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Cardiac mechanics in heart transplant recipients with and without transplant vasculopathy – Combined approach of longitudinal, radial and circumferential strain with torsion

Doctoral Thesis

To attain the degree of medical doctor at the Medical Faculty of Hamburg University

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1. Introduction

1.1 Heart failure and treatment by heart transplantation

The presence of heart failure is a major public health problem with a steadily increasing patient population reaching about 23 million patients worldwide and over 5,8 million patients in the United States [1,2]. Especially due to the increasing age, incidence and prevalence of heart failure are increasing, representing a leading cause of death and hospitalization in the elderly [3]. In relation to the increasing expectancy in life, as well as new options in treatment of heart failure, patients are reaching a more severe stage of heart failure and increase in numbers, representing the cohort of end-stage heart failure patients [4,3]. End-stage heart failure patients are characterized by advanced structural heart disease and symptoms of heart failure being present at rest or at minimal physical activity already receiving optimal medical treatment and device therapy. These patients are summarized in group D of the ABCD classification of the American College of Cardiology (ACC)/ American Heart Association (AHA) and have functional impairment corresponding to New York Heart Association (NYHA) class III-IV [4,3]. The outcome of this population is poor with a 1-year survival rate of 50%, requiring special therapeutic interventions to correct reversible causes of worsening heart failure (see figure 1).

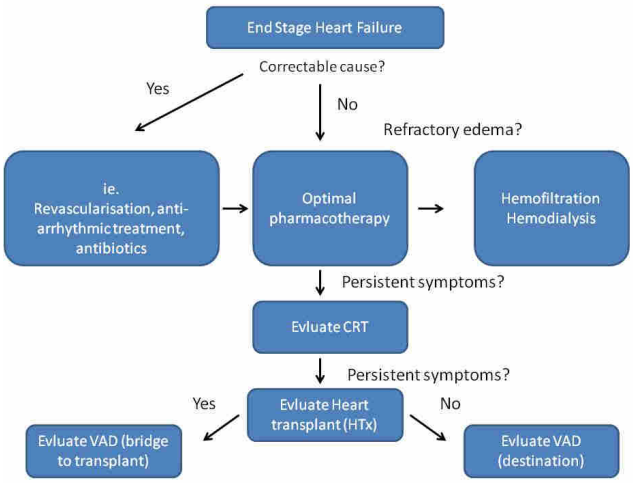

Figure 1 Management of end stage heart failure

However, despite the advances in pharmacologic and device based treatment of heart failure, morbidity and mortality remains to be very high in this patient cohort, so that surgical treatment represents an option consisting of treatment with left ventricular assist devices (LVAD) or heart transplantation [5,4]. Heart transplantation is a reliable therapeutic option for patients with end-stage heart failure [6]. During the last years, 1 year survival remained high after transplantation for ischemic (84%) and non-ischemic (86%) reasons [7]. In addition, progression in immunosuppresive therapy resulted in a decrease of acute rejection to 22% after 1 year and 36% after 3 years [7]. Although the current results show that heart transplant is a feasible option, organ shortage is still a problem to be solved in the background of a declining trend of subjects to donate organs [8,7] and future strategies of allocating the organ to the recipient are needed [9]. The International Society of Heart and Lung Transplantation outlined indications and criteria for listing patients with heart failure [10] the criteria were especially focusing on cardiopulmonary stress testing, hemodynamic data from right heart catheter, co-morbidities and cardiovascular risk factors. In a more condensed fashion, characteristics to consider for heart transplantation are outlined in table 1.

Patients to consider	**Contraindications**
End stage heart failure with severe symptoms	Active Infection
Motivates, well informed, emotionally stable	Current alcohol or drug abuse
Complying with intensive treatment after operation	Significant renal disease (creatinine clearance <50mL/min)

	Significant liver disease
	Emotionally instability or mental illness
	High fixed pulmonal vascular resistance

Table 1 Heart transplantation: indications and contraindications

1.2 Imaging and its role in the care for heart transplant recipients during follow-up

After the first successful heart transplant in a human being in the 1960s, there was the need to monitor patients for the organ function and the complications inherent in allograft transplants. Although there were major breakthroughs in the surgical technique and diagnostic methods, improved by molecular research, the outcome of patients after transplant are still worsened by diseases specifically resulting from the necessary immunosuppressive therapy and the developing transplant vasculopathy (TVP) [11,12]. Immunosuppressive therapy demands inclusion of a broad spectrum of pharmacokinetic and pharmacodynamic aspects which have to be considered [11,13]. The doctoral thesis focuses on imaging aspects being of use in surveillance of organ function, indicators of rejection and declining organ function. The main stay to evaluate the organ function is echocardiography and its ability to monitor systolic function by measures like ejection fraction or fractional shortening of the left ventricle [14]. However, in the previous years only cardiac magnetic resonance imaging (CMR) was capable of providing full two- and three-dimensional motion analysis through tracking of magnetic tags. The disadvantage in this technique is the needed amount of time and the high cost in conjunction with a low spatial and temporal resolution [15,16]. Relying on the same technique is speckle tracking echocardiography, using natural acoustic markers as tracking tags during the cardiac

cycle [17-20]. The advantage of echocardiography is the fact that during contraction new acoustic markers fade into the imaging plane in contrast to MRI, were all tags together fade in and out during image acquisition, limiting the analysis to only a part of the heart cycle. Although CMR is not the standard tool for detection of TVP, current results strengthen the use of CMR for characterization of HTR and the probability by tissue analysis and corresponding lesions of progressive TVP in the myocardium [21-23]. One of the limiting factors in the general use of CMR is the progressive worsening renal function of HTR due to the immunosuppressive therapy and the arising cautious use of contrast agents like gadolinium [7]. This disadvantage is not present in the use of echocardiography, as the patients have no disadvantage by repeated use of echocardiography to assess the organ function [24].

Current study results strengthen the use of echocardiography in HTR and maybe as well TVP through assessment of cardiac mechanics by speckle tracking echocardiography. The progress made in imaging from one dimensional tissue velocity imaging assessing the regional myocardial function and its corresponding sub-clinical abnormalities resulting in a more sensitive diagnosis of rejection in HTR [25,26] to evaluation of the cardiac function by two- and even three-dimensional echocardiography [27-29]. Diagnosis regarding rejection is often made by endomyocardial biopsy, however aspects of declining organ function, besides parameters of systolic function, are reflected by strain and in this case, especially by radial strain and torsion of the cardiac myocytes [30-33]. Although strain analyses is a rather new aspect in echocardiography, the options open a door to evaluate the function of the heart beside standard echocardiography only focusing on systolic function of the heart and thereby missing important aspects of declining organ function.

1.3 Definition and causes of transplant vasculopathy

Transplant vasculopathy is considered to be a result of constant immunosuppressive therapy and resulting in progressive intimal proliferation leading finally to rising morbidity and mortality in HTR [12]. TVP represents a form of chronic rejection reaction and manifests in diffuse atherosclerosis and myointimal proliferation in the coronary arteries [13] resulting in ischemia and infarction. However, the most often used therapy of relevant coronary artery disease by angioplasty and coronary bypass grafting prove no benefit in treatment of TVP [34]. After 5 years of follow up, TVP is present in nearly 50% of patients and is a major cause of adverse outcome in the first post transplantation year [34,13]. More intense immunosuppression is supposed to inhibit progress of TVP and especially treatment regimes incorporating sirolimus and the newer medication everolimus are the most promising candidates [35,13]. An important tool to assess presence of TVP is intravascular ultrasound (IVUS) and thus facilitates diagnosis of TVP. In this context, everolimus could proof superiority in minimizing TVP and its progress as shown through IVUS measurements [36]. However, IVUS still relies on invasive techniques to position the Doppler wire in the coronary arteries and thus contrast media is still needed resulting in possible renal function impairment. TVP shares the aspect of narrowing of coronary arteries as reported from coronary artery disease and thus could be also sharing aspects of modern imaging techniques, a field still in need of further research.

1.4 Aims and hypothesis of the doctoral thesis

The architecture of the left ventricle is composed of the complex three dimensional patterns of myocardial layers, contributing to myocardial deformation.

Echocardiographic strain imaging has been developed to assess regional myocardial function and proofed to be useful to gain understanding in the pathophysiology and diagnosis of cardiac ischemia and infarction [37,38]. As TVP resembles aspects to coronary artery disease, one would suggest similar changes in patients with TVP regarding strain measurements. In addition, relying only on systolic function parameters is not ideally suited to detect changes in organ function or acute rejection in HTR [33,31,25,20,39].

The hypothesis of this doctoral thesis is that cardiac mechanics is changed after heart transplantation in terms of longitudinal, circumferential and radial strain and strain rate in comparison to normal values in strain and strain rate described in cohorts of the general population. Further, TVP patients show changes in strain and strain rate as described in coronary artery disease, thus strain imaging could facilitate the non-invasive diagnosis of TVP presence in HTR. In addition, strain imaging is useful to assess long term function after heart transplantation during follow-up, providing more information as solely relying on systolic function parameters. Imaging provides more information in HTR than the use of reliable biomarkers as HTR often show equivalent concentration to patients with structural heart disease and a large part of the HTR suffer from impaired renal function, influencing biomarker concentration further. The doctoral thesis aims to underline the importance of imaging in patients after heart transplantation for follow up and non-invasive assessments of organ function.

2. Material and Methods

2.1 Patients and study cohort

The study population consists of 41 patients (33 men and 8 women) with a median age of 54 years ($1^{st}/3^{rd}$ Quartile 45.7/65.3 years). The indication for heart transplantation was made in 17 patients (41,2%) due to ischemic coronary artery disease and in 24 patients (58,8%) due to non-ischemic reasons. Treatment and follow-up of patients in evaluation for heart transplantation or after transplantation is organized in a heart transplant and heart failure outpatient clinic staffed with a combined team of cardiologists and cardiovascular surgeons. During a scheduled outpatient visit each patients receives a blood draw to measure concentration of immunosuppressive medication and also a standardized echocardiography is performed to evaluate the organ function. As time points in the natural history after transplantation, the cohort evaluated in this study was retrospectively analyzed regarding strain and strain rate immediately after transplantation and 1 and 3 years. To monitor function of the transplanted organ, especially N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured to assess volume load and wall stress of the left ventricle. Further, as immunosuppressive therapy can influence renal function and thus the concentration of NT-proBNP, creatinine concentration is also measured during every outpatient visit. As current standard of care, presence of transplant vasculopathy is assessed by coronary angiography and classified according to the guidelines outlined by the ISHLT [12].

2.2 Principles of strain in echocardiography

The concept of tracking tissue motion by Doppler ultrasound was used since the last century to investigate cardiac pathophysiology. In this background (see figure 2) continuous-wave Doppler (A) analyzes the frequency shift of the returning echoes

compared with original frequency of the ultrasound beam and both, pulsed-wave Doppler (B) and color Doppler (C) use the phase shift between consecutive echoes (figure 2) [37].

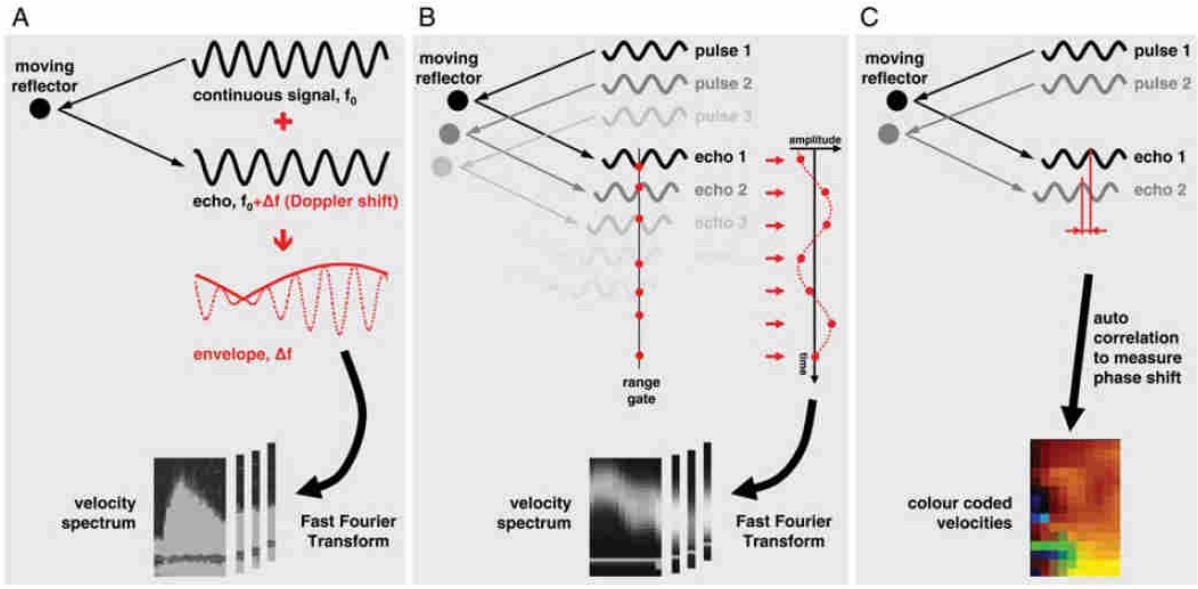

Figure 2 Schematics of different Doppler techniques (from reference [37])

Since the myocardium is constructed complex in nature and Doppler techniques measure velocities only in one dimension, different planes of the region of interest have to be examined. Therefore, this technique has the main disadvantage of being angle dependent upon its use, resulting in underestimated velocities if the ultrasound beam is not well aligned (figure 3). Regarding the different course of the myocardial tissue layers constructing the left ventricle, each component adds to myocardial deformation [37]. From studies exploring the deformation of myocardial tissue, the arrangement of the myocardial layers is described as two continuous helical fiber geometries. The subendocardial layer shows a right-handed fiber geometry changing to left-handed fiber geometry in the subepicardial region. In the complex geometry, the estimation of velocities and deformation rely on the same Doppler techniques as used with pulsed-wave and color Doppler echocardiography for blood flow, in these

cases using a special wall filter. The filter is a high-pass filter for imaging of blood velocities and a low-pass filter to display wall-motion [37].

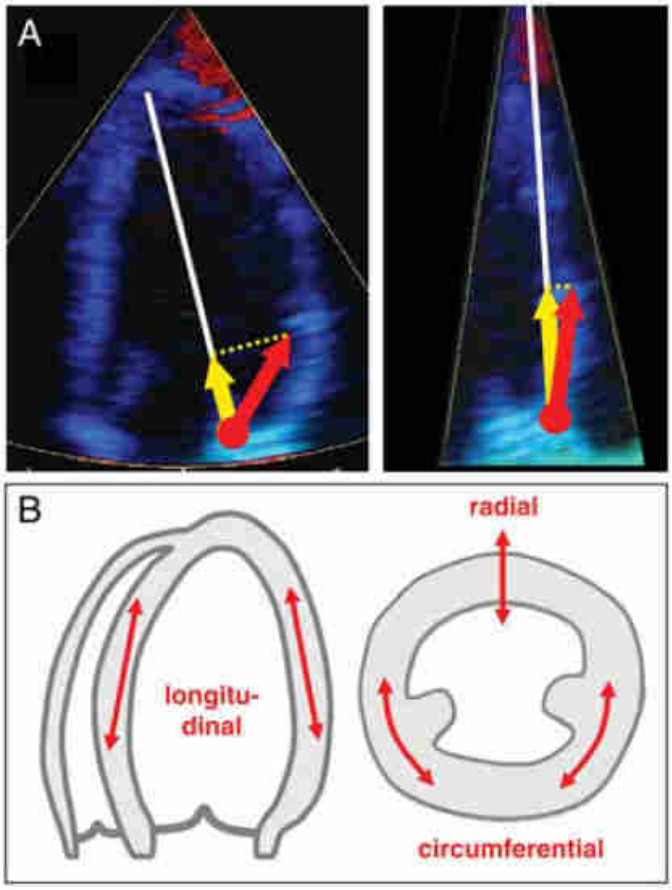

Figure 3 Principles for using Doppler ultrasound techniques with A showing an example of minimizing angle dependency by narrowing of the sector and B motion and deformation components that can be interrogated by Doppler (from reference [37]).

As shown in figure 3 strain, commonly referred to as “stretching” but meaning “deformation” in a more scientific approach, can be obtained from different perspectives and regions of interest resulting in values for longitudinal, circumferential and radial strain. Deformation of an object is present during differential motion of the object, whereby spatial derivation of velocity will result in strain rate (the velocity difference per time unit) and spatial derivation of displacement will result in strain (motion difference per length unit) (see figure 4) [40-42].

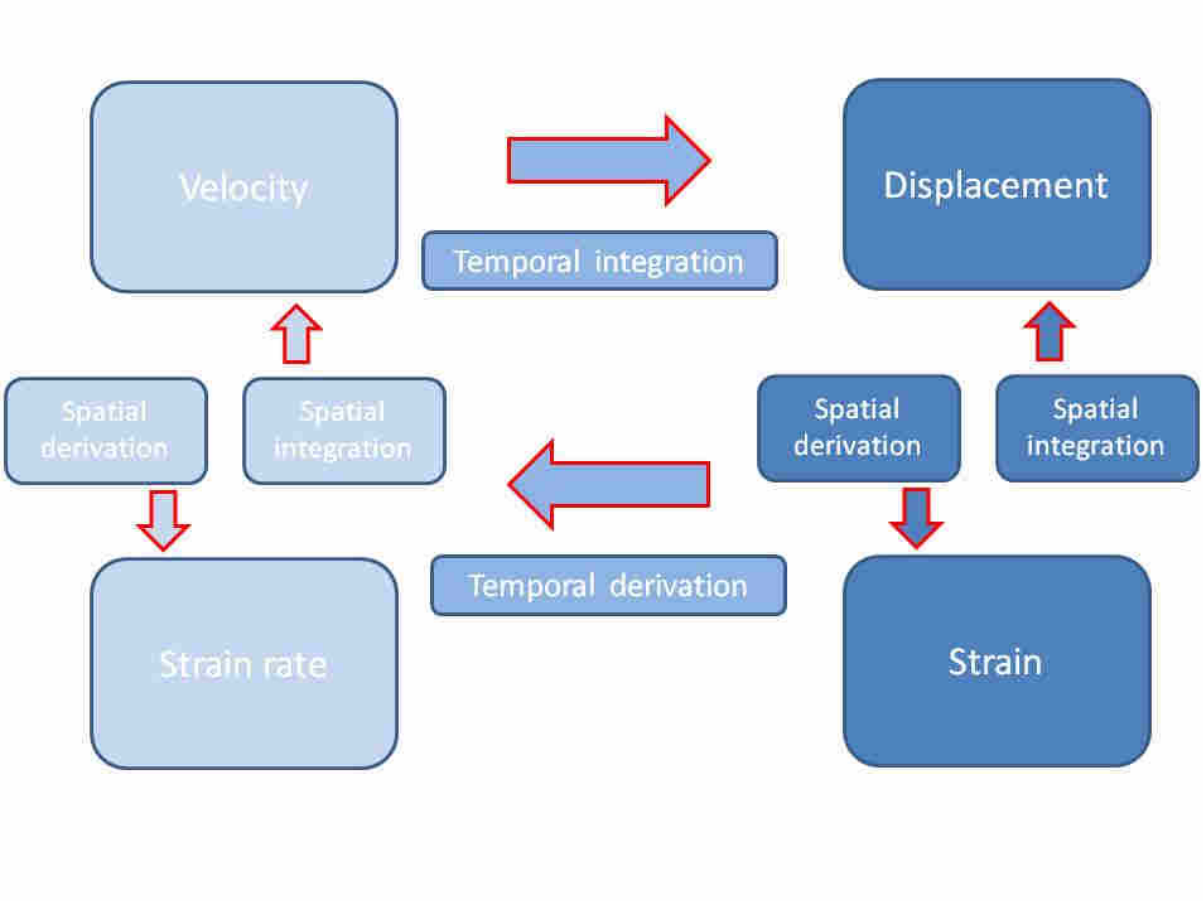

Figure 4 Relation of strain and strain rate as measures of velocity per time unit (strain rate) and displacement per length unit (strain).

In this context, speckle tracking echocardiography is a relatively new, largely angle-independent technique to assess myocardial function [14,43,44,37]. The speckles seen in B-mode grayscale images of the myocardium result from constructive and destructive interference of ultrasound backscattered from structures smaller than the ultrasound wavelength [37]. These speckles can be tracked in the ultrasound images frame by frame through the previous images, thus providing regional displacement information and derivation of parameters of myocardial function like velocity, strain and strain rate. Although speckle tracking echocardiography is nearly angle

independent, spatial resolution has to be of good quality and frame rate high enough to trace the speckles picture by picture.

One of the major advantages in speckle tracking echocardiography is the semi-automatic assessment by a vendor specific algorithm. From the picture loop the myocardium is manually defined, ensuring the most of the wall thickness is incorporated in the region of interest, leaving out the pericardium. After this procedure automatic tracking is processed and needs eventually manual correction, where tracking was not successful. One of the major advantages of speckle tracking is the option to measure strain in any direction and not only towards or away from the probe as in the case of Doppler tissue imaging [37]. This enables also to measure circumferential and radial strain, both being difficult to measure with conventional Doppler techniques in imaging. Of note in this context is that speckle tracking echocardiography is not fully angle independent as resolution is better in the direction of the ultrasound beam rather than the perpendicular direction.

2.3 Echocardiography in heart transplant recipients and follow-up

Echocardiographic measurements

All patients underwent echocardiography with a Vivid E9 ultrasound system (GE Healthcare, 9900 Innovation Drive, Wauwatosa, WI 53226, U.S.A.). A M5S transducer was used with single-crystal matrix to acquire all pictures. The 2D strain imaging was performed off-line with an EchoPac work station provided by GE Healthcare (GE EchoPac 12.0). 2D strain is a research tool that uses inherent features of a 2D image defined as natural acoustic markers for frame-to-frame tracking of the myocardial tissue in any direction within the tracking plane. By this method, 2D strain capabilities of tracking and quantifying full, two-dimensional motion

are comparable to those utilized with tagged CMR [45,38,46,19,20,15,16]. For evaluation user-defined automated subendocardial borders are traced throughout 1 cardiac cycle for calculation of myocardial velocity, longitudinal strain (LS) and strain rate (LSR) radial strain (RS) and strain rate (RSR). In addition, circumferential strain and strain rates (CS and CSR) were obtained. The values for LS/LSR were obtained from in apical 4-, 2- and 3-chamber views. Circumferential strain (CS) and RS were obtained from 6 segments in short-axis views of the left ventricle at the level of the papillary muscle. In addition to strain value obtained at the segmental level, we also calculated global LS, CS, and RS as an average of strain values obtained from the 6 segments in respective views. Assessment of LV strain was regarded as suboptimal when either: speckle tracking could not be obtained for at least 4 of the 6 myocardial segments in apical 4-chamber or short-axis views. The 2D-ST measurement also includes the torsion analysis. After processing the parasternal short-axis view at the level of the papillary muscle (SAX-PM) rotation analysis of the muscle was performed.

In addition to the conventional assessed variables parameters focusing on the systolic function of the transplanted organ were measured using the biplane Simpson method and fractional shortening measured in M-Mode pictures [24].

During follow-up coronary angiography was performed if new symptoms of chest pain or progressive dyspnea at exertion were detected. Angiography was also scheduled in cases of declining organ function and new detected impaired function of the transplanted organ. When renal function was normal or showed only mild impairment, angiography was planned every year in conjunction with endomyocardial biopsy.

2.4 Statistics

3. Results

3.1 Baseline characteristics

The HTR cohort consists of 41 patients (33 men and 8 women), the median age of the treated patients was 54 years (45.7/65.3 years). For biomarker concentrations, the HTR without diagnosis of TVP had median NT-proBNP values of 2202 pg/mL after transplantation, 347 pg/mL at 1 year and 253 pg/mL after 3 years. For creatinine the concentration was 1.4 mg/dL after transplantation and 1.2mg/dL after 1 and 3 years. Patients with TVP during follow-up had NT-proBNP concentrations of 2950 pg/mL after transplantation and 450 pg/mL after 1 and 347 pg/mL after 3 years. Creatinine was 1.7 mg/dL after transplantation, 1.8 mg/dL after 1 year and 1.5mg/dL after 3 years. Acute rejection of the heart transplant was present in 2 of 7 TVP (28,6%) patients and 3 of 34 HTR (8,8%). The immunosuppressive therapy used were calcineurin-inhibitors (CNI; Tacrolimus or Cyclosporine A) in 16 (39%) patients, mammalian target of rapamycin inhibitors (mTOR inhibitors Everolimus (EVE) in 15 (36.6%) patients or combination of CNI with EVE in 10 (24,4%) patients. The baseline characteristics are shown in table 2.

	After transplant (N=41)	**1 Year (N=41)**	**3 Years (N=41)**
Age	54 (45.7, 65.3)	54 (45.7, 65.3)	54 (45.7, 65.3)
Gender No. (%)	8 (19.5)	8 (19.5)	8 (19.5)
TVP No. (%)	0	5 (17.1)	7 (17.1)
Ejection Fraction (%)	64.6 (55.1, 71.8)	62.7 (57.9, 71.1)	62.9 (59.4, 70.4)
Fractional Shortening	33.4 (30, 44.1)	35.5 (28.8, 40.8)	34.4 (29.7, 40.2)

Creatinine mg/dL	1.4 (1.2, 1.7)	1.3 (1, 1.7)	1.3 (1.1, 1.6)
NT-proBNP pg/mL	2576.5 (460.1, 6125.7)	399.8 (184.4, 811.4)	286.6 (157.8, 547.9)
Global LS Strain (%)	15.4 (-16.8/-13.1)	-16.3 (-17.4/-14.5)	-17.2 (-17.8/-15.3)
Global RS strain (%)	39.7 (21.2, 57.4)	40.6 (29, 56.5)	34 (16.6, 51.8)
Global CS strain (%)	-18.8 (-26, -14.9)	-17.6 (-21.5, -13.1)	-17 (-21.4, -13.4)

Table 2 Baseline characteristics of the overall cohort

3.2 Systolic parameters of transplant function

Parameters of systolic function were assessed at every outpatient visit. During the follow-up immediately after transplantation, after 1 year and after 3 years, patients without TVP showed an EF of 66.7% (54.8%/72.7%), after 1 year 65.7% (59.0%/71.6%) and 64.3% (60.1%/70.8%) after three years describing no relevant change during the time line (p=0.81). Fractional shortening was 34% (29.4%/42.8%), after 1 year 35.1% (28.0%/40.3%) and 35.7% (30.2%/40.3%) after three years with the same trend without relevant change (p=0.97). Patients with TVP during the follow-up had an ejection fraction of 67.9% (63.0%/75.7%) after transplantation, 60.7% (51.3%/65.7%) after 1 year and 61.7% (58.7%/70.1%) after three years (p=0.45). Fractional shortening was also without relevant change in patients with TVP with 33.2% (27.1%/44.9%) after transplantation, 36.7% (22.8%/40.6%) after 1 year and 33.8% (31.5%/39.0%) after three years (p=0.65).

3.3 Longitudinal strain and strain rate in heart transplant recipients with and without transplant vasculopathy

The overall cohort showed an improvement of global longitudinal strain from baseline to 1 and 3 years with -14.2% (-16.9,-12.3) to -16.1% (-17.5,-14.3) and -16.7% (-18,-13.7), p=0.036. For patients developing TVP, global longitudinal strain was not

different from baseline up to the maximum of 3 years -16.6% (-16.7, -13.8) to -16.4% (-17.3,-14.7) and -17.6% (-18.7,-16.9) with p=0.21. Most segments showed no relevant change of LSR in the cohort with and without TVP. Relevant changes in LSR could be reported in patients without TVP in the segments inferior and inferoseptal (p=0.0022 and 0.04) with an impairment and anteroseptal with a trend to improve in terms of LSR (p=0.03). See table 3,4 and figure 5.

Variable	HTR without TVP (N=34)			P-Value	HTR with TVP (N=7)			P-value
	After Transplant	1 year	3 years		After Transplant	1 year	3 years	
Global LS [%]¶	-14.2 (-16.6,-12.6)	-16.2 (-17.9,-14.2)	-16.4 (-19.7, 13.7)	0.036	-16.6 (-16.7,-13.8)	-16.4 (-17.3,-14.7)	-17.6 (-18.7,-16.9)	0.21
LS basal anterior	-14.5 (-16.8,-10)	-14.4 (-19.7,-8.8)	-18.5 (-21.0,-12.8)	0.18	-11.9 (-15.8,-8.2)	-10 (-16.4,-8.8)	-19.4 (-22.9,-12.6)	0.074
LS basal anteroseptal	-14.7 (-18,-11,3)	-15 (-18.1,-10.6)	-16.5 (-19.2,-12.7)	0.37	-11.8 (-16.1,-8.9)	-13.8 (-17.9,-8.9)	-17.1 (-19.9,-11.1)	0.16
LS basal inferoseptal	-14.8 (-19.2,-12.6)	-15.6 (-16.5,-12.3)	-14.5 (-17.4,-13.2)	0.55	-11.6 (-16.5,-9.5)	-17.6 (-19.4,-8.9)	-14.7 (-16.8,-9.5)	1.00
LS basal inferior	-18.9 (-20,-14.3)	-17 (-21.3,-13.6)	-17.8 (-19.1,-12.7)	0.64	-13.1 (-19,-8.4)	-16.1 (-18.1,-11.7)	-14.2 (-18.7,-7.2)	1.00
LS basal inferolateral	-14.8 (-20.6,-11.7)	-16.2 (-20.9,-14.2)	-18.8 (-22.8,-14.2)	0.43	-10.9 (-14.3, -9.5)	-11.5 (-12.1,-9.7)	-15 (-19.4,-8.7)	0.25
LS basal anterolateral	-14.7 (-21.0,-12.1)	-17.6 (-21.7,-13.1)	-16.1 (-19.2,-12.5)	0.61	-13.0 (-16.7,-12.1	-15.2 (-19.4,-10.2)	-16.4 (-24.8,-13.9)	0.45
LS mid anterior	-12.5 (-15.9,-11.7)	-13.8 (-17.4,-10.1)	-16.8 (-20.6,-14.4)	0.082	-12 (-14.7,-11.7)	-12.7 (-15.8,-11.2)	-17.9 (-19.7,-14.2)	0.25
LS mid anteroseptal	-12.4 (-17.4,-8.1)	-17.9 (-21.1,-10)	-20.6 (-24.7,-19.1)	0.0057	-17.8 (-20.4,-14.4)	-12.9 (-15.9,-11.7)	-20.7 (-23.3,-13.6)	0.47
LS mid inferoseptal	-15.1 (-19,-13.5)	-16.5 (-19.2,-13.9)	-15.8 (-18.7,-13)	0.69	-12 (-18.2,-9.1)	-16.4 (-21.9,-8.5)	-15.2 (-18.5,-8.5)	0.45
LS mid inferior	-17.5 (-21.6,-14.8)	-17.4 (-19.1,-14)	-16.7 (-20.5,-12.6)	0.93	-11.9 (-17.5,-8)	-13.3 (-20.6,-10.5)	-14.4 (-16.8,-8.4)	0.82
LS mid inferolateral	-13.4 (-16.3,-10.4)	-14.3 (-19.3,-10.4)	-17.7 (-21.8,-14.1)	0.062	-10.6 (-14.7,-7.8)	-10.5 (-12.8,-9.6)	-16.2 (-16.8, -8.3)	0.44
LS mid anterolateral	-14.2 (-17.1,-12.6)	-16.4 (-19.5,-15.2)	-14.4 (-18.0,-11.3)	0.078	-13.9 (-18.2,-12.3)	-12.8 (-13.7,-0.2)	-13.5 (-17.3,-11.8)	0.17
LS apical anterior	-19.1 (-24.7,-9.5)	-18.2 (-25.7,-11.3)	-18.5 (-26.4,-14.8)	0.38	-14.2 (-17.7,-12.2)	-21.6 (-23.7,-12.5)	-22.4 (-24.9,-11.1)	0.82
LS apical septal	-17.7 (-21.6,-11.1)	20.3 (-23.1,-14.5)	-16 (-21.1,-11.7)	0.30	-11.9 (-18.7,-8)	-16.1 (-23.6,-12.9)	-16.2 (-20.5,-11.7	0.074
LS apical inferior	-19.1 (-28.9,-14.2)	-20.2 (-23,-15.5)	-20.5 (-26.3,-15.5)	0.72	-10.8 (-17.5 -7)	-19 (-28.1, -12)	-20 (-22.5, -15.4)	0.11
LS apical lateral	-16.4 (-19.4,-10.9)	-20.4 (-23.6,-14.9)	-16.3 (-23.8,-12.3)	0.033	-12.9 (-20.5, -9.5)	-14.9 (-20.3,-12.2)	-16 (-18.2,-13.2)	0.28

Table 3 Longitudinal strain in patients with and without TVP

¶ LS is measured in the unit %

Variable	HTR without TVP (N=34)			P-Value	HTR with TVP (N=7)			P-value
	After Transplant	1 year	3 years		After Transplant	1 year	3 years	
LSR basal anterior*	-1.0 (-1.5, -0.8)	-0.9 (-1.2, -0.7)	-1.1 (-1.4, -0.6)	0.73	-0.9 (-1.3, -0.5)	-1.1 (-1.4, -0.9)	-1.0 (-1.6, -0.6)	0.82
LSR basal anteroseptal	-1,0 (-1,4, -0,8)	-0,9 (-1,2, 0,8)	-1,0 (-1,2 –0,7)	0.48	-1,1 (-1,5,-0,6)	-1,0 (-1,3, -0,8)	-1,4 (-1,3, -0,6)	0.46
LSR basal inferoseptal	-1.0 (-1.2, -0.8)	-0.9 (-1.2, -0.8)	-0.8 (-1.0, -0.7)	0.22	-1.2 (-1.7, -0.7)	-0.9 (-1.1, -0.6)	-0.7 (-0.9, -0.6)	0.091
LSR basal inferior	-1.5 (-1.9, -1.1)	-1.3 (-1.4, -1.0)	-1.2 (-1.4, -1.0)	0.0022	-1.0 (-1.5, -0.8)	-1.1 (-1.5, -0.6)	-1.0 (-1.4, -0.6)	0.82
LSR basal inferolateral	-1.6 (-1.8, -1.3)	-1.4 (-1.8, -1.0)	-1.5 (-1.9, -1.3)	0.36	-1.3 (-1.6, -0.8)	-1.0 (-1.4, -0.9)	-1.4 (-1.5, -0.9)	0.55
LSR basal anterolateral	-1.2 (-1.6, -1.1)	-1.3 (-1.5, -1.0)	-1.6 (-1.8, -1.0)	0.97	-1.1 (-1.7, -0.5)	-1.2 (-1.3, -0.8)	-1.1 (-1.7, -0.9)	0.82
LSR mid anterior	-1.0 (-1.2, -0.9)	-1.0 (-1.2, -0.7)	-1.1 (-1.3, -0.7)	0.54	-0.7 (-1.2, -0.6)	-1 (-1.1, -0.8)	-1.1 (-1.2, -0.7)	0.35
LSR mid anteroseptal	-1.1 (-1.3, -0.8)	-1.4 (-1.5, -1.1)	-1.4 (-1.6, -1.2)	0.031	-1.1 (-1.5, -0.9)	-0.9 (-2.0, -0.8)	-1.1 (-1.8, -0.7)	1.00
LSR mid inferoseptal	-1.1 (-1.2, -0.9)	-1.1 (-1.2, -0.9)	-0.9 (-1.1, -0.8)	0.044	-0.9 (-1.1, -0.8)	-0.9 (-1.3, -0.8)	-0.7 (-1.1, -0.6)	0.45
LSR mid inferior	-1.2 (-1.5, -1.1)	-1.2 (-1.3, -0.9)	-1.2 (-1.3, -1.0)	0.069	-0.9 (-1.2, -0.8)	-1.1 (-1.4, -0.6)	-0.8 (-1.0, -0.7)	0.55
LSR mid inferolateral	-1.1 (-1.4, -0.8)	-1.1 (-1.3, -0.9)	-1.3 (-1.6, -1.1)	0.19	-0.8 (-1.5, -0.7)	-0.8 (-1.6, -0.7)	-1.0 (-1.1, -0.7)	0.65
LSR mid anterolateral	-1.1 (-1.4, -0.9)	-1.1 (-1.3, -0.9)	-1.1 (-1.4, -0.7)	0.26	-0.9 (-1.7, -0.7)	-1 (-1.1, -0.7)	-0.9 (-1.3, -0.6)	0.45
LSR apical anterior	-1.3 (-1.6, -1.0)	-1.2 (-1.6, -1.0)	-1.3 (-1.9, -1.0)	0.66	-1.1 (-1.5, -0.9)	-1.4 (-1.7, -1.1)	-1.3 (-1.6, -0.9)	0.82
LSR apical septal	-1.4 (-1.7, -1.1)	-1.3 (-1.6, -1.1)	-1.1 (-1.7, -1.0)	0.70	-0.8 (-2, -0.7)	-1.26 (-1.7, -1.0)	-1.0 (-1.2, -0.9)	0.14
LSR apical inferior	-1.4 (-1.9, -1.1)	-1.4 (-1.6, -1.2)	-1.4 (-1.9, -1.3)	0.35	-1.4 (-1.4, -0.6)	-1.5 (-1.7, -1.0)	-1.4 (-1.5, -1.0)	0.47
LSR apical lateral	-1.3 (-1.6, -1.1)	-1.2 (-1.8, -1.1)	-1.1 (-1.8, -1.0)	0.30	-1.2 (-1.9, -0.7)	-0.9 (-1.4, -0.9)	-1.0 (-1.4, -0.9)	0.93

Table 4 Longitudinal strain rate in patients with and without TVP

*LSR is measured in the unit /s

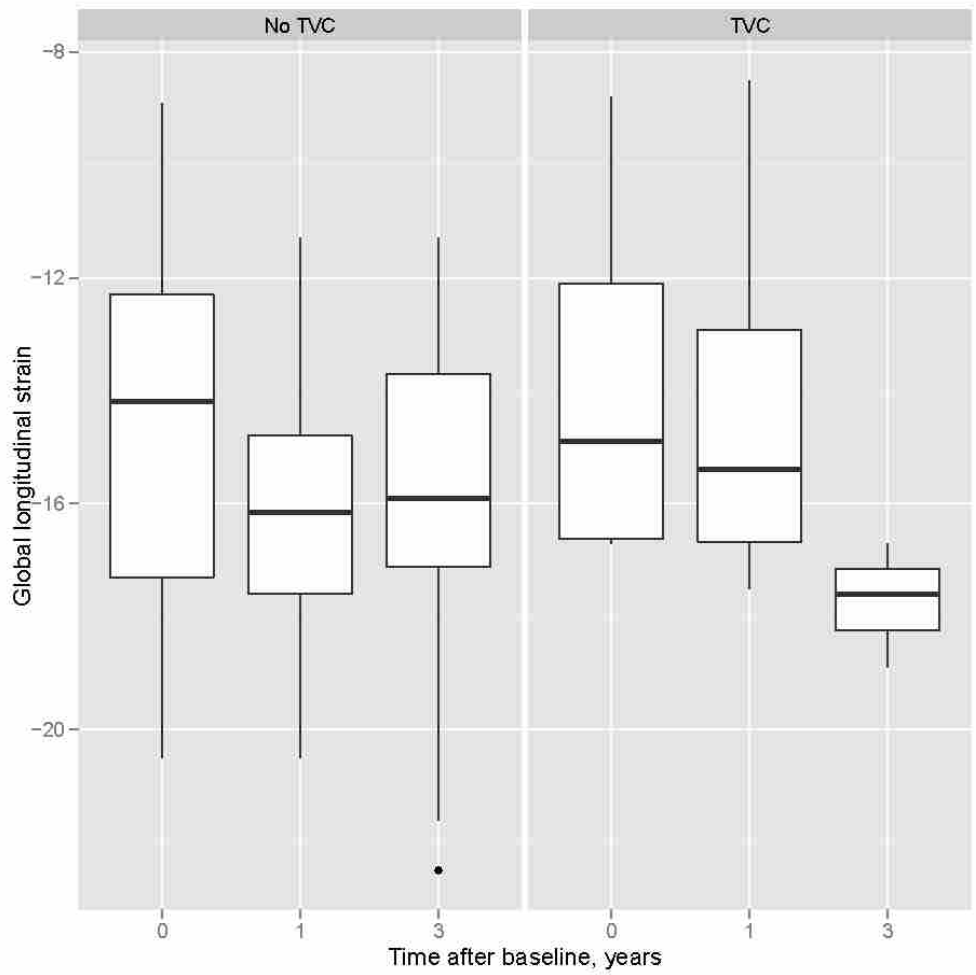

Figure 5 Global longitudinal strain in HTR with and without TVP during the follow-up.

3.4 Radial and circumferential strain and strain rate in heart transplant recipients with and without transplant vasculopathy

For both cohorts of patients global radial and circumferential strain was derived as described in the methods section. Global radial strain had a trend to decline during follow-up in patients without TVP and reported values of 42.2% (23.2%/59.5%) after transplantation, 40.6% (27.3%/53.7%) after 1 year and 34.0% (15.5%/54.5%) after 3 years, however showing no relevant change with p=0.72. The same trend could be described in patients with TVP and a global radial strain of 37.6% (17.7%/69.7%) after transplantation, 37.7% (37.0%/62.2%) after 1 year and 26.8% (14.2%/45.3%) after 3 years this trend was also not relevant with p=0.78. Global circumferential strain did show no relevant changes in patient without TVP with -17.5% (-21.9%/ -14.9%) after transplantation and -17.6% (-22.5%/-12.6%) after 1 year and -18.1% (-22.7%/-15.3%) after 3 years (p=0.44). In patients with TVP global circumferential strain did show a decreasing trend with -26.2% (-31.0%/-17.4%) after transplant, -20.0% (-28.4%/-18.1%) after 1 year and -13.5% (-17.2%/-12.8%) after three years with no statistical relevance in this described trend (p=0.24). Regarding strain rates only the circumferential strain in the inferolateral segement did present with an impairment during follow-up in patients without TVP (p=0.019). See table 5, 6 and figure 6+7.

Variable	HTR without TVP (N=34)			P-Value	HTR with TVP (N=7)			P-value
	After Transplant	1 year	3 years		After Transplant	1 year	3 years	
Global CS	-17.5 (-21.9/-14.9)	-17.6 (-22.5/-12.6)	-18.1 (-22.7/-15.3)	0.44	-26.2 (-31.0/-17.4)	-20.0 (-28.4/-18.1)	-13.5 (-17.2/-12.8)	0.24
CS* anterior	-21.7 (-26,-19.5)	-21.1 (-26.1,-16.1)	-20.2 (-25.7,-13.4)	0.54	-32(-41.6,-18.3)	-26.7 (-30.3,-19.9)	-15.7 (-20.5,-11.2)	0.17
CS anterolateral	-27.9 (-31.4,-21.8)	-24.6 (-31,-17.9)	-24.2 (-27.4,-16.9)	0.26	27.8 (-40.5,-21.4)	-26.1 (-29.3, -18)	-17.4 (-27.6,-13.5)	0.47
CS inferolateral	-15 (-21.3,-10.3)	-12.3 (-21.1, -7.4)	-17.5 (-21.2, -12)	0.94	-25.1 (-32.8,-16.2)	-14.9 (-26,-14)	-11.6 (-21.7, -6.9)	0.91
CS inferior	-14.5 (-19.1,-10.6)	-14.3 (-20.7,-10.1)	-16 (-23.5,-11.3)	0.56	-21.1 (-28.1,-9.5)	-14.1 (-25,-10.3)	-13.9 (-14.5, -7)	0.47
CS inferoseptal	-12.6 (-17.3,-4.8)	-8.6 (-19.4, -5.5)	-13.4 (-21.4,-10.9)	0.059	-22.7 (-25,-10.6)	-9.7 (-19.2,-5.4)	-10.7 (-14.4, -7)	0.78
CS anteroseptal	-23.9 (-28,-18.9)	-20.6 (-26.2,-16)	-23.6 (-28.7,-13.7)	0.55	-22.2 (-34.3,-14.2)	-23.2 (-31.8,-15.5)	-19.7 (-24.8,-8.3)	0.78
Global RS	42.2 (23.2/59.5)	40.6 (27.3/53.7)	34.0 (15.5/54.5)	0.72	37.6 (17.7/69.7)	37.7 (37.0/62.2)	26.8 (14.2/45.3)	0.78
RS* anterior	42.7 (16, 59.4)	38 (27, 56)	32.3 (13.1, 45)	0.77	41.2 (20.2, 74)	36.9 (31.3, 56.1)	14.6 (13.7, 31.9)	0.78
RS anterolateral	43.8 (17.6, 57.9)	34.5 (20.5, 53.1)	30.7 (13.8, 41.3)	0.54	39.8 (22.8, 67.5)	35.7 (20.5, 56.6)	19.2 (13.7, 37.1)	0.78
RS inferolateral	41.7 (27.9, 61.0)	42.5 (29.2, 58.1)	35.1 (15.6, 54.5)	1.00	38.5 (17.7, 72.3)	50.8 (40.5, 63.5)	20.7 (15.2, 37)	0.78
RS inferior	41.7 (25.8, 53.2)	43.2 (30.8, 62,0)	35.8 (19.9, 55.2)	0.39	34.8 (13.5, 67.7)	49.3 (38.2, 62.5)	37.1 (14, 58.9)	0.78
RS inferoseptal	43.1 (20.1, 56.9)	47.4 (26.8, 60)	36.4 (19.2, 57.1)	0.90	35.9 (15.2, 69.8)	51.4 (38.9, 65.5)	34 (15.3, 52.1)	0.78
RS anteroseptal	40.2 (25.9, 56.8)	41.4 (22.4, 58)	33.7 (21, 51.6)	0.90	35.6 (17.1, 66.7)	36.5 (17.9, 56)	35.0 (12.5, 55.4)	0.78
TR‡ anterior	4.3 (1.4, 7.1)	3.8 (-2.0, 4.5)	2.9 (-3.2, 6.2)	0.056	4.7 (0.3, 7.3)	4.1 (2.8, 5.8)	4.4 (-4.1, 5.6)	0.78
TR anterolateral	3.4 (-3.4, 5.3)	1.69 (-3.0, 3.5)	1.6 (-2.3, 5.0)	0.12	0.2 (-2.8, 3.8)	3.1 (0.2, 5.2)	2.7 (-8.1, 3.5)	0.47
TR inferolateral	3.3 (0.9, 6.5)	3.7 (1.6, 5.1)	-1.9 (-4.7, 5.8)	0.22	5.1 (0.4, 10.7)	4.6 (4.5, 5.8)	3.5 (-0.7, 5.1)	0.24
TR inferior	-3.1 (-7.4, 2.7)	-3.5 (-5.9, -1.4)	-2.4 (-3.7, 2.6)	0.23	0.3 (-3.6, 7.8)	2.3 (-2.5, 3.5)	-1.1 (-7.7, 2.9)	0.37
TR inferoseptal	2.3 (-4.8, 4.4)	1.6 (-3.5, 2.5)	-2.0 (-3.6, 4.3)	0.62	4.1 (-0.2, 10.6)	2.9 (-0.4, 4)	0.8 (-4.3, 6.4)	0.78
TR anteroseptal	-2.3 (-6.3, 3.8)	-1.8 (-4.7, 2.3)	-1.6 (-4.9, 3.9)	0.90	0.5 (-3.8, 4.8)	0.7 (-3.1, 4.5)	-5.6 (-10.7, -0.2)	0.050

Table 5 Circumferential and radial strain in patients with and without TVP

[β]CS and RS are measured in the unit %

Variable	HTR without TVP (N=34)			P-Value	HTR with TVP (N=7)			P-value
	After Transplant	1 year	3 years		After Transplant	1 year	3 years	
CSR[Ω] anterior	-1.9 (-2.3, -1.4)	-1.7 (-2.0, -1.4)	-1.7 (-2.0, -1.1)	0.40	-3.1 (-3.4, -1.8)	-2.1 (-2.4, -1.9)	-1.3 (-1.6, -1.0)	0.17
CSR anterolateral	-2.2 (-2.4, -1.8)	-2.1 (-2.2, -1.6)	-1.7 (-2.4, -1.2)	0.62	-3.2 (-3.6, -2.1)	-2.2 (-2.3, -2.1)	-1.8 (-2.2, -1.5)	0.37
CSR inferolateral	-1.6 (-1.9, -1.2)	-1.3 (-1.5, -0.9)	-1.3 (-1.5, -0.8)	0.019	-2.6 (-2.9, -1.5)	-1.6 (-2.3, -1.4)	-1.13 (-2.3, -1.0)	0.91
CSR inferior	-1.5 (-1.9, -1.2)	-1.5 (-1.7, -1.0)	-1.2 (-2.0, -1.0)	0.19	-2.0 (-2.3, -1.2)	-2.1 (-2.3, -1.7)	-1.5 (-2.2, -1.0)	0.78
CSR inferoseptal	-1.3 (-1.8, -1.0)	-1.4 (-1.8, -1.1)	-1.3 (-2.0, -1.1)	0.79	-2.3 (-2.6, -1.3)	-1.8 (-2.1, -1.4)	-1.4 (-1.5, -0.8)	0.37
CSR anteroseptal	-2.0 (-2.3, -1.6)	-1.7 (-1.9, -1.2)	-1.7 (-2.1, -1.1)	0.073	-2.6 (-3.3, -1.6)	-2.7 (-7.2, -1.9)	-1.7 (-1.8, -0.9)	0.37
RSR anterior	1.9 (1.5, 2.4)	2.0 (1.3, 2.4)	1.5 (1.2, 2.1)	0.90	2.4 (1.7, 5.7)	2.5 (1.9, 3.9)	2.9 (1.4, 3.9)	0.78
RSR anterolateral	1.9 (1.3, 2.6)	1.8 (1.3, 2.4)	1.5 (1.2, 1.8)	0.88	2.7 (2.2, 4.1)	2.3 (1.6, 3.1)	2.7 (1.4, 4.7)	0.37
RSR inferolateral	2.1 (1.7, 2.7)	2.2 (1.6, 2.7)	2.0 (1.3, 2.3)	0.42	2.5 (1.8, 5.1)	2.5 (1.8, 2.6)	3.2 (1.8, 4.1)	0.95
RSR inferior	2.2 (1.7, 2.7)	2.4 (1.8, 2.8)	1.8 (1.3, 2.3)	0.57	2.7 (1.9, 4.5)	2.8 (2.1, 4.3)	3.4 (2.0, 4.7)	0.78
RSR inferoseptal	2.4 (1.7, 2.7)	2.4 (1.9, 3.1)	1.6 (1.3, 2.0)	0.56	2.7 (2.1, 4.0)	3.3 (2.1, 4.2)	3.4 (1.8, 5.3)	1.00
RSR anteroseptal	2.0 (1.7, 2.7)	1.9 (1.4, 2.4)	1.4 (1.4, 1.9)	0.39	2.8 (1.9, 4.2)	2.7 (2.0, 3.2)	3.1 (1.5, 5.3)	0.78

Table 6 Circumferential and radial strain rate in patients with and without TVP

[Ω]CSR and RSR are measured in the unit /s

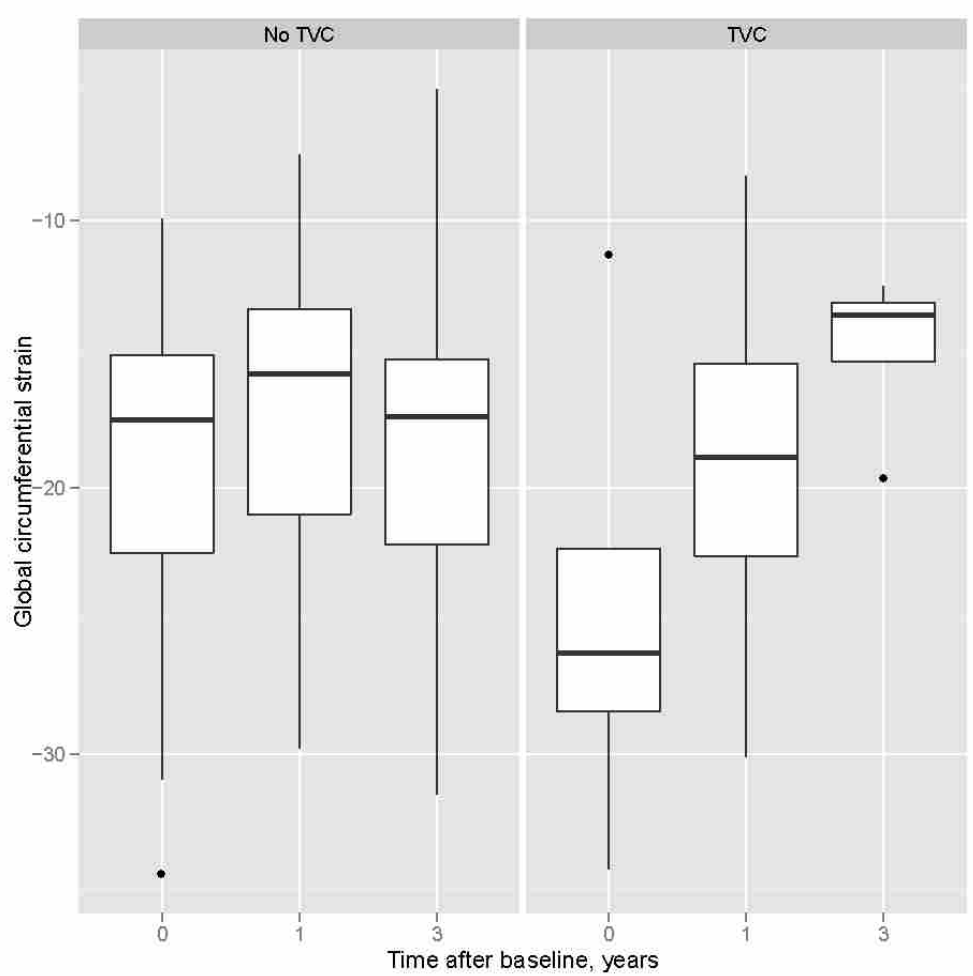

Figure 6. Global circumferential strain in HTR with and without TVP during the follow-up.

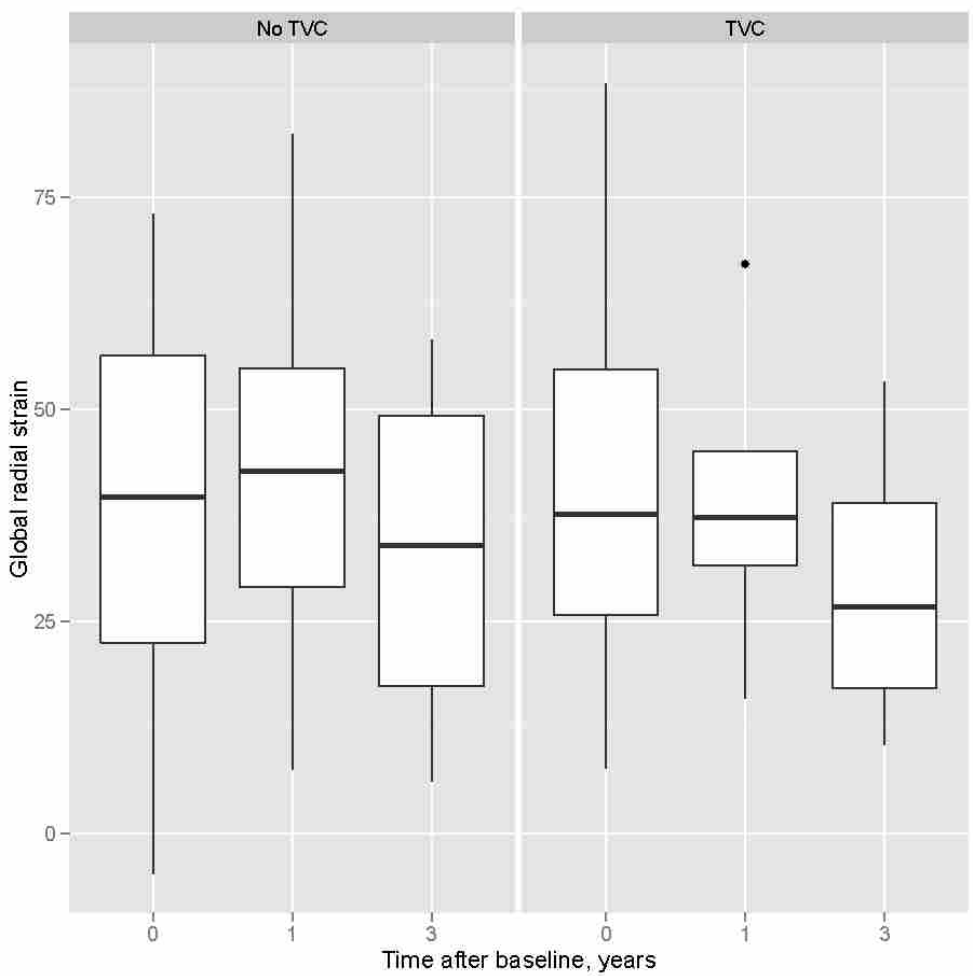

Figure 7. Global radial strain in HTR with and without TVP during the follow-up.

3.5 Torsion in heart transplant recipients with and without transplant vasculopathy

In both patient cohorts there is a reduction of torsion with the time after transplantation, showing an impairment of counterclockwise rotation at the base of the left ventricle. However, this is noticed in both patients with and without TVP. Although there is a marked reduction in rotation, this shows no relevant p value alteration for any segment in both cohorts. See table 7.

Variable	HTR without TVP (N=34)			P-Value	HTR with TVP (N=7)			P-value
	After Transplant	1 year	3 years		After Transplant	1 year	3 years	
TR‡ anterior	4.3 (1.4, 7.1)	3.8 (-2.0, 4.5)	2.9 (-3.2, 6.2)	0.056	4.7 (0.3, 7.3)	4.1 (2.8, 5.8)	4.4 (-4.1, 5.6)	0.78
TR anterolateral	3.4 (-3.4, 5.3)	1.69 (-3.0, 3.5)	1.6 (-2.3, 5.0)	0.12	0.2 (-2.8, 3.8)	3.1 (0.2, 5.2)	2.7 (-8.1, 3.5)	0.47
TR inferolateral	3.3 (0.9, 6.5)	3.7 (1.6, 5.1)	-1.9 (-4.7, 5.8)	0.22	5.1 (0.4, 10.7)	4.6 (4.5, 5.8)	3.5 (-0.7, 5.1)	0.24
TR inferior	-3.1 (-7.4, 2.7)	-3.5 (-5.9, -1.4)	-2.4 (-3.7, 2.6)	0.23	0.3 (-3.6, 7.8)	2.3 (-2.5, 3.5)	-1.1 (-7.7, 2.9)	0.37
TR inferoseptal	2.3 (-4.8, 4.4)	1.6 (-3.5, 2.5)	-2.0 (-3.6, 4.3)	0.62	4.1 (-0.2, 10.6)	2.9 (-0.4, 4)	0.8 (-4.3, 6.4)	0.78
TR anteroseptal	-2.3 (-6.3, 3.8)	-1.8 (-4.7, 2.3)	-1.6 (-4.9, 3.9)	0.90	0.5 (-3.8, 4.8)	0.7 (-3.1, 4.5)	-5.6 (-10.7, -0.2)	0.050

Table 7 Torsion at the papillary muscle level

4. Discussion

4.1 Organ function and surveillance during follow-up

The surveillance of adequate organ function during follow-up is a major cornerstone in a good long-term prognosis after transplantation of a solid organ and especially after heart transplantation. Echocardiography is a non-invasive method without harm to the patient, capable to assess systolic as well as diastolic function of the heart [47,25,26,14,11]. However, the organ function cannot be simply reduced to systolic and diastolic function as the contraction is much more complex in nature and concentrates on an organ with a 3-dimensional structure. Therefore, there is the need to investigate the mechanics of the transplanted heart, to understand early and sub-clinical decline of organ function after transplantation and during follow-up which is not mirrored by measures of systolic function alone.

The results of this retrospective study could show that patients after heart transplantation on stable immunosuppressive therapy have a normal ejection fraction and fractional shortening, two important measures of systolic function of the left ventricle [24], during follow-up. However, all patients in this study, including patients with transplant vasculopathy, representing a major factor of morbidity and mortality after transplantation, did as well show normal systolic function during the whole follow-up time. Since transplant vasculopathy shows similarities to coronary artery disease, there was the suggestion that sub-clinical changes in the mechanical contraction process, as reflected by strain and strain rate measurements, could add to detect patients with TVP, as these could show the same characteristics as patients with coronary artery disease [38,37]. The current standard in detection of TVP is still coronary angiography with all risks of an invasive diagnostic procedure, reaching

from renal impairment, to complications of the vascular access site, stroke, myocardial infarction or even, on rare occasions, to death. An important tool in diagnosing relevant TVP is intravascular ultrasound; therefore this imaging modality is recommended by the ISHLT [12] and can be used to assess the progress and the severity of TVP [36].

During the follow-up period of patients with heart transplantation multiple co-morbidities can occur, which interfere with sufficient immunosuppressive therapy, whereby most patients were either using a CNI based therapy or mTOR (39% to 36.6%). The use of mTOR is described to reduce the incidence of TVP but has side effects limiting its use immediately after transplantation like an impaired wound healing [35,36]. A therapy regime based upon mTOR was selected in 24.4% and was the preferred regime in patients with TVP, as mTOR are reported to reduce the progression of TVP and renal impairment [35], two of the main factors for adverse outcome in HTR [7]. The data regarding echocardiographic changes in HTR about the preferred medication is however rather scarce, but first data from renal transplantation suggest that there are no major changes in standard echocardiography upon comparison of a CNI based therapy to mTOR [48]. One of the major problems which is related to TVP is the higher rate of allograft rejection which was reported significantly more often in patients with TVP with 28.8% in comparison to 8.4% in patients without TVP.

4.2 The imaging perspective

The study shows that patients after heart transplantation depict a changed pattern in cardiac mechanics in comparison to healthy controls. Although stable patients after transplantation show an increase regarding global LS after transplantation or a preserved function, values are still lower as reported as normal values in the general

population with a lower limit for LS of -18.5% [38,37]. On the other hand some study groups also reported strain values in healthy controls mirroring the same results as in the studied patient cohort. The in Norway conducted HUNT Study described a decrease in strain with age and thus healthy patients in this cohort had strain values with a mean of -15.8% for men and -17.6% in women for the age range of 40-60 years [41,42]. Using these described values, organ function under immunosuppressive therapy was preserved using longitudinal strain reference values. The same finding with a preserved CS and CSR could be reported from both groups of HTR with and without TVP. However, RS and RSR was preserved as reported from the general population with 44.5% [37] after transplantation and at the time point of 1 year but decreased at the 3 year follow-up. As a reason of low numbers, this finding was not relevant but elucidates changes in the cardiac mechanics due to need of permanent immunosuppression, also affecting the cardiac structure [13]. During contraction, LV geometry causes simultaneous contraction and stretch and as a consequence for longitudinal and circumferential contraction with a transmural and apex-to-base heterogeneity [49,50]. This fact could also been shown in this cohort of HTR during follow-up with a preserved contractility, and an apex-to-base gradient with higher strains in the apex and midsegmental walls in comparison to the base of the LV [37,49,50]. The contraction in longitudinal and circumferential direction does not simply result in radial thickening but also shearing in groups of myocytes. In the normal heart, shearing deformation amplifies the shortening of myocytes by 15%, resulting in a more than 40% in radial thickening leading to larger than 60% change in ejection fraction [43,44]. The results of our study describe a preserved radial contraction at baseline and after 1 year but a considerable decline in all HTR patients, resulting in a continuous process of organ alteration with immunosuppression changing radial mechanics in the first place.

On the other hand the results show that cardiac function can be monitored by speckle tracking derived strain more reliably as by ejection fraction or fractional shortening, both aiming at the left ventricular systolic function, alone. Patients with a stable immunosuppressive regimen show a preserved function during the follow-up as monitored with 2D-ST strain.

The presence of TVP shows parallels to coronary artery disease with narrowing of larger epicardial arteries but also shows differences with widespread affection of the microcirculation of the vascular bed. In patients with coronary artery disease strain is decreased relating to the declining function of the myocardium, strain was described to be -11% in patients with chronic ischemic heart disease and about -5% in scarring of the heart [38,37]. The patients with known TVP in this study cohort presented with no difference regarding LS, CS and RS, as well as torsion. However, these patients presented with a significant increase of episodes of acute rejection during follow-up indicating are sever decrease of organ viability. As reported from animal experiments, radial strain is a sensitive variable to assess organ function and is among the first parameters with impaired organ function or rejection [31,33]. Thus, even in comparison to patients with acute rejection, HTR show a trend of decreasing radial strain over time, maybe elucidating the adverse effect of immunosuppression on the level of cardiomyocyte layers. Radial strain seems to be a sensitive measure to monitor organ function, as well as during diagnosis of impaired organ function. This contrasts the altered pattern in LS and CS as fact of CAD, however this might relate to the more epicardial stenosis in CAD and more microvascular involvement in HTR.

Torsion of the left ventricle was only available at the base or papillary muscle level so that twist as comparison between apical and papillary muscle level could not be calculated. However, patients with HTR show a decrease in angle over time maybe

additionally elucidating the declining function of the organ over time, mimicking some of the features that were also described for dilated cardiomyopathy [37,51].

Of future interest is also the additional use of CMR imaging in TVP patients as these subjects can show scarring in the myocardium possibly related to TVP during the follow-up of the individual patient [21,22]. However, this imaging modality was not used in this study cohort, as most patients had an impaired renal function so that additional examinations needing contrast media were not performed.

4.3 The biomarker perspective

In healthy individuals, only low BNP levels are measured, whereas in states of increased myocardial stretch, like heart failure or myocardial infarction, *BNP* expression is increased [52]. Recent studies already showed the value of BNP as well as NT-proBNP for improved diagnosis of heart failure [53,54]. However, there are also limitations for the sole use of natriuretic peptides. The diagnosis of heart failure is not 100% specific when using natriuretic peptides as biomarker, as increased natriuretic peptide concentrations reflect structural heart disease and presence of cardiovascular risk factors. Apart from age and ventricular function, obesity, atrial arrhythmias, renal function and heart disease beyond heart failure influence natriuretic peptide concentrations [52]. In this study cohort of HTR NT-proBNP concentration was increased, elucidating the fact that structural heart disease is present after transplantation or a side effect of immunosuppressive therapy with left ventricular hypertrophy, arterial hypertension and different other cardiovascular risk factors [13]. One of the major interfering factors with the use of natriuretic peptides is the impaired renal function in all patients in this study cohort as a result of the immunosuppressive medication. Therefore, the declining concentration of NT-proBNP documents the preserved organ function but was not able to

differentiate patients with and without TVP, as both cohorts had increased concentrations above the limit to detect structural heart disease or hear failure.

Apart from the current gold standard, represented by natriuretic peptides, none of the currently proposed biomarkers meet all criteria but some come very close in doing so [52,55]. Main reason for the complex process of evaluating such markers is that different pathophysiologic states like pressure or volume overload can finally manifest in heart failure. It is still a continuous process when the heart function is impaired reaching from an at-risk but structurally normal organ to cardiac injury, ventricular dysfunction and finally symptomatic heart failure.

In addition to the mentioned B-type natriuretic peptie, midregional pro atrial natriuretic peptide (MR-proANP) has emerged as a promising biomarker in patients with congestive heart failure [56]. MR-proANP and the B-type natriuretic peptides exhibited similar associations to previous or prevalent cardiovascular disease, and echo-cardiographic data. In subgroups with confounding conditions (female sex, obesity, renal dysfunction), MR-proANP did not exhibit stronger associations to echocardiographic data than the B-type natriuretic peptides and was not superior in diagnosing heart failure in patients with atrial fibrillation due to the different release pattern [57,56]. In the population studies there was a moderate to strong correlation of the biomarkers with age, diabetes, hypertension, smoking, renal function, prevalence of coronary artery disease and heart failure. Males showed lower MR-proANP concentrations than females [58]. In general, MR-proANP was not inferior to BNP in diagnosing heart failure, however it offers additional information in patients within the grey zone of BNP concentrations between 100-500 pg/mL and in obese patients [52]. In the PRIDE study MR-proANP was an independent predictor of heart failure diagnosis and provided information beyond BNP or NT-proBNP suggesting a superior accuracy in combining both natriuretic peptides [59].

Although troponin concentration was not measured in the samples of this study cohort, a promising biomarker candidate would be highly-sensitive determined troponin. According to the universal definition of myocardial infarction [60], cardiac troponins I and T are the biomarkers of choice to diagnose acute myocardial necrosis. Evolution of troponin tests has recently led to the determination of troponin via high-sensitivity assays [61]. Regarding the pathology represented by elevated hs TnI concentrations; the mechanisms are numerous like myocardial infarction type 1 and 2 (with and without coronary heart disease), inflammation, apoptosis and cytotoxicity as a result of cardiac remodeling and contribute to elevated troponin I concentrations [62,63]. It is known from population-based studies that troponin T correlates with cardiovascular risk factors, age and impaired renal function [64,63]. Estimation of troponin in at-risk subjects, like older community dwelling individuals showed the additive information regarding incident heart failure or cardiovascular death, mirroring the pathophysiology of different causes of heart failure and the resulting structural changes to the heart itself [63,65,66]. In patients after heart transplantation, there was a good correlation of proven acute rejection and concentration of a high-sensitive troponin I test [67]. During episodes of rejection the troponin I concentration is increased maybe paving the way for troponin as a future promising biomarker in HTR as well. The combination of NT-proBNP and troponin proved to be a possible alternative to surveillance endomyocardial biopsy in pediatric HTR [68].

4.4. The use of additional strain analysis in heart transplant recipients

The additional analysis of cardiac mechanics proves to be useful in HTR since sub-clinical changes of the myocardial function can be detected besides the standard echocardiography to assess systolic and diastolic function of the heart. Although

there was no evidence of differentiatin HTR with TVP and without trends in the cardiac mechanics could be pointed out characterizing HTR more in detail. Longitudinal strain is not different in HTR patients to the general population regarding recent results of the HUNT Study [41,42]. However, as reported during acute rejection, radial strain shows a declining trend over time, maybe as a result of immunosuppression and the related side effects. Circumferential strain was also declining during the follow-up but only in patients with TVP elucidating this type of vasculopathy more in detail. However, as the numbers were low in both cohorts, these reported observations were not significant in statistical testing but are different from findings in the general population. Biomarkers are important to monitor symptoms of heart failure but are inconclusive in differentiating patients with and without TVP. Future biomarkers, like highly-sensitive determined troponin I deserves further merit, but was not tested in the current study cohort.

In conclusion strain analysis in HTR could show alterations in cardiac mechanics to the general population but was not able to differentiate patients with and without TVP in contrast to coronary artery disease. Longitudinal strain is preserverd in patients with stable immunosuppressive therapy but declining organ function might be more correctly mirrored by radial strain.

Limitations

The first limitation in our study was the low number of patients in each cohort; therefore some data might lack the statistical relevance due to a small number of patients. Further, follow-up was not performed always by the same physician therefore quality of imaging, being essential in the use of speckle tracking echocardiography, varies during the reported time. The study is retrospective in nature and relies on picture data routinely acquired during outpatient visits.

5. Summary

This medical doctoral thesis could show the change in cardiac mechanics after heart transplantation and the importance of adding new diagnostic features in non-invasive imaging to a patient cohort with severe co-morbidities. Longitudinal strain is a sophisticated function parameter capable of detecting sub-clinical structural changes in transplanted organs which are not detected by systolic function parameters like ejection fraction and fractional shortening. The cohort of patients after heart transplantation and those patients with transplant vasculopathy during follow-up however, could not be separated by strain imaging alone. A further finding in this study was the impairment of heart transplant recipients in terms of radial and circumferential strain during follow-up as a response of declining organ function during the needed immunosuppressive therapy. On the other hand the reported findings stress that patients under stable immunosuppressive therapy have no different profiles in terms of longitudinal strain and systolic function parameters, speaking in favor on non-invasive imaging and especially strain analysis during follow-up. The standard in terms of detecting relevant transplant vasculopathy remains coronary angiography although the information by angiography is relevantly augmented by strain analysis.

Different readily variables, which are of proven use in heart failure patients, cannot be transferred easily in this setting of care for HTR. Natriuretic peptides are often increased in HTR in patients as a result of renal failure induced by the immunosuppressive therapy. Maybe highly-senstive determined troponin I could be of future use in this setting.

The use of strain imaging allows detecting changes missed by standard echocardiography especially in terms of sub-clinical changes and decreasing function

of the transplanted organ. Cardiac mechanics are changed during the course of heart transplantation and understanding the different features of patients mechanics during heart action could improve care in the future.

6. Abbreviations

2D-ST	2-dimensional speckle tracking
CMR	Cardiac magnetic resonance imaging
CNI	Calcineurin inhibitor
CS	Circumferential strain
CSR	Circumferential strain rate
EF	Ejection fraction
EVE	Everolimus
FS	Fractional shortening
HTR	Heart transplant recipient
LS	Longitudinal strain
LSR	Longitudinal strain rate
mTOR	Mammalian target of rapamycin
Nt-proBNP	N-terminal pro B-type natriuretic peptide
RS	Radial strain
RSR	Radial strain rate
TVP	Transplant vasculopathy

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10. Affirmation (Eidesstattliche Versicherung) *[als letztes Blatt in die Dissertation einzubinden]*

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