Echocardiographic Stratification of Acute Coronary Syndrome

Thesis

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Acknowledgments

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LIST OF PAPERS

I Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K, Smiseth OA, Edvardsen T, Skulstad H. Strain echocardiography predicts acute coronary occlusion in patients with non-ST-segment elevation acute coronary syndrome. Eur J Echocardiogr 2010 In press (e-published)

II Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K, Hol PK, Smith HJ, Smiseth OA, Edvardsen T, Skulstad H. Strain echocardiography and wall motion score index predicts final infarct size in patients with non-ST-segment-elevation myocardial infarction. Circ Cardiovasc Imaging 2010; 3:187-94.

III Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K, Smiseth OA, Edvardsen T, Skulstad H. Post systolic shortening is a strong predictor of viability in patients with non ST-segment elevation myocardial infarction. Subittet to: J Am Soc Echocardiogr

IV Grenne B, Eek C, Sjoli B, Skulstad H, Aakhus S, Smiseth OA, Edvardsen T, Brunvand H. Changes of myocardial function in patients with non-ST-elevation acute coronary syndrome awaiting coronary angiography. Am J Cardiol 2010; 105:1212-8.

SELECTED ABBREVIATIONS

AUC = Area Under the Curve

CE-MRI = Contrast Enhanced Magnetic Resonance Imaging

ECG = Electrocardiogram

IRA = Infarct related Artery

LAD = Left Anterior Descending

LCX = Left Circumflex

LVEF = Left Ventricular Ejection Fraction

MI = Myocardial Infarction

NSTEMI = Non ST segment Elevation Myocardial Infarction

NSTE-ACS = Non ST segment Elevation Acute Coronary Syndrome

PSS = Post Systolic Shortening

RCA = Right Coronary Artery

ROC = Receiver Operating Characteristic

STE = Speckle Tracking Echocardiography.

STEMI = ST segment Elevation Myocardial Infarction

UAP = Unstable Angina Pectoris

WMS = Wall Motion Score

WMSI = Wall Motion Score Index

INTRODUCTION

Acute coronary syndrome

The acute coronary syndrome comprises three different entities, ST elevation myocardial infarction (STEMI), Non ST elevation myocardial infarction (NSTEMI) and unstable angina (UAP). These share a common cause, namely impaired supply of oxygenated blood to the myocardium, which is again caused by atherosclerotic or thrombotic narrowing or occlusion in the coronary arteries. This in turn may lead to ischemic symptoms, impaired myocardial function and myocardial necrosis. Patients with acute myocardial infarction are upon first medical contact dichotomized according to their presenting electrocardiogram (ECG). Patients with STEMI are perceived to have total occlusion of an epicardial coronary artery and a large area of myocardium at risk of necrosis. Prognosis after myocardial infarction (MI) is closely linked to the size of the infarct, and to residual left ventricular (LV) function.[1] Hence, treatment is aimed at limiting infarct size and preserving LV function by restoration of flow, either medically by thrombolysis or mechanically by percutaneous coronary intervention (PCI). Patients with NSTEMI are rarely treated with acute reperfusion. They are stabilized medically, and those with high risk features are recommended to undergo coronary angiography within 48-72 hours, with subsequent revascularization if indicated.

The ECG is insensitive towards detection of acute coronary occlusion and substantial infarction.[2,3] Registry data have revealed that the culprit lesion is occluded in 24% of patients with NSTEMI, and that these patients suffer worse outcomes.[4] There is also a large overlap in final infarct size between STEMI and NSTEMI patients.[5] Therefore, there is a need for methods to rapidly identify patients with acute occlusion and/or substantial infarction, in the absence of ST-segment elevation.

Detection of myocardial ischemia by echocardiography.

This whole thesis is based on detection and quantification of ischemia and necrosis through detection and quantification of changes in myocardial systolic function. The close relationship between myocardial systolic function and ischemia was first elegantly demonstrated by Tennant and Wiggers in 1935.[6] Acute ischemia induces sequential changes in regional myocardial function; initially reduced systolic contraction and later systolic distention. These changes occur and may be detected within few seconds after abrupt cessation of blood supply.[7] Transthoracic echocardiography is today the most widely used diagnostic tool for evaluation of global and regional myocardial systolic function. Several other imaging modalities have been developed for evaluation of myocardial function. However, no other modality yield the unique combination of detailed real-time information, high spatial and temporal resolution and comprehensive information on cardiac structure and function, in addition to being cheap, non-invasive and rapidly available. If assessment of myocardial function is to be implemented in initial evaluation of patients with suspected MI, the above mentioned properties give echocardiography several advantages compared to other imaging modalities.

Echocardiographic parameters of systolic function

Several echocardiographic parameters are in use for quantification of myocardial systolic function. The most widely used is the left ventricular ejection fraction (LVEF),[8,9] which represents the stroke volume as a fraction of the end diastolic volume:

$$LVEF = \frac{\text{Stroke volume}}{End\ diastolic\ volume}$$

LVEF is widely validated as a prognostic indicator after acute MI,[10] but has several disadvantages, including high interobserver variability.[11] In addition, it is a measure of global and not regional function. Compensatory increased contractions in non-ischemic regions may result in only small changes in LVEF, and masque large areas with impaired function. Wall motion score (WMS) is another widely used parameter of LV systolic function.[12] It is based on visual assessment of systolic endocardial excursion on an ordinal scale, most often in a 16 segments model.[13] Segments are scored as 1= normal, 2=hypokinetic, 3=akinetic and 4=dyskinetic. Wall motion score index (WMSI) is calculated as the mean of analyzed segments. Compared to LVEF it is less affected by regional hyperkinesia, but is limited by dependence of the experience and the subjective interpretation of the observer.

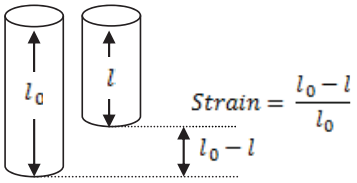
Tissue Doppler provides information about velocities in tissue relative to a transmitter. Through the Doppler equation

$$v = \frac{\Delta f \, x \, c}{2 f_0 \, x \cos\theta}$$

velocity (v) is calculated based on the shift in frequency between transmitted and received frequency (Δf). Velocity of sound in tissue (c) and the transmitted frequency (f_0) are known constants. The measurement is angle dependant, but misalignment of up to 25° will only underestimate true velocity by up to approximately 10%. Myocardial velocities are obtained from pulsed Doppler recordings or color coded 2D images. Applied on images from the apical view, these measurements provide quantitative information on myocardial longitudinal function. Decreased systolic velocity has been demonstrated in ischemic myocardium.[14] Displacement can be calculated from the time integral of velocity, providing information on translation of the myocardial region. Both velocity and displacement data are hampered by tethering; the measurements are affected by velocity and displacement in neighboring regions. Together with the emergence of strain echocardiography, this may be why velocity based assessment of myocardial function has not reached widespread clinical use, despite being available for more than a decade.

Strain echocardiography

Strain is a dimensionless measure of the deformation that occurs upon application of stress. It represents the fractional or percentage change between the unstressed and stressed dimension. Theoretically, it can be calculated along any given axis. Throughout systole, the myocardium shortens along a longitudinal axis, thickens along a radial axis and shortens along a circumferential axis. These deformations are caused by generation of active force, through myocardial muscle fiber contraction. Hence, quantification of strain along any of these axes represents a measure of deformation and consequently contractile function in the assessed region.



Strain Doppler echocardiography

To overcome the tethering problems inherent in velocity measurements, strain Doppler echocardiography was developed. The basis of Doppler-based strain is the velocity gradient; if two points measured from a set distance from a transmitter have different velocities, the difference in velocity represents the instant rate of deformation between the two points, the strain rate. Strain is then obtained through the time integral of strain rate. During the last decade, extensive research has been performed on myocardial systolic function using both strain and strain rate,[15] in a variety of clinical and experimental settings. Results have been

promising, but clinical use is still scarce. Even though the tethering issues were largely overcome by strain Doppler, other issues have limited clinical application; since measurements are based on a velocity gradient, the signal is noisy and separation between signal and artifact can be difficult. The angle dependency is much greater for strain than velocity,[16] making careful alignment of the axes very important. Post processing is time consuming, and requires a certain level of experience and expertise in order to make the correct interpretation.

Speckle tracking echocardiography

A novel approach to strain echocardiography has been developed called "Speckle tracking Echocardiography" (STE). This modality uses conventional 2D cine loop images for calculation of strain. Instead of calculating strain from velocity, strain is calculated directly from tracking consistent pixel patterns (speckles) from frame to frame. Speckles can be tracked in all directions, eliminating the angle dependency in Doppler strain. This implies that deformation can also be assessed along circumferential and radial axes, in addition to longitudinal. However, since linear resolution parallel to the ultrasound beam is limited only by the ultrasound wavelength (typically 0.5-1mm) while resolution perpendicular to the beam is limited by the ultrasound beam with, longitudinal strain has a theoretical advantage. STE has been validated against sonomicrometry and tagged magnetic resonance imaging (MRI), both clinically and experimentally, under ischemia and different loading conditions.[17] Compared to Doppler strain, the signal is less noisy, post processing can be performed much more rapidly, and semi automatic algorithms have also been developed. The latter may facilitate clinical utilization. STE is based on 2D images, and the signal-to-noise ratio is dependent on image quality. Reverberations, drop-outs and poor image quality may represent sources of error. Automatic algorithms to accept or discard analyzed segments are developed and refined, but should not replace visual confirmation of tracking. Feasibility and reproducibility has proven excellent.[18]

Summary

There is a close relationship between myocardial perfusion and myocardial systolic function. In this thesis, we wanted to assess whether impaired perfusion could be identified and quantified by echocardiographic estimates of myocardial systolic function. This may solve a clinical problem, namely accurately identifying NSTE-ACS patients at high risk of adverse events. Above, several different methods to estimate myocardial systolic function are summarized. Paradoxically, despite substantial technological development and improvements in image quality, the echocardiographic parameters most used today were developed decades ago. The primary objective of our studies was to show that echocardiography, irrespective of method, is a feasible tool for risk stratification of patients with NSTE-ACS. Without prejudice, new and older modalities were compared with respect to their ability to detect and quantify myocardial ischemia and/or necrosis.

AIMS OF THE THESIS

General Aims

The general objective of this thesis was to determine the value of echocardiography for stratification of patients with non ST-segments elevation acute coronary syndrome (NSTE-ACS). Specifically, we sought to assess whether echocardiographic estimates of systolic function could be used to identify patients at high risk.

Specific aims

I To investigate in a clinical study the ability to identify patients with acute coronary occlusion by echocardiographic parameters of global and regional systolic function.

II To investigate the relationship between echocardiographic parameters of myocardial systolic function prior to revascularization and final infarct size, as measured by MRI. Specifically, we assessed the ability to identify patients with substantial infarction.

III To investigate the ability of post systolic shortening (PSS) to predict recovery of systolic function in patients with NSTEMI and impaired regional systolic function at baseline, and to compare the added value of PSS compared to angiographic and other parameters.

IV To investigate temporal changes in myocardial systolic function between hospital admittance and subsequent coronary angiography 1-2 days later.

MATERIAL

Study population (paper I-III)

The studies were conducted on Oslo University Hospital (OUS), Rikshospitalet, which is a tertiary coronary care center providing coronary angiography and intervention services. Consecutive patients from referring hospitals were screened for enrollment upon arrival. Between May 2007 and June 2008, 150 patients (40 women), 58±9 (mean±SD) years of age were enrolled. Inclusion criteria were age ≥ 18 years, a clinical diagnosis of NSTE-ACS and planned coronary angiography within 3 days of index admission. Time from index hospital admission to coronary angiography was 2.2±0.7 (range 1-3) days. Major exclusion criteria were: prior MI, evidence of STEMI (ST-elevation > 0.1mV [0.2mV in precordial leads V_1-V_3]) in two or more contiguous leads on any ECG during index admission, bundle branch block with QRS > 120ms, severe valvular disease, previous heart surgery, extensive comorbidity with short life expectancy, atrial fibrillation with heart rate > 100 or any condition interfering with the patient's ability to comply.

A total of 756 patients were screened for inclusion, of whom 150 (20%) were included. Patient characteristics are summarized in table 1. The major reasons for exclusion were; previous MI (n=212), delayed referral (n=193), previous CABG (n=193), comorbidity (n=30), and wide QRS (n=22). Only 4 patients refused participation, and no patients were excluded due to poor echocardiographic image quality.

Patients paper I

In paper I, the entire 150 patients enrolled were examined. Of these, 124 (83%) were referred with a diagnosis of NSTEMI based on elevated troponin I or T, the remaining 26 (17%) had UAP. All patients underwent coronary angiography the same day they arrived at OUS. Echocardiography was performed immediately prior to coronary angiography. The latter was important to ensure that the echocardiogram reflected status prior to revascularization.

Patients paper II

In paper II, the primary objective was to determine the relationship between myocardial systolic function and final infarct size in patients with NSTEMI. From the total population, 61 patients aged 57±9 years (13 women) underwent examination with late enhancement magnetic resonance imaging to determine final infarct size, 9±3 months after inclusion. All patients had NSTEMI evident by elevated troponin I or T at baseline.

Patients paper III

In paper III, the objective was to determine the ability of PSS to predict improvement in systolic function among patients with NSTEMI and impaired regional systolic function at baseline. From the total population of 150 patients, 35 patients aged 56.3±10 years (5 women) had a combination of NSTEMI, an identified culprit lesion, impaired regional systolic function at baseline, successful complete revascularization and a follow up echocardiogram 9±3 months after inclusion. Impaired systolic function at baseline was defined as at least one segment with WMS ≥ 2 within the culprit region.

Study population paper IV

This study was conducted at Sykehuset Sørlandet, Arendal, which is a local hospital with invasive cardiologic services. Inclusion criteria were: 1) Acute anginal pain lasting for at least 10 minutes and clinically classified as unstable angina pectoris or NSTEMI; 2) A history of chest pain less than 3 days; 3) indication for coronary angiography according to current guidelines. Exclusion criteria were similar to study I-III, except patients with previous myocardial infarction were not excluded. 102 patients were included, and

retrospectively grouped according to discharge diagnosis as having NSTEMI, UAP or non coronary chest pain.

Table 1. Patient characteristics

Patients	**n=150**	
Age (years)	57.7 ± 9.0	
BMI (kg/m^2)	27 ± 3.6	
Risk Factors	n	%
Male gender	110	73 %
Current smoker	55	37 %
Hypercholesterolaemia	39	26 %
Hypertension	60	40 %
Diabetes Mellitus	12	8 %
History of CAD	8	5 %
Troponin positive	123	82 %
Medication		
Aspirin	149	99 %
Clopidogrel	146	97 %
LMWH	144	96 %
β-blocker	122	81 %
Statin	135	91 %
Warfarin	1	1%
ACE/ARB	40	27 %
Gp2b3a inh.		

BMI indicates body mass index; CAD, coronary artery disease; LMWH, low molecular weight heparin; ACE, angiotensin converting enzyme, ARB, Angiotensin receptor blocker; GpIIbIIIa, glycoprotein IIbIIIa.

METHODS

Echocardiography

Echocardiography was performed in the left lateral decubital position, using a Vivid 7 scanner, equipped with a 2.5 MHz probe (GE Vingmed, Horten, Norway). In short axis view, three consecutive cycles were obtained at the basal-, mid ventricular- and apical level. From the apical view, three consecutive cycles were obtained in four chamber-, two chamber- and long axis view. Frame rate ranged from 69±12 (Study III) to 74±9 (study IV) frames/s. In study I-III, echocardiography was performed immediately prior to coronary angiography, and at follow up 9±3 months later. In study IV, echocardiography was performed at admittance, immediately prior to coronary angiography, and at follow up 99±20 days later. LVEF was calculated using the modified Simpson's rule from two- and four chamber images. WMSI was calculated in a 16 segments model.[13] As all echocardiographic methods in this thesis rely on the quality of 2D grayscale images, great care was taken to acquire high quality images. Mitral inflow velocity (E) was recorded by pulsed Doppler with the sample volume placed between the leaflet tips. Early diastolic mitral annular velocity (e') was recorded by tissue Doppler using color mode, and calculated by averaging values from septum and the lateral wall in four chamber view. The E/e' ratio correlates to LV filling pressure,[19] and is reported in study IV. All images were digitally stored, and later analyzed off-line in a blinded fashion.

Strain analysis

In this thesis, speckle tracking was used to estimate strain. This relatively new algorithm calculates segmental deformation by tracking acoustic markers from within the myocardium on a frame-to-frame basis. A region of interest (ROI) was manually drawn, and adjusted if tracking was not optimal. Quality of tracking was assessed both by the automatic algorithm within the software, as well as visually. Segments with suboptimal tracking were discarded. Filters for temporal and spatial smoothing were kept in default position, to avoid introducing potential confounding. In papers I-III, peak negative systolic strain was used as a measure of segmental systolic function in the longitudinal and circumferential directions, peak positive systolic strain in the radial direction. In paper IV, peak systolic strain was used, representing the point on the strain curve that has the largest absolute value within systole. The software output generates strain values in an 18 segments model, which was converted to 16 segments by averaging strain values from adjacent segments in four chamber- and long axis view. Global longitudinal strain (GLS), global circumferential strain (GCS) and global radial strain (GRS) were obtained by averaging values from analyzed segments.

In paper I a new term; the *"functional risk area"* was introduced. Previously, experimental studies have demonstrated an excellent correlation between the ischemic risk area and the area of regional systolic dysfunction.[21,22] We therefore assessed the size of the area with impaired systolic function, defined as the number of adjacent segments with systolic dysfunction. Systolic dysfunction was defined separately using WMS and strain, and segments with WMS ≥ 2 or segmental longitudinal strain $\geq -14\%$ were defined as dysfunctional.

Torsion has been introduced as a measure of global LV systolic function,[20] and was used in paper II. It was measured by speckle tracking, and calculated as the difference in rotation between the basal and apical planes.

In paper III, PSS was used as a predictor of recovery of systolic function. PSS was measured in long axis view by STE, and defined as the segmental shortening in diastole beyond minimum systolic segment length, as percentage of end diastolic segment length; i.e.

peak negative strain in diastole minus peak negative strain in systole (figure 1). If maximum segmental shortening was within systole, PSS was set to zero. Hence, PSS could only take negative values. Duration of systole was defined in apical long axis view as the time from peak R in the ECG to the first frame where the aortic valve was closed.

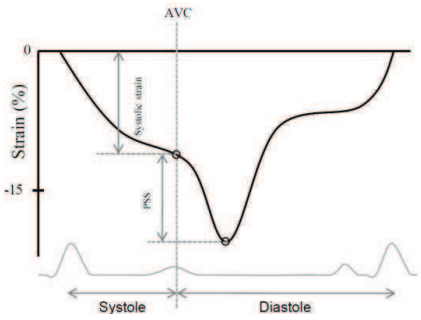


Figure 1 *PSS was defined as segmental shortening in diastole beyond minimum systolic segment length.*

In paper III and IV, strain values from the culprit territory, based on a standardized division of the LV into three vascular beds (LAD, LCx and RCA), were used in accordance with established recommendations.[13]

Coronary angiography

Coronary angiography was performed on clinical indication by standard (Judkins) technique,[23] using digital imaging acquisition and storage. Revascularization was not part of study protocol, and PCI was performed at the discretion of the operator. Cine loops in multiple angles were stored, and all analyses were performed off-line, blinded to the results of the echocardiographic analyses. TIMI-flow was noted, and acute occlusion was defined as TIMI-flow 0 or 1 in the infarct related artery (IRA). Acute occlusions were differentiated from chronic total occlusions by angiographic appearance (thrombus, collaterals, calcification), and by the ease with which a guide wire could cross the lesion. Occlusive lesions were classified as being either in the proximal or mid part of a major coronary artery, as opposed to in a distal part or branch (paper I). The number of diseased vessels (diameter stenosis ≥50%) was noted, and patients with significant stenosis were dichotomized as having single- or multi vessel disease.

Magnetic resonance imaging (MRI)

Contrast enhanced MRI (CE-MRI) has a high spatial resolution, and is considered the gold standard for assessment of infarct size.[24] For clinical use, it is limited by cost, availability and time consumption. In paper II, CE-MRI was used as the reference method to assess infarct size at follow up 9±3 months after inclusion. An example is demonstrated in figure 2.

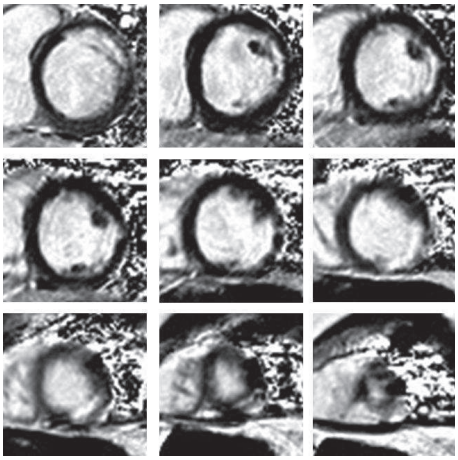


Figure 2. *Short axis MRI images from basis (upper left) to apex (lower right), demonstrating late enhancement in the lateral wall.*

The delay between the infarct and assessment of final infarct size allows LV remodeling and shrinkage of infarct size to complete.[25] Imaging was performed on 61 patients, using a 1.5-T units (Magnetom Sonata, Siemens, Erlangen, Germany) on 29 patients, and a 3-T

units (Philips Medical Systems, Best, The Netherlands) on 32 patients. Late enhancement images were obtained 10-20 minutes after intravenous injection of 0.1 to 0.2 mmol/kg gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany) in multiple short-axis slices covering the entire LV. Typical image parameters were slice thickness 8mm, gap 2mm, inversion time 270ms. On each short axis image, total myocardial area as well as area of infarcted myocardium was manually drawn (PACS, Sectra, Sweden). Final infarct size was calculated as infarct volume as percentage of total myocardial volume. Segmental transmurality was calculated in a 16 segments LV model as infarct volume divided by myocardial volume pr. segment, and segments with ≥ 50% contrast enhancement were judged transmurally infarcted.[26] Both short and long term mortality have been demonstrated to be increased in patients with infarct size ≥12%.[1,27] Therefore, patients were dichotomized by infarct size using 12% as cut off.

Statistical methods

Data were presented as n (percentage) for categorical variables, mean ± standard deviation (SD) for continuous variables with normal distribution, and median (inter quartile range) for continuous variables with skewed distributions. Infarct size and WMSI are typical examples of variables with skewed distributions. Distributions were assessed by graphically by histograms and Q-Q plots. Categorical variables were analyzed using Chi-square test or Fishers Exact test. For continuous variables, differences between groups were analyzed using student *t* test (two samples or paired samples), one way analysis of variance (ANOVA), Mann-Whitney U test or Kruskal-Wallis test as appropriate. In paper II, the relationship between parameters of systolic function and infarct size was assessed by univariate linear regression (least squares). Similarly, in paper III, multivariate linear regression was used to determine predictors of recovery of systolic function. Logistic regression was used to identify predictors of acute coronary occlusion (paper I) and infarct size ≥ 12% (paper II). Inter- and intra observer variability was calculated by intra class correlation coefficient in randomly selected patients.

Receiver operator characteristic (ROC) analyses were used in paper I-III, primarily to assess discrimination, and also to determine optimal cut-off levels to maximize sensitivity and specificity. An example is demonstrated in figure 3. The area under the curve (AUC) is a parameter of discriminating ability. AUC with 95% confidence interval are reported, and compared according to the method described by Hanley and McNeil,[28] using dedicated software (MedCalc Software v. 10.3.1.0, Mariakerke, Belgium). All other statistical analyses were performed on SPSS v. 13 (SPSS Inc. Chicago, IL).

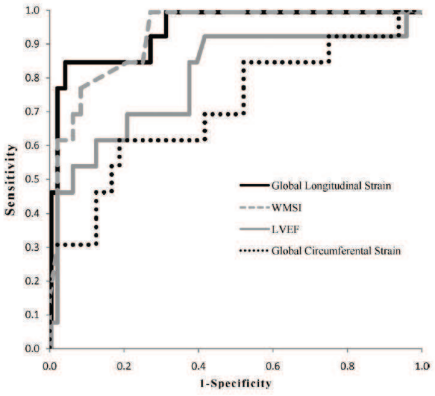


Figure 3. *ROC analysis set to identify infarct size ≥ 12% of to LV myocardial volume*

SUMMARY OF RESULTS

Paper I

In this study, we hypothesized that NSTE-ACS patients with acute occlusion of the infarct related artery (IRA) have impaired systolic global LV function, and a larger area of myocardium with impaired systolic function, compared to patients with a patent IRA.

Acute coronary occlusion was found in 33 patients (22%). All the assessed echocardiographic parameters of LV systolic function were significantly impaired in patients with acute occlusion compared to patients with a patent IRA: LVEF; 54.9±9.6 vs. 59.1 ±7.6%, p=0.02, WMSI; 1.16 (1.03 - 1.36) vs. 1.00 (1.00 - 1.13), p<0.001, global longitudinal strain; -15.0±2.4 vs. -17.4±2.5%, p<0.001. In addition, the area with impaired systolic function was increased: risk area by WMS; median 3 (IQR 0.5 - 4) vs. 0 (IQR 0 - 2) segments, p<0.001, risk area by strain; median 7 (IQR 4.5 – 9) vs. 2 (IQR 0 - 5) segments, p<0.001. No significant differences were found in clinical or electrocardiographic parameters. Troponin T was significantly increased in patients with acute occlusion (1.0±1.1 vs. 0.3±0.7 µg/l, p<0.01). The latter is likely to reflect a larger amount of myocardial necrosis.

ROC analysis demonstrated that the functional risk area estimated as the number of adjacent segments with longitudinal strain ≥ -14% had the best ability to identify patients with acute occlusion (AUC 0.81 [95% confidence interval 0.74 – 0.88], p<0.001). With cut off at ≥ 4 segments, we find sensitivity 85% and specificity 70%.

Paper II

In this study, we assessed the ability of strain echocardiography and established indices of LV systolic function to predict final infarct size. Previously, infarct size ≥ 12% has been associated with increased mortality, and we specifically assessed the ability to identify individual patients with infarct size ≥12%.

Infarct size followed a right skewed distribution, with median 5.4% and IQR 1.7 – 11.4%. 13 patients (21%) had infarct size ≥12%. All echocardiographic parameters of LV systolic function demonstrated significant correlation to final infarct size. WMSI (r=0.74, p<0.001) and GLS (r=0.68, p<0.001) demonstrated the strongest correlations.

The ability to identify patients with infarct size ≥ 12% was excellent for GLS (AUC 0.95 [95% CI 0.86 – 0.99]) and WMSI (AUC 0.93 [[95% CI 0.83 – 0.98]). Both were superior to LVEF, GCS, GRS and torsion. No clinical or electrocardiographic criteria were able to identify patients with infarct size ≥ 12%. Logistic regression demonstrated that combining echocardiographic parameters did not increase discriminating power. At follow up, a persistent impairment of LV systolic function was found in patients with infarct size ≥12% compared to those with smaller infarcts (GLS -14.1±2.0% vs. -17.5±2.2%, p<0.001).

Paper III

PSS has previously been associated with viable myocardium. The association between PSS and change in systolic function between baseline (before revascularization) and follow up 9±3 months after successful revascularization was assessed in this study. Change in systolic function was calculated as difference in longitudinal strain values at baseline and follow up (ΔStrain).

PSS was present in 32 patients (91%) at baseline, mean -1.9±1.4%. In the myocardial territory supplied by the infarct related artery, mean ΔStrain was -3.3±2.9 %. Improved systolic function was found 30 patients (86%).

Systolic function at baseline was found to be a confounder of improvement , as a larger absolute ΔStrain was found in patients with poor function at baseline (correlation between

ΔStrain and baseline function; r=-0.58, p<0.001). After adjustment for the confounding effect of baseline systolic function, PSS and angiographic severity of the culprit lesion were significant predictors of ΔStrain. In a multivariate regression model, PSS had the strongest prognostic power (PSS standardized β = 0.38, angiographic severity standardized β = 0.33).

Paper IV

Temporal changes in patients with suspected NSTE-ACS awaiting coronary angiography have not previously been determined.

In patients with NSTEMI, we found a small but significant deterioration in longitudinal global strain from -16.1±2.6% at admittance to -15.0±2.6% before coronary angiography (p<0.001). This was due to deterioration in longitudinal strain in the territory supplied by the infarct related artery from -14.2±4.2% to -12.0±4.1% (p<0.001), whereas strain in remote area was unchanged. This deterioration was most pronounced in patients with total occlusion of the infarct related artery at coronary angiography. No change was observed in LVEF or global circumferential strain. No change in LV systolic function was observed in patients with UAP or non coronary chest pain.

DISCUSSION

Study design and protocol

This study was designed, and the protocol was written, to assess whether echocardiography may be a useful tool for stratification of patients with NSTE-ACS, with respect to extent of coronary pathology and myocardial necrosis. For the findings in clinical studies like these to be applicable to a general population, some conditions concerning patient selection, choice and use of methods and end points must be fulfilled. These will be discussed below.

Patient selection

All clinical studies will have inclusion and exclusion criteria. Still, it is important that the studied population as closely as possible resembles patients in an unselected population. In our studies I-III, assessment was limited to patients who were referred for coronary angiography, as the studies were performed at the referral centre. This of course may introduce a selection bias. Nevertheless, we sought to identify patients with acute coronary occlusion or substantial MI, who may benefit from acute reperfusion therapy. Patients with MI who are not referred for coronary angiography following MI are also unlikely to be candidates for acute revascularization. Still, we may have missed some of the most seriously ill patients, who may have died or become too unstable for transport while awaiting coronary angiography, thus introducing a bias towards patients with less serious disease. On the other hand, some patients with suspected or confirmed NSTE-ACS may have been stabilized medically, and never been referred to coronary angiography. These patients may suffer from less serious disease, introducing a bias towards more seriously ill patients in the studied population. By including study IV in this thesis, we are able to provide data from the initial period during which patients are stabilized. In studies I-III, findings are limited to patients without previous MI. As it is difficult to differentiate acute from chronic MI by echocardiographic estimates of LV systolic function, this selection was necessary.

Patients with a delay of more than three days before arrival were excluded from our studies. The main reason for this is that we wanted to study a population treated according to current guidelines, which recommend a delay of 72 hours at most.[29] Good compliance to guidelines in the studied population is confirmed by the large proportion of patients on dual platelet inhibition, beta blockers and LMWH. The number of patient excluded due to delayed referral was relatively large, (n=193). As patients with less serious disease may be more likely to wait longer, this may also introduce a bias towards patients with more serious disease.

A large scale registry study including more than 30,000 NSTEMI patients, also excluding those with previous MI or CABG, found a prevalence of an occluded IRA of 24%.[4] This is virtually identical to our population, where an occluded IRA was found in 33 out of 150 patients (22%), and may indicate that the frequency of serious disease in our population does not deviate substantially from what would be expected in an unselected population.

Our population is relatively young (mean age 58 years). The reason for this is probably found in the exclusion criteria. Patients excluded due to previous MI (mean age 66 years), delayed referral (mean age 65 years) and previous CABG (mean age 69 years) were all significantly older (all $p<0.01$). This, however, does not imply that our findings apply only to younger patients. In all studies, we tested whether age was a confounder or effect modifier, and did not find any evidence of such. In addition, the age of the patients studied ranged from 37 to 79 years, thus representing a broad age spectrum.

Selection and use of methods

Another important issue concerning whether findings are applicable to a broader population, is the choice and use of methods. Post-hoc application of numerous tests, calculation of indexes and reporting positive findings will result in over fitting of statistical models, and poor reproducibility of results. To avoid this, it is important that analyses are predefined, and that findings are consistent using different methods. In our studies, all parameters used to estimate LV function (volumes, LVEF, global and regional systolic strain, WMSI, and PSS) were used according to study protocol. The echocardiographic methods have differences, which will be discussed in detail below, but findings are consistent. For example, acute coronary occlusion results in short and long term impairment of LV systolic function, measured by either strain echocardiography, LVEF or WMSI. Likewise, patients with infarct size ≥12% have impaired LV systolic function compared to patients with smaller infarcts, regardless of method.

One important caveat that is difficult to avoid concerning the general applicability of findings, is the quality of the data used in the analysis. One would expect that the quality of the echocardiographic images and image analysis is superior when performed by a scientist for research purposes, compared to examinations and analysis performed in a clinical setting by clinicians. The reported feasibility in our studies is indeed very high, and probably higher than could be expected in a clinical setting. Thus, we do not have data on the robustness of our methods, and trials in a clinical setting are needed to clarify this issue. Technological developments may reduce the impact of this limitation. Images may be transferred on-line with minimal time delay for interpretation in high volume centers. In addition, automatic algorithms for assessment of strain are developed (Automated Function Imaging (AFI), GE Vingmed, Horten, Norway) which reduce the time and skill needed for interpretation. Developments in scanner technology also have made acquisition of high quality images easier, and this development is likely to continue. One must also not forget that this limitation applies to all methods used to evaluate patients, and even biochemical and electrocardiographic data are in need of skilled interpretation.

The use of different observers to perform analysis of different parameters is an important strength in our studies. Also, strict blinding procedures are necessary to avoid observer bias. In our studies, blinding was performed by applying random identification numbers generated by an independent investigator to each patient, and the code was broken only after all analyses were performed. The procedure was repeated for analysis of follow up tests. This ensures that no results were influenced by the results of other analysis.

Choice and use of end points

Use of hard end-points like death or recurrent MI would require a greatly increased study population and longer follow up than was available. For studies that rely on surrogate end-points, like ours, it is important that these are well defined and clinically meaningful.

In study I, we used acute coronary occlusion as end-point, and patients were dichotomized accordingly. Acute coronary occlusion was defined as TIMI flow 0 or 1 in the IRA. The rationale behind using this as an end-point is two sided. Identification of patients with acute occlusion is important, because acute coronary occlusion is an independent predictor of poor prognosis.[4] In addition, patients with acute coronary occlusion are logically the ones most likely to benefit from acute reperfusion therapy, as this may restore flow and salvage viable myocardium.

The main problem using acute coronary occlusion as an endpoint is the diversity of the coronary anatomy. The same vessel will, in different patients, have differences in diameter

and length, and thus differences in the size of the perfusion territory. Interestingly though, infarct size was no different in patients with a proximal occlusion vs. distal occlusion or occlusion in a side branch (median 8.6% vs. median 8.3%, p=0.98, unpublished data). This may be because patients with proximal occlusions are more likely to develop ST segment elevations, and these patients were excluded from our study.

In paper II, we used infarct size measured by CE-MRI as end point. The association between final infarct size and subsequent mortality and adverse events is well established,[1,27,30-33] and infarct size is much used as a surrogate end point. Stratification based on early assessment of the predicted infarct size is also likely to facilitate tailored treatment algorithms for NSTEMI patients. CE-MRI is today considered the gold standard for estimation of final infarct size.[34] The association between LV systolic function and infarct size is well established in chronic MI,[35] and also shortly after reperfusion in STEMI patients.[36] No study to date has attempted echocardiographic prediction of infarct size *prior* to reperfusion in NSTEMI patients.

Infarct size can be assessed both on a linear scale and dichotomized at a given cut point. In study II, both methods were used. We present scatter plots and regression coefficients demonstrating a linear relationship between infarct size as percentage of LV myocardial volume and different echocardiographic estimates of LV systolic function. In order to estimate sensitivities and specificities of a method, it is necessary to dichotomize the study population. It is important that the chosen cut point has a clinical correlate. On small populations, cut points which fit the data set can be chosen that erroneously over estimate the discriminating ability of a method. We suggest infarct size ≥12% as cut point. This is primarily based on two previous studies, which demonstrate increased mortality in patients with infarct size ≥12%.[1,27] An infarct size of 12% may intuitively seem small. However, one large trial found 12% to be median infarct size in STEMI patients treated by acute reperfusion.[27] More recently, mean final infarct size estimated with modern CE-MRI methods was found to be 10% in patients with reperfused *anterior* STEMI (LAD as infarct related artery).[37] One small study found infarct size measured by CE-MRI ≥18% to be associated with increased risk of adverse events,[30] suggesting using a cut off set higher. However, it is intuitively reasonable to at least attempt to identify NSTEMI patients with infarct size larger than a typical STEMI patient, and a cut point set higher would in our opinion be too conservative. Still, applying 18% as cut point on our material uniformly yields *increasesed* discriminating power of all parameters of LV systolic function, compared to a cut off at 12%. Even LVEF, the parameter that performs least well, achieves an AUC of 0.89, compared to 0.80 using 18% as cut point. Thus, we chose to use 12% as cut off not because it by chance fitted our data, but since in our opinion it is the one that is the most clinically meaningful, and is associated with increased mortality.

In studies III and IV, the end point was changes in global and regional LV systolic function, measured by longitudinal strain. In study III, we assessed viability, defined as the crude difference in systolic function prior to revascularization compared to follow up, 8±3 months later. This definition is the one that carries immediate clinical and prognostic information for the individual patient. Today, contrast enhancement on MRI comprising less than 50% of a segment is often used synonymous to viability. It is important, however, to remember that CE-MRI only represents a *surrogate* measure of viability. Indeed, in the study validating CE-MRI as a measure of viability, the ability to improve contractile function after revascularization was used as reference method.[26] In addition, the validation study was performed on patients with predominantly chronic CAD, and the

findings do not necessarily translate to the setting of acute MI. True viability corresponds to the ability to improve contractile function. Therefore, we feel this is the definition that should be used when such data are available.

Assessment of viability was performed after adjustment for systolic function at baseline. This adjustment is very important, but often not applied in studies assessing potential markers of viability.[38,39] Patients with a large impairment at baseline, will also have larger absolute potential of recovery. Thus, absolute recovery will be larger in patients with major impairment compared to minor, by statistical "regression to the mean". The strong correlation between viability (ΔStrain) and baseline systolic function confirms this confounding effect. Failure to adjust for systolic function at baseline may result in paradoxical findings, as factors may be identified as predictors of viability, simply through being associated with the level of baseline impairment. Indeed, PSS *is* associated with the level of baseline impairment, and is a significant predictor of viability in unadjusted analysis. This does not necessarily imply that PSS has any clinical value in predicting viability. However, PSS remains significant after adjustment for baseline function, confirming it to be an *independent* predictor of viability, and therefore clinically valuable. In our study, several potential factors that may affect viability, including PSS, angiographic severity of the IRA and levels of TnT, were studied. After adjustment for baseline systolic function, we found PSS to be the strongest independent predictor of viability. This easily measured parameter may facilitate identification of patients who potentially will and those who will not benefit from revascularization.

In study IV, we demonstrate changes in LV systolic function in patients with NSTEMI awaiting coronary angiography. As discussed below, strain echocardiography is an excellent tool for identification of small but significant changes in LV systolic function. Our findings are merely descriptive, and we have no data to describe what causes this deterioration. Potentially, changes may be caused by factors within the myocardium, as a result of ischemia, infarct expansion and development of edema. In addition, changes may be caused by alterations in blood supply to the myocardium. Indeed, atherothrombosis is a highly dynamic, process. Even with anticoagulation and triple platelet inhibition, there is a high incidence of recurrent ischemia and infarction in patients awaiting coronary angiography.[40] Irrespective of the cause, the observed changes are important, as they persist at follow up. This provides a rationale for early intervention in patients with NSTEMI, to improve long term LV systolic function.

The discriminating ability of ST segment deviations in the ECG was not a primary objective in our studies. Still, the ECG is the most widely used tool for risk stratification of patients with chest pain in the acute phase, and the association between ECG changes and acute coronary occlusion and infarct size are reported in paper I and II, respectively. Findings are consistently disappointing. Neither the sum of ST segment deviations nor prevalence of an ischemic ECG was increased in patients with acute coronary occlusion. Patients with ischemic changes in the presenting ECG had increased infarct size compared to patients with normal or non specific findings. However, ischemic ECG changes were found in only 7 out of 13 patients (54%) with substantial infarction (infarct size ≥12%), and prevalence of ischemic ECG findings was not statistically different from patients with smaller infarcts. Therefore, in ACS patients without ST-segment elevation, the ECG is not an accurate tool to stratify patients with respect to coronary pathology or extent of myocardial necrosis. An example is demonstrated in Figure 4.

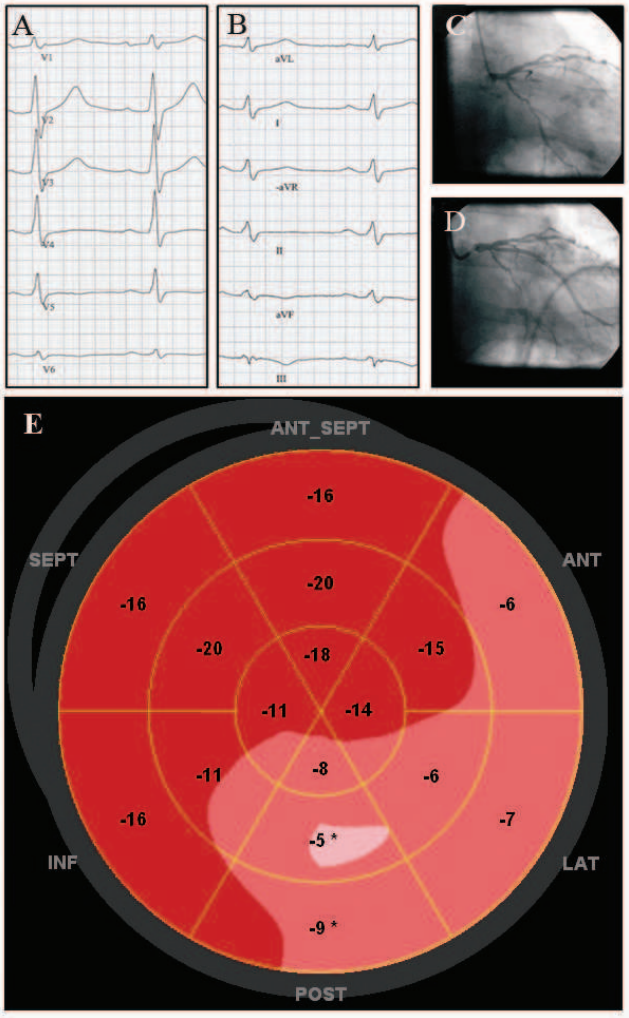


Figure 4. *Example of a patient with acute MI without ST-segment deviations. ECG is shown in panel A and B. Coronary angiography revealed thrombotic occlusion of a large intermediate branch. White arrow in panel C indicates site of occlusion, panel D shows the result after PCI with stent was performed. A bulls eye plot of strain values in panel E demonstrate impaired systolic function in the lateral wall. MRI images from the same patient are demonstrated in figure 2.*

DETAILED DISCUSSION OF ECHOCARDIOGRAPHIC METHODS.

Strain echocardiography and LVEF were used in all papers in this thesis. In papers I and II, we also used WMSI for quantification of LV systolic function. LVEF is the measure most widely used clinically. Guidelines on treatment of heart failure and prevention of sudden death consistently use LVEF to stratify patients.[41-44] The effect of a new treatment is often measured by its effect on LVEF.[45-47] Nevertheless, LVEF has several limitations. Agreement between observers and reproducibility is suboptimal.[11] This is important, since inaccuracy in measurements introduces noise. From a research point of view, this necessitates increased sample sizes to demonstrate differences between groups or effects of treatment. Clinically, it reduces diagnostic accuracy. In our studies, the performance of LVEF was consistently inferior to that of strain echocardiography and WMSI for prediction of acute coronary occlusion and final infarct size. In study II, we found a relative reduction of 9 percentage points in LVEF in patients with infarct size ≥ 12% compared to patients with smaller infarcts. Nevertheless, the ability to identify individual patients was significantly inferior to strain. In study IV, a small but significant impairment of longitudinal systolic strain was demonstrated, while no significant difference was evident by LVEF. This may well be because LVEF is an inaccurate measure of LV systolic function, and a larger sample would be needed to demonstrate such a difference.

Another drawback of LVEF is that is insensitive to smaller areas with impaired systolic function. Acute coronary occlusion and myocardial infarction predominantly cause *regional* impairment of LV systolic function. Increased contractions in remote areas may decrease the impact on LVEF, thereby concealing regional impairments.

WMSI demonstrated discriminating ability similar to strain echocardiography in our papers I and II. WMSI is an established parameter of LV systolic function, validated as a prognostic indicator after MI, superior to LVEF.[48] It is, however, semi quantitative, experience dependent and based on subjective interpretation of myocardial motion. Since all normal segments are scored 1, WMSI is not affected by increased contractions in remote myocardium, and is therefore more sensitive towards detection of small regions with impaired systolic function compared to LVEF. Calculation of an exact WMSI is quite rapidly obtained, does require use of simple mathematic calculation. Even more rapid is a rough count of the number of segments with decreased contractions. The experienced cardiologist can perform such an estimate within 1-2 minutes, based on three apical projections. In our study, only 30 out of 143 segments with impaired contractions were akinetic or dyskinetic (WMS = 3 or 4). Therefore, we find a close association between WMSI and the number of segments with WMS larger or equal to 2 ($r=0.96$, $p<0.001$). The correlation between this "segment count" and infarct size is similar to WMSI ($r=0.73$, vs. $r=0.74$, both $p<0.001$). Visual assessment of how many segments demonstrating WMS larger or equal to 2 may represent the fastest method to estimate final infarct size. In stable patients, time consumption is not very important. However, if echocardiographic methods are to be used for risk stratification of patients with suspected ACS, a less time consuming method is likely to be applied more often. For identification of patients with infarct size ≥12%, a finding of 3 or more segments with WMS ≥2 yield a sensitivity of 100% and specificity of 71%.

Strain echocardiography was used in all papers in this thesis, for quantification of LV deformation. Strain echocardiography represents an accurate validated measure of LV systolic function.[16,17] It has been shown to be superior to visual assessment of wall motion in detection and quantification of regional systolic dysfunction.[49] Recent developments

facilitate assessment of strain from 2D images (speckle tracking), which has reduced post processing, time consumption and has largely overcome the angel dependency limitation of Doppler strain.[17] Global longitudinal strain by speckle tracking has been introduced and validated as a measure of LV systolic function,[50] and has proven superior to LVEF and WMSI for prediction of all cause mortality.[51]

One important feature of strain is that it is measured on a linear scale. This enables quantification of differences too small to be detected by the ordinal 4 level scale of WMS, especially when analyzed on a regional or segmental basis. Thus, sensitivity towards detection of small but clinically significant differences is increased. The small but significant decrease is systolic function between admittance and coronary angiography demonstrated in paper IV is an example of this.

Importantly, strain echocardiography enables not only quantification of deformation, but also timing of such. This is important when assessing patients with dyssynchrony. Recently, regional differences in timing of contractions, "mechanical dispersion", are demonstrated to be a predictor of malignant arrhythmias.[52] In paper III, strain was used both to quantify systolic function, but also PSS. PSS occurs within the first 100-150 ms after aortic valve closure. When the aortic valve is not visualized, as is the case in apical four-chamber and two-chamber view, it is difficult visually to ascertain if myocardial deformation occurs within systole or in the early phase of diastole. This may lead to erroneous overestimation of segmental *systolic* function, if myocardial deformation occurs predominantly within *diastole*. This limitation of visual assessment is overcome by use of strain echocardiography.

As opposed to LVEF, reproducibility is excellent for strain measured by speckle tracking. Intra class correlation coefficient for LV global strain for both inter and intra observer variability has previously been reported > 0.90,[18] which is confirmed in our studies. As mentioned above, this is important both from a clinical and research point of view.

Longitudinal vs. circumferential strain, radial strain and torsion

Systolic myocardial deformation is complex, comprising shortening along longitudinal and circumferential axes, and as a consequence, thickening along a radial axis. In addition, LV torsion, a result of oppositely directed rotation of the apical and basal planes, has been introduced and validated as a measure of LV global systolic function.[20] Doppler strain can only be measured parallel to the ultrasound beam, and is therefore only feasible in the longitudinal direction. Speckle tracking is feasible for measuring strain in all three directions, as well as assessment of LV rotation and torsion. When directly compared, longitudinal and circumferential strain by speckle tracking have previously demonstrated similar ability to predict final infarct size in patients with STEMI.[35]

In study II, we used strain in all directions as well as LV torsion for early estimation of final infarct size. We found the performance of longitudinal strain to be superior compared to circumferential strain, radial strain and torsion. There are several possible reasons for this, both methodological and physiological. Methodologically, longitudinal strain has the advantage of tracking motion parallel to the ultrasound beam. Resolution in this direction is limited by wavelength, typically 0.5-1mm. Circumferential and radial strains are dependant of tracking motion in all directions compared to the ultrasound beam. Resolution perpendicular to the ultrasound beam is limited by line density. Echocardiographic ultrasound probes are non-linear, and lateral resolution is therefore also dependant on depth. Poor resolution leading to suboptimal tracking may therefore be one reason for the poor

performance of circumferential and radial strains.

Another factor is that strain in the latter directions are based on short axis images, where the image planes are difficult to accurately define. In addition, there is considerable through plane motion, especially in the basal parts of the heart. Since the mitral annular plane moves 10-12mm in the apical direction during systole, different regions of the myocardium is assessed through one cardiac cycle. If the echocardiographic plane in end systole extends into the left atrium, severe differences in strain may occur. This may be the reason why some investigators have chosen to use only circumferential strain from the mid ventricular level to assess global LV systolic function.[53]

CLINICAL PERSPECTIVE

The main objective of this thesis was to develop methods to stratify patients with NSTE-ACS based on echocardiographic assessment of LV systolic function. The NSTE-ACS population is very heterogenous. Since the introduction of more sensitive biochemical markers of myocardial necrosis, an increasing number of patients with NSTE-ACS are diagnosed with myocardial infarction.[54] A majority of these patients have a patent IRA, develop small infarctions, and have a good prognosis. Therefore, emphasis must be applied to identification of the minority of patients with more serious disease. Our findings clearly demonstrate that echocardiography represent an accurate tool to identify patients with acute coronary occlusion or substantial MI. These patients comprise a significant proportion of the NSTE-ACS population, and may benefit from acute reperfusion therapy.

Previous studies have found that acute revascularization of patients with NSTEMI is not associated with any harm,[55] and a clear benefit in patients at high risk.[40,55] Immediate revascularization is unlikely to be feasible in all patients with NSTE-ACS, due to the large volume of patients, and difficulty in providing an exact early diagnosis in patients with chest pain. Therefore, stratification is important in order to identify patients at high risk.

The rationale for acute reperfusion therapy in NSTEMI patients is similar to that in STEMI patients; myocardial salvage and reduction of final infarct size. Whether this can be achieved in the NSTEMI population has never been unequivocally demonstrated. Reduction in infarct size by acute angioplasty was the primary end point of the "Acute Balloon Angioplasty vs. Traditional Early Invasive Treatment of Non-ST-Elevation Myocardial Infarction" (DaNSTEMI2) trial (ClinicalTrials.gov Id: NCT00493584). Unfortunately, this trial was terminated prematurely due to insufficient patient inclusion. Nevertheless, there is little reason to believe that acute reperfusion would not be beneficial in a patient with acute coronary occlusion and substantial MI, with or without ST segment elevation.

This thesis was named "**Echo**cardiographic **Str**atification of **A**cute **C**oronary **S**yndrome" (Echo-Str-ACS). Str-ACS phonetically resembles the Norwegian word "*straks*", which translates into "immediately", reflecting our view on when echocardiography could with benefit be performed on patients with suspected ACS.

Conclusions

General conclusion:

Our studies confirm that echocardiography is a valuable tool for risk stratification and evaluation of patients with NSTE-ACS. Patients with acute coronary occlusion or substantial MI can be accurately identified by echocardiography, providing means to identify patients who may benefit from urgent reperfusion therapy. PSS estimated by strain echocardiography prior to revascularization is an independent predictor of viability. Strain echocardiography also demonstrates a progressive impairment of LV systolic function in patients awaiting coronary angiography.

Specific conclusions:

I. LVEF, WMSI and global are impaired in patients with acute coronary occlusion, while risk area measured by strain or WMS is increased in patients with acute coronary occlusion, compared to patients with a patent IRA. Strain echocardiography and WMS are superior to LVEF for identification of individual patients with acute coronary occlusion.

II. There is a significant linear relationship between final infarct size assessed by CE-MRI and global longitudinal-, radial- and circumferential strain, LVEF and WMSI. For identification of individual patients with substantial MI (≥12%), WMSI and global longitudinal strain has excellent discriminating power, superior to LVEF, torsion, radial- and circumferential strain.

III. In patients with NSTEMI, PSS assessed by strain echocardiography prior to revascularization is a strong independent predictor of viability in patients who undergo successful revascularization. The predictive power is superior to biochemical estimates of myocardial necrosis and angiographic severity of the IRA.

IV. During the first 24 hours after admittance for NSTE-ACS, there is a progressive impairment of LV systolic function assessed by longitudinal systolic strain. This impairment is most pronounced in patients with an occluded IRA at time of angiography, and also most pronounced in the myocardial region supplied by the IRA.

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Paper I

Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K,

Smiseth OA, Edvardsen T, Skulstad H.

Strain echocardiography predicts acute coronary occlusion in patients

with non-ST-segment elevation acute coronary syndrome.

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Paper II

Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K,

Hol PK, Smith HJ, Smiseth OA, Edvardsen T, Skulstad H.

Strain echocardiography and wall motion score index predicts final infarct size in patients with non-ST-segment-elevation myocardial infarction.

Circ Cardiovasc Imaging 2010; 3:187-94.

Paper III

Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K,

Smiseth OA, Edvardsen T, Skulstad H.

Post systolic shortening is a strong predictor of viabilityin patients with non ST-elevation myocardial infarction.

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Paper IV

Grenne B, Eek C, Sjoli B, Skulstad H, Aakhus S,

Smiseth OA, Edvardsen T, Brunvand H.

Changes of myocardial function in patients with non-ST-elevation acute coronary syndrome awaiting coronary angiography.

Am J Cardiol 2010; 105:1212-8.