The role of advanced echocardiography in patients with ischemic heart disease

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CHAPTER ONE

General introduction and outline of the thesis

Global longitudinal strain: clinical use and prognostic implications in contemporary practice

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ABSTRACT

Assessment of left ventricular systolic function is pivotal for the diagnosis, risk stratification and management of patients with cardiovascular disease. Left ventricular ejection fraction is the most frequently used parameter to characterise left ventricular systolic function and is usually included in practice guidelines to select the therapeutic strategies. However, left ventricular ejection fraction has many limitations, not only in terms of reproducibility of the measurement but also in terms of not being accurate enough to detect early left ventricular systolic dysfunction. Myocardial strain imaging using echocardiography has shown that left ventricular global longitudinal strain is more sensitive to detect subclinical left ventricular systolic dysfunction and is more reproducible than left ventricular ejection fraction. This review article is a practical guide on the technical aspects of left ventricular global longitudinal strain measurements and summarises the available evidence on the clinical use of this parameters. Furthermore, we provide a glimpse into future clinical applications derived from left ventricular global longitudinal strain that are being increasing used in clinical practice.

INTRODUCTION

Non-invasive evaluation of left ventricular (LV) systolic function by echocardiography remains one of the most pivotal measures in clinical cardiology. Although conventionally quantified by means of the LV ejection fraction (EF), it has become evident that this parameter is subject to a number of limitations. LVEF can be normal in the presence of impaired LV systolic function, since it does not reflect intrinsic myocardial contractility.[1] In addition, LVEF is highly load-dependent, and suffers from significant intra- and inter-observer variability.[2] Assessment of myocardial strain can potentially overcome many of the limitations of LVEF in assessing LV systolic function. Speckle tracking echocardiography permits assessment of myocardial strain in 3 spatial directions (longitudinal, radial and circumferential) independent of the angle of insonation of the ultrasound beam. Longitudinal strain is probably the most frequently type of strain used to characterise LV systolic function in clinical practice. This review article focuses on the practical aspects of measuring LV global longitudinal strain (GLS), reviews the clinical implications of impaired LV GLS strain and provides a glimpse into the future clinical applications of this technology.

ASSESSMENT OF LEFT VENTRICULAR GLOBAL LONGITUDINAL STRAIN

The LV myocardium consists of two helical, opposing layers of myocardial fibres (endocardial/right-handed and epicardial/left-handed) surrounding a circumferential, mid-ventricular layer. When these layers contract, the myocardium shortens in the longitudinal and circumferential directions and thickens in the radial direction (Figure 1).

The introduction of speckle tracking echocardiography has allowed for a more comprehensive analysis of LV systolic function when compared to LVEF by assessing myocardial deformation in these 3 directions. Speckle tracking echocardiography can be performed off-line on 2-dimensional echocardiographic data by tracking myocardial "features" throughout the cardiac cycle. Strain can be measured in different directions (longitudinal, circumferential and radial), and is conventionally expressed as a percentage, defined as relative change in length/thickness of the LV myocardium in relation to its original length/thickness (i.e. it is unitless). LV GLS is calculated from 4-, 3- and 2-chamber apical views (Figure 2), whereas LV global circumferential strain and LV global radial strain are computed from short-axis images. LV GLS measured with speckle tracking echocardiography has the largest body of evidence in clinical

practice, since 1) images obtained from the axial views for LV GLS measurement have better lateral resolution than short-axis images, 2) LV GLS is obtained from the entire length of the LV and therefore includes a greater amount of myocardial tissue, when compared to the short-axis views and 3) radial and circumferential strain demonstrate lower reproducibility than LV GLS.[3]

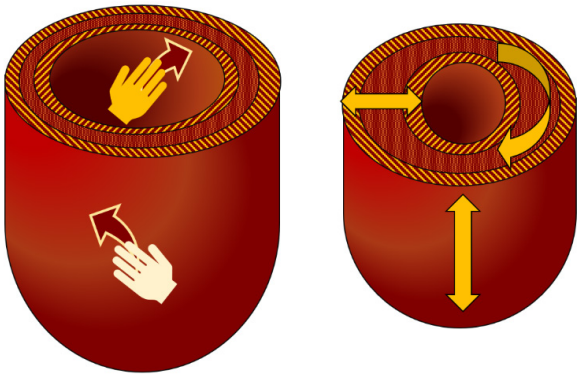

Figure 1. Schematic representation of the left ventricular myocardial wall. On the left, the left ventricular myocardial wall is formed by three layers: the subendocardial layer with the fibres arranged in the direction of a right-handed helix (hand and arrow), the subepicardial layer with the fibres oriented as a left-handed helix (hand and arrow) and the mid-myocardial with the fibres oriented circumferentially. When the subendocardial and subepicardial layers shorten in opposite directions and the mid-myocardial layer shortens in the circumferential direction, the ventricle shortens in the longitudinal and circumferential direction and thickens in the radial direction (arrows).

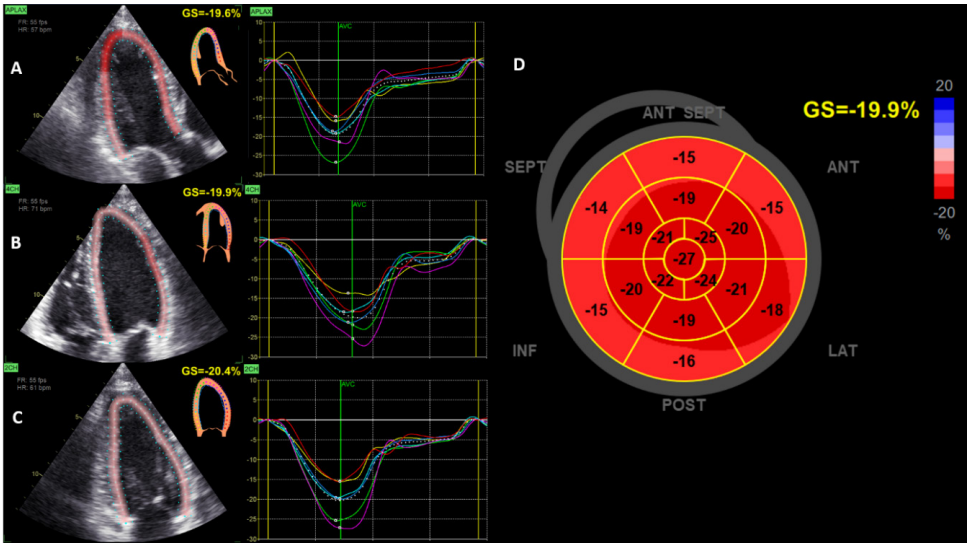

Figure 2. Left ventricular global longitudinal strain assessment with two-dimensional speckle tracking echocardiography. The figure demonstrates analysis of left ventricular global longitudinal strain (GLS) from the 3- (A), 4- (B) and 2-chamber (C) and views, with the respective

time to strain curves. The value of global longitudinal strain is displayed in each view. Panel D provides the polar map with the regional values and the global longitudinal strain value calculated from the 17 segments which is within the normal values.
Abbreviations: ANT, anterior; ANT_SEPT, anteroseptal; APLAX, apical long-axis view; GS, global strain; INF, inferior; LAT, lateral; POST, posterior; SEPT, septal.

When measuring LV GLS, good image quality is a prerequisite, ideally with a minimum frame rate of 40 frames/second. The LV endocardium is traced manually and the thickness of the region of interest where speckles will be tracked, is adjusted to exclude the papillary muscles and the pericardium. The region of interest is also adjusted to exclude the LV outflow tract and the left atrium. Reliable tracking of all myocardial segments throughout the cardiac cycle should be verified visually, and as a rule of thumb, views should be excluded from analysis if insufficient tracking (indicated by the software) is present in one or more myocardial segments. Current platforms still provide LV GLS as negative values since it measures shortening of the myocardium in the longitudinal direction. Therefore, more negative values of LV GLS denote better LV systolic function. However, current recommendations acknowledge the use of LV GLS in absolute values since it may be easier to understand that lower values of LV GLS represent worse LV systolic function.[4]The accuracy and reproducibility of the measurement of LV GLS relies on the experience of the observer and the image quality. However, previous study has shown that the intraclass correlation coefficient for the measurement of LV GLS were significantly better than those reported for LVEF, independently of the image quality.[5] Teaching interventions consisting of tutorial review of reference cases and group discussions have improved the interobserver variability for visual estimation of LVEF.[6] However, similar exercises have not shown such an impact on the measurement of LV GLS and only improved moderately the standard deviation and coefficient of variance of segmental longitudinal strain.[5]

LV GLS: normal values

In a large meta-analysis, including more than 2500 healthy volunteers (mean age 47±11 years, 51% male), normal values of LV GLS ranged from –15.9% to –22.1% [mean 19.7%; 95% confidence interval: -20.4% to -18.9%].[7] Although all were healthy individuals, clinical characteristics (e.g. age, gender, body mass index and blood pressure), as well as vendor-specific software used for longitudinal strain analysis, may explain the variation in LV GLS. LV GLS appears to be more impaired in the elderly, as well as in males.[8] Furthermore, LV GLS is also heart-rate dependent, with increased heart rates being associated with reduced LV GLS values in healthy subjects.[9] Guidelines do not yet describe threshold values of LV GLS, but suggest that -20% (± 2%) may be considered normal.[10]

CLINICAL APPLICATIONS OF LV GLOBAL LONGITUDINAL STRAIN

Early detection of LV systolic dysfunction and heart failure

LV GLS is a more sensitive marker of LV dysfunction than LVEF, and this is attributed to: 1) the longitudinal orientation of subendocardial LV fibres, which are susceptible to ischaemia, and 2) compensatory increase in circumferential fibre function in the presence of longitudinal dysfunction, whereby LVEF is maintained in the normal range.[1] Impaired LV GLS has been reported in asymptomatic patients with type 2 diabetes mellitus and normal LVEF suggesting the presence of early structural changes of the myocardium (increased myocardial triglyceride content, accumulation of ceramides, reactive fibrosis), i.e. the hallmarks of diabetic cardiomyopathy.[11, 12] In individuals with hypertension, LV GLS can be impaired despite having a normal LVEF.[7] These findings could be explained by the increased afterload and the response of the myocardium with hypertrophy.[13] In addition, obesity has been associated with a reduction in LV GLS independently of increased blood pressure, LV mass and circulating insulin.[14] These cardiovascular risk factors: diabetes, hypertension and obesity, are highly prevalent and frequent co-exist. They have been associated with cardiovascular events such as myocardial infarction, heart failure and cardiovascular mortality in various population-based studies.[8, 15-17] The Copenhagen City Heart Study included 1296 participants (mean age 57 years, 42% male) with a body mass index of 25 kg/m^2 and a prevalence of diabetes of 9% and hypertension of 38%.[8] The mean LV GLS was -18% and individuals within the lowest quartile of LV GLS (>-15.8%) were significantly older, had significantly higher values of blood pressure, heart rate and body mass index and the prevalence of hypertension was the highest (52%). After a median follow-up of 11 years, 12% of participants presented with heart failure, acute myocardial infarction, or cardiovascular death. Each 1% deterioration in LV GLS was independently associated with a 12% increased risk of the composite endpoint.[8]

Why is LV GLS an earlier marker of LV systolic dysfunction than LVEF in these populations? This was elegantly demonstrated by Stokke and coworkers in a mathematical model:[1] each 1% reduction in myocardial shortening (GLS) should be compensated by 0.5% increase in circumferential shortening, 0.9 mm increase in wall thickness or a reduction in LV end-diastolic volume by 6 to 9 ml in order to maintain LVEF. This dependency of LVEF on wall thickness and end-diastolic volume support the use of LV GLS as an alternative measure of LV systolic function.

Identification of LV hypertrophy aetiologies

LV GLS may aid in the differentiation of the causes of LV hypertrophy. Certain characteristic patterns are evident: patients with mutation positive sarcomeric hypertrophic cardiomyopathy usually demonstrate regionally impaired LV GLS in the regions where hypertrophy is most prominent.[18] In contrast, cardiac amyloidosis is characterized by relative sparing of the LV apical segments (Figure 3).[19]

The clinical implications of impaired LV GLS in patients with hypertrophic cardiomyopathy have been demonstrated in several studies.[20, 21] LV GLS is usually impaired in these patients, despite having normal LVEFs.[21]In a systematic review, including 3154 patients with hypertrophic cardiomyopathy, the mean LVEF ranged between 62% and 72% whereas LV GLS was impaired and ranged between -9% and -16.%. The different vendors used to analyse LV GLS could partly explain the relatively wide range of values. However, it is important to note that hypertrophic cardiomyopathy is a very heterogenous disease and that the magnitude of myocyte disarray is probably the main determinant of functional and structural abnormalities whereas replacement fibrosis and microvessel disease, which can also impact on LV GLS, are related to LV mass, sex and local autocrine factors.[22] The majority of studies have shown that impaired LV GLS is associated with an increased risk of ventricular arrhythmias, heart failure symptoms and all-cause mortality.[21, 23]

In cardiac amyloidosis, LV GLS has also shown incremental prognostic value over a current prognostic staging algorithm including cardiac troponin T, N-terminal pro-brain natriuretic peptide and free light chain serum levels.[23] Among 150 patients with biopsy-proven light chain amyloidosis and LVEF≥55%, a value of LV GLS ≥-14.8% was associated with a hazard ratio of 2.68 for the occurrence of all-cause mortality.

Coronary artery disease

LV subendocardial muscle fibres are predominantly oriented in a longitudinal direction. Since the subendocardium is most susceptible to ischaemia, it is therefore not surprising that LV GLS is affected by coronary artery disease earlier than LVEF. Speckle tracking echocardiography can be used in patients with coronary artery disease during both rest and stress (exercise or pharmacological).[24] Measuring LV GLS from images obtained during stress echocardiography does however, present a number of technical challenges: 1) increased heart rate influences LV GLS values, 2) image quality is often suboptimal and 3) STE cannot be performed in conjunction with contrast agents.

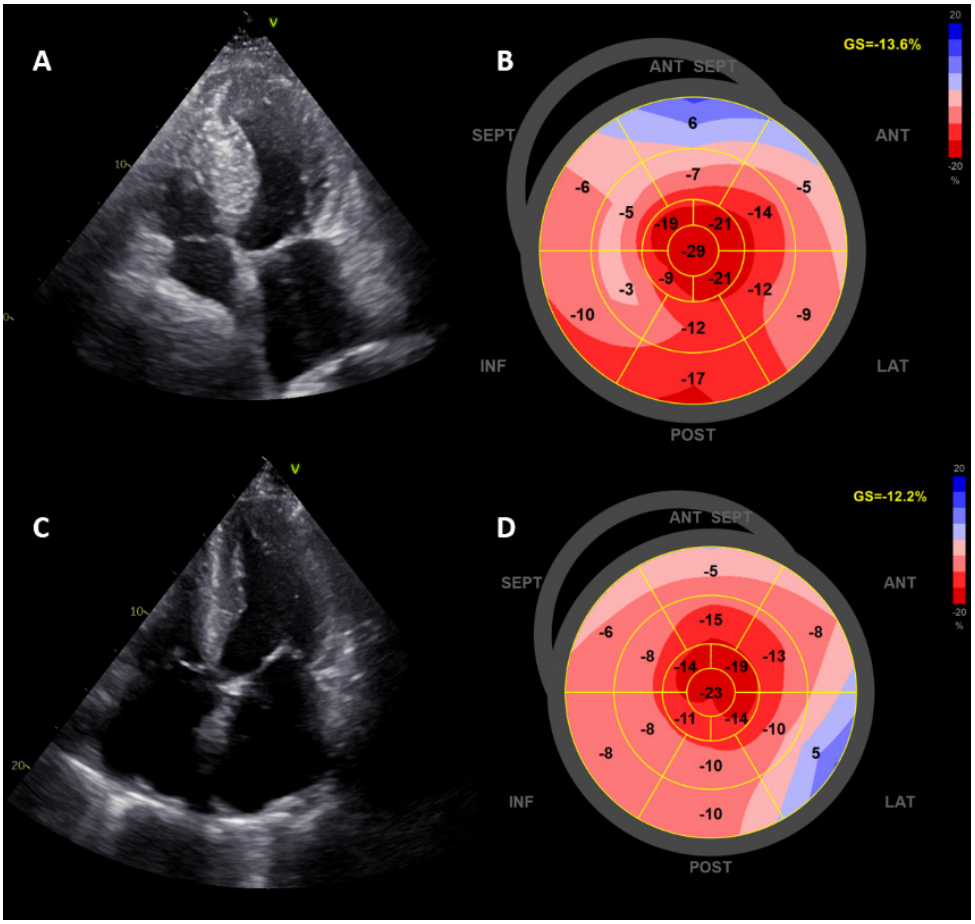

Figure 3. Left ventricular global longitudinal strain to differentiate between mutation positive sarcomeric hypertrophic cardiomyopathy and cardiac amyloidosis. In panel A, the apical 4-chamber view of a 66 year-old patient known with mutation positive hypertrophic cardiomyopathy. The thickness of the septum was 28 mm and the left ventricular ejection fraction was 55%. In panel B, the polar map shows markedly impaired longitudinal strain in the septal mid and basal areas and the global longitudinal strain is impaired (-13.6%). Panel C shows the apical 4-chamber view of a 75 year-old patient diagnosed with light chain amyloidosis. There is concentric hypertrophy of the left ventricle and the ejection fraction is 56%. Based on speckle tracking echocardiography analysis, the left ventricular global longitudinal strain is impaired (-12.2%) with typical sparing of the longitudinal strain values in the apical segments.
Abbreviations: ANT, anterior; ANT_SEPT, anteroseptal; GS, global strain; INF, inferior; LAT, lateral; POST, posterior; SEPT, septal.

Nevertheless, LV GLS has shown to be an important prognostic parameter in the risk stratification of patients after acute myocardial infarction as well as in those with chronic coronary syndromes.[25, 26] A previous study has shown that LV GLS was better correlated with myocardial infarct size (as assessed by cardiac magnetic resonance) than LVEF in 61 patients with myocardial infarction.[27] Strain imaging has the potential to identify significant coronary stenosis in patients who present with stable angina, as well as non-ST-segment elevation myocardial infarction.[28] Furthermore, the pattern of longitudinal strain values as provided by the polar-plot offers additional information on the affected coronary artery and the extent of myocardial damage.[24] Recent work by Huttin et al,[29] demonstrated an association between LV GLS and adverse remodelling (increased LV end-diastolic volume or LV-end systolic volume (>15% to 20%)) (pooled multivariable odds ratio [OR] = 1.38, 1.13-1.70, p=0.002), which is incremental to conventional echocardiographic parameters for predicting adverse LV remodelling. Furthermore, LV GLS has been demonstrated to predict recovery of LV systolic function post-infarct. In a study by Mollema et al,[30] baseline LV GLS (-13,7%) yielded a sensitivity of 86% and a specificity of 74% to predict LV functional recovery at one year follow-up.

Valvular heart disease

Decisions on surgical and transcatheter intervention for valvular heart disease are mainly based on the severity of valve disease, while LVEF assumes a more prominent role in asymptomatic patients. Due to the load-dependent nature of LVEF, as well as a fraction of the LV volume which is pumped into the LA during systole, LVEF overestimates systolic function in the context of mitral regurgitation.[31] LV GLS is less load-dependent than LVEF, and has proven to be a good predictor of post-operative LVEF in severe mitral regurgitation. LV GLS >-19.9% was an independent predictor of long-term LV systolic function after mitral valve repair in a study of 233 patients with moderate to severe primary mitral regurgitation.[32]

Aortic valve replacement is recommended in patients with asymptomatic, severe aortic stenosis and LVEF<50%. LVEF however, has limited sensitivity in the context of a hypertrophic LV. Impaired LV GLS has been correlated with LV fibrosis, and is associated with the development of symptoms and mortality in asymptomatic, severe aortic stenosis.[33] Furthermore, LV GLS also predicts recovery of LV function after aortic valve replacement for aortic stenosis.[34] Although, contemporary guidelines do not recommend routine use of LV GLS, the evidence showing that LV GLS is associated with prognosis in patients with severe aortic stenosis is growing.[35] Current guidelines still advocate a conservative strategy in patients with asymptomatic severe aortic regurgitation, preserved LVEF and a non-dilated left ventricle. LV GLS may already be

impaired in such patients and has been associated with the development of symptoms or LVEF deterioration in a group of 67 individuals with moderate to severe AR and preserved LVEF.[36, 37]

Cardio-oncology

The prevalence of cardiotoxicity as a result of chemotherapy may vary from 13%-42%, and is influenced by individual risk, combination chemotherapy and dosages.[38, 39] At present, the mainstay of LV systolic function monitoring during chemotherapy, still remains the LVEF.[38] When employing this parameter, cardiotoxicity is defined as a decrease of >10% in the LVEF, to an LVEF <53%.[38] Early cardiac impairment can be demonstrated with LV GLS, i.e. when the LVEF is still within the normal range, and LV GLS values predict the subsequent decline in LVEF.[40, 41] Even though the impact on management has not been validated, guidelines from the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend the routine use of LV GLS for surveillance of patients receiving potentially cardiotoxic chemotherapy regimens. A relative percentage reduction in LV GLS of >15% from baseline, has been proposed to define cardiotoxicity.[38] Prospective studies are required to inform on the therapeutic role of LV GLS in cardio-oncology, i.e. if early cardioprotective therapy will translate into improved outcomes.

RESEARCH-BASED APPLICATIONS OF LV GLOBAL LONGITUDINAL STRAIN

Speckle tracking echocardiography allows for more detailed analysis of the LV, such as automated analysis of layer-specific GLS of the LV myocardial wall (endocardium, mid-myocardial, epicardium; respectively) (Figure 4). Particularly in ischaemic heart disease, layer-specific analysis is of interest since the myocardial damage after acute myocardial infarction may not be transmural. Layer-specific analysis of LV GLS can accurately discriminate between transmural and non-transmural myocardial infarction and has also been associated with outcome.[42, 43] The use of layer-specific strain analysis remains experimental, due to the lack of reference values, high inter-vendor variability and suboptimal reproducibility.[10]

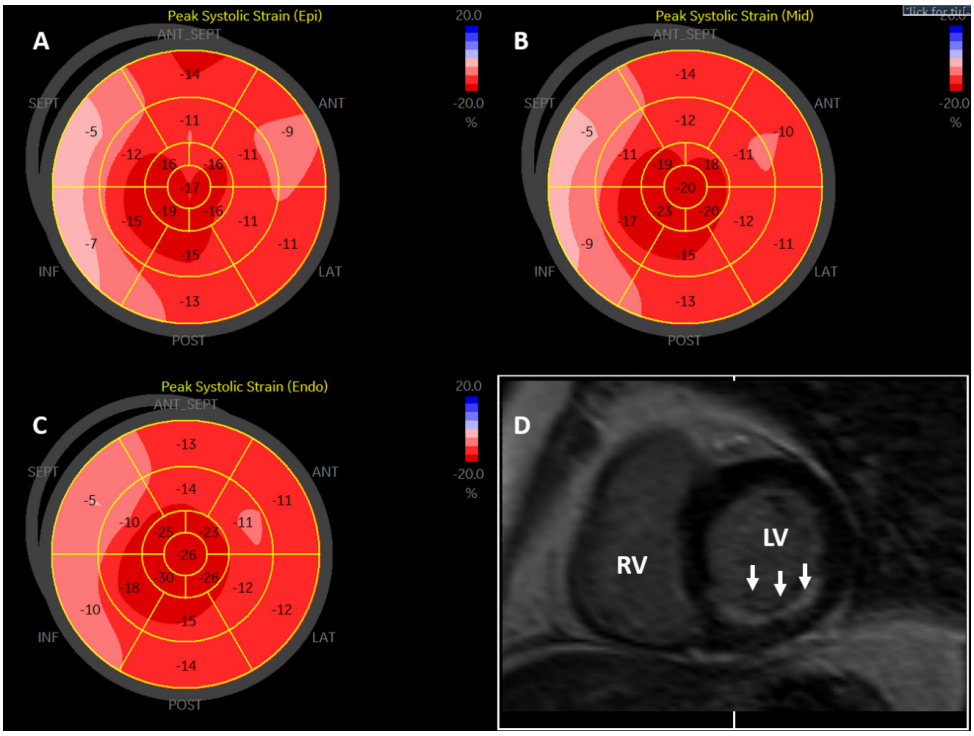

Figure 4. Layer-specific left ventricular global longitudinal strain. Example of a patient with subendocardial inferoposterior myocardial infarction. The polar maps show the regional longitudinal strain values of the epicardial (A), mid-myocardial (B) and endocardial (C) layers. Panel D shows a short-axis view of the left ventricle acquired with late gadolinium contrast enhanced cardiac magnetic resonance. Note the subendocardial infarction (arrows). The polar maps of longitudinal strain show more impaired values in the infarcted regions.
Abbreviations: ANT, anterior; ANT_SEPT, anteroseptal; INF, inferior; LAT, lateral; LV, left ventricle; POST, posterior; RV, right ventricle; SEPT, septal.

LV mechanical dispersion is defined as the standard deviation of time from the onset of the Q/R-wave on the surface ECG to the peak longitudinal strain of 17 LV segments (Figure 5).[44, 45] LV mechanical dispersion reflects the degree of heterogeneity in myocardial contraction, and has been linked to the occurrence of ventricular arrhythmias in variety of cardiac diseases.[44, 45] LV mechanical dispersion appears particularly useful in patients with ischaemic heart disease and heart failure, where it has shown incremental value to LVEF for the prediction of adverse events.[44-46]

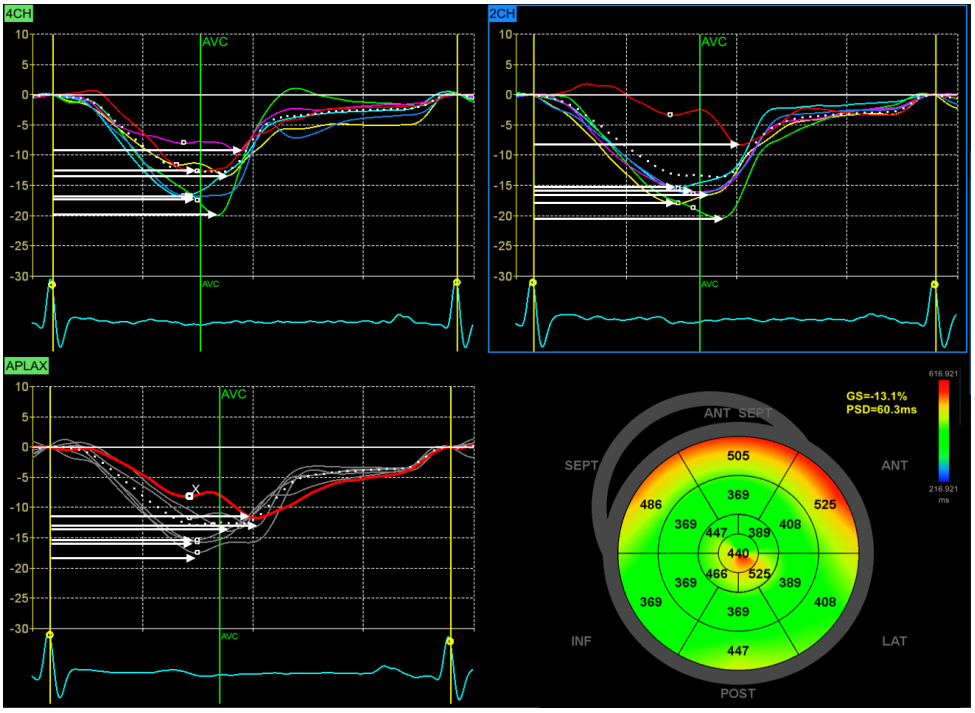

Figure 5. Assessment of left ventricular mechanical dispersion. Left ventricular mechanical dispersion is calculated as the standard deviation of the time from the onset of the QRS complex on the surface ECG, to the peak longitudinal strain in 17 segments of the left ventricle. The time to peak longitudinal strain curves are displayed in the apical long-axis (APLAX), 2-chamber and 4-chamber views (white arrows). The polar map showing the time to peak longitudinal strain is displayed. The global longitudinal strain (GS) was -13.1% while the left ventricular mechanical dispersion (PSD) is 60.3 ms.
Abbreviations: ANT, anterior; ANT_SEPT, anteroseptal; INF, inferior; LAT, lateral; POST, posterior; SEPT, septal.

Finally, measurement of LA strain allows a comprehensive assessment of LA function, including the various phases (LA reservoir, LA conduit, and active LA contraction (booster pump)) of the cardiac cycle[49] (Figure 6). LA strain however, remains technically challenging due to the thin LA wall, discontinuity of the LA contour due to pulmonary vein ostia and the ostium of the LA appendage, lack of dedicated LA strain analysis software and uncertainty regarding normal values. Nevertheless, LA strain has shown promise in the evaluation of diastolic function and in predicting outcomes of patients with atrial fibrillation.[50-51]

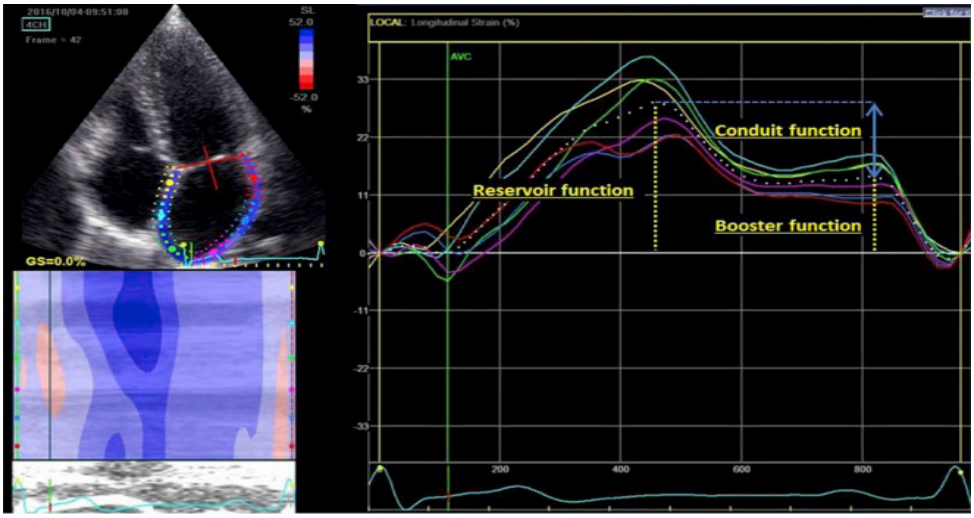

Figure 6. Research based apllications of speckle tracking echocardiography with two-dimensional echocardiography. The figure demonstrates left atrial (LA) strain analysis. The LA endocardium is manually traced in the apical 4-chamber view, and the region of interest is adjusted to fit the thickness of the LA wall. Strain curves for individual LA segments are illustrated. LA strain is measured as the peak global longitudinal strain during ventricular systole, which is indicated by the dotted line within the strain curves.

AIMS AND OUTLINE OF THIS THESIS

The objective of this thesis was to evaluate the role of advanced echocardiography for the risk stratification and possible treatment guidance of patient with ischemic heart disease.

In **Part I**, we gained more insight into left ventricular mechanics. We determined (near) normal reference values and gained better understanding of advanced echocardiographic parameters in subjects with no structural heart disease across a wide age range. **Chapter 2** is predominantly focused on level and layer-specific LV GLS whereas **Chapter 3** is mainly focused on left atrial parameters derived from advanced echocardiography and the conventional electrocardiogram. **Part II**, focusses on the role of advanced echocardiography in patients with ischemic heart disease. **Chapter 4** evaluated the effect of guideline based therapy on LV systolic functional recovery. **Chapter 5** provides more insight into LV mechanics and the value of multilayer LV GLS in adverse remodeling. **Chapter 6** describes the prognostic value of layer-specific LV GLS in patients with mildly reduced or preserved LVEF. **Chapter 7** investigates clinical

correlates of LV mechanical dispersion and the long term prognostic value of LV mechanical dispersion. Finally, **Chapter 8** investigates the association of LV mechanical dispersion with the amount of myocardial scar burden and its prognostic implications.

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