Aus der II. Medizinischen Klinik
Klinikum Coburg

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INAUGURAL-DISSERTATION

The emerging role of stress speckle tracking in viability world

zur Erlangung der Doktorwürde

der medizinischen Fakultät der Julius-Maximilians-Universität Würzburg

vorgelegt von

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Würzburg, September 2017

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Tag der mündlichen Prüfung: 02.05.2019

Der Promovend ist Facharzt für Innere Medizin und Kardiologie

Acknowledgement

The generosity and great support of Professor Dr. Johannes Brachmann had been of great value to bring up this work to light. His vast knowledge and experience were the source of many useful channels in our work. Moreover, I thank him for the personal advices which helped me a lot through my career. His meticulous review of related literature and discussion and his valuable additions were indispensible for finalizing this work.

Words can't express my deep and faithful appreciation for Professor Hany Negm, "Professor and past Head of Cardiology department, Cairo University". He has always been a father and a role model to be followed. His guidance and help had major impact on my personal life before my scientific one.

Beside him, I am thankful for all the consultants and colleagues in Coburg, especially Dr. Christian Mahnkopf the head of Cardiac MRI unit, for utilizing his internationally recognized experience in this work.

I am deeply grateful for Professor Dr. T. Bley for reviewing this work. Moreover, I am thankful for the deep evaluation and guidance to produce this thesis in such shape.

To my family and friends, your support is the leading factor of inspiration and motivation in my life.

Ahmed Saleh 2017

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AMI	Acute myocardial infarction	8
LV	Left ventricle	9
DSE	Dobutamine stress echocardiography	9
SPECT	Single photon emission computed tomography	9
PET	Positron emission tomography	9
STEMI	ST segment elevated myocardial infarction	12
LBBB	Left bundle branch block	14
MMP	Metalloprteinase	18
vWF	Von Willbrand factor	19
ADP	Adenosine diphosphate	19
TXA	Thromboxane A	19
GP	Glycoprotein	19
COX	Cyclooxygenase	19
RAAS	Renin angiotensin aldosterone system	23
CK	Creatine kinase	29
CV	Coefficient of variation	29
Tn	Troponin	30
ECG	Electrocardiogram	31
RWMA	Resting wall motion abnormalities	34
PTCA	Percutaneous transluminal coronary angioplasty	37
AHA	American heart association	38
CMRI	Cardiac MRI	55
18-FDP	Fluorine-18 deoxyglucose	61
COPD	Chronic obstructive lung disease	77
FPS	Frame per second	78
PCI	Percutaneous coronary intervention	82

Introduction

The first descriptions of what would today be recognized as «viable myocardium» appeared in the 1970s, when it was observed that ventricular dysfunction reverted after revascularization in some patients with antecedents of acute myocardial infarction (AMI). **Chatterjee K. et al, 1973.**

The concept of viability is the opposite of that of necrosis, which implies an irreversible alteration in contractility. In patients with severe left ventricular dysfunction of ischemic origin, revascularization leads to improvements in ventricular function, survival and prognosis. Such improvements may be due to the presence of myocardial viability. **Mahrholdt H. et al, 2002.**

Simple diagnostic methods such as the electrocardiogram, resting echocardiography, and ventriculography are available to detect myocardial necrosis. Although such methods are not helpful in detecting myocardial viability, even without resorting to specific diagnostic techniques, revascularization is known to improve survival in 50% of patients with severe left ventricular dysfunction of ischemic origin. **Hayat S.A. et al, 2006.**

Assessing myocardial viability poses two difficulties. In the first place, viability is not a dichotomous concept, as there are degrees of viability ranging from complete absence to total normality. In the second place, the lack of a standard reference model means that precise assessment of myocardial viability is not possible at present, so that results obtained with current assessment methods may be open to discussion. **La Canna GL. et al, 2000.**

Identifying myocardial hibernation is of clinical relevance, as it represents potentially salvageable myocardial tissue. Coronary revascularization in this context is likely to improve contractile performance, LV systolic function, and, in turn, overall morbidity and mortality. However, hibernating myocardium, if left untreated, has the potential to transform into clinically overt heart failure. Revascularization, via either percutaneous angioplasty or coronary bypass surgery, is the primary avenue

of restoring coronary blood flow, unless natural collaterals are formed from the primary diseased vessel. **Ling L.H. et al,2006.**

Dobutamine stress echocardiography (DSE) is used to assess myocardial contractile reserve. Low-dose dobutamine (5 to 10 $\mu g/kg^{-1}/min^{-1}$) can lead to increased contractility in dysfunctional segments that are viable. Myocardial contrast echocardiography is another tool to determine viability through using acoustically active gas-filled micro-bubbles as contrast agent that have a diameter smaller than red blood cells and remain confined within the intravascular space. Single-photon emission computed tomography (SPECT) is a widely available modality with well-established clinical and prognostic validation. **Baer FM. et al, 2000.**

Early studies demonstrated that myocardial ischemia and infarction could be distinguished by analysis of positron emission tomography (PET) images of the perfusion tracer. The uptake of FDG by the myocardium and scan quality depend on many factors such as dietary state, cardiac workload, sympathetic drive, and the presence and severity of ischemia. **Duncan BH. et al, 2000.**

Cine imaging with gradient echo sequences provides information on global LV function, regional wall motion, and thickening. An important advance has been the application of gadolinium-chelated contrast agents to detect perfusion defects, microvascular obstruction, and areas of scarred tissue/fibrosis. This technique allows assessment of the transmurality of necrosis. The transmural extent of infarction correlates with the likelihood of functional recovery of dysfunctional myocardium after revascularization. **Selvanayagam et al, 2006.**

Two-dimensional (2D) speckle-tracking echocardiography is a novel ultrasound method used to assess myocardial deformation parameters derived from standard 2D grayscale

images. Two-dimensional speckle-tracking echocardiography has only been used in a few studies for its diagnostic and prognostic utility in studying myocardial ischemia and viability**. Becker M. et al, 2008.**

Previous studies demonstrated that echocardiographic strain imaging has the potential to discriminate between viable and nonviable tissue. **Becker M. et al, 2006.**

Aim of work

Aim of work

To evaluate global and regional myocardial function and viability in patients with ST elevated myocardial infarction after successful revascularization through primary PCI using stress speckle tracking echocardiography in comparison to cardiac MRI in order to:

1. Assess the feasibility and accuracy of stress speckle tracking to risk stratify STEMI patients after revascularization.

2. Evaluation of stress speckle tracking in detection of functional recovery and viability of global and regional myocardial function following successful revascularization in STEMI patients.

Review of literature

1. Myocardial infarction

Myocardial infarction, commonly known as a heart attack, is the irreversible necrosis of heart muscle secondary to prolonged ischemia. This usually results from an imbalance in oxygen supply and demand, which is most often caused by plaque rupture with thrombus formation in a coronary vessel, resulting in an acute reduction of blood supply to a portion of the myocardium. **McManus DD. et al, 2011.**

The new universal definition clarified that a myocardial infarction should be diagnosed by detection of rise and/or fall of cardiac biomarker values (preferably troponin) with at least one value above the 99th percentile of the upper reference limit and with at least one of the following: Symptoms of ischemia; New or presumably new significant ST-T changes or new LBBB; Development of pathological Q waves in the ECG; Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality; Identification of an intracoronary thrombus by angiography or autopsy. **Steg PG. et al, 2012.**

Cardiac death with symptoms suggestive of myocardial ischemia, and presumably new ECG changes or new LBBB, but death occurring before blood cardiac biomarkers values are released or before cardiac biomarker values would be increased. Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values. **Thygesen K. et al, 2007**

Epidemiology

Ischemic heart disease is the leading cause of death worldwide. Cardiovascular diseases cause 12 million deaths throughout the world each year, according to the third monitoring report of the World Health Organization. They cause half of all deaths in several industrialized countries and are one of the main causes

of death in many developing countries; they are the major cause of death in adults everywhere. **Mendis S. et al, 2011.**

Of particular concern are projections from the World Heart Federation that the burden of atherosclerotic cardiovascular disease in developing countries will increasingly become commensurate with that seen in industrialized countries. With a decline in infectious disease-related deaths, in conjunction with accelerated economic development and life-style changes that promote atherosclerosis, rates of ischemic heart disease and myocardial infarction are expected to sharply increase in developing countries, especially such countries in Eastern Europe, Asia, and parts of Latin America. **Go AS. et al, 2013.**

According to the WHO, 17.3 million deaths in 2008 were attributable to cardiovascular disease, with 7.3 million (42% of all cardiovascular deaths) being due the result of a myocardial infarction (Figure 1). **Mendis S. et al, 2011.**

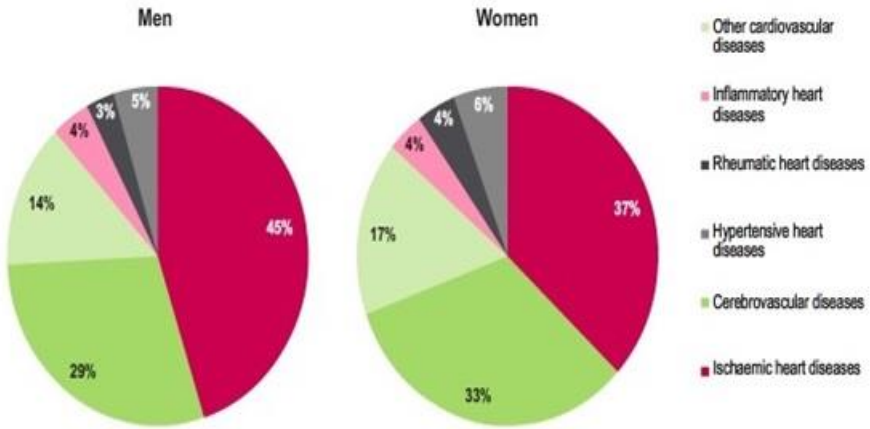


Figure 1. Prevalence of different forms of cardiac diseases in men and women. **Mendis S. et al, 2011.**

The incidence of cardiovascular disease increases with age, with acute myocardial infarction being rare in childhood and adolescence. Most patients who develop an acute myocardial infarction are older than 60 years. Elderly people also tend to have higher rates of morbidity and mortality from their infarcts. Age (≥75 y) is the strongest predictor of 90-day mortality in patients with STEMI undergoing percutaneous coronary intervention. A continued focus on improving outcomes for these high-risk patients is needed. **Gharacholou SM. et al, 2011.**

Pathology of STEMI

Atherosclerosis is a chronic vascular disease that is characterized by endothelial dysfunction, intimal hyperplasia, inflammation, smooth muscle proliferation, and deposition of lipids and formation of microvessels within the vascular wall. The focal nature of atherosclerosis results in formation of discrete plaques. Key components of the plaque include a fibrous cap, composed of smooth muscle cells and fibroblasts, an overlying layer of endothelial cells, and an internal core that contains cholesterol and other lipids, macrophages, foam cells (which are derived from macrophages), other inflammatory cells, and extracellular matrix (Figure 2). **Kumar et al, 2011.**

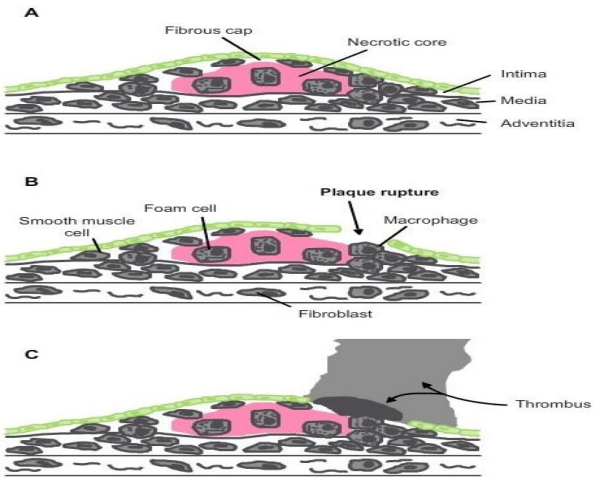


Figure 2. Pathology of plaque formation and rupture. **Kumar et al, 2011.**

Some plaques are more vulnerable to rupture than others. Important characteristics of the vulnerable plaque include a thin fibrous cap, a large, lipid-rich, hypocellular core, and the presence of leukocytes, which produce metalloproteinases (MMPs) and other factors that trigger extracellular matrix degradation and apoptosis, within the fibrous-cap. **Sharma M. et al, 1997**

Platelets play a central role in the development of thrombi and subsequent ischemic events, and this process of platelet-mediated thrombus formation involves adhesion, activation, and aggregation. Plaque rupture exposes subendothelial collagen, a highly thrombogenic material, which serves as a site of plate -let adhesion, activation, and aggregation. Activated platelets undergo a series of steps including: shape change, adhesion to endothelial cells of vessels, aggregation, and the secretion of granules that perpetuate the cycle (figure 3). **Savi P. et al, 1996.**

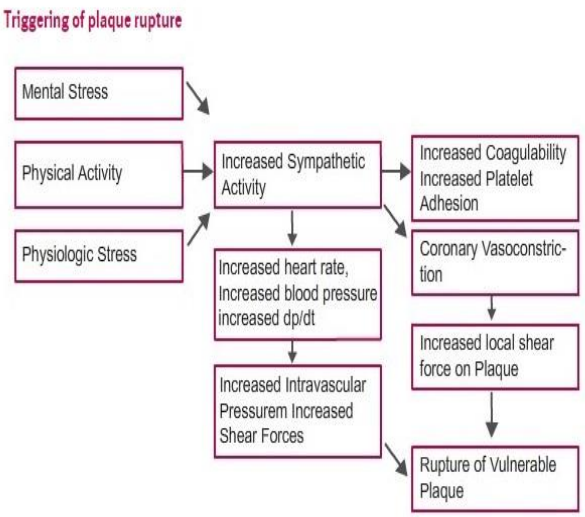


Figure 3. Triggers of plaque rupture. **Savi P. et al, 1996.**

An adhesive glycoprotein, von Willebrand factor (vWF), allows platelets to stay attached to the subendothelial vessel wall (via GP Ib) despite high shear forces. Following adhesion, platelets are activated to secrete a variety of agonists which are pro-

aggregatory molecules, such as thrombin, serotonin, adenosine diphosphate (ADP), and thromboxane A(TXA)(Figure 4). These agonists, which further augment the platelet activation process, bind to specific receptor sites on the platelets to activate the GP IIb/IIIa receptor complex, the final common pathway to platelet aggregation. Once activated, the GP IIb/IIIa receptor undergoes a conformational change that enables it to bind with fibrinogen. **Born GV. et al, 1970.**

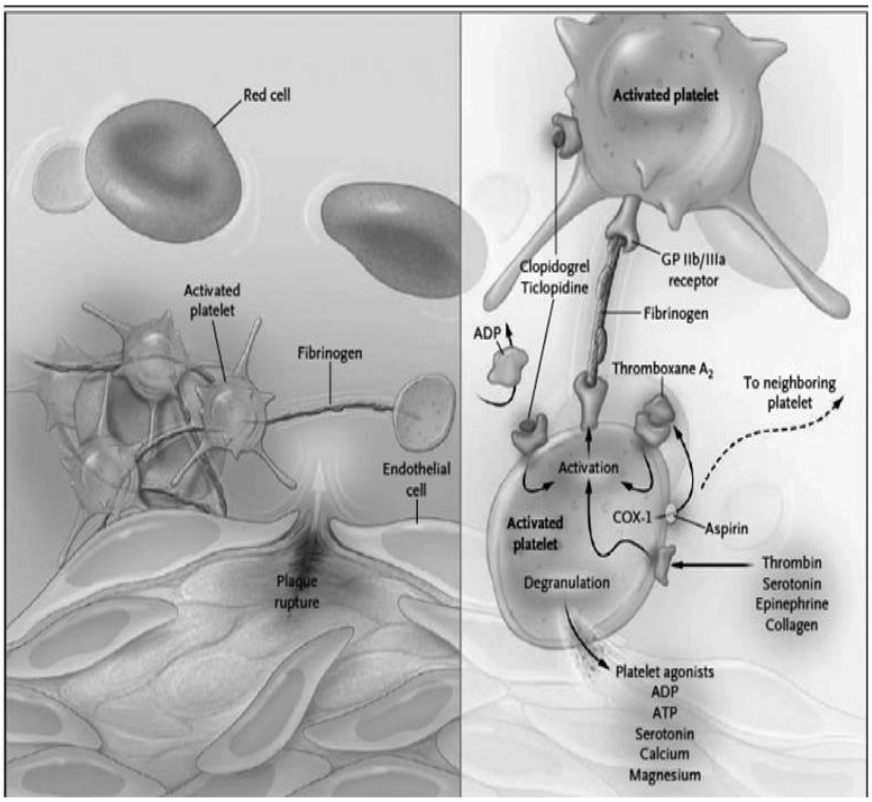


Figure 4 : The disruption of an atherosclerotic plaque results in exposure of highly thrombogenic material. In patients with atherothrombosis, the activation of platelets and coagulation are inseparable, reciprocally self-amplifying processes. The inhibition of platelets alone does not block the coagulation activators. GP denotes glycoprotein, ADP adenosine diphosphate, and COX-1 cyclooxygenase-1. **Mohler E.R. et al, 2007.**

Factors leading to myocardial infarction

Table 1. Causes of Myocardial Infarction without coronary atherosclerosis

Coronary Artery Disease Other than Atherosclerosis
Arteritis Granulomatous (Takayasu disease) Polyarteritis nodosa Mucocutaneous lymph node (Kawasaki) syndrome Disseminated lupus erythematosus Rheumatoid spondylitis Ankylosing spondylitis
Trauma to coronary arteries Laceration Thrombosis Iatrogenic Radiation (radiation therapy for neoplasia)
Coronary mural thickening with metabolic disease or intimal proliferative disease Mucopolysaccharidoses (Hurler disease) Homocystinuria Fabry's disease Amyloidosis Juvenile intimal sclerosis (idiopathic arterial calcification of infancy) Intimal hyperplasia associated with contraceptive steroids or with the postpartum period Pseudoxanthoma elasticum

Coronary fibrosis caused by radiation therapy
Luminal narrowing by other mechanisms Spasm of coronary arteries (Prinzmetal angina with normal coronary arteries) Spasm after nitroglycerin withdrawal Dissection of the aorta Dissection of the coronary artery
Emboli to Coronary Arteries
Infective endocarditis Nonbacterial thrombotic endocarditis Papillary fibroelastoma of the aortic valve ("fixed embolus") Thrombi from intracardiac catheters or guidewires

Pathophysiology of STEMI

Left Ventricular Function

Systolic Function

Upon interruption of antegrade flow in an epicardial coronary artery, the zone of myocardium supplied by that vessel immediately loses its ability to shorten and perform contractile work. Four abnormal contraction patterns develop in sequence: (1) dyssynchrony, that is, dissociation in the time course of contraction of adjacent segments; (2) hypokinesis, reduction in the extent of shortening; (3) akinesis, cessation of shortening; and (4) dyskinesis, paradoxical expansion, and systolic bulging . **Schuster EH. et al, 1980**

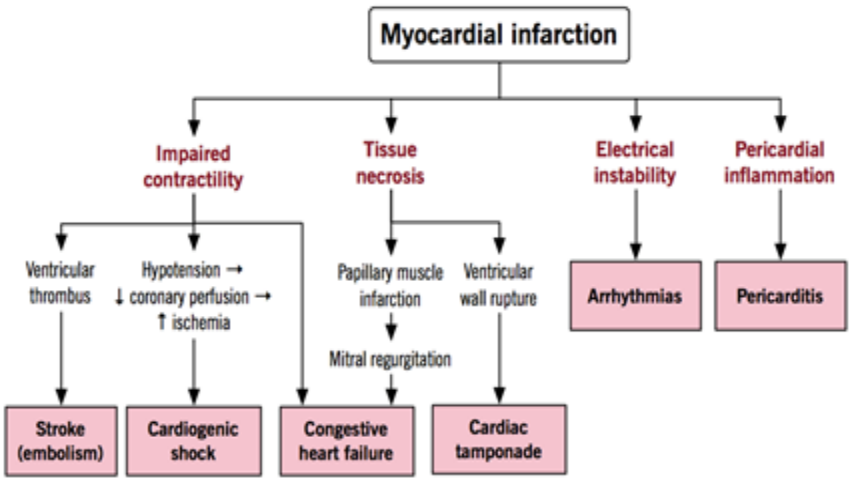


Figure 5. Consequences of Myocardial Infarction. **Chaudhry et al, 2005**

Increased motion of the non-infarcted region subsides within 2 weeks of infarction, during which time some degree of recovery often occurs in the infarct region as well, particularly if reperfusion of the infarcted area occurs and myocardial stunning diminishes. **White HD. et al, 1987**

If a sufficient quantity of myocardium undergoes ischemic injury (Figure 5), left ventricular pump function becomes depressed; cardiac output, stroke volume, blood pressure, and peak dP/dt decline and end-systolic volume increases. **Sadanandan S. et al, 2001**

As necrotic myocytes slip past each other, the infarct zone thins and elongates, especially in patients with large anterior infarcts, leading to infarct expansion. As the ventricle dilates during the first few hours to days after infarction, regional and global wall stress increase according to Laplace's law. The degree of ventricular dilation, which depends closely on infarct size, patency of the infarct-related artery and activation of the renin-angiotensin-aldosterone system (RAAS), can be favorably modified by inhibitors of this system, even in the absence of symptomatic left ventricular dysfunction. **McMurray J. et al, 2006**

The likelihood of developing clinical symptoms such as dyspnea and ultimately a shock-like state correlate with specific parameters of left ventricular function. The earliest abnormality is a ventricular stiffness in diastole, which can be observed with infarcts that involve only a small portion of the left ventricle on angiographic examination. When the abnormally contracting segment exceeds 15 percent, the ejection fraction may decline and elevations of left ventricular end-diastolic pressure and volume occur. **Hochman JS. et al, 2003**

Clinical heart failure accompanies areas of abnormal contraction exceeding 25 percent, and cardiogenic shock, often fatal, accompanies loss of more than 40 percent of the left ventricular myocardium. Unless infarct extension occurs, some improvement in wall motion takes place during the healing phase, as recovery of function occurs in initially reversibly injured (stunned) myocardium. **Pitt B. et al, 2005**

Diastolic Function

The diastolic properties of the left ventricle change in infarcted and ischemic myocardium. These alterations associate with a decrease in the peak rate of decline in left ventricular pressure , an increase in the time constant of the fall in left ventricular pressure, and an initial rise in left ventricular end-diastolic pressure. As with impairment of systolic function, the magnitude of the diastolic abnormality appears to relate to the size of the infarct. **Mads J. Andersen et al, 2013**

Ventricular Remodeling

As a consequence of STEMI, the changes in left ventricular size, shape, and thickness involving both the infarcted and the non-infarcted segments of the ventricle described earlier occur and are collectively referred to as *ventricular remodeling*, which can in turn influence ventricular function and prognosis. A combination of changes in left ventricular dilation and hypertrophy of residual non-infarcted myocardium causes remodeling. **Guo X. et al, 2005**

Clinical Features of STEMI

PRODROMAL SYMPTOMS

The patient's history remains crucial to establishing a diagnosis. The prodrome is usually characterized by chest discomfort, resembling classic angina pectoris, but it occurs at rest or with less activity than usual and can therefore be classified as unstable angina. **Brener SJ. et al, 2006**

NATURE OF PAIN

The pain of STEMI varies in intensity; in most patients, it is severe and in some instances intolerable. The pain is prolonged, usually lasting for more than 30 minutes and frequently for a number of hours. The discomfort is described as constricting, crushing, oppressing, or compressing; often the patient complains of a sensation of a heavy weight or a squeezing in the chest. Although the discomfort is typically described as a choking, viselike, or heavy pain, it can also be characterized as a stabbing, knifelike, boring, or burning discomfort. The pain is usually retrosternal in location, spreading frequently to both sides of the anterior chest, with predilection for the left side. **Singh JP. et al, 2003**

Some patients note only a dull ache or numbness of the wrists in association with severe substernal or precordial discomfort. In other patients, the discomfort of STEMI radiates to the shoulders, upper extremities, neck, jaw, and interscapular region, again usually favoring the left side. In patients with preexisting angina pectoris, the pain of infarction usually resembles that of angina with respect to location. However, it is generally much more severe, lasts longer, and is not relieved by rest and nitroglycerin. **Gregoratos G. et al, 2001**

SILENT STEMI AND ATYPICAL PRESENTATION

Nonfatal STEMI can be unrecognized by the patient and discovered only on subsequent routine electrocardiographic or

postmortem examinations. Of these unrecognized infarctions, approximately half are truly silent, with the patients unable to recall any symptoms whatsoever. The other half of patients with so-called *silent infarction* can recall an event characterized by symptoms compatible with acute infarction when leading questions are posed after the electrocardiographic abnormalities are discovered. Unrecognized or silent infarction occurs more commonly in patients without antecedent angina pectoris and in patients with diabetes and hypertension. **Davis TM. et al, 2004**

Atypical presentations of STEMI include the following:
(1) heart failure (i.e., dyspnea without pain beginning de novo or worsening of established failure)
(2) classic angina pectoris without a particularly severe or prolonged episode
(3) atypical location of the pain
(4) central nervous system manifestations, resembling those of stroke, secondary to a sharp reduction in cardiac output in a patient with cerebral arteriosclerosis
(5) apprehension and nervousness
(6) sudden mania or psychosis
(7) syncope
(8) overwhelming weakness
(9) acute indigestion
(10) peripheral embolization. **Davis TM. et al, 2004**

Laboratory Findings

Serum Markers of Cardiac Damage

Necrosis compromises the integrity of the sarcolemmal membrane that is compromised and intracellular macromolecules (serum cardiac markers) begin to diffuse into the cardiac interstitium and ultimately into the microvasculature and lymphatics in the region of the infarct (figure 6).The rate of appearance of these macromolecules in the peripheral circulation depends on several factors including intracellular location, molecular weight, local blood and lymphatic flow, and the rate of elimination from the blood. **Jaffe AS. et al, 2006**

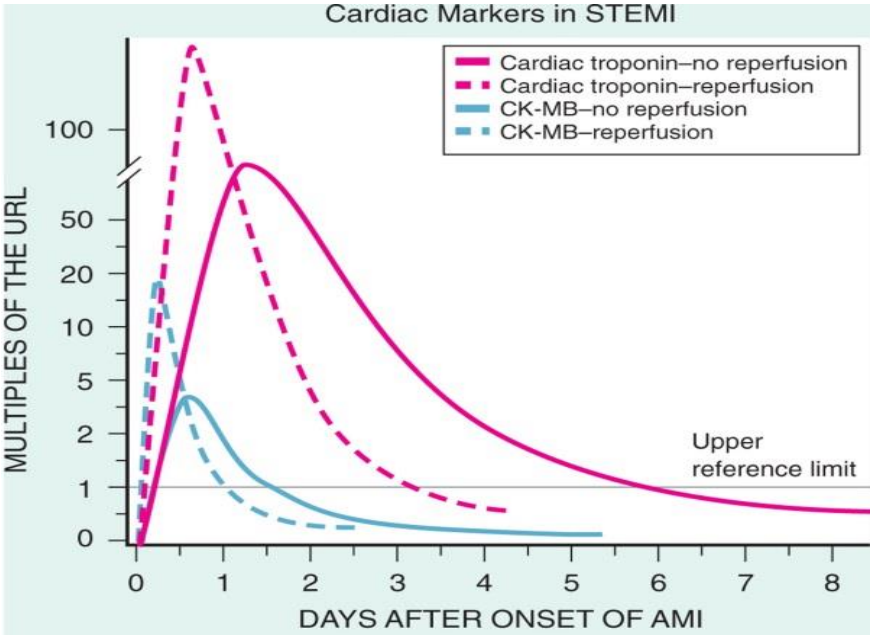


Figure 6: The zone of necrosing myocardium is shown at the top of the figure, followed in the middle portion of the figure by a diagram of a cardiomyocyte that is in the process of releasing biomarkers. Cardiac troponin levels rise to about 20 to 50 times the upper reference limit (the 99th percentile of values in a reference control group) in patients who have a "classic" acute myocardial infarction (MI) and sustain sufficient myocardial necrosis to result in abnormally elevated levels of the MB fraction of creatine kinase (CK-MB). Clinicians can now diagnose episodes of micro-infarction by sensitive assays that detect cardiac troponin elevations above the upper reference limit, even though CK-MB levels may still be in the normal reference range (not shown). CV = coefficient of variation. **Jaffe AS. et al, 2006**

CREATINE KINASE ISOENZYMES

Three isoenzymes of CK exist (MM, BB, and MB). Extracts of brain and kidney contain predominantly the BB isoenzyme; skeletal muscle contains principally MM but does contain some MB (1 to 3 percent); and cardiac muscle contains both MM and MB isoenzymes. Although small quantities of CK-MB isoenzyme occur in tissues other than the heart, elevated levels of CK-MB may be considered, for practical purposes, to be the result of MI (except in the case of trauma or surgery). **Roger VL. et al, 2006**

MYOGLOBIN

This monomeric protein is released into the circulation from injured myocardial cells and can be detected within a few hours after the onset of. Peak levels of serum myoglobin are reached considerably earlier (1 to 4 hours) than peak values of serum CK. Because of its lack of cardiac specificity, an isolated measurement of myoglobin within the first 4 to 8 hours after the onset of chest discomfort in patients with a non-diagnostic ECG should not be relied on to make the diagnosis of MI. **Roger VL. et al, 2006**

CARDIAC-SPECIFIC TROPONINS

Although both TnT and TnI are present in cardiac and skeletal muscle, they are encoded by different genes and their amino acid sequence differs. This permits the production of antibodies that are specific for the cardiac form (cTnT and cTnI) and has led to the development of quantitative assays for cTnT and cTnI that have been approved for clinical use. Several studies have confirmed the reliability of these new quantitative assays for detecting myocardial injury, and measurement of cTnT or cTnI is now at the of the new diagnostic criteria for MI. **Apple FS. et al, 2003**

Diagnosis of STEMI

Electrocardiography

The ECG is the most useful and feasible diagnostic tool for the initial evaluation, early risk stratification, triage, and guidance of therapy in patients who have chest pain. There is currently a growing trend for 12-lead ECGs to be recorded in the field by paramedics and transmitted by cellular telephone or fax to the target emergency department. It is conceivable that emergency department physicians will be involved in triaging patients in the prehospital phase to hospitals offering primary percutaneous coronary intervention (PCI), which is now recognized to be a superior reperfusion strategy than thrombolytic therapy. **Keeley et al,2003**

Some of the patients who have acute chest pain and ST elevation may subsequently have an increase in cardiac markers without any further ECG changes (no ST resolution, no new Q-wave development, and no T-wave inversion). These patients may have non-STEMI with baseline ST elevation, or pseudo STEMI, On the other hand, there are patients who have transient ST elevation who have ST resolution without an increase in the cardiac markers. Although some of them may have acute pericarditis, Prinzmetal angina, or aborted myocardial infarction, many simply have transient early repolarization. **Dowdy L. et al, 2004**

ECG changes during the acute phase of ST-elevation myocardial infarction

Shortly after occlusion of a coronary artery, serial ECG changes are detected by leads facing the ischemic zone, as shown in Fig. 2. First, the T waves become tall, symmetrical, and peaked (grade 1 ischemia); second, there is ST elevation (grade 2 ischemia) without distortion of the terminal portion of the QRS; and third, changes in the terminal portion of the QRS complex may appear (grade 3 ischemia). The changes in the terminal portion of the QRS are explained by prolongation of the electrical conduction in the Purkinje fibers in the ischemic region. The delayed conduction decreases the degree of cancellation resulting in an increase in R-wave amplitude in leads with terminal R wave and a decrease in the S-wave amplitude in leads with terminal S wave on the surface ECG. **Wong CK. et al, 2005.**

ISCHEMIA AT A DISTANCE

Patients with new Q waves and ST-segment elevation diagnostic for STEMI in one territory often have ST-segment depression in other territories. These additional ST-segment changes, which imply a poor prognosis, are caused either by ischemia in a territory other than the area of infarction, termed *ischemia at a distance*, or by reciprocal electrical phenomena. A good deal of attention has been directed to associated ST-segment depression in the anterior leads, when it occurs in patients with acute inferior STEMI. **Zimetbaum PJ. et al,2003**

However, despite the clinical importance of differentiation among causes of anterior ST-segment depression in such patients, including anterior ischemia, inferolateral wall infarction, and true reciprocal changes, such a differentiation cannot be made reliably by electrocardiographic or even vector-cardiographic techniques. Although precordial ST-segment depression associates more commonly with extensive infarction of the lateral, or inferior septal segments, rather than anterior wall subendocardial ischemia, imaging techniques such as echocardiography are necessary to ascertain whether an anterior wall motion abnormality is present. **De Luca G. et al, 2005**

Role of Echocardiography

Echocardiography is an accurate, noninvasive test that is able to detect evidence of myocardial ischemia or necrosis.

Severe ischemia produces regional wall motion abnormalities (RWMAs) that can be visualized echocardiographically within seconds of coronary artery occlusion. These changes occur prior to the onset of electrocardiographic changes or the development of symptoms. The Regional wall motion abnormalities reflect a localized decrease in the amplitude and rate of myocardial excursion, as well as a blunted degree of myocardial thickening and local remodeling. **Lang RM. et al, 2005**

Assessment of segmental function and overall LV performance provides prognostic information and is essential when MI is extensive, as judged by use of enzymatic criteria, or when MI is complicated by shock or profound HF. In part, this assessment is done to identify potentially surgically correctable complications and to detect true ventricular aneurysms, false ventricular aneurysms, or thrombi. **Møller JE. et al, 2008**

Imaging is also useful in detecting pericardial effusion, concomitant valvular or congenital heart disease, and marked depression of ventricular function that may interdict treatment in the acute phase with beta-adrenergic blockers. Echocardiography is also helpful in delineating recovery of stunned or hibernating myocardium. **Hillis GS. et al, 2006**

Doppler echocardiography is particularly useful in estimating the severity of mitral or tricuspid regurgitation; in detecting ventricular septal defects secondary to rupture; in assessing diastolic function; in monitoring cardiac output, as calculated from flow velocity and aortic outflow tract area estimates; and in estimating pulmonary artery systolic pressure. **Perez de Isla et al,2006**

Normal walls show a progressive increase in contractility (motion and thickening). Dead segments have poor motion and no thickening, and contractility fails to increase with high stimulation. Viable but jeopardized myocardium (ischemic myocardium) shows a biphasic response, wherein the contractility increases at lower doses of dobutamine and declines with perceptible wall-motion abnormalities at high doses of dobutamine. This kind of response is characteristic of ischemic myocardium and is most often the result of coronary stenosis. **Davi G. et al, 2007**

Percutaneous Coronary Interventions for Myocardial Revascularization

In 1929, a young surgical resident from Germany was tooling around in an attempt to find a safe and effective way to inject drugs for cardiac resuscitation. He anesthetized his left elbow, inserted a catheter into his antecubital vein, and confirmed the position of the catheter tip in the right atrium by use of radiography, thus performing the first documented human cardiac catheterization. **Mueller RL et al, 1995**

Forssmann further elaborated on his experiments to include intracardiac injection of contrast material through a catheter placed in the right atrium. By 1958, Mason Sones had performed selective coronary arteriography in a series of more than 1,000 patients. **Dotter CT. et al, 1964; Forssmann W. et al, 1974**

Melvin Judkins, a radiologist who had studied coronary angiography with Sones, introduced a series of specialized catheters and created his own system of coronary imaging in

1967 and perfected the transfemoral approach. **Mueller RL. et al, 1995**

Meanwhile in 1974 Andreas Gruentzig in Zurich substituted a balloon-tipped catheter for the rigid dilator and inaugurated the first peripheral balloon angioplasty in a human. **Gruentzig A. et al, 1979**

After perfecting coronary angioplasty in animals, Gruentzig then went on to perform intraoperative balloon angioplasty on the human heart for the first time. Soon thereafter, Gruentzig and his colleagues described their technique of percutaneous transluminal coronary angioplasty (PTCA) as used in a series of 50 patients. **Hurst JW. et al, 1986**

This Gruentzig technique was widely adopted and universally applied. The era of percutaneous coronary intervention had arrived. This technique quickly evolved into applications such as coronary atherectomy (1986) and coronary stenting (1987) and by 1997, angioplasty had become one of the most common medical interventions in the world. **Trikalinos TA. et al, 2009**

Currently, mortality rates for PCI from experienced operators in large series range from 0.5 to 1.7 percent. Overall, the improvements in devices, the use of stents, and aggressive antiplatelet therapy have significantly reduced the incidence of major peri-procedural complications of PCI in the last 20 to 25 years. This is evidenced by the fact that, the need for emergent coronary bypass surgery (CABG) decreased in two series from 1.5% in 1992 to 0.14% in 2000,and from 2.9% in 1979 to 1994 to 0.3% in 2000 to 2003. **Keeley EC. et al, 2003**

Primary percutaneous coronary intervention (PCI) to restore coronary blood flow is the current standard of care for ST-elevation myocardial infarction (STEMI) PCI. It carries a class IA recommendation from the American College of Cardiology (ACC)/American Heart Association (AHA) and 2005 Society for Cardiovascular Angiography and Interventions (SCAI) PCI guidelines. In addition the Centers for Medicare & Medicaid Services (CMS)/The Joint Commission have established a door-

to-balloon time of less than 90 minutes as one of the core clinical performance measures. **Keeley EC. et al, 2003**

Drug-Eluting Stents

Drug-eluting stents are metal stents that have been coated with a polymer containing an anti-proliferative agent, gradually released over time after the stent is inserted. Theoretically, this should provide sustained inhibition of the neointimal proliferation (the process that is responsible for restenosis) occurring as a result of vascular injury. The so-called first-generation drug-eluting stents released sirolimus, rapamycin, a natural cytostatic macrocyclic lactone with potent antiproliferative, anti-inflammatory, and immunosuppressive effects, acting by inhibiting the activation of the mammalian target of rapamycin (mTOR), ultimately causing arrest of the cell cycle, or paclitaxel, a chemotherapeutic agent that suppresses assembly and stabilization of microtubule. **Morice M. et al, 2002**

The Randomized Study utilizing the sirolimus-eluting Velocity Balloon Expandable Stent (RAVEL) demonstrated a stupendous 0% rate of restenosis, as measured by angiography, and complete inhibition of neointimal hyperplasia in the group that received a sirolimus-eluting stent. While 23% of the control group at one year required percutaneous revascularization of the treated lesion, the study group that received a sirolimus-eluting stent group required 0% revascularization. This study led to the approval of the device in Europe. **Moses JW. 2003**

The SIRIUS trial confirmed the safety and efficacy of the sirolimus-eluting stent in single, previously untreated coronary artery lesions, with a lower rate of in-stent restenosis than found with otherwise identical bare-metal stents (3.2% vs. 35.4%, $P<0.001$). More studies confirmed that DES appeared to be superior to bare-metal stents (BMS) and to balloon angioplasty in reducing the magnitude of neointimal proliferation, the incidence of clinical restenosis, and the need for vascular re-intervention. **Stone GW. et al, 2007**

2. Risk Stratification after STEMI

Initial risk stratification should be performed early with the use of information available at the time of presentation. However, risk assessment is a continuous process that requires recalibration on the basis of data obtained during the hospital stay. Such data include the success of reperfusion therapy, events that occur during the hospital course (such as hemorrhagic complications), and the findings from noninvasive and invasive testing, particularly as they relate to the assessment of LV systolic function. **O'Gara et al, 2013**

For example, in patients treated with fibrinolytic therapy, clinical and ECG indicators of failed reperfusion identify individuals who should undergo urgent coronary angiography with intent to perform PCI. In addition, the emergence of HF or significant LV systolic dysfunction is among the strongest predictors of higher-mortality risk after STEMI. Stable patients with a low risk of complications may be candidates for early discharge. **Wijeysundera HC. 2007**

Among patients with STEMI managed with fibrinolysis, it has been suggested that an uncomplicated course after 72 hours of hospitalization identifies a group with sufficiently low risk to enable discharge. **Borgia F. et al, 2010**

Use of Noninvasive Testing for Ischemia before Discharge:
Recommendations
CLASS I
1. Noninvasive testing for ischemia should be performed before discharge to assess the presence and extent of inducible ischemia in patients with STEMI who have not had coronary angiography and do not have high-risk clinical features for which coronary angiography would be warranted .(Level of Evidence: B)

CLASS IIb
1. Noninvasive testing for ischemia might be considered before discharge to evaluate the functional significance of a non-infarct

artery stenosis previously identified at angiography. (Level of Evidence: C)
2. Noninvasive testing for ischemia might be considered before discharge to guide the post-discharge exercise prescription. Level of Evidence: C. **O'Gara et al, 2013**

Noninvasive testing for ischemia provides valuable information about the presence of residual ischemia in patients who have not undergone cardiac catheterization during initial management of STEMI and may be useful in assessing the functional significance of a non-infarct artery stenosis identified at angiography. In the latter instance, stress imaging to localize ischemia would be appropriate. Exercise testing early after STEMI may also be performed to
1) Assess functional capacity and the ability to perform tasks at home and at work,
2) Evaluate the efficacy of medical therapy, and
3) Assess the risk of a subsequent cardiac event. Symptom-limited exercise testing is a key feature of the intake evaluation for enrollment in a program of cardiac rehabilitation2weeks after discharge. **Thomas RJ. et al, 2010**

Low-level exercise testing after MI appears to be safe if patients have undergone in-hospital cardiac rehabilitation, including low-level exercise; have had no symptoms of angina or HF; and have a stable baseline ECG 48 to 72 hours before the test. **Thomas RJ. et al, 2010**

Two different protocols have been used for early post-MI exercise testing: the traditional submaximal exercise test (done at 3 to 5 days in patients without complications) or a symptom-limited exercise test (done at 5 days or later) without stopping at a pre-specified target heart rate or metabolic equivalent level. RCTs of early exercise testing after PCI have excluded patients with recent MI. **Jain A. et al, 1993**

Limited data exist on the safety of early symptom-limited exercise testing after MI; therefore, clinical judgment must be

used. Pharmacological stress myocardial perfusion imaging has been shown to have predictive value for post-infarction cardiac events and is useful and safe in patients who are unable to exercise. **Jain A. et al, 1993**

The optimum timing for provocative testing for ischemia after STEMI remains unresolved. It is argued that a pre-discharge exercise test may provide psychological benefit to the patient and will permit detection of profound ischemia or other indicators of high risk that could be associated with post-discharge cardiac events that might occur before a symptom-limited stress test scheduled weeks later. A pre-discharge study also provides parameters for exercise prescription in the first few days after return home, before enrollment in cardiac rehabilitation. **Roffi M. et al, 2003**

On the other hand, deferring exercise testing until approximately 3 weeks after STEMI in clinically low-risk patients appears safe and reasonable and enables more optimal assessment of functional capacity. It is the consensus of the writing committee that patients without complications who have not undergone coronary angiography and who might be potential candidates for revascularization should undergo provocative testing before hospital discharge. In patients with non-infarct artery disease who have undergone successful PCI of the infarct artery and have an uncomplicated course, it is reasonable to proceed with discharge and plans for close clinical follow-up with stress imaging within 3 to 6 weeks. **Gibbons RJ. et al, 2006**

Viable myocardium refers to reversible dysfunctional myocardium resulting from CAD. Reversible myocardial dysfunction in the setting of chronic CAD has been referred to as “hibernating myocardium.” Earlier descriptions of this entity emphasized the presence of a match between the decrease in myocardial perfusion and the presence of regional dysfunction. However, more recent studies have shown that contractility may

be reduced despite the presence of normal or only moderately reduced myocardial perfusion at rest. **Meluzin J. et al, 1998**

Most stress echocardiography protocols are centered on the detection of contractile reserve and have used inotropic stimulation with dobutamine. **Naqvi T. et al, 1999**

However, other modalities of stress echocardiography have been applied, including exercise, post-premature ventricular contraction stimulation, enoximone, and low-dose dipyridamole. **Eichhorn E. et al, 2003**

In comparison with the assessment of viability using nuclear perfusion tracers or contract echocardiography, a lower extent of interstitial fibrosis and greater percentage of viable myocytes are needed for the detection of contractile reserve by dobutamine echocardiography. **Nagueh et al, 1999**

This probably accounts for the higher sensitivity but lower specificity of myocardial perfusion imaging compared with dobutamine echocardiography in the detection of viable myocardium. Both low- and high-dose protocols have been shown to be useful for detection of viability. Earlier studies examined low-dose dobutamine, whereas other investigators emphasized the importance of reaching at least 85% of target heart rate in an attempt to uncover the presence of ischemia. **Nagueh et al, 1999**

Wall thickness should be assessed on the resting echocardiographic images. Segments that are thinned and bright (likely a result of advanced fibrosis) rarely recover. It is also useful to examine the mitral inflow pattern, particularly in patients who have received adequate medical therapy at the time of imaging. A pattern of restrictive LV filling is associated with few viable segments and a low likelihood of functional recovery after revascularization. **Eichhorn E. et al, 2003**

Baseline imaging should include assessment for the presence of significant valvular disease that may alter surgical plans. After adequate baseline data have been obtained, dobutamine infusion is begun. An initial infusion of dobutamine at 2.5 μg/kg/ min, with gradual increase to 5, 7.5, 10, and 20μg/kg/min, is frequently used. **Elsasser A. et al,1997**

The advantage of the higher dose dobutamine is the potential to elicit ischemia. Dysfunctional myocardium responds to dobutamine in one of 4 ways that are most likely to be appreciated when the response to both high and low doses of dobutamine are considered. These responses include biphasic response (augmentation at a low dose followed by deterioration at a higher dose), sustained improvement (improvement in function at a low dose without deterioration at higher doses), worsening of function, and no change in function. **Bito V. et al ,2005**

The sensitivity of dobutamine echocardiography in predicting functional recovery (which varies depending on the protocol used) ranges from 71% to 97%, with a specificity ranging from 63% to 95%. **Bito V. et al, 2005**

Patients with a large area of viable myocardium (> 25% of LV) have a high likelihood of improvement in EF and a better outcome after revascularization compared with patients with less or no contractile reserve. **Bito V. et al, 2005**

Although presence of viability has been defined in various ways, it is recommended that improvement by at least one grade in two or more segments be demonstrated. A substantial amount of viable myocardium detected by low-dose dobutamine echocardiography has been shown to prevent ongoing remodeling after revascularization and to be associated with persistent improvement of heart failure symptoms and a lower incidence of cardiac events. **Iyer V. et al, 2005**

Cardiac MRI in post-STEMI assessment

Myocardial infarction (MI) can be detected with high resolution using a protocol known as late gadolinium enhancement CMR. Gadolinium is given intravenously and CMR is performed after a delay, using an inversion recovery sequence. Little gadolinium enters areas of normal myocardium, because there is uniform tightly packed muscle, and gadolinium is an extracellular contrast agent. However, the extracellular compartment is expanded in areas of MI because of cellular rupture, and therefore differential distribution occurs. **Elliot et al, 2005**

The kinetics of entry of gadolinium into the MI territory is delayed and the optimal time for imaging of the distribution of gadolinium is after 10 to 15 minutes. By nulling (forcing to near-zero) the normal myocardial signal with adjustment of the inversion time, the area of infarction can be demonstrated with extremely high contrast relative to the black normal myocardium. A simple mnemonic is that "bright is abnormal." **Wu E. et al, 2001**

The transmural distribution of MI can be visualized in vivo for the first time using this technique because of its high resolution. Animal models have validated this In humans, late gadolinium enhancement CMR detects Q wave and non-Q-wave MI accurately and with such high sensitivity that small MIs can be demonstrated that are usually not apparent using gated perfusion single-photon emission computed tomography (SPECT; also, microinfarcts can be shown after percutaneous coronary intervention. **Wagner A. et al, 2003**

In the acute setting, the extent of late gadolinium enhancement is related to the magnitude of cardiac enzyme release and the functional outcome after recovery. Late gadolinium enhancement CMR reveals a permanent record of MI (both acute and chronic) and is proving very useful clinically for the diagnosis of MI in cases of doubt, or when other techniques are

inconclusive. The technique has clarified the pathological significance of Q waves after MI. It has good inter-study reproducibility, suggesting a useful role in studies of therapies for limiting MI in the acute setting. In the setting of acute MI, data have shown that the area at risk from coronary occlusion can be determined from T2-weighted imaging because the severely ischemic but non-infarcted myocardium becomes edematous; this significantly lengthens T2, which increases the signal. **Selvanayagam JB. et al, 2005**

The increase in T2 signal persists for many days, allowing edema to be imaged well after the acute event. The area at risk (T2 scan) is larger than the final infarction (late gadolinium enhancement scan) when myocardial salvage has occurred with physical or pharmacological intervention. This makes the combination of these two scans very attractive for studies of techniques to improve salvage and thence prognosis. Late gadolinium enhancement has been shown to be a major predictor of cardiac events in patients without a history of infarction, but in whom infarction is nonetheless present. **Moon JC. et al, 2002**

Further work has shown that CMR can differentiate between the densely bright infarct core and the adjacent peri-infarct zone, which appears with lower signal intensity because of the admixture of infarct and viable tissue. The greater the extent of the peri-infarct zone, the greater the likelihood of future cardiac death and events. **Mahrholdt H. et al, 2002**

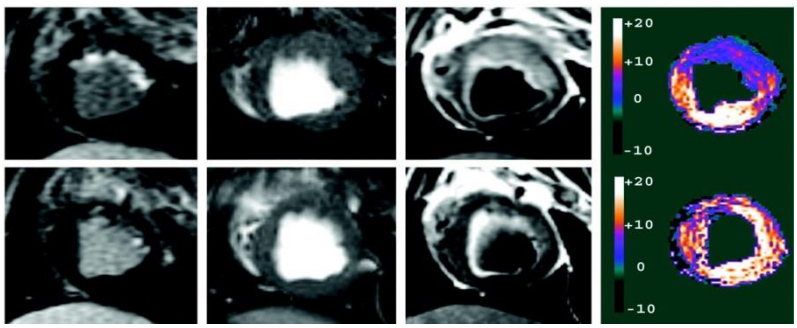


Figure 7: MRI findings in subendocardial infarction. **Aletras AH. et al, 2006**

3. Assessment of myocardial viability

The first descriptions of what would today be recognized as «viable myocardium» appeared in the 1970s, when it was observed that ventricular dysfunction reverted after revascularization in some patients with antecedents of acute myocardial infarction (AMI). The concept of viability is the opposite of that of necrosis, which implies an irreversible alteration in contractility. In patients with severe left ventricular dysfunction of ischemic origin, revascularization leads to improvements in ventricular function, survival and prognosis. Such improvements may be due to the presence of myocardial viability. **Chatterjee K. et al, 1973.**

From the clinical perspective, viable myocardium can be defined as myocardium in which contractile function is expected to improve, or in which remodelling can be avoided, once blood flow has been restored.

Simple diagnostic methods such as the electrocardiogram, resting echocardiography, and ventriculography are available to detect myocardial necrosis. Assessing myocardial viability poses two difficulties. In the first place, viability is not a dichotomous concept, as there are degrees of viability ranging from complete absence to total normality. In the second place, the lack of a standard reference model means that precise assessment of myocardial viability is not possible at present, so that results obtained with current assessment methods may be open to discussion. **Schulz R. et al, 2000**

MECHANISMS OF VIABLE DYSFUNCTIONING MYOCARDIUM

In myocardium which suffers acute, subacute or persistent perfusion defects, nonfatal ischemia can occur, and in such cases viability is maintained but resting contractile function is altered. Responses to such nonfatal ischemia include stunning and hibernation. In both of these states, cell dysfunction may be reversed once coronary flow is restored. The terms myocardial hibernation and stunning are currently accepted within the cardiology community, although their clinical application has

been limited because they are difficult to determine precisely. The myocardium is said to be stunned when transitory post-ischemic contractile dysfunction is present after coronary flow has been restored. After revascularization, contractile dysfunction persists temporarily and is followed by late recovery. Hibernating myocardium is believed to be the consequence of discordance between flow and function, in which contractile function is altered as a response to a reduction in blood flow. **Redwood SR. et al, 1998**

Various mechanisms may be responsible for flow defects, including persistent perfusion defects at rest, reductions in the coronary flow reserve, or repeated episodes of ischemia and accumulated stunning. Recovery of contractile function once coronary flow is restored is, however, independent of the mechanism that produces hibernation. As with viability, hibernation should not be considered a dichotomous concept, but can be conceived of as a reaction involving progressive tissue dedifferentiation, which can eventually result in apoptosis. The more severe and longer-lasting the ischemic injury, the greater the degree of myocardial degeneration. In general, the study of viability in pre-revascularization patients means studying hibernating myocardium. **Redwood SR. et al, 1998**

In viable myocardium, cell membrane integrity is typically retained, and there is some mitochondrial activity, together with an active glucose metabolism, existence of coronary flow, and the presence of contractile reserve. AMI produces irreversible myocardial damage, and the extent of this damage will determine functional recovery in the ventricular wall and the possibility of avoiding remodelling. Irreversible damage to the myocytes alters their metabolism and contractile function, and leads to their replacement with scar tissue and subsequent loss of contractile muscle mass. **St. Louis J.D. et al, 2000**

IMPORTANCE OF DEFINING VIABILITY IN PRE-REVASCULARIZATION PATIENTS

Assessing myocardial viability is of particular interest in patients in whom regional contractility is severely affected, as it helps to determine which segments of ventricular wall are viable

and may be suitable for revascularization. In over 50% of patients with antecedents of electrocardiographically documented infarct, viable myocardial regions and necrotic tissue exist side by side. However, the prior existence of necrosis does not necessary affect segment contractility. In a prospective study, regional contractile dysfunction was observed in 33% of patients who had ischemic cardiomyopathy but no electrocardiographic evidence of infarct, and functional recovery after revascularization was found to occur in 85% of the dysfunctioning segments. From the point of view of prognosis, the most important factor is the existence of severe global ventricular dysfunction. In patients with coronary disease, depressed ejection fraction, and cardiac insufficiency - with or without angina - assessing myocardial viability can be helpful in deciding whether there is an indication for revascularization. The prevalence of viable myocardium in patients with ischemic cardiomyopathy and global contractile dysfunction of the left ventricle is considerable, and ranges between 29% and 55% depending on the series**. Taneja A. K. et al, 2010**

Determining viability in patients with left ventricular dysfunction is also important from the prognostic point of view. When treated conservatively, patients with depressed ventricular function and signs of viability have higher mortality than patients without viability. Likewise, revascularization has been shown to improve long-term prognosis in the former group, which may be explained by an improvement in overall ventricular function in patients with viability. In patients with ischemic cardiomyopathy, functional recovery after revascularization is a sufficient but not necessary condition for improved prognosis, as cases in which revascularization does not increase left ventricular ejection fraction may also present a favourable course. Where viability is present, revascularization improves both prognosis and functional class in these patients. **J. E. Møller, K et al, 2003.**

Determining the extent of viable myocardium to be revascularized allows thresholds to be defined above which improvements in global ventricular functioning and patients' functional capacity can be expected. Studies with cardiac magnetic resonance imaging (CMRI) in patients with AMI have

shown that the recovery of contractile function in ventricular segments depends on the extent of viable myocardium in the thickness of the ventricular wall. **L. E. J. Thomson et al, 2004.**

Diagnostic testing of myocardial viability

Living myocardium is characterized by preserved ventricular wall thickness, the presence of contractile reserve, cell membrane integrity, active myocyte metabolism, and the existence of blood perfusion. Diagnostic techniques for studying myocardial viability are based on detecting one or more of these markers. The preservation of ventricular wall thickness and contractile reserve are usually investigated using echocardiography or stress CMRI. Myocyte membrane integrity and blood perfusion can be evaluated using gammagraphy with thallium or technetium contrasts, positron emission tomography (PET), and contrast CRMI. PET and CRMI spectroscopy can detect metabolic defects in nonviable myocardium. **K. Shan G. et al, 2004**

The importance of these markers is relative, as myocardial necrosis may not be transmural and may coincide with viable myocardium in the same segment of the ventricular wall. The ideal diagnostic technique would be one which provided sufficient spatial resolution to determine the quantity of viable myocardium in the same ventricular segment. Of all the techniques mentioned, CMRI provides the best spatial resolution. **L. E. J. Thomson, et al 2004**

The image-based diagnostic techniques used in cardiology aim to identify the presence and extent of viable myocardium using noninvasive methods. Such techniques include dobutamine echocardiography, thallium and technetium scintigraphy, PET and more recently CMRI. The choice of technique to be used will be based on availability and experience. Because of its high sensitivity, PET has generally been considered the gold standard for determining viability; however, its limitations and cost have restricted its use. **P. G. Camici et al, 2008**

Markers of myocardial viability

Ventricular wall thickness

Studies have indicated that nonviable myocardium is frequently associated with a significant thinning of the ventricular wall. When myocardial necrosis leads to considerable myocyte loss, a process of fibrosis begins which results in loss of myocardial wall thickness. The small number of living myocytes remaining is insufficient to recover contractility once reperfusion is achieved after revascularization. **La Canna GL. et al, 2000**

Echocardiography

This is a quick and accessible method for estimating reductions in thickness in the akinetic or dyskinetic wall. Increased refraction may also be a sign of fibrosis. When using echocardiography, a reduction in the diastolic thickness at rest to below 5 mm, and the presence of akinesia or dyskinesia, indicate nonviable myocardium. Such a finding has high negative predictive accuracy for viability, and means that more complex diagnostic procedures can be avoided. Conversely, a diastolic thickness of over 5 mm provides a sensitive (100%), but not very specific (28%) marker of viability. Although echocardiography is accessible and economic, its limited specificity and poor reproducibility mean that it is of little practical use. Where wall thickness is reduced, more specific markers need to be used. **Cho S. et al, 2002.**

Contractile reserve

One objective of revascularizing viable myocardium is to recover contractile function. Echocardiography and stress CMRI can be used to determine the level of contractile reserve in viable myocardium, and to predict its functional recovery. However, even where contractile reserve is not shown to exist, viability may still be present. In some patients with a small

proportion of viable myocardium, revascularization may not lead to recovery of contractility in the myocardial wall, but it can avoid ventricular remodelling. **Klein C. et al, 2002.**

Stress echocardiography

Contractile reserve is demonstrated using echocardiography in combination with stress-inducing protocols based on progressive exercise or continuous perfusion of drugs such as dipyridamole, nitroglycerin, postextrasystolic potentiators, enoximone and the catecholamines (including isoprenaline, adrenaline, dopamine and dobutamine). Enoximone is a positive inotropic drug which inhibits cyclic adenosine monophosphate (cAMP) phosophodiesterase, and in preliminary studies in small numbers of patients, it has shown the greatest diagnostic precision of the drugs listed, with a sensitivity and specificity of 88% and 89%, respectively. However, dobutamine stress echocardiography is the most widely used and best-documented stress echocardiographic technique for detecting myocardial viability. Dobutamine preferentially stimulates beta-1-adrenergic receptors. At low doses (5 and 10 μg/kg/min) it produces more of an inotropic than a chronotropic effect, leading to improved contractility in the hibernating myocardium. **Cho S. et al, 2002**

At higher doses, both the inotropic effect and heart rate are increased, thereby increasing oxygen consumption and ischemia in territories irrigated by stenosed coronary arteries. When significant coronary stenosis exists, once the existence of contractile reserve has been demonstrated at low doses of dobutamine, contractility worsens at ischemic doses. The result is a two-phase response consisting of initial improvement, indicating viability, and later worsening due to the flow defects which produce the induced ischemia. Such a two-stage response is characteristic of hibernating myocardium, and predicts recovery of ventricular function after revascularization. **Cho S. et al, 2002**

In comparison with single photon emission computed tomography (SPECT) and PET, dobutamine stress echocardiography shows greater specificity in the diagnosis of

myocardial viability (81% against 73%) and lower sensitivity (84% against 90%). **Sawada S. et al, 2000**

Cardiac magnetic resonance imaging

Infarcted viable myocardium may have lost contractile function because of perfusion defects, which produce significant stenosis in the coronary artery involved. In this case, when stress is induced by progressive doses of dobutamine or exercise, the result is the two-stage response described previously. Long experience with stress echocardiography means this procedure has been widely studied. However, some patients may not have an adequate ultrasonic window, and in these cases cardiac magnetic resonance imaging (CMRI) provides a useful alternative which has also proved reliable in identifying viable myocardium. **Gerber BL. et al, 2002**

With CMRI the window for studying the heart is not limited, and equipment incorporating the latest technical advances will ensure a quick and accurate exploration. Significant systolic thickening of any segment of the akinetic or dyskinetic ventricular wall observed using stress CMRI is indicative of viability. This marker is more accurate if it is combined with the wall thickness analysis referred to earlier. Although the monitoring of patients undergoing CMRI is complicated, there should be no additional risk if qualified personnel are available and adequate procedures are used. **Gerber BL. et al, 2002**

Gated SPECT

Obtaining isotopic images of myocardial perfusion, synchronized with electrocardiogram and gated SPECT, permits the simultaneous evaluation of perfusion and contractility at a global and segmental level. When this technique was used to assess viability by studying contractile reserve during dobutamine perfusion at 10 μg/kg/min, it provided a sensitivity of 96% and a specificity of 78% (the capacity of dobutamine gated SPECT at rest to predict contractile recovery after revascularization in dyssynergic myocardial regions. **Dilsizian Vet. al,2005**

Positron Emission Tomography

Cardiac positron emission tomography (cardiac PET) involves the administration of a tracer, Rubium-82, Ammonium-13, Water-15, and Fluorine-18 deoxyglucose (18-FDP). Of these various positron-emitting radiotracers, which are peripherally introduced, a glucose analogue; Fluorine-18 deoxyglucose (18-FDP), is the most validated radiotracer for cardiac PET metabolism. Glucose 11-C, free fatty acid (FFA), and Oxygen are also metabolism tracers, however glucose is the preferred metabolite for assessment of ischemic or hypoxic myocardium. The most commonly used criterion to identify viable myocardium is the uptake and metabolism of 18-FDP, which is dependent on viable myocytes, with viable glucose transporters. Viable myocardium displays normal perfusion and normal 18F-FDG uptake, hibernating myocardium displays reduced perfusion and preserved 18F-FDG uptake but, scarred tissue will display no perfusion and absent 18F-FDG uptake. **Lautamäki R. et al,2009**

Strain rate imaging

An increase in strain rate, defined as the tissue velocity gradient between two points within a myocardial territory, by more than −0.23 (1/s) with low-dose dobutamine (10 μg/kg body weight) has a sensitivity of 83% and a specificity of 84% for predicting viability compared to FDG PET . **Bansal M. et al, 2010**

It was found that global LV strain, the change in the length of a region of interest from end-diastole to end-systole, assessed with novel automated function imaging (AFI) using speckle tracking from 2D gray-scale images, predicted patients who had an improvement in LV ejection fraction following myocardial infarction. Baseline AFI of −13.7% had a sensitivity of 86% and a specificity of 74% to predict LV functional recovery at 1 year. Also, longitudinal strain and strain rate imaging at rest and low-

dose dobutamine were shown to be predictors of functional recovery after revascularization. **Bansal M. et al, 2010.**

4. Strain rate imaging

Cardiac motion and deformation occur in three dimensions. The heart rotates and repositions (circumferential), shortens and dilates in longitudinal direction and thickens and relaxes in radial orientation during cardiac cycle. **Perk G. et al, 2007**

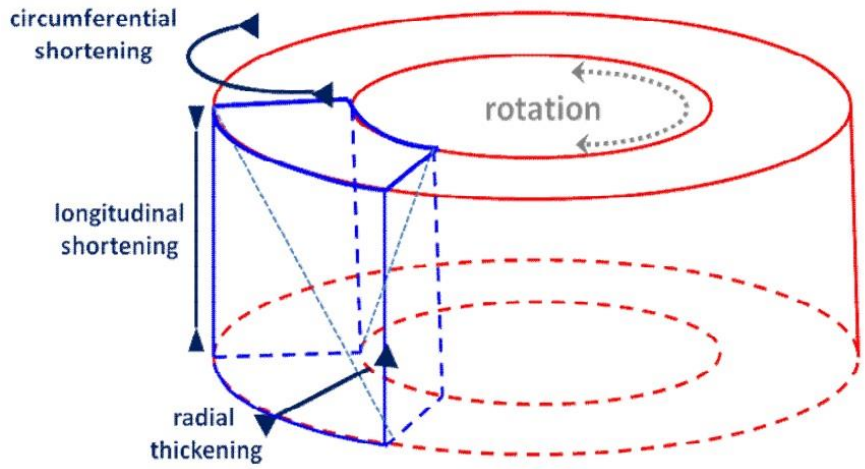


Figure 8. 3D-illustration of a hypothetical myocardial segment. Myocardial motion and deformation consist of three major components: longitudinal, radial and circumferential. The total deformation of a myocardial segment is very complex and includes shortening, thickening and rotatory movement. **A. Stoylen et al, 2015**

Definitions related to Motion; Velocity and Displacement

The amount of motion normalized to time is defined to be the velocity of the object. It is thus the displacement of the object divided by the time required to make the displacement. [The object in Tissue Tracking Echocardiography (TTE) is mainly a single point or a Region of Interest (ROI).] Hence, its unit is cm/s. Velocity is used to describe how fast the myocardium moves in a particular direction. During systole myocardium travels towards apex and velocities are positive in nature. During diastole heart muscle moves to its initial position and diastolic velocities are negative. Displacement is the measure defining how far a myocardial segment moves from an initial point. In fetal

echocardiography its unit is mm and indicated positively. **Dandel M. et al, 2009**

Definitions related to Deformation

Strain

Strain (S) is defined as the deformation of an object, normalized to its original shape. In a one-dimensional concept the only possible deformation is lengthening or shortening. This is illustrated in Figure 9. **Blessberger H. et al, 2010**

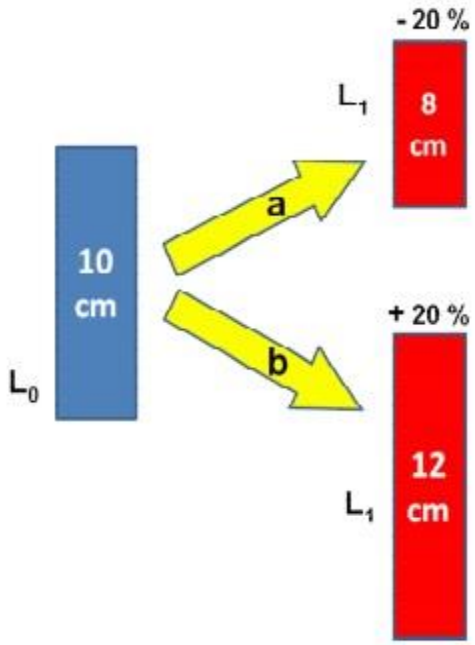


Figure 9: Strain pattern of a region of the heart in the longitudinal direction. L0; original length at end diastole, L; length after deformation. At the right lower corner a Strain curve example. **Blessberger H et al, 2010**

By convention, the expression is defined in such a way that lengthening is represented as a positive value for S, while shortening is represented by a negative value (Figure 10). When the length of an object is known before (at the state of L0) and at the end of deformation (L1 at a random time frame) Lagrangian strain can be defined.

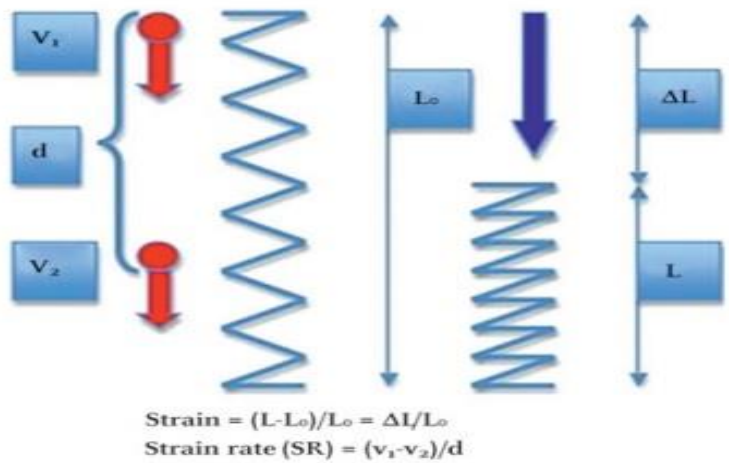


Figure 10. Acquisition of Lagrangian strain through shortening and lengthening of cardiac tissue. **A. Stoylen et al, 2015**

However the deformation of the object can also be expressed relative to the length at a previous time instance (natural strain). According to this approach it is possible to evaluate the amount of deformation occurring during an infinitesimal time interval. For cardiac applications, it has been suggested that it may be more appropriate to measure natural strain, since the values measured are less dependent on the definition of the initial length L0 rather than on a previous time instance. **Blessberger H. et al, 2010**

Speckle-tracking echocardiography has recently emerged as a quantitative ultrasound technique for accurately evaluating myocardial function by analyzing the motion of speckles identified on routine 2-dimensional sonograms. It provides non-Doppler, angle-independent, and objective quantification of myocardial deformation and left ventricular systolic and diastolic dynamics. By tracking the displacement of the speck-les during the cardiac cycle, strain and the strain rate can be rapidly measured offline after adequate image acquisition. **Geyer H. et al, 2010**

The term speckle tracking implies that this technique is principally based on the analysis of speckles during the cardiac

cycle. Single speckles are merged in functional units (kernels) that are in turn univocally identifiable given the peculiar disposition of the speckles. As a result, each kernel constitutes a sort of ultrasound fingerprint that can be tracked by software during the entire cardiac cycle. **Geyer H. et al, 2010**

According to the indications derived from the literature and to reduce random noise, each sample for a speckle-tracking echocardiographic analysis must be obtained by averaging at least 3 consecutive heart cycles, setting the frame rate of the routine 2-dimensional image acquisition between 60 and 110 frames per second. **Buchalter MB. et al, 1990**

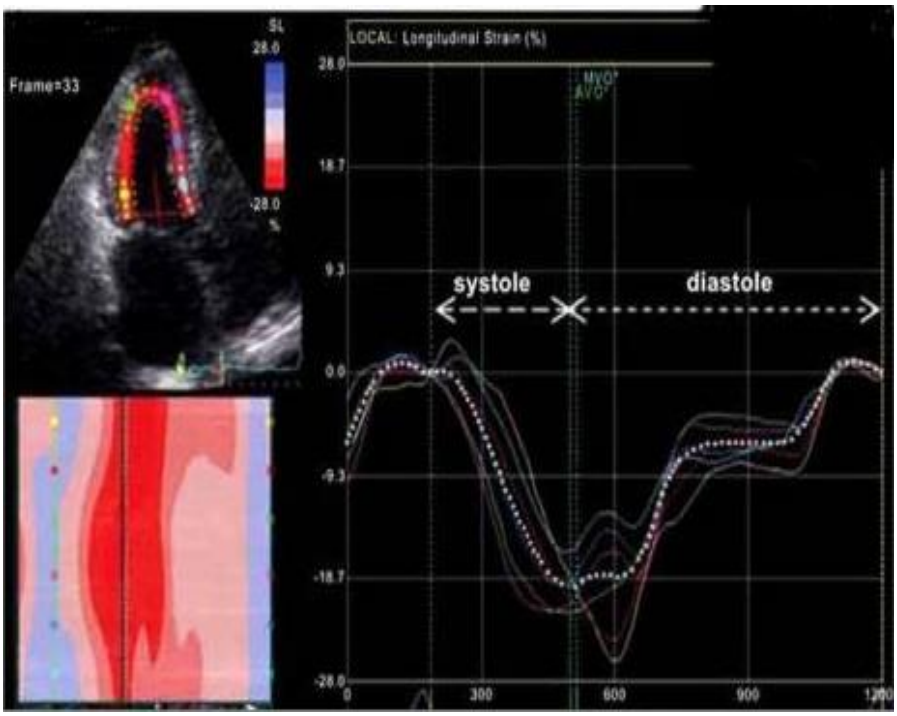


Figure11. Speckle-tracking echocardiographic analysis of myocardial deformation showing measurements of longitudinal strain**. Dandel M. et al, 2009**

Term Definition

Table2 . Speckle-Tracking Echocardiographic Terminology

How to Obtain Strain Parameters

Strain	Myocardial deformation
Strain rate	Myocardial deformation rate velocity
Longitudinal strain	Base-to-apex–directed deformation
Radial strain	Myocardial deformation directed radially toward the center of the left ventricular cavity
Circumferential strain	Left ventricular myocardial shortening observed in a short-axis

Image Acquisition

Images for speckle-tracking echocardiographic analysis, currently performed offline, are obtained and recorded by using conventional 2-dimensional gray scale echocardiography during breath holding with stable electrocardiographic tracing. Care must be taken to obtain true apical and short-axis images using standard anatomic landmarks in each view and to avoid foreshortening of the analyzed myocardial structure, thus allowing a more reliable delineation of the endocardial border. The optimal frame rate for the 2-dimensional image acquisition is set between 60 and 110 frames per second. **Shaw SM. et al, 2008**

These settings are recommended to combine high temporal resolution with acceptable spatial definition and to enhance the feasibility of the frame-to-frame tracking technique. It is recommended to begin with speckle-tracking echocardiographic analysis of an apical long-axis chamber view to select the frame corresponding to the aortic valve closure, which is a useful reference for the subsequent analysis. Apical 4- and 2-chamber view acquisitions are necessary for longitudinal strain and peak atrial longitudinal strain analysis. **Altiok E. et al, 2012**

Short-axis recordings, useful for radial strain, circumferential strain, and rotation analysis, are obtained from a standard parasternal probe position for the basal plane and from a more distal anterior or anterolateral position for the apical plane. To standardize acquisitions, the basal plane is identified as the plane including the tips of the mitral leaflets, whereas the apical plane is identified dis-tally to the papillary muscles as the plane just proximal to the level at which LV cavity end-systolic obliteration occurs. Particular attention should be paid to making the LV cross section as circular as possible. **Altiok E. et al, 2012**

Offline Analysis

Recordings are processed using specific acoustic-tracking software usually available on dedicated workstations, allowing for an offline semi-automated analysis of speckle-based strain. The endocardial surface of the myocardial segment analyzed is manually traced in apical and/or short axis views by a point-and-click approach. An epicardial surface tracing is then automatically generated by the system, thus creating a region of interest. After manual adjustment of the region of interest width and shape, the software automatically divides the region of interest into 6 segments, and the resulting tracking quality for each segment is automatically scored as either acceptable or unacceptable, with the possibility of further manual correction. Segments for which no adequate image quality can be obtained are rejected by the software and excluded from the analysis. **Belghiti H. et al, 2008**

Last, once the region of interest is optimized, the software generates strain curves for each selected myocardial segment. From these curves, the operator can obtain regional and global (by averaging values observed in all segments) peak and time-to-peak values. If the longitudinal strain analysis is performed in all 3 apical views, the software automatically generates a topographic representation of all 17 analyzed segments (bull's-eye acquisition). **Belghiti H. et al, 2008**

Clinical Applications

In general, speckle-tracking echocardiography may allow an unprecedented in-depth evaluation of myocardial systolic and diastolic dynamics across a broad range of physiologic and pathologic conditions beyond traditional echocardiographic techniques. For example, not only has a good correlation between longitudinal strain and the left ventricular ejection fraction (LVEF) been shown in several studies, but in addition, longitudinal strain provides a quantitative myocardial deformation analysis of each LV segment, also allowing for early systolic dysfunction detection in patients with a preserved LVEF. **Takigiku K. et al, 2012**

- Hypertension

Arterial hypertension is an ideal model for assessing the changes in different varieties of deformation occurring hand in hand with the development of LV concentric geometry (concentric remodeling and concentric LV hypertrophy). This is a crucial issue because experiences using standard echocardiography have shown that impairment of midwall fractional shortening of the circumferential fibers precedes the reduction of the LVEF. **Anwar A. et al, 2013**

Speckle-tracking echocardiography has furthered the understanding that the interaction of the different deformations is much more complex under these circumstances. In particular, it seems that longitudinal and radial strain are impaired when circumferential strain is still normal and LV torsion, also maintained in the normal range, acts as mechanistic compensation to preserve a normal ejection fraction (EF). **Anwar A. et al, 2013**

- Diabetes

In asymptomatic diabetic patients with a preserved LVEF, it has been shown that speckle-tracking echocardiography has the potential for detecting subclinical LV systolic dysfunction, which is unmasked by the alteration of longitudinal strain. In this view,

speckle-tracking echocardiography might provide useful information about the development of subclinical myocardial dysfunction in the diabetic setting before the overt appearance of diabetic cardiomyopathy. This evidence confirms previous experiences using either color tissue velocity imaging or Doppler-derived strain rate imaging. **Nakai H. et al, 2009**

- Coronary Artery Disease

It was reported that a lower longitudinal strain value in asymptomatic patients without wall motion abnormalities is a strong predictor of stable ischemic cardiomyopathy. **Choi JO. et al, 2009**

Studies in patients with acute myocardial infarction found that longitudinal strain is related to peak levels of cardiac troponin T and the LV infarct size. Moreover, when measured immediately after reperfusion therapy, longitudinal strain is an excellent predictor of LV remodeling and adverse events, such as congestive heart failure and death. **Choi JO. et al, 2009**

In addition, it has been shown that longitudinal strain correlates with the global and regional extent (transmurality) of scar tissue as evaluated by contrast-enhanced MRI.

A radial peak strain cutoff value of 17.2% predicts LV functional recovery after revascularization with accuracy similar to that of a cutoff value of 43% hyper-enhancement on MRI. A cutoff value of –4.5% for regional longitudinal strain discriminates between segments with a viable myocardium and those with transmural scar tissue on contrast-enhanced MRI, with sensitivity of 81.2% and specificity of 81.6%. **Bansal M. et al, 2008**

Recently, speckle-tracking echocardiography was used to validate an analysis of post-systolic motion, identified as LV regional myocardial motion after aortic valve closure, and showed that the post-systolic index represents an important quantitative marker for analysis of the ischemic myocardium.

However, data from studies on large populations are still lacking. **Voigt JU. et al, 2004**

- Valvular Heart Disease

Speckle-tracking echocardiographic analysis in patients with valvular heart disease has been mainly performed for the evaluation of LV function with stress (exercise or pharmacologic) testing. In asymptomatic patients with degenerative mitral regurgitation undergoing valvular surgery, limited exercise-induced longitudinal LV contractile recruitment, as assessed by speckle-tracking echocardiography with global longitudinal strain, predicts postoperative LV dysfunction. **Lancellotti P. et al,2008**

In patients with aortic stenosis or aortic regurgitation immediately after aortic valve replacement, there is a substantial increase in radial and circumferential strain, suggestive of how these myocardial deformation parameters critically depend on LV load conditions. **Becker M. et al,2007**

- Heart Failure

It has been shown that in hypertensive patients with heart failure and in patients with heart failure and a normal EF, LV longitudinal strain progressively deteriorates from New York Heart Association class I to class IV, with additional LV radial and circumferential systolic impairment occur-ring in New York Heart Association functional classes III and IV. **Park SJ. et al,2008**

As for LV rotation and torsion analysis, Park et al reported that systolic twisting, torsion, and diastolic untwisting are significantly increased in patients with mild diastolic dysfunction. In patients with advanced diastolic dysfunction and increased filling pressures, these parameters are normalized or reduced. **Kosmala W. et al,2008**

- Mechanical Dyssynchrony

Cardiac resynchronization therapy is an effective treatment option for patients with New York Heart Association functional

class III and IV heart failure who have an LVEF of 35% or less and QRS prolongation and who remain symptomatic despite optimal medical therapy. However, about 30% of patients fail to show a substantial benefit with cardiac resynchronization therapy, and several efforts have been made in recent years to identify non-responders be-fore implantation. A variety of echocardiographic parameters potentially suitable for predicting the response to cardiac resynchronization therapy have been tested. **Tanaka H. et al, 2009**

In a recent multicenter trial, none of 12 conventional and tissue Doppler-based echocardiographic indices of dyssynchrony was shown to be a reliable predictor of the response to cardiac resynchronization therapy. **Tops LG. et al, 2009**

However, strain parameters recently have been shown to have good reproducibility and accuracy in discriminating healthy patients from cardiac resynchronization therapy volumetric responders. **Nesser HG. et al, 2009**

- Cardiomyopathies

In patients with nonobstructive hypertrophic cardiomypathy and a preserved EF, speckle-tracking echocardiography has shown the capability to identify early major abnormalities of all strain components of myocardial deformation (longitudinal, circumferential, and radial strain). Another potential clinical application of speckle-tracking echocardiography is for differentiation of hypertrophic cardiomyopathy from athlete's LV hypertrophy based on the lower longitudinal strain values in patients with hyper-trophic cardiomyopathy who have a normal LVEF. **Stefani L. et al, 2009**

Patients and Methods

Forty nine patients were enrolled from Mai 2013 until December 2014 from the coronary care unit (CCU) at the hospital in Coburg. The Patients were diagnosed with ST elevation myocardial infarction patients based on their ECG, laboratory findings and symptoms at admission. A follow up study was undertook at 6 weeks after STEMI.

A written consent was taken from all recruited patients after clarifying the details of Stress-Echo and MRI- procedures and the possible complications. All obtained clinical and personal data was objected to medical data protection.

Inclusion criteria

Patients with acute ST elevation myocardial infarction documented by ECG, elevated cardiac enzymes, cardiac Troponin I and conventional echocardiography study.

Exclusion criteria

1- Patients with very poor acoustic window due to marked obesity or Chronic Obstructive Pulmonary Disease (COPD).
2- Patients with arrhythmia either ventricular or supraventricular.
3- Patients with absolute contraindications to stress test.
4- Patients with congenital heart diseases
5- Patients who are contraindicated to perform a cardiac MRI test (with pacemaker, cochlear implants and patients with diagnosed claustrophobia).
6- Acute myocardial infarction <4 days
7- Known relevant left main coronary artery stenosis or three vessel disease.
8- Manifest congestive heart failure
9- Hypertrophic obstructive cardiomyopathy
10- Acute pericarditis, myocarditis and endocarditis
11- Aortic dissection

All patients were subjected to

1- Full medical history. The onset, duration and progression of symptoms were precisely obtained from all patients.
2- Complete clinical examination, including heart and lung auscultation, checking of signs of manifested cardiac decompensation (peripheral edema, jugular venous distention or palpation of liver).
3- Standard 12 leads resting ECG.
4- Conventional resting transthoracic echocardiography study.
5- Dobutamine stress echocardiography (low dose dobutamine at 4 days and full stress dobutamine testing at 6 weeks).
6- Automated functional imaging (Speckle tracking) echocardiography study of left ventricle.
7- Cardiac MRI as the gold standard method in detecting myocardial viability.

Echocardiography

Examinations were performed with a digital ultrasonic device system (Vivid 9 2013, GE Vingmed Ultrasound, Horten, Norway). The patients were examined 96 hours after revascularization using M4S probe in left lateral position. In harmonic mode 2.0/4.3 MHz with maximal frame per second (FPS) count available at necessary sector width. Range of FPS was from 64 to 112 with mean value 83. **Lang RM. et al, 2015**

Conventional echocardiography study was done including 2D based M-mode measures of cardiac chambers and Ejection Fraction (EF%), pulsed and continuous wave Doppler studies, Color Doppler study, calculation of ejection fraction by Simpson`s method and analysis of wall motion abnormalities. Regional wall motion abnormalities were analyzed using wall motion score. **Lang RM. et al, 2015**

Dobutamine stress Echocardiography

All patients underwent low dose dobutamine stress echocardiography 4 days post-STEMI as well as a full dobutamine stress testing follow up study at 6 weeks.
-Patient was prepared for standard stress testing after obtaining a written consent.
-Intravenous access was obtained.
-Digital images were acquired at baseline (these loops are displayed and used as reference throughout the infusion).
-Continuous electrocardiogram and blood pressure monitoring were established.
-Dobutamine infusion began at a dose of 10 μg/kg/min.
-The infusion rate is increased every 3 minutes to doses of 20, 30, and 40 μg/kg/min.
-Peak images were acquired before termination of the infusion.
-Post-stress images were recorded after return to baseline.
-The patient was monitored until he or she returns to baseline status.

Whereas atropine was added in 0.5 mg fractional doses after the second stage of infusion up to the total dose of 2 mg. The infusion of dobutamine was stopped when age-adjusted HR limit was reached or when patients experiences criteria for terminating (angina pectoris or dyspnea)For safety reasons, the presence of minimum two persons during each study was mandatory. **Lancellotti P. et al, 2016**

Then total wall motion score were divided by number of analyzed segments i.e. 17 segments in order to calculate the wall motion score index with normal wall motion score index is 1 and higher values represented progressive greater degrees of left ventricular dysfunction. **Lancellotti P. et al, 2016**

Strain rate obtained by Speckle Tracking study

Left ventricle (LV) was recorded in 2D cine-mode in 3 views: - apical 4 chambers, apical 2 chambers and apical 3 chambers. Then LV was studied by offline analysis through the external

work station. Three points were selected in each view (2 points at the base and 1 point at the apex) then the program automatically tracked the endocardial border of LV in each view. Regional and global strain of LV were calculated automatically and expressed in Bull's eye form based on 17 myocardial segmentation system that showed average global strain and peak systolic strain of each myocardial segment giving it a specific color according to value of peak systolic strain. Color ranges between dark red for normal myocardial segments and dark blue for severely dyskinetic segments with hypokinetic and akinetic segments between those colors. The parameters were defined as the peak deformation in longitudinal direction achieved for assessed segment during systole, before the aortic valve closure. Correlations were calculated for global and regional longitudinal strain in all segments. **Bansal M. et al, 2013**

Cardiac MRI

Magnetic resonance imaging was performed using a 1.5-T scanner (Magnetom Vision Plus, Siemens, Erlangen, Germany) and a phased array body coil. Breath-hold cine images with a time resolution of 35 ms were acquired. Approximately 10 to 20 min after intravenous injection of 0.1 mmol/kg gadopentetate dimeglumine, late enhancement images were obtained from the long-axis views, followed by multiple short-axis slices covering the entire left ventricle. **Zhang S. et al, 2014**

A breath-hold segmented magnetization-prepared turbo gradient echo sequence was used. The basal and midventricular short axis slices were divided into6 segments, and the apical short axis slices were divided into 4 segments. In our study, findings in the apex were not used. In each of the LV segments, the area of the entire myocardium was manually drawn. Infarct was defined as areas with pixel intensities > 2 SD of the mean pixel intensity in normal myocardium in the same slice. In each segment, the infarct size was calculated as percentage of the total segment area. The total infarct size was reported as percent of

LV mass and in units of grams of the infarcted myocardium. **Zhang S. et al, 2014**

Primary PCI

After laboratory and electrocardiographically confirmation together with the presented symptoms of STEMI, the patients were transferred urgently to the heart catheter laboratory. A primary PCI was conducted through one of the interventional cardiology consultant through arterial access (either radial or femoral artery). No parallel admission of thrombolytic therapy was conducted.

Statistical analysis

Statistical analysis was performed using MedCalc V.12.1.4. (Frank Schoonjans Belgium). Continuous variables were expressed as means and standard deviations. Mean values were compared with t Student test for paired variables. Chi square test was used to test the dichotomous variables distribution. For comparison of parameters obtained by STE and AFI Pearson correlation coefficients were calculated and Bland–Altman analysis performed. For interobserver variability assessment we calculated coefficients of variance. Duration of STE and AFI calculations and interobserver agreement were assessed in the group of 12 randomly selected subjects. Receiver-operating characteristic (ROC) curves were constructed, and areas under curves were measured to determine cutoff values with maximum sensitivity and specificity. A p value < 0.05 was considered statistically significant. We performed a multivariate regression analysis to find the best method for estimating final infarct size using MRI as the reference method.

Results

We examined 49 patients in whom ST elevated myocardial infarction was diagnosed depending on the clinical presentation, ECG results and laboratory findings. The patients were subjected to primary PCI procedures in less than 6 hours of symptoms beginning. They were examined with echocardiography at rest and at low dobutamine stress on 4 days and at rest and high dobutamine stress on 6 weeks to determine the global and regional strain rate values. All patients were evaluated through cardiac MRI as a gold standard method of determining myocardial viability at 4 days and 6 weeks as well.

Women accounted for 49% of our study cohort (No. 24) whereas Men were 51% of the patients (No. 25). Thirty-one patients were hypertensive while twenty-one were already diagnosed with diabetes before admission with STEMI. Twenty-one of the studied group were smokers (57%) and twenty-four showed either elevated lipid profile or were taking lipid-lowering drugs. Five patients had experienced a previous acute coronary syndrome in their medical history while eight of them had previous coronary interventions (PCI) with stent implantation (Table 3).

The mean age in our study group was 64 years old $\pm$ 9.7 and mean Body mass index was 25 kg/m^2 $\pm$ 3.7. Troponin levels at 4 days post-infarction were 0.65 ng/ml $\pm$ 0.8 while at the control exam on 6 weeks were 0.24 ng/ml $\pm$ 0.4. Pro-BNP levels at 4 days were 696.0 pg/ml $\pm$ 404 and at 6 weeks showed an improvement to a level of 547 0 pg/ml $\pm$ 281 (Table 4).

	Number	Percentage
Gender		
Male	25	51%
Female	24	49%
Hypertension		
Non-hypertensive	18	36.7%
Hypertensive	31	63.3%
Diabetes mellitus		
Non-diabetics	28	57.1%
Diabetics	21	42.9%
Smoking		
Non-smoker	28	57.1%
Smoker	21	42.9%
Hyperlipidemia		
No	25	51%
Yes	24	49%
Previous ACS		
No	44	89.8%
Yes	5	10.2%
Previous PCI		
No	41	83.7%
Yes	8	16.3%

Table 3 . Demographics of patients who were enrolled in the study. ACS (Acute coronary syndrome) . PCI (percutaneous coronary intervention)

				Deviation
Age	39	84	64.39	9.781
BMI	19	33	25.41	3.774
EF (4d)	27	63	47.41	8.715
EF (6w)	25	66	49.67	8.680
Global SR-Rest (4d)	-18.3	-7.5	-14.147	2.8157
Global SR-Stress (4d)	-22.5	-6.9	-16.292	3.7278
Global SR-Rest (6w)	-19.9	-7.1	-15.745	3.3786
Global SR-Stress (6 w)	-22.8	-6.5	-17.245	4.1164
Regional SR-Rest (4d)	-13	7	-3.53	4.491
Regional SR-Stress (4d)	-18	11	-8.27	5.674
Regional SR-Rest (6w)	-16	4	-7.65	4.608
Regional SR-Stress (6w)	-23	10	-13.86	6.272
Troponin-4d	0.01	4.04	0.6544	0.82580
Troponin-6w	0.00	1.90	0.2458	0.40400
Pro-BNP-4d	73	12,377	696.0	404
Pro-BNP-6w	54	14,512	547.0	281

Table 4 . Mean and standard deviation of Age, Body mass index (BMI), Ejection fraction (EF), Global and regional strain rate at rest and under stress (SR-Rest, SR-Stress) at 4 days and 6 weeks, Troponin levels at 4 days and 6 weeks and Pro-Brain Natriuretic Peptide at 4 days and 6 weeks.

Gender difference was not significant in both global and regional, resting and stress strain obtained with speckle tracking neither at 4 days nor at 6 weeks, p value > 0.5. Hypertension was a significant factor in determining global stress strain rate at 4 days, p value 0.16, while it did not have any significance at resting and stress strain at 6 weeks. Diabetes mellitus (DM) was highly significant in affecting global strain rate at rest and at stress on 4 days, p value 0.017 and 0.001 respectively. At 6 weeks follow up, DM was not significant at rest or at stress. Both smoking and Hyperlipidemia have not shown any significance in relation to global and regional, resting and stress strain obtained with speckle tracking. Throughout the patients who had a previous ACS showed significance in affecting global stress strain

at 6 week, p value 0.3. The patients with previous stenting had significantly lower global and regional strain rate at stress at both 4 days and 6 weeks in comparison to patients with no history of PCI, p value 0.02 and 0.12 respectively. The significance of such values were determined on the basis of improvement or worsening the strain rate values in resting and stress studies at 4 days and at 6 weeks of follow up.

Age and BMI were not significant to affect global stress strain, whether as an improvement or worsening, at the performed follow up study at 6 weeks. Whereas Troponin showed a significance of predicting the worsening of stress strain values at the follow up with a p value of 0.005. Pro-BNP level had also shown a statistical significance in detecting the global stress strain outcome at 6 weeks with a p value of 0.2 (Figure 12).

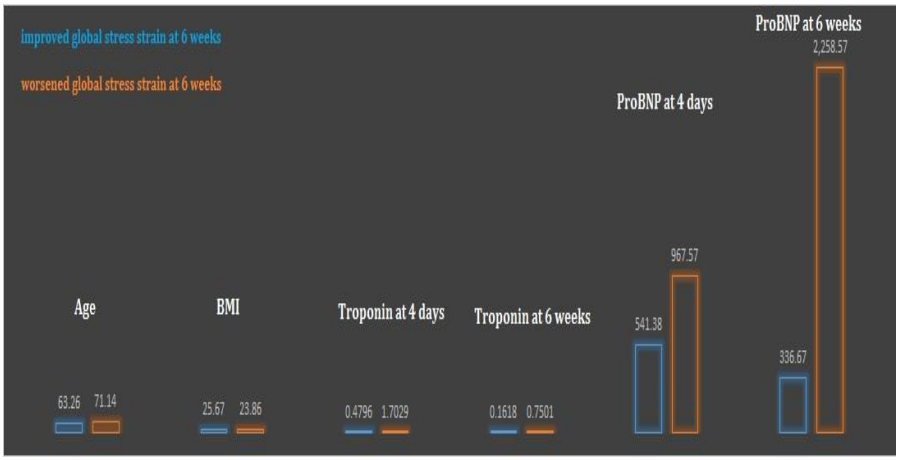


Figure 12 . Mean values of Age, BMI, Troponin at 4 days and 6 weeks and ProBNP at 4 days and 6 weeks in a comparison based on improvement and worsening the global stress strain values.

Based on the same concept, Age and BMI were not significant in determining the positive or negative regional stress strain outcome at 6 weeks. While Troponin had shown a statistical significance in predicting the negative regional outcome with a p value of 0.13. Pro-BNP was also significant in determining the regional stress strain outcome at 6 weeks with a p value of 0.43.

Troponin levels at 6 weeks showed a moderate correlation with global stress strain obtained with speckle tracking at 6 weeks with r value of 0.43 and p value <0.001. ProBNP exhibited a moderate correlation with global stress strain obtained with speckle tracking at 6 weeks with r value of 0.41 and p value of 0.003 (Figure 13 and figure 14).

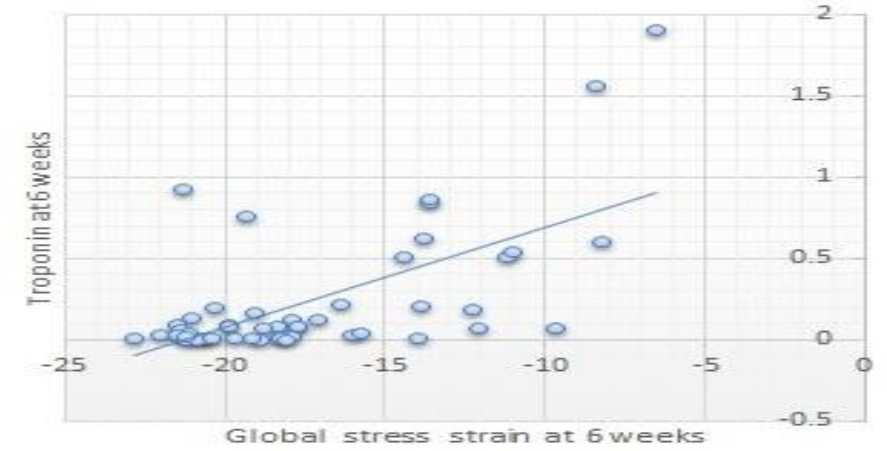


Figure 13.Correlation between Troponin levels and global stress strain at 6 weeks.

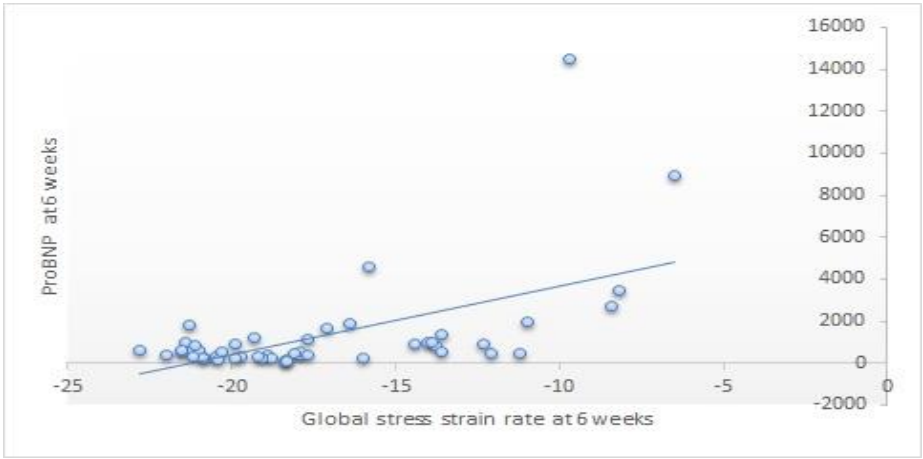


Figure 14. Correlation between ProBNP levels and global stress strain at 6 weeks.

Meanwhile, Troponin values at 6 weeks showed a strong correlation with regional stress strain rate at 6 weeks with a r value of 0.64 and p value <0.001. ProBNP levels at 6 weeks indicated a strong correlation as well with regional stress strain

at 6 weeks with a r value of 0.66 and p value <0.0001 (Figure 15 and 16).

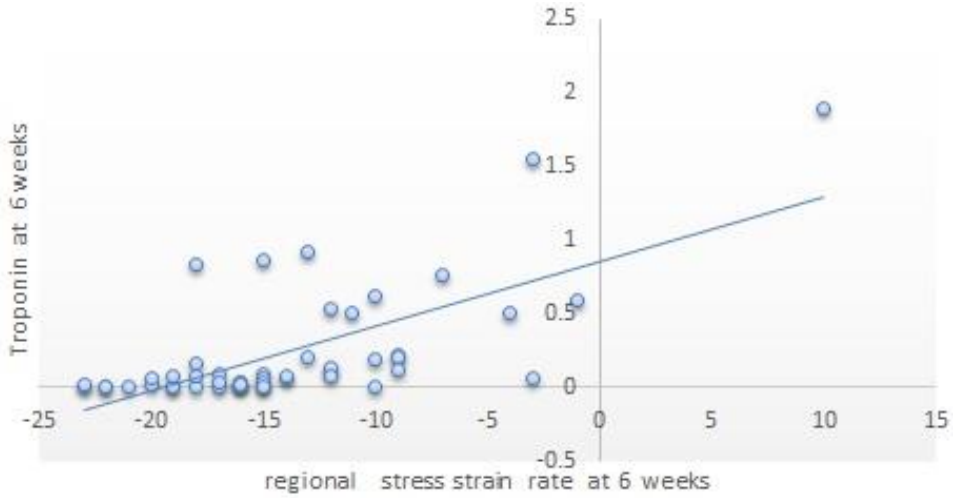


Figure 15.Correlation between Troponin levels at 6 weeks and regional stress strain at 6 weeks.

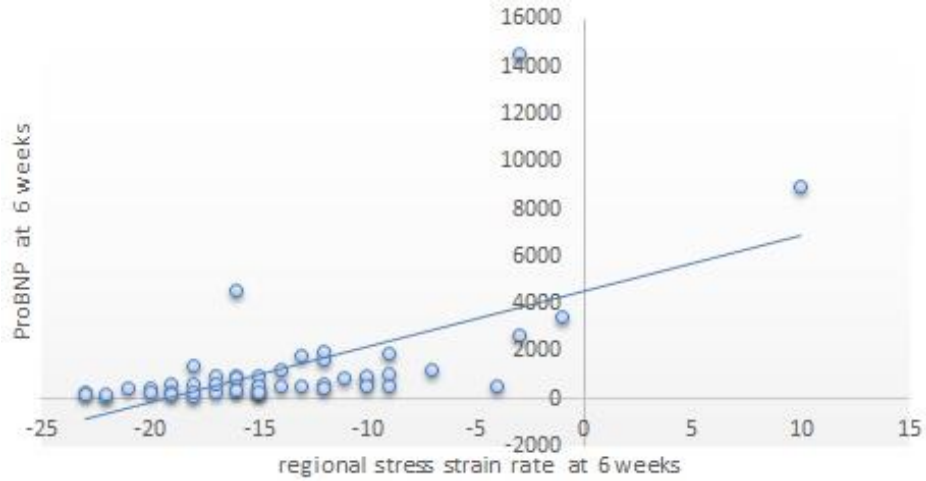


Figure 16. Correlation between ProBNP levels at 6 weeks and regional stress strain at 6 weeks.

A statistical agreement was conducted to detect the most appropriate method in determining post-infarction ischemia at 4

days in relation to cardiac MRI at the different level of myocardial walls. Dobutamine stress echocardiography revealed a kappa value of 0.72 with a p value of 0.04 while global strain rate at rest showed a kappa value of 0.79 with a p value of 0.006. Global strain rate under stress had a kappa value of 0.89 with a p value of 0.0001 (Figure 17).

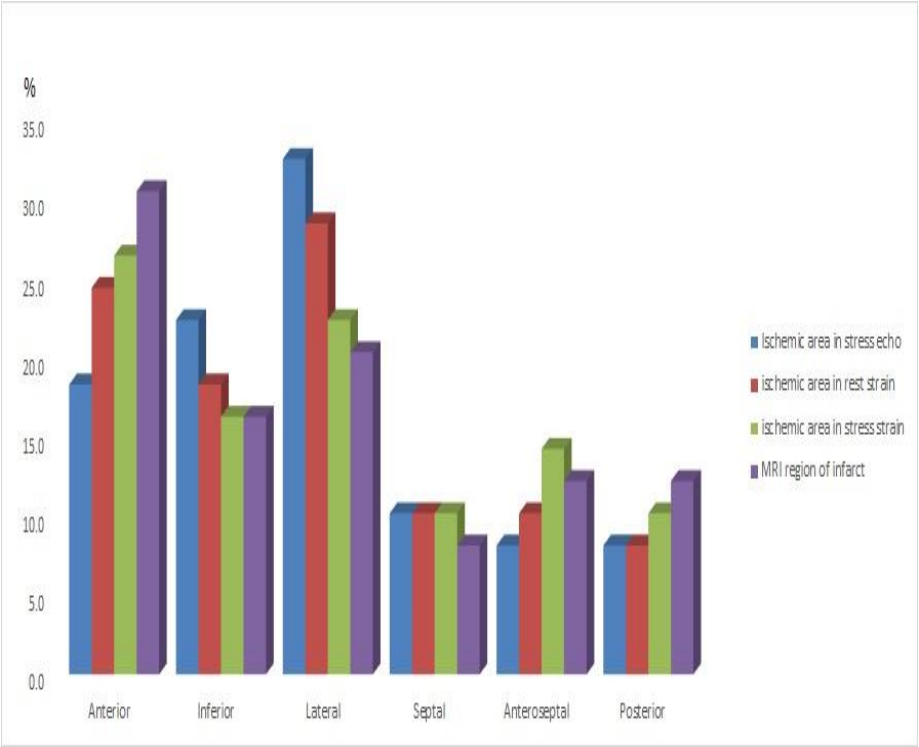


Figure 17. Agreement analysis at 4 days comparing different echocardiographic methods to cardiac MRI in detecting post-MI ischemia.

Moreover, the same analysis was performed to distinguish the different echocardiographic data obtained through dobutamine stress, resting strain rate and stress strain rate at 4 days in correlation to the ischemic territory in coronary angiography. In this analysis an agreement was found between wall motion analysis revealed by dobutamine stress echocardiography with kappa value of 0.25 and p value of 0.1. Using resting strain revealed an agreement with a kappa value of 0.32 and p value of

0.04. Obtaining strain rate at stress raised the agreement to a kappa value of 0.46 with a p value of 0.001(Figure 18).

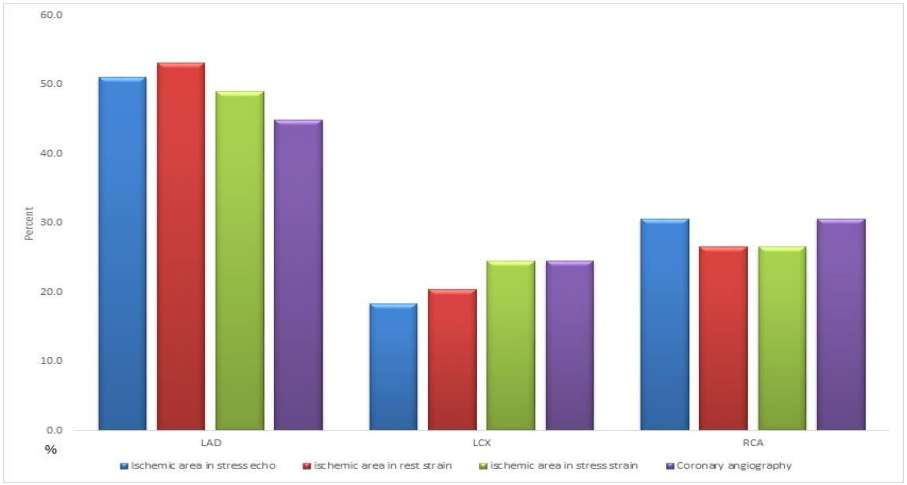


Figure 18. Agreement analysis at 4 days comparing different echocardiographic methods to coronary angiography findings in detecting post-MI ischemia.

Global stress strain rate obtained from speckle tracking showed different levels in relation to the MI extent at 6 weeks. A sub-endocardial MI (<50% extension of left ventricular wall as measured by cardiac MRI) had a mean value of -18,9± 4.8 while a non-transmural infarction (50%-90% extension of left ventricular wall) showed a mean value of -9.6 ± 5.2. On the other hand, a transmural infarction (100% involvement of left ventricular wall) indicated a mean value of -4.9± 4.4. (Figure 19).

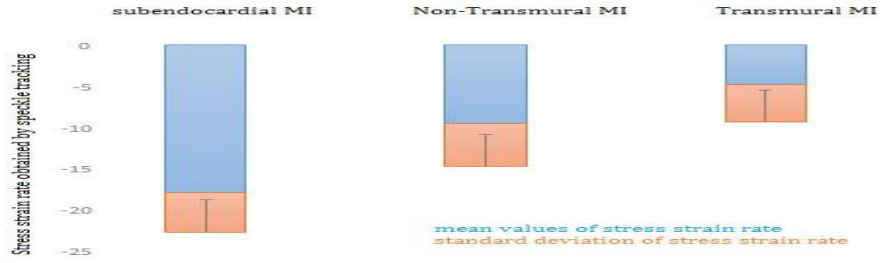


Figure 19. Mean values and standard deviation of global stress strain obtained by speckle tracking as differentiated by extent of infarction in cardiac MRI.

Regional stress strain rate at 6 weeks also was able to discriminate various forms of myocardial infarction extension through left ventricular wall with a mean value of -19.5 ±3.9 in sub-endocardial infarction. In non-transmural MI, a mean value of regional stress strain of -12.1±5.2 was detected. Furthermore a mean value of -1.9±2.5 was demonstrated in patients with transmural MI (Figure 20).

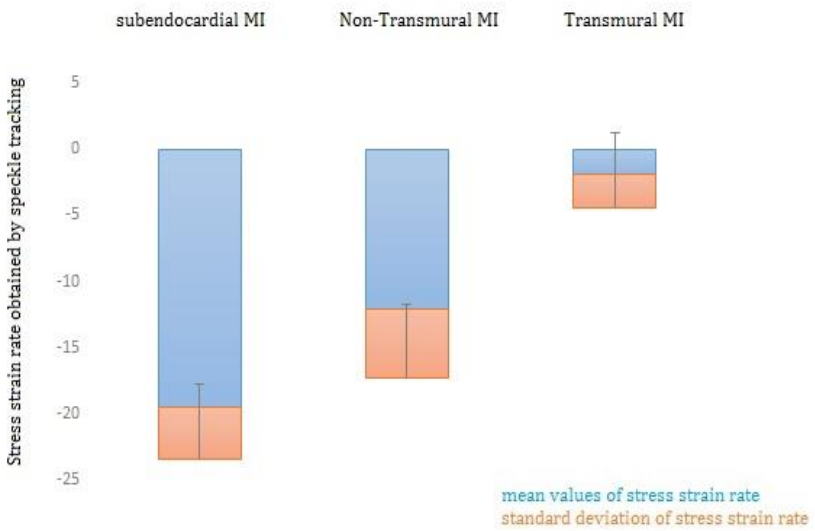


Figure 20. Mean values and standard deviation of regional stress strain obtained by speckle tracking as differentiated by extent of infarction in cardiac MRI.

We conducted a Receiver-operating characteristics (ROC analysis)in order to detect the sensitivity and specificity of various diagnostic modus obtained from echocardiography (normal stress echocardiography, resting strain stress obtained by speckle tracking and speckle tracking stress strain stress) in relation to cardiac MRI viability.

It revealed a 60% sensitivity and 74.29% specificity while applying wall motion abnormalities detected by dobutamine stress echocardiography (AUC, Area under the curve 0,677) Figure 21.

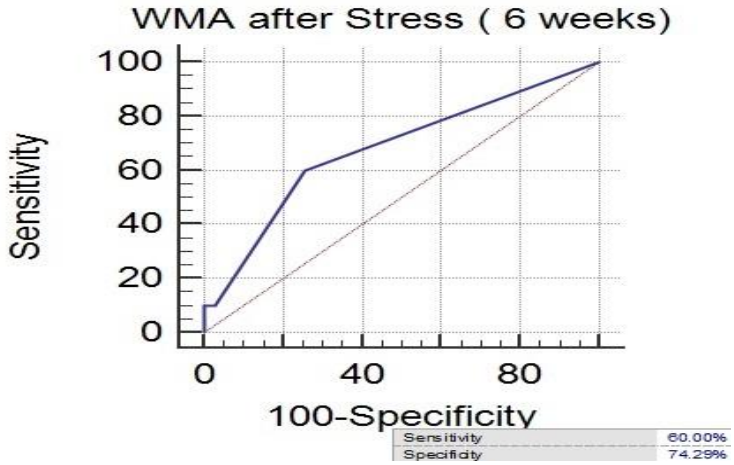


Figure 21. Sensitivity and specificity of dobutamine stress in detecting viability at 6 weeks in comparison with cardiac MRI.

Global resting strain rate was 74.09% sensitive and 60% specific in detecting myocardial viability in relation to cardiac MRI (AUC 0.764) at a cut-off value of -10.4 in differentiating transmural from non-transmural infarction and a cut-off value -17.65 differentiating subendocardial from non-transmural infarction. Figure 22.

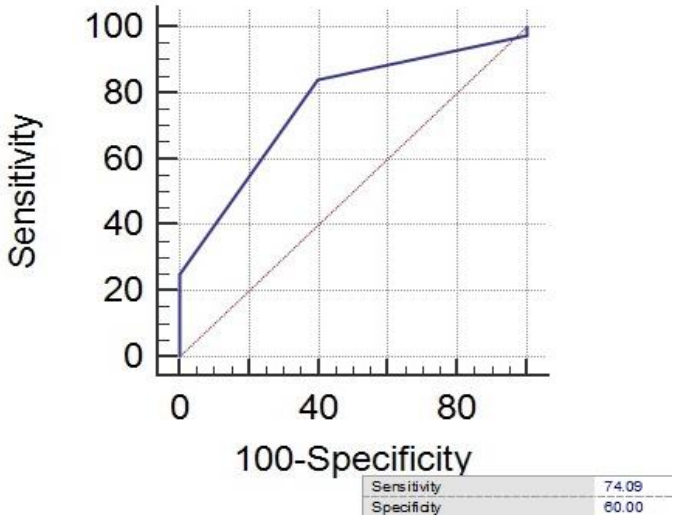


Figure 22 Sensitivity and specificity of resting strain rate obtained by speckle tracking in detecting viability at 6 weeks in comparison with cardiac MRI.

Obtaining strain rate under stress by speckle tracking provided a 81.82% sensitivity and 82.6% specificity to detect transmural from non-transmural infaction at a cut-off value of -10.15. Meanwhile it carried a 76.92% sensitivity and 79% specificity to detect sub-endocardial from non-transmural infarction at a cut-off value of -18.

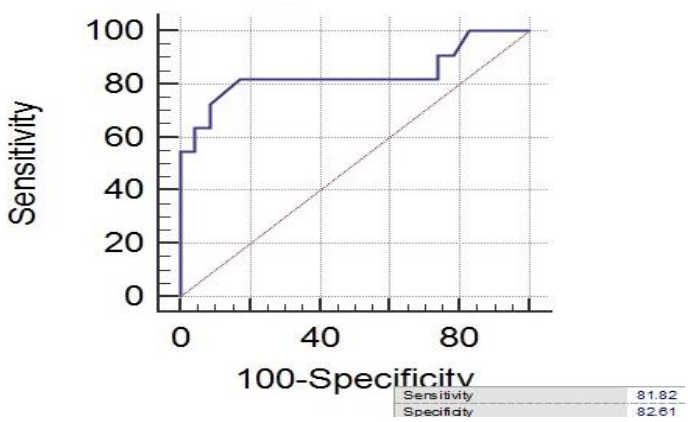


Figure 23: Sensitivity and specificity of stress strain rate obtained by speckle tracking in detecting viability at 6 weeks in comparison with cardiac MRI

We performed a multivariate regression analysis to find the best method for detecting myocardial viability at 6 weeks, using Cardiac MRI as the reference method. That disclosed a regression coefficient of 0.182 with significance level of p value 0.0022 as of using dobutamine stress in detecting viability. Utilization of regional strain rate showed a regression coefficient of 0.168 with a p value of 0.0034. A regression of 0.501 with a significance level of <0.0001 was raised by using global strain rate at rest (Figures 24,25).

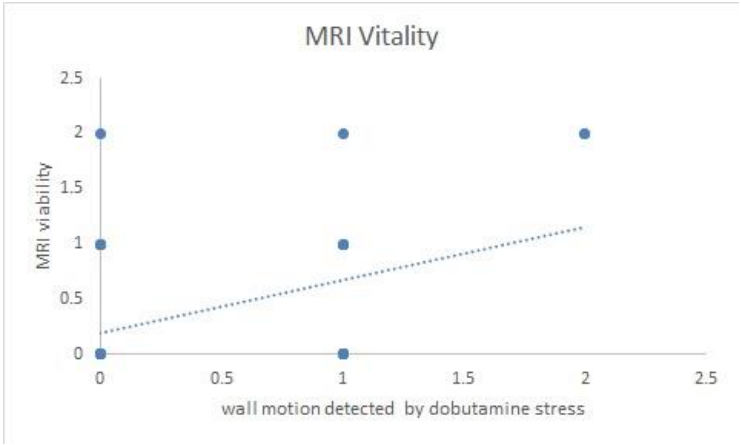


Figure24. regression analysis of wall motion abnormality detected by dobutamine stress in myocardial viability in relation to cardiac MRI.

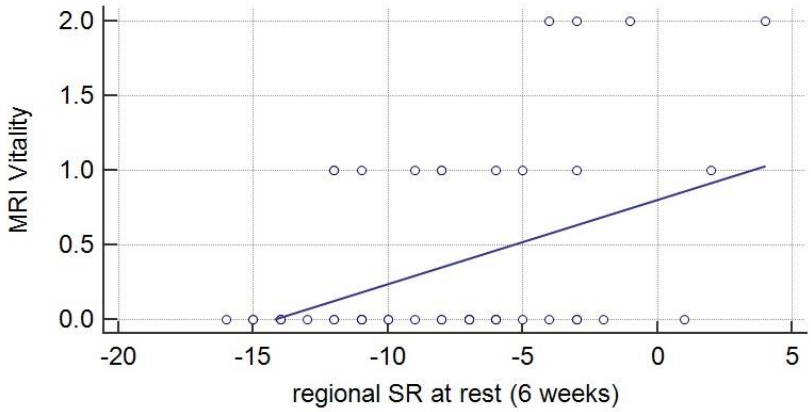


Figure 25. regression analysis of regional strain rate values at rest in myocardial viability in relation to cardiac MRI.

Regional strain rate values under stress divulged a highly significant regression with a coefficient of 0.776 and a p value <0.0001. While the highest significance was obtained by global stress strain rate with a regression coefficient of 0.8 and a significance level of <0.0001. Figures 26,27,28.

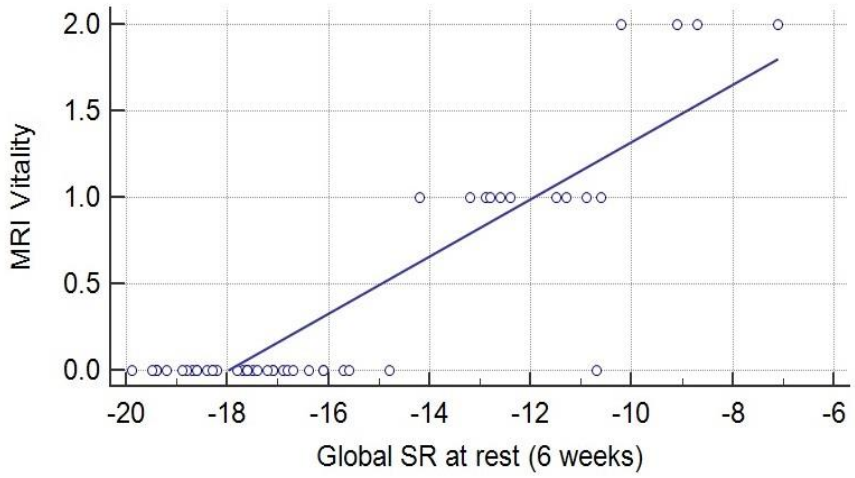


Figure 26. regression analysis global strain rate at rest in assessing myocardial viability in relation to cardiac MRI.

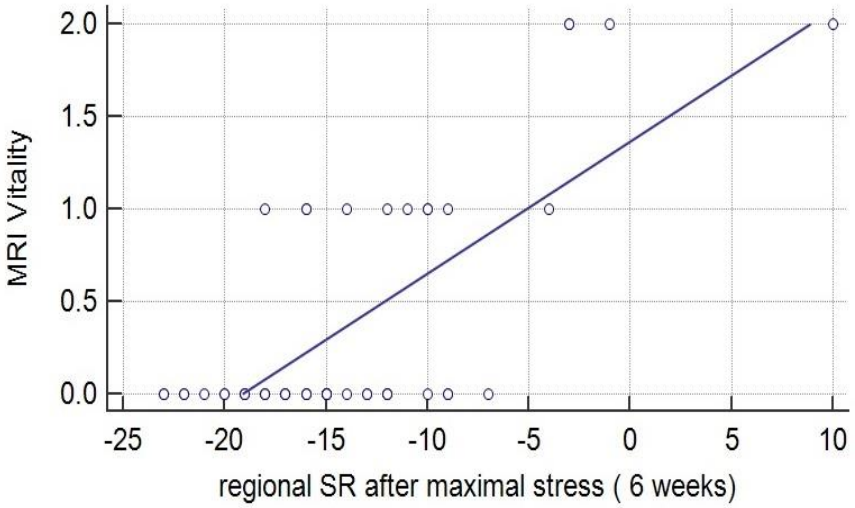


Figure 27. regression analysis of regional stress strain rate in evaluating myocardial viability in relation to cardiac MRI.

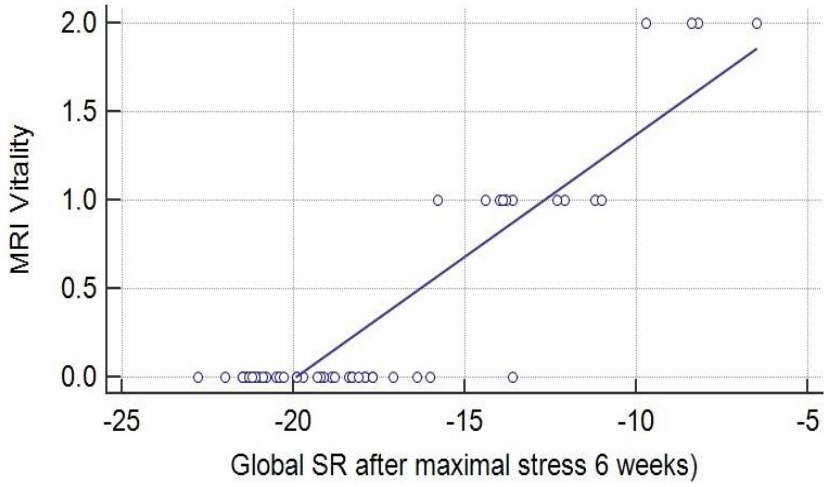


Figure 28. regression analysis of global strain rate speckle tracking under dobutamine stress in myocardial viability in relation to cardiac MRI.

A one year follow up of the patient perceived a 4 cases of hospital re-admission due to cardiology-related symptoms (2 patients with recurrent chest pain, one patients dyspnea on mild exertion NYHA III and one patient with cardiac syncope). Global stress strain rate obtained from speckle tracking showed 80% sensitivity and 77.5% specificity at a cut-off value of -9.1 to predict hospital re-admission (Figure 29).

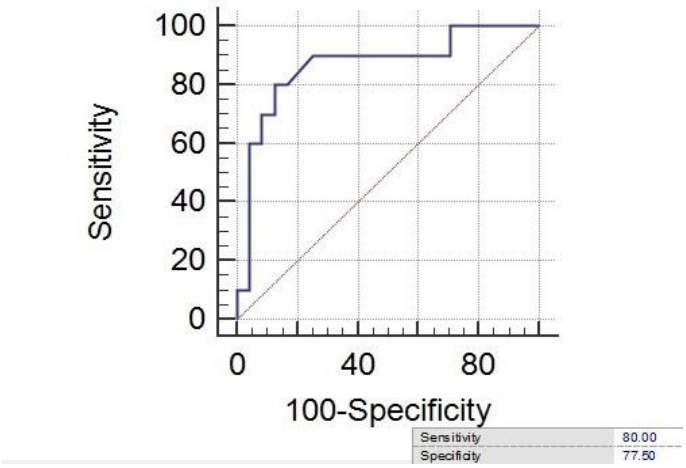


Figure 29. Predicting hospital re-admission from stress speckle tracking

From those 4 patients, two were diagnosed with acute coronary syndrome depending on the laboratory findings and ECG changes (one patient with unstable angina pectoris and one patient with NSTEMI). A cut-off value of -8.4 had shown a 69.23% sensitivity and 73.5% specificity to predict the recurrence of acute coronary syndrome (Figure 30).

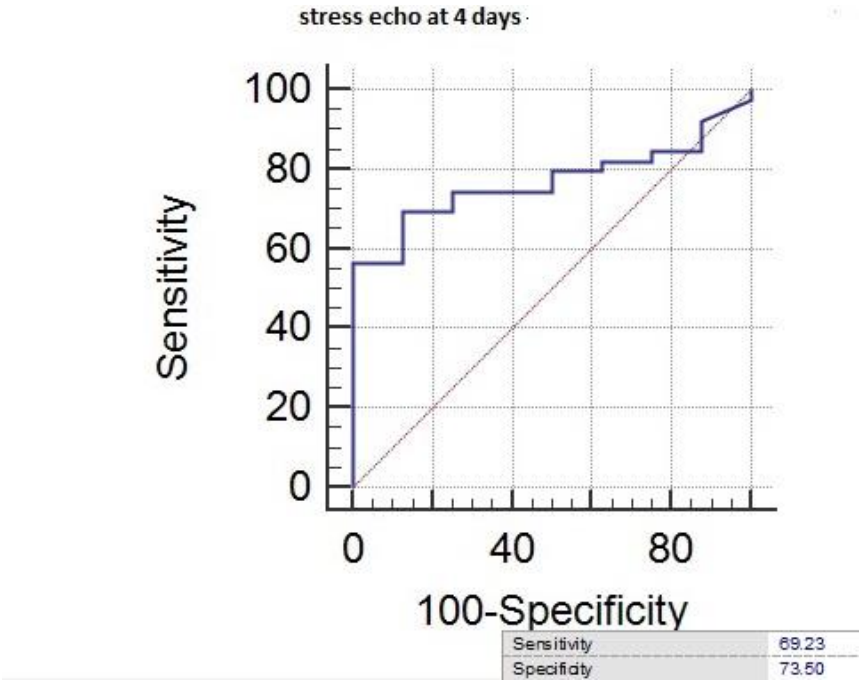
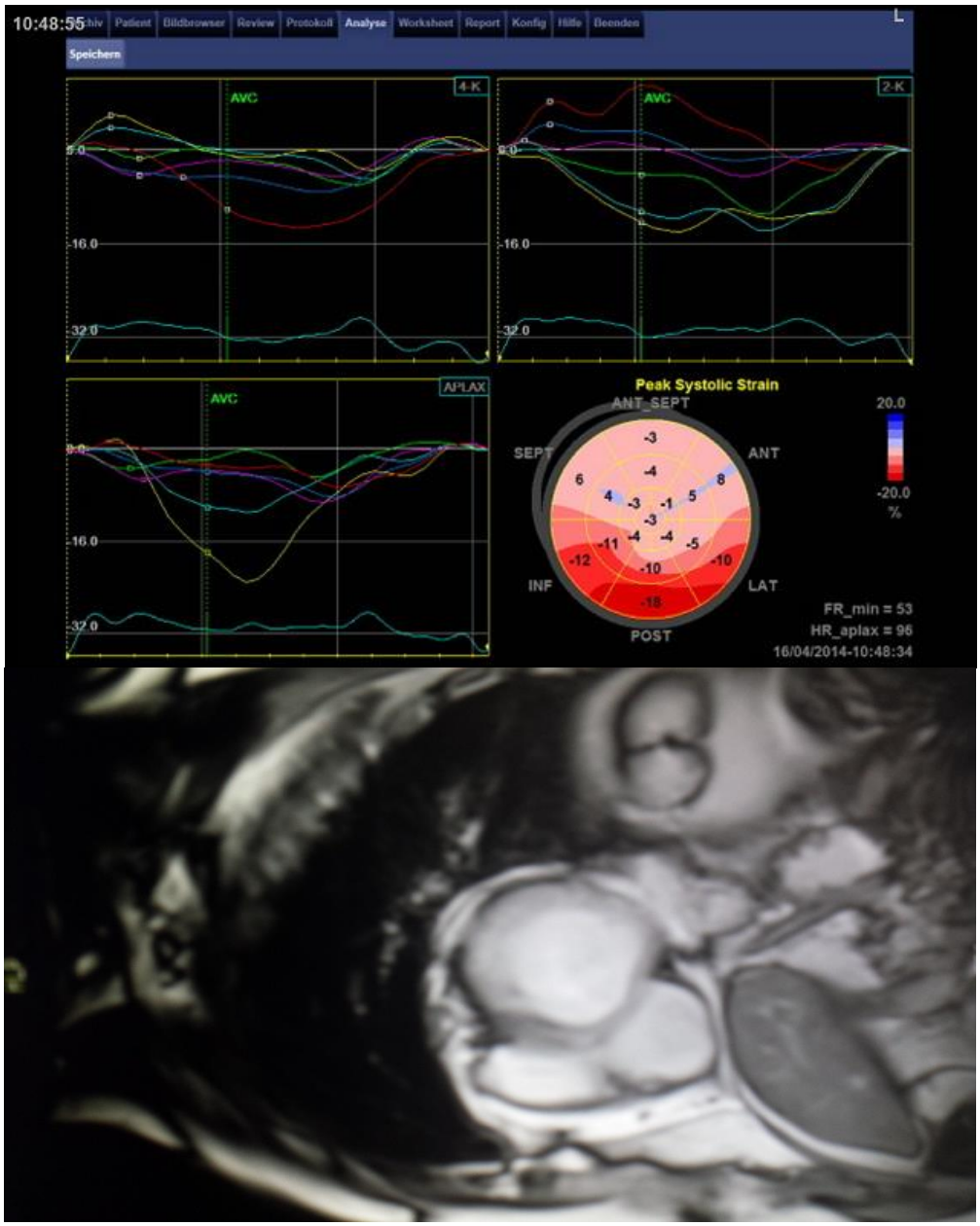
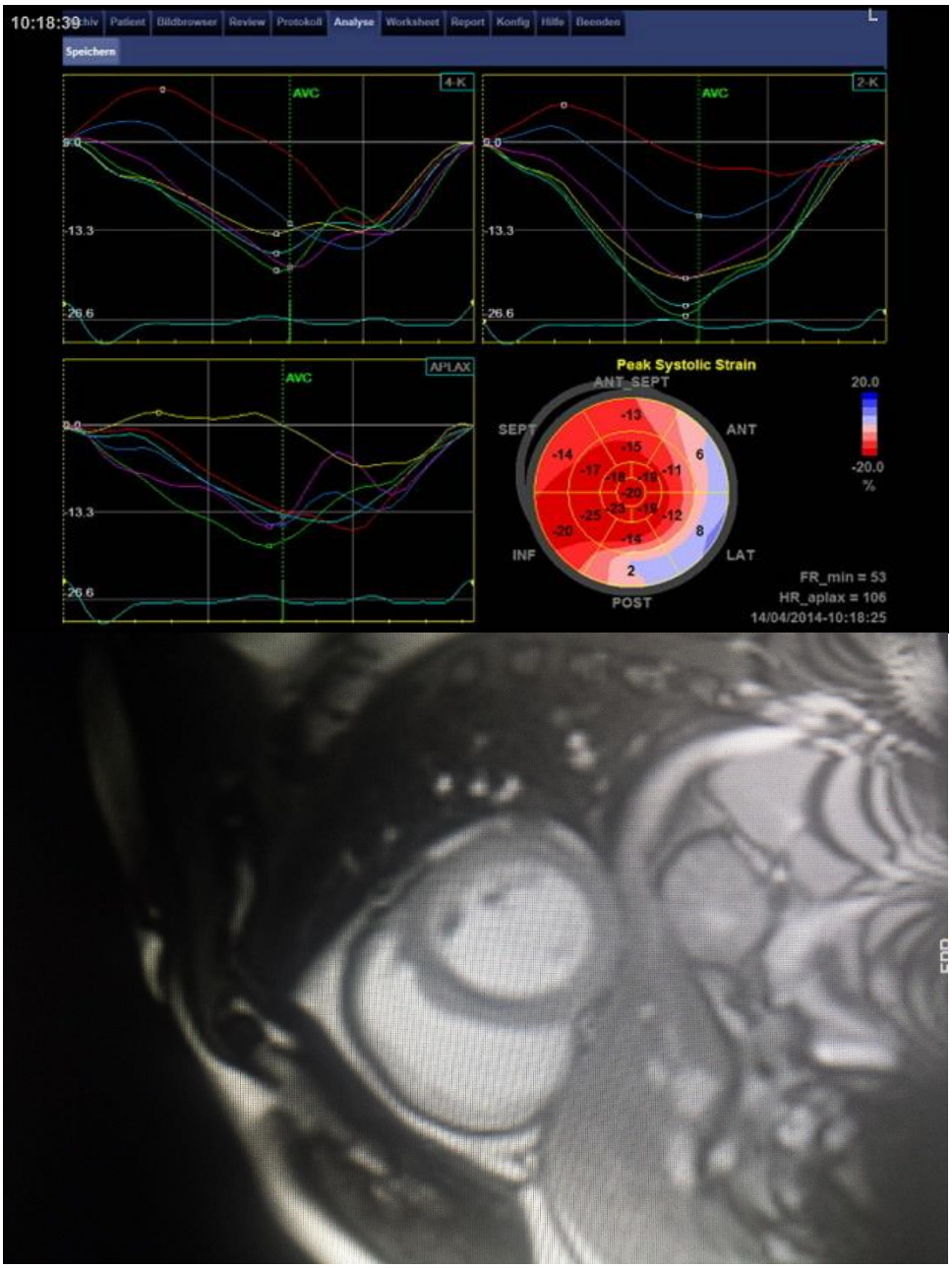


Figure 30. Predicting recurrence of acute coronary syndrome events from stress speckle tracking.



Case I.

Figure 31. Stress speckle tracking 6 weeks after STEMI revealing a massive transmural involvement of anterior wall . Cardiac MRI on the same day revealing same results and confirming the speckle data. The cardiac function didn't improve and the patient received primary prophylactic ICD as a result of ischemic cardiomyopathy.



Case II.

Figure 32. Stress speckle tracking showing moderate involvement of lateral myocardial wall 6 weeks after PCI of LCX lesion presenting with STEMI. In cardiac MRI a non-transmural involvement of myocardium of the lateral wall could be seen.

Discussion

Forty nine patients were enrolled from Mai 2013 until December 2014 from the coronary care unit (CCU) at Coburg hospital. The Patients were diagnosed with ST elevation myocardial infarction patients based on their ECG, laboratory findings and symptoms at admission. A follow up study was undertook at 6 weeks after STEMI.

They were examined with echocardiography at rest and at low dobutamine stress on 4 days and at rest and high dobutamine stress on 6 weeks to determine the global and regional strain rate values. All patients were evaluated through cardiac MRI as a gold standard method of determining myocardial viability at 4 days and 6 weeks as well.

The results as shown in chapter 5 have revealed a powerful and promising role of utilization of stress speckle tracking whether as an evaluating tool for post-myocardial infarction viability assessment or as an effective risk stratification value just before hospital discharge after STEMI. The obtained stress strain rate from speckle tracking have correlated with cardiac MRI as gold standard method.

A Norwegian experimental study, which took place in 2010 tried to simulate a clinical stress test applied in coronary artery disease with a constant coronary stenosis of about 80%, causing a 35% flow reduction at rest. This level of experimental stenosis, allowing flow reserve during dobutamine application combined with hypoperfusion, was crucial in obtaining the increased deformations during the inotropic challenge. **Assami et al, 2010**

The study demonstrated that the spatial sensitivity of the speckle tracking high-resolution ultrasound allows a focused assessment of specific layers of the myocardium and a graded assessment of parts of the myocardial wall with a different sensitivity to reduced coronary reserve. Thus, when applying an inotropic challenge to the hypoperfused ventricular wall, the mid-myocardial layers in longitudinal and circumferential directions demonstrated the highest sensitivity by increasing the

deformation measured by ET strain. This heterogeneous response was also evident by the lack of response of subendocardial and midendocardial radial ET strain. This observation is compatible with previous studies **Jamal F et al, 2001**, as sub-midendocardial radial ET strain might need cross-fiber activation of all layers and therefore might not be significantly activated when not all myocardial layers normalize their contractility. **Rademakers et al, 1994**

Hong Ran et al evaluated in 2012 whether myocardial strain under adenosine stress calculated from two-dimensional echocardiography by automatic frame-by-frame tracking of natural acoustic markers enables objective description of myocardial viability in clinic.

Two-dimensional echocardiography and two-dimensional speckle tracking imaging (2D STI) at rest were performed first and once again after adenosine was infused at 140 ug/kg/min over a period of 6 minutes in 36 stable patients with previous myocardial infarction. **Hong Ran et al, 2012**

Radionuclide myocardial perfusion/metabolic imaging served in his study as the "gold standard" to define myocardial viability was given in all patients within 1 day. Two-dimensional speckle tracking images were acquired at rest and after adenosine administration.

An automatic frame-by-frame tracking system of natural acoustic echocardiographic markers was used to calculate 2D strain variables including peak-systolic circumferential strain (CS peak-sys), radial strain (RS peak-sys), and longitudinal strain (LS peak-sys). **Hong Ran et al, 2012**

Accordingly, in nonviable group strain values showed no significant changes during adenosine administration. After adenosine administration, RS peak-sys and LS peak-sys in viable group increased significantly compared with nonviable group. Obtained strain data were highly reproducible and affected in

small intra-observer and inter-observer variability. A change of radial strain more than 9.5% has a sensitivity of 83.9% and a specificity of 81.4% for viable whereas a change of longitudinal strain more than 14.6% allowed a sensitivity of 86.7% and a specificity of 90.2%. **Hong Ran et al, 2012**

In 2005, longitudinal strain was evaluated to determine the value of regional deformation when compared to cardiac MRI. SRs and SRe were significantly lower in subendocardial infarction compared with normal myocardium. Moreover, they established a direct relationship between SRI, transmurality, and infarct size. Linear regression analysis showed that both SRs and Sm of the infarct area had a significant correlation with the infarct size. SRs of the transmural infarcted segments were significantly decreased when compared with non-transmural, subendocardial MI, and normal segments; SRs and SRe were also significantly reduced in subendocardial infarction compared with normal subjects. **Zhang et al, 2005**

In a correlative functional/histo-pathologic closed-chest animal study, it was shown that SRs and strain could also clearly differentiate non-transmural from transmural infarction. **Weidemann et al, 2003**

Standard Strain rate analysis, demands manual tracing of the myocardium whereas automated function imaging (AFI) offers more convenient (based on selection of three points) assessment of longitudinal strain. Nevertheless, feasibility and correlation between both methods were not thoroughly examined until 2014, especially during tachycardia at peak stage of dobutamine stress echocardiography (DSE).

A polish study assessed correlations between STE and AFI derived peak systolic longitudinal strain values for global and regional parameters, feasibility, time of analysis and inter-observer agreement. The novel, simplified AFI technique offered similar feasibility, lower coefficient of variance both during rest and peak stress stage significantly (about two times) shorter time needed for analysis. **Wierzbowska et al, 2014**

However, investigating strain Doppler echocardiography performed immediately after revascularization by percutaneous coronary intervention predicted the extent of myocardial scar, determined by contrast-enhanced magnetic resonance imaging. **Vartdal et al, 2007**

A good correlation was found between the global strain and total infarct size (R 0.77, $p< 0.00001$). A multi-variate regression analysis showed that global peak strain and serum glutamic oxaloacetic transaminase correlated with the infarct size measured by MRI ($p <0.0001$ and $p < 0.001$, respectively). Furthermore, a clear inverse relationship was found between the segmental strain and the transmural extent of infarction in each segment. **Vartdal et al, 2007**

The authors concluded that global strain parameter is a valuable predictor of the total extent of myocardial infarction and may therefore be an important clinical tool for risk stratification in the acute phase of myocardial infarction.

Limitations

1- Heart rate variability played a negative role in strain rate offline analysis. The analysis was aborted and many patients were therefore excluded from the study. Patients with atrial fibrillation were as well excluded as the program couldn't overcome the heart rate variability during the study.

2- Failure of obtaining a perfect acoustic window during performing the echocardiography remains a critical limitation in markedly obese patients or hyper-inflated thoracic wall.

3- Single center study with relatively limited number of studied objects.

4- Patients with pacemakers, central nervous system aneurysm clips, cochlear implants, implanted neural stimulator or patients with insulin pump were not appropriate to be examined through cardiac MRI.

Conclusion

Strain rate obtained from speckle tracking during stress is a powerful method of detecting myocardial viability after STEMI and provide dependable results in comparison to strain rate obtained at rest.

It's safe, fast and reproducible. It elucidates the Inter- and Intra-observer variability of normal stress echocardiography.

It is a highly sensitive and specific test in correlation to the gold standard method (cardiac MRI).

Moreover, it carries a promising role in post-myocardial infarction risk stratification with a reasonable prediction of reversible coronary events or hospital re-admission.

Recommendations

Performing stress echocardiography with a parallel obtaining of strain rate through speckle tracking 96 h after myocardial infarction and at 6 weeks is important to detect both risk stratification and viability.

Conducting a multi-centric study for more data validation and eventually applying the data in the appropriate guidelines criteria.

Conducting the study with a large number of patients will help to overcome the limitation of statistical accuracy at low number data.

Encouraging the manufacturing companies of echocardiography machines to provide a solution for heart rate variability problems through offline processing and analysis.

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bei Schriftwechsel bitte angeben: **20180611 01**

Unbedenklichkeitsbescheinigung

Projekt: The emerging role of stress speckle tracking in viability world

Sehr geehrter Herr Dr. Saleh,

zu Ihrer Anfrage vom 11.06.2018 nimmt die Ethik-Kommission wie folgt Stellung:

Die Bewertung klinikinterner qualitätssichernder Maßnahmen gehört nicht in den Zuständigkeitsbereich der Ethik-Kommission. Zudem sind für qualitätssichernde Maßnahmen auch keine Ethikkommissionvoten notwendig.

Eine Befürwortung oder ein Votum kann daher für die von Ihnen angestrebte Qualitätssicherungsmaßnahme durch die Ethik-Kommission nicht erfolgen.

Mit freundlichen Grüßen

Prof. Dr. med. Eva-Bettina Bröcker
Seniorprofessorin
Vorsitzende der Ethik-Kommission

Ausgefertigt im Auftrag

Ass. jur. Katharina Reith
Geschäftsführerin der Ethik-Kommission