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Novel Echocardiographic Modalities for Evaluation
of Pathophysiology and Diagnostic in Heart Failure
with Normal Ejection Fraction

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Abbreviations and Acronyms used

E/A	ratio of early peak (E) to late peak (A) mitral flow velocities
E/E'	LV filling index
E'/A'	early (E') to late (A') diastolic velocity ratio of mitral annulus
ECM	extracellular matrix
EDP	end-diastolic pressure
EDPVR	end-diastolic pressure-volume relationship
EF	ejection fraction
HFNEF	heart failure with normal ejection fraction
HFREF	heart failure with reduced ejection fraction
IVRT	isovolumetric relaxation time
LA	left atrium
LV	left ventricle
LVMI	LV mass index
NT-pro BNP ...	N-terminal pro-brain natriuretic peptide
SR	strain rate
SR _E	early diastolic peak of strain rate
SR _{IVR}	strain rate during isovolumetric relaxation
TDI	tissue Doppler imaging

Introduction

Among all patients presenting the clinical syndrome of heart failure, approximately one-half of them have preserved left ventricular ejection fraction,¹ known most usually as heart failure with normal ejection fraction (HFNEF). It is noteworthy to consider that these heart failure patients have similar outcomes compared to those with reduced ejection fraction (HFREF). Among both HFREF and HFNEF patients, the mortality rate lies up to 22% which is about 10-fold higher than in an age-matched control population.^{2, 3} In the last two decades, HFNEF is becoming a growing public health issue since its prevalence² is increasing relative to HFREF at the rate of 1% and it is therefore turning into the most frequent form of heart failure. Also their morbidity is similar and a 1-year hospitalization rate of 50% is relatively high.

In accordance with these discouraging epidemiological trends, pathophysiological mechanisms underlying HFNEF as well as diagnostic and therapeutic strategies still remain unclear.^{4, 5} In general, the medical therapy of heart failure seems to be highly evidence-based and validated through numerous studies. However, all large heart failure trials were related to HFREF patients, whereas HFNEF patients were excluded since their prognostic role was at that time unknown and therefore underestimated. In contrast to the outcome improvements observed in patients with HFREF in the last decades, the mortality has remained unchanged in patients with HFNEF,² emphasizing the apparent lack of evidence-based medical therapies. The recent treatment trials in HFNEF which only transferred known beneficial therapies strategies from HFREF studies showed neutral results and thus failed to improve outcomes in HFNEF. A major limitation to advances in therapy and survival of the patients with HFNEF is the relative uncertainty about the fundamental pathophysiological mechanisms and overall inconsistency in the diagnostic definition and procedures.

Nevertheless, the clinical studies and epidemiological trials taught us that older age and the female gender seem to be capable of predisposing the development of HFNEF.⁶⁻⁹ Further risk factors for cardiac limitations in HFNEF include arterial hypertension, diabetes mellitus, obesitas and thus metabolic syndrome. The changes in LV and LA remodelling shown in this risk population can lead to a decreased ventricular compliance and abnormal diastolic filling, causing symptoms of pulmonary

congestion.^{6, 7, 10,11} In the clinical routine, these patients can be identified by signs of LV hypertrophy, LA dilatation,¹² and abnormal filling properties measured by echocardiography or by increased BNP-levels.¹³ However, those who are stable at rest but suffer from exercise intolerance are difficult to diagnose, especially when they are younger, have a low degree of comorbidity, and when echocardiography reveals borderline results without any evidence of severe LV hypertrophy and LA dilatation. The cardiac status of these patients often remains cryptic and cardiac dysfunction may remain unrecognized, in particular if additional diagnostic assessments including exercising testing were not performed.

Pathophysiology of HFNEF

Other than HFREF patients which are characterized by LV dilation, eccentric LV hypertrophy, and low wall thickness, patients with HFNEF are considered to have a non-dilated LV, concentric LV hypertrophy or at least a concentric LV remodelling, and preserved LVEF.¹⁴⁻¹⁶ A normal pressure-volume loop of the left ventricle during one heart beat is divided into 4 haemodynamic phases: isovolumetric contraction and ejection, isovolumetric relaxation and filling, determined by regular pressure-volume relationship. Under physiological conditions, LV pressure rapidly decays after systole isovolumetric relaxation, allowing low filling pressures and adequate diastolic filling. Whereas patients with reduced EF have a predominantly systolic dysfunction, those with HFNEF are thought to have a predominantly diastolic dysfunction. The latter includes abnormalities of active relaxation and passive stiffness which lead to an elevated LV diastolic filling pressure.^{11, 17}

Elevated LV filling pressure will increase pressure in the pulmonary system and thus cause pulmonary congestion and oedema which is responsible for the main symptom in HFNEF – dyspnoea. Besides pulmonary congestion and dyspnoea, exercise intolerance in these patients is thought to be due to an inability to increase cardiac output sufficiently during exercise due to impaired physiological compensatory Frank-Starling mechanism.^{11, 17-19}

The underlying pathogenic mechanisms leading to the clinical symptomatology in patients with HFNEF still remain controversial.^{14, 20, 21} Besides cardiac limitations²²⁻²⁴ clinical symptoms of heart failure can be caused by non-cardiac diseases^{9, 25, 26} like

lung diseases, anaemia, hyperthyreosis, or a lack of physical endurance.²⁷ Those diseases, similar to valvular diseases, hypertrophic (obstructive) cardiomyopathy, and acute ischemia have to be ruled out before establishing the diagnosis of HFNEF.²⁸ Currently, left diastolic but also non-diastolic abnormalities are discussed as possible reasons for HPNEF. Non-diastolic abnormalities may include an impairment in ventricular-vascular coupling,^{7, 9, 11, 25, 26, 29} systolic LV dyssynchrony^{30, 31} or chronotropic incompetence^{26, 32} as possible contributors to the heart failure symptomatology of those patients, while pathologies inducing changes in chamber compliance lead to diastolic abnormalities of the left ventricle. The latter include cardiac hypertrophy, changes in the extracellular matrix with accumulation of fibrosis,^{24, 25, 28} microangiopathy,^{16, 33-35} and/or intracellular changes in the myocyte.³⁶⁻³⁹ These pathophysiological changes will impair diastolic filling,²² increase left atrial (LA) size³⁶ with a reduction of LA reserve, and decrease in LV ventricular compliance, which are key mechanisms for diastolic dysfunction.

LV hypertrophy

Diastolic filling is clearly compromised by LV hypertrophy, since the hypertrophied heart may have a delayed relaxation and decreased compliance. Therefore, the presence of severe LV hypertrophy is used as a surrogate parameter for diastolic dysfunction in the current recommendations of a study group of the ESC.^{30, 40} This seems to be appropriate not only for hypertrophy triggered by increased blood pressure, but also for cardiac hypertrophy due to structural heart diseases.

Left atrial dysfunction

Increased LV stiffness increases the work done by the left atrium at each cardiac cycle, which underlies the conventional mitral flow Doppler measurements. Therefore, chronic alterations in LV compliance might impair the function of LA and finally lead to LA enlargement,³⁶ which is also a predictor of mortality.¹² LA volume is, in a manner similar to that of LV hypertrophy, used as a surrogate parameter for diastolic dysfunction in the guidelines.⁴¹ LA enlargement will increase the risk of atrial fibrillation (another surrogate of diastolic dysfunction), a factor which seems to have an impact on mortality and morbidity, especially in patients with HFNEF.²⁸

Ischemia

Active relaxation is highly energy-dependent. Therefore diastolic dysfunction due to delayed relaxation seems to be important. In the long run, ischemia will trigger changes in cardiac hypertrophy and ECM remodelling, and will therefore eventually alter LV compliance as well.³³ Not only coronary artery disease may cause ischemia, but already endothelial dysfunction³⁵ can cause diastolic dysfunction.

Extracellular matrix (ECM)

The accumulation of extracellular matrix may compromise diastolic function, since LV compliance will be decreased by the amount of stiff collagen within the myocardium.²⁸ Furthermore, cross links between those collagen fibres, e.g. by non-enzymatic connections of advanced glycation end products may aggravate this problem, especially in diabetic patients.²⁴

Intracellular changes in the myocyte

Changes within the myocyte are also associated with a change in LV compliance. Changes in titin isoforms, which will change the spring-like function in diastole, were found to be involved at least in severe forms of HFNEF.³⁹ Moreover, changes in the calcium balance will impair active relaxation and therefore, normalization of this haemostasis appears to be pathophysiologically important for treating diastolic dysfunction with altered relaxation.

Diagnostic of HFNEF

Recent recommendations from a study group of the European Society of Cardiology (ESC) explain in detail how to diagnose HFNEF on the basis of LV diastolic dysfunction.¹⁶ For the diagnosis of HFNEF, three obligatory conditions need to be satisfied:

- 1) Signs and/or symptoms of heart failure are required.
- 2) Moreover, systolic function has to be preserved or only mildly abnormal with a calculated EF of over 50% in a non-dilated ventricle (LV end diastolic volume index < 97 ml/m²).

- 3) Furthermore and more importantly, the ESC study group defines that evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness are required to make the proper diagnosis of HFNEF.

Therefore, the ESC recommendation indicates that HFNEF is always associated with – if not caused by – diastolic dysfunction and therefore could be termed heart failure with normal EF and diastolic dysfunction (HFNEF with diastolic dysfunction). The above-mentioned diagnosis criteria 1) and 2) can be easily investigated e.g. by clinical evaluation, spiroergometry and regular echocardiography. However, the diagnosis of LV diastolic impairment is a challenge which needs special echocardiographic techniques or invasive measurements in clinical routine.

Invasive parameters of LV diastolic dysfunction

A gold standard for diagnosing LV dysfunction during relaxation and diastolic filling includes the invasive catheter-based procedure. LV relaxation is determined by an index Tau, the time constant derived by fitting a monoexponential equation to the LV pressure decay during early diastole and filling pressures by direct measurement of end-diastolic pressure in LV (LVEDP) or mean pulmonary capillary wedge pressure (PCWP). An increased relaxation index Tau ($> 48\text{ms}$), an elevated LVEDP ($> 16\text{ mmHg}$) or PCWP ($> 12\text{ mmHg}$) allow the diagnosis of diastolic dysfunction.²⁸ However, a normal LVEDP or PCWP does not exclude an impairment of LV compliance, since the pressure has to be interpreted in respect to the relation of the volume status. Chamber stiffness can be measured using conductance catheters and examining the position of a pressure-volume relationship on a diastolic pressure-volume plot, determining the slope of the LV pressure-volume relationship during diastole (EDPVR). It was recently shown that the diastolic stiffness constant (defined by an exponential fit over the end diastolic pressure-volume points during a transient preload reduction) discriminates HFNEF patients from controls.²⁸ Nevertheless, invasive measurements cannot be acquired in all patients for this purpose of diagnosis. This holds true particularly if they are not suitable to perform exercise testing in order to clarify mild symptomatic disturbances manifested only at stress.

Echocardiographic parameters of LV diastolic dysfunction

The role of echocardiography in diagnosing HFNEF involves an assessment of LVEF and the detection of diastolic dysfunction. These two criteria are absolutely essential. Although echocardiography does not measure indexes of diastolic function directly, it is widely available and without risks to the patient, and thus echocardiography has become the method of choice in clinical practice.⁴²

Conventional flow Doppler

Transmitral flow Doppler with the analysis of mitral inflow patterns plays an important role in the diastolic function evaluation.⁴³ This type of measurement includes the peak early transmitral filling (E) velocity, atrial contraction (A) velocity, E/A ratio, E velocity deceleration time (DT), and isovolumic relaxation time (IVRT); The main limitation of mitral flow measurements is its dependence on age, tachycardia, conduction disease, and mitral regurgitation which affect the filling pattern independently of diastolic function.^{43, 44} Whereas the transmitral filling pattern can reliably predict the presence of elevated LV filling pressures in HFREF, the predictive value is weak or absent in patients with preserved LVEF.⁴⁵⁻⁴⁷ Since most parameters derived from mitral flow Doppler assessment showed a variable outcome in terms of their predictive value for HFNEF, their use alone is no longer recommended as a first-line diagnostic approach to diastolic LV dysfunction. The pulmonary vein flow Doppler approach and/or a measurement of mitral colour M-mode propagation velocity (Vp) in colour flow Doppler might be helpful in patients with a more severe dysfunction but these are difficult to perform and showed a significant observer dependence.

Tissue Doppler imaging (TDI)

Tissue Doppler imaging is a novel modality which allows us to measure velocity of myocardial tissue motion and thus TDI can overcome limitations encountered with flow Doppler measurements for the evaluation of diastolic dysfunction. Mitral annular longitudinal motion pattern includes systolic (S'), early diastolic (E'), and atrial (A') velocity amplitude,^{48, 49} and is usually evaluated at the septal and lateral annulus in the apical view. The E' velocity is the key parameter for the evaluation of diastolic function since it decreases with impaired LV relaxation^{48, 49} independently of LA pressure. Left ventricular filling pressures can be estimated from the ratio of

transmitral E velocity and E' velocity (E/E'), known as LV filling index. The E/E' correlates strongly with wedge pressure, mean LV diastolic pressure, or LVEDP,^{48, 50, 51} as demonstrated in patients with both reduced and preserved LVEF,^{51, 52} whereas in decompensated HFREF, the correlation may be modest.⁵³

Therefore, according to recent ESC recommendations, the use of tissue Doppler analysis has become more and more important. Especially, the LV filling Index has been suggested as the key parameter for the diagnosis of HFNEF.¹⁷ Since mitral annular velocities at the septal site reveal lower amplitudes than at the lateral site, the use of mean E/E' value from both sites is recommended. A filling index of E/E' above 15 indicated elevated LV filling pressures and E/E' lower than 8 normal LV filling pressures.^{10, 50} Therefore, the value of 15 is used as a positive cut-off in the guidelines to diagnose HFNEF with diastolic dysfunction. In this context, TDI measurements also show the limitations provided by this wide uncertain "grey zone" of E/E' between 8 and 15. Other echocardiographic parameters are currently under discussion to improve such diagnostics. TDI during exercise, three dimensional echocardiography,⁵⁰ deformation (strain, strain rate) imaging might optimize echocardiographic diagnostic approach in the future.

Strain imaging

Myocardial deformation imaging can evaluate myocardial contraction and relaxation in all three directions; longitudinal, radial, and circumferential.⁵⁴ Several studies demonstrated decreased systolic LV strains in patients with HFNEF, suggesting that LV systolic function may be impaired in HFNEF.⁵⁵⁻⁵⁸ Also, global LV diastolic strain rate measured during isovolumic relaxation (SR_{IVR}) and during early diastole (SR_E) correlate inversely with LV Relaxation index Tau.⁵⁵ The ratio of transmitral E velocity and SR_{IVR} (E/SR_{IVR}) predicts an elevated wedge pressure, providing an index of LV filling. In addition, the parameters of ventricular torsion and diastolic untwisting have been reported as the measures of elastic recoil during early diastole.⁵⁹

In conclusion, it is known that the clinical criteria for diagnosis of HFNEF are unsatisfactory mainly due to the high percentage of false positive results. This is particularly evident for the detection of preclinical heart diseases or of patients with mild symptoms. However, it is crucial to detect a LV dysfunction at an early stage to

prevent the progress of heart failure. Early stages of LV dysfunction are difficult to identify, frequently not recognized, and currently still rely on complex invasive measurements.

Aims

The focus of these studies is on the role of echocardiography in diagnosing diastolic dysfunction among heart failure patients with normal ejection fraction. Especially new techniques are investigated and validated in comparison with the invasive gold standard method in order to improve the diagnostic and prognostic accuracy of HFNEF. Additionally, the new methods should help us to understand the pathophysiology in HFNEF.

Results (own original studies)

1. 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 Aug 7;116(6):637-47.)

Kasner, M., Westermann, D., Steendijk, P., Gaub, R., Wilkenshoff, U., Weitmann, K., Hoffmann, W., Poller, W., Schultheiss, H.-P., Pauschinger, M., Tschöpe, C.

To carry out the diagnosis of HFNEF, a direct evidence of impaired diastolic function is required. In this regard, the most reliable method is the measurement of left ventricular pressure-volume relationships using a conductance catheter system. This technique solely allows assessment of LV stiffness, a specific volume-independent parameter; however it is not applicable for widespread clinical use because it is highly invasive. For clinical routine work, non-invasive imaging techniques such as echocardiography are preferable. This is, to our knowledge, the first study to correlate various established conventional flow and novel tissue Doppler echocardiographic indexes with the data obtained by conductance catheterization in HFNEF populations and then compared these with the control collective. We found in HFNEF patients with confirmed diastolic dysfunction that single indexes of flow Doppler echocardiography were not accurate enough to establish a correct diagnosis. Although the accuracy improved after adding several parameters of the mitral and pulmonary venous flow analysis, their use in early or mild forms of the disease still cannot be recommended. Novel tissue Doppler imaging, which measures the velocity of myocardial movement instead of indirectly blood flow during the systolic and diastolic phase, was a significantly superior technique in identifying early disturbances of both LV relaxation and stiffness. The proportion of the blood flow and myocardial tissue velocity during early diastolic filling phase, known as the LV filling index correlated the most strongly with invasive obtained diastolic pressure and stiffness. Among all echocardiographic parameters investigated, the LV filling index was identified as the most reliable non-invasive diagnostic tool for determining diastolic dysfunction in HFNEF. This study provides cut off values and equations for an estimation of LV relaxation, filling pressure and stiffness in HFNEF which may improve clinical diagnostic routine.

Kasner, M., Westermann, D., Steendijk, P., Gaub, R., Wilkenshoff, U., Weitmann, K., Hoffmann, W., Poller, W., Schultheiss, H.-P., Pauschinger, M., Tschöpe, C. 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 Aug 7;116(6):637-47.

DOI: <http://dx.doi.org/10.1161/CIRCULATIONAHA.106.661983>

2. Global strain rate imaging for the estimation of diastolic function in HFNEF compared with pressure-volume loop analysis. (Eur J Echocardiogr. 2010 Oct;11(9):743-51.)

Kasner, M., Gaub, R., Sinning, D., Westermann, D., Steendijk, P., Hoffmann, W., Schultheiss, H.-P., Tschöpe, C.

In this similarly designed study a further novel echocardiographic modality, myocardial deformation imaging, was put into focus in order to investigate its diagnostic value in HFNEF. Strain and strain rate measurements are quantitative indexes of cardiac deformation which give direct information on intrinsic myocardial function and therefore may detect even subtle diastolic abnormalities. The Speckle tracking technique allows tracing of myocardium from simple 2-dimensional grey images throughout the cardiac cycle in all directions, whereas tissue Doppler imaging only in one. This method provides assessment of global 2D strain / rate, independent of translational motion and through-plane motion effects, which are known limitations of Doppler imaging. Several global strain and strain rate parameters during systolic and diastolic phase – divided into isovolumetric relaxation, early and late diastolic filling – were correlated with LV relaxation and stiffness indexes obtained by gold standard conductance catheterization in HFNEF and controls. These correlations were compared with the results of established tissue Doppler parameter. The distinctive value of this study lies in simultaneously performed strain measurements during invasive pressure-volume loop registration and thus minimized haemodynamic differences occurring due to heart rate variability, loading conditions or other factors. The study results showed that systolic deformation is not affected in this HFNEF population. The findings of diastolic strain rate parameters were closely related to the invasive diastolic indexes in patients with HFNEF. However, when compared with tissue Doppler and particularly LV filling indexes, 2D strain rate revealed similar accuracy in detecting increased LV stiffness. In conclusion, results did not provide any significant advantages of diastolic strain rate over tissue Doppler filling index in the routine diagnostic of HFNEF. Nevertheless, strain rate could be helpful for additional analysis in patients with borderline results and for a better understanding of myocardial pathomechanisms in HFNEF.

Kasner, M., Gaub, R., Sinning, D., Westermann, D., Steendijk, P., Hoffmann, W., Schultheiss, H.-P., Tschöpe, C. Global strain rate imaging for the estimation of diastolic function in HFNEF compared with pressure-volume loop analysis. Eur J Echocardiogr. 2010 Oct;11(9):743-51.

DOI: <http://dx.doi.org/10.1093/ejehocard/jeq060>

3. Simultaneous estimation of NT-proBNP on top to mitral flow Doppler echocardiography as an accurate strategy to diagnose diastolic dysfunction in HFNEF. (Int J Cardiol. 2011 May 19;149(1):23-9)

Kasner, M., Gaub, R., Westermann, D., Kaplan, H., Akpulat, S., Steendijk, P., Schultheiss, H.-P., Tschöpe, C.

In clinical practice, conventional echocardiography is a crucial non-invasive diagnostic approach in attempting to ascertain diastolic dysfunction in HFNEF. According to the recent guidelines, mitral flow Doppler echocardiography has not been recommended any more as a first-line diagnostic of isolated diastolic dysfunction because of its limited accuracy. Since N-terminal pro-brain natriuretic peptide (NT-pro BNP) is proven to reveal a high negative predictive value in order to rule out heart failure, including diastolic heart failure, the question remains whether an additional determination of the NT-pro BNP on top to the conventional flow Doppler echocardiography may be an accurate alternative diagnostic approach, if tissue Doppler is not available. This study is of enormous importance for everyday clinic routine. First, the accuracy of NT-proBNP was validated by comparing its plasma levels with the “gold standard” for analysing diastolic function; measurements of pressure-volume (PV) relationships were made to test the hypothesis whether plasma NT-proBNP as an additional criterion can improve the conventional mitral flow Doppler analysis for the diagnostic of HFNEF. This was then compared with the corresponding data taken from use of an invasive approach. Additionally, follow-up analysis was performed to investigate the predictive role of NT-proBNP already in patients with mild HFNEF compared to echocardiographic analysis. We found that in patients with HFNEF, abnormal NT-proBNP plasma levels reflect already mild impairments of LV relaxation or stiffness. When added to mitral flow Doppler analysis, NT-proBNP improved the accuracy of conventional echocardiography concerning the diagnostics of HFNEF, up to the level of tissue Doppler analysis. Its plasma levels correlate with the degree of a cardiac remodelling process which determines collagen content directly from endomyocardial biopsies in patients with HFNEF. These findings have proven that NT-proBNP is not just a haemodynamic marker but that it is also indicating cardiac remodelling processes which may support its clinical role in outlining the prognosis and treatment response in patients with HFNEF. And finally, a superior role of NT-proBNP in predicting hospitalization compared to echocardiography indexes was shown.

Kasner, M., Gaub, R., Westermann, D., Kaplan, H., Akpulat, S., Steendijk, P., Schultheiss, H.-P., Tschöpe, C. Simultaneous estimation of NT-proBNP on top to mitral flow Doppler echocardiography as an accurate strategy to diagnose diastolic dysfunction in HFNEF. *Int J Cardiol.* 2011 May 19;149(1):23-9

DOI: <http://dx.doi.org/10.1016/j.ijcard.2009.11.035>

4. Diastolic tissue Doppler indexes correlate with the degree of collagen expression and cross-linking in heart failure and normal ejection fraction. (J Am Coll Cardiol. 2011 Feb 22;57(8):977-85)

Kasner, M., Westermann, D., Lopez, B., Gaub, R., Escher, F., Köhl, U., Schultheiss, H.-P., Tschöpe, C.

One of the postulated pathophysiologic mechanisms in HFNEF also includes the role of the extracellular matrix, in particular the amount of cardiac collagen. It is believed that enhanced myocardial fibrosis could be associated with an increase of myocardial passive properties, LV stiffness and is thus critical for reduced compliance and impaired diastolic filling in HFNEF. This study aimed to determine the amount of cardiac collagen in endomyocardial biopsies taken from HFNEF patients and to prove the association of myocardial fibrosis with diastolic dysfunction. An additional objective was to evaluate how reliable echocardiographic indexes of LV stiffness are in recognizing the changes of myocardial collagen. Compared to controls, patients with HFNEF showed increased myocardial collagen content, predominantly collagen type-I. Collagen-I is also known for its stiff molecular properties and is thus responsible for increased passive ventricular stiffness in HFNEF, compromising diastolic filling of the LV. In agreement with this we found a direct correlation of cardiac collagen type I with diastolic dysfunction and cardiac performance in HFNEF which were associated with reduced exercise tolerance. An interesting finding was the enhanced collagen cross-linking and lysyl-oxidase expression in comparison to that of control patients, indicating the presence of an early remodelling process in HFNEF. This association suggested that not only the quantity but also the quality of myocardial collagen influences the compliance characteristics and performance of the LV in HFNEF. A further valuable finding was the evidence of a relationship between diastolic tissue Doppler velocities, particularly LV filling index and collagen type I content as well as cross-linking expression, whereas conventional flow Doppler measurements did not reveal any significant correlations here. The latter implicates the ability of tissue Doppler imaging to reflect the alteration of haemodynamic LV properties due to structural changes of the extracellular matrix, already present among mild forms of HFNEF. Therefore, tissue Doppler imaging should substantiate a method of choice for the evaluation of diastolic function in HFNEF.

Kasner, M., Westermann, D., Lopez, B., Gaub, R., Escher, F., Kühl, U., Schultheiss, H.-P., Tschöpe, C. Diastolic tissue Doppler indexes correlate with the degree of collagen expression and cross-linking in heart failure and normal ejection fraction. J Am Coll Cardiol. 2011 Feb 22;57(8):977-85

DOI: <http://dx.doi.org/10.1016/j.jacc.2010.10.024>

5. Left ventricular dysfunction induced by nonsevere idiopathic pulmonary arterial hypertension: a pressure-volume relationship study. (Am J Respir Crit Care Med. 2012 Jul 15;186(2):181-9.)

Kasner, M., Westermann, D., Steendijk, P., Dröse, S., Poller, W., Schultheiss, H.-P., Tschöpe, C.

Severe increase of right ventricular pressures can compromise diastolic filling of the left ventricle to the extent of diastolic heart failure. The underlying pathomechanisms in patients with an early form of idiopathic pulmonary hypertension (IPAH) still remain unclear. Particular enquiring here is the impact of the right ventricle on the LV function. This is the first study in humans with IPAH which performed pressure-volume loops analysis obtained by conductance catheterization in order to detect complex haemodynamic changes of diastolic ventricular interaction (DVI) at rest, during preload reduction and during atrial pacing mimicking stress conditions, compared to the controls and patients with diastolic dysfunction. In patients with IPAH, increased pulmonary pressures lead to impaired ventricular interaction characterized by an increased right to left end-diastolic transseptal pressure gradient and non-uniform relaxation of the septum. A 2-fold increased diastolic internal flow was shown with an ineffective volume shift between the segments. This resulted in reduced LV compliance and elevated diastolic filling pressures, in terms of diastolic dysfunction in the absence of prior intrinsic LV disease. However systolic function was preserved as evidenced by normal LV contractility and ejection fraction. During pacing at 120/min in patients with IPAH, decreased stroke volume and cardiac output failed to increase significantly, similar to the case of patients with an intrinsic LV diastolic dysfunction. In IPAH, preload reduction during inferior vena cava occlusion neutralized the transseptal gradient inducing expansion of LV end-diastolic volume and consecutive end-diastolic pressure drop, indicating a better LV filling, which was associated with improvement of cardiac output. Haemodynamic changes which are observed and then documented via DVI are proven to be accompanied with exercise tolerance in patients with IPAH, as obtained by a pathologic 6-minute walk test, ergometry performance, and a significantly elevated plasma level of NT-proBNP. These effects were already present in patients with only mild and moderate pulmonary hypertension, suggesting that it may aggravate their clinical manifestation and furthermore that these patients might profit from early therapy.

Kasner, M., Westermann, D., Steendijk, P., Dröse, S., Poller, W., Schultheiss, H.-P., Tschöpe, C. Left ventricular dysfunction induced by nonsevere idiopathic pulmonary arterial hypertension: a pressure-volume relationship study. *Am J Respir Crit Care Med.* 2012 Jul 15;186(2):181-9.

DOI: <http://dx.doi.org/10.1164/rccm.201110-1860OC>

Discussion

The diagnosis of heart failure despite normal EF involves with considerable difficulties in everyday clinic routine, and the pathogenesis of those patients still remains unclear. On the basis of publications presented here in this cumulative thesis, the role of several new echocardiographic methods validated by invasive standard measurements will be discussed, as well as their additional diagnostic effects on the established conventional non-invasive methods and markers. Furthermore, this will elaborate on the pathophysiologic associations between cardiac remodelling in terms of collagen accumulation and induction of a diastolic dysfunction using novel echocardiographic tools for a more reliable functional characterization of the heart. And finally the influence of the right ventricle on the left ventricle and their interaction during diastolic phase will be evaluated as an additional pathophysiological effect in patients with idiopathic pulmonary hypertension and compared with a HFNEF population. All of the publications presented here focus on patients with HFNEF.

Evaluating cardiac dysfunction in patients with HFNEF is a complex and not unequivocal undertaking which still requires the exact analysis of left ventricular haemodynamic function. Disturbed LV stiffness and impaired LV relaxation are considered to be a cardinal mechanism of diastolic dysfunction in HFNEF,¹¹ despite preserved LV contractility. In this regard the invasive measurement of LV stiffness is becoming increasingly important. A measurement of this includes simultaneous recordings of LV pressure and volume in order to provide pressure-volume loops. Using the changes and shift of pressure-volume loops during a transient preload reduction makes it possible to measure LV distensibility. Also an exact LV stiffness can be determined by means of recorded invasive data. This method was performed in all studies with HFNEF patients where non-invasive diagnostic methods were tested. The first study could prove that increased LV stiffness represents a crucial pathomechanism in HFNEF patients. In our further study¹⁷ the role of LV stiffness in HFNEF at rest and under exercise was elaborated and thus an exact haemodynamic phenotype of those patients could be described. In agreement with findings of large population-based heart failure trials,^{1, 2} our HFNEF patients with increased LV

stiffness were associated with a higher prevalence of concomitant diseases, arterial hypertension and diabetes mellitus, known to be linked with diastolic dysfunction. They also showed concordant findings regarding their decreased LV volumes and larger left atrial volume index⁶⁰ confirming that impaired LV filling impairs mitral inflow and gives rise to LA enlargement. However our HFNEF population demonstrated LA dimensions which were near those within the normal range, probably due to the shorter duration of heart failure in our relatively young population, as compared to other studies with older HFNEF patients. Nevertheless, higher LV mass index and increased LV mass-to-volume ratio were shown in HFNEF suggesting a presence of their structural remodelling.

In conclusion, the invasive pressure-volume measurements in HFNEF aid us to better understand their complex pathophysiology and can also serve for validation of non-invasive methods which are more applicable in clinical routine work.

Several studies showed that other, non-diastolic mechanisms could be involved in patients with HFNEF and in particular an impairment of systolic function.^{61, 62} They used a novel echocardiographic technique, *Speckle tracking*, which allowed a characterization of myocardial deformation and thus even more subtle changes in LV function than reduction in ejection fraction. However, a systolic dysfunction like that obtained from previously described invasive haemodynamic measurements was found in none of our studies on HFNEF patients. Moreover, no impairment of arterioventricular coupling and LV elastance could be evidenced by the analysis of an endsystolic pressure-volume relationship. Those are volume-independent systolic LV characteristics for which impairment has been reported as a possible mechanism responsible for exercise intolerance in HFNEF. In line with the latter, the results from a validation study of Speckle tracking for the diagnosis of HFNEF also showed no systolic abnormalities in terms of impaired systolic deformation as proven by preserved global longitudinal 2D strain in this study. In direct comparison with invasive pressure-volume measurements, it could be evidenced again that myocardial deformation was diminished solely during diastole including reduced strain rate in both the early (SR_E) and late (SR_L) phase. This was also the case for the ratio index E/SR_E . In general, a systolic dysfunction in patients with HFNEF is however not unlikely, but it is essential that a global pump function is not distinctly

reduced. In conclusion, our HFNEF patients were characterized by isolated diastolic dysfunction which should be taken into consideration when comparing these with results from other studies on HFNEF. This is a form of early and mild myocardial dysfunction which was associated with exercise intolerance despite preserved systolic function. Thereby, exercise limitation were evaluated objectively by a 6-min walking test or a cardiopulmonary bicycle exercise test. In our further study,⁶³ invasive-measured LV stiffness found to be directly and independently associated with exercise limitation as obtained by VO_2 and VE/CO_2 , known to be the most objective test for assessment of cardiac exercise capacity. Failing cardiac reserve in these patients was also accompanied by lower exercise performance and elevated NT-proBNP values.

Interestingly, the amount of cardiac collagen accumulation in HFNEF, as proven by endomyocardial biopsies, correlated significantly with LV filling index E/E' , an echocardiographic surrogate parameter for LV stiffness. This relationship was supported in particular by a connection to collagen I expression, which is known to possess extreme tensile properties. This association was also confirmed with invasive-measured LV stiffness.⁶⁴ Thus a specific cardiac functional phenotype evidenced by novel imaging modalities was associated with specific morphological changes in terms of cardiac remodelling. By this, not only a quantitative collagen accumulation but also a qualitative change of extracellular matrix by increased collagen cross-linking and lysyl-oxidase expression were linked with diastolic parameters from tissue Doppler imaging and LV filling index E/E' . This association suggested that quantity and quality of myocardial collagen influence the compliance characteristics and performance of the LV in HFNEF. Correlation of diastolic TDI parameters with increased cardiac collagen expression and cross-linking implicates that TDI reflects the haemodynamic properties of the LV already present among mild forms of HFNEF. Therefore, in middle-aged patients with symptoms manifested solely during exercise conditions, TDI should substantiate a method of choice for the evaluation of diastolic function.

Additional to the intrinsic LV abnormalities in HFNEF which are detected more accurately by novel echocardiographic modalities tissue Doppler imaging and Speckle tracking imaging, there are also "extraventricular" causes that can

compromise diastolic LV filling such as pericardial constraint and diastolic ventricular interaction. This effect is well known in a severe pulmonary hypertension with excessive pressure and volume overload of the enlarged right heart compromising LV filling.⁶⁵ Even more, we were able to show for the first time that even non-severe idiopathic pulmonary arterial pressure significantly influences diastolic ventricular interaction and impairs the filling and compliance of the LV in the absence of a prior intrinsic LV disease. LV dysfunction can induce exercise intolerance *per se* and may contribute to the symptoms of patients with mild IPAH who attempt to stretch beyond their pulmonary limitations. Haemodynamic changes induced by diastolic ventricular interaction are shown to be accompanied by neurohumoral activation as evidenced by elevated NT-proBNP levels. From a clinical point of view the mechanism described in the study is of great relevance since both patients with pulmonary hypertension and patients with diastolic dysfunction are manifested similarly by dyspnoea and exercise intolerance, especially in an early stage.

The association of increased LV stiffness and exercise intolerance in HFNEF patients is in line with invasive studies which showed increased passive cardiac stiffness in patients with more severe heart failure symptoms¹⁸ but also in mild HFNEF.⁶⁶ This was also supported by large population-based studies carried out using a non-invasive approach to measure diastolic stiffness.¹¹ The non-invasive data of these studies were also able to show that an increased filling index occurs in those HFNEF patients without any volume overload and subsequent enlargement of the LV. This is supported by the coherent results of Zile et al.^{10, 17}

However, there is an ongoing debate whether non-diastolic limitations of the cardiovascular function may be superior to LV diastolic dysfunction in limiting exercise capacity in HFNEF patients, including LV dyssynchrony,^{6, 7} LV contractility,¹¹ arterial-ventricular coupling^{30, 67}, and chronotropic incompetence.^{6, 10, 17, 68-70} LV dyssynchrony, arterial-ventricular coupling and LV contractility were not found to have a major abnormality in our studies. The latter finding is in contrast to that of Tan et al.^{7, 71} who found impairments in LV contractility, at least in elderly with more severe concomitant diseases including coronary artery disease and atrial fibrillation. Thus, different mechanisms contribute additionally to the exercise intolerance, and

this depends on the development of risk factors, including aging, ischemia and arrhythmias.

Beyond the heterogeneous and hitherto incompletely understood pathophysiology there is also an inconsistency in definition and diagnostic evaluation of HFNEF, particularly when guidelines reveal borderline results and in patients without a long history of typical risk factors, left ventricular hypertrophy and left atrial dilatation.⁷² The cardiac status of these patients often remains cryptic, and cardiac dysfunction may remain unrecognized if invasive conductance catheter measurements are not performed. These invasive procedures are cost-intensive, require high-tech equipment and have potential risks to patients that limit their widespread application. Although it does not directly measure diastolic function, echocardiography is widely available and has therefore become the first method of choice in clinical practice.⁴² However, it is commonly known that the most-used technique flow Doppler echocardiography cannot provide unequivocal evidence of diastolic dysfunction in HFNEF. Their parameters (E/A ratio, IVRT, DT, and pulmonary vein Doppler)⁵⁰ do not permit any direct measurement of LV relaxation, stiffness, or filling pressure.^{73, 74} Even though it has been demonstrated that mitral flow Doppler echocardiography can reliably estimate LV end-diastolic pressure in patients with a reduced EF (Guidelines ASE/ESC 2009) this is not evident in HFNEF.^{47, 50} The difference between these findings can be explained by a dependence of the E velocity on both left atrial pressure and LV relaxation. In HFREF patients, LV relaxation is certainly impaired and thus the E and E/A ratio are predominantly dependent on LA pressure. In contrast to HFREF, in HFNEF patients LV relaxation is variably prolonged, and therefore the E and E/A remain to be dependent on both LV relaxation and LA pressure. In concordance are the findings of our study which validated tissue Doppler echocardiography in diagnosing diastolic dysfunction in HFNEF by direct comparison to invasive pressure-volume measurements. Concerning the measurements of LV relaxation, only a weak association between flow Doppler IVRT and invasive index Tau was found, whereas tissue Doppler imaging early diastolic mitral velocity (E') correlated significantly better. This proves that tissue Doppler imaging can reflect LV function and tissue properties than more accurately indirect flow measurements can. Regarding the valuation of LV filling pressures, the association of TDI parameters

with LVEDP were stronger than those of flow indexes E/A and DT, probably due to their biphasic response at rising filling pressures. Importantly, increasing preload has minimal impact on the E' velocity when LV relaxation is impaired and pseudonormalization does not occur when left atrial pressure is elevated.^{48, 49}

Further improvement of TDI is evident due to its strong relation to the most specific volume-independent index of diastolic dysfunction, LV stiffness. We found that the TDI indexes E' and E'/A' correlated more closely with LV stiffness than any conventional echocardiography index did. Similarly, the dimensionless E/E' index, which is recently introduced as an echocardiographic measure of LA pressure and LV filling,^{47, 50, 75-77} showed the best correlation with diastolic parameters from PV loop measurements. We could also show that using accepted cut-offs, the mitral flow Doppler correctly identified only 70% of HFNEF patients with diastolic dysfunction whereas TDI detected 81% and the LV filling index E/E' 86%. In conclusion, TDI was a more reliable technique to identify early disturbances of both LV relaxation and stiffness. This is in agreement with ESC recommendations and finding⁷⁸ of TDI to be the strongest echocardiographic predictor of exercise intolerance.

However, neither mitral flow nor TDI are direct measures of LV filling and thus do not provide specific information on intrinsic passive diastolic properties of the LV.⁷⁹ Also, the LV filling index E/E' has some limitations in characterization of diastolic function,^{2, 10, 43} due to its wide borderline values between a normal (< 8) and increased index (> 15). This is particularly the case when left atrial pressure is low, in mild form of disease with borderline symptoms. Here, the question arises whether novel techniques such as myocardial deformation imaging might in fact improve the diagnostics of HFNEF.

Strain and strain rate measurements are new quantitative indexes of intrinsic cardiac deformation⁸⁰ and when obtained by the Speckle tracking technique, they are angle-independent and not affected by translational motion and other through-plane motion effects in contrast to myocardial TDI.^{28, 43, 81, 82} These characteristics of a new imaging modality had initially promised more accurate diagnoses of LV dysfunction in HFNEF,⁵⁵ not only in systolic but also in diastolic phase. Thus, strain rate in both early and late diastole was proved to be impaired in HFNEF. However up-to-date the method is, there still remains the question how reliable it is in detecting subtle

haemodynamic changes, particularly in LV stiffness. With our further study this new method was validated and compared for the first time with gold standard PV analysis. Although there are strong correlations with LV relaxation Tau, end-diastolic pressure and stiffness coefficient, strain rate measurements alone did not appear to reveal significant advantages over TDI measurements in our HFNEF population. On the basis of ROC curve analyses, none of the strain rate indexes was significantly superior to the established TDI analysis including LV filling index E/E'. Therefore, due to required post-acquisition analysis, the widespread clinical application of global strain rate is not really rational but may be useful when TDI reveals unclear results or when regional motion disturbances may occur.

Since actually none of the applied non-invasive methods appear to be completely accurate solely, a comprehensive examination is required, incorporating several imaging modalities in the evaluation. A further aggravating factor involves a limited equipment disposal of those new techniques in general. It is therefore suggested to overcome this issue by using additional parameters for the conventional echocardiography, particularly when TDI is not available. Additional criteria suggested by ESC include LV mass and LA volume,²⁹ as well as BNP plasma levels.^{28, 83} BNP is known to rise when LV wall tension and filling pressure rise,⁸⁴⁻⁸⁶ and these have been already proven to be useful in diagnosing heart failure.^{28, 87, 88} Several small cohort studies^{73, 74, 89-92} showed a high accuracy of natriuretic peptides in diagnosing diastolic dysfunction in HFNEF. On the contrary, in large population-based trials, BNP measurement has revealed a highly negative and thus not an acceptable, positive predictive value. Thus BNP has been recommended to be used to rule out heart failure patients, but not to detect diastolic dysfunction in HFNEF as a sole parameter. We investigated for the first time in a prospective study the diagnostic accuracy of a proposed strategy to use additional NT-proBNP measurements which were superior to echocardiographic analysis in detecting diastolic dysfunction in HFNEF. First, the pressure-volume analysis proved that NT-proBNP was related not only to LV relaxation but also to LV stiffness in HFNEF. Hereby in high selected population the cut-off to rule out diastolic dysfunction was lower than proposed, at the value of 125 pg/ml. Furthermore, our findings showed that such additional measurements of NT-proBNP – which are better than those of simple, conventional echocardiography (E/A) – reveal results similar to those found

using TDI. Such an alternative diagnostic strategy to detect diastolic dysfunction in HFNEF revealed clinically acceptable accuracy in regard to sensitivity (93%) and specificity (74%). And lastly, according to follow-up evaluation, NT-proBNP was not only a diagnostic marker but revealed also prognostic information of our mild HFNEF patients showing increasing hospitalization frequency with increasing NT-proBNP levels. This is in agreement with recent trials showing that HFNEF is associated with an inverse mortality and morbidity rate^{2, 3} seen also in younger population, as reported in a population-based study.⁸

In conclusion, a comprehensive assessment which also includes potential limitations of echocardiography is required to accurately interpret LV systolic and diastolic function in HFNEF. Novel echocardiographic approaches are likely to improve our understanding of the pathophysiology, upgrade the noninvasive haemodynamic evaluation, and provide important diagnostic and prognostic information in these patients.

Summary

This thesis is focused on studies investigating the role of novel echocardiographic modalities for the evaluation of LV diastolic function in heart failure with a normal ejection fraction. New non-invasive techniques have been validated against the invasive gold standard catheterization method in order to provide the diagnostic and prognostic accuracy of HFNEF.

Despite of high prevalence and mortality in HFNEF, the exact pathomechanisms are still uncertain and diagnostic procedures unreliable. Conventional echocardiography, a widespread non-invasive method of choice yielded low sensitivity and specificity in direct comparison with pressure-volume relationship analysis. Novel tissue Doppler diastolic velocity parameters provided strong correlation with LV relaxation and stiffness, crucial haemodynamic determinants of diastolic dysfunction. They showed significantly higher diagnostic accuracy in early and mild forms of LV dysfunction. In particular, the LV filling index E/E' correlated with passive cardiac properties like the LV stiffness coefficient. An additional study demonstrated that tissue Doppler velocities including E/E' index were associated with myocardial collagen amounts and the level of cardiac fibrosis obtained from endomyocardial biopsies, which have impact on LV stiffness. Besides tissue Doppler imaging, further echocardiographic modality, and deformation imaging also reflected intrinsic myocardial changes which showed a significant correlation of diastolic strain rate with relaxation index and LV stiffness. By this, deformation parameters were not found to be superior to the tissue Doppler imaging in diagnostic HFPEF. However, in the settings of clinical routine where extended echocardiographic analysis is not available, a simple diagnostic tool with an additional determination of NT-proBNP level to the conventional echocardiography improved the diagnostic accuracy up to the level of tissue Doppler imaging and showed a prognostic value by predicting a re-hospitalisation rate involving HFNEF. New techniques extended the understanding of pathophysiology in HFNEF as evidenced by their relation to cardiac fibrosis, and by their clarifying diastolic ventricular interactions in primary pulmonary arterial hypertension.

The bottom line of these evaluated studies is that novel echocardiographic methods optimize diagnostic accuracy in HFNEF based on an improved characterization of intrinsic myocardial properties.

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Eidesstattliche Erklärung

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

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wird bzw. 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.

April, 2013

Mario Kasner

