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DISSERTATION

Prediction of Short–Term Outcomes in Patients with Idiopathic Dilated Cardiomyopathy Referred for Transplantation using Standard Echocardiography and Strain Imaging

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1. Preamble

Idiopathic dilated cardiomyopathy (DCM) is considered the most common cause of chronic heart failure syndrome in Western countries. Despite advanced pharmacologic treatment DCM remains a progressive condition with high mortality rates (1). A possible treatment option for end-stage idiopathic DCM is heart transplantation (HTx), yet the waiting time on HTx list continues to increase and many patients die on the waiting lists. The criteria used for patient listing for HTx or high-urgency HTx are of vital importance, thus the need for more reliable predictors of the time course of heart failure (HF) has become increasingly important. Although many studies analyzing the long term predictors of HF course have been published (2-5), the data on short term prognostic markers in patients with DCM, which could be helpful in HTx listing, are scarce.

2. Background

2.1. Dilated cardiomyopathy

2.1.1. Definition and epidemiology

The World Health Organization (WHO) defines DCM as a condition in which the ventricular chambers exhibit increased diastolic and systolic volume and a low (<40%) ejection fraction (1,2). The prevalence of DCM in the adult population in Western countries is 1-1,5% and as already mentioned it is considered as the most common cause of chronic HF syndrome. The natural history of the condition is progressive. Despite improved treatment, the mortality rate for dilated cardiomyopathy remains high, with a median period of survival of 1.7 years for men and 3.2 years for women (1). A minority of patients with recent-onset DCM improve spontaneously, even some sick enough initially to be considered for cardiac transplantation. Cost, disability, and morbidity of DCM are among the highest of any disease (3-5).

2.1.2. The place of DCM in the classification of cardiomyopathies

The 1995 WHO/ISFC (International Society and Federation of Cardiology) classification of cardiomyopathies was based mainly on the anatomic descriptions of cardiac chambers in systole and diastole, but the pathopysiologic background, natural history and response to treatment of these conditions were not considered. Therefore recently an American Heart Association scientific group prepared a new classification (6), where DCM and restrictive cardiomyopathy are defined as mixed cardiomyopathies (predominately non-genetic). Hypertrophic cardiomyopathy, caused by mutations in contractile proteins, Ion channelopathies, arrythmogenic right ventricular dysplasia (cardiomyopathy) and left ventricular noncompaction, which also have genetic reasons, were defined as genetic cardiomyopathies. As acquired cardiomyopathies the following were classified: peripartum, tachycardia-induced, stress-provoked (Tako-Tsubo syndrome) cardiomyopathies and myocarditis. Genetic cardiomyoapthies without unique phenotype and with multiorgan involvement (eg. Duchenne muscular dystrophy, Friedriech ataxia, myotonic dystrophy) were considered secondary.

2.1.3. Etiology

Heart chamber dilation can be caused or accelerated by the following processes and agents (7):

- Genetic reasons (autosomal dominant, autosomal recessive, X-linked inheritance)
- Specific heart muscle diseases (myocardial ischemia, valvular heart disease, chronic systemic hypertension)
- Metabolic diseases (nutritional deficiencies, endocrine disorders (e.g. diabetes mellitus hypothyroidism, thyrotoxicosis, Cushing disease, pheochromocytoma), electrolyte disturbances (e.g. hypocalcemia, hypophosphatemia)
- Infections (viral, bacterial, rickettsial, mycobacterial, fungal, spirochetal, parasitic)
- Toxins (e.g. alcohol, anthracyclines, antiretroviral agents, cocaine, lithium, phenothiazines)
- Systemic, autoimmune diseases (e.g, systemic lupus erythematosus, amyloidosis, sarcoidosis)
- Peripartum state
- Tachyarrythmias (supraventricular, ventricular, atrial fluter)
- Arrhythmogenic right ventricular dysplasia or cardiomyopathy

- Neuromuscular dystrophies (e.g. X-linked cardioskeletal myopathy)
- Hematologic disorders (e.g, chronic anemia, as in sickle cell disease or thalassemia)
- Idiopathic DCM.

The variety of possible etiologic factors shows how heterogeneous the phenotype of dilated cardiomyopathy is. Thus differential diagnosis of DCM might also be very complicated. Idiopathic DCM can be considered only when after rigorous evaluation all other possible etiologic factors are excluded; and even then idiopathic DCM makes up more than a half of patients with DCM.

A lot of scientists work to elucidate the possible reasons for idiopathic DCM, most of them concentrating on genetic and autoimmune mechanisms. Transmitted genetic alterations responsible for familial DCM have already been identified. However none of the other revealed genetic or autoimmune system alterations can independently cause idiopathic DCM.

Genetics

Three main categories of genetic mechanisms are involved in the development of DCM: single gene defects, altered expression of normal genes and polymorphic variations in modifier genes. Familial dilated cardiomyopathies are associated with multiple single gene mutations, usually encoding cytoskeletal, nuclear membrane, or contractile proteins, including desmin, titin, and troponin T. The transmission is usually autosomal dominant, although autosomal recessive and X-linked inheritance is also known (8).

In all types of cardiomyopathies, when heart failure progresses, altered expression of normal, so called wild-type genes can be found. The examples are as follows: downregulation of beta1-adrenoreceptors, ATPase genes, upregulation of atrial natriuretic peptide (ANP), ACE, tumor necrosis factor (TNF) alfa, endothelin, etc. (9)

The last genetic mechanism, which could probably contribute to the genesis of idiopathic DCM, is based on polymorphic variations (slightly different size or number) of modifier genes. These are not so rare in population, and usually they do not cause any differences in function and are considered normal. Yet some of these polymorphisms can cause differences in the function of encoded proteins, which might be considered as biological variation, but also might account for a higher susceptibility for disease or different response to treatment. Polymorphic variants of genes encoding angiotensin converting enzyme (ACE), angiotensin AT1 receptors, beta2-adrenoreceptors, alfa1 adrenoreceptors with or without beta1-adrenoreceptor polymorphism and endothelin receptor type A are known to influence the natural history of cardiomyopathies. Moreover pharmacogenomic studies have shown that polymorphic variations also influence the different response to medications.

Autoimmunity

Several immune regulatory abnormalities have been identified in DCM, including humoral (10), and cellular autoimmune reactivity against myocytes (11), decreased natural killer cell activity (12), and abnormal suppressor cell activity (13). It is possible that certain antibodies present in DCM may have important functional implications (14). For example, anti–beta1-adrenergic receptor antibodies could modify beta-adrenergic receptor activity and produce chronic increases in signal transduction that are harmful to the failing heart (15).

Human leukocyte antigens (HLAs) associations have also been identified in DCM. This suggests a possible immunologic etiology for this disease. However, specific HLAs are present in <50 percent of patients with DCM, and the heterogeneity of these antigens does not point to a unique site for a putative disease-associated gene (17). Thus, although the autoimmune hypothesis is an attractive candidate for the etiology of idiopathic DCM, it still remains unproved.

2.1.4. Pathological anatomy: macroscopic and microscopic features

DCM is characterized by initial dilation of left ventricle (LV) and later of all four cardiac chambers with myocyte hypertrophy and diminished systolic function. However the degree of hypertrophy is often less than might be expected given the severe dilation present. Total cardiac mass in DCM is increased. Grossly visible scars may be present in both ventricles: most of them are small, but some may be large and transmural. Scarring occurs in the absence of significant narrowing of the epicardial coronary arteries. The cardiac valves are intrinsically normal, and intracavitary thrombi, particularly in the ventricular apex, also as mural endocardial plaques (from the organization of thrombi) are not uncommon (8,9).

Microscopic study reveals extensive areas of interstitial and perivascular fibrosis, particularly involving the left ventricular subendocardium. Small areas of necrosis and cellular infiltrate are also seen. There is marked variation in myocyte size; some myocardial cells are hypertrophied, and others are atrophied. In isolated cardiac myocytes, the major cellular phenotypic change is a marked increase in cell length without a concomitant increase in diameter.

No viruses or other etiological agents have been identified with any regularity in tissue from patients with DCM. Particularly disappointing has been the failure to identify any

immunological, histochemical, morphological, ultrastructural, or microbiological marker that might be used to establish the diagnosis of idiopathic DCM or to clarify its cause (8,9).

2.1.5. Pathophysiology

Neuroendocrine system

The progression of HF is consistent in patients with different etiologies, as it is ultimately driven by very similar biologically active molecules, regardless of the inciting cause (18). Compensatory mechanisms that are activated after the initial decline in the pumping capacity of the heart are able to modulate LV function within the physiologic range. Therefore the functional capacity of the patient at the beginning is preserved or depressed only minimally. The early activation of the adrenergic nervous system (ANS) and salt-water retaining renin-angiotensin system (RAS) preserve cardiac output by increasing heart rate and contractility and expanding the plasma volume. In order to reduce wall stress hypertrophy develops. To counteract the excessive vasoconstriction resulting from excessive activation of ANS and RAS, the family of vasodilatory molecules, including natriuretic peptides, prostaglandins (PGE2, PGEI2) and nitric oxide, is activated (18-20). Yet for a longer time all these compensatory mechanisms show adverse affects, such as altered gene expression, resulting in changes in cardiac myocytes, growth and remodelling and apoptosis. Excessive adrenergic stimulation has a toxic effect on the myocytes and results in their necrosis. Angiotensin II through collagen deposition enhances myocardial fibrosis.

Changes at the myocyte and myocardium level

In addition to excessive neuroendocrine stimulation, altered expression of genes causes defects of their encoded proteins or regulatory mechanisms and further enhances myocardial contractile dysfunction. These phenomena may be divided into two groups: changes in intrinsic and in modulated heart function. The intrinsic heart function means the contraction and relaxation of the myocardium in the resting state, which is not influenced by hormonal or neural factors. Modulated heart function might be stimulated or inhibited by extrinsic factors (neurotransmiters, cytokines, autocrine/paracrine substances and hormones). It is very important for the response to the changed physiologic conditions or physical stimuli (20).

The changes in intrinsic function in the failing heart comprise an altered length-tension relation, a blunted force-frequency response and signals responsible for the abnormal cellular and chamber remodelling (20). As during remodelling cardiac myocytes become greatly lengthened relative to transverse diameter, the wall stress, which is one of the determinants of myocardial oxygen consumption, increases (20,22,23). Moreover myocyte energy production is inadequate due to deficiencies in subcellular ion flux mechanisms or the myosin ATPase cycle (20,21). All this places the heart at energetic disadvantage and further contributes to contractile dysfunction.

Most of the changes in the modulated heart function occur in beta-adrenergic signal transduction (24). The ability of beta-adrenergic stimulation to increase heart rate and contractility is affected in the failing heart due to the changes in receptors, G-proteins and adenylate cyclise, which influence myocardial reserve and exercise responses. Nevertheless the inhibition of modulated heart function is also abnormal in heart failure as a result of the reduced parasympathetic drive (9,20).

At the myocardial level firstly the myocyte loss contributes to pump dysfunction in heart failure. Myocyte loss can occur via toxic mechanisms, producing necrosis, or by programmed cell death, producing apoptosis (9). There is experimental evidence that myonecrosis might be triggered by elevated levels of circulating or tissue norepinephrine, or by excessive stimulation with angiotensin II or endothelin (25,26). It has been proved in *in vitro* and *in vivo* models that apoptosis can be triggered by multiple factors taking part in the pathogenesis of heart failure, such as myocardial stretch, norepinephrine, TNF, oxidative stress, angiotensin II. Yet all the currently available assessments of myocyte apoptosis in failing hearts have been performed on explanted hearts from heart transplantation recipients, many of whom were receiving inotropic support. As catecholamines are also known to provoke apoptosis, it remains unclear whether apoptosis occurs only in end-stage HF or whether it contributes to progression of cardiac remodelling and systolic dysfunction (18).

After the death of myocytes the deposition of fibrillar collagen in the extracellular matrix occurs. This “replacement fibrosis” as well as perivascular fibrosis around the intramyocardial blood vessels can be triggered by angiotensin II, endothelin and aldosterone. It might contribute to the progression of contractile dysfunction.

Recently it has been suggested that within the failing myocardium collagenolytic enzymes, known as metalloproteinases (MMPs), become activated. They lead to the progressive degradation of the extracellular matrix, which accounts for the LV wall thinning and dilation.

TNF and other cytokines and peptide growth factors that are expressed in the failing myocardium are capable of activating MMPs (18).

Changes in left ventricular geometry and architecture

There are two different opinions about the role of LV remodelling. Some investigators view it as the end-organ response to long–lasting neurohormonal stimulation and to changes occurring at myocardial level; others suggest that LV remodelling might contribute independently to the progression of heart failure (27,28) and first of all by the increase in LV wall stress. The increase in LV end-diastolic wall stress occurs as a result of the increase in LV size and the change in its geometry from ellipsical to a more spherical shape. Given that the load of the ventricle at end-diastole contributes to the afterload that the ventricle faces at the onset of systole, it follows that LV dilation itself increases the work and also the oxygen utilization. This increase in afterload created by LV dilation together with LV wall thinning occurring during the remodelling contributes to the decrease in cardiac output (18,29). The high end-diastolic wall stress might lead to episodic hypoperfusion of the subendocardium, with a resultant worsening of LV function (18,30) and increased oxidative stress, with a resultant activation of genes sensitive to free radical generation (eg., TNF and interleukin-1beta).

Moreover, in the dilated spherical ventricle the papillary muscles are pulled apart, which results in incompetence of the mitral valve and the development of "functional mitral regurgitation" (41). First of all this causes the loss of forward blood flow, and secondly the regurgitant flow further overloads the ventricle.

It seems that, when the deleterious changes in cardiac function and remodelling are advanced enough, they become self–sustaining and are capable of driving disease progression independently of the neurohormonal status of the patient.

2.1.6. Symptoms

Most of the patients remain asymptomatic for a long time and are not aware of their disease. First clinical presentation may be abrupt with acute pulmonary edema, systemic or pulmonary emboli or even sudden death, but more often patients present with typical signs and symptoms of chronic heart failure such as breathlessness, in particular exertional dyspnoea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, peripheral edema, palpitations,

hepatomegaly, cachexia, raised jugular venous pressure and other symptoms. Arrhythmias are also common in these patients.

Even though the severity of LV dysfunction only weakly correlates with symptoms, they alone can be used to classify the severity of chronic heart failure and to monitor the response to treatment. The New York Heart Association (NYHA) classification is one of the most widely used: (8,9,42).

- NYHA Class I – no limitations of physical activity;
- NYHA Class II – slight limitation of physical activity – symptoms with ordinary level of exertion (e.g. walking upstairs);
- NYHA Class III – marked limitation of physical activity – symptoms with minimal levels of exertion (e.g. dressing);
- NYHA Class IV – symptoms at rest.

The more recent classification of HF stages by American College of Cardiology/American Heart Association (ACC/AHA) involves also patients, without heart disease, yet with the risk factors: the ones who would profit from early HF treatment. The HF stages according to ACC/AHA HF classification are:

- Stage I – high risk for developing heart failure (HF). Patient description:
  - ✓ Hypertension
  - ✓ Coronary artery disease
  - ✓ Diabetes mellitus
- Stage II – asymptomatic HF. Patient description:
  - ✓ Previous MI
  - ✓ LV hypertrophy or systolic dysfunction
  - ✓ Asymptomatic valvular disease
- Stage III – symptomatic HF. Patient description:
  - ✓ Known structural heart disease
  - ✓ Shortness of breath and fatigue
  - ✓ Reduced exercise tolerance
- Stage IV - refractory end-stage HF. Patient description:
  - ✓ Marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions).

Stage II of this classification corresponds to NYHA class I, stage III to NYHA classes II and III, and stage IV to NYHA class IV. Stage I patients have only risk factors. However heart failure should not only be treated at symptomatic stages, but also prevented through the early treatment of risk factors and, when present, asymptomatic left ventricular (LV) dysfunction.

2.1.7. Diagnosis

Diagnosis is established by appropriate symptoms, physical examination, electrocardiography (ECG), chest X-ray, cardiac imaging (usually echocardiography, but might also be cardiac magnetic resonance or computed tomography) and cardiac catheterization. Additional information is provided by blood analysis, urinalysis and plasma natriuretic peptide concentration.

Electrocardiogram

ECG may reveal signs of left ventricular hypertrophy such as increased QRS voltage in the standard and precordial leads, ST segment and T wave abnormalities and left atrial abnormality. Arrhythmias and sinus tachycardia are common with non-specific T wave changes and poor R wave in anterior chest leads. It has been suggested that a completely normal ECG is very unlikely in a person with heart failure, but its positive predictive value is low in the elderly where ECG abnormality is common (8,9,42).

Chest X-ray

The main role for a chest radiograph is to exclude other causes for dyspnea—such as pleural effusion, pneumothorax, lung carcinoma, or pneumonia. Cardiothoracic ratio is only of moderate value in identifying heart failure as the cause of breathlessness. Echocardiography has replaced chest radiography as the method of determining cardiac chamber dimensions. However, in acute deterioration pulmonary congestion with interstitial edema, pleural effusions and Kerley B lines might be seen (8,9,42).

Echocardiography

The characteristic DCM features, such as impaired left ventricular contractility, reduced cardiac output and elevated left ventricular end-diastolic pressure, can be evaluated by echocardiography. From standard 2D and M-Mode images left ventricular global and regional systolic function and right ventricular systolic function can be qualitatively evaluated, LV end-systolic and end-diastolic dimensions or volumes, revealing LV dilatation can be obtained

and the ejection fraction can be calculated. Apical four chamber view is most suitable for the evaluation of LV dilation relative to other chambers; it also reveals the sphericity of the left ventricle. In DCM myocardial walls are often thin. Apical views are also suitable for the measurement of left ventricular volumes and for calculation of LV ejection fraction by the Simpson method. When severe LV dilatation is present a careful search for apical LV thrombus might be indicated, as also in the case of atrial fibrillation – a search for atrial thrombi (43,44).

The subcostal views are helpful when looking for signs of right heart insufficiency: congested hepatic veins and absence of inspiratory inferior caval vein collapse (44).

Doppler imaging reveals reduced aortic ejection velocity and velocity-time integral, indicating a reduced stroke volume. Associated mitral regurgitation usually of moderate severity is also usually seen, and a slow rate of rise in velocity of mitral regurgitant jet (dP/dt) shows an inreased LV pressure in early systole. Pulmonary pressures can be estimated from the velocity in the tricuspid regurgitant jet. The LV diastolic filling can be evaluated from left ventricular inflow by Doppler methods. In the early DCM stages a reduced E wave velocity and increased A wave velocity show impaired early diastolic relaxation. With further deteriorating LV function, left atrial pressure and LV end-diastolic pressure increases, resulting in an increase in E wave velocity and a decrease in A wave velocity (43,44).

Cardiac magnetic resonance imaging

Magnetic resonance imaging provides high-resolution images of cardiac structure and ventricular function. Contrast agents such as gadolinium can provide information on inflammation, fibrosis and myocardial perfusion. Valve function can also be assessed, although with less reliability than myocardial structure and function. Although becoming mainstream in large hospitals, the expense of the equipment and its lack of portability makes it of limited use in clinical routine (9).

Cardiac catheterization

Cardiac catheterization is firstly performed to exclude coronary artery disease. It also allows measurement of intracardiac pressures, estimation of cardiac output, detection of valve abnormalities, quantification of left ventricular ejection fraction, and the detection of epicardial coronary artery disease. Diastolic function can be assessed in detail. The ventricular biopsy performed during catheterization might be useful in revealing myocarditis.

Cardiopulmonary exercise test

Functional capacity is assessed from the clinical history or preferably measured by an exercise test. The cardiopulmonary exercise test measures the integrated response of the

pulmonary, cardiovascular, and muscular systems to a steadily increasing workload. The assessment of a normal work capacity is made by evaluation of the peak oxygen consumption (VO_2max). Although this parameter depends not only on cardiac reserve, but also on age, gender, muscle mass, deconditioning and pulmonary diseases, it is still widely used as a prognostic factor and criterion for HTx listing (8,9,42).

Laboratory examinations

B-type natriuretic peptide (BNP) is secreted by the heart, and the plasma concentration is elevated in left ventricular hypertrophy or dysfunction (systolic or diastolic), and particularly in those with heart failure. The current European and North American heart failure guidelines suggest that the measurement of the plasma concentration of BNPs or NT-proBNP can be useful in confirming or refuting a diagnosis of heart failure, particularly at the time of first presentation in the acute setting. However although normal BNP or NT-proBNP values suggest normal LV function, high values do not necessarily show severe HF. Apart from cardiac causes, natriuretic peptide elevation may be caused by renal dysfunction, pulmonary diseases, pulmonary embolism, sepsis, cirrhosis, hyperthyroidism and other high output states, etc. (95,96).

Additional laboratory parameters can reveal concomitant liver and kidney diseases, diabetes and other diseases.

2.1.8. Treatment principles

Management of DCM focuses on relieving symptoms and improving quality of life and prognosis. It consists of non-pharmacologic, pharmacologic and surgical treatment (45). Non-pharmacologic treatment involves patient and family education, weight monitoring, dietary restrictions, smoking cessation, alcohol intake reduction, vaccination, physical exercise training and others measures.

Pharmacological treatment

Drugs used for heart failure treatment can be roughly divided into two groups: those mainly reducing symptoms, and those acting on the neurohormonal system and improving outcomes.

- ***Drugs reducing symptoms***
  - ✓ Diuretics

Diuretics are useful in relieving symptoms caused by fluid overload (pulmonary congestion, peripheral oedema). There are no randomized, controlled trials that might have shown their benefit in terms of outcome and prognosis. However, the direct aldosterone antagonist spironolactone, which blocks aldosterone salt and water retaining effects, reduces mortality in patients with severe chronic heart failure (42,45,46).

- ✓ Cardiac glycosides

It is thought that digoxin acts by inhibiting sodium-potassium ATPase, thereby increasing intracellular sodium concentration. It results in increased transmembranous sodium-calcium exchange and increased calcium concentration and thereby improved myocardial contractility. Due to its vagomimetic properties it decreases conduction through the atrioventricular and sinoatrial node. It also has direct sympathoinhibitory affect and reduces renin activity. Due to its positive inotropic and negative chronotropic effects digoxin is used to reduce the symptoms of HF and to control the heart rate in patients with supraventricular arrhythmias (42,45,46).

- ***Drugs acting on the neurohormonal system***

- ✓ Renin-angiotensin-aldosterone system

Inhibition of the renin-angiotensin system can be achieved by counteracting the angiotensin I conversion to biologically active angiotensine II (angiotensin converting enzyme (ACE) inhibitors) or by inhibiting the action of angiotensin II by blocking AT1 receptors (angiotensin receptor 1 antagonists (ARB)). The weakened action of angiotensin II results in light venodilation, reduced baroreceptor sensitivity, slower break-down of bradicinine, increased excretion of H_20 and sodium and thereby in reduced blood pressure. Nevertheless, suppressed action of local angiotensin II retards left ventricular remodelling or even starts reverse remodelling.

Angiotensin converting enzyme inhibitors were the first neurohormonal blocking agents with mortality reducing effect in patients with heart failure. They also reduce symptoms and hospitalization of patients with moderate to severe heart failure or left ventricular dysfunction and are recommended as first line therapy for such patients.

Angiotensin receptor 1 antagonists can be used as an alternative in patients who are intolerant of ACE inhibitors. They are as effective as ACE inhibitors in reducing mortality of patients with chronic heart failure. Some studies speak for the advantages of combination therapy with ACE inhibitors and ARBs.

As mentioned above, aldosterone antagonists also improve outcomes if provided for patients with severe heart failure. By blocking aldosterone they increase excretion of H_20 and sodium, and it seems that they also inhibit left ventricular remodelling (42,45,46).

- ✓ Sympathetic nervous system

Beta-adrenoblockers reduce sympathetic activation by reversibly inhibiting beta adrenorecepors. The selective beta-blockers inhibit beta1 adrenoreceptors distributed mainly in the heart, and unselective beta-blockers inhibit also beta2 adrenoreceptors found in vascular and bronchial smooth musculature. Reduced sympathetic activation of the heart results in reduced myocardial contractility and reduced heart rate, and thereby it reduces myocardial oxygen demand. Due to slower heart rate the duration of diastole increases and myocardial oxygen supply ameliorates.

Beta-blockers were once contraindicated for patients with heart failure, because of their negative inotropic and chronotropic action. Later a number of large randomized clinical trials showed that they reduce the mortality and significantly improve the prognosis of these patients. However, not all the drugs in the class have this beneficial effect, and only metoprolol, carvedilol and bisoprolol are highly recommended in heart failure (42,45,46).

- ***Others***

- ✓ Anticoagulation and antiarrhythmic therapy

Patients with DCM are known to be prone to thromboembolic complications. However, anticoagulation is recommended only for patients with chronic atrial fibrillation. In patients with sinus rhythm the benefit of long-term anticoagulation is controversial.

Although arrhythmias are not rare in patients with DCM, the use of antiarrhythmics does not seem to improve the survival of these patients. In the case of atrial fibrillation heart rate should be controlled, as the sinus rhythm is unlikely to be sustained. In patients with low left ventricular ejection fraction and evidence of non-sustained ventricular tachycardia on ambulatory ECG, implantation of a cardiac defibrillator should be considered (42,45,46).

- ✓ Immunoadsorption

Another rather controversial treatment modality is immunoadsorption. Its principle is the neutralization of circulating autoantibodies found in some patients with DCM. The usual target of immunoadsorption is anti–beta1-adrenergic receptor antibodies, as they are thought to modify beta-adrenergic receptor activity and to produce chronic increases in signal transduction that are harmful to the failing heart (15). Although some studies have

documented the benefit of immunoadsorption, it remains unclear whether it produces long–term benefit. Nevertheless, as mentioned above, the role of circulating autoantibodies in DCM progression has not been elucidated.

Surgical treatment and devices

As mentioned above, in patients with low left ventricular ejection fraction and evidence of non-sustained ventricular tachycardia on ambulatory ECG, implantation of a cardiac defibrillator should be considered. Implantable cardiac defibrillators are devices recognizing ventricular arrhythmias and delivering shock to terminate them. They are thought to improve the survival by up to 30% (42,45).

In patients with DCM, bundle branch block patterns on ECG are not rare and a wide QRS complex is associated with worse outcomes. Left bundle branch block results in delayed depolarization and contraction of the lateral left ventricular free wall, which is thought to contribute to disease progression. Therefore, in patients with wide QRS complexes, NYHA functional class III-IV and LVEF <35%, cardiac resynchronization therapy might be beneficial in improving functional capacity. It uses specially designed biventricular pacemakers, which pace the right and left ventricle simultaneously, thereby improving patients exercise capacity, quality of life and survival (42,45).

A treatment modality for the patients with end-stage heart failure who do not respond to conservative therapy is heart transplantation. For patients who are listed for heart transplantation but who can not be stabilized on a heart failure regimen including inotropic agents, ventricular assist devices (VAD), automatic pumps taking over the work of heart, have become standard. The first ones ventricular VAD were extracorporeal pulsatile pumps, later intracorporeal pulsatile and intracorporeal continuous flow VADs were developed. A next stage would be a total artificial heart. Approximately 25% to 30% of patients undergoing transplantation are bridged to transplant with a mechanical support device. Approximately 65% to 70% of patients supported with a left ventricular assist device (LVAD) alone survive to undergo transplantation (47).

About a decade ago partial left ventriculotomy, the Batista procedure, was considered to be an alternative to heart transplantation. This ventricular reduction surgery entails the resection of a region of myocardium. The rationale for the procedure is provided by the law of Laplace: a reduction in the overall radius of the left ventricular chamber should serve to decrease wall tension, resulting in an increase of overall efficiency of the heart. In spite of benefit seen in some cases, the mortality after the operation remained high (48). It was

demonstrated how improvement in systolic function following partial ventriculectomy is accompanied by worsening diastolic function, resulting in overall impaired cardiac function (49). Concerns arising from these convincing findings have obliterated enthusiasm for the procedure, and it is no longer commonly performed.

Correction of mitral insufficiency can also be performed in order to reduce volume overload resulting from the regurgitant blood, and to increase forward blood flow.

Heart transplantation as treatment method for DCM

Despite major advances in the treatment of severe myocardial failure, a sizable number of patients with terminal or progressive myocardial dysfunction are fated to die or be severely limited by symptoms. In these patients heart transplantation (HTx) has become standard therapy. Evidence-based immunosuppressive strategies have decreased morbidity and mortality, making survival routine. Most infections and rejections are either preventable or treatable, and the temporary pretransplant use of VADs no longer portends a poor prognosis following transplantation. Although cardiac allograft vasculopathy and malignancy limit long-term survival, 1-, 3-, and 10-year survival rates are 83%, 75%, and 45%, respectively. Thus, heart transplantation is now widely accepted as a modality for prolonging life and improving its quality in carefully selected patients (42).

The current generally accepted indications for heart transplantation include advanced heart failure, New York Heart Association (NYHA) Function Class III-IV, refractory angina, and recurrent life-threatening arrhythmias. HTx should be considered in patients who:

- have severe symptoms despite aggressive and appropriate medical treatment;
- have a poor 1-year and 2-year prognosis;
- are not candidates for other accepted surgical alternatives to transplantation;
- do not have comorbid conditions that could have a negative impact on postoperative recovery and long-term survival (93).

Still, because of the shortage of donor hearts, even following these instructions the waiting time on pre-transplantation list increases dramatically. According to the data of the Organ Procurement and Transplantation Network (91) the median waiting time for HTx increased from 60 days in 1999 to 308 days in 2004.

In order to give priority to the patients with the highest risk of dying from heart failure Eurotransplant changed the organ allocation system in the year 2000. According to the currently used algorithm a donor heart is first allocated to the critically ill patients listed with high-urgency

status. In order to obtain U status for Eurotransplant listing, idiopathic DCM patients must fulfil one of the following criteria (94):

- continuous intravenous inotropic therapy;
- assist device complications;
- documented intractable recurrent ventricular rhythm disorders;

Approximately 45% patients listed for HTx have cardiomyopathy (92) and a large proportion of them – DCM. While some of them remain stable or even improve during the waiting time, the others deteriorate quickly. Nevertheless it is possible that HTx is sometimes performed too early, the reason for the heart transplantation being just an available donor. Therefore, it is crucial to determine the prognostic predictors, priority, and optimal timing for heart transplantation among patients with severe cardiac failure.

2.1.9. Prognostic markers in end-stage DCM

Several potential prognostic markers, including gender, age, sex, etiology, left ventricular ejection fraction (LVEF), transmitral filling E/A wave ratio, E-wave deceleration time (DT), mitral and tricuspid regurgitation, pulmonary wedge pressure (PWP), peak exercise oxygen consumption (VO_2max), levels of plasma norepinephrine, atrial and B-type natriuretic peptides (ANP, BNP), heart fatty acid binding protein (H-FABP), have been widely reported in patients with severe cardiac failure (50-64). However, the predictors of outcomes varied from study to study and in most of them long–term (>24 month) outcomes were chosen.
Now a widely accepted 1-year and 2-year prognostic factor also used as selection criterion for HTx is VO_2max. It is considered that HF patients who have markedly reduced exercise capacity (VO_2max <10 ml/kg/min) have poor prognosis and should be listed for HTx, and that patients with good exercise capacity (VO_2max >18 ml/kg/min) have a good prognosis and do not need transplantation. However, VO_2max has several limitations, as it is affected not only by cardiac reserve but also by age, gender, muscle mass, deconditioning and pulmonary diseases. Therefore it has to be used in combination with other parameters (93).
Numerous studies demonstrated the impact of diastolic dysfunction on long-term clinical prognosis in DCM. Most of them concluded that in HF patients restrictive filling pattern, characterized by high transmitral E wave velocity, low A wave velocity, high E/A ratio and short transmitral E wave deceleration time, is associated with more expressed symptoms,

poor prognosis and high mortality (50-54). Werner et al. (51) noted that during the follow-up of DCM patients an increase in A wave velocity and decrease in E/A ratio were associated with clinical improvement, whereas opposite changes were present at the deterioration. Similar data concerning DT were described by Shen et al. (65). Pinamonti et al. (50) further classified patients with restrictive filling pattern at the baseline in two groups with different outcomes: the group where restrictive filling pattern persisted during short–term (3 month) follow-up was associated with higher long–term mortality and worse outcomes than the group where restrictive filling pattern disappeared. On the other hand Rihal et al. (54) demonstrated that in these patients diastolic dysfunction correlated only with congestive symptoms, whereas only systolic variables were the predictors of survival.

Interesting data come from Fauchier et al., who used radionuclide angiography and found that intraventricular, but not interventricular dyssynchrony is an independent long term predictor of cardiac events in DCM patients (34).

Prediction of short-term outcomes in patients with end-stage idiopathic DCM is also of crucial importance. As mentioned above, while some of the patients listed for HTx remain stable or even improve during the waiting time, others deteriorate quickly. As hemodynamic compromise progresses from moderate to severe in a patient waiting heart transplantation, not only the risk of dying before transplantation can be performed increases, but the results after transplantation also worsen. Thus the prediction of short–term outcomes would help to select patients who need more intense follow-up because of expected rapid clinical deterioration and possible need for urgent transplantation or mechanical circulatory support. The latter, started timely, could halt further deterioration, decrease the likelihood of death before transplantation can occur, and reverse metabolic, cellular, and nutritional compromise (47).

Data regarding short-term outcomes of end-stage idiopathic DCM are scarce. Huang et al. demonstrated that transpulmonary resistance (TPR) and cardiac index (CI) have powerful predictive values in terms of 6 and 12 month outcomes in patients with severe heart failure secondary to ischemic or nonischemic DCM (66). However both of these parameters require invasive investigation, and for routine examination less invasive methods would be preferred.

Over the last decade new techniques have emerged, offering new examination possibilities. The information gained using these methods might contribute to the routinely used parameters. One of these new techniques is strain imaging.

2.2. Strain imaging

2.2.1. Definition

First of all the distinction between motion and deformation should be noted. Displacement and velocity are motion, while strain and strain rate describe deformation. A moving object does not undergo deformation until every part of it moves with the same velocity, which means that its shape remains unchanged.

Strain (S) is a dimensionless parameter measuring the deformation of an object relative to its original shape. It is expressed as the fractional or percent change from the original dimension. The Langrangian formula used to quantify the strain is as follows:

$$S = \frac{L - L_0}{L_0} = \frac{\Delta L}{L_0} \qquad (1)$$

where S is strain, L_0 is the initial length (Lagrangian strain), L is the instantaneous length during contraction (Eulerian or natural strain) and ΔL is the absolute change in length. (Fig. 1)

Strain rate (SR) is the local rate of deformation or strain per unit time, which equals the velocity difference per length unit:

$$SR = \frac{S}{\Delta t} = \frac{(\Delta L / L_0)}{\Delta t} = \frac{(\Delta L / \Delta t)}{L_0} = \frac{\Delta V}{L_0} \qquad (2)$$

where ΔV is the velocity gradient in the segment studied. (67,68)

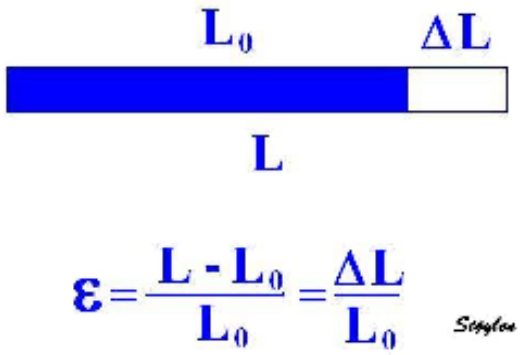


Figure 1. *Langrangian formula used to quantify strain (68)*

2.2.2. Myocardial strain

The term strain in relation to the heart was first used by Mirsky and Parmley to describe myocardial deformation (69). The heart, like all three dimensional objects, shows strain in three dimensions. In the heart, the usual directions are longitudinal, circumferential and radial/transmural (Fig. 2). As the ventricle contracts, its muscles shorten in the longitudinal and circumferential dimensions (a negative strain) and thickens in the radial dimension (a positive strain). However, the human eye can only evaluate radial thickening and strain imaging techniques offer the possibility to assess myocardial deformation in all three dimensions.

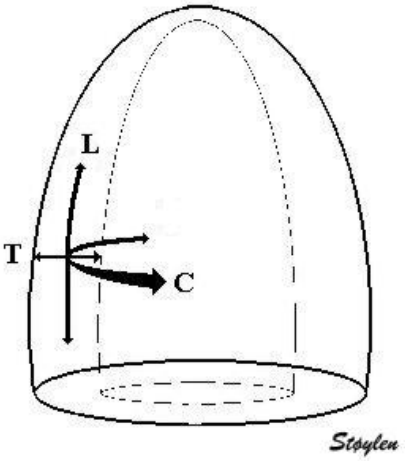


Figure 2. *Myocardial strain dimensions. T – transverse (radial), L – longitudinal, C – circumferential (68).*

Heart muscle is generally considered incompressible, which means that the volume remains constant during the deformation. Thus, radial thickening has to be balanced by longitudinal plus circumferential shortening. As all the strain components are interrelated, one component may be representative of all the regional function (68).

It seems that SR correlates with a rate of change in pressure (dP/dt) and therefore is a parameter reflecting contractility, whereas S is an analog of regional ejection fraction (70). As would be expected, in the heart increasing preload is associated with increasing strain at all levels of wall stress, and increasing afterload is associated with a reduction of strain. SR is thought to be less related to the load conditions (70,71).

Currently myocardial strain and strain rate can be acquired using tissue Doppler imaging (TDI) or speckle tracking techniques.

2.2.3. Strain imaging by TDI

The TDI techniques measure the velocity of myocardium relative to the transducer. During the systole the velocity of myocardium displacement increases from the apex to the base, reflecting the contraction of the base toward the relatively fixed apex. This velocity difference along the myocardial wall is defined as velocity gradient. Velocity per length unit equals the strain per time unit or strain rate:

$$VG = \frac{(v_2 - v_1)}{L} = \frac{\Delta v}{\Delta x} = \frac{v(x) - v(x + \Delta x)}{\Delta x} = SR \qquad (3)$$

where VG is velocity gradient and Δx is called the offset distance or the strain length (Fig.3a and b).
Thus strain rate by tissue Doppler is calculated from the velocity gradient of two points over a segment with a fixed distance. In the latest software, instead of measuring the velocities at the ends of offset distance, the velocity gradient is calculated by linear regression of all pixel velocities within the Δx.
By integrating the SR values, S values are obtained. With imperfect data, this method tends to make the TDI strain imaging less sensitive to errors in velocity measurements, as the value is an average of more measurements (68).
The main limitations of this method are sensitivity to noises, angle dependency and poor reproducibility (68,71).

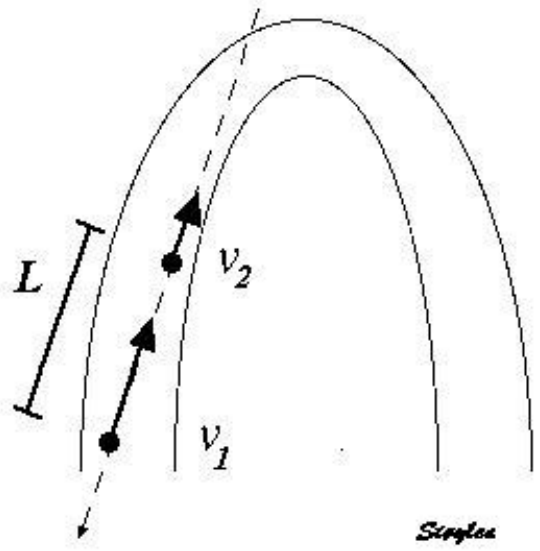


Figure 3a. *Longitudinal velocity gradient by TDI. Where v1 and v2 are two different velocities measuredat two different points. L is the distance between these points. Velocity gradient is given in the formula (3) (68).*

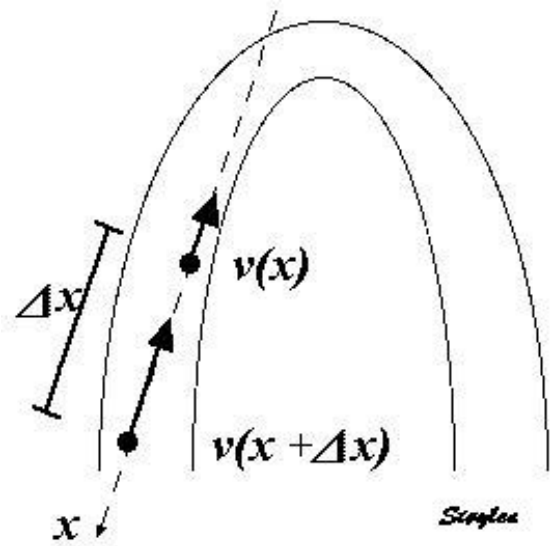


Figure 3b. *Strain rate measured by TDI, as the velocities of a segment with fixed length. As shown in the formula, both SR (2) and VG (3) formulas result in the same ratio (68).*

2.2.4. Strain imaging by speckle tracking

Speckle tracking is a more recent non-Doppler based method that measures myocardial deformation by tracking speckles in two–dimensional (2D) ultrasonic images. The speckles are highly reproducible ultrasound reflectors within the tissue. Their random distribution ensures that each myocardial segment has a unique pattern, a fingerprint. As the myocardium moves from one frame to another the position of this fingerprint will shift slightly, but the distribution of speckles in it remains fairly constant; thereby it can be identified and followed through the consecutive frames. From the change of the fingerprint position, deformation can be measured (Fig. 4a and b) (68). As from 2D images the baseline length (Langrangian strain) can be acquired, strain values are calculated directly by the Langrangian formula:

$$S = \frac{L - L_0}{L_0} = \frac{\Delta L}{L_0} \qquad (4)$$

The advantage of this method is that it tracks speckles in 2 dimensions, along the wall, not along the ultrasonic beam, and therefore is angle independent and gives a true strain. Yet the quality of the measurements might be affected by too low or too high frame rate. Too low frame rate results in excessive displacement of the speckles between the frames, and too high frame rate is associated with high levels of noise. The optimal frame rate for 2D speckle tracking is 50-70 frames per second (FPS) (67,68,71).

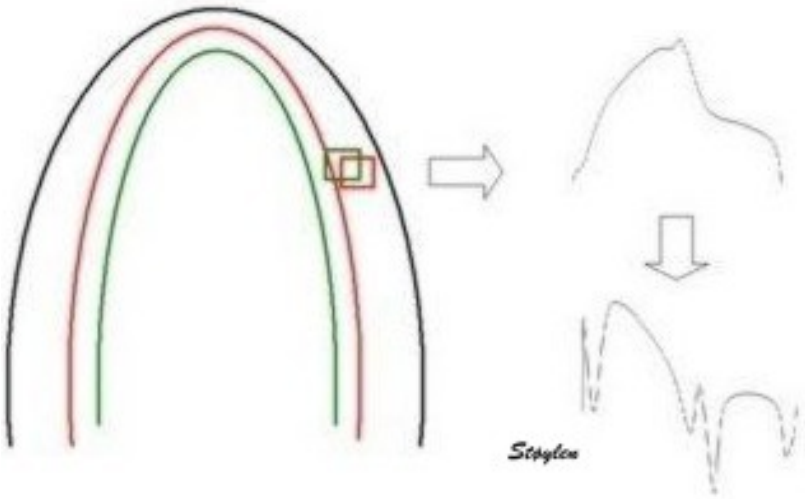
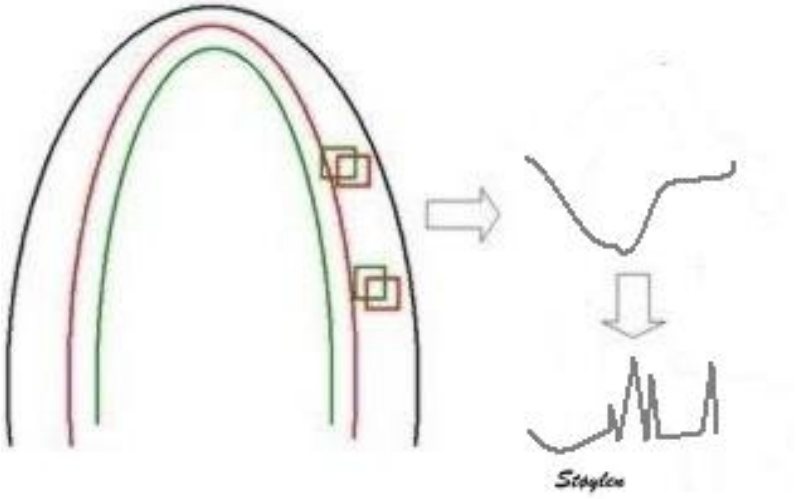


Figure 4a. *Fingerprint displacement . Upper curve demonstrates displacement and lower curve – velocity, obtained by tracking the fingerprint through a whole cardiac cycle (68).*



Picture 4b. *From two fingerprints relative displacement and hence strain and strain rate can be obtained (68).*

Non-Doppler strain imaging can be performed offline. It requires only one cardiac cycle, but as already mentioned the images must have high resolution. First of all the myocardial end-systolic frame must be defined in the apical long axis (APLAX) view, where the aortic valve is directly visible. The aortic valve closure (AVC) time is marked, and the time from ECG R wave to AVC is measured. This is used by the software as reference point in the other loops. The mitral valve opening (MVO) is easily seen in any apical view. AVC and MVO together allow accurate timing of systole and diastole.

Within the end-systolic frames an estimation of LV myocardium is traced. The software automatically defines the epicardial and mid-myocardial line and processes them on the loop. Endocardial border is identified by edge detection, based on black-and-white

recognition on the single frame, and myocardium is defined by estimation of thickness. This can be corrected by the investigator if needed. As mentioned above, myocardial deformation and motion are analyzed by identifying fingerprints of speckles and measuring their frame to frame changes. The myocardium is then automatically divided into six segments and the analyzed values within the middle points of these segments are then displayed as traces in specific diagrams, showing different parameters (strain, SR, displacement, velocities) derived from speckle velocities. With the same principle all the standard apical and parasternal views can be analyzed (67).

2.2.5. Parameters

The parameters that can be gained by strain rate imaging can be divided into those relating to timing and magnitude (71). The standard timing parameters are the time to onset of systole and time to relaxation; standard magnitude parameters are peak systolic and diastolic strain rates and peak systolic strain. End-systolic strain is the parameter combining time and magnitude. Calculating the standard deviation of the mean value of time from R to peak systolic strain in different myocardial segments allows the evaluation of systolic dyssynchrony.

The examples of normal strain and strain rate patterns are given in Figures 5 to 10. The images were obtained during personal examinations performed at the German Heart Institute Berlin (Deutsches Herzzentrum Berlin, DHZB).

2.2.6. Clinical applications

- *LV function*. Maximal elastance, based on creating pressure volume loops at various levels of pressure and volume through alteration of preload and afterload, is the gold standard for global assessment of LV function, albeit of limited clinical feasibility (71). Peak and mean SR measured by TDI showed high correlation with elastance, much higher than that of strain or tissue velocity (72). In another study mean systolic SR and mean systolic strain measured by 2D strain imaging both showed high sensitivity and specificity in the detection of LV systolic dysfunction (73). These promising results suggest that in future strain imaging could be used for more precise evaluation of LV function.

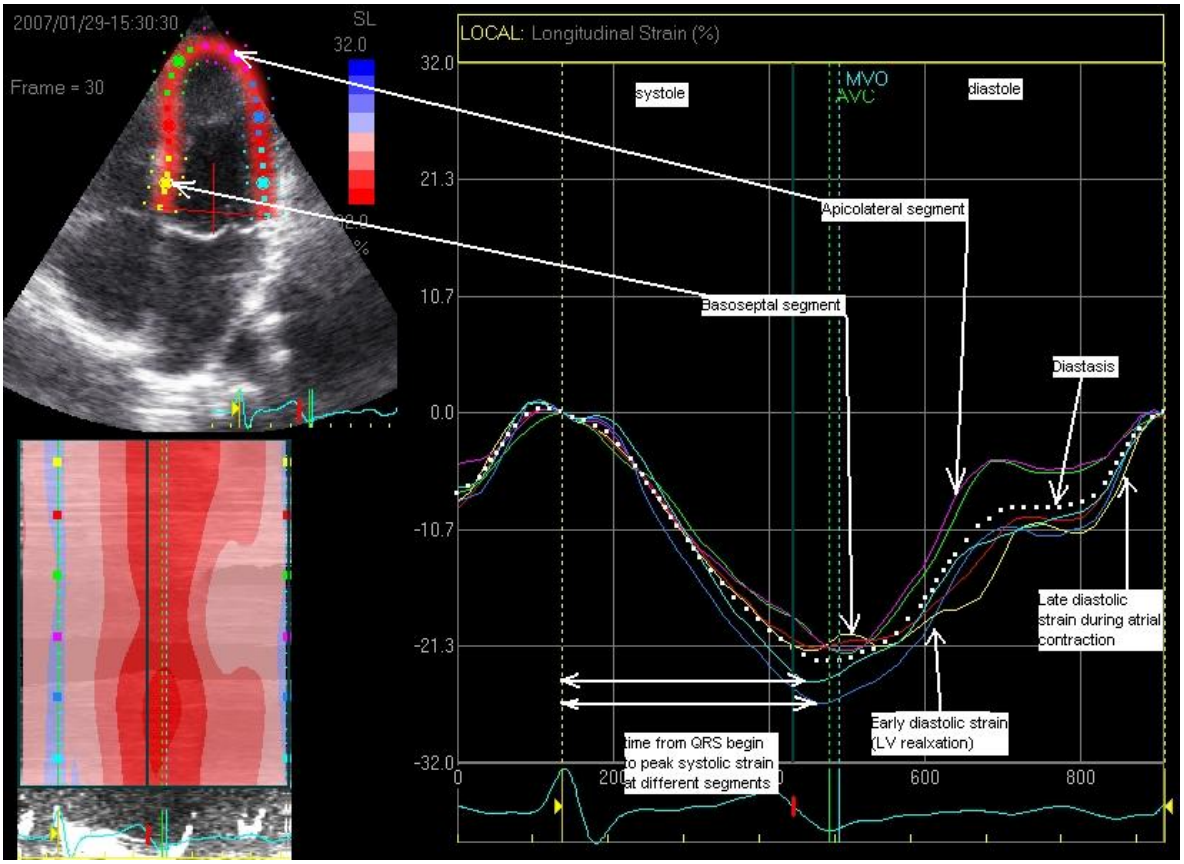


Figure 5. ***Normal longitudinal strain pattern.*** *In the color diagram red indicates shortening (negative strain) and blue lengthening (positive strain). Myocardium is divided into six segments, and their strains are displayed in the diagram as colored lines. White dotted line on the diagram represents global strain (mean of segmental strains). In this case: endsystolic strain -23.3%; synchronous systolic function (as peak systolic strain in separate segments occurs at the same time).*

- *Myocardial disease*. Numerous studies have elucidated the utility of strain rate imaging in the detection of myocardial diseases even in their subclinical stages, also as myocardial involvement in non-cardiac diseases, such as amyloidosis, diabetic heart disease, beta-thalassemia, Friedriech ataxia and others (74-78). It is also helpful in distinguishing between hypertrophic cardiomyopathy, athelete's heart and hypertrophy caused by hypertension (79,80). Nonetheless, in the case of global disease, where the site specificity of SR is not required, it remains unclear whether SR offers any advantages in comparison to tissue velocity (71).
- *Valvular heart disease*. Recently improvement in myocardial strain and SR values after percutaneus aortic replacement was reported (81). Also it is being suggested that subclinical myocardial dysfunction revealed by SR imaging might help to decide about the timing for surgical intervention (82).

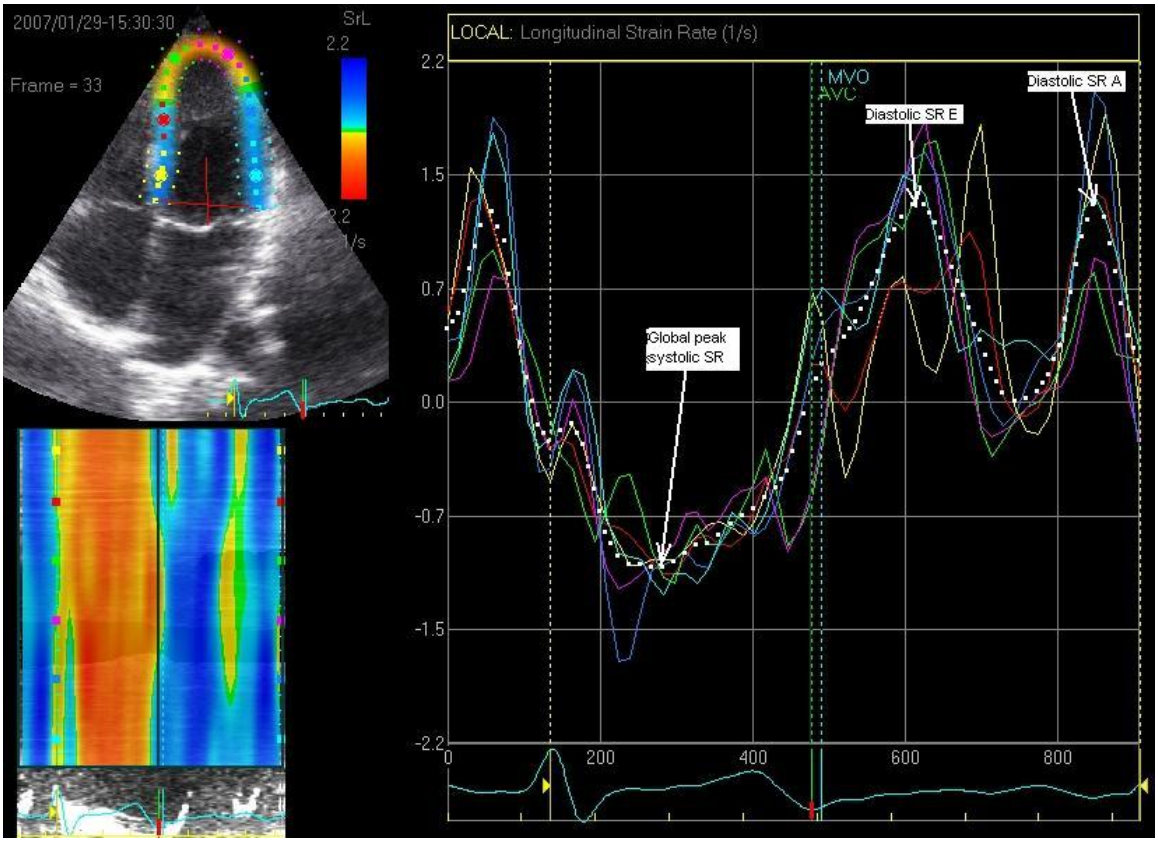


Figure 6. ***Normal longitudinal strain rate pattern***. *Colored lines indicate segmental strain rates and a dotted line global strain rate. In this case: peak systolic strain rate -1.1/s, diastolic SR E – 1.2/s, diastolic SR A – 1.1/s.*

- *Diastolic dysfunction*. Current evaluation of diastolic function is based on the analysis of the load dependent transmitral flow, and a direct parameter showing the stiffness of myocardium would be of great value. Such a parameter could be the diastolic strain and strain rate. Yet although some studies have used strain imaging for the evaluation of diastolic function (85,86), its value remains unclear.

- *Stress echocardiography and detection of ischemia.* Numerous studies have been performed using strain imaging to assess the myocardial response to stress and to evaluate stunned, acutely ischemic myocardium or myocardial infarct. Myocardial viability is usually assessed by the changes in systolic and diastolic SR, time to relaxation and degree of post systolic thickening (71). It was validated in several studies. In one of them myocardial viability was assessed by positron emission tomography (83), and in another study the recovery of segmental function after revascularization was used to assess the viability (84). They both defined certain cut-off values of SR increment for the prediction of viability and documented that SRI was more accurate than TVI.

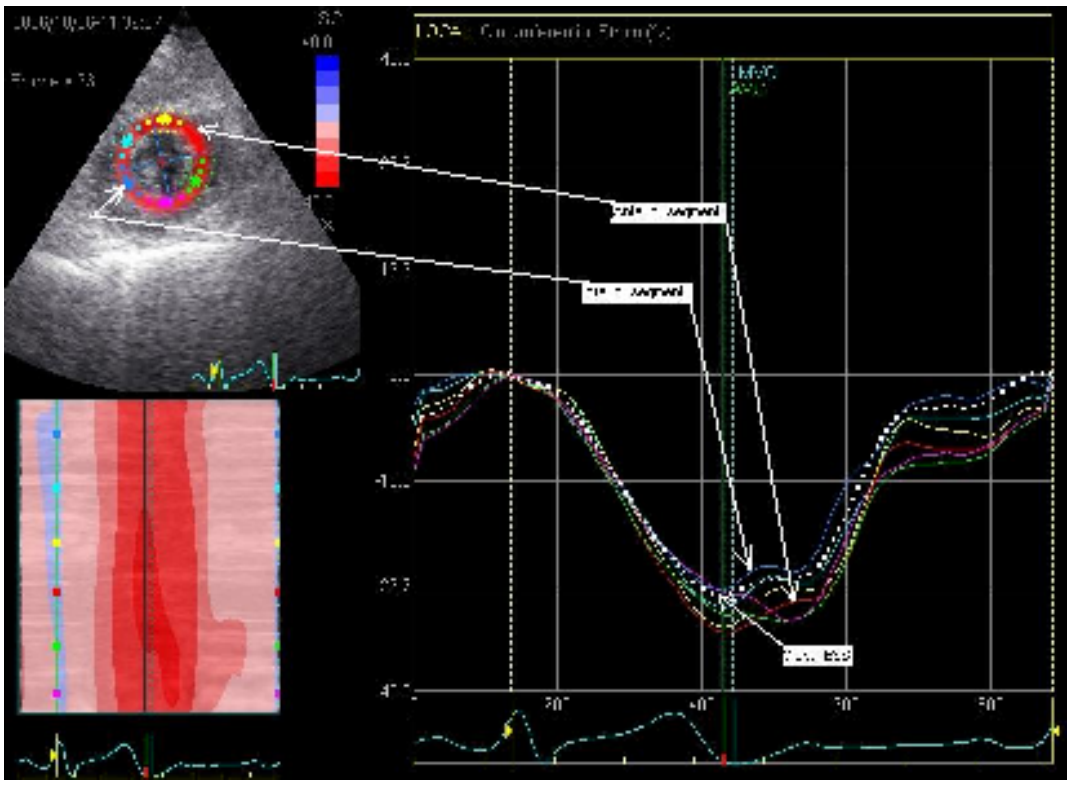


Figure 7. ***Normal circumferential strain pattern.*** *In the color diagram red indicates shortening (negative strain) and blue lengthening (positive strain). In this case: global ESS – 27.1%, synchronous systolic function (as peak systolic strain in separate segments occurs at the same time); clearly seen early and late diastolic phases.*

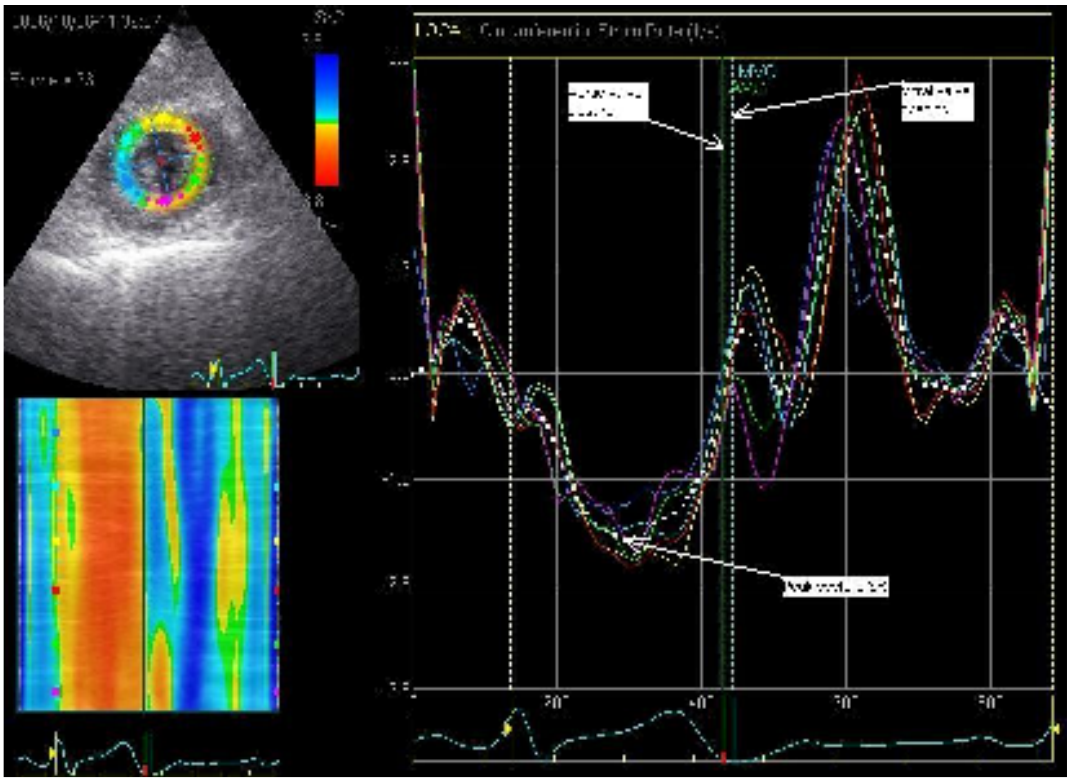


Figure 8. ***Normal circumferential strain rate pattern****. Colored lines indicate segmental strain rates, a dotted line global strain rate. In this case: peak systolic strain rate -1.9 /s, diastolic SR E – 2.5 /s, diastolic SR A – 0.7 /s.*

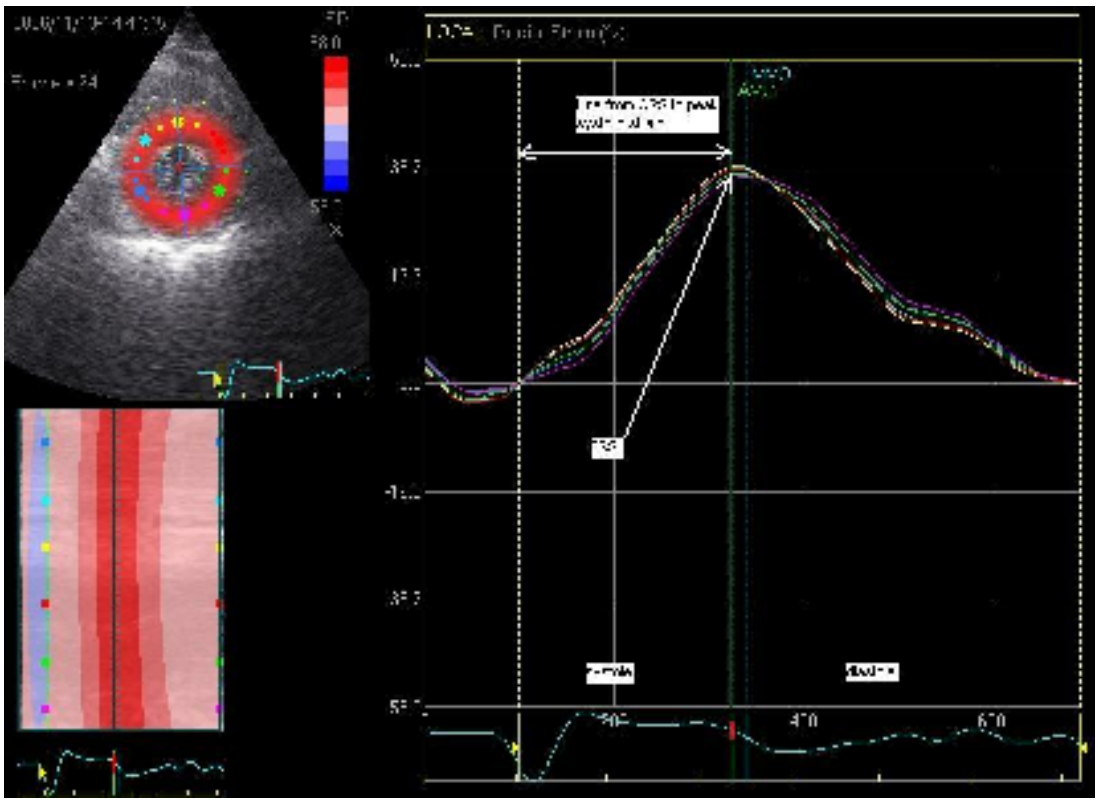


Figure 9. ***Normal radial strain pattern.*** *In the color diagram red indicates thickening (positive strain), blue thinning (negative strain). In this case: global ESS – 38.7 %, synchronous systolic function (as peak systolic strain in separate segments occurs at the same time).*

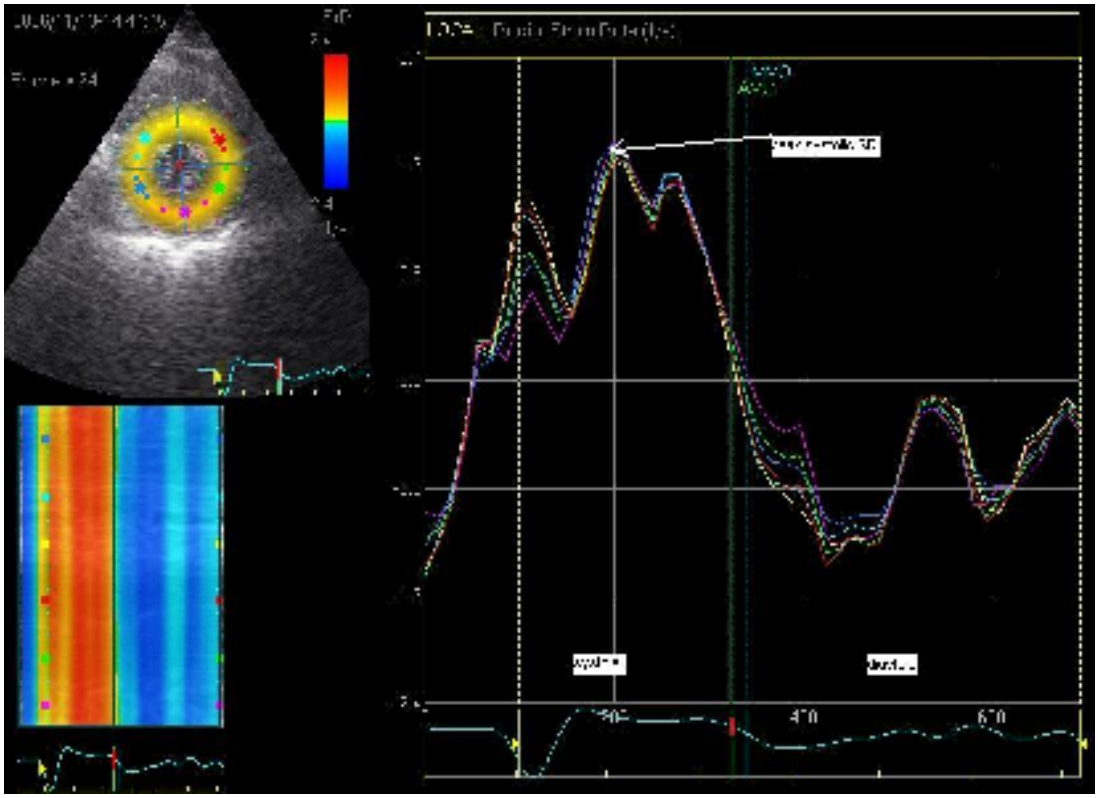


Figure 10. ***Normal radial strain rate pattern****. Colored lines indicate segmental strain rates, dotted line global strain rate. In this case: peak systolic strain rate -1.6 /s.*

- *Right ventricular function.* The evaluation of right ventricular function with SR imaging, although feasible, remains challenging. For TDI strain measurements RV wall is too thin to permit adequate regression line, and 2D strain is not defined yet for RV evaluation (71).

Clearly strain rate imaging is a very promising technique, opening up new possibilities in diagnostics and in understanding the pathologic mechanisms of diseases. However, no consensus about its clinical application has been found yet and ongoing research is required to clarify the true value of this method (71).

3. Study

3.1. Objective

The aim of this study was to find echocardiographic short-term prognostic factors of idiopathic DCM course and to investigate whether if the synchronicity of left ventricular systolic function influences the clinical stability of these patients.

3.2. Methods

3.2.1. Patient selection and study design

As stated above, dilated phenotype can be caused by various etiologic factors, which might result in significant differences in prognosis, echocardiographic features etc. Therefore, to obtain as homogenous group as possible, we considered only patients with idiopathic DCM for our study, and excluded those with clear etiologic factors. Thus, patients with previous myocardial infarction, specific myocardial diseases, acute myocarditis during the last months, valvular heart disease or *cor pulmonale* were excluded from the study.

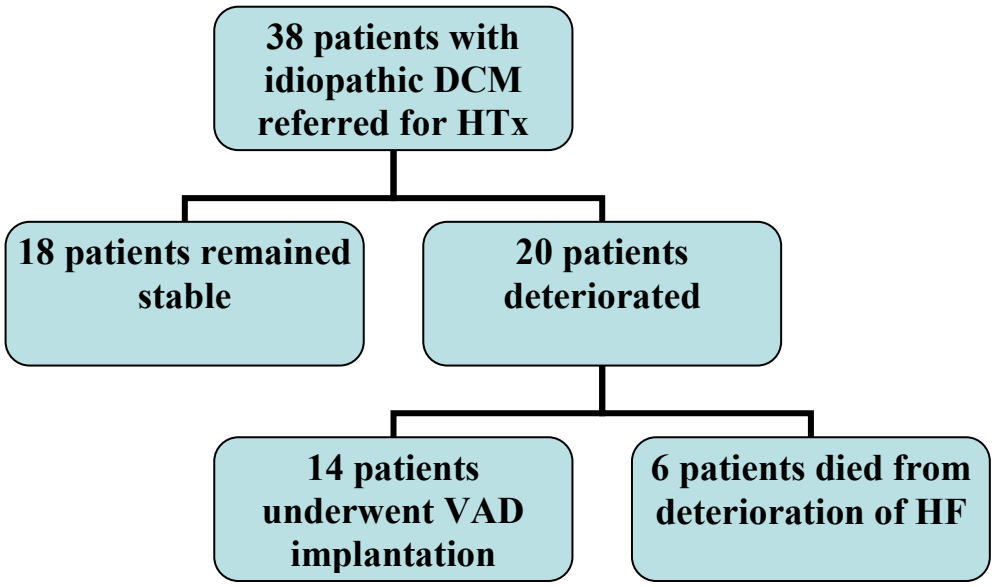


Figure 11. ***Outcome of patients referred for HTx***

Finally 38 consecutive stable patients with idiopathic DCM referred for HTx in the years 2006 and 2007 were included in the study. The inclusion criteria were: left ventricular ejection fraction (LVEF) <30%, left ventricular enddiastolic diameter (LVEDD) >55mm, coronarography without relevant stenosis of any of the main coronary arteries and no need for inotropic cardiac support.

At the baseline all of the patients underwent transthoracic echocardiography, during which also the images for off-line 2D strain imaging were stored. Exercise testing for evaluation of peak oxygen consumption (VO_2max) was performed in all patients and NT-proBNP values were also measured on the same day.

After six months the patients were grouped into the two arms according to whether their clinical status had remained stable or deteriorated.

3.2.2. Echocardiographic examination and strain imaging

During transthoracic echocardiography standard parameters such as left ventricular ejection fraction (LVEF), left ventricular enddiastolic and endsystolic diameters (LVEDD, LVESD), left atrial diameter (LAD), left ventricular enddiastolic volume (LVEDV), transmitral E/A-wave ratio and E-wave deceleration time (DT) and others were obtained.

To evaluate the heterogeneity and synchronity of left ventricular function 2D strain imaging was chosen, because it is more reliable (higher reproducibility), easy to perform and less time consuming in comparison to TDI derived strain imaging. In each patient we stored echocardiographic loops obtained from short-axis views at the level of the mitral valve (SAX-MV) as well as apical long-axis (APLAX), four-chamber (4CH) and two-chamber (2CH) views for off-line strain imaging. The inner endocardial border was traced manually. The software provided high quality of strain and strain rate analysis by rejecting all echocardiographic images and manual tracings of insufficient quality. After this controlling radial, circumferential and longitudinal strain and strain rate measurements were performed to acquire global endsystolic strains (ESS) and maximal systolic strain rate (SSR_{max}). For evaluation of diastolic function diastolic strain rate during the passive ventricular filling (DSR_E) and diastolic strain rate during ventricular filling due to atrial contraction (DSR_A) were measured and their ratio ($DSR_{E/A}$) was calculated.

The coefficient of variance, which is the ratio of standard deviation and the mean, was used to quantify intraventricular dyssynchrony and dyssynergy. Thus the coefficient of variance

of time interval between the beginning of QRS complex and peak systolic strain of each segment was considered dyssynchrony index.

$$IVDS = \frac{SD(t_{PSS})}{M(t_{PSS})}$$

where IVDS = intraventricular dyssyynchrony, t_{PSS} = time to peak systolic strain, SD = standard deviation and M = mean value.
Similarly the coefficient of variance of ESS at each segment was used for estimation of endsystolic dyssynergy.

$$ESDSn = \frac{SD(ESS)}{M(ESS)}$$

where ESDSn = endsystolic intraventricular dyssynergy, ESS = endsystolic strain, SD = standard deviation and M = mean value.
The examples of strain and strain rate patterns in DCM are given in the Figures 12-16. The images were obtained during personal examinations performed at the German Heart Institute Berlin (Deutsches Herzzentrum Berlin, DHZB) on patients included in the study.

3.2.3. Statistical analysis

For statistical analysis SPSS version 11.5 was used. All data are reported as mean value ± 1 standard deviation (SD). Comparisons between the groups were made using the Mann-Whitney U test or Fisher exact test. Differences were considered significant at $p < 0.05$ (two-sided). Correlations between the variables were calculated using the Pearson method. Receiver operating characteristic (ROC) curves and odds ratios were obtained to evaluate the discriminatory value of different parameters in order to test their prognostic accuracy in prediction of rapid HF deterioration. Sensitivity, specificity and negative and positive predictive values were calculated for the chosen cut-off values of these parameters.

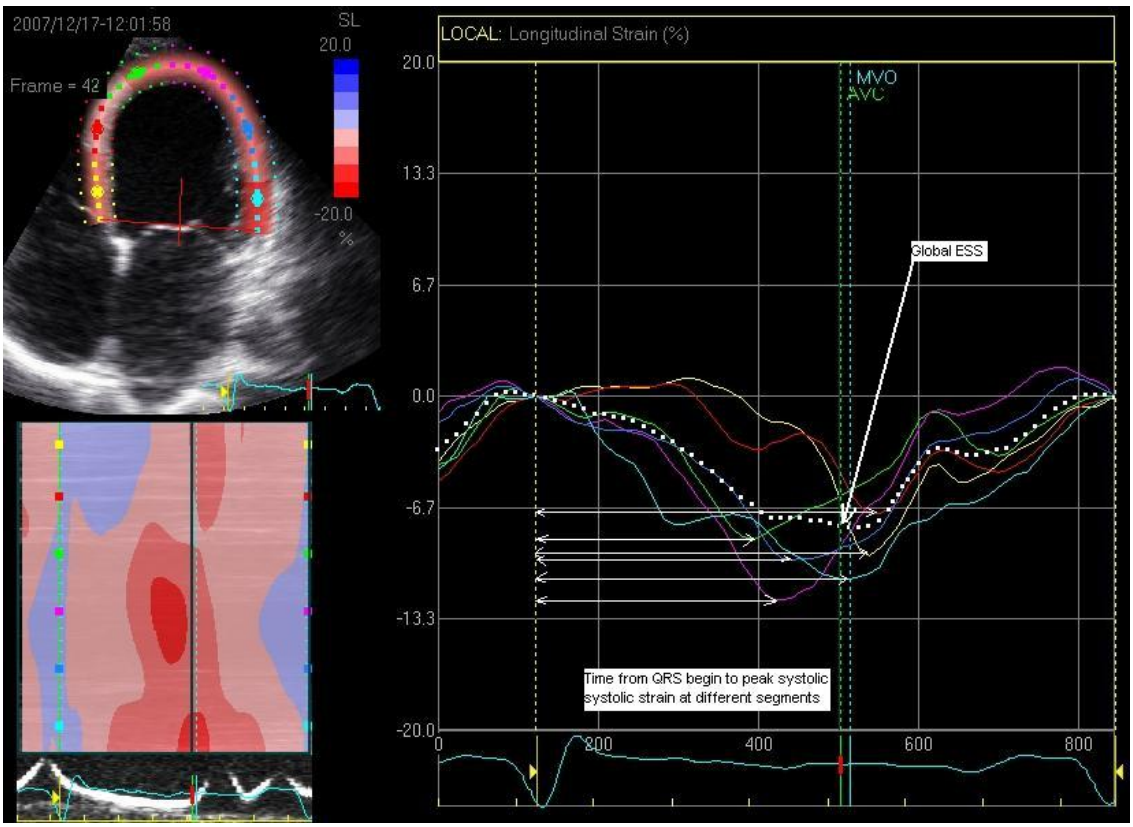


Figure 12. ***Abnormal longitudinal strain pattern in a patient with severe IDCM.*** *Reduced endsystolic strain (-7.1%). Relevant systolic dyssynchrony (white arrows indicate segmental peak systolic strain occurring not at the same time).*

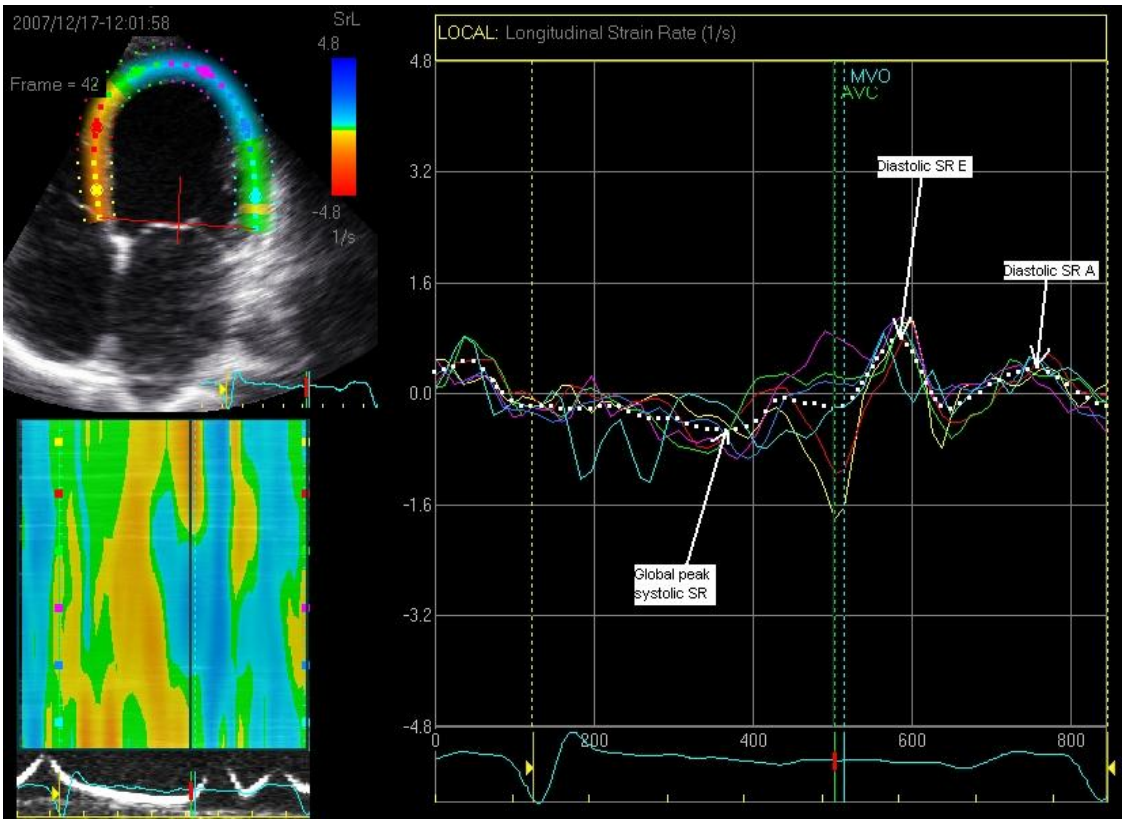


Figure 13. ***Abnormal longitudinal strain rate pattern.*** *Very low peak systolic strain rate (-0.48 /s); diastolic strain rate E > A, also note differences between segmental SR,*

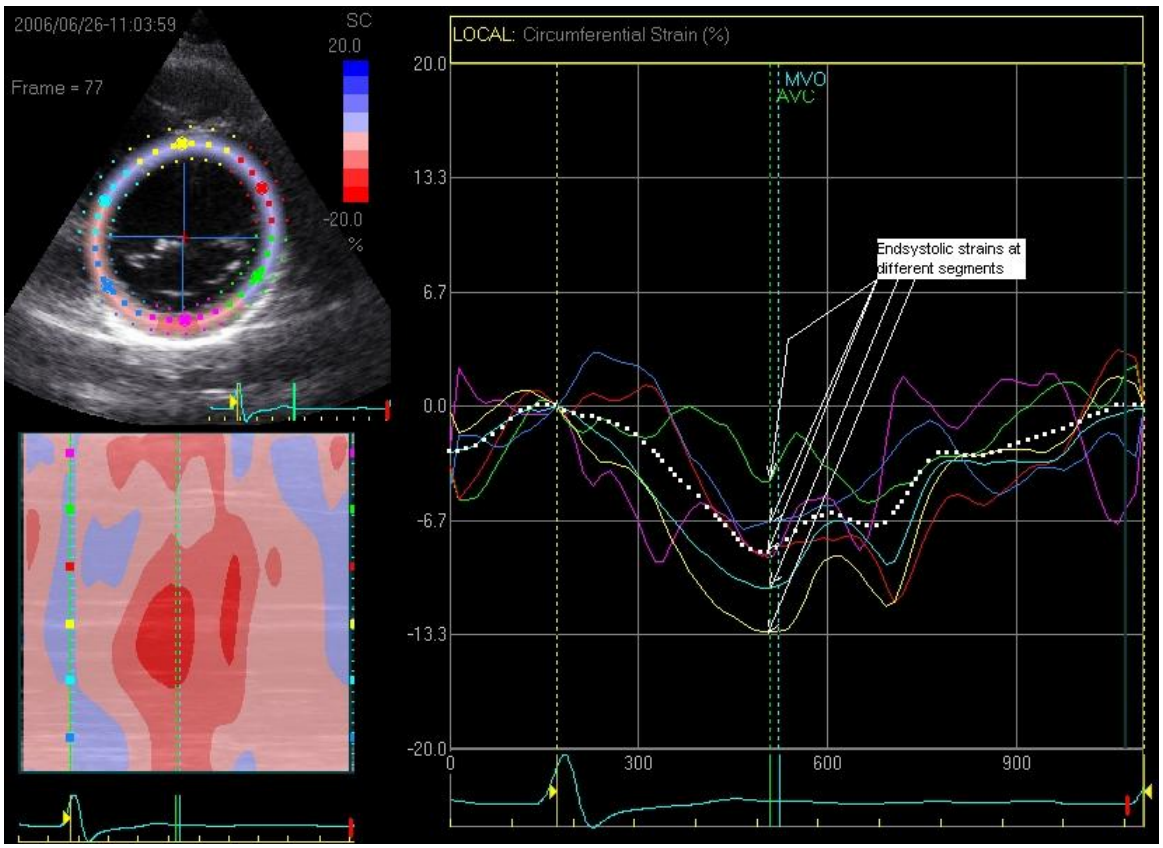


Figure 14. ***Abnormal circumferential strain pattern.*** *Low ESS (-9.3%), systolic dyssynchrony (segmental peak systolic strains occur not at the same time), systolic dyssynergy (note differences between segmental ESS).*

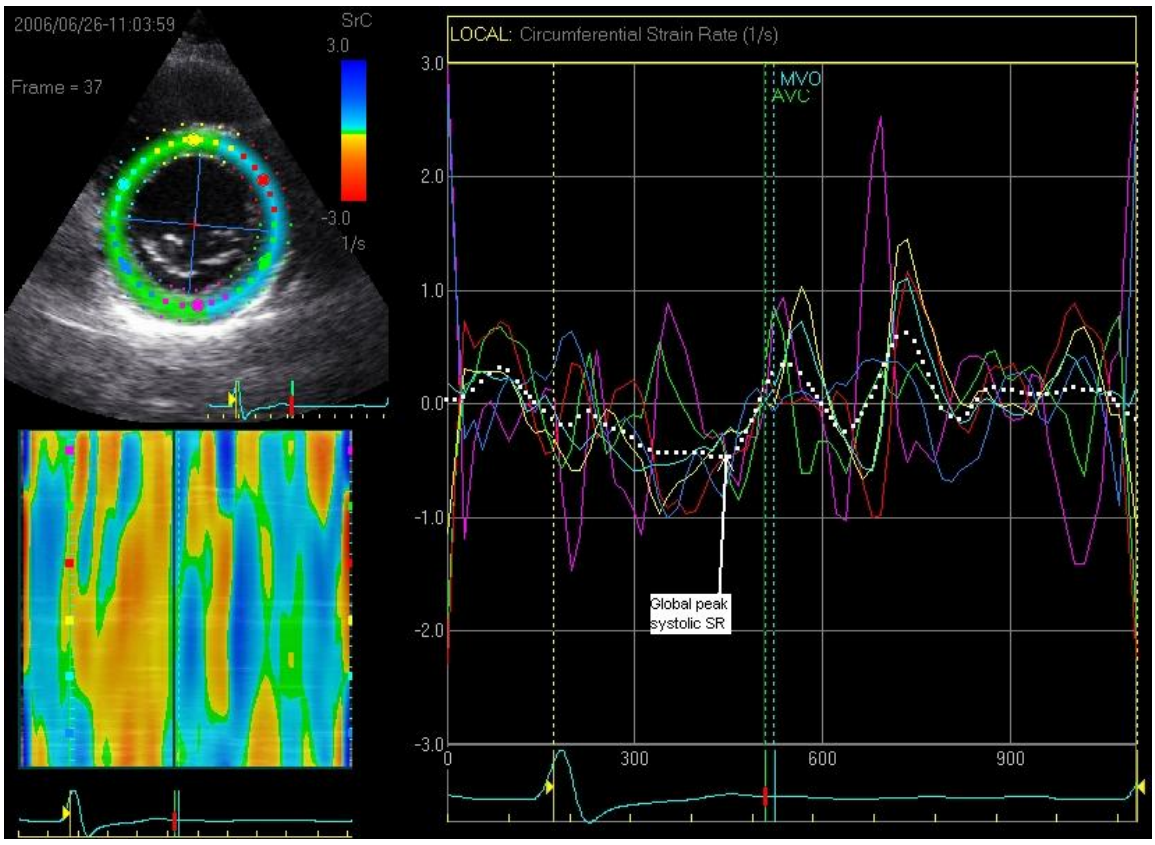


Figure 15. ***Abnormal circumferntial strain rate pattern.*** *Low peak systolic strain rate (-0.48 /s);, also note differences between segmental SR.*

3.3. Results

3.3.1. Study group characteristics

During the first 6 months after inclusion in the study, 18 patients (47%) remained stable; the other 20 showed severe cardiac deterioration. Fourteen of them (70%) underwent ventricular assist device implantation and six (30%) – died from progressing HF.

In the group of stable patients the mean age was 48±10 years and in the group of unstable patients 50±13 years. The distribution of NYHA classes, concomitant diseases, immunadsorbtion and cardiac resynchronization therapy did not significantly differ between the groups and is outlined in table 1. Some of the data is also depicted in figures 17-20.

Peak oxygen consumption (VO_2max) also did not show significant differences between the groups at the baseline. However, the unstable group had significantly higher NT-proBNP values (table 1).

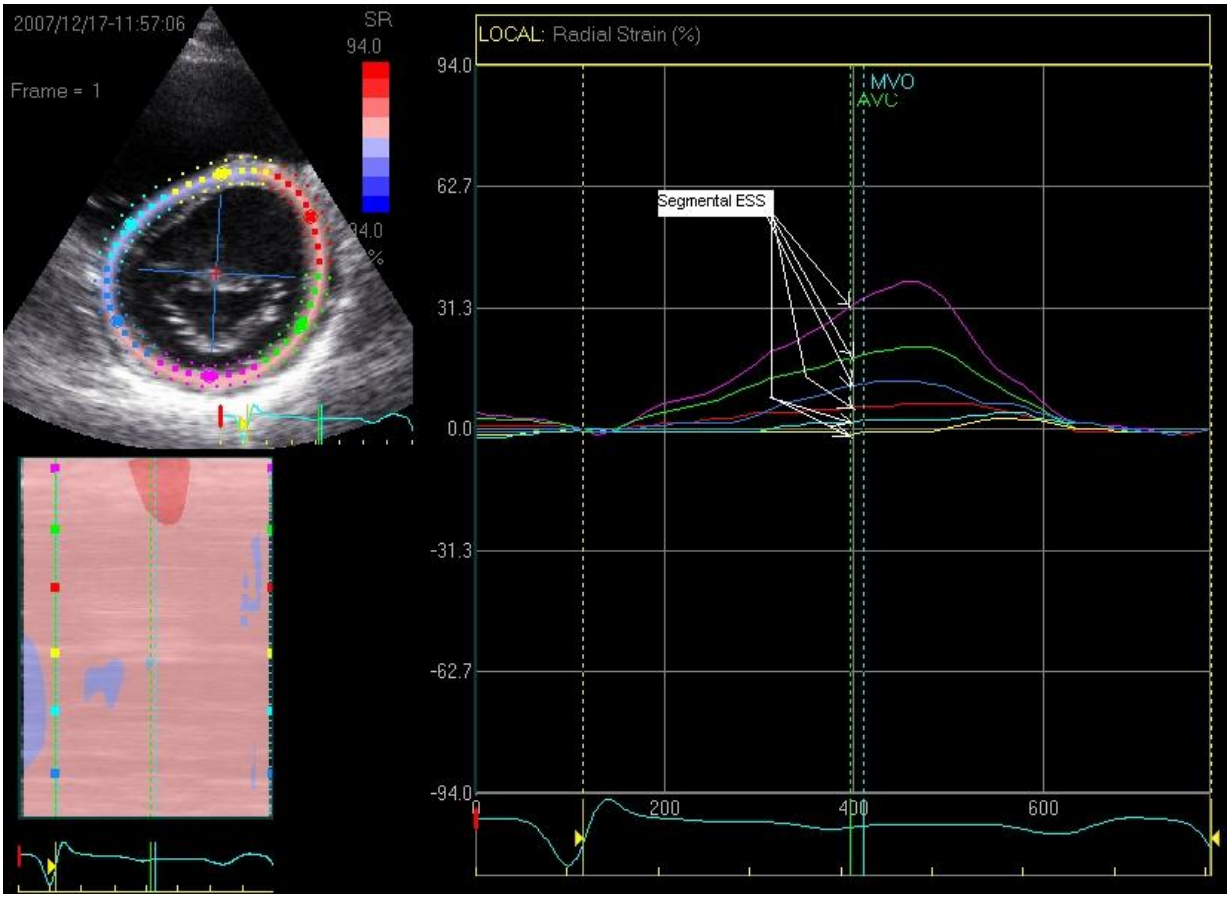


Figure 16. ***Abnormal radial strain pattern.*** *Low global ESS (15.2 %), synchronous systolic function (peak segmental systolic SR), systolic dyssynergy (note segmental ESS differences).*

Table 1. ***Baseline study group characteristics***

	Stable patients	**Unstable patients**	**P**
Women / men	1 (6%) / 17 (92%)	2 (10%) / 18 (90%)	0.2
Age, years (mean±SD)	48±10	50±13	0.71
Atrial fibrillation	6 (33%)	7 (35%)	0.9
Secondary pulmonary hypertension	5 (28%)	6 (30%)	0.88
Diabetes mellitus	5 (28%)	8 (40%)	0.43
Hyperlipidemia	11 (61%)	6 (30%)	0.19
Compensated renal insufficiency	5 (28%)	7 (35%)	0.43
Nicotine abuse	4 (22%)	3 (15%)	0.57
Immunoadsorption	14 (78%)	11 (55%)	0.51
Cardiac resynchronization	5 (28%)	4 (20%)	0.38
NYHA (II / III),	11 (61%) / 7 (39%)	10 (50%)/ 10 (50%)	0.32
VO_2 max, ml/kg/min	15.3±5.9	11.6±6.02	0.11
NT-proBNP*, pg/ml	1950±2555	6058±6547	0.019

***** *shows a statistically significant difference between the groups*

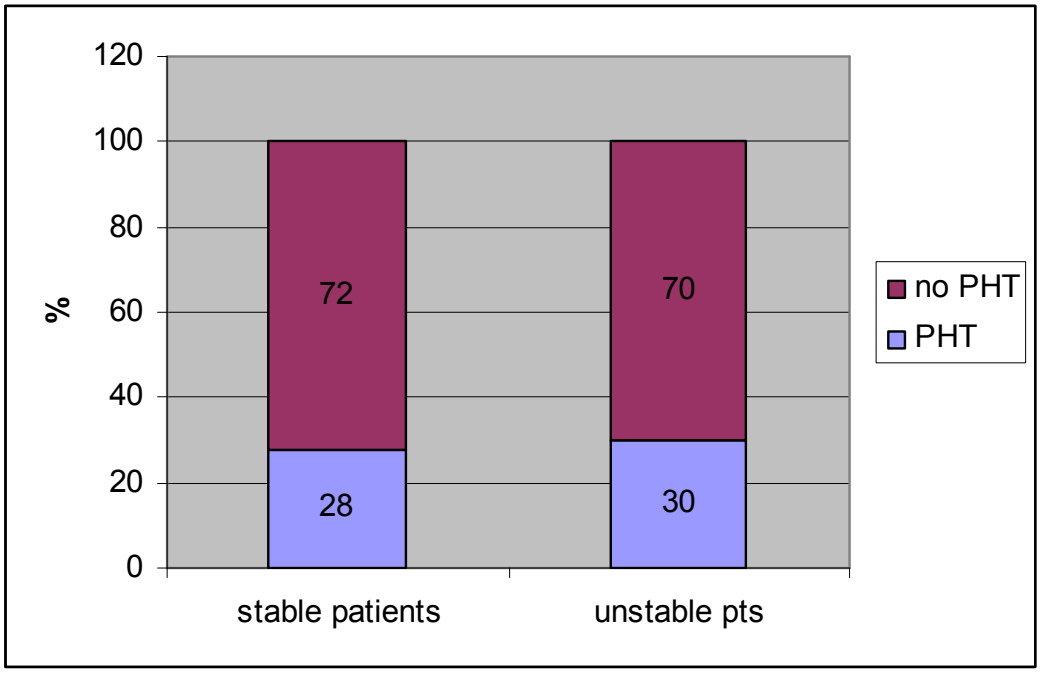


Figure 17. ***Distribution of secondary pulmonary hypertension.***
PHT – pulmonary hypertension, pts – patients.

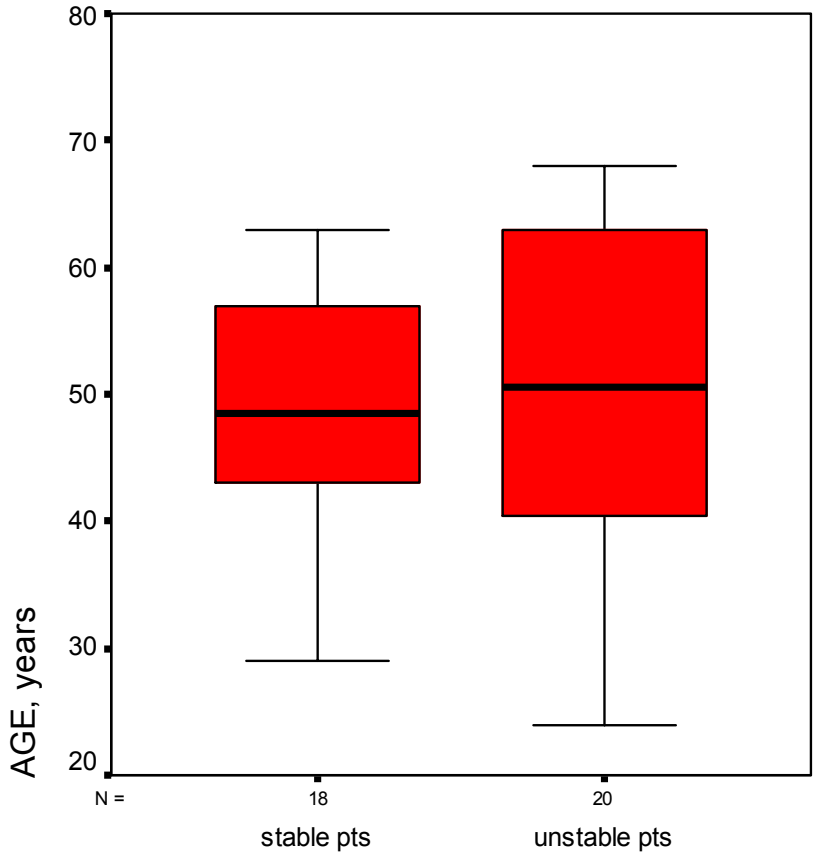


Figure 18. ***Age distribution between the groups***
pts – patients

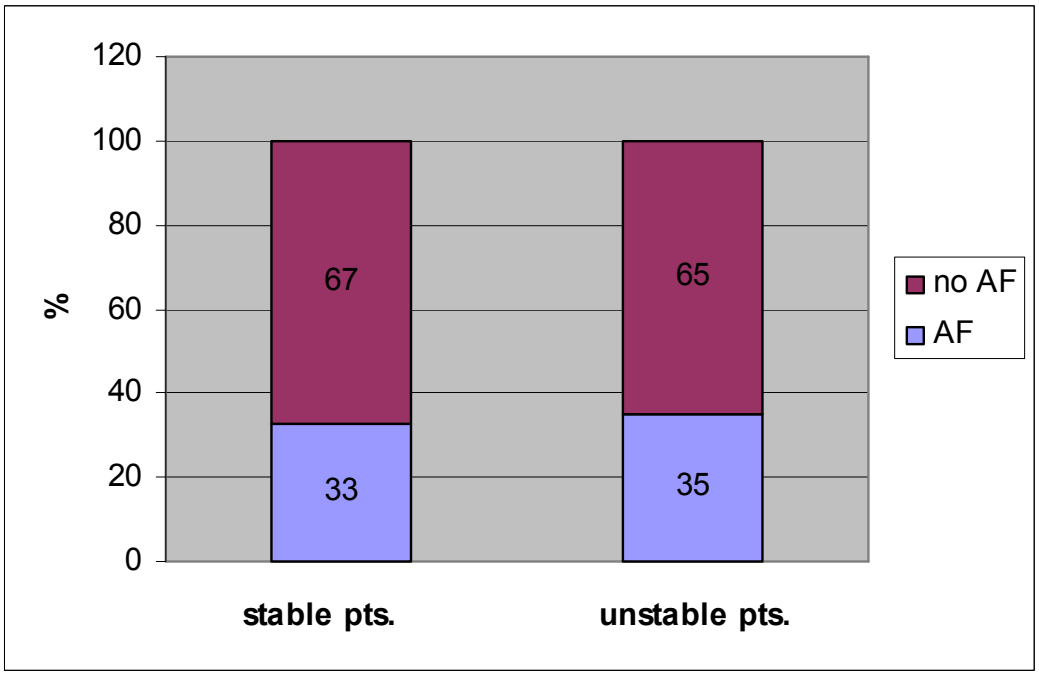


Figure 19. ***Distribution of atrial fibrillation.***
AF – atrial fibrillation, pts – patients.

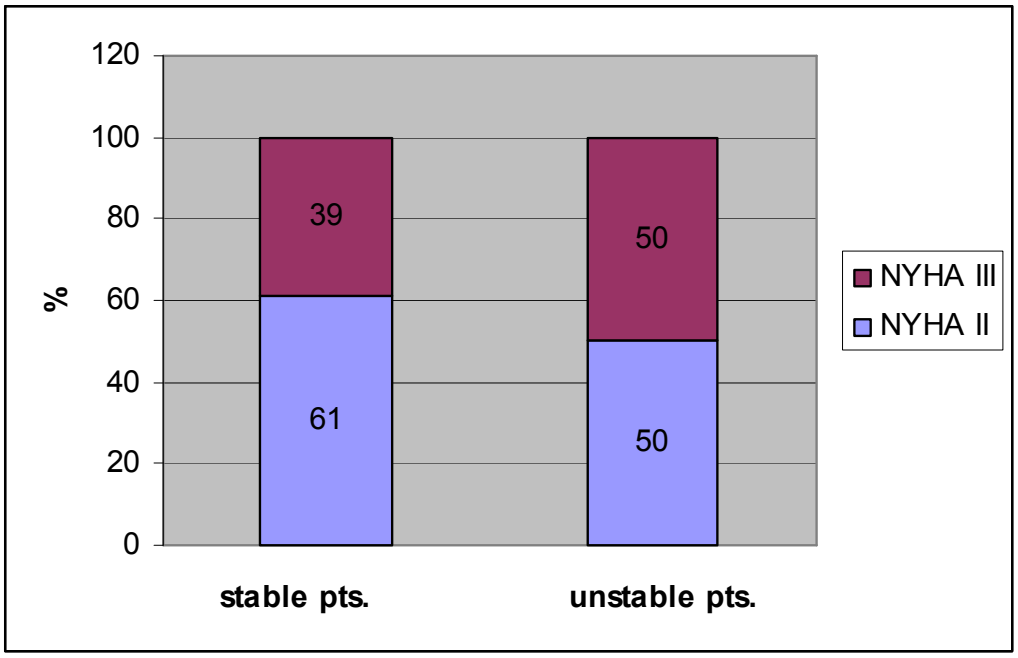


Figure 20. ***Distribution of NYHA classes.*** *Pts – patients*

3.3.2. Systolic standard echocardiographic parameters

All of the patients included in the study had a very low LV ejection fraction (<30%), which did not differ between the groups. Other standard echocardiograhic parameters for systolic function also did not show any significant differences (table 2). Left ventricular dimensions and diastolic volume were even slightly higher in the group of stable patients, but not significantly. No differences were observed in LV longitudinal and transverse axis relation. However, stable patients tended to have higher stroke volumes and smaller left atria, but also not significantly.

3.3.3. Systolic 2D strain imaging parameters

Stable patients appeared to have significantly higher global longitudinal endsystolic strains (ESS), and peak systolic strain rates (SSR_{max}) in comparison to unstable patients: longitudinal ESS -7.2±3.5% vs. -4.9±2.4% ($p<0.05$) and longitudinal SSR_{max} -0.44±0.13s^{-1} vs. -0.34±0.1s^{-1} ($p<0.05$). Radial and circumferential ESS and SSR_{max} were also higher in the group of stable patients, but the differences were not significant (table 3). Moreover it was noticed that unstable patients in comparison to stable patients had more marked radial, circumferential and longitudinal systolic dyssynergy between the separate myocardial segments. However the differences did not reach statistical significance.

Table 2. ***Baseline values of standard ehocardiographic systolic parameters***

Parameter	Stable patients	Unstable patients	P
LVEF, %	22.1±3.8	19.6±5.4	0.32
LVEDD, mm	73.3±13.5	71.4±9.2	0.63
LVESD, mm	65±7.2	60.5±13.7	0.27
LVEDV, ml	287±99	270±74	0.59
SV, ml	63.1±13	54.4±17.3	0.22
LV axis relation	1.27±0.17	1.29±0.12	0.58
LA, mm	40.2±13.8	45.8±7	0.21
MI (0 / I / II / III)	5 (28%) / 9 (50%) / 4 (22%) / 0	4 (20%) / 10 (50%) / 3 (15%) / 1 (5%)	0.72

Table 3. ***Baseline values of strain imaging derived systolic parameters***

Parameter	Stable patients	Unstable patients	P
Radial ESS, %	12.6±8.9	8,2±5.5	0.085
Radial SSR_{max}, s^{-1}	0.68±0.35	0.52±0.21	0.1
Circumferential ESS, %	-7.3±3.5	-5.8±1.7	0.14
Circumferential SSR_{max}, s^{-1}	-0.49±0.22	-0.43±0.11	0.29
Longitudinal ESS,* %	-7.2±3.5	-4.9±2.4	0.028
Longitudinal $SSR_{max,}$* s^{-1}	-0.44±0.13	-0.34±0.1	0.018

***** *shows a statistically significant difference between the groups*

3.3.4. Synchronicity of LV systolic function

Intraventricular systolic circumferential and longitudinal dyssynchrony indexes were found to be significantly higher in patients who tended to deteriorate in the near future than in those who remained stable over the next 6 months (0.24±0.13 vs. 0.16±0.05 ($p<0.05$) and 0.36±0.18 vs. 0.22±0.08 ($p<0.005$), respectively). The synchronicity of intraventricular

radial systolic thickening was also more altered in the group of unstable patients, but the difference was not statistically significant (table 4, figure 21).

Table 4. ***Baseline values of strain imaging derived synchronity indexes.***

Parameter	Stable patients	Unstable patients	P
Radial dyssynchrony index	0.14±0.06	0.17±0.11	0.27
Circumferential dyssynchrony index*	0.16±0.05	0.24±0.13	0.034
Longitudinal dyssynchrony index *	0.22±0.08	0.36±0.18	0.004

**shows a statistically significant difference between the groups*

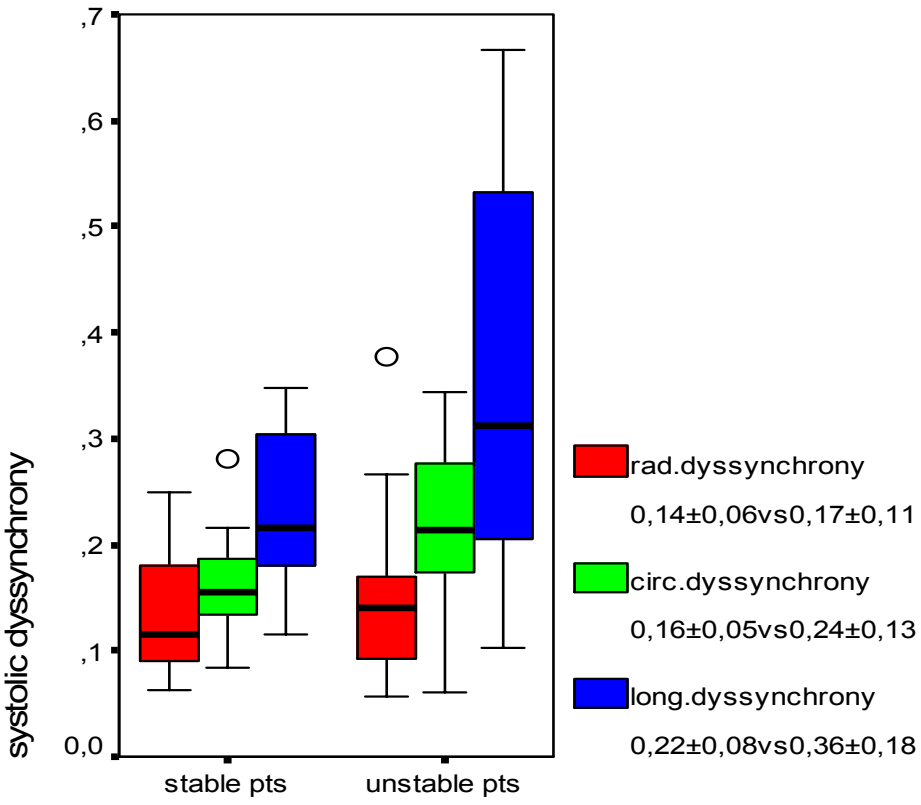


Figure 21. ***Boxplot representing radial, circumferential and longitudinal systolic dyssynchrony differences between the groups.*** *Pts – patients.*

3.3.5. Diastolic standard echocardiographic and 2D strain imaging parameters

At the baseline the patients who remained stable had less altered diastolic function in comparison to those with rapid HF progression: transmitral E/A-wave ratio 1.3±1 vs. 2.9±1.3

($p<0.005$), E-wave deceleration time (DT) 139±34.5ms vs. 103±22.4ms ($p<0.01$). Better diastolic function in these patients was also shown by parameters derived from strain imaging: strain rate during late diastolic ventricular filling (DSR_A) 0.42±0.13s^{-1} vs. 0.19±0.12s^{-1} ($p<0.001$), $DSR_{E/A}$ 1.4±0.9 vs. 3.5±2.5 ($p<0.005$). Strain rate during early diastolic filling (DSR_E) did not differ between the groups (Table 5, figures 22-24).
Diastolic function was not evaluated for the patients with chronic fibrillation.

Table 5. ***Baseline values of diastolic paramters.***

Parameter	**Stable patients**	**Unstable patients**	**P**
VE,* m/s	0.65±0.24	0.96±0.32	0.015
VA,* m/s	0.74±0.73	0.37±0.15	0.014
EA*	1.3±1.1	3±1.3	0.002
DT*, ms	139±34.5	102.7±22.4	0.004
DSR_E, s^{-1}	0.53±0.27	0.47±0.21	0.516
DSR_A,* s^{-1}	0.42±0.14	0.19±0.12	0.000
$DSR_{E/A}$,*	1.34±0.86	3.45±2.4	0.004

***** *shows a\statistically significant difference between the groups*

3.3.6. Correlation with other prognostic markers

Standard echocardiographic and strain imaging parameters, that showed differences between the two groups were further analyzed. We evaluated the correlations between them and NT-proBNP, which is routinely used to reflect the severity and prognosis of heart failure. Logarithmic transformation of NT-proBNP values was performed to obtain the normal distribution of data.
Highly significant correlations are listed in table 6. The strongest correlations were observed between NT-proBNP and diastolic parameters, especially diastolic SR (DSR_A), VE and E/A (figures 25-26). None of the standard echocardiographic parameters depicting systole correlated with NT-proBNP. Longitudinal ESS, systolic SR and longitudinal dyssynchrony index appeared to have moderate correlation with NT-proBNP. However, circumferential and radial strain parameters did not show any significant correlation with this marker.
No correlations were observed between any of these parameters and VO_2max.

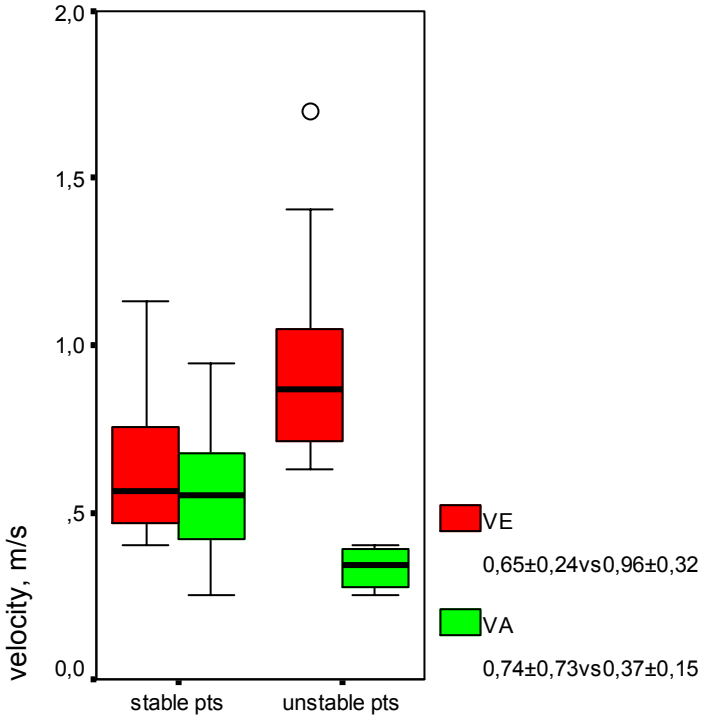


Figure 22. ***Diastolic flow Doppler parameters.***
Boxplot representing differences in diastolic transmitral flow velocities between the groups
Pts – patients, VE – E wave velocity, VA – A wave velocity.

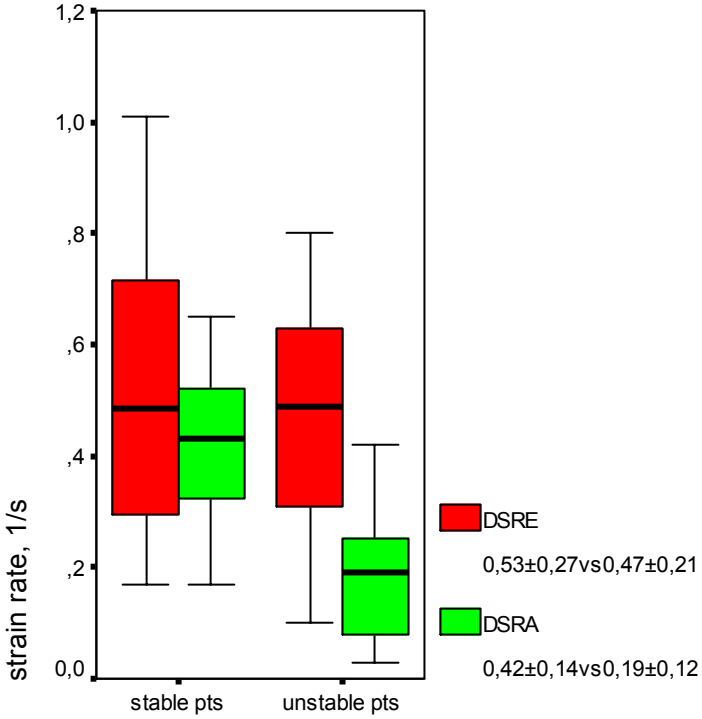


Figure 23. ***Boxplot representing diastolic strain rate differences between the groups.***
Pts – patients, SR – strain rate, DSRE - diastolic strain rate E wave, DSRA – diastolic strain rate A wave.

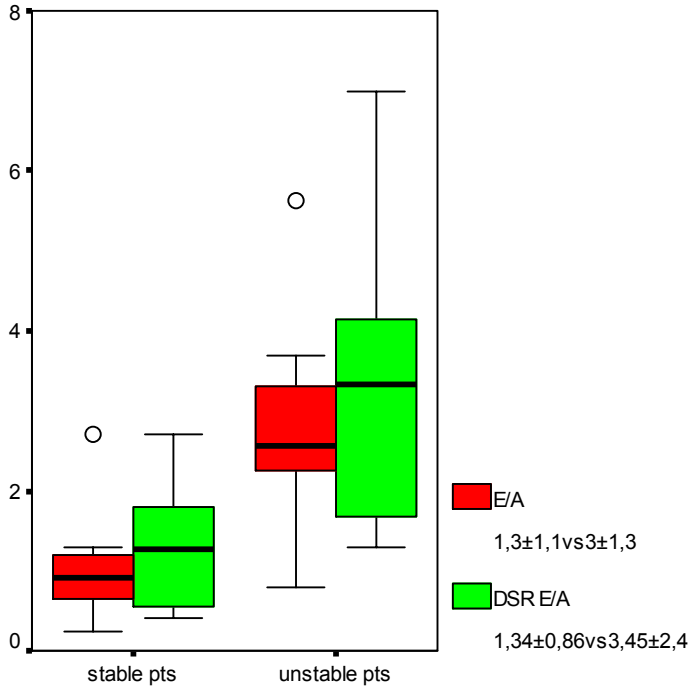


Figure 24. ***Boxplot representing differences of diastolic filling patterns between the groups.***
Pts – patients, DSRE/A - diastolic strain rate E wave.

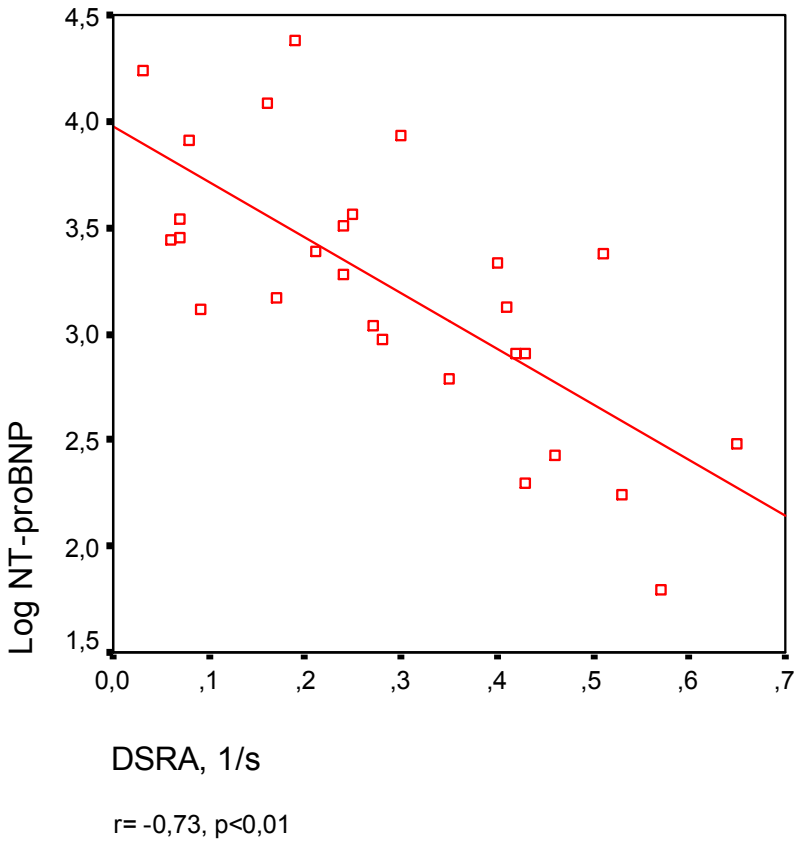


Figure 25. ***Negative correlation between NT-proBNP and diastolic SR A wave.***
NT-proBNP – N-terminal-pro-B-type natriuretic peptide, DSRA – diastolic strain rate A wave.

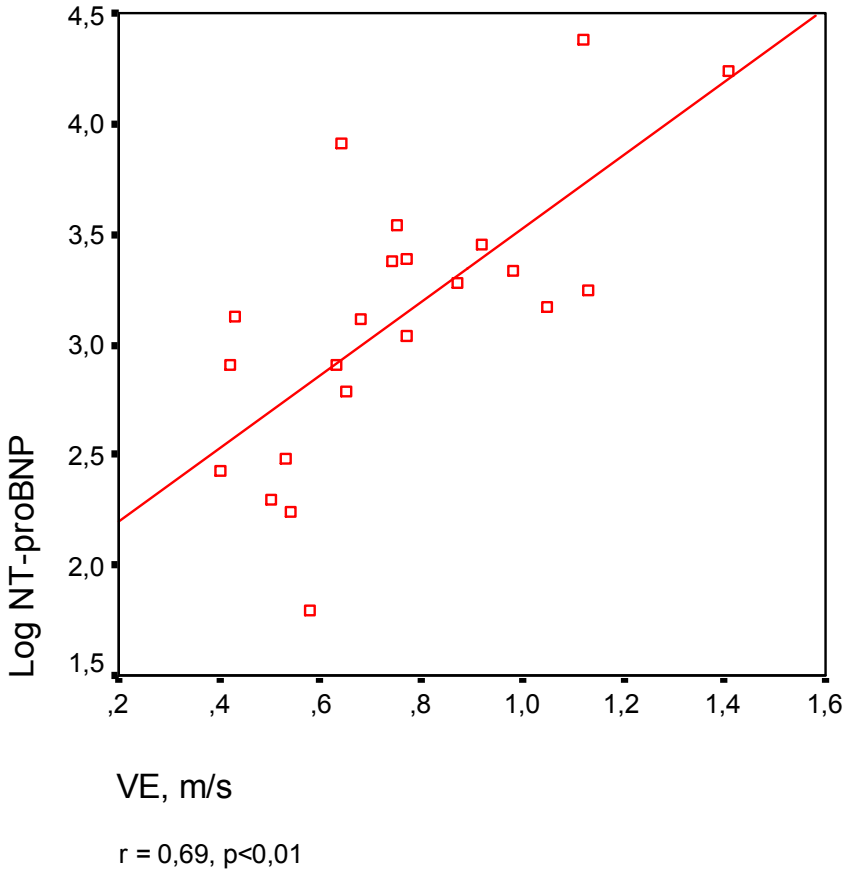


Figure 26. ***Positive correlation between NT-proBNP and diastolic E wave velocity.***
NT-proBNP – N-terminal-pro-B-type natriuretic peptide, DSRA – diastolic strain rate A wave.

Table 6. ***Significant correlations between NT-proBNP and echocardiographic parameters.***

Parameter	**r**	**P**
VE	0.69	<0.01
E/A	0.68	<0.01
DSR_A	-0.73	<0.01
$DSR_{E/A}$	0.39	<0.05
Longitudinal ESS	0.46	<0.01
Longitudinal SR	0.38	<0.05
Longitudinal dyssynchrony index	0.34	<0.05

3.3.7. Predictive value

The receiver operating characteristic (ROC) curves for certain parameters were obtained to test their accuracy in the prediction of rapid clinical deterioration in patients with end-stage idiopathic DCM (Figure 27). Sensitivity, specificity and positive and negative predictive values were calculated for the chosen cut-off points (Table 5). As flow Doppler E wave and late diastolic SR (DSR_A) showed very high significant differences between the groups and strongest correlations with NT-proBNP, their ratio was also tested as a new parameter for HF progression. The highest predictive values for rapid clinical deterioration had E-wave DT<100ms, $DSR_A<0.3s^{-1}$, $DSR_{E/A}>2$ and $VE/DSR_A>2$ (88%, 89%, 85% and 83% respectively).

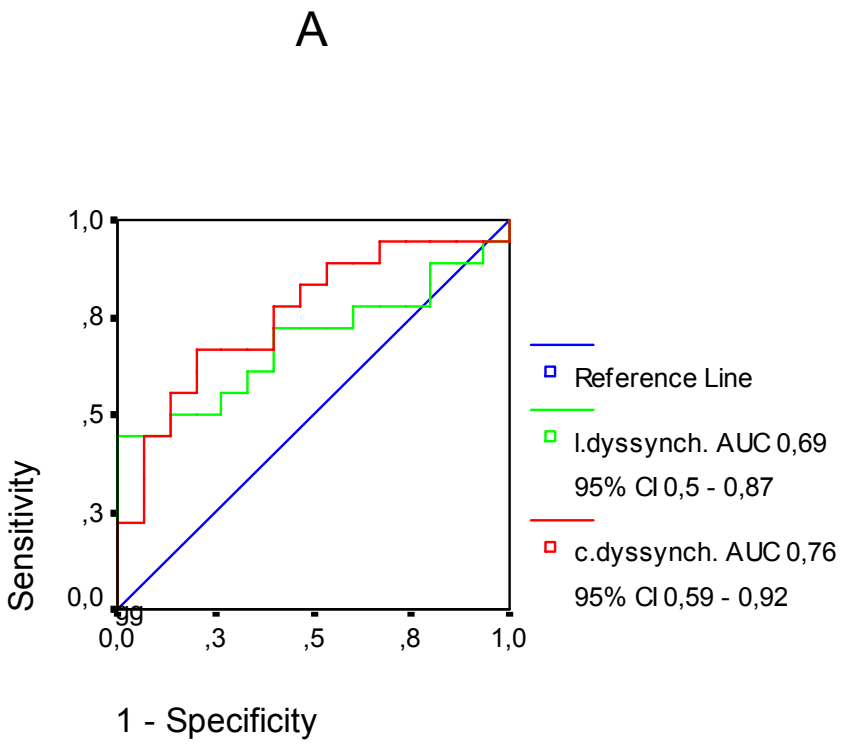
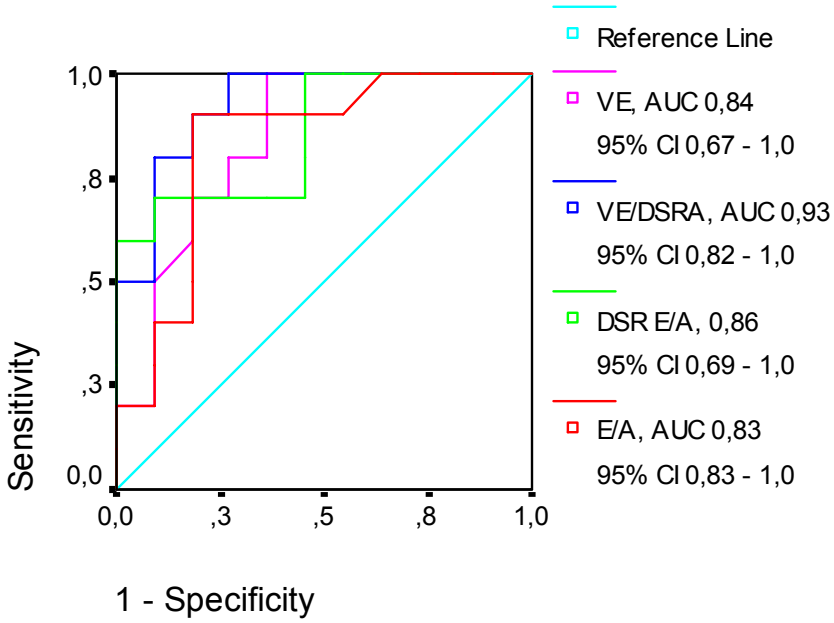


Figure 27. ***Receiver-operating characteristic (ROC) curves for prediction of rapid clinical deterioration in patients with end-stage idiopathic DCM.*** The high values for the areas under the curves (AUC) indicate the value of circumferential and longitudinal dyssynchronies (A) and diastolic parameters (B and C) in identifying the patients with possible rapid deterioration.

B



C

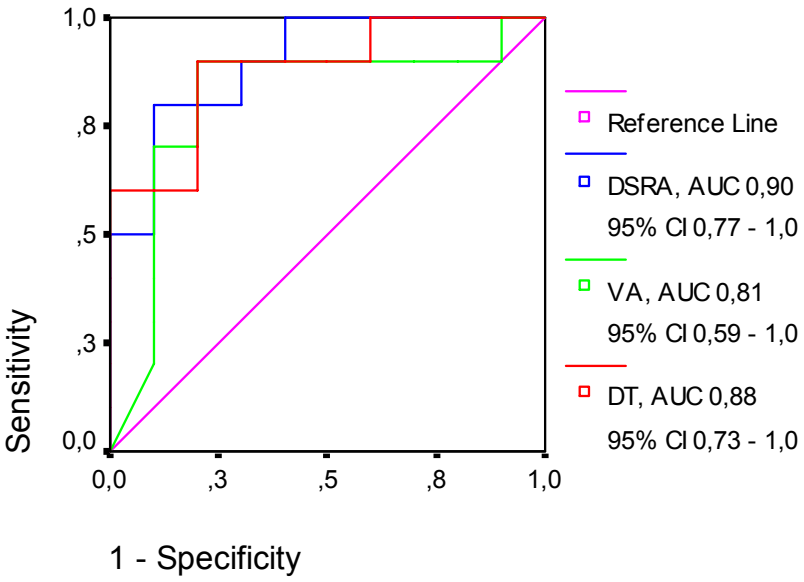


Figure 27 (*continued*)

Table 7. ***Sensitivity, specificity and positive and negative predictive values of certain parameters***

Parameters	Cut-off	PPV	NPV	Sensitivity	Specificity
Circumferential dyssynchrony	>0.16	68%	73%	83%	53%
Longitudinal dyssynchrony	>0.22	68%	68%	75%	61%
E/A	>1.5	79%	91%	78%	91%
DT, ms	<100	88%	59%	91%	50%
DSR_A, s^{-1}	<0.3	89%	90%	94%	83%
$DSR_{E/A}$	>2	85%	63%	65%	83%
VE/DSR_A	>2	83%	90%	82%	91%

PPV – positive predictive value, NPV – negative predictive value

In addition the risk of clinical deterioration was evaluated by calculating the odds ratios for the same cut-off values. All the above mentioned parameters had odds ratios and 95% confidence intervals above 1, which indicates their value in risk prediction. Yet some of them had very wide confidence intervals. The narrowest confidence intervals had odds ratios calculated for strain parameters. These are outlined in the table 8.

Table 8. ***Odds ratios of certain parameters.***

	Odds ratio	95% CI	
		Lower	Upper
$DSR_A \leq 0{,}3\ s^{-1}$	22.5	3.1	161.5
$DSR_{E/A} \geq 2$	9.2	1.5	56.3
Circ.dyssynchrony ≥ 0,16	5.7	1.2	28.4
Long.dyssynchrony ≥ 0,16	4.7	1.2	18.9

3.4. Discussion

3.4.1. Short–term prognosis in patients with end-stage idiopathic DCM

The intention of our study was to find simple short-term prognostic factors of idiopathic DCM course. Although several studies have identified prognostic markers in patients with DCM, the discriminatory power of these classic parameters (etiology, duration of disease, LV ejection fraction, NYHA functional class, ventricular tachycardia, cardiothoracic ratio, systolic blood pressure, pulmonary vascular resistance and others) appeared to be less accurate in patients with severe end-stage heart failure. Moreover there are only few data concerning short-term predictors in end-stage DCM.

Huang et al. reported total pulmonary vascular resistance and cardiac index to be predictors of short-term outcomes in patients with non-ischemic DCM (66). Yet these parameters require invasive procedures, and therefore are not very suitable for clinical routine.

Our study group was restricted to symptomatic patients accepted for transplantation with very low LVEF (≤ 30%) and potentially worst prognosis at the baseline, which made it different from the other studies mostly investigating patients with higher LVEF, better LV function and more favorable prognosis.

The results show that such a highly available non-invasive method as echocardiography might be a useful tool in evaluating short term prognosis of end-stage DCM patients. Besides the standard flow Doppler parameters E/A and DT, the strain imaging parameters DSR_A and $DSR_{E/A}$ appeared to have high sensitivity and predictive values for clinical deterioration. Circumferential and longitudinal dyssynchrony also seem to contribute to clinical instability. Although in comparison to diastolic parameters they have lower sensitivity and specificity, the 95% CI of their odds ratios are above 1, which shows their prognostic relevance. Our data suggest that these parameters could significantly contribute to the routine follow-up of end-stage DCM patients. Their value in reflecting prognosis of HF is also supported by the significant correlation with NT-proBNP. However, although NT-proBNP tests are highly available and simple to perform, they have some major limitations. First of all it should not be forgotten that although normal NT-proBNP values show good LV function, high values do not necessarily show severe HF. Apart from cardiac causes, NT-proBNP elevation may be caused by renal dysfunction, pulmonary diseases, pulmonary embolism, sepsis, hyperthyroidism, liver cirrhosis, other high output states, etc. (95, 96). This would not be a problem of echocardiography including strain imaging. We did not see any correlations

between these echocardiographic parameters and VO_2max, but this most probably shows the inaccuracy of VO_2max, as it depends on many other factors, such as muscle mass, age, gender, deconditioning of the patient and pulmonary diseases.

3.4.2. Diastolic dysfunction

We found that diastolic dysfunction is a valuable predictor of short-term outcomes in end-stage DCM patients. The patients with deterioration in our study had at the baseline more expressed restrictive filling patterns measured by pulsed Doppler and by strain rate imaging, a shorter transmitral E-wave deceleration time and also slower myocardial strain rate during late diastolic filling (DSR_A). At certain cut-off values these parameters were highly predictive for short-term clinical deterioration, and their odds ratios for clinical deterioration were above 1. Furthermore DSR_A, VE and E/A showed strong correlations with NT-proBNP, which is known to reflect the severity and prognosis of heart failure (95,96). We tried to construct the new parameter combining flow Doppler VE and strain imaging DSR_A, as both of these parameters differed significantly between the two groups and showed strong correlations with NT-proBNP. The new VE/DSR_A also appeared to have high sensitivity and positive predictive value for fast clinical deterioration in end-stage idiopathic DCM. However it remains unclear whether this provides any additional information.

Our results correspond in part with those of other studies, which have concluded that short transmitral E wave deceleration time and persisting restrictive left ventricular filling pattern are associated with worse clinical course and high mortality in HF patients (50-53). However, in most of them-long term (>24 month) outcomes were chosen.

It is known that early ventricular diastolic filling is determined mainly by the pressure gradient between the ventricle and the atrium, which depends on ventricular relaxation and atrial diastolic pressure (87). At the baseline of our study patients in the unstable group had higher transmitral E wave velocities (VE) and shorter E wave deceleration times (DT) in comparison to the patients who remained stable, and yet DSR_E in the two groups did not differ. Assuming that diastolic SR reflects diastolic deformation or lengthening of myocardium, and flow Doppler parameters describe transmitral flow, it appears that in patients susceptible to clinical deterioration LV restrictive filling patterns result from the increasing pressure gradient between LV and left atrium, without further deterioration of LV relaxation.

Late diastolic filling occurs due to atrial contraction, and ventricular compliance plays an important role here (87). DSR_A, while showing myocardial lengthening during late diastolic filling, reflects myocardial compliance. Thus, significant differences in DSR_A between the stable and clinically deteriorated patients in our group support the importance of myocardial compliance for the clinical course of DCM.

In healthy persons myocardial compliance also contributes the ventricular systolic function, as according to the Frank-Starling law the contraction force depends on the initial length of each sarcomere. It is clear that the more the sarcomere is stretched during diastole, the more bindings between actin and myosin complexes occur and therefore contraction becomes stronger (87). In a dilated ventricle this should be of less importance, as the sarcomeres are overstretched. However, worsening myocardial compliance decreases LV filling and thereby leads to a decrease in cardiac output and increase in left atrial and later pulmonary and right ventricular pressures.

3.4.3. Dyssynergy and dyssynchrony of left ventricular systolic function

It appears that in end-stage HF longitudinal systolic shortening might be of crucial importance for the heart pump function. On the other hand longitudinal function might be the last one to be affected in the dilated left ventricle. We analyzed separately systolic radial, circumferential and longitudinal strains to evaluate the heterogeneity of ventricular function. As expected, at the baseline the patients who tended to deteriorate in the following months had lower SSR_{max} and global ESS values, and also as more marked differences in endsystolic strains in separate segments. However, only the differences between longitudinal global ESS and SSR_{max} values were statistically significant. Besides that, only longitudinal, and not circumferential or radial systolic strain values correlated with NT-proBNP values.

It also seems that the poor synchronity of both longitudinal and circumferential shortening might play a role in rapid progression of heart insufficiency, as the peak systolic strain occurring not at the same time in separate myocardial segments leads to higher energy demand needed to develop adequate pressure in the ventricle to open the aortic valve. In our study we found that the patients who tended to deteriorate in the following months had at the baseline more expressed circumferential and longitudinal, but not radial dyssynchrony in comparison to the patients who remained stable. These two parameters might also be used as

risk factors, as their prognostic significance is reflected by the area under curve on ROC curves and odds ratios above 1.

The substantial contribution of longitudinal and circumferential motion to the systolic function of left ventricle was also documented by Bogaert and Rademakers, who performed strain analysis in healthy adults using MRI (88). Recently some other studies have also been published demonstrating that left ventricular wall motion is not always diffusely hypokinetic and that regional heterogeneity of left ventricular function is frequently present (31-38, 89,90). Julliere et al. found thallium-201 myocardial perfusion anomalies in IDCM patients which they associated with the heterogeneity of myocardial function and wall stress (33). Bach et al. compared the heterogeneity of left ventricular function in normal subjects and IDCM patients and correlated it with myocardial oxidative metabolism. They concluded that myocardial segments with higher regional oxidative metabolism have better contractile function (40). Thereby the more hypokinetic segments the ventricle has, the more limited is its energy reserve.

Concerning the synchronicity of left ventricular systolic function, it was documented that patients with HF had more expressed intraventricular dyssynchrony than normal subjects (32,40) which did not correlate with the QRS complex duration (37). Fauchier et al. found that intraventricular dyssynchrony evaluated by radionuclide angiography, but not interventricular is an independent long-term predictor of cardiac events in DCM patients (34). The data of Takemoto et al. also speak for the role of intraventricular dyssynchrony in idiopathic DCM. They found, that in these patients beta-blocker therapy, whose efficacy for HF treatment is well proved, diminished the intraventricular segmental dyssynchrony (39). Yet to our knowledge the impact of ventricular systolic synchronicity on the clinical stability of idiopathic DCM patients has never been tested.

This systolic heterogeneity and dyssynchrony of failing myocardium do not seem surprising in view of all the complex changes occurring at the myocyte, myocardial and ventricular levels. All these changes, and especially myocyte loss, excessive fibrosis and extracellular matrix degradation, might also result in the loss of normal fiber arrangement in myocardium, and the latter is significant for the complex adaptations related to optimal energy transfer from myocardium to the blood in the normal heart (97). It is obvious that abnormal fiber orientation can contribute to the loss of synchronicity and homogeneity of systolic function. Consequently the severity of ventricular heterogeneity and dyssynchrony should reflect the extent of the pathologic changes in myocardium, and thereby predict the further short-term clinical course.

3.4.4. The role of strain imaging in predicting short term clinical deterioration

It is clear that strain imaging offers new possibilities in the evaluation of patients with idiopathic DCM. Systolic intraventricular dyssynchrony and diastolic strain imaging parameters, such as DSR_A and $DSR_{E/A}$, as well as flow Doppler and strain imaging VE/DSR_A appear to be valuable risk factors, predicting possible rapid clinical deterioration. Even though their prognostic value is just slightly higher than that of flow Doppler derived E/A and DT, they can contribute a lot to the clinical examination of individual patient.

A number of conditions, such as atrial fibrillation, severe mitral regurgitation and pacemaker rhythm, are known to make diastolic flow Doppler parameters imprecise. However, this might not have relevant influence on strain imaging. Thus as a next step we are planning a study to analyze its prognostic value in these situations.

It should not be forgotten that HF syndrome is very complex, and there cannot be one universal criterion suitable for decision making. Before making a decision concerning an individual patient, physicians should consider all the pathophysiological processes taking place because of the disease. Exactly here strain imaging might be very useful: it enables evaluation of pathological processes, which play an important role in the progression of HF, but cannot be analyzed with any other technique. Moreover, the method is non-invasive, easy to perform, not time consuming and well reproducible.

3.5. Conclusion

In idiopathic DCM patients with similar LVEF (<30%), further cardiac stability appeared to be related to the severity of alterations in LV systolic synchronicity and diastolic function. The high predictive values of transmitral flow Doppler and 2D-strain parameters for the short-term (<6 month) course of HF recommend echocardiography as a valuable tool for the guidance of HTx-listing decisions, which could add to such widely used parameters as natriuretic peptides or peak oxygen consumption. Adding strain imaging to routine follow-up would make the approach to the individual patient more comprehensive, and thereby patient selection for more intense follow-up or even for HU listing or VAD implantation would become more precise.

4. Summary

In the light of continuous prolongation of the waiting time on heart transplantation (HTx) lists, the need for reliable predictors of the time course of heart failure (HF) has become increasingly important. Thus, the aim of our study was to evaluate the prognostic value of echocardiography including 2D strain imaging in patients with end-stage idiopathic dilated cardiomyopathy (IDCM).

The study population comprised 38 consecutive stable IDCM patients referred for HTx. At the baseline all of them underwent standard echocardiography, during which views for radial, circumferential and longitudinal strain and strain rate measurements were stored. Strain imaging was used to acquire radial, circumferential and longitudinal endsystolic strains (ESS), peak systolic strain rates (SSR_{max}), as well as early and late diastolic strain rate (DSR_E and DSR_A, respectively). Dyssynchrony indexes were also calculated from strain images. For quantification of systolic intraventricular dyssynchrony the coefficient of variance of time interval from the beginning of QRS complex to peak systolic strain at separate segments was used. Echocardiographic parameters were analyzed to find significant differences between the groups. Their value in predicting the time course of HF during the following 6 months was tested.

During the first 6 months after inclusion in the study, 18 patients remained stable; the other 20 showed severe cardiac deterioration and finally 14 of them underwent ventricular assist implantation and 6 died, although initially there were no significant differences in peak oxygen consumption, left ventricular size, ejection fraction or other parameters describing systolic function. However, at the baseline, patients who remained stable had lower NT-proBNP values and less altered diastolic function in comparison to those with rapid HF progression. Thus, stable patients had significantly lower flow Doppler and strain imaging derived E/A ratios, longer transmitral E wave deceleration time and higher late diastolic strain rate (DSR_A) values). They also had significantly lower systolic circumferential and longitudinal dyssynchrony indexes and higher longitudinal systolic strain and strain rate values. Diastolic parameters correlated strongly with NT-proBNP, which is known to be elevated in patients with HF, whereas systolic dyssynchrony indexes showed moderate correlations with this marker. No correlations between peak oxygen consumption and echocardiographic parameters were observed.

At certain cut-off values flow Doppler and strain imaging derived diastolic parameters, as well as systolic dyssynchrony indexes showed high predictive values for cardiac stability

over the next 6 months. Highest positive predictive values for rapid HF progression were found for transmitral E deceleration time (DT) <100ms, late diastolic strain rate (DSR_A) <0.3/s and strain imaging derived E/A ratio ($DSR_{E/A}$) >2 (88%, 89% and 85%, respectively). The index obtained by combining flow Doppler and strain imaging (VE/DSR_A) was also tested, and its value, which was >2, had a predictive value for rapid HF progression of 83%. Thus in patients with advanced idiopathic DCM and similar LVEF (<30%), further cardiac stability appeared to be related to the severity of alterations in LV systolic synchronicity and diastolic function. Transmitral flow Doppler and strain imaging parameters can be recommended as short-term prognostic factors in these patients. Moreover, strain imaging is a very useful method, as it allows a better understanding of HF pathophysiology and throws light on the progress of this syndrome in individual patients. This extensive approach to the problem is essential while making decisions of vital importance, such as patient listing for high-urgency Tx.

5. Abbreviations

2D – two dimensional

2CH – two-chamber

4CH – four-chamber

ACE – angiotensin converting enzyme

ANP – atrial natriuretic peptide

ANS – adrenergic nervous system

APLAX – apical long axis

ARB – angiotensin receptor 1 blockers

AT1 – angiotensin receptor 1

ATP – adenosintriphosphate

AVC – aortic valve closure

BNP – brain (B-type) natriuretic peptide

CI – cardiac index

DCM –dilated cardiomyopathy

DSR_E – diastolic strain rate E wave

DSR_A – diastolic strain rate A wave

$DSR_{E/A}$ – diastolic strain rate E and A wave ratio

DT – E-wave deceleration time

E/A – VE and VA ratio

ECG – electrocardiography

ESS – global endsystolic strain

HF – heart failure

HLA – human leukocyte antigens

HTx –heart transplantation

ISFC – international society and federation of cardiology

LAD – left atrial diameter

LV – left ventricle

LVEF – left ventricular ejection fraction

LVEDD – left ventricular enddiastolic diameter

LVEDV – left ventricular enddiastolic volume

LVESD – left ventricular endsystolic diameter

MCS – mechanical circulatory support

MI – myocardial infarction

MMP – metalloproteinase

MVO – mitral valve opening

NYHA – New York Heart Association

NT-proBNP – N-terminal proBNP

PGE – prostaglandin E

PWP – pulmonary wedge pressure

RAS – renin-angiotensin system

RV – right ventricle

S – strain

SAX-MV – short-axis mitral view

SR – strain rate

SSR_{max} – maximal systolic strain rate

TDI – tissue Dopper imaging

TNF – tumor necrosis factor

TPR – transpulmonary resistance

VE – E wave velocity

VA – A wave velocity

VAD – ventricular assist devices

VO_2max – peak exercise oxygen consumption

WHO – World Health Organization

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Erklärung

„Ich, Ruta Jasaityte, erkläre, dass ich die vorgelegte Dissertationsschrift mit dem Thema: „Prediction of Short–Term Outcomes in Patients with Idiopathic Dilated Cardiomyopathy Referred for Transplantation using Standard Echocardiography and Strain Imaging" selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe."

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