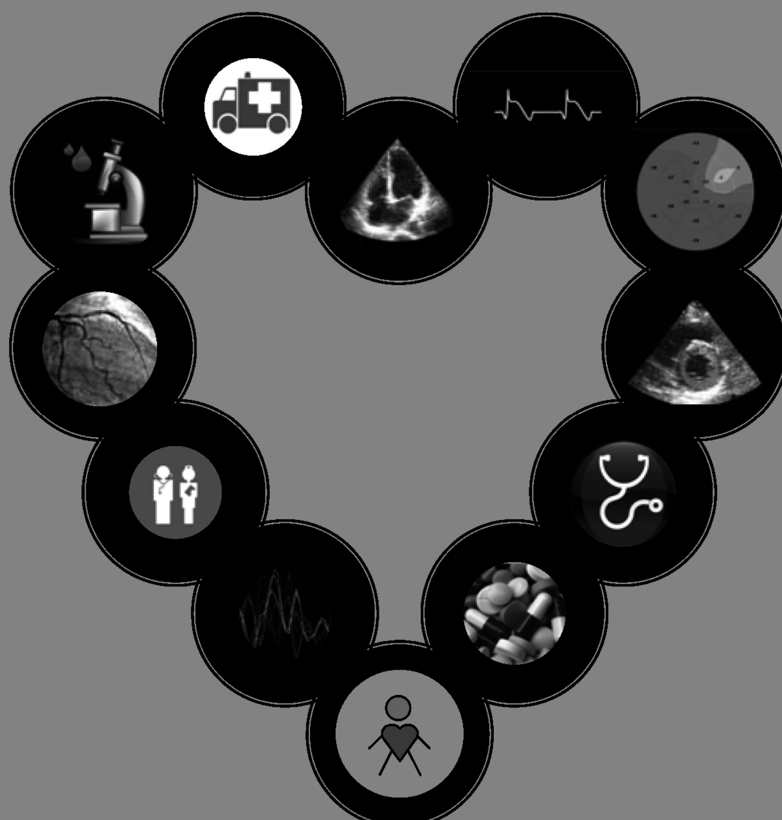
Improving risk stratification after acute myocardial infarction : focus on emerging applications of echocardiography

Antoni, M.L.



Chapter 1

General Introduction and Outline of the Thesis

Introduction

Coronary heart disease is still the leading cause of death in the Western world.[1] With an estimated number of 7.2 million deaths worldwide, 12% of all global deaths are caused by coronary heart disease.[1] The major contributor to mortality among patients who die as a result of coronary artery disease is an acute myocardial infarction and therefore the current guidelines concerning the management of ST-segment elevation myocardial infarction (STEMI) patients from the American College of Cardiology, American Heart Association and the European Society of Cardiology are focused on the optimization of care and outcome of this population.[2 3] In the Leiden University Medical Center, the MISSION! protocol was designed in 2004, which represents an all-phases integrated guideline-implementation program for patients with STEMI. The aim of MISSION! was to improve the care around STEMI patients by incorporating the most recent international guidelines in the pre-hospital, in-hospital and out-patient clinic phases up to one-year follow-up after the index infarction and thereby maximizing the use of evidence-based medicine in real life.
In the past decades, primary percutaneous coronary intervention (PCI) has improved the outcome of STEMI patients significantly and has been currently established as the preferred treatment.[2 3] Several studies have shown that patients treated with primary PCI have a significantly improved short-term outcome reflected by both a reduction in morbidity and mortality when compared to patients treated with thrombolytic therapy.[4] Even more important, these favorable results are sustained during long-term follow-up, and primary PCI is found to be superior to any type of thrombolytic therapy, even when reperfusion was delayed because of transfer to a primary PCI center.[4] However, despite aggressive therapy with primary PCI, mortality rates after STEMI are still substantial. Recent studies reported cumulative event rates ranging from 5% at 90 days to 6% at 1 year and 14% at 3 years for all-cause mortality.[5-7]

On the other hand, the improved survival of STEMI patients in combination with the aging population resulted in a growing number of patients with chronic ischemic heart disease, which imposes a significant socioeconomic burden in the Western countries.[8] Therefore, secondary prevention of cardiovascular events including reinfarction and heart failure plays

a key role in the medical management of STEMI patients and risk stratification has been studied extensively with the aim to improve the outcome of this patient population.
In this context, several risk scores have been developed to stratify patients hospitalized with STEMI. However, most of them have been developed from patient cohorts treated with thrombolysis.[9-12] One of the first validated and clinically useful risk score was the thrombolysis In Myocardial Infarction (TIMI) score, derived from fibrinolytic therapy trials.[13] The TIMI score incorporates clinical and electrocardiographic characteristics including age, systolic blood pressure, heart rate, Killip classification, cardiovascular risk factors (diabetes mellitus, hypertension and angina pectoris), weight, infarct localization (on the electrocardiogram) and time to treatment. The other widely used risk score developed in the thrombolytic era is the Global Registry for Acute Coronary Events (GRACE) score, based on a large registry of patients across the entire spectrum of acute coronary syndromes.[9] The GRACE score also incorporates clinical and electrocardiographic characteristics (age, heart rate, systolic blood pressure, creatinine, Killip classification, cardiac arrest at admission, increased cardiac markers, ST-segment deviation and anemia) and has been well validated.[9 14] Interestingly, the GRACE score has shown to be of predictive value for all forms of acute coronary syndromes (STEMI, non-STEMI and unstable angina patients) and for short-term (in-hospital) and long-term follow-up (up to 4 years).[9 14 15]

Currently, in the western countries, patients with STEMI are preferably treated with primary PCI resulting in limited infarct size and preserved left ventricular systolic function.[3 4] Recently, a few studies have focused on developing risk scores for STEMI patients treated with primary PCI.[7 16-18] De Luca et al. proposed a score to predict all-cause mortality at 30 days.[18] Age, anterior infarction, Killip class, ischemic time, procedural success and multivessel disease were independent predictors of all-cause mortality.[18] More recently, the CADILLAC risk score selected seven risk factors (age, Killip class, baseline left ventricular ejection fraction, anemia, renal insufficiency, triple-vessel disease, and post-procedural TIMI flow grade) which are readily available at time of intervention for the prediction of long-term mortality.[7 16 17]

Interestingly, many of the predictors included in the novel risk scores are the same predictors identified by the risk scores developed in the thrombolytic era. Especially heart rate has been included in most risk scores and appears to provide important prognostic information in STEMI patients. Although the association between heart rate and outcome has been described extensively, understanding the relationship between heart rate and adverse events remains challenging. It is likely that heart rate is both a causative factor and an indicator of pathophysiologic processes. Heart rate influences myocardial oxygen demand and supply and consequently, also myocardial perfusion which may explain the strong relationship observed between heart rate and adverse outcome in STEMI patients.[19 20] In addition, previous experimental studies with coronary artery occlusions have shown that hemodynamic status and neurohumoral status at the time of occlusion can alter the extent and severity of myocardial ischemic damage and myocardial necrosis.[21] As a consequence, patients with an elevated heart rate at admission may develop more extensive infarction due to an increased vulnerability of the border zone. Therefore, an elevated heart rate can make the border zone more prone to an extension of the infarct due to an increased myocardial oxygen demand. Finally, in the novel risk scores developed in STEMI patients treated with primary PCI, the importance of infarct size is emphasized as one of the most powerful determinants of long-term survival.[22 23] Hence, patients with a large infarct size despite primary PCI should be followed up closely and aggressive medical treatment is warranted to prevent sudden cardiac death and the development of congestive heart failure.

Infarct size

There are several approaches available for the quantification of infarct size.[24] The most commonly applied approach in clinical practice is measuring the level of biochemical markers. Although the assessment of infarct size with biochemical markers including peak levels of creatine phosphokinase and troponin T is less direct, serial measurements during the first 24 hours to determine peak values have shown to be useful in daily practice.[25 26] In the setting of primary PCI, peak values can be missed due to rapid washout after reperfusion and correlations between area under the curve of peak values and infarct size are difficult. On the other hand, the rapid washout may result in a higher peak, but potentially smaller area under the curve, which is a more accurate reflection of infarct size. In addition, several studies have demonstrated a direct correlation of peak cardiac troponin T and creatine phosphokinase levels with histopathologic infarct size and infarct size assessed with cardiac magnetic resonance imaging.[27-29]

Besides biochemical markers, advances in cardiac imaging currently enable the quantification of infarct size using multiple methods which vary widely in their technical requirements, benefits, limitations, and costs. Magnetic resonance imaging is a well-validated, robust technique to assess infarct size and has been used in several trials as a surrogate endpoint in STEMI patients, because of its unique ability to depict the transmural extent of the infarction and it permits quantification and localization of microvascular damage.[30] Coronary occlusion and reperfusion initiate a progression of changes within the myocardium that result in signal intensity increases on T1-weighted gadolinium-enhanced cardiac magnetic resonance images. It is hypothesized that delayed gadolinium enhancement within ischemic injured myocardium is related to an increase in interstitial space caused by the loss of cellular integrity in necrotic myocytes and by the development of tissue edema. Previous studies performing serial magnetic resonance imaging have indicated that gadolinium enhancement may change over time following STEMI. Multiple mechanisms, including infarct shrinkage, partial volume effects, and overestimation owing to early imaging, have been proposed to explain the changes over time. Especially, during the first week after reperfusion of an infarction, a reduction in enhancement is observed and therefore, it is recommended to perform magnetic resonance imaging at least one week after STEMI. Nevertheless, the use of cardiac magnetic resonance imaging in daily practice remains suboptimal due to the limited availability, high costs and time consumption associated with the examination.

More available is single-photon emission computed tomography (SPECT) myocardial perfusion imaging, which assesses the perfusion defect as a measure of infarct size. SPECT imaging has been validated clinically, is more available in the daily practice and a close correlation has been observed between infarct size assessed by SPECT imaging and the amount of fibrosis.[25] Besides the assessment of infarct size, SPECT may be used to identify myocardial stunning early after myocardial infarction and can predict the improvement of left ventricular function during follow-up.[31 32] In addition, ECG gating of myocardial perfusion images enables the assessment of remaining ischemic territories and provides information regarding global as well as regional LV systolic function. On the other hand, radiation exposure is one of the limitations of SPECT imaging and serial examinations using this modality are therefore not preferred.

Finally, the assessment of residual left ventricular function is also an indirect, but clinically useful measurement of infarct size. In clinical practice, two-dimensional (2D) echocardiography is frequently performed to evaluate left ventricular function and stratify risk after STEMI.[33] Both left ventricular ejection fraction and wall motion score index are strong predictors of mortality after STEMI.[33 34] Where left ventricular ejection fraction reflects global left ventricular systolic function, wall motion score index allows better evaluation of regional dysfunction of the left ventricle. However, both measurements may be misleading early after STEMI, due to the presence and extent of salvaged but still stunned myocardium.[35 36] In addition, these traditional parameters of left ventricular function have several limitations and are influenced by the presence of arrhythmias, cardiomyopathies, valvular heart disease, and ventricular loading. Left ventricular ejection fraction is load dependent and may appear normal in patients with remote, compensatory hyperkinesis, despite myocardial damage at the infarct zone. For wall motion score index, the assessment of regional function remains subjective, is more difficult and requires a certain level of expertise.[37] Recently, novel echocardiographic modalities have been introduced which may overcome these limitations.[38] These novel techniques provide more insight into cardiac mechanics and especially in patients after STEMI, the application of deformation imaging is very promising.[39] Several studies have already shown that more subtle changes in left ventricular function can be detected with this technique and the ability to differentiate between different levels of infarct is excellent.[40-43]

Role of echocardiography after acute myocardial infarction

Echocardiography is a relatively simple, inexpensive and easily accessible modality that allows dynamic imaging of the heart and has therefore been incorporated by several guidelines for clinical decision-making and management of cardiac patients.[33] Despite the introduction of several advanced novel imaging techniques in the past years, 2D echocardiography still remains a highly utilized imaging modality.[44] In STEMI patients, 2D echocardiography is frequently used, because it is a low-cost and safe modality, which can be applied early after the index infarction at bedside and has proven to be valuable during the follow-up of the patients.[40] In the acute phase, echocardiography can be used to establish the diagnosis and location of myocardial infarction and to evaluate the presence of potential mechanical complications. Before discharge, using 2D echocardiography, left ventricular function can be assessed with left ventricular ejection fraction and wall motion score index, which have been established as important prognostic parameters in this patient population.[34] Although the importance of left ventricular function early after STEMI has been studied extensively, the evolution of left ventricular function during the follow-up has not been completely elucidated, especially in patients treated with primary PCI and relatively preserved left ventricular function. Over the years, multiple factors have been identified to contribute to left ventricular remodeling at different stages.[45] So far, it has been shown that infarct size, infarct healing and ventricular wall-stress influence the left ventricular remodeling process significantly.[46] However, studies have demonstrated that patients with comparable infarct sizes differ in the extent of left ventricular remodeling.[47] Serial echocardiography can be used to assess the changes during follow-up and may provide more insight in defining patients with an increased risk of developing left ventricular remodeling and related adverse outcome.[34 35 48] Besides left ventricular systolic function, more studies are focusing on the role of diastolic function and right ventricular function in the remodeling process after STEMI leading to heart failure.[49 50] In addition, echocardiographic techniques continue to evolve and several novel modalities have been introduced using automated function imaging and facilitating the assessment of myocardial mechanics and myocardial tissue characterization.

Novel echocardiographic imaging modalities

Among the several novel echocardiographic modalities that have been introduced, the assessment of myocardial strain appears to be currently the most feasible (Figure 1).[40] Initially, the assessment of myocardial strain was based on tissue Doppler imaging. Using tissue Doppler imaging, myocardial displacement can be assessed by filtering out the high velocities of the blood flow and only recording lower velocities of the myocardium. However, the disadvantage of tissue Doppler imaging is the angle- and load-dependency, limitations which can be overcome by speckle-tracking imaging.[40]

Speckle-tracking imaging is a relatively novel technique which describes myocardial deformation by analyzing motion with frame-to-frame tracking of movement of natural acoustic markers on standard ultrasonic images. With this technique strain and strain rate of a myocardial segment can be calculated as the percentage change in lengthening or shortening during myocardial contraction and the velocity of the displacement, respectively.[40] Strain and strain rate accurately reflect intrinsic measures of myocardial contractility and offer the opportunity to examine cardiac motion in several directions. The myocardium of the left ventricle is constructed by a complex orientation of myocardial fibers. In the presence of ischemia, the subendocardial fibers are the first to be affected due to hypoperfusion.

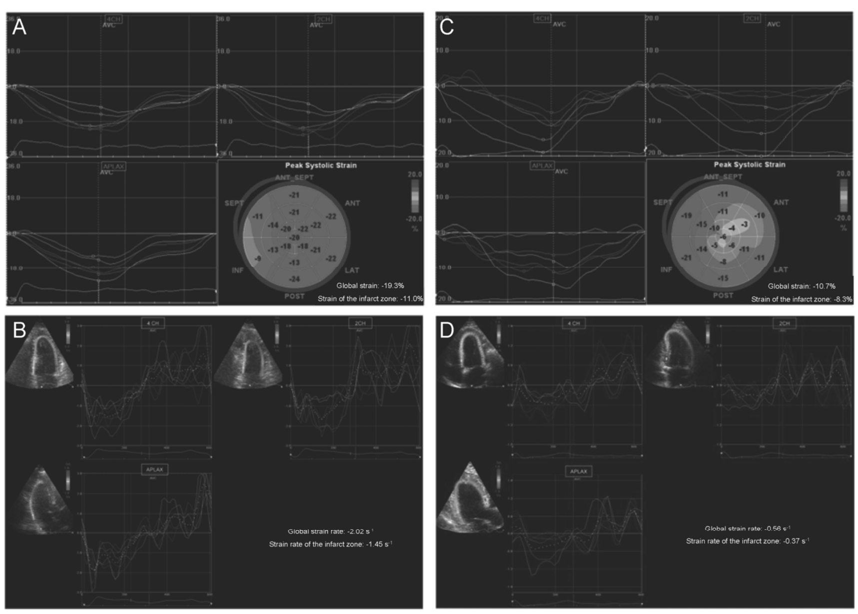


Figure 1.

Examples of longitudinal strain (A, C) and strain rate (B, D) curves from the three apical views of the left ventricle. Preserved strain (A) and strain rate (B) versus diminished strain (C) and strain rate (D).

The longitudinal function of this subendocardial layer can be accurately measured by longitudinal strain and strain rate. Both measurements have been validated extensively against sonimicrometry and magnetic resonance imaging and have demonstrated to be useful in the evaluation of ischemia, viability and the detection of subclinical left ventricular dysfunction.[38 39 43 51-54] Importantly, this novel technique enables the detection of subtle myocardial dysfunction and has been demonstrated to be superior to conventional measurements of left ventricular function.[55] Besides for left ventricular function, strain imaging may also be applied to evaluate left atrial and right ventricular function (Figures 2 and 3).[56 57] Using speckle-tracking echocardiography, subtle changes over time in left atrial and right ventricular function can be evaluated, which may contribute to the remodeling process after STEMI. In addition, strain and strain rate measurements are obtained semi-automated from regional segments of the myocardium using dedicated software.

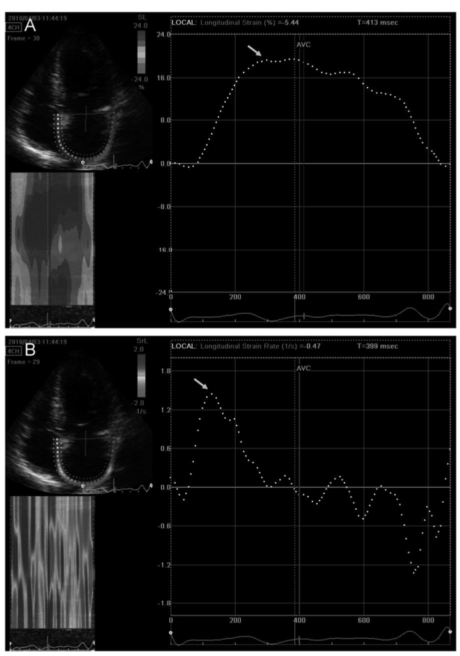


Figure 2.

Example of left atrial longitudinal strain (A) and strain rate (B) from the apical 4-chamber view.

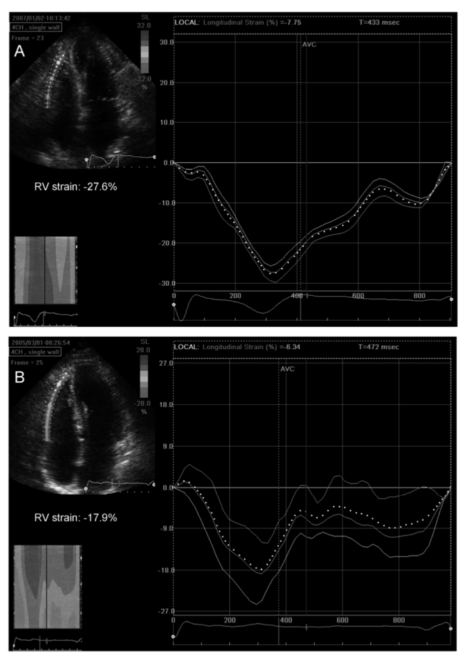


Figure 3.

Examples of patients with normal (A) and impaired (B) right ventricular longitudinal strain from the apical 4-chamber view.

Automated function imaging is an important step in making advanced imaging techniques applicable in daily practice.[58] Especially in echocardiography where subjective assessment is a well-known limitation, the interpretation of less experienced users and variability between different observations may be improved by automated function imaging.
Another application using speckle-tracking imaging is the evaluation of the presence of left ventricular dyssynchrony. By assessing the timings of the deformation of the left ventricular segments, more information can be obtained concerning the efficiency of myocardial contraction (Figure 4). Left ventricular contraction normally occurs in a highly coordinated manner, but as a consequence of myocardial infarction, the normal activation of the left ventricle may be disturbed and contraction becomes dyssynchronous.

Dyssynchrony reflects a reduced efficiency of the global ventricular function and has been recognized as a significant contributor to increased morbidity and mortality in patients with congestive heart failure. In STEMI patients, dyssynchrony develops in an early phase after the infarction and is an important determinant of left ventricular remodeling during follow-up.[59]

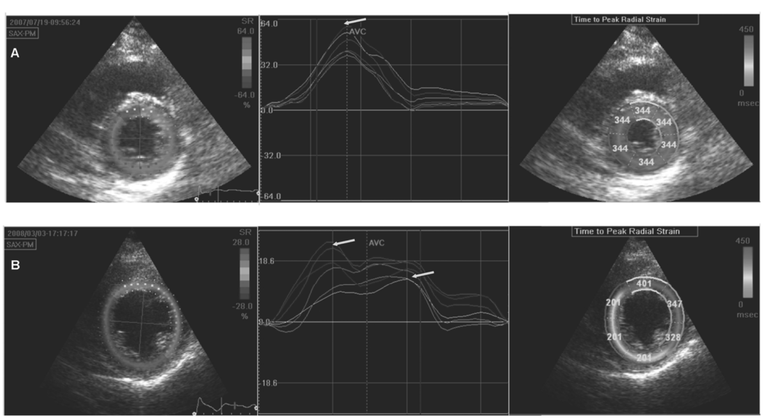


Figure 4.

Examples of LV dyssynchrony measurements using speckle-tracking radial strain analyses. Panel A demonstrates a patient without LV dyssynchrony. Panel B depicts a patient with LV dyssynchrony and a time delay of 200 ms, where the anterior segment was the latest activated segments. The arrows depict the timings of the earliest and latest activated segments.

Finally, integrated backscatter imaging is an interesting echocardiographic technique that permits evaluation of the ultrasound reflectivity of the myocardium.[60] The ultrasound reflectivity can be calibrated against the signal of the pericardium, the cardiac structure that contains the most fibrosis and thereby provides an estimate of the amount of myocardial fibrosis.[61] The presence of increased myocardial fibrosis may have a detrimental effect on myocardial function which can be identified before left ventricular dysfunction is observed with conventional echocardiographic techniques.

Outline of the Present Thesis

Although the mortality and morbidity of STEMI patients has improved significantly, due to the improved survival of STEMI patients and the aging population, the number of patients with ischemic heart failure is growing and determines a significant socioeconomic burden in the Western world. The aim of the current thesis is to evaluate clinical characteristics and the role of echocardiography to improve the risk stratification of contemporary patients admitted with STEMI and treated with primary PCI. In particular, novel echocardiographic deformation imaging was applied to characterize both left ventricular systolic function and left ventricular diastolic function early after STEMI, during follow-up and in chronic ischemic patients.

Part I Clinical Risk Factors

In the first part, clinical risk factors in patients admitted with STEMI are studied. The risk factors that are described are widely available during hospitalization and are therefore relevant for the daily clinical practice. **Chapter 2** describes the frequency and distribution of the culprit lesions in the coronary tree in relation to infarct size as assessed with peak cardiac enzymes and left ventricular function. **Chapter 3** investigates the procedural success and clinical outcome in patients ≥75 years. **Chapters 4 and 5** evaluate the role of heart rate in the contemporary STEMI population, a well-established predictor of adverse outcome in patients with coronary artery disease. Finally, **Chapter 6** combines traditional risk factors to construct a clinically applicable risk score for the prediction of cardiovascular mortality and heart failure during short-term and long-term follow-up.

Part II Systolic Function after Acute Myocardial Infarction

In part II, left ventricular systolic function is evaluated extensively with traditional echocardiographic parameters, speckle-tracking imaging and integrated backscatter imaging. **Chapters 7 and 8** evaluate the role of global longitudinal peak systolic strain as a surrogate marker for left ventricular ejection fraction and wall motion score index for the evaluation of left ventricular systolic function. **Chapter 9** discusses the importance of right ventricular function in this population. Finally, **Chapter 10** discusses the value of calibrated backscatter imaging for the characterization of left ventricular fibrosis in both the infarcted and non-infarcted myocardium.

Part III Diastolic Function after Acute Myocardial Infarction

Part III describes the importance of assessing left ventricular diastolic function after STEMI. **Chapter 11** provides more insight in the different aspects of left atrial function during baseline and follow-up. **Chapter 12** describes a novel technique for the noninvasive assessment of total atrial conduction time in relation to the development of new-onset atrial fibrillation. Finally, **Chapter 13** evaluates the role of left atrial function in relation to adverse outcome.

Part IV Chronic Ischemic Heart Disease

Part IV focuses on the role of echocardiography in chronic ischemic patients, mainly in relation with novel treatment possibilities. **Chapter 14** describes the prognostic value of global longitudinal peak systolic strain together with traditional echocardiographic parameters in a large cohort of patients with chronic ischemic heart disease.
Chapter 15 evaluates the prevalence of left ventricular dyssynchrony early after STEMI and the relation with long-term outcome including the development of heart failure.
Chapter 16 investigates the effect of cardiac resynchronization therapy on diastolic function quantified with myocardial deformation imaging. Finally, **Chapter 17** describes the role of echocardiography in the evaluation of the effect of intramyocardial bone marrow cell therapy.

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