS to analyze the myocardial systolic performance of the LV in patients with cardiovascular diseases.

**Publication of the Selected Study:**

**Daniel A. Morris,** Kyoko Otani, Tarek Bekfani, Kiyohiro Takigiku, Chisato Izumi, Satoshi Yuda, Konomi Sakata, Nobuyuki Ohte, Kazuaki Tanabe, Katharina Friedrich, York Kühnle, Satoshi Nakatani, Yutaka Otsuji, Wilhelm Haverkamp, Leif-Hendrik Boldt, Masaaki Takeuchi. **Multidirectional Global Left Ventricular Systolic Function in Normal Subjects and Patients with Hypertension: Multicenter Evaluation. J Am Soc Echocardiogr. 2014** May;27(5):493-500. https://doi.org/10.1016/j.echo.2014.01.017

**Selected Study 2 – New Parameter to Analyze the Diastolic Function of the LV:**

**Hypothesis / Goal of the Selected Study:**

Current standard LV parameters to analyze the diastolic function of the LV are based on annular and flow analyses of the mitral valve (namely, the septal and lateral annular early diastolic peak velocity [e`] by TDI and the ratio of the early diastolic mitral inflow peak velocity (E) on the septal or lateral e` [i.e., the mitral E/e` ratio]). New LV diastolic parameters focused on myocardial analyses rather than mitral annular analyses could provide a global and direct (i.e., in all LV segments) diastolic analysis of the LV. Hence, the goal of the selected study of the author was to determine first the normal range of new myocardial and global diastolic parameters such as LV early diastolic strain rate (LVSRe) and the ratio of mitral E / LVSRe and then to determine the clinical relevance of these new LV myocardial diastolic parameters.

**Summary and Results of the Selected Study:**

As it has been stated in the introduction section, while conventional mitral annular parameters such as septal and lateral annular mitral e` velocities and their corresponding derived indexes (i.e., the septal E/e` and the lateral E/e` ratios) demonstrated usefulness to analyze indirectly the diastolic function of the LV in patients with preserved LVEF,[70-85] these conventional parameters

reflect mainly a mitral-annular functional analysis rather than a global or myocardial LV diastolic analysis (i.e., in all LV segments). Hence, the purpose of the author and his research group was to determine the clinical relevance of new diastolic parameters, which would help analyze the global and myocardial LV diastolic function in patients with preserved LVEF. In effect, the authors studied the usefulness and clinical relevance of LV early diastolic strain rate (LVSRe) and of the ratio of mitral E / LVSRe (both new global LV diastolic parameters) in a multicenter study including 477 patients with cardiovascular risk factors and preserved LVEF. In addition, in this multicenter study, a large cohort of healthy subjects was also analyzed (n = 377) to determine the lower and upper limits of normality of these new global LV diastolic parameters. In this respect, analyzing the large cohort of healthy subjects, the lower limit of normality of LVSRe was $1.00s^{-1}$. The upper limit of normality of its derived parameter, the mitral E / LVSRe ratio, was 71.5. Besides, by analyzing the cohort of patients with cardiovascular risk factors such as arterial hypertension, diabetes mellitus, or coronary artery disease (CAD) and preserved LVEF, both LVSRe and its derived parameter (the mitral E / LVSRe) enabled to detect LV diastolic alterations, which was even better than standard diastolic parameters such as the mitral E/e` ratio, LAVI, and TR regurgitation peak velocity (i.e., rate of detection of LV diastolic abnormalities: using LVSRe 71%, using E/LVSRe ratio 57%, using the septal-lateral E/e` ratio 25%, using LAVI 22%,

and using TR velocity 9.1%). In line with these findings, adding LVSRe to the conventional and recommended approach to detect LV diastolic dysfunction led to significantly higher detection of LV diastolic dysfunction (an absolute increase of 18.9% [from 14.3% to 33.2%], p-value < 0.01) in comparison with using this approach without LVSRe. In agreement with these findings, an abnormal LVSRe or elevated mitral E / LVSRe ratio were significantly linked to heart failure hospitalization at 2 years (OR 3.5 [95%CI 1.05-12] and OR 3.6 [95%CI 1.3-9.8]), even after adjustment by age and sex and better than conventional annular diastolic parameters such as the septa-lateral mitral e` velocities and the septal-lateral mitral E/e` ratio.

**Publication of the Selected Study:**

**Daniel A. Morris,** Masaaki Takeuchi, Satoshi Nakatani, Yutaka Otsuji, Evgeny Belyavskiy, Radhakrishnan Aravind Kumar, Athanasios Frydas, Martin Kropf, Robin Kraft, Esteban Marquez, Engin Osmanoglou, Maximilian Krisper, Clemens Köhncke, Leif-Hendrik Boldt, Wilhelm Haverkamp, Carsten Tschöpe, Frank Edelmann, Burkert Pieske, Elisabeth Pieske-Kraigher. **Lower Limit of Normality and Clinical Relevance of Left Ventricular Early Diastolic Strain Rate for the Detection of Left Ventricular Diastolic Dysfunction. Eur Heart J Cardiovasc Imaging. 2018** Aug 1;19(8):905-915. https://doi.org/10.1093/ehjci/jex185

**Selected Study 3 – New Parameter to Analyze the Systolic Function of the RV:**

**Hypothesis / Goal of the Selected Study:**

New myocardial and global RV parameters such as RV global longitudinal systolic strain (RV global strain) and RV free wall longitudinal systolic strain (RV free wall strain) are accurate measurements to analyze the systolic function of the RV. However, despite these advances, there remained uncertainty about the potential usefulness of RV global and free wall strain to detect early or subtle RV systolic dysfunction in patients with heart failure with reduced or preserved LVEF. Hence, the goal of the selected study of the author was to determine first the normal range of these new myocardial RV systolic parameters such as RV global and free wall strain, and then to determine the clinical relevance of these new RV systolic parameters to detect an early or subclinical RV systolic dysfunction in patients with heart failure.

**Summary and Results of the Selected Study:**

As has been previously mentioned, while conventional echocardiographic RV systolic parameters such as TAPSE, S-TDI, and FAC have demonstrated to have clinical and prognostic relevance in patients with cardiovascular diseases,[3,86,97-101] recent studies using new myocardial and global RV parameters such as RV global and free wall strain have suggested that these new parameters could be more accurate to analyze the systolic function of the RV than the previous

conventional RV parameters (i.e., TAPSE, RV S-TDI, and FAC).[102-111] Nonetheless, despite these advances, there remained uncertainty about the potential usefulness of RV global and free wall strain to detect early or subtle RV systolic dysfunction in patients with heart failure with reduced or preserved LVEF. In addition, the lower limit of normality of these RV parameters was not known, which would be of pivotal importance to determine a normal or abnormal RV strain and thereby, a normal or abnormal RV systolic function. Hence, the purpose of the author and his research group was to investigate the potential usefulness of RV global and free wall strain to detect subtle RV systolic dysfunction and to determine the lower limit of normality of these new RV parameters by analyzing a large cohort of healthy adult subjects. In this respect, the authors investigated the potential usefulness and clinical relevance of RV global and free wall strain in a multicenter study including 426 patients with heart failure (218 with preserved LVEF and 208 with reduced LVEF) and 216 asymptomatic patients. In addition, in this multicenter study, a large cohort of healthy adult subjects was also analyzed (n = 238) to determine the lower limit of normality of RV global and free wall strain. In this regard, analyzing the large cohort of healthy subjects, the lower limit of normality of RV global strain was 17% and of RV free wall strain was 19%. Besides, analyzing the cohort of patients with heart failure, RV global and free wall strain enabled to detect RV systolic dysfunction, which was even better than standard parameters such as

TAPSE, S-TDI, and FAC (i.e., rate of detection of RV systolic abnormalities in patients with reduced LVEF: using RV global strain 58%, using RV free wall strain 46%, using TAPSE 38%, using S-TDI 38%, and using FAC 28%; rate of detection of RV systolic abnormalities in patients with preserved LVEF: using RV global strain 11%, using RV free wall strain 10%, using TAPSE 6%, using S-TDI 5%, and using FAC 5%). In line with these findings, RV global and free wall strain enabled to detect subtle RV systolic dysfunction despite normal TAPSE, S-TDI, or FAC in heart failure patients (mainly those with reduced LVEF). Moreover, the symptomatic status and functional capacity in patients with heart failure were significantly associated with RV global and free wall strain (OR > 5.0; p-value < 0.01).

**Publication of the Selected Study:**

**Daniel A. Morris**, Maximilian Krisper, Satoshi Nakatani, Clemens Köhncke, Yutaka Otsuji, Evgeny Belyavskiy, Aravind K Radha Krishnan, Martin Kropf, Engin Osmanoglou, Leif-Hendrik Boldt, Florian Blaschke, Frank Edelmann, Wilhelm Haverkamp, Carsten Tschöpe, Elisabeth Pieske-Kraigher, Burkert Pieske, Masaaki Takeuchi. **Normal Range and Usefulness of Right Ventricular Systolic Strain to Detect Subtle Right Ventricular Systolic Abnormalities in Patients with Heart Failure: A Multicentre Study. Eur Heart J Cardiovasc Imaging. 2017** Feb;18(2):212-223. https://doi.org/10.1093/ehjci/jew011

**Selected Studies 4 and 5 - New Parameter to Analyze the Function of the LA:**

**Hypothesis / Goal of the Selected Studies:**

The standard parameter to analyze the LA is a volumetric measurement named LA volume index (LAVI) (namely, the maximal LA volume indexed by BSA). New LA parameters focused on functional analyses rather than on size could provide important clinical information on functional LA alterations, even despite a preserved volumetric measurement of the LA (such as LAVI). Hence, the goal of the selected study of the author was to determine first the normal range of new myocardial and functional parameters of the LA such as LA global reservoir strain (LA strain), and then to determine the clinical relevance of this new functional LA parameter to detect an early or subclinical LA dysfunction despite a preserved volumetric measurement of the LA (i.e., despite a normal LAVI).

**Summary and Results of the Selected Studies:**

As has been highlighted in the introduction section, while conventional and volumetric LA echocardiographic parameters such as LAVI demonstrated to have clinical and prognostic relevance in patients with cardiovascular diseases,[3,66-69] recent studies using new myocardial and functional myocardial parameters such as LA global longitudinal reservoir strain (LA strain) have

suggested that this new parameter could be more accurate and sensitive than LAVI to detect functional LA alterations and thus, having potential clinical usefulness.[112-115] However, despite these advances regarding this new functional LA parameter, there remained uncertainty about the potential clinical relevance of LA strain in patients with preserved LVEF. In addition, the lower limit of normality of LA strain was not known, which would be of pivotal importance to determine a normal or abnormal LA strain and thereby, a normal or abnormal LA function. Hence, considering these remaining issues concerning the potential clinical usefulness of LA strain, the purpose of the author and his research group was to analyze the potential usefulness and clinical relevance of LA strain in patients with preserved LVEF and to determine the lower limit of normality of this new LA parameter by analyzing a large cohort of healthy subjects. In this respect, the author and his research group conducted a multicenter study in 10 university hospitals from Japan and Germany to determine the lower limit of normality of LA strain by analyzing a large cohort of healthy adult subjects (n = 329). In addition, in a second study, the authors aimed to determine the clinical relevance and usefulness of LA strain in patients with preserved LVEF by analyzing a cohort of 517 patients in sinus rhythm, without severe valvular heart disease, and with some cardiovascular risk factor such as arterial hypertension, diabetes mellitus, or history of coronary artery disease and preserved LVEF.

In effect, by analyzing the large cohort of healthy subjects, the lower limit of normality of LA strain was 23%. Besides, studying the potential usefulness and clinical relevance of LA strain, this new parameter enabled to detect subtle LA functional alterations despite a non-altered measurement of LAVI in patients with preserved LVEF and sinus rhythm (i.e., rate of early or subtle LA alterations detected by LA strain 29.4%). In addition, the symptomatic status, functional capacity, and heart failure hospitalization in these patients were significantly associated with LA strain, even in patients with normal LAVI and after adjustment by age and sex. Furthermore, LA strain was significantly a more sensitive parameter of LV diastolic dysfunction compared with LAVI. In fact, adding LA strain to LAVI into the conventional and recommended approach to detect LV diastolic dysfunction led to significantly higher detection of LV diastolic dysfunction (relative and absolute increases 73.3% and 9.9%; rate of detection of LV diastolic dysfunction: from 13.5% to 23.4%; $p < 0.01$) in comparison with using this approach but without LA strain.

**Publication of the Selected Studies:**

**Daniel A. Morris,** Masaaki Takeuchi, Maximilian Krisper, Clemens Köhncke, Tarek Bekfani, Tim Carstensen, Sabine Hassfeld, Marc Dorenkamp, Kyoko Otani, Kiyohiro Takigiku, Chisato Izumi, Satoshi Yuda, Konomi Sakata, Nobuyuki Ohte, Kazuaki Tanabe, Engin Osmanoglou, York Kühnle, Hans-Dirk Düngen, Satoshi Nakatani, Yutaka Otsuji, Wilhelm Haverkamp, Leif-Hendrik Boldt. **Normal Values and Clinical Relevance of Left Atrial Myocardial Function Analysed by Speckle-Tracking Echocardiography: Multicentre Study. Eur Heart J Cardiovasc Imaging. 2015** Apr;16(4):364-72. https://doi.org/10.1093/ehjci/jeu219

**Daniel A. Morris,** Evgeny Belyavskiy, Radhakrishnan Aravind-Kumar, Martin Kropf, Athanasios Frydas, Kerstin Braunauer, Esteban Marquez, Maximilian Krisper, Ruhdja Lindhorst, Engin Osmanoglou, Leif-Hendrik Boldt, Florian Blaschke, Wilhelm Haverkamp, Carsten Tschöpe, Frank Edelmann, Burkert Pieske, Elisabeth Pieske-Kraigher. Potential **Usefulness and Clinical Relevance of Adding Left Atrial Strain to Left Atrial Volume Index in the Detection of Left Ventricular Diastolic Dysfunction. J Am Coll Cardiol Img. 2018** Oct;11(10):1405-1415. https://doi.org/10.1016/j.jcmg.2017.07.029

# Discussion

The findings of these studies analyzing large cohorts of patients with CV diseases and risk factors have highlighted and demonstrated the potential usefulness and clinical relevance of new myocardial parameters such as LV strain, RV strain, and LA strain. In addition, these studies have provided the lower limit of normality of these new myocardial parameters, which could be of pivotal importance in determining normal or abnormal cardiac function using these new parameters.

## Clinical Relevance and Lower Limit of Normality of a New Myocardial LV Systolic Parameter: LV Global Longitudinal Systolic Strain (GLS)

As stated in the introduction section, the analysis of the systolic function of the LV is of key importance in evaluating the symptomatic status and prognosis of patients with cardiovascular diseases.[1-4] In effect, LVEF using the biplane Simpson method by echocardiography remains the standard parameter to analyze the cardiac function or more specifically the systolic function of the LV in patients with different cardiovascular diseases.[3,97] However, in the last years several studies have highlighted some major limitations of this standard systolic parameter such as its high dependence on

systemic and intracardiac changes in volume and pressure,[31-35] since LVEF is rather a volumetric than a myocardial parameter. Thus, taking into consideration these major limitations of LVEF, technological and clinical studies began to investigate the potential usefulness of new functional systolic parameters among which has stood out LV global longitudinal systolic strain (i.e., GLS), a myocardial rather volumetric parameter, using new technologies such as speckle-tracking echocardiography.[36-65] In this respect, several studies suggested the potential usefulness of this new myocardial parameter to detect subclinical LV systolic dysfunction, despite a normal LVEF.[45,46,48-58,60-65] Notwithstanding this, few studies demonstrated the rate and clinical relevance of subtle or early LV systolic dysfunction detected by GLS in common cardiovascular diseases such as arterial hypertension. In addition, the lower limit of normality of GLS, which would provide the right cutoff to determine a subclinical LV systolic dysfunction using GLS, was also poorly studied in large cohorts of healthy subjects. Hence, the purpose of the author and his research group was to determine the clinical relevance of GLS in patients with arterial hypertension and to determine the lower limit of normality of this new parameter by analyzing a large cohort of healthy subjects. In this respect, as it has been previously shown in this document, the author and his research group conducted a multicenter study in 10 university hospitals from Japan and Germany to

determine the clinical relevance and usefulness of GLS in patients with arterial hypertension and to determine the lower limit of normality of this new parameter by including a large cohort of healthy subjects.[116] Three hundred twenty-three healthy adult subjects and 310 patients with arterial hypertension were included in this multicenter study.[116] By analyzing the healthy cohort, the lower limit of normality of GLS was 17%, and GLS could detect early or subtle LV systolic function in 46.1% (i.e., 143 out of 310) of patients with arterial hypertension, despite preserved LVEF.[116] In addition, by integrating GLS in the global systolic performance of the LV (i.e., by averaging the longitudinal, radial, and circumferential systolic function/strain [global systolic index]), the functional capacity and symptomatic status were significantly correlated with the systolic performance of the LV including GLS (i.e., with the global systolic index).[116] Thus, the findings from this study have provided the clinical relevance and lower limit of normality of GLS and of a new global LV systolic parameter (the global systolic index),[116] which could have significant importance in the assessment of LV systolic dysfunction in patients with preserved LVEF.

## Clinical Relevance and Lower Limit of Normality of a New Myocardial LV Diastolic Parameter: LV Global Longitudinal Early Diastolic Strain Rate (LVSRe)

LV diastolic dysfunction plays a pivotal role in the symptomatology, functional capacity, and dyspnea in patients with cardiovascular diseases, mainly in those with preserved LVEF without severe valvular or congenital heart disease.[66-69] In this respect, current LV diastolic parameters such as septal and lateral annular early diastolic peak velocities (e`) and its derived parameters the septal and lateral mitral E /e` ratio remain as the standard measurements to detect LV diastolic dysfunction.[66-69] However, these annular mitral parameters have limitations such as their local or annular functional analysis rather than a global or myocardial LV diastolic analysis (i.e., in all LV segments). Hence, the purpose of the author and his research group was to determine the clinical relevance of new diastolic parameters, which would help analyze the global or myocardial diastolic function of the LV. In effect, the authors investigated the potential usefulness and clinical relevance of LV early diastolic strain rate (LVSRe) and of the ratio of mitral E / LVSRe (both new global LV diastolic parameters) in a multicenter study including 477 patients with cardiovascular risk factors and preserved LVEF.[117] In addition, in this multicenter study, a large cohort of healthy subjects was also analyzed (n = 377) to determine the lower and upper limits of normality of these new

global LV diastolic parameters.[117] In this respect, analyzing the large cohort of healthy subjects, the lower limit of normality of LVSRe was 1.00$s^{-1}$ and the upper limit of normality of its derived parameter, it is the mitral E / LVSRe ratio, was 71.5.[117] Besides, by analyzing the cohort of patients with cardiovascular risk factors such as arterial hypertension, diabetes mellitus, or CAD and preserved LVEF, both LVSRe and its derived parameter (the mitral E / LVSRe) enabled to detect LV diastolic alterations, which was even better than standard diastolic parameters such as the mitral E/e` ratio, LAVI, and TR regurgitation peak velocity (i.e., rate of detection of LV diastolic abnormalities: using LVSRe 71%, using E/LVSRe ratio 57%, using the septal-lateral E/e` ratio 25%, using LAVI 22%, and using TR velocity 9.1%).[117] In line with these findings, adding LVSRe to the conventional and recommended approach to detect LV diastolic dysfunction led to significantly higher detection of LV diastolic dysfunction (i.e., an absolute increase of 18.9% [from 14.3% to 33.2%], p-value < 0.01).[117] In agreement with these findings, an abnormal LVSRe or elevated mitral E / LVSRe ratio were significantly linked to heart failure hospitalization at 2 years (OR 3.5 [95%CI 1.05-12] and OR 3.6 [95%CI 1.3-9.8]), even after adjustment by age and sex and better than conventional annular diastolic parameters such as the septa-lateral mitral e` velocities and the septal-lateral mitral E/e` ratio.[117] Thus, the findings from this study have provided the clinical relevance and

lower limit of two new global LV diastolic parameters (LVSRe and its derived parameter [mitral E / LVSRe ratio]),[117] which could have significant importance in the assessment of LV diastolic dysfunction in patients with preserved LVEF.

**Clinical Relevance and Lower Limit of Normality of New Myocardial RV Systolic Parameters: RV Global Longitudinal Systolic Strain and RV Free Wall Longitudinal Systolic Strain**

Conventional echocardiographic parameters of the RV such as TAPSE, S-TDI, and FAC demonstrated clinical and prognostic relevance in patients with cardiovascular diseases.[3,86,97-101] Nonetheless, recent studies using new sensitive and global parameters such as RV global longitudinal systolic strain (RV global strain) and RV free wall longitudinal systolic strain (RV free wall strain) have suggested that these new parameters could be more accurate to analyze the systolic function of the RV than conventional RV parameters (i.e., TAPSE, RV S-TDI, and FAC).[102-111] However, despite these advances, there remained uncertainty about the potential usefulness of RV global and free wall strain to detect early or subtle RV systolic dysfunction in patients

with heart failure with reduced or preserved LVEF. In addition, the lower limit of normality of these new RV parameters was not known, which would be of pivotal importance to determine a normal or abnormal RV strain and thereby, a normal or abnormal RV systolic function. Hence, considering these gaps in evidence on RV global and free wall strain, the purpose of the author and his research group was to study the potential usefulness of RV global and free wall strain to detect subtle RV systolic dysfunction and to determine the lower limit of normality of these new RV parameters by analyzing a large cohort of healthy subjects. In this respect, the authors investigated the potential usefulness and clinical relevance of RV global and free wall strain in a multicenter study including 426 patients with heart failure (218 with preserved LVEF and 208 with reduced LVEF) and 216 asymptomatic patients.[118] In addition, in this multicenter study, a large cohort of healthy adult subjects was also analyzed (n = 238) to determine the lower limit of normality of RV global and free wall strain.[118] In this regard, analyzing the large cohort of healthy subjects, the lower limit of normality of RV global strain was 17% and of RV free wall strain was 19%.[118] Besides, by analyzing the cohort of patients with heart failure, RV global and free wall strain enabled to detect RV systolic dysfunction, which was even better than standard parameters such as TAPSE, S-TDI, and FAC (i.e., rate of detection of RV systolic abnormalities in patients with reduced LVEF: using RV global

strain 58%, using RV free wall strain 46%, using TAPSE 38%, using S-TDI 38%, and using FAC 28%; rate of detection of RV systolic abnormalities in patients with preserved LVEF: using RV global strain 11%, using RV free wall strain 10%, using TAPSE 6%, using S-TDI 5%, and using FAC 5%).[118] In line with these findings, RV global and free wall strain detected subtle RV systolic dysfunction despite normal TAPSE, S-TDI, or FAC in heart failure patients (mainly in those with reduced LVEF).[118] Moreover, the symptomatic status and functional capacity in patients with heart failure were significantly associated with RV global and free wall strain.[118] Thus, the findings from this study have provided the clinical relevance and lower limit of new myocardial RV systolic parameters,[118] which could have significant importance in analyzing the systolic function of the RV in clinical practice.

## Clinical Relevance and Lower Limit of Normality of a New Myocardial and Functional LA Parameter: LA Global Longitudinal Reservoir Strain (LA Strain)

The maximal LA volume indexed by body surface area (LAVI) is the conventional LA parameter to detect LA remodeling or LA alterations in patients with cardiovascular diseases.[3,66-69] Nonetheless, recent studies using myocardial and mainly functional parameters such as LA global longitudinal reservoir strain (LA strain) have suggested that this new functional parameter could be more accurate and sensitive than LAVI to detect functional LA alterations and thus, have potential clinical usefulness.[112-115] However, despite these advances regarding new functional LA parameters, there remained uncertainty about the potential clinical relevance of LA strain in patients with preserved LVEF. In addition, the lower limit of normality of this new LA functional parameter was not known, which would be of pivotal importance to determine a normal or abnormal LA strain and thereby, a normal or abnormal LA function. Hence, considering these remaining issues concerning the potential clinical usefulness of LA strain, the purpose of the author and his research group was to analyze the potential usefulness and clinical relevance of LA strain in patients with preserved LVEF and to determine the lower limit of normality of this new LA parameter by analyzing a large cohort of healthy subjects. In this respect, the author and his research group

conducted a multicenter study in 10 university hospitals from Japan and Germany to determine the lower limit of normality of LA strain by analyzing a large cohort of healthy adult subjects (n = 329).[119] In addition, in a second study, the authors aimed to determine the clinical relevance and usefulness of LA strain in patients with preserved LVEF by analyzing a cohort of 517 patients in sinus rhythm, without severe valvular heart disease, and with some cardiovascular risk factor such as arterial hypertension, diabetes mellitus, or history of coronary artery disease and preserved LVEF.[120] In effect, analyzing the large cohort of healthy subjects, the lower limit of normality of LA strain was 23%.[119] Besides, analyzing the potential usefulness and clinical relevance of LA strain, this new parameter enabled to detect subtle LA functional alterations despite a non-altered measurement of LAVI in patients with preserved LVEF and sinus rhythm (i.e., rate of early or subtle LA alterations detected by LA strain 29.4%).[120] In addition, the symptomatic status, functional capacity, and heart failure hospitalization in these patients were significantly associated with LA strain, even in patients with normal LAVI and after adjustment by age and sex.[120] Furthermore, compared with LAVI, LA strain was significantly more helpful in determining LV diastolic dysfunction.[120] In fact, adding LA strain into the conventional and recommended approach to detect LV diastolic dysfunction led to significantly higher detection of LV diastolic dysfunction than using

only LAVI in the current recommended approach.[120] Thus, the findings from these studies have provided the clinical relevance and lower limit of a new myocardial LA functional parameter (LA strain),[119,120] which could have significant importance in assessing patients with cardiovascular diseases and preserved LVEF in clinical practice.

## Summary

The findings of these studies analyzing large cohorts of healthy subjects and patients with CV diseases and risk factors have highlighted and demonstrated the potential usefulness and clinical relevance of new functional and myocardial parameters such as LV strain, RV strain, and LA strain. In addition, these studies have provided the lower limit of normality of these new myocardial parameters, which could be of pivotal importance in determining normal or abnormal cardiac function using these new parameters. Nonetheless, further studies should validate these findings and expert consensus should recommend these new myocardial parameters before introducing these new LV, RV, and LA functional analyses into clinical practice.

## References

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2021;42(36):3599-3726.

2. Marwick TH, Gillebert TC, Aurigemma G, et al.. Recommendations on the Use of Echocardiography in Adult Hypertension: A Report From the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). Eur Heart J Cardiovasc Imaging. 2015;16(6):577-605.

3. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update From the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70.

4. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2022;43(7):561-632.

5. Folse R, Braunwald E. Determination of Fraction of Left Ventricular Volume Ejected Per Beat and of Ventricular End-Diastolic and Residual Volumes. Experimental and Clinical Observations With a Precordial Dilution Technic. Circulation. 1962;25:674-85.

6. Holt JP. Estimation of the Residual Volume of the Ventricle of the Dog's Heart by Two Indicator Dilution Technics. Circ Res. 1956;4(2):187-95.

7. Bartle SH, Sanmarco ME. Measurement of Left Ventricular Volume by Biplane Angiocardiography and Indicator-Washout Techniques: A Comparison in the Canine Heart. Circ Res. 1966;19(2):295-306.

8. Kennedy JW, Baxley WA, Figley MM, Dodge HT, Blackmon JR. Quantitative Angiocardiography. I. The Normal Left Ventricle in Man. Circulation. 1966;34(2):272-8.

9. Krayenbühl HP, Bussmann WD, Turina M, Lüthy E. Is the Ejection Fraction an Index of Myocardial Contractility? Cardiologia. 1968;53(1):1-10.

10. Sonnenblick EH. Correlation of Myocardial Ultrastructure and Function. Circulation. 1968;38(1):29-44.

11. Pombo JF, Troy BL, Russell RO. Left Ventricular Volumes and Ejection Fraction by Echocardiography. Circulation. 1971;43(4):480-90.

12. Fortuin NJ, Hood WP Jr, Craige E. Evaluation of Left Ventricular Function by Echocardiography. Circulation. 1972;46(1):26-35.

13. Teichholz LE, Cohen MV, Sonnenblick EH, Gorlin R. Study of Left Ventricular Geometry and Function by B-scan Ultrasonography in Patients With and Without Asynergy. N Engl J Med. 1974;291(23):1220-6.

14. Feigenbaum H, Zaky A, Nasser WK. Use of Ultrasound to Measure Left Ventricular Stroke Volume. Circulation. 1967;35(6):1092-9.

15. Schiller NB, Acquatella H, Ports TA, et al. Left Ventricular Volume From Paired Biplane Two-Dimensional Echocardiography. Circulation. 1979;60(3):547-55.

16. Folland ED, Parisi AF, Moynihan PF, Jones DR, Feldman CL, Tow DE. Assessment of Left Ventricular Ejection Fraction and Volumes by Real-Time, Two-Dimensional

Echocardiography. A Comparison of Cineangiographic and Radionuclide Techniques. Circulation. 1979;60(4):760-6.

17. Starling MR, Crawford MH, Sorensen SG, Levi B, Richards KL, O'Rourke RA. Comparative Accuracy of Apical Biplane Cross-Sectional Echocardiography and Gated Equilibrium Radionuclide Angiography for Estimating Left Ventricular Size and Performance. Circulation. 1981;63(5):1075-84.

18. Solomon SD, Skali H, Anavekar NS, et al. Changes in Ventricular Size and Function in Patients Treated With Valsartan, Captopril, or Both After Myocardial Infarction. Circulation. 2005;111(25):3411-9.

19. Thune JJ, Køber L, Pfeffer MA, et al. Comparison of Regional Versus Global Assessment of Left Ventricular Function in Patients With Left Ventricular Dysfunction, Heart Failure, or Both After Myocardial Infarction: The Valsartan in Acute Myocardial Infarction Echocardiographic Study. J Am Soc Echocardiogr. 2006;19(12):1462-5.

20. deFilippi CR, Christenson RH, Kop WJ, Gottdiener JS, Zhan M, Seliger SL. Left ventricular ejection fraction assessment in older adults: an adjunct to natriuretic peptide testing to identify risk of new-onset heart failure and cardiovascular death? J Am Coll Cardiol. 2011;58(14):1497-506.

21. Ky B, French B, May Khan A, et al. Ventricular-arterial Coupling, Remodeling, and Prognosis in Chronic Heart Failure. J Am Coll Cardiol. 2013;62(13):1165-72.

22. Frigerio M, Lunati M, Pasqualucci D, et al. Left ventricular ejection fraction overcrossing 35% after one year of cardiac resynchronization therapy predicts long-term survival and freedom from sudden cardiac death: single center observational experience. Int J Cardiol. 2014;172(1):64-71.

23. de Groote P, Fertin M, Duva Pentiah A, Goéminne C, Lamblin N, Bauters C. Long-term functional and clinical follow-up of patients with heart failure with recovered left ventricular ejection fraction after β-blocker therapy. Circ Heart Fail. 2014;7(3):434-9.

24. Rantner B, Pohlhammer J, Stadler M, et al. Left ventricular ejection fraction is associated with prevalent and incident cardiovascular disease in patients with intermittent claudication - results from the CAVASIC Study. Atherosclerosis. 2015;239(2):428-35.

25. Narayan HK, Finkelman B, French B, Plappert T, Hyman D, Smith AM, Margulies KB, Ky B. Detailed Echocardiographic Phenotyping in Breast Cancer Patients: Associations With Ejection Fraction Decline, Recovery, and Heart Failure Symptoms Over 3 Years of Follow-Up. Circulation. 2017;135(15):1397-1412.

26. Lupón J, Díez-López C, de Antonio M, et al. Recovered heart failure with reduced ejection fraction and outcomes: a prospective study.Eur J Heart Fail. 2017;19(12):1615-1623.

27. Wang Y, Xiong L, Xu Q, et al. Association of left ventricular systolic dysfunction with mortality in incident peritoneal dialysis patients. Nephrology (Carlton). 2018;23(10):927-932.

28. Aimo A, Januzzi JL Jr, Vergaro G, et al. Left ventricular ejection fraction for risk stratification in chronic systolic heart failure. Int J Cardiol. 2018;273:136-140.

29. Lundorff IJ, Sengeløv M, Godsk Jørgensen P, et al. Echocardiographic Predictors of Mortality in Women With Heart Failure With Reduced Ejection Fraction. Circ Cardiovasc Imaging. 2018;11(11):e008031.

30. Angaran P, Dorian P, Ha ACT, et al. Association of Left Ventricular Ejection Fraction with Mortality and Hospitalizations. J Am Soc Echocardiogr. 2020;33(7):802-811.

31. Kumar A, Anel R, Bunnell E, Habet K, Neumann A, Wolff D, et al. Effect of large volume infusion on left ventricular volumes, performance and contractility parameters in normal volunteers. Intensive Care Med. 2004;30:1361–9.

32. Kumar A, Anel R, Bunnell E, Zanotti S, Habet K, Haery C, et al. Preload-independent mechanisms contribute to increased stroke volume following large volume saline infusion in normal volunteers: a prospective interventional study. Crit Care. 2004;8:R128–36.

33. ten Brinke EA, Klautz RJ, Tulner SA, et al. Haemodynamics and left ventricular function in heart failure patients: comparison of awake versus intra-operative conditions. Eur J Heart Fail. 2008;10:467–74.

34. Chemaly ER, Chaanine AH, Sakata S, Hajjar RJ. Stroke volume-to-wall stress ratio as a load-adjusted and stiffness-adjusted indicator of ventricular systolic performance in chronic loading. J Appl Physiol. 2012;113:1267–84.

35. Mérillon JP, Ennezat PV, Guiomard A, Masquet-Gourgon C, Aumont MC, Gourgon R. Left ventricular performance is closely related to the physical properties of the arterial system: Landmark clinical investigations in the 1970s and 1980s. Arch Cardiovasc Dis. 2014;107(10):554-62.

36. Heimdal A, Støylen A, Torp H, Skjaerpe T. Real-time strain rate imaging of the left ventricle by ultrasound. J Am Soc Echocardiogr. 1998;11(11):1013-9.

37. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. J Am Soc Echocardiogr 2004;17:630–3.

38. Leitman M, Lysyansky P, Sidenko S, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr. 2004;17:1021-9.

39. Ingul CB, Torp H, Aase SA, Berg S, Stoylen A, Slordahl SA. Automated analysis of strain rate and strain: feasibility and clinical implications. J Am Soc Echocardiogr. 2005;18:411-8.

40. Modesto KM, Cauduro S, Dispenzieri A, et al. Two-dimensional acoustic pattern derived strain parameters closely correlate with one-dimensional tissue Doppler derived strain measurements. Eur J Echocardiogr. 2006;7(4):315-21.

41. Rappaport D, Adam D, Lysyansky P, Riesner S. Assessment of myocardial regional strain and strain rate by tissue tracking in B-mode echocardiograms. Ultrasound Med Biol. 2006;32(8):1181-92.

42. Hurlburt HM, Aurigemma GP, Hill JC, et al. Direct ultrasound measurement of longitudinal, circumferential, and radial strain using 2-dimensional strain imaging in normal adults. Echocardiography. 2007;24(7):723-31.

43. Delgado V, Mollema SA, Ypenburg C, et al. Relation between global left ventricular longitudinal strain assessed with novel automated function imaging and biplane left ventricular ejection fraction in patients with coronary artery disease. J Am Soc Echocardiogr. 2008;21(11):1244-50.

44. Lancellotti P, Cosyns B, Zacharakis D, et al. Importance of left ventricular longitudinal function and functional reserve in patients with degenerative mitral regurgitation: assessment by two-dimensional speckle tracking. J Am Soc Echocardiogr. 2008;21(12):1331-6.

45. Kosmala W, Wong C, Kuliczkowska J, Leano R, Przewlocka-Kosmala M, Marwick TH. Use of body weight and insulin resistance to select obese patients for echocardiographic assessment of subclinical left ventricular dysfunction. Am J Cardiol. 2008;101(9):1334-40.

46. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J. 2008;29:1283–89.

47. Brown J, Jenkins C, Marwick TH. Use of myocardial strain to assess global left ventricular function: a comparison with cardiac magnetic resonance and 3-dimensional echocardiography. Am Heart J. 2009;157:102.e1–5.

48. Ng AC, Delgado V, Bertini M, et al. Findings from left ventricular strain and strain rate imaging in asymptomatic patients with type 2 diabetes mellitus. Am J Cardiol 2009;104:1398–401.

49. Narayanan A, Aurigemma GP, Chinali M, Hill JC, Meyer TE, Tighe DA. Cardiac mechanics in mild hypertensive heart disease: a speckle-strain imaging study. Circ Cardiovasc Imaging. 2009;2(5):382-90.

50. Liu YW, Tsai WC, Su CT, Lin CC, Chen JH. Evidence of left ventricular systolic dysfunction detected by automated function imaging in patients with heart failure and preserved left ventricular ejection fraction. J Card Fail. 2009;15:782–89.

51. Nguyen JS, Lakkis NM, Bobek J, Goswami R, Dokainish H. Systolic and diastolic myocardial mechanics in patients with cardiac disease and preserved ejection fraction: impact of left ventricular filling pressure. J Am Soc Echocardiogr 2010;23:1273–80.

52. Ernande L, Rietzschel ER, Bergerot C, et al. Impaired myocardial radial function in asymptomatic patients with type 2 diabetes mellitus: a speckle-tracking imaging study. J Am Soc Echocardiogr. 2010;23:1266–72.

53. Nucifora G, Schuijf JD, Delgado V, et al. Incremental value of subclinical left ventricular systolic dysfunction for the identification of patients with obstructive coronary artery disease. Am Heart J. 2010;159:148–57.

54. Ho E, Brown A, Barrett P, et al. Subclinical anthracycline- and trastuzumab-induced cardiotoxicity in the long-term follow-up of asymptomatic breast cancer survivors: a speckle tracking echocardiographic study. Heart. 2010;96:701–7.

55. Leitman M, Lysiansky M, Lysyansky P, et al. Circumferential and longitudinal strain in 3 myocardial layers in normal subjects and in patients with regional left ventricular dysfunction. J Am Soc Echocardiogr. 2010;23(1):64-70.

56. Imbalzano E, Zito C, Carerj S, et al. Left ventricular function in hypertension: new insight by speckle tracking echocardiography. Echocardiography. 2011;28:649–57.

57. Yip GW, Zhang Q, Xie JM, et al. Resting global and regional left ventricular contractility in patients with heart failure and normal ejection fraction: insights from speckle-tracking echocardiography. Heart 2011;97:287–94.

58. Kouzu H, Yuda S, Muranaka A, et al. Left ventricular hypertrophy causes different changes in longitudinal, radial, and circumferential mechanics in patients with hypertension: a two-dimensional speckle tracking study. J Am Soc Echocardiogr. 2011;24:192–9.

59. Altiok E, Neizel M, Tiemann S, et al. Quantitative analysis of endocardial and epicardial left ventricular myocardial deformation-comparison of strain-encoded cardiac

magnetic resonance imaging with two-dimensional speckle-tracking echocardiography. J Am Soc Echocardiogr. 2012;25:1179-88.

60. Sengupta SP, Caracciolo G, Thompson C, Abe H, Sengupta PP. Early impairment of left ventricular function in patients with systemic hypertension: new insights with 2-dimensional speckle tracking echocardiography. Indian Heart J. 2013;65(1):48-52.

61. Miyoshi H, Oishi Y, Mizuguchi Y, et al. Contribution of obesity to left atrial and left ventricular dysfunction in asymptomatic patients with hypertension: A two-dimensional speckle-tracking echocardiographic study. J Am Soc Hypertens. 2014;8(1):54-63.

62. Ballo P, Nistri S, Cameli M, et al; Working Group Nucleus on Echocardiography of the Italian Society of Cardiology. Association of left ventricular longitudinal and circumferential systolic dysfunction with diastolic function in hypertension: a nonlinear analysis focused on the interplay with left ventricular geometry. J Card Fail. 2014;20(2):110-20.

63. Ishizu T, Seo Y, Kameda Y, et al. Left ventricular strain and transmural distribution of structural remodeling in hypertensive heart disease. Hypertension. 2014;63(3):500-6.

64. Tadic M, Majstorovic A, Pencic B, et al. The impact of high-normal blood pressure on left ventricular mechanics: a three-dimensional and speckle tracking echocardiography study. Int J Cardiovasc Imaging. 2014;30(4):699-711.

65. Celic V, Tadic M, Suzic-Lazic J, et al. Two- and three-dimensional speckle tracking analysis of the relation between myocardial deformation and functional capacity in patients with systemic hypertension. Am J Cardiol. 2014;113(5):832-9.

66. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr. 2009;22(2):107-33.

67. Nagueh SF, Smiseth OA, Appleton CP, et al. 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. Eur Heart J Cardiovasc Imaging. 2016;17(12):1321-1360.

68. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539-50.

69. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019;40(40):3297-3317.

70. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol. 1997;30(6):1527-33.

71. Nagueh SF, Mikati I, Kopelen HA, Middleton KJ, Quiñones MA, Zoghbi WA. Doppler Estimation of Left Ventricular Filling Pressure in Sinus Tachycardia. A New Application of Tissue Doppler Imaging. Circulation. 1998;98(16):1644-50.

72. Nagueh SF, Bachinski LL, Meyer D, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a

novel means for an early diagnosis before and independently of hypertrophy. Circulation. 2001;104(2):128-30.

73. Nagueh SF, McFalls J, Meyer D, et al. Tissue Doppler imaging predicts the development of hypertrophic cardiomyopathy in subjects with subclinical disease. Circulation. 2003;108(4):395-8.

74. Dokainish H, Zoghbi WA, Lakkis NM, Quinones MA, Nagueh SF. Comparative accuracy of B-type natriuretic peptide and tissue Doppler echocardiography in the diagnosis of congestive heart failure. Am J Cardiol. 2004;93(9):1130-5.

75. Dokainish H, Zoghbi WA, Lakkis NM, Al-Bakshy F, Dhir M, Quinones MA, Nagueh SF. Optimal noninvasive assessment of left ventricular filling pressures: a comparison of tissue Doppler echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters. Circulation. 2004;109(20):2432-9.

76. Bruch C, Grude M, Müller J, Breithardt G, Wichter T. Usefulness of tissue Doppler imaging for estimation of left ventricular filling pressures in patients with systolic and diastolic heart failure. Am J Cardiol. 2005;95(7):892-5.

77. Kasner M, Westermann D, Steendijk P, et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. Circulation. 2007;116(6):637-47.

78. Dokainish H, Nguyen JS, Sengupta R, Pillai M, Alam M, Bobek J, Lakkis N. Do additional echocardiographic variables increase the accuracy of E/e' for predicting left ventricular filling pressure in normal ejection fraction? An echocardiographic and invasive hemodynamic study. J Am Soc Echocardiogr. 2010;23(2):156-61.

79. Dini FL, Ballo P, Badano L, et al. Validation of an echo-Doppler decision model to predict left ventricular filling pressure in patients with heart failure independently of ejection fraction. Eur J Echocardiogr. 2010;11(8):703-10.

80. Prasad A, Hastings JL, Shibata S, et al. Characterization of static and dynamic left ventricular diastolic function in patients with heart failure with a preserved ejection fraction. Circ Heart Fail. 2010;3(5):617-26.

81. Kuznetsova T, Thijs L, Knez J, Herbots L, Zhang Z, Staessen JA. Prognostic value of left ventricular diastolic dysfunction in a general population. J Am Heart Assoc. 2014;3(3):e000789.

82. Maragiannis D, Schutt RC, Gramze NL, et al. Association of Left Ventricular Diastolic Dysfunction with Subclinical Coronary Atherosclerotic Disease Burden Using Coronary Artery Calcium Scoring. J Atheroscler Thromb. 2015;22(12):1278-86.

83. Matsushita K, Minamishima T, Goda A, et al. Comparison of the reliability of E/E' to estimate pulmonary capillary wedge pressure in heart failure patients with preserved ejection fraction versus those with reduced ejection fraction. Int J Cardiovasc Imaging. 2015;31(8):1497-502.

84. Cameli M, Sparla S, Losito M, et al. Correlation of Left Atrial Strain and Doppler Measurements with Invasive Measurement of Left Ventricular End-Diastolic Pressure in Patients Stratified for Different Values of Ejection Fraction. Echocardiography. 2016;33(3):398-405.

85. Zhou D, Huang Y, Fu M, Cai A, Tang S, Feng Y. Prognostic value of tissue Doppler E/e' ratio in hypertension patients with preserved left ventricular ejection fraction. Clin Exp Hypertens. 2018;40(6):554-559.

86. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23(7):685-713.

87. Donal E, Behagel A, Feneon D. Value of left atrial strain: a highly promising field of investigation. Eur Heart J Cardiovasc Imaging 2015;16:356–7.

88. Cameli M, Mandoli GE, Loiacono F, Dini FL, Henein M, Mondillo S. Left atrial strain: a new parameter for assessment of left ventricular filling pressure. Heart Fail Rev. 2016;21(1):65-76.

89. Donal E, Galli E, Schnell F. Left Atrial Strain: A Must or a Plus for Routine Clinical Practice? Circ Cardiovasc Imaging. 2017;10(10):e007023.

90. Cameli M, Mandoli GE, Mondillo S. Left atrium: the last bulwark before overt heart failure. Heart Fail Rev. 2017;22(1):123-131.

91. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left Atrial Structure and Function, and Left Ventricular Diastolic Dysfunction: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;73(15):1961-1977.

92. Donal E, Galli E, L'Official G. The left atrium: A reservoir and a witness for risk of symptoms and cardiovascular complications. Eur J Prev Cardiol. 2019;26(10):1015-1017.

93. Bytyçi I, Bajraktari G, Lindqvist P, Henein MY. Compromised left atrial function and increased size predict raised cavity pressure: a systematic review and meta-analysis. Clin Physiol Funct Imaging. 2019;39(5):297-307.

94. Dal Canto E, Remmelzwaal S, van Ballegooijen AJ, et al. Diagnostic value of echocardiographic markers for diastolic dysfunction and heart failure with preserved ejection fraction. Heart Fail Rev. 2022;27(1):207-218.

95. Khan MS, Memon MM, Murad MH, et al. Left atrial function in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Eur J Heart Fail. 2020;22(3):472-485.

96. Mandoli GE, Sisti N, Mondillo S, Cameli M. Left atrial strain in left ventricular diastolic dysfunction: have we finally found the missing piece of the puzzle? Heart Fail Rev. 2020;25(3):409-417.

97. Galderisi M, Cosyns B, Edvardsen T, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2017;18(12):1301-1310.

98. Gorter TM, Hoendermis ES, van Veldhuisen DJ, et al. Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Eur J Heart Fail. 2016;18(12):1472-1487.

99. Lee JZ, Low SW, Pasha AK, Howe CL, Lee KS, Suryanarayana PG. Comparison of tricuspid annular plane systolic excursion with fractional area change for the evaluation of right ventricular systolic function: a meta-analysis. Open Heart. 2018;5(1):e000667.

100. Ren B, Spitzer E, Geleijnse ML, et al. Right ventricular systolic function in patients undergoing transcatheter aortic valve implantation: A systematic review and meta-analysis. Int J Cardiol. 2018;257:40-45.

101. Fan J, Liu X, Yu L, et al. Impact of tricuspid regurgitation and right ventricular dysfunction on outcomes after transcatheter aortic valve replacement: A systematic review and meta-analysis. Clin Cardiol. 2019;42(1):206-212.

102. Leong DP, Grover S, Molaee P, et al. Nonvolumetric echocardiographic indices of right ventricular systolic function: validation with cardiovascular magnetic resonance and relationship with functional capacity. Echocardiography. 2012;29(4):455-63.

103. Focardi M, Cameli M, Carbone SF, et al. Traditional and innovative echocardiographic parameters for the analysis of right ventricular performance in comparison with cardiac magnetic resonance. Eur Heart J Cardiovasc Imaging. 2015;16(1):47-52.

104. Lu KJ, Chen JX, Profitis K, et al. Right ventricular global longitudinal strain is an independent predictor of right ventricular function: a multimodality study of cardiac magnetic resonance imaging, real time three-dimensional echocardiography and speckle tracking echocardiography. Echocardiography. 2015;32(6):966-74.

105. Vizzardi E, Bonadei I, Sciatti E, Pezzali N, Farina D, D'Aloia A, Metra M. Quantitative analysis of right ventricular (RV) function with echocardiography in chronic heart failure with no or mild RV dysfunction: comparison with cardiac magnetic resonance imaging. J Ultrasound Med. 2015;34(2):247-55.

106. Kühn A, Meierhofer C, Rutz T, et al. Non-volumetric echocardiographic indices and qualitative assessment of right ventricular systolic function in Ebstein's anomaly: comparison with CMR-derived ejection fraction in 49 patients. Eur Heart J Cardiovasc Imaging. 2016;17(8):930-5.

107. da Costa Junior AA, Ota-Arakaki JS, Ramos RP, et al. Diagnostic and prognostic value of right ventricular strain in patients with pulmonary arterial hypertension and

relatively preserved functional capacity studied with echocardiography and magnetic resonance. Int J Cardiovasc Imaging. 2017;33(1):39-46.

108. Moreira HT, Volpe GJ, Marin-Neto JA, et al. Right Ventricular Systolic Dysfunction in Chagas Disease Defined by Speckle-Tracking Echocardiography: A Comparative Study with Cardiac Magnetic Resonance Imaging. J Am Soc Echocardiogr. 2017;30(5):493-502.

109. Werther Evaldsson A, Ingvarsson A, Smith JG, et al. Echocardiographic right ventricular strain from multiple apical views is superior for assessment of right ventricular systolic function. Clin Physiol Funct Imaging. 2019;39(2):168-176.

110. Kim J, Alakbarli J, Yum B, et al. Tissue-based markers of right ventricular dysfunction in ischemic mitral regurgitation assessed via stress cardiac magnetic resonance and three-dimensional echocardiography. Int J Cardiovasc Imaging. 2019;35(4):683-693.

111. Kavurt AV, Paç FA, Koca S, Mutlu Mıhçıoğlu A, Yiğit H. The evaluation of right ventricular systolic function in patients with repaired Tetralogy of Fallot by conventional echocardiographic methods and speckle tracking echocardiography: compared with the gold standard cardiac mangenetic resonance. Echocardiography. 2019;36(12):2251-2258.

112. Mondillo S, Cameli M, Caputo ML, Lisi M, Palmerini E, Padeletti M, Ballo P. Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. J Am Soc Echocardiogr. 2011;24(8):898-908.

113. Morris DA, Parwani A, Huemer M, et al. Clinical significance of the assessment of the systolic and diastolic myocardial function of the left atrium in patients with paroxysmal atrial fibrillation and low CHADS(2) index treated with catheter ablation therapy. Am J Cardiol. 2013;111(7):1002-11.

114. Santos AB, Kraigher-Krainer E, Gupta DK, et al. Impaired left atrial function in heart failure with preserved ejection fraction. Eur J Heart Fail. 2014;16(10):1096-103.

115. Miyoshi H, Oishi Y, Mizuguchi Y, Iuchi A, Nagase N, Ara N, Oki T. Association of left atrial reservoir function with left atrial structural remodeling related to left ventricular dysfunction in asymptomatic patients with hypertension: evaluation by two-dimensional speckle-tracking echocardiography. Clin Exp Hypertens. 2015;37(2):155-65.

116. Morris DA, Otani K, Bekfani T, et al. Multidirectional global left ventricular systolic function in normal subjects and patients with hypertension: multicenter evaluation. J Am Soc Echocardiogr. 2014;27(5):493-500.

117. Morris DA, Takeuchi M, Nakatani S, et al. Lower limit of normality and clinical relevance of left ventricular early diastolic strain rate for the detection of left ventricular diastolic dysfunction. Eur Heart J Cardiovasc Imaging. 2018;19(8):905-915.

118. Morris DA, Krisper M, Nakatani S, et al. Normal range and usefulness of right ventricular systolic strain to detect subtle right ventricular systolic abnormalities in patients with heart failure: a multicentre study. Eur Heart J Cardiovasc Imaging. 2017;18(2):212-223.

119. Morris DA, Takeuchi M, Krisper M, et al. Normal values and clinical relevance of left atrial myocardial function analysed by speckle-tracking echocardiography: multicentre study. Eur Heart J Cardiovasc Imaging. 2015;16(4):364-72.

120. Morris DA, Belyavskiy E, Aravind-Kumar R, et al. Potential Usefulness and Clinical Relevance of Adding Left Atrial Strain to Left Atrial Volume Index in the Detection of Left Ventricular Diastolic Dysfunction. J Am Coll Cardiol Img. 2018;11(10):1405-1415.

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## Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,

- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,

- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

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