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DOPPLER TISSUE IMAGING IN ST-ELEVATION MYOCARDIAL INFARCTION

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"The only reason for time is so that everything doesn't happen at once"

Albert Einstein (1879-1955)

To Katarina, Hanna, Simon and Melker

ABSTRACT

Highly available, noninvasive and cost-effective, echocardiography remains a keystone in the evaluation of patients with coronary artery disease (CAD). Echocardiographic assessment of cardiac function at rest and during dobutamine stress has direct clinical implications. Conventional echocardiographic parameters however, are partly based on visual interpretation of cardiac motion, thereby subject to interobserver variability, especially in patients with poor image quality. As a complement, myocardial velocity imaging techniques such as Doppler tissue imaging (DTI) offer quantitative markers of cardiac function.

In the present study, we explored the feasibility and diagnostic value of DTI in the evaluation of left and right ventricular function, the presence of inducible ischemia and myocardial viability in patients with ST-elevation myocardial infarction (STEMI).

In 90 patients with STEMI (64 men and 26 women aged 65±13 years) echocardiography was performed at day 1, 5–7 days and 6 months after admission. At day 5–7, dobutamine stress echocardiography (DSE) with wall motion analysis (WMA) was performed, followed by coronary angiography within 24 hours. Using DTI, systolic, early and late diastolic myocardial velocities were recorded near the mitral annulus at 4 left ventricular (LV) sites, and near the tricuspid annulus in the right ventricular free wall. The myocardial performance index (MPI), a Doppler-based, combined measure of systolic and diastolic function, was calculated as the sum of the isovolumic time intervals divided by the ejection time derived from DTI at the 4 LV sites. Forty-one aged-matched healthy subjects served as controls.

In patients with complete normalization of conventional parameters of LV function at follow-up, peak systolic as well as early diastolic LV myocardial velocities were significantly reduced compared with those in healthy subjects, possibly reflecting a residual subendocardial damage.

Using peak systolic velocity in the right ventricular (RV) free wall as a marker of RV function, sensitivity and specificity of DTI in identifying patients with electrocardographic signs of RV infarction (ST-elevation in ECG lead V4R) were 89% and 71%, respectively. Furthermore, peak RV systolic velocities remained reduced in patients with RV infarction, even after resolution of ECG changes and were still evident at 6 months' follow-up.

Use of the MPI as a marker of ischemia during DSE was shown to be feasible, and although the majority of patients did not achieve an optimal level of stress, relative changes in MPI between rest and peak stress offered reasonable diagnostic properties, superior to those of WMA. Sensitivity and specificity for detection of left anterior descending, left circumflex and right coronary artery disease were 80% and 87%, 59% and 80% and 85% and 72%, respectively.

Finally, we found that MPI during low-dose dobutamine infusion exhibits a specific pattern, similar to that of WMA, predicting late recovery of LV systolic function.

In conclusion, the use of DTI during echocardiography at rest and during dobutamine stress is feasible and allows evaluation of LV and RV function in the acute as well as the late phase after a STEMI. Furthermore, changes in MPI derived from DTI during DSE identify patients with residual CAD and predict late recovery of LV function, independently of age, troponin level and time to reperfusion treatment.

LIST OF PUBLICATIONS

This thesis is based on the following original papers, which will be referred to by their Roman numerals.

I. Witt N, Alam M, Svensson L, Samad BA. Tricuspid annular velocity assessed by Doppler tissue imaging as a marker of right ventricular involvement in the acute and late phase after a first ST-elevation myocardial infarction. *Echocardiography 2010;27:139-145*

II. Witt N, Samad BA, Frick M, Alam, M. Detection of left ventricular dysfunction by Doppler tissue imaging in patients with complete recovery of visual wall motion abnormalities six months after a first ST-elevation myocardial infarction. *Clinical physiology and functional imaging 2007;27:305-308*

III. Witt N, Alam M, Frick M, Samad BA. Diagnostic value of myocardial performance index derived from Doppler tissue imaging during dobutamine stress echocardiography – detection of residual coronary artery disease after initial reperfusion therapy in patients with ST-elevation myocardial infarction. *Submitted for publication*

IV. Witt N, Alam M, Frick M, Samad BA. Myocardial performance index derived from Doppler tissue imaging during dobutamine stress echocardiography predicts late recovery of left ventricular function in patients with ST-elevation myocardial infarction. *Submitted for publication*

CONTENTS

LIST OF ABBREVIATIONS

BP	Blood pressure
CAD	Coronary artery disease
DSE	Dobutamine stress echocardiography
DTI	Doppler tissue imaging
EF	Ejection fraction
ET	Ejection time
HR	Heart rate
IVCT	Isovolumic contraction time
IVRT	Isovolumic relaxation time
LV	Left ventricle/ventricular
MI	Myocardial infarction
MPI	Myocardial performance index
NSTEMI	Non ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
PW	Pulsed-wave
RV	Right ventricle/ventricular
STEMI	ST-elevation myocardial infarction
TAPSE	Tricuspid annular plane systolic excursion
WMA	Wall motion analysis

INTRODUCTION

CORONARY ARTERY DISEASE

Coronary artery disease (CAD) is a leading cause of death and a major cause of morbidity in the western world. Risk factors include age, heredity, obesity, physical inactivity, smoking and the presence of diabetes mellitus, hypertension and dyslipidemia. New therapeutic options for prevention and treatment of CAD have resulted in an increasing number of patients surviving a cardiovascular event. The positive effects of new therapies however, are at least partly outweighed by the increasing incidence in the aging population [1].

Pathophysiology and clinical spectrum

Early mechanisms initiating the process of atherosclerosis precede clinical manifestations of coronary artery disease by decades [2]. A complex process where deposition and oxidation of lipids is accompanied by endothelial dysfunction, infiltration of inflammatory cells and proliferation of smooth muscle cells and fibrous tissue results in progressively increasing plaque, consisting of a lipid core with a fibrous cap (Fig. 1). An initial outward growth of the atherosclerotic plaque, commonly referred to as positive remodeling, is followed by inward growth, compromising the vessel lumen, ultimately limiting coronary blood flow.

When the balance between metabolic demands and oxygen delivery is shifted during exercise, myocardial ischemia is induced, either silent or clinically manifested as stable angina pectoris. Symptoms are typically evoked by a certain level of exertion, ranging from mild to strenuous exercise.

A combination of mechanical forces from coronary blood flow and degradation of collagen and other matrix proteins in the fibrous cap may lead to rupture or fissuring of the atherosclerotic plaque, thereby exposing factors triggering coagulation and thrombus formation [3] (Fig. 1). The clinical manifestations include unstable angina pectoris, non ST-elevation and ST-elevation myocardial infarction (NSTEMI, STEMI), and sudden cardiac death.

Atherosclerotic plaque

Plaque rupture

Thrombus formation

Figure 1. Rupture of an atherosclerotic plaque with subsequent thrombus formation limiting coronary blood flow.

Medical treatment

Treatment of CAD is based on modification of atherosclerosis progression, inhibition of thrombotic mechanisms and limitation of myocardial oxygen consumption. HMG-CoA reductase inhibitors, known as statins, have been documented to slow the rate of atherosclerosis progression and lower the risk of myocardial infarction and death in patients with CAD [4]. Inhibitors of angiotensin-converting enzyme (ACE-inhibitors) also seem to reduce the risk of cardiac events, beyond the level of their antihypertensive effect [5]. Anti-ischemic medication, including beta-blocking agents, calcium channel inhibitors and nitrates, limit oxygen consumption through reduction of heart rate (HR), blood pressure (BP), preload and afterload. Antithrombotic treatment targets different mechanisms of coagulation, where platelet inhibition is a fundamental component in treatment of stable, as well as unstable CAD. Inhibition of the enzyme cyclooxygenase by aspirin, the ADP receptor by thienopyridines and the GP2b/3a receptor on the surface of platelets, all independently contribute to reduction of clinical events [6]. In order to counteract the prothrombotic mechanisms in unstable CAD, antiplatelet therapy is combined with anticoagulation, for many years represented by unfractionated heparin, later replaced by low-molecular-weight heparins and direct inhibitors of thrombin and factor X [7-9]. In patients with STEMI, the presence of a thrombus completely occluding a coronary vessel requires prompt actions to restore normal coronary blood flow, thereby limiting the extent of myocardial necrosis. The introduction of fibrinolytic agents offered specific means of reperfusion, improving prognosis in STEMI patients [10].

Invasive treatment

Since its introduction in 1960, coronary artery bypass surgery (CABG) has been considered the gold standard of revascularization for CAD, especially in patients with multivessel- and left main disease [11]. Technical progress in the field of percutaneous coronary intervention (PCI), however, now allows treatment of an increasing proportion of patients throughout the whole spectrum of CAD. Large-scale trials established the positive prognostic effects of an early invasive strategy in patients with NSTEMI [12]. Furthermore, for patients with STEMI, primary PCI has emerged as the reperfusion treatment of choice, at least in centers with close access to invasive facilities [13].

ANATOMICAL AND PHYSIOLOGICAL ASPECTS OF NORMAL LEFT AND RIGHT VENTRICLES

Left and right ventricular geometry

There are some distinct differences in the geometry of the two ventricles. The left ventricle (LV) is cylindrical or conical, with an almost circular cross-sectional shape. The three-dimensional structure of the anteriorly oriented right ventricle (RV) is more complex, having the shape of a modified ellipsoid with a semilunar short axis appearance (Fig. 2).

The muscular part of the ventricular wall (the myocardium) is arranged in 3 layers with different orientation. In the LV, the superficial layer is obliquely arranged with a spiral-like course from the base to the apex, whereas the mid-layer is circumferential, and the inner layer longitudinally oriented. This complex microstructure of the LV wall has important implications for normal ventricular contraction and relaxation. In contrast, the RV wall mainly consists of a superficial layer with circumferentially oriented muscle fibers and a deep layer, where fibers are longitudinally oriented. Despite these differences, there is continuity between the muscle layers of the right and left ventricular wall, resulting in functional interdependence between the two ventricles [14].

Figure 2. Schematic view of the interrelation between the right (RV) and left (LV) ventricles. (Kovalova S, *Eur J Echocardiogr* 2005;6:15-23) Reprinted with the permission of Oxford University Press.

The contractile unit

Myocardial contraction and relaxation is based on function of the contractile units, or sarcomeres inside the cardiac myocytes. The sarcomere is a protein complex consisting of myosin and troponin, attached to thin actin filaments. The contractile process is initiated by an action potential releasing calcium ions from the sarcoplasmic reticulum. As a result of calcium binding, troponin changes shape, exposing binding sites for myosin at the actin filaments. This allows cross-bridging between myosin and actin, initiating contraction. Energy-dependent calcium ion reuptake into the sarcoplasmic reticulum results in decreasing intracellular calcium concentrations and reversal of the cross-bridging between myosin and actin filaments, thereby initiating myocardial relaxation [15].

Mechanisms of left ventricular systolic contraction

The systolic phase begins after closure of the mitral valve. Intraventricular pressure increases, initially without any volume change, representing the isovolumic contraction period. As the aortic valve opens, blood passes out into the aorta, representing the ejection period. Contraction in the different muscle layers of the myocardium causes a complex deformation pattern of the LV, resulting in volume reduction during systolic

ejection. Contraction of the obliquely oriented fibers of the superficial layer causes rotation and twisting of the LV, in opposite directions at the base and apex [16]. Circumferential and longitudinally oriented fibers are responsible for concentric radial compression and shortening of the LV by atrio-ventricular (AV) plane displacement [17]. The contribution of the individual directions of contraction to overall LV systolic function depends on several factors, including age, preload, afterload, heart rate and contractility [18, 19].

Left ventricular diastolic relaxation and filling

Relaxation of the LV is an active, energy-requiring process, dependent on calcium reuptake into the sarcoplasmic reticulum. The diastolic phase begins with closure of the aortic valve. Similar to isovolumic contraction, there is an initial isovolumic period, followed by a rapid increase in LV volume during early filling. Rotation during systolic contraction resulting in increasing LV wall tension is reversed during diastole. Untwisting, or elastic recoil, results in suction of blood from the atrium into the LV [20]. During late diastole, atrial contraction contributes to the late phase of LV filling [21]. Factors determining the proportion of LV filling during early and late phases of diastole include the rate of myocardial relaxation, LV compliance and left atrial (LA) pressure [22].

Right ventricular function

As a result of serial connection, stroke volumes of the two ventricles are equal. However, in contrast to the LV, the RV is connected to a low-resistance vascular system, explaining some of its anatomical and physiological characteristics, including a thinner muscular wall and a lower systolic pressure compared with the LV. Diastolic filling of the RV depends on several factors, including heart rate, right atrial (RA) pressure and RV compliance. Right ventricular systolic contraction is a result of longitudinal shortening with AV-plane displacement, radial compression from the lateral free wall and interaction with LV contraction [23, 24]. Right ventricular contractility and stroke volume are mainly determined by loading conditions. Changes in RV preload (e.g. in dehydration) may have significant impact on stroke volume, resulting in low cardiac output and systemic hypotension. Furthermore, compared with the LV, the RV is more sensitive to changes in afterload and even a moderate increase in pulmonary vascular resistance may lead to a significant reduction of RV stroke volume [25].

The coronary circulation

Myocardial blood flow is supplied by the coronary arteries (Fig. 3). Two main vessels, the left coronary artery (LCA) and the right coronary artery (RCA) arise from the aorta, in the left and right sinus of Valsalva. The common take-off of the LCA, the left main stem, splits into the left anterior descending artery (LAD) and the left circumflex artery (LCx). Originating from the LAD, septal and diagonal branches supply the interventricular septum, the anterior and lateral wall of the LV, while obtuse marginal branches from the LCx mainly supply the lateral, posterolateral and posterior LV wall segments. Originating from the RCA, posterolateral (PLA) and posterior descending

(PDA) arteries supply LV posterolateral and inferior segments and the inferior interventricular septum. However, the anatomical distribution of the coronary circulation exhibits wide variation. According to the origin of the PDA, three main patterns may be distinguished, where right dominance is the most common (PDA originating from the RCA), followed by codominance and left dominance (PDA originating from the LCx). In a recent study using multislice computed tomography, the frequencies of right-, left- and codominance were 88.1%, 8.5% and 3.4%, respectively [26]. In a right dominant system, blood flow to the RV is mainly supplied by the RCA, where acute marginal branches supply the anterolateral wall and the PDA supplies the posterior and inferoseptal region, while branches from the LAD supply the apical segments of the RV. Furthermore, branches mainly from the RCA supply the sinoatrial node and the atrioventricular node of the conduction system, explaining the frequent occurrence of arrhythmias associated with acute occlusion of the RCA [27]. Anomalies of the coronary circulation are seen in approx. 1–1.5 % of the population. Most common anomalies include separate origin of the LAD and LCx from the aorta, ectopic origin of the LCx from the right coronary sinus and ectopic coronary origin from the posterior sinus of Valsalva [28].

Figure 3. Normal distribution of the coronary arteries

As a result of extravascular compression from the contracting myocardium during systole, coronary blood flow to the LV occurs predominantly during diastole (Fig. 4). In contrast, blood flow in the RCA is more homogeneously distributed over the cardiac cycle because of the thinner wall and lower systolic pressure of the RV. Coronary blood flow is regulated by intrinsic as well as by extrinsic mechanisms, including endothelium-derived vasoactive substances, circulating catecholamines and autonomic nervous tone [29]. By means of autoregulation, coronary blood flow is maintained at different levels of systemic blood pressure (BP), ranging from 60 to 200 mmHg (Fig. 4).

Figure 4. Blood flow in the left coronary artery – relationship to aortic pressure during systole and diastole. Reprinted with the permission of Richard E. Klabunde. www.CVphysiology.com 2009.

IMPACT OF ISCHEMIA ON LEFT AND RIGHT VENTRICULAR FUNCTION - PATHOPHYSIOLOGICAL AND CLINICAL ASPECTS

The ischemic cascade

In the presence of obstructive CAD, an increasing level of exercise results in coronary flow abnormalities, thereby shifting the balance between myocardial oxygen demand and delivery to an ischemic state. Similarly, rupture of an atherosclerotic plaque and thrombus formation in unstable CAD results in limitation or inhibition of regional coronary blood flow with subsequent induction of ischemia. A decrease in oxygen-dependent production of adenosine triphosphate (ATP) ultimately causes impaired membrane transportation of calcium in the sarcoplasmic reticulum, thereby affecting the activation and deactivation of cross-bridges between myosin and actin filaments in the sarcomere. This impairment of the fundamental mechanisms of cardiac myocyte function is clinically manifested as diastolic and systolic dysfunction. In experimental studies it has been demonstrated that after induction of ischemia, regional diastolic dysfunction precedes changes in systolic function, followed by ECG changes and finally symptoms of angina [30, 31]. Thus, it is evident that the clinical presentation of myocardial ischemia is just the top of an iceberg consisting of the event chain initiated by coronary flow abnormalities. This is commonly referred to as the ischemic cascade [32] (Fig. 5).

INCREASING
MYOCARDIAL
OXYGEN
DEMAND

ANGINA

ISCHAEMIC ST DEPRESSION

GLOBAL LV DYSFUNCTION

REGIONAL SYSTOLIC DYSFUNCTION

REGIONAL DIASTOLIC DYSFUNCTION

PERFUSION ABNORMALITY

NORMAL LV FUNCTION

INCREASING EXERCISE

Figure 5. The classic ischemic cascade.

Left ventricular systolic function

As early as in 1935 Tennant and Wiggers demonstrated the effects of coronary occlusion on regional LV systolic function [33]. Further 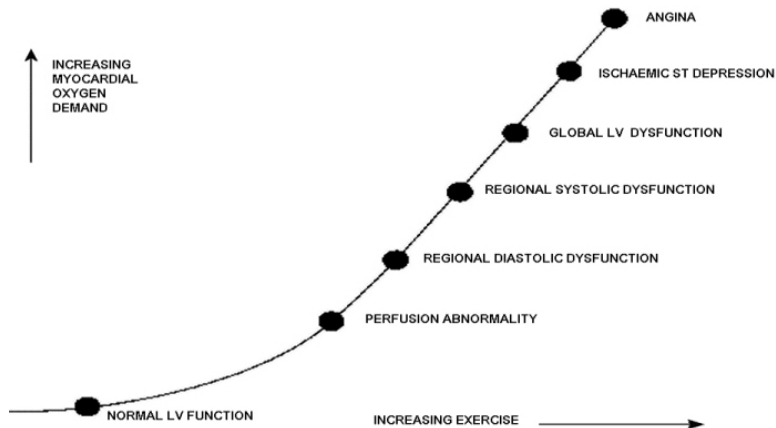studies established the almost linear relationship between regional myocardial blood flow and systolic contraction [34, 35]. Impaired regional systolic function is seen within seconds of coronary occlusion, followed by a return to normal function in less than a minute after restoration of blood flow [36]. If ischemia is prolonged, myocardial necrosis may occur, starting in the subendocardium where metabolic demands are higher and oxygen tension is lower compared with the subepicardial region [37]. Continued necrosis progresses towards the subepicardial myocardium, becoming transmural if myocardial perfusion is not restored. Experimental studies suggest that reduction in twisting and rotation of the LV may play an important role in ischemic systolic dysfunction [38]. This hypothesis is supported by results of *in vivo* studies in patients with MI [39]. The presence of inducible myocardial ischemia is a strong predictor of cardiac events, including mortality [40]. The risk increases with the extent of ischemia and the number of vessel territories involved [41]. Ischemic LV systolic dysfunction is clinically manifested as heart failure. Symptoms include shortness of breath, fatigue and fluid retention. The presence of left ventricular systolic dysfunction is a strong predictor of mortality in patients with CAD [42].

Left ventricular diastolic function

As previously discussed, diastolic dysfunction is an early manifestation of ischemia, preceding changes in systolic function as well as ECG changes and symptoms. Mechanisms of ischemia-induced diastolic dysfunction include reduced or delayed relaxation and untwisting as well as increased wall stiffness [43-45]. Asymptomatic LV diastolic dysfunction with preserved systolic function may be present in up to one third of patients with stable CAD, in whom the presence of moderate to severe diastolic dysfunction is a strong predictor of hospitalization for heart failure as well as for cardiac

death [46]. In patients with chronic ischemic cardiomyopathy, diastolic function may improve after revascularization [47]. The prognostic implications of diastolic dysfunction in patients suffering from myocardial infarction (MI) have been established in several small studies, and confirmed in a recent meta-analysis showing an almost threefold increase in all-cause mortality in the presence of severe diastolic dysfunction [48].

Stunning, hibernation and myocardial viability

Although transient after short exposure to myocardial hypoperfusion, LV systolic dysfunction may be persistent after prolonged or repeated episodes of ischemia. This phenomenon, commonly referred to as myocardial stunning [49], has been extensively studied in animal models [50] as well as in a variety of clinical situations. Exercise-induced ischemia may lead to LV systolic dysfunction evident even after resolution of ECG changes and symptoms [51]. In patients with acute myocardial infarction, systolic dysfunction may persist for weeks after successful reperfusion [52]. Thus, stunning is defined as persistent post-ischemic myocardial dysfunction in viable tissue despite restoration of normal myocardial perfusion. During the past 30 years, cellular and molecular mechanisms involved in myocardial stunning have been subject to intensive research, where interest has been focused on the effect of oxygen-derived free radicals and calcium regulation [53, 54].

In contrast to the perfusion-function mismatch characterizing myocardial stunning, the combination of chronic hypoperfusion and myocardial dysfunction is the typical finding in hibernating myocardium. Introduced by Rahimtoola in 1985, the term myocardial hibernation has been frequently used to describe the adaptation of myocardial tissue to chronic hypoperfusion [55]. Micro-structural as well as metabolic changes have been demonstrated to play a role in the pathogenesis of hibernating myocardium [56]. Morphological abnormalities of cardiac myocytes, including loss of contractile units and alterations of the interstitial architecture are accompanied by accumulation of glycogen and increasing numbers of mitochondria with an abnormal shape [57]. Although experimental studies support the definition of myocardial stunning and hibernation as two distinct forms of ischemic myocardial dysfunction, there is probably some functional overlap, mainly regarding hibernation and repetitive stunning [58].

A common characteristic of stunned and hibernating myocardium is the potential for recovery of contractile function, referred to as myocardial viability. By definition, functional recovery is spontaneous in stunning, but has to be preceded by revascularization and restoration of myocardial perfusion in hibernating myocardium. The presence of myocardial viability is a prognostic marker in patients with LV dysfunction and CAD, identifying patients who benefit from revascularization [59]. Moreover, there is a relationship between the extent of viable myocardium and the probability of functional recovery as well as the risk of future adverse events [60].

Right ventricular function

Substantial interest has been directed towards the impact of ischemia on RV function. Experimental studies demonstrate that occlusion of the RCA is rapidly followed by RV dysfunction. However, in contrast to LV function, RV function is immediately improved by reperfusion after one hour of occlusion. In fact, global RV function may

recover without extensive residual infarction, even after several hours of coronary occlusion [61]. Differences in loading conditions, wall tension and thereby oxygen demand may partly explain why the RV is less sensitive to ischemic injury [62]. Furthermore, even if antegrade flow in the RCA is completely inhibited, RV myocardial perfusion may be supplied by branches from the LCA as well as by acutely developed collaterals [63]. In post-mortem studies, right ventricular involvement has been demonstrated in up to 60% of patients dying from posterior as well as anterior MI [64]. However, a minority of patients and exclusively those with posterior infarction, present with clinical manifestations of RV infarction, including jugular venous distention and systemic hypotension [65, 66]. Hemodynamic impairment may be even more pronounced in the presence of concomitant LV dysfunction or atrial fibrillation. The diagnosis of RV infarction is commonly based on clinical signs, electrocardiographic, echocardiographic or angiographic parameters [67, 68]. Treatment is focused on maintaining adequate RV preload and heart rate. Furthermore, reperfusion treatment is associated with a favorable short-term prognosis and results in rapid recovery of RV function. However, positive prognostic effects seem to depend specifically on successful reperfusion of RV branches [69]. The prognostic implications of RV infarction have been addressed in several studies, with conflicting results [70, 71]. A recent meta-analysis, however, confirmed the prognostic value, showing a relative risk of death of 2.59 (95% CI 2.02–2.31, p<0.00001 in the presence of RV infarction [72].

ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT AND RIGHT VENTRICULAR FUNCTION IN THE NORMAL AND ISCHEMIC HEART

Historical perspective

The idea of using ultrasonographic imaging in medicine originated from industrial use of ultrasound to detect flaws in metal during the 1920s. The first ultrasonographic image of the heart was presented by the Swedish cardiologist Inge Edler and the German physicist Helmuth Hertz in 1953 (Fig. 6). Based on their pioneering work and the achievements in the field of computer technology during the following decades, echocardiography has evolved into an indispensable tool in modern cardiology, allowing real-time, high-resolution imaging for morphological as well as functional assessment of the heart. The application of Doppler techniques established echocardiography as the gold standard for evaluation of valvular heart disease, and also allowed the development of new quantitative methods for assessment of ventricular function based on myocardial tissue velocity imaging. For many years, the combination of echocardiography and stress testing, either pharmacologic or by means of physical exercise, has been a keystone in the evaluation of myocardial ischemia and viability. Finally, specific contrast agents developed for ultrasonographic imaging have improved image quality and extended the use of echocardiography to include the evaluation of myocardial perfusion.
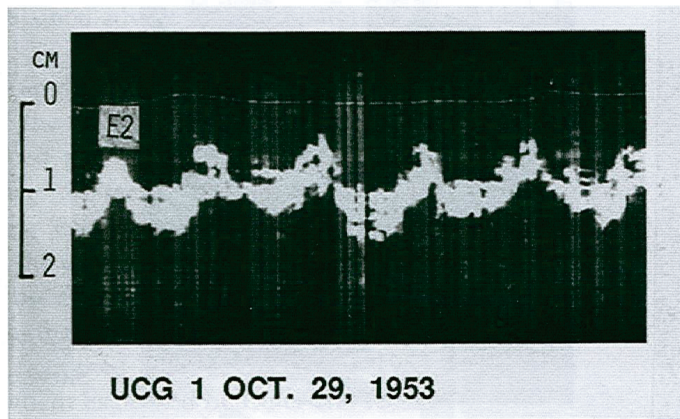
Figure 6. The first ultrasonographic image of the heart.

Assessment of left ventricular systolic function

Left ventricular systolic function may be expressed in many different ways, including contractility, stroke volume and ejection fraction (EF), the latter frequently used in echocardiography. Although the clinical impact of changes in EF largely depends on loading conditions, the prognostic implications of LV systolic dysfunction expressed as EF are undisputed [73, 74]. Furthermore, LVEF is useful in selecting patients who would benefit from specific therapies such as cardiac resynchronization pacemakers and implantable cardioverter defibrillators [75].

With the exception of three-dimensional imaging, echocardiographic methods for quantification of LVEF are based on assumptions of LV geometry. This has been considered as a major limitation of methods based on one-dimensional recordings of linear changes in LV dimensions, e.g. the Teichholz method, where geometrical assumptions ignore the influence of regional differences in systolic function [76]. Frequently used in clinical practice, estimation of LVEF by means of visual assessment, or eyeballing, has been shown to correlate to reference methods such as radionuclide imaging [77], but it is subject to significant interobserver variability, and is therefore inappropriate for serial evaluation [78]. The method of choice for quantification of LVEF recommended by the American Society of Echocardiography (ASE) is the biplane method of discs (also known as the modified Simpson's method). End-systolic and end-diastolic volumes are estimated from apical 2-chamber and 4-chamber views by dividing the LV into a number of elliptical discs and LVEF is calculated as the difference between end-diastolic and end-systolic volumes divided by the end-diastolic volume. Although new applications such as second harmonic imaging and the use of contrast agents have improved image quality, the accuracy of the biplane method of discs still depends on complete endocardial border definition. The evolution of 3D echocardiography has allowed the calculation of LV volumes independently of geometrical assumptions. Benefiting from this advantage, 3D echocardiography proved to be more accurate in determining LV volumes and EF when compared with 2D imaging [79, 80].

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While assessment of LVEF is essential for evaluation of patients with heart failure and valvular heart disease, the localization and extent of regional changes in LV systolic function have important clinical implications for patients with CAD. Recommended by the ASE, a 16-segment model has become the gold standard for echocardiographic assessment of regional LV wall motion [81]. Each myocardial segment is assigned a wall motion score (1, normal; 2, hypokinesis; 3, akinesis and 4, dyskinesis) and the relationship between LV segments and the distribution of the coronary arteries allows the identification of culprit lesions in acute MI as well as in stable CAD (Fig. 7).

Figure 7. The 16-segment model for assessment of regional LV wall motion. (Becher H, *Heart* 2004;90:vi23-vi30) Reprinted with the permission of the BMJ Publishing Group Ltd.

In order to overcome the limitations of suboptimal image quality, surrogate variables independent of volume calculations have been proposed for the estimation of LVEF. Left-ventricular long-axis displacement of the AV plane towards the apex is linearly correlated to LVEF by radionuclide angiography and a mean displacement of 10 mm or more is highly predictive of an EF of > 50% [82]. During the last two decades, parameters derived from myocardial velocity imaging techniques have been extensively used as markers of LV systolic function. These will be further discussed in subsequent sections.

Assessment of left ventricular diastolic function

As previously discussed, left ventricular filling during diastole is a complex process involving passive as well as active mechanisms of the left atrium and ventricle. The multifactorial nature of LV diastolic function therefore constitutes a major challenge in echocardiographic evaluation of patients with heart disease. On the other hand, it allows the use of several different parameters reflecting ventricular filling, providing a more complete assessment of LV diastolic function. Alterations in LV morphology such as hypertrophy should raise the suspicion of diastolic dysfunction because of the frequent causal relationship. Conversely, an increase in left atrial (LA) volume is often a result of elevated LV filling pressures secondary to diastolic dysfunction, although other causes have to be considered. Pressure-related indices of LV diastolic function may also be derived from Doppler recordings of tricuspid and pulmonary valvular flow profiles. Thus, in the absence of increased pulmonary vascular resistance or severe pulmonary hypertension, pulmonary artery diastolic pressure derived from recordings of pulmonary regurgitation flow correlates to LA pressure, thereby reflecting LV diastolic function [83]. Based on the fundamental mechanics of LV filling, pulsed wave Doppler recordings of the flow profiles of early and late filling in combination with recordings of pulmonary venous flow are frequently used for the assessment of LV diastolic function (Fig. 8). At early stages of diastolic dysfunction, disturbances in LV relaxation are reflected by a shift in the proportion between early and late filling (commonly referred to as the ratio between mitral E and A waves, the E/A ratio) and a prolongation of the E wave deceleration time. With increasing severity of diastolic dysfunction and progressively increasing LV filling pressures, the contribution of left atrial contraction to LV filling decreases, thereby resulting in normalization of the mitral inflow profile and the E/A ratio (often referred to as pseudonormalization). Additional recordings while the patient is performing the Valsalva maneuver as well as recordings of pulmonary venous flow profiles often allow distinction between normal and pseudonormal filling patterns. The most severe form of diastolic dysfunction is characterized by a restrictive filling pattern with a high peak E velocity, a short E deceleration time and a high E/A ratio. Changes in the isovolumic relaxation time (IVRT) also reflect diastolic function. At early stages of diastolic dysfunction delayed LV relaxation results in prolongation of the IVRT, whereas a restrictive filling pattern is typically associated with a short IVRT. Although useful in many clinical situations, analysis of mitral inflow has to be interpreted with caution as the different components may be influenced by extrinsic factors such as loading conditions. Moreover, in the presence of tachy-arrythmias, especially atrial fibrillation and flutter, analysis of E/A ratio and E deceleration time may be impossible. In addition to transmitral flow patterns, assessment of intraventricular flow propagation by means of color M-mode recordings is useful in the evaluation of diastolic function. As a result of the decrease in relaxation-related suction force present in diastolic dysfunction, the pressure gradient between the LA and LV is diminished, thereby slowing flow propagation towards the apex. Especially when used in conjunction with mitral E velocity, flow propagation velocity is correlated to LV filling pressure [84]. Assessment of diastolic function is probably the most common clinical application of myocardial velocity imaging techniques such as Doppler tissue imaging (DTI). A decrease in peak early velocity is typically seen at all stages of diastolic dysfunction. This will be further discussed in a following section.
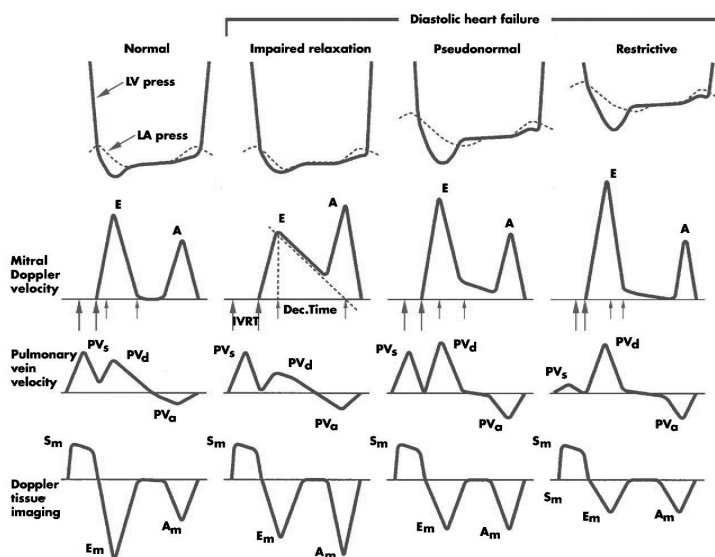
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Figure 8. Left ventricular (LV) and left atrial (LA) pressures during diastole, transmitral Doppler LV inflow velocity, pulmonary vein Doppler velocity, and Doppler tissue velocity. A, velocity of LV filling contributed by atrial contraction; Am, myocardial velocity during filling produced by atrial contraction; Dec. Time, E-wave deceleration time; E, early LV filling velocity; Em, myocardial velocity during early filling; IVRT, isovolumic relaxation time; PVa, pulmonary vein velocity resulting from atrial contraction; PVd, diastolic pulmonary vein velocity; PVs, systolic pulmonary vein velocity; Sm, myocardial velocity during systole. (Leite-Moreira, *Heart* 2006;92:712-718) Reprinted with permission of the BMJ Publishing Group Ltd.

Assessment of right ventricular function

Considering the complex geometry of the RV, it is obvious that accurate calculation of end-diastolic and end-systolic volumes from echocardiographic images would require advanced mathematical models not suitable for daily clinical practice. Nevertheless, changes in RV area between systole and diastole measured in the apical 4-chamber view, i.e. RV fractional area change (RVFAC), have been used as a surrogate for RVEF and have been shown to correlate well with RVEF as assessed by magnetic resonance imaging (MRI) [85]. By using three-dimensional echocardiography, RVEF may be assessed independently of volume assumptions, resulting in low variability and a high level of correlation with MRI [86]. However, RVFAC and 3D echocardiography are time-consuming and both methods depend on optimal image quality. Therefore, evaluation of RV function in daily practice is often based on visual assessment and simple surrogate parameters. Readily appreciated by means of visual assessment, alterations in RV morphology may reflect changes in RV contractility and afterload. Thus, a decrease in RV contractility resulting from a RVMI is frequently followed by dilatation and a change in shape of the RV. Analysis of tricuspid AV plane systolic excursion (TAPSE) in the RV lateral free wall offers a simple, quantitative surrogate parameter of RV function [87], also demonstrated to predict outcome in a variety of

clinical settings, including heart failure [88]. Finally, as previously discussed, the LV contributes significantly to RV function, mainly through septal interaction. Thus, simultaneous observation of LV performance is essential for a complete assessment of RV function.

DOBUTAMINE STRESS ECHOCARDIOGRAPHY

Detection of inducible ischemia is fundamental for risk assessment in patients with known or suspected CAD [89]. The choice of method for cardiac stress testing is based on multiple factors, including pre-test probability of disease, the patient's ability to exercise and the need for ischemia-localizing information and assessment of viability [90]. Since being introduced in the 70s, stress echocardiography (SE) has evolved as one of the gold standard methods for detection of inducible myocardial ischemia and viability [91, 92]. Recently, SE was shown to provide incremental prognostic information, above that of clinical and exercise-ECG data in patients with suspected CAD [93]. The basic principle of SE is the demonstration of new wall motion abnormalities induced by myocardial ischemia which, in turn, may be achieved by physical exercise (bicycle or treadmill), pacing or pharmacological stress. Common agents used for pharmacological stress include the synthetic catecholamine dobutamine and vasodilators such as adenosine and dipyridamole. For the latter two, ischemia is induced by dilatation of vessels in the myocardial microcirculation resulting in a redistribution of flow from stenosed to non-stenosed coronary vessels. Dobutamine induces ischemia through β_1-receptor stimulation, increasing heart rate, contractility and to a less extent systolic blood pressure. The diagnostic properties of different stress modalities are comparable and the choice between exercise-induced and pharmacological stress as well as between different pharmacological agents is influenced by other factors such as exercise capacity and available recourses [90]. However, one important advantage of dobutamine SE (DSE) is that it allows not only detection of ischemia, but also the evaluation of myocardial viability, thereby minimizing the number of tests needed for complete assessment.

Set-up and protocol

A typical contemporary set-up for DSE includes continuous ECG monitoring, an infusion pump for intravenous administration of dobutamine and a digital ultrasound-image acquisition system with adequate software, including harmonic imaging for optimal endocardial border detection. Intravenous contrast agents for LV opacification may be used in cases of suboptimal image quality as well as for myocardial perfusion studies. Various dobutamine protocols are used but typically, infusion is started at a rate of 5 µg/kg/min, increased every 3 min to 10, 20, 30 and 40 µg/kg/min during continuous ECG monitoring. If target HR ($\geq$ 85% of the predicted maximum HR) is not achieved, i.v. atropine may be added in 0.25 mg doses up to a maximum of 1–2 mg. Digital images are acquired at rest, during low dose infusion (10 µg/kg/min), at peak stress and during recovery. Termination criteria include detection of new wall motion abnormalities in > 1 segment, reaching target heart rate, onset of complex arrhythmias and intolerable symptoms.

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Image interpretation

Images are preferably interpreted in a side-by-side manner, allowing direct comparison at different dose stages. Regional wall motion is analyzed by using the previously mentioned 16-segment model proposed by the ASE. An increase in wall motion score (i.e. decreased systolic wall thickening) in at least 2 adjacent segments during stress is considered diagnostic for inducible ischemia. Similarly, a decrease in wall motion score (i.e. increased systolic wall thickening) in at least 2 adjacent segments during low-dose dobutamine implies the presence of myocardial viability. When examining patients with LV dysfunction, different reaction patterns may be recognized during dobutamine stress. A biphasic response refers to increased contractility during low-dose dobutamine infusion, followed by deterioration at peak stress, indicating the presence of viable myocardium in combination with inducible ischemia (i.e. hibernation). Increased contractility at low dose may also be followed by further improvement at peak stress, typically seen in viable myocardium after revascularization (i.e. stunning). In non-viable myocardium the response to dobutamine stress is either early deterioration at low dose or no change at all. In addition to the magnitude, analyzing the timing of wall motion may add diagnostic information, as contraction as well as relaxation is delayed during ischemia [94]. Attention should also be paid to LV dimensions and global systolic function. Although more frequently seen with exercise-induced stress, LV cavity dilatation and a decrease in LVEF during stress may indicate the presence of extensive CAD [95]. Visual wall motion analysis (WMA) is limited by interobserver variability [96]. Therefore, various parameters have been proposed for quantitative analysis during stress. Although still not completely incorporated into clinical practice, promising results have been seen in studies of parameters derived from myocardial velocity imaging, including peak systolic velocities and deformation indices such as strain and strain rate [97, 98].

Detection of coronary artery disease

As with other non-invasive tests, induction of ischemia during DSE depends on an optimal level of stress [99]. Thus, inability to achieve the target heart rate decreases sensitivity by way of false-negative results [100]. Other factors decreasing the probability of ischemia detection by DSE include the presence of LV hypertrophy and one-vessel disease [101]. Conversely, false-positive results, reducing specificity, are seen in patients with left bundle branch block and hypertension [102, 103]. Moreover, ischemic wall motion abnormalities may be induced during stress in patients with impaired coronary flow reserve due to microvascular dysfunction, even in the absence of significant epicardial CAD [104]. Analysis of pooled data from 17 studies in which the accuracy of stress echocardiography and myocardial perfusion imaging compared with an angiographic gold standard was examined showed sensitivity and specificity of 80% and 86%, respectively, for detection of CAD by DSE [92] (Figure 9a). An equal level of accuracy for DSE and myocardial perfusion imaging was seen, although sensitivity was slightly lower and specificity higher for DSE. There is a trend towards improved accuracy of DSE in more recent studies, probably reflecting the enhanced image quality achieved by new applications such as harmonic imaging and intravenous contrast agents [105, 106].

Prediction of left ventricular functional recovery

As previously discussed, assessment of myocardial viability has important clinical implications in patients with CAD. Based on its availability and low cost, DSE has been extensively used for the prediction of functional outcome in patients with ischemic LV dysfunction. In a meta-analysis of studies comparing DSE with perfusion imaging, DSE had sensitivity and specificity of 74% and 86%, respectively, for the prediction of functional outcome in post-MI patients (Fig. 9b). Corresponding values for the prediction of functional recovery after revascularization in patients with chronic ischemic LV dysfunction were 74% and 80%, respectively [92] (Fig. 9c). Compared with perfusion imaging, DSE seems to be less sensitive but significantly more specific in the prediction of functional outcome.

a   b   c

Figure 9. Sensitivity and specificity of dobutamine stress echocardiography and myocardial perfusion imaging for detection of coronary artery disease (a), prediction of left ventricular functional recovery after myocardial infarction (b) and revascularization for chronic ischemic left ventricular dysfunction (c). (Schinkel A. F. L. *Eur Heart J* 2003;24:789-800) Reprinted with the permission of Oxford University Press.

Safety

The safety of DSE has been analyzed in large populations including previously healthy subjects with suspected CAD as well as in patients with recent MI [107, 108]. Minor side effects of dobutamine infusion, including non-cardiac chest pain, hypotension and nausea are common, occurring at a frequency of 4–11%, whereas severe, life-threatening complications such as complex ventricular arrhythmias, MI and death are rare [109].

DOPPLER TISSUE IMAGING

Historical perspective and technical aspects

Named after the Austrian physicist Christian Doppler (1803–1853), the Doppler effect describes the change in frequency of waves when the observer is moving relative to the source, quantified by the Doppler equation (Fig. 10). Doppler suggested this effect in his studies on stars of different colors published in 1843 [110]. In 1845, Buys Ballot, a Dutch professor of mathematics and physics, confirmed the Doppler effect as regards

sound waves by using a group of musicians playing a calibrated note on a train in the Utrecht–Amsterdam line. In modern technology and science, the Doppler effect has several practical applications including underwater acoustics, astronomical measurements and medical imaging.

$$f = \left(\frac{v}{v + v_s} \right) f_0$$

Figure 10. The Doppler equation for calculation of frequency shift. f, observed frequency; v, the velocity of waves in the medium; v_s, the velocity of the source, relative to the medium; f_0, actual frequency of waves from the source.

The history of Doppler ultrasonography for detection of heart motion dates back to the early 1960s [111]. In the following decade, it was postulated that Doppler-based quantification of myocardial velocities could be of value for assessment of regional myocardial function. However, clinical application of myocardial velocity imaging was not shown to be feasible until 30 years later [112]. Since then, improvement of ultrasonographic imaging and computer technology has enabled the development of modern systems with digital image acquisition for off-line analysis and frame rates allowing temporal resolution at a level required for analysis of tissue velocities as well as for timing of cardiac motion.

In contrast to the low-amplitude and high-velocity signals obtained from blood flow, Doppler signals from myocardial tissue are characterized by high amplitude and low velocities; typically 10 times lower than those of normal blood flow in the heart. Myocardial velocities may be recorded either on line by pulsed wave spectral Doppler (Doppler tissue imaging, PW DTI) or off line by color coded Doppler 2D images (CC DTI), the former measuring peak velocities at a specific depth along a scanning line whereas the latter measures mean myocardial velocities in any segment within a complete scanning sector [113]. Velocities may be recorded either at the AV plane level (annular velocities) or at any myocardial segmental level between the base and apex. In the following, however, the term myocardial velocity will be exclusively used. Offline analysis of CC DTI recordings allows the calculation of additional parameters derived from myocardial velocities, including AV plane displacement (the time integral of velocity) and deformation indices as strain and strain rate, representing relative change in the length of a myocardial segment and its time rate. Careful adjustment of filter settings and gain as well as scale and sweep velocity is important for optimal signal quality. In modern ultrasound machines, presets are available for tissue velocity recordings.

Recording and interpretation of myocardial velocity data

Recording of myocardial velocities allows the analysis of regional changes in LV and RV contraction and relaxation as well as their temporal relationship to different phases of the cardiac cycle. Typically, PW DTI recordings include peak systolic as well as early and late diastolic velocities (Fig. 11). As analysis is performed on line, the region

of interest has to be pre-specified and measurements in multiple segments require repeated recordings. In contrast, color-coded recordings allow off-line analysis and tracking of regional data from any point of interest within the scanned sector. As previously discussed, off-line analysis of CC DTI recordings also allows calculation of derived parameters such as strain and strain rate.
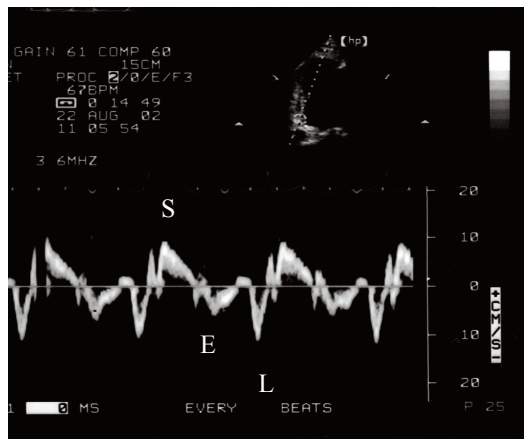

Figure 11. Myocardial systolic (S), early (E) and late (L) diastolic velocities recorded at the septal left-ventricular site, near the mitral annulus by means of pulsed-wave Doppler tissue imaging in the apical 4-chamber view.

Validation

Establishing the relationship to hemodynamic parameters as well as to results of non-invasive gold standard methods has been important for the validation of myocardial velocities as markers of cardiac function. Several studies with simultaneous echocardiographic and invasive hemodynamic evaluation have demonstrated the correlation between myocardial systolic and diastolic velocities and invasive indices of LV systolic and diastolic function, such as the peak positive and negative first derivates of LV pressure (dP/dt_{max}) and the time constant of isovolumic relaxation (Tau, $\square$) [114, 115]. The ratio between the early diastolic velocity of mitral inflow and myocardial diastolic velocity assessed by DTI (E/E´) has been shown to correlate with LV filling pressures [116]. Doppler-derived myocardial velocities are considered to be relatively insensitive to loading conditions, although conflicting results from experimental and clinical studies have been reported [117-119]. Comparative studies have also confirmed the relationship between average systolic velocities and LVEF assessed by gold-standard methods [120]. Similarly, RV systolic myocardial velocities correlate with invasive hemodynamic indices of RV systolic function as well as with RVEF in radionuclide angiography [121, 122]. In addition to validation, demonstration of feasibility and reproducibility as well as determination of reference values for healthy subjects have been important steps towards the introduction of myocardial velocity imaging techniques in clinical practice [123]. In the absence of heart disease,

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significant negative correlation are seen between age and LV velocities, more pronounced for diastolic than systolic velocities. In contrast, no such correlations are seen as regards the RV. Furthermore, myocardial velocities are higher in the basal compared with the apical parts of the ventricles.

Clinical applications

As a measure of global systolic function, the average of systolic myocardial velocities from multiple LV sites correlates with LVEF, and a cut-off value of > 7.5 cm/s has been shown to be an accurate predictor of normal LVEF [124]. Furthermore, reduced LV myocardial systolic velocity has been considered as a marker of systolic LV dysfunction in subclinical disease [125]. The peak systolic velocity in the RV free wall correlates relatively well with global RV systolic function and a value of < 11.5 cm/s predicts RVEF of < 45% with sensitivity and specificity of 90% and 85%, respectively. Currently, the use of myocardial diastolic velocities for evaluation of LV diastolic function is probably the most well established clinical application of DTI. As previously mentioned, there is a clear relationship between E/E´ and LV filling pressure. A value of > 15 identifies patients with elevated filling pressures, whereas a value of < 8 is highly predictive of a normal filling pressure [126]. Typically, early diastolic myocardial velocity is reduced at all stages of diastolic dysfunction and this is therefore useful for distinction between normal and pseudonormal filling patterns as well as to differentiate between restrictive cardiomyopathy and constrictive pericarditis [127]. Numerous studies have demonstrated the prognostic value of Doppler-derived myocardial velocities in different disease states including heart failure, hypertension and CAD [128-130]. Although not recommended in current guidelines, the temporal relationships between systolic velocity parameters at different LV sites have been used to assess intraventricular dyssynchrony and to predict the response to cardiac resynchronization therapy in heart failure patients [131].

Finally, myocardial velocities and deformation indices have been used as quantitative markers of ischemia and viability during stress echocardiography. In a study including 242 patients undergoing DSE for suspected CAD, the diagnostic value of systolic myocardial velocities was equal to that of visual WMA [132]. Assessment of myocardial velocities during dobutamine stress is feasible, with relatively high reproducibility, especially for systolic velocities in basal myocardial segments [133]. In healthy subjects, peak systolic velocities in basal segments typically increase 100% at peak stress compared with 50–75% in patients with CAD. The best discriminators of disease, however, seem to be the absolute values of systolic velocities at peak stress [97]. Furthermore, deformation indices such as strain rate have been shown to add incremental diagnostic value to WMA during DSE for suspected CAD [134]. In patients with ischemic LV dysfunction, changes in systolic myocardial velocities during low-dose dobutamine infusion have been used for the assessment of myocardial viability and prediction of LV recovery after revascularization [135]. The use of strain rate imaging during DSE has been shown to add incremental value to WMA in the assessment of myocardial viability and prediction of LV functional recovery after revascularization [136].

THE MYOCARDIAL PERFORMANCE INDEX

In 1995 Tei *et al.* proposed a new index of combined systolic and diastolic LV function based on time intervals from Doppler measurements of mitral inflow and LV outflow (the Tei-index) [137]. The Tei-index is calculated by dividing the sum of the isovolumic contraction and relaxation time intervals by the ejection time (Fig. 12). The rationale for the use of such an index is that in many disease states systolic and diastolic dysfunction coexist. As a result, prolongation of the isovolumic intervals as well as shortening of the ejection time reduces the time for effective pumping. Thus, taking both systolic and diastolic aspects of ventricular function into account, the Tei-index could be a more sensitive measure of disease than parameters separately assessing systolic or diastolic function. In their first description of the Tei-index, the authors demonstrated its feasibility and reproducibility, established reference values for healthy subjects and showed that the index increased with disease severity in patients with dilated cardiomyopathy. In subsequent publications, the diagnostic and prognostic values of the Tei-index have been established in a variety of clinical settings including ischemic heart disease, heart failure and valvular heart disease [138-140]. Similarly, a RV Tei-index has been used as a marker of RV function in patients with pulmonary hypertension, MI and congenital heart disease [141-143]. Moreover, applied during DSE, the Tei-index, also named the myocardial performance index (MPI) has been used as a marker of inducible ischemia and contractile reserve [144, 145] as well as for prediction of prognosis after MI [146]. An alternative mode of calculating the MPI from time intervals derived by DTI has been proposed [147] (Fig 13). Values of MPI derived from DTI correlate with values of the conventionally measured Tei-index but are typically higher. Moreover, although conflicting results have been reported, MPI derived from DTI seems to be less sensitive to loading conditions than the conventionally measured Tei-index [148].

Figure 12. Calculation of the myocardial performance index (MPI) from Doppler recordings of mitral inflow and left ventricular outflow. MPI=(ICT + IRT) / ET = (a – b) / b. ET, ejection time; ICT, isovolumic contraction time; IRT, isovolumic relaxation time; LV, left ventricle. (Tekten T. *Echocardiography* 2003;20:503-10) Reprinted with the permission of John Wiley and sons.

Figure 13. Calculation of the myocardial performance index (MPI) from Doppler tissue imaging recordings. MPI = (a – b) / b.
Am, diastolic velocity during atrial contraction; Em, early diastolic velocity; Sm, systolic velocity. (Tekten T. *Echocardiography* 2003;20:503-10) Reprinted with the permission of John Wiley and sons.

AIMS OF THE THESIS

The aims of this thesis was to evaluate the use of Doppler tissue imaging as a complement to conventional echocardiographic parameters at rest and during dobutamine stress in patients with acute ST-elevation myocardial infarction, and with specific focus on:

- The use of RV systolic velocities for the detection of RV infarction and for the assessment of RV function over time.

- Evaluation of myocardial velocities in patients with complete recovery of conventional echocardiographic parameters of LV function at late follow-up.

- The application of MPI derived from DTI during DSE as a quantitative marker of inducible ischemia.

- The value of MPI derived from DTI during DSE as a predictor of late recovery of LV systolic function.

PATIENTS AND METHODS

Patients

The study population consisted of 90 patients included in the Swedish Early Decision reperfusion Study (SWEDES) in which reperfusion treatment with thrombolysis was compared with primary PCI in patients with STEMI [149]. Patients were enrolled at Södersjukhuset, Stockholm, Sweden, between November 2001 and May 2003. Inclusion criteria were characteristic chest pain with a duration of a maximum of 6 h, the presence of ST-segment elevation of at least 1 mm in two contiguous leads and diagnostic serial changes in serum cardiac troponin T concentrations ($\geq$0.2 μg/L). All patients received reperfusion therapy by means of thrombolysis (n=45) or primary PCI (n=45). Additional pharmacological treatment was introduced according to recommendations in present guidelines. A symptom-limited bicycle stress test was performed prior to discharge.

Healthy subjects

In Study II, 41 healthy subjects (27 male and 14 female, age 57 ± 13 years, 7 smokers) without a history of cardiovascular disease, diabetes mellitus or hypertension and with a normal resting ECG and echocardiogram served as controls. In Study I, a subgroup of 31 healthy subjects was used, as the age distribution was slightly different compared with that in Study II.

METHODS

ECG

Standard 12-lead electrocardiograms with the addition of the right precordial lead V4R were recorded at presentation and the day after admission. Electrocardiographic criteria for inclusion are defined above. Right ventricular infarction was defined as an ST-segment elevation of $\geq$ 1 mm in lead V4R.

Echocardiography

Echocardiographic recordings were made using a Hewlett-Packard Sonos 5500 (Andover, Mass, USA) phased-array system with DTI technology and a variable frequency transducer (2.0–4.0 MHz). Subjects were examined in the left lateral decubitus position at day 1 (within 24 hours after admission), 5–7 days and 6 months after admission. Images were stored digitally on magneto-optical discs for off-line measurements and were analyzed separately by a physician blinded to clinical data. Recordings and calculations of cardiac dimensions were made according to the recommendations of the American Society of Echocardiography (ASE) [81]. If image quality allowed adequate endocardial border detection, global LV systolic function expressed as EF was calculated by the biplane method of discs. Alternatively, EF was

assessed visually by two physicians and in case of disagreement, a consensus decision was made. Regional LV function was assessed in a 16-segment model as proposed by the ASE [81]. Parameters of LV diastolic function including the ratio between transmitral E-wave and A-wave velocities, mitral E-wave deceleration time, isovolumic relaxation time and pulmonary venous flow pattern were assessed using PW flow Doppler recordings of mitral inflow and LV outflow as well as of pulmonary venous flow. Right ventricular function was assessed by TAPSE in M-mode recordings of the RV lateral free wall.

Dobutamine stress echocardiography

Stress echocardiography was performed at day 5–7 after admission. During continuous 12-lead ECG monitoring, dobutamine was infused at rates of 5, 10, 20, 30 and 40 µg/kg/min. If the target HR ($\geq$ 85% of the predicted maximum HR) was not achieved, iv atropine was added at 0.25 mg doses up to a maximum of 1 mg. Echocardiographic recordings including DTI were obtained at rest, during low-dose infusion (10 µg/kg/min.) and peak stress. Images were stored digitally and analyzed separately.

Wall motion analysis

For interpretation of DSE results, digitally stored images were displayed in a side-by-side manner allowing simultaneous assessment of recordings at different levels of stress. Using the 16-segment model, each segment was assigned a wall motion score (1 = normokinesia, 2 = hypokinesia or 3 = akinesia or dyskinesia). Wall motion score index (WMSI) was calculated as the sum of wall motion scores divided by the number of segments assessed. Inducible ischemia was defined as worsening of wall motion in at least 2 adjacent segments during stress. In segments with normal wall motion at rest, an ischemic response was defined as a change to hypokinesia or akinesia/dyskinesia at peak stress. In segments with hypokinesia or akinesia/dyskinesia at rest, an ischemic response was defined as either an improvement at low dose with a subsequent worsening at peak stress (biphasic response) or a continued hypokinesia at low dose, followed by further worsening to akinesia/dyskinesia at peak stress [150]. Myocardial viability was defined as an improvement of wall motion between rest and low dose (i.e. a change from akinesia to hypo- or normokinesia, or a change from hypokinesia to normokinesia) in at least 2 adjacent segments [151].

Doppler tissue imaging

Left and right ventricular longitudinal myocardial velocities were recorded using pulsed-wave DTI. For the LV, peak systolic, and early and late diastolic velocities were recorded from the septal, lateral, inferior and anterior sites near the mitral annulus in apical 2- and 4-chamber views. Similarly, for the RV, myocardial velocities were recorded from the lateral free wall near the tricuspid annulus in the apical 4 chamber view. The custom filter settings for DTI recordings were used with adjustment of the low pass filter (50Hz) and gain for optimal image quality. A 1.7 mm sample volume was used. All parameters were calculated as mean values of three consecutive cycles. In Study II, the mean myocardial velocity from the 4 LV sites was used as a measure of global systolic function. E/E' was calculated by dividing the peak early diastolic

velocity of mitral inflow by the peak early diastolic myocardial velocity from the septal LV site.

Myocardial performance index

From DTI recordings at rest and during dobutamine stress, MPI was calculated as the sum of the time intervals corresponding to isovolumic contraction and relaxation divided by the interval corresponding to ejection time (Fig. 13).

Coronary angiography

Coronary angiography was performed within 24 hours after DSE. All angiograms were assessed visually and significant stenosis was defined as luminal narrowing of at least 50% in two different projections. Patients with the culprit lesion located in the RCA were considered to have RV involvement if the occlusion was located proximal to the first RV branch. According to national guidelines at the present time, PCI was performed if ischemia was present in a preceding bicycle stress test.

Statistical analysis

Statistical analyses were performed using SPSS Statistical software versions 16 and 17 (SPSS Inc., Chicago, Illinois, USA). Numerical values are expressed as means and one standard deviation. According to their distributions, comparisons of continuous variables between groups were made using Student's unpaired t test or the Mann–Whitney U test. Paired samples t tests were used for comparisons within groups. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Analysis of variance (ANOVA) with Bonferroni correction was used for comparisons of more than two groups. A p-value of < 0.05 was considered statistically significant. In Studies I, III and IV, receiver operating characteristics (ROC) curves were used to determine cut-off values for RV systolic velocity and MPI. In order to assess inter- and intra-observer variability, a second analysis in 20 randomly selected patients was made 1 month later by the first, as well as a second reviewer. In Study I, variability was calculated as the absolute difference between observations divided by their mean. In Studies III and IV, variability of WMA was expressed as the level of agreement (Kappa) in the classification of results as positive or negative for ischemia and viability. For MPI, variability was assessed using Cronbach's alpha and the Bland–Altman method [152]. In Study IV, multivariable logistic regression analysis was used to assess the value of MPI as a predictor of LV functional recovery.

Ethics

This study was approved by the Local Ethics Committee of the Karolinska Institute in Stockholm. All patients gave their informed consent to participate.

RESULTS

Study flow-chart

Time courses, methods and numbers of patients in Studies I–IV are presented bellow.

| Day 0-1 ECG Echo | Day 5-7 Echo DSE Angio | | 6 months Echo | |

Study I
n=71

Study II
n=68

Study III
n=77

Study IV
n=76

Clinical characteristics and outcome

Baseline characteristics of the 90 patients included in the study are presented in Table 1. One patient was excluded after withdrawal of consent prior to DSE and control angiography. One patient with ischemic stroke on day 2 after admission was also excluded. There were 3 in-hospital deaths, of which 2 occurred during the first 24 hours and 1 at day 3 after admission. One patient died and 3 patients were admitted because of MI during the first 6 months after discharge.

Table 1. Baseline clinical characteristics of MI patients

	n = 90
Age (yr)	65±13
Sex (M/F)	64 (71%) / 26 (29%)
Smokers	21 (23%)
Diabetes	18 (20%)
Hypertension	25 (28%)
History of MI	13 (14%)
TL/PCI	45 / 45
Ant/Inf MI	32 (36%) / 58 (64%)
ST-elevation V4R	23 (26%)
Trop T (µg/L)	6.5 ± 6.1

MI, myocardial infarction; TL, thrombolysis; PCI, percutaneous coronary intervention; Ant, anterior; Inf, inferior; Trop. T, Troponin T.

Right ventricular infarction (Study I)

Electrocardiographic signs of RV involvement (ST-elevation in V4R) were present in 17 (24%) of the patients included in Study I. In 15 of these, the culprit coronary lesion was located in the RCA with 13 (87%) proximal to the first RV branch. In patients without ST-elevation in V4R the culprit lesion was in the LAD in 24 (44%), the LCx in 5 (9%) and the RCA in 25 patients (46%). Of the latter, 3 patients (12%) had an occlusion proximal to the first RV branch. In 3 patients persistent ST-elevation in V4R was seen the day after admission. Clinical signs of RV infarction including hypotension and jugular venous distention were seen in 4 patients (24%), of whom all had a proximal RCA occlusion. Analysis of RV myocardial systolic velocity and TAPSE during the first 24 hours after admission identified patients with RV infarction with sensitivity of 89% and 82% and specificity of 71% and 76%, respectively (cut-off values 13 cm/s for RV systolic velocity and 20 mm for TAPSE). In patients with RV infarction, a significant increase in RV systolic velocity and TAPSE was seen between day 1 and the 6-month follow-up. However, RV systolic velocity at follow-up was still significantly lower than in patients without RV infarction (12.3 ± 2.3 vs. 14.2 ± 2.4 cm/s, $p < 0.01$).

Coronary angiography and revascularization procedures

As a result of incomplete reperfusion or recurrent ischemia, urgent coronary angiography with revascularization was performed during the first 48 hours after admission in 14 of the 45 patients initially treated with thrombolysis. No angiographic follow-up at day 5–7 was carried out in these patients. Seventy-two patients underwent control angiography at day 5–7. Of these, 17 were subject to revascularization by way of PCI (10 patients initially treated with thrombolysis and 7 patients initially treated with primary PCI). Between discharge and 6 months' follow-up, 13 patients underwent revascularization procedures (10 PCI, 3 CABG). Angiographic data from primary PCI, urgent secondary PCI or control angiography were available in 89 patients. Prior to

revascularization procedures, 41 patients (46%) had 1-vessel disease, 31 (35%) had 2-vessel disease and 18 (20%) had 3-vessel disease.

Detection of coronary artery disease (Study III)

Dobutamine stress echocardiography

Dobutamine stress echocardiography was performed in 77 patients (53 men and 24 women, aged 64±13 years). Side effects resulting in termination of dobutamine infusion included frequent premature ventricular contractions (1 patient) and hypotension (2 patients). Blood pressure increased marginally during dobutamine infusion ($136 \pm 22 / 81 \pm 14$ mmHg at rest to $145 \pm 19 / 83 \pm 13$ mmHg at peak stress). Target HR was achieved in 34 patients (mean $89 \pm 6\%$ of the age-predicted maximum HR), whereas in the remaining 44 patients, HR did not reach target levels (mean $76 \pm 9\%$ of the age-predicted maximum HR).

Wall motion analysis

Of 1232 segments, 1164 were analyzed at rest, 1158 at low dose and 1148 at peak stress. An ischemic response was observed in 33 patients (43%). Sensitivity and specificity of WMA for the diagnosis of LAD, LCx and RCA disease were 64% and 87%, 53% and 84%, and 60% and 81%, respectively.

Myocardial performance index during dobutamine stress

From recordings at the 4 LV sites in 77 patients, 308 MPI values were obtained, each considered to be a measure of regional LV function. Changes in MPI during dobutamine stress and the relationship to the presence of stenosis in the supplying coronary artery are illustrated in Fig. 14.

Figure 14. MPI at rest and during dobutamine stress in regions supplied by stenosed and non-stenosed vessels.

At rest and low dose, no significant differences were seen between the groups. At peak stress, however, MPI values were significantly higher at LV sites supplied by stenosed vessels. The relative change in MPI between rest and peak stress in regions supplied by stenosed and non-stenosed vessels is presented in Fig.15. From analysis of ROC curves it was evident that the relative change in MPI between rest and peak stress was a better discriminator of CAD compared with absolute values of MPI at peak stress (area under the curve 0.82, 95% CI 0.77–0.87, *p < 0.001* for relative change and 0.71, 95% CI 0.65–0.77, *p < 0.001* for absolute values at peak stress). A cut-off value of a 15% increase in MPI identified stenosis with sensitivity and specificity of 59% and 80% for the LCx and 85% and 72% for the RCA. For the LAD, corresponding values were 87% and 80% when the anterior LV site was used and 67% and 86% for the septal site.

Figure 15. Relative change in MPI between rest and peak stress in regions supplied by stenosed and non-stenosed vessels.

Prediction of LV functional recovery (Study IV)

Wall motion analysis

Improvement of wall motion in the infarct region during low-dose DSE was observed in 42 of 76 patients (55%). Sensitivity, specificity and negative and positive predictive values for the prediction of LV regional wall motion recovery were 82%, 84%, 76% and 88%, respectively.

Myocardial performance index

Anterior and inferior infarct regions were identified on the basis of the location of wall motion abnormalities at rest. Changes in MPI in infarct- and remote regions during low-dose DSE are presented in Fig. 16.

Figure 16. MPI at rest, during low-dose dobutamine and at 6 months' follow-up in infarct regions with and without subsequent functional recovery as well as in non-infarct regions.

Decreasing MPI values during low-dose dobutamine infusion were observed in patients with subsequent recovery of wall motion. Conversely, an increase in MPI during DSE was seen in patients without functional recovery. Fig. 17 displays relative changes in MPI between rest and low-dose dobutamine infusion in patients with and without functional recovery. Analysis of the ROC curve showed that with a cut-off value of 0% and a specificity level of 84%, changes in MPI during low-dose DSE predict LV functional recovery with sensitivity and negative and positive predictive values of 87%, 81% and 89%, respectively (AUC 0.86, 95% CI 0.77–0.95, $p < 0.001$). Changes in MPI values paralleled changes in wall motion over time. Thus, at 6 months' follow-up, MPI values in patients with recovery of LV function were no longer significantly different from those in non-infarct regions. In patients without recovery of wall motion, MPI values remained at baseline levels, significantly higher than those of non-infarct regions.
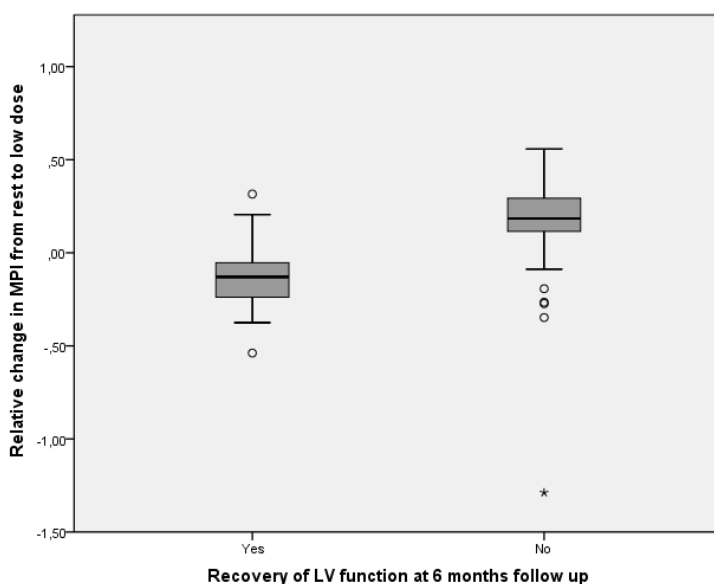
Figure 17. Relative change in MPI during low-dose dobutamine infusion in infarct regions with and without subsequent functional recovery

Temporal changes in LV function (Studies II and IV)

Study II

At baseline (day 5–7), LV systolic function in patients with subsequent normalization of wall motion was significantly better compared with patients in whom wall motion abnormalities persisted. This was evident for all measures of LV systolic function, i.e. LVEF, WMSI and mean systolic myocardial velocity (S mean). Regarding LV diastolic function, however, conventional echocardiographic parameters did not differ significantly between the groups, whereas mean early diastolic myocardial velocity (E mean) was significantly higher and E/E' significantly lower in patients with complete recovery of wall motion.

Table 2 displays the temporal changes in different parameters of LV function between baseline and follow-up (also including baseline DTI parameters not published in Study II). Although still reduced after 6 months, a small but significant increase in LVEF was seen in patients with persistent wall motion abnormalities ($45 \pm 7.0\%$ to $48 \pm 8.2\%$, $p < 0.01$). Mean systolic myocardial velocities increased significantly in both groups, but the difference between groups was still evident at follow-up (7.1 ± 1.4 cm/s for patients with persistent wall motion abnormalities and 8.3 ± 1.3 cm/s for patients with complete recovery of wall motion, $p < 0.01$). With the exception of a significant increase in E-deceleration time in patients with persistent wall motion abnormalities, conventional parameters of LV diastolic function remained unchanged over time. A significant decrease in E/E' was seen in both groups whereas early diastolic myocardial velocity increased significantly only in patients with complete recovery of wall motion (8.6 ± 2.4 cm/s to 9.3 ± 1.3 cm/s, $p < 0.01$).

At follow-up, systolic as well as diastolic myocardial velocities were significantly lower and E/E' was significantly higher in patients with complete recovery of wall motion compared with healthy subjects.

Table 2. Temporal changes in LV function (Study II)

	Persistent wall motion abnormalities n=49		Complete recovery of wall motion n=19	
	Day 5–7	6 months	Day 5–7	6 months
Systolic function				
LVEF (%)	45 ± 7.0	48 ± 8.2**	56 ± 5.0	57 ± 4.4
WMSI	1.6 ± 0.4	1.5 ± 0.4	1.2 ± 0.2	1.0*
S mean (cm/s)	6.5 ± 1.2†	7.1 ± 1.4**	7.6 ± 1.2	8.3 ± 1.3**
Diastolic function				
E/A ratio	1.1 ± 0.6	1.0 ± 0.5	1.1 ± 0.3	1.1 ± 0.26
E-dec time (ms)	206 ± 56	262 ± 66*	215 ± 36	218 ± 42
IVRT (ms)	93 ± 34	102 ± 24	96 ± 17	91 ± 17
E mean (cm/s)	7.2 ± 1.8††	7.4 ± 2.0	8.6 ± 2.4	9.3 ± 1.3**
L mean (cm/s)	8.8 ± 2.3††	8.6 ± 2.1	9.6 ± 1.7	10.4 ± 2.4
E/E'	11 ± 4.9†	8.3 ± 2.8**	9.1 ± 2.7	6.5 ± 2.3**

S mean, mean systolic myocardial velocity from 4 LV sites; E mean, mean early diastolic myocardial velocity from 4 LV sites; L mean, mean late diastolic myocardial velocity from 4 LV sites
* $p < 0.001$ compared with day 5–7
**$p < 0.01$ compared with day 5–7
† $p < 0.01$ compared with patients with complete recovery of wall motion
†† $p < 0.05$ compared with patients with complete recovery of wall motion
 p-values for between-group comparisons are only presented for unpublished data

Study IV

Parameters of LV systolic and diastolic function (including myocardial velocity data not included in Study IV) at baseline and follow-up are presented in Table 3. Similar to findings in Study II, baseline global LV systolic function was better in patients with subsequent functional recovery (LVEF 49 ± 7.2% vs 44 ± 7.8 for patients without functional recovery, $p < 0.05$). However, this was not reflected by differences in regional systolic dysfunction expressed as peak systolic myocardial velocity (S peak) at the LV infarct site or by differences in WMSI. Conventional parameters of diastolic function were equal in the two groups at baseline, whereas peak early diastolic myocardial velocity (E peak) at the LV infarct site was significantly higher and E/E' significantly lower for patients with recovery of LV function (8.0 ± 2.2 cm/s vs. 6.5 ± 2.2 cm/s, $p < 0.01$ for E peak and 8.6 ± 2.6 vs. 11 ± 5.3, $p < 0.05$ for E/E'). In patients with recovery of LV function, significant changes over time were seen for all systolic

as well as DTI-based diastolic parameters of LV function. In contrast, no such changes were observed in patients without functional recovery.

Table 3. Temporal changes in LV function (Study IV)

	MI No recovery of LV function (*n*=31)		MI Recovery of LV function (*n*=45)	
	Day 5–7	**6 months**	**Day 5–7**	**6 months**
Systolic function				
LVEF (%)	44 ± 7.8	45 ± 9.7	49 ± 7.2	54 ± 5.8*
WMSI	1.5 ± 0.4	1.5 ± 0.4	1.4 ± 0.3	1.2 ± 0.3*
S peak (cm/s)	7.0 ± 1.4	6.7 ± 1.5†	7.5 ± 1.5	8.1 ± 1.6**
Diastolic function				
E/A ratio	0.9 ± 0.4	1.0 ± 0.4	1.2 ± 0.6	1.1 ± 0.5
E-dec time (ms)	216 ± 63	258 ± 55*	224 ± 49	233 ± 53
IVRT (ms)	97 ± 31	103 ± 20	94 ± 16	95 ± 20
E peak (cm/s)	6.5 ± 2.2†	6.5 ± 2.1†	8.0 ± 2.2	8.8 ± 1.9**
L peak (cm/s)	8.9 ± 2.2	8.3 ± 1.9†	9.0 ± 1.7	9.7 ± 2.1
E/E'	11 ± 5.3††	12 ± 6.1†	8.6 ± 2.6	7.3 ± 2.2***
MPI	0.81 ± 0.27	0.86 ± 0.25†	0.75 ± 0.22	0.58 ± 0.11*

S peak, peak systolic myocardial velocity at LV infarct site ; E peak, peak early diastolic myocardial velocity at LV infarct site ; L peak, peak late diastolic myocardial velocity at LV infarct site.

* *p* < 0.001 compared with day 5−7

** *p* < 0.01 compared with day 5−7

*** *p* < 0.05 compared with day 5−7

† *p* < 0.01 compared with patients with recovery of LV function

† † *p* < 0.05 compared with patients with recovery of LV function

p-values for between-group comparisons are only presented for unpublished data

GENERAL DISCUSSION

Right ventricular infarction (Study I)

Early diagnosis of RV involvement in patients with STEMI is important. Although not always present, hemodynamic impairment may appear suddenly, requiring specific treatment considerations. The ischemic right ventricle is less compliant and therefore depends on adequate preload and heart rate to maintain a normal stroke volume and cardiac output. Hence, pharmacological agents affecting these parameters must be used with caution and plasma volume expansion as well as temporary pacing are often indicated. Moreover, attention should be paid to the coronary anatomy as the patency status of RV branches from the RCA may affect long-term prognosis in patients with RV infarction [69]. Among different methods for diagnosis of RV infarction, ECG remains the most simple and available, allowing very early recognition of RV involvement, even in the pre-hospital phase. The presence of ST-elevation in right precordial leads, especially V4R, has been extensively used for identification of RV infarction and the correlation with echocardiographic, scintigraphic and invasive hemodynamic evidence of RV involvement has been established [153-155]. These ECG changes, however, are transient and sometimes disappear within the first few hours of onset [67], as also evident in our study, where resolution of ST changes in V4R was observed within 24 hours in 82% of the patients. Gold standard methods for evaluation of RV function such as cardiac magnetic resonance imaging and invasive hemodynamic measurements are time-consuming and usually not suitable for early assessment. In contrast, echocardiography has evolved as a simple tool for early evaluation of patients with acute MI. Right ventricular dysfunction may be appreciated visually by the presence of wall motion abnormalities, or by quantitative methods such as fractional area change [85]. In an acute setting, however, suboptimal imaging conditions may limit the feasibility of methods requiring complete endocardial border detection. Therefore, easily assessable surrogate parameters of RV function such as peak systolic myocardial velocity and TAPSE are attractive options for echocardiographic evaluation of patients with suspected RV infarction. Indeed, the results of previous studies show not only that RV systolic velocity and TAPSE correlate well with RVEF, but also that they may identify patients with RV involvement in the acute phase of MI [68, 122, 156, 157]. In our study, RV free wall velocity of < 13 cm/s identified the vast majority of patients initially presenting with ST-elevation in V4R. However, the application of this cut-off value resulted in a relatively low specificity of 71% which probably is an overestimation of the true specificity because of selection bias from exclusion of patients with well-known causes of reduced RV myocardial velocities. Nevertheless, in this context, false-positive results have acceptable clinical consequences, mainly consisting of increased attention to clinical signs of hemodynamic impairment. Furthermore, it cannot be ruled out that some of the false-positive results actually reflected persistent RV dysfunction following transient RV ischemia.

In our study, use of an angiographic definition would have resulted in identification of fewer RV infarctions compared with an ECG-based definition (13 and 17 patients, respectively). It must be pointed out though, that the presence of ST-elevation in V4R

reflects transmurality of RV ischemia, not necessarily implicating extensive myocardial necrosis. Distribution of the coronary vessels supplying the RV is multi-territorial, with contribution from the right as well as the left coronary arteries. Branches arising from the LAD mainly supply the apical part, representing a limited proportion of the entire RV. In our study, patients in whom RV infarction was associated with an occlusion in the LAD or distal RCA did not develop hemodynamic impairment. In contrast, clinical manifestations of RV infarction were relatively common in patients with proximal RCA occlusions. Hemodynamic impairment may be even more severe if the proximal occlusion affects right atrial branches thereby compromising perfusion of the right atrium, and resulting in loss of atrial contribution to RV diastolic filling [158]. Thus, early angiographic assessment allows identification of patients at risk of hemodynamic impairment. However, in the absence of invasive facilities, echocardiographic assessment remains an important diagnostic tool in patients with RV infarction. This also holds true for serial assessment and follow-up of RV function over time. Right ventricular function typically exhibits relatively rapid recovery after infarction, even in the absence of reperfusion of the culprit vessel [159, 160]. Mechanisms protecting the RV from extensive permanent ischemic dysfunction include abundant collaterals, a favorable balance between oxygen supply and demand and a coronary flow profile allowing diastolic as well as systolic perfusion of the RV myocardium [63, 161, 162].

In contrast, the results of our study suggest that residual RV myocardial damage may persist even at late follow-up. Although increased over time, systolic RV myocardial velocities in patients with RV infarction remained reduced compared with those in patients without RV infarction. These findings have been confirmed in a recent study in which peak systolic velocity and RV MPI were used for evaluation of RV function in the early and late phase after a first inferior MI [163]. The possible prognostic implications of these persistent abnormalities, however, were not addressed in either of the studies.

Detection of coronary artery disease (Study III)

The impact of ischemia on different aspects of LV function is classically described by the sequential chain of events in the ischemic cascade (Fig. 5). Initial abnormalities in coronary blood flow are followed by regional diastolic dysfunction, systolic wall motion abnormalities, ischemic ST-depression and finally symptoms. The temporal relationship between these events may contribute to the understanding of differences in diagnostic properties of various stress tests. It is evident that observation of perfusion abnormalities would be the most sensitive tool for detection of CAD. Indeed, most comparative studies show a slightly higher sensitivity for myocardial perfusion imaging vs. DSE with WMA [92]. The additive value of perfusion in regard to function is further illustrated by the increase in sensitivity in the detection of CAD seen with myocardial contrast echocardiography compared with WMA alone [164].

Quantitative markers of ischemia – diastolic indices

The ischemic cascade also forms a rationale for the use of diastolic indices as markers of ischemia during stress. Experimental as well as clinical studies have consistently shown that regional diastolic dysfunction occurs within seconds of ischemia induction, followed by regional systolic wall motion abnormalities and global LV dysfunction

[31, 165]. A linear relationship has been established between the extent of ischemia and regional diastolic myocardial velocities [166]. In clinical practice, conventional parameters of diastolic function have been difficult to apply in stress echocardiography because of the load-dependency of mitral inflow. In contrast, DTI-derived parameters such as diastolic myocardial velocity and E/E' seem to be sensitive to stress-induced ischemia [167, 168], although specificity is negatively influenced by the presence of other causes of diastolic dysfunction such as LV hypertrophy and diabetes mellitus. Interestingly, the results of a recent study also demonstrate a link between stress-induced ischemia and reduced LV diastolic untwisting during isovolumic relaxation [169].

Quantitative markers of ischemia – systolic indices

Moving upwards along the temporal axis of the ischemic cascade, a further shift of the balance between oxygen supply and demand towards ischemia results in the occurrence of regional systolic wall motion abnormalities, being the focus of WMA in stress echocardiography. However, although widely used for detection of myocardial ischemia, stress echocardiography is limited by the subjective nature of WMA [96, 170]. Therefore, great interest has been directed towards potential quantitative markers of stress-induced ischemia. In addition to the diastolic indices discussed above, changes in the displacement of the atrioventricular plane during exercise and myocardial systolic velocities assessed by DTI during dobutamine stress have been shown to identify patients with CAD [132, 171]. Moreover, myocardial systolic velocities during DSE seem to be superior to WMA for the detection of CAD in patients with left bundle branch block [172]. The main limitation of using myocardial velocities during stress for the identification of ischemic segments is the interaction between different myocardial regions, or tethering of segments. Thus, myocardial velocities in one segment may be affected by stress-induced hyperkinesia in adjacent segments as well as by overall cardiac motion. This phenomenon was illustrated in a previous study, were myocardial systolic velocities during dobutamine stress failed to localize regional ischemia as assessed by myocardial perfusion imaging, but accurately identified patients with any ischemic response [173]. The problem with tethering segments may be overcome by the use of myocardial deformation indices such as strain and strain-rate, both proposed as more specifically assessing regional myocardial function [174, 175]. Indeed, the use of strain-rate has been shown to add incremental diagnostic value to conventional wall motion analysis in patients undergoing dobutamine stress echocardiography because of suspected CAD [134]. Deformation imaging is limited mainly by poor reproducibility and dependency on recording angle and image quality [98].

Myocardial performance index

The temporal resolution of myocardial velocity imaging techniques allows analysis of the impact of ischemia on the velocity profile over the entire cardiac cycle. In the normal myocardium, early systolic shortening is seen as a positive, high amplitude velocity with short duration, corresponding to isovolumic contraction. Induction of ischemia results in a gradual decrease of amplitude, ultimately reversed to a large negative isovolumic contraction velocity in the presence of severe ischemia [176]. Similarly, with increasing ischemia, myocardial shortening continues after aortic valve closure and into the isovolumic relaxation phase, a phenomenon referred to as postsystolic shortening [177]. These findings are consistent with the effects of ischemia

on isovolumic time intervals observed during flow Doppler recordings [178, 179], forming the rationale of using MPI for detection of ischemia. In patients undergoing DSE, Ling *et al.* showed that among different time intervals and indices from flow Doppler recordings, MPI was the best discriminator for identification of an ischemic response [144]. First described by Tei *et al*, MPI was calculated from conventional systolic and diastolic Doppler time intervals of aortic and mitral flow, and therefore considered to be a marker of global rather than regional LV function [137]. The application of myocardial velocity imaging techniques such as DTI offers an alternative way of calculating MPI [147]. It should be noted, however, that the different approaches using flow-derived or DTI-derived MPI do not yield identical results. Typically, DTI-derived MPI requires higher cut-off values for distinction between normal and dysfunctional myocardium. Nevertheless, both assess the relationship between isovolumic and ejection phases, and when DTI-derived MPI is averaged from different LV sites, they have been shown to correlate in healthy subjects as well as in patients with LV dysfunction [180, 181].

In the present study, MPI was separately analyzed at different LV sites. We found that changes in MPI during dobutamine stress may identify myocardial regions supplied by stenosed coronary vessels. Thus, MPI was used for detection of CAD at a regional vessel territory level as opposed to the analysis of individual myocardial segments used in WMA. Theoretically, temporal resolution of the myocardial velocity profiles obtained during DTI would also allow assessment of MPI in a segment-based manner. However, the typical gradual changes in myocardial velocities seen from basal to apical segments of the LV would be a potential source of error, especially in the apical region, where little longitudinal shortening occurs. Different imaging angles at different levels would further complicate the analysis. Analysis of MPI at basal LV sites resulted in fairly accurate detection of stenoses in major coronary vessels. The main limitation of this approach is the individual variation in coronary anatomy. While the LAD most often supplies the anteroseptal and anterior parts of the LV, the perfusion territories of the LCx and the RCA exhibit substantial variation between dominant and codominant variants [26]. Moreover, we did not analyze MPI at the true posterior LV site, possibly resulting in failure to detect stenoses in major posterolateral branches. These facts may help to explain the lower sensitivity observed as regards detection of LCx disease.

Although not a pre-specified objective of the study, we found that despite a suboptimal level of stress in a majority of the patients, regional changes in MPI identified the presence of CAD with reasonable sensitivity. In contrast, sensitivity of conventional assessment with WMA was far below the level usually seen for DSE. This discrepancy agrees well with the fact that WMA is exclusively based on assessment of changes during systole, whereas MPI reflects both systolic and diastolic changes in LV function, the latter appearing at an earlier stage in the ischemic cascade. Thus, analysis of MPI during stress seems to be particularly useful when target HR is not achieved, constituting a potential clinical application in patients with ongoing beta-blocker treatment.

Myocardial viability and recovery of LV function (Studies II and IV)

Assessment of myocardial viability and prediction of LV functional recovery have important clinical implications in patients with ischemic LV dysfunction. The presence or absence of viability may affect decision-making prior to revascularization and the probability of persisting LV dysfunction may influence timing of cardiac resynchronization therapy and the use of implantable cardioverter defibrillators. In the present study, we evaluated the use of MPI during DSE for prediction of LV functional recovery in patients presenting with a STEMI.

The timing of follow-up was based on a balance between the expected delay in LV recovery and the risk of new ischemic events. As previously discussed, induction of ischemia by limitation of coronary blood flow immediately results in impaired LV function followed by gradual recovery after restoration of myocardial perfusion. The time course of this improvement depends on several factors, including the severity and duration of ischemia as well as the presence of residual myocardial hypoperfusion, ranging from days up to several months. The width of this time span probably reflects the composition of metabolic and structural abnormalities seen in ischemic LV dysfunction. Brief episodes of ischemia mainly result in metabolic changes involving calcium turnover and oxygen free radicals as in myocardial stunning, whereas chronic hypoperfusion, typical of hibernating myocardium, is associated with cellular structural changes such as accumulation of glycogen, myofibril loss and fibrosis [53, 54, 182]. Moreover, following MI, coexistence of stunned, hibernating and necrotic myocardium can be expected, further complicating the prediction of functional recovery.

Assessment of viability

Apart from being determinants of delay in LV recovery, the metabolic and structural abnormalities seen in necrotic and viable but dysfunctional myocardium may help to explain some properties of different methods for assessment of viability. Necrotic myocardium is characterized by microvascular damage and loss of myocyte membrane integrity (i.e. metabolic activity). In contrast, viable myocardium typically exhibits intact membrane integrity and a variable degree of perfusion abnormalities. Therefore, imaging modalities incorporating both perfusion and metabolism are ideal methods for assessment of myocardial viability. Positron emission tomography (PET) with tracing of ^{18}F-fluorodeoxyglucose (FDG) is considered as the gold standard for assessment of viability and has been shown to be useful in patient selection prior to revascularization [183]. The use of PET for assessment of viability in clinical practice, however, is limited by low availability. More available and widely used, myocardial perfusion imaging with single-photon computed tomography (SPECT) has been shown to detect viable myocardium accurately and to predict LV recovery in patients with ischemic LV dysfunction [184, 185]. However, in the acute phase after MI, SPECT seems less accurate in predicting recovery of LV function [186]. The evolution of cardiac magnetic resonance imaging (MRI) has offered a new modality for viability assessment and the addition of gadolinium contrast agents allows assessment of infarct transmurality, being highly predictive of LV functional recovery [187, 188]. Although increasing, the availability of MRI is still limited and the need for simple methods with high availability in daily practice is apparent. Fulfilling these criteria, DSE has been frequently used for assessment of myocardial viability and several studies have established the value of DSE for prediction of LV functional recovery [92]. Assessment

of viability by DSE is based on detection of contractile reserve. Thus, metabolic and other structural changes are not taken into account, probably at least partly explaining the lower sensitivity for prediction of functional recovery seen with DSE when compared with SPECT in chronic ischemic LV dysfunction. The introduction of myocardial contrast agents allowed simultaneous assessment of contractile reserve and microvascular integrity, thereby increasing sensitivity for prediction of LV functional recovery [189]. Moreover, analysis of systolic velocity indices at rest and during dobutamine stress has also been proved to add diagnostic information in the assessment of myocardial viability [190, 191]. Data on diastolic parameters, however, are limited.

Viability, diastolic function and myocardial performance index

Left-ventricular relaxation is partly an active, energy-requiring process and therefore it is not surprising that diastolic function is independently associated with the presence of myocardial viability [192, 193]. Furthermore, in viable myocardium, diastolic function may improve during low-dose dobutamine infusion [194]. Results from a recent experimental study showed that analysis of diastolic strain-rate during low-dose DSE accurately distinguished transmural from nontransmural myocardial infarction [195]. Given these facts, incorporating diastolic parameters of LV function in the assessment of myocardial viability seems appealing. We tested this concept using a combined index of systolic and diastolic function and showed that changes in MPI derived from DTI during low-dose DSE seem to exhibit a specific pattern allowing prediction of functional recovery in patients with LV dysfunction following MI. These findings are consistent with the results of previous studies in which flow Doppler-derived MPI during DSE in patients with recent MI has been evaluated [145, 196]. In healthy controls as well as in patients with contractile reserve, a decrease in MPI resulting from a shortening of isovolumic time intervals relative to ejection time was seen during low-dose dobutamine infusion. Conversely, an increase in MPI resulting from failure to shorten isovolumic intervals was seen in patients without contractile reserve. Furthermore, an increase in MPI during low-dose DSE was an independent predictor of subsequent LV dilatation and adverse events. These changes in MPI reflect the complex response to inotropic stimulation seen in normal and dysfunctional myocardium. By decreasing the duration of isovolumic intervals, a greater part of the cardiac cycle may be used for diastolic filling, thereby enabling an increase in stroke volume. In patients with ischemic LV dysfunction, limitation of the ability to increase stroke volume during dobutamine stimulation is associated with failure in shortening of isovolumic time intervals [197]. This link between impaired relaxation and an abnormal response to inotropic stimulation further emphasizes the important role of diastolic function in myocardial viability. Indeed, we found that baseline early diastolic myocardial velocities were higher and E/E' was lower in patients with recovery of LV function.

A positive outcome in our study was defined as recovery of regional systolic wall motion in the infarct region, and although significant improvement of LVEF was seen in patients with recovery of regional LV function, the predictive value of changes in MPI during DSE cannot be applied to recovery of global systolic function. Furthermore, as outcome was dichotomized, we did not analyze the magnitude of changes in MPI during DSE as a predictor of the extent of recovered myocardium. Previous data from MI patients, however, have shown that there is a significant

correlation between the amount of myocardium showing a contractile reserve and the degree of change in MPI during dobutamine infusion [145].

Temporal changes in ventricular function and residual myocardial damage

Although based on different populations the results of studies II and IV exhibit some similarities. In Study IV, global systolic function and DTI-based diastolic indices of LV function were better in patients with subsequent functional recovery. Similar findings in Study II probably reflect the fact that patients with complete recovery of wall motion abnormalities represented a homogeneous group of patients with viable myocardium, whereas patients with persistent wall motion abnormalities constituted a mix of patients with viable as well as non-viable infarct regions. Recovery of LV function in patients with viability may explain the small improvement in LV systolic function seen over time in this group. Despite the differences in baseline systolic and diastolic parameters, MPI values did not differ significantly between groups, although absolute values were lower in patients with LV functional recovery. DTI-derived diastolic parameters improved over time in both groups in Study II, whereas in Study IV, diastolic function remained depressed at follow-up in patients without functional recovery. These findings are consistent with the results of previous studies, representing a phenomenon sometimes referred to as "diastolic stunning" [198]. The results of Study II show that despite normalized standard echocardiographic parameters of LV function, systolic and diastolic LV velocities in MI patients are significantly reduced compared with those in healthy subjects, possibly representing residual subendocardial damage. At the opposite end of the temporal spectrum, reduced myocardial velocities have been shown to represent very early stages of heart disease, possibly preceding clinical manifastation by years [199]. This ability to predict development of disease may be useful for risk assessment and timing of intervention. The clinical value of retrospective findings such as the reduced myocardial velocities observed in Study II however, is probably limited.

CONCLUSIONS

The purpose of this study was to evaluate the use of myocardial velocity data from PW DTI as quantitative markers of LV and RV function at rest and during dobutamine stress in patients with STEMI. Recording and calculation of velocities and time intervals was shown to be feasible with reasonable inter- and intraobserver variability.

The results of the study suggest that:

- Peak RV systolic myocardial velocity is a sensitive marker of RV infarction, allowing assessment of RV function in the early as well as the late phase after a first STEMI.

- Analysis of changes in the myocardial performance index during dobutamine stress echocardiography identifies the presence of coronary artery disease, even at suboptimal levels of stress.

- A decrease in MPI during low-dose dobutamine infusion predicts recovery of regional left ventricular function over time.

- Improvement of diastolic function is parallel to recovery of systolic function and is restricted to patients with viable myocardium.

- Despite normalized standard echocardiographic parameters of LV function, systolic and diastolic myocardial velocities remain reduced compared with healthy subjects at late follow-up, possibly representing residual myocardial damage.

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