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

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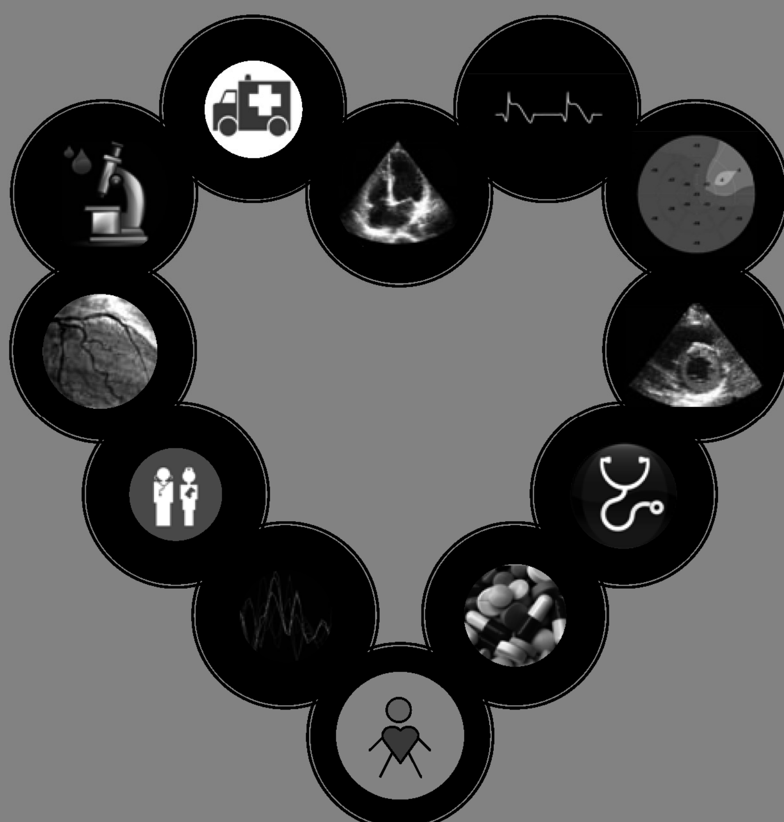
Summary, Conclusions and Future Perspective



Summary

The general introduction (**Chapter 1)** of this thesis gives an overview of the epidemiology of ST-segment elevation myocardial infarction (STEMI) and the current focus of the guidelines concerning the management of these patients. In the past decades changes in the treatment and outcome of STEMI patients have influenced the risk stratification of this population and the focus has been shifted to the evaluation of infarct size. Furthermore, the role of echocardiography in the risk stratification after STEMI is addressed including the evolving echocardiographic techniques.

The aim of the current thesis was to evaluate the clinical characteristics of this contemporary population of STEMI patients and to assess the value of echocardiography for the improvement of the risk stratification of these patients. First, the current population of STEMI patients treated with primary percutaneous coronary intervention is described in **Part I**, where clinical parameters are being evaluated in relation to short- and long-term outcome. In **Part II**, the role of conventional and novel echocardiographic techniques is being evaluated for the assessment of left ventricular (LV) systolic function and the importance of LV diastolic function is addressed in **Part III**. Finally, the role of echocardiography in patients with chronic ischemic heart disease is studied in **Part IV**.

Part I Clinical Risk Factors

Chapter 2 describes the frequency and distribution of the culprit lesions in the coronary tree in 1533 patients in relation to infarct size. The majority of the lesions were located in the left anterior descending coronary artery (LAD, 45%), followed by the right coronary artery (RCA, 38%) and left circumflex coronary artery (LCX, 14%). LAD and LCX lesions resulted in higher peak cardiac enzymes than RCA lesions. In addition, proximal LAD and LCX lesions resulted in significantly worse LV function compared to mid or distal lesions. This study indicates that plaque rupture is more likely to occur in the proximal LAD and RCA and the location of lesions was related to infarct size.

The aim of **Chapter 3** was to investigate the procedural success and clinical outcome in patients ≥75 years. In a total of 1002 consecutive patients, 161 patients (16%) were 75 years or older. Patients in the age group ≥75years were less likely to be male and had a

lower prevalence of risk factors for coronary artery disease. Interestingly, similar initial procedural success were observed between the younger and older patients, although patients ≥75 years had significantly longer time delays than patients <75years. It was observed that in-hospital mortality was significantly higher in the elderly patients and age was only a significant independent predictor of 90-day mortality. After 3 months, low ejection fraction and diabetes were more important predictors. This study demonstrates that despite significantly higher 90-day mortality in older patients, surviving patients have the potential to gain advantage from aggressive reperfusion, optimal medication and regular follow-up.

In **Chapter 4** the role of heart rate at admission is evaluated in the contemporary STEMI population, a well-established predictor of adverse outcome in patients with coronary artery disease. A total of 1492 patients were evaluated and the median heart rate at admission was 72bpm. After adjustment for known risk factors, an admission heart rate of ≥72bpm was associated with a larger infarct size as assessed with both peak cardiac enzymes and left ventricular ejection fraction. In addition, the event rate (cardiovascular mortality, reinfarction and hospitalization for heart failure) at 30 days was significantly higher in patients with a heart rate of ≥72bpm compared to patients with a heart rate <72bpm. Moreover, elevated admission heart rate was an independent predictor of adverse 30-day outcome. This study clearly demonstrates the prognostic importance of this simple cardiovascular parameter in STEMI patients treated with primary percutaneous coronary intervention (PCI).

Chapter 5 describes the role of discharge heart rate in relation to long-term mortality. The population comprised 1453 STEMI patients treated with primary PCI. Resting heart rate was measured before discharge and all patients were followed prospectively for the occurrence of all-cause mortality and cardiovascular mortality. During the median follow-up duration of 40 months, 83(6%) patients died of which 52(4%) died from cardiovascular disease. After adjusting for parameters reflecting a greater infarct size and the presence of heart failure, heart rate at discharge remained a strong predictor of long-term mortality. Patients with a heart rate of ≥70bpm had a 2 times increased risk of cardiovascular mortality at 1 year and 4 year follow-up compared to patients with a heart rate <70bpm. In addition, every increase of 5bpm in heart rate at discharge was associated with a 29% and 24% increased risk of cardiovascular mortality at 1 and 4 year follow-up, respectively. This study shows that in STEMI patients treated with primary PCI and optimal medical therapy, heart rate at discharge was an important predictor of long-term mortality even after adjustment for parameters reflecting a greater infarct size and the presence of heart failure.

Chapter 6 evaluates clinical, angiographic and echocardiographic data to construct a clinically applicable risk score for the prediction of cardiovascular mortality and heart failure during short-term and long-term follow-up. Multivariate regression analyses identified age ≥70 years, Killip class ≥2, diabetes, LAD as culprit vessel, three vessel disease, peak cardiac troponin T level ≥3.5µg/l, LV ejection fraction ≤40% and heart rate at discharge ≥70bpm as relevant factors for the construction of the risk score. The discriminatory power of the model as assessed with the areas under the receiver operating characteristic curves was good and patients could be allocated to low (1%), intermediate (6%), or high (24%) risk categories. This study demonstrates that 8 parameters which are readily available during the hospitalization of STEMI patients treated with primary PCI can accurately stratify patients into low, intermediate and high risk categories.

Part II Systolic Function after Acute Myocardial Infarction

In **Chapter 7** the role of global longitudinal peak systolic strain as a surrogate marker for LV ejection fraction and wall motion score index for the evaluation of LV systolic function was investigated. A total of 659 patients were evaluated and baseline echocardiography was performed to assess LV function with traditional parameters and strain and strain rate. During follow-up, 51 patients (8%) reached the primary endpoint (all-cause mortality) and 142 patients (22%) the secondary endpoint (a composite of revascularization, reinfarction and hospitalization for heart failure). Strain and strain rate were both significantly related with all endpoints. After adjusting for clinical and echocardiographic parameters, strain was independently related to all endpoints and was found to be superior to LV ejection fraction and wall motion score index. Patients with global strain and strain rate higher than -15.1% and $-1.06s^{-1}$, demonstrated HRs of 4.5 (95%CI 2.1–9.7) and 4.4 (95%CI 2.0–9.5) for all-cause mortality, respectively. This study indicates that strain and strain rate were superior to

LV ejection fraction and wall motion score index in the risk stratification for long-term outcome.

Chapter 8 assessed the evolution of LV function after STEMI using global longitudinal peak systolic strain during 1 year follow-up. A total of 341 patients with echocardiography performed at baseline, 3, 6 and 12 months were evaluated. Improvement of LV function based on global strain and was observed in 72% of the patients. No differences were observed between patients with early and late improvement. Independent predictors of recovery of LV function appeared to be the LAD as culprit vessel, peak cardiac troponin T level, diastolic function and baseline global strain. The study demonstrates the potential value of global strain for the prediction of recovery of LV function in STEMI patients.

Chapter 9 focuses on the importance of right ventricular (RV) function. RV function was quantified with RV fractional area change (RVFAC), tricuspid annular plane systolic excursion (TAPSE) and RV strain. RVFAC, TAPSE and RV strain were all univariable predictors of worse outcome. After multivariable analysis, only RVFAC (HR 0.96, 95%CI 0.92–0.99) and RV strain (HR 1.08, 95%CI 1.03–1.13) independently predicted the composite endpoint (all-cause mortality, reinfarction and hospitalization for heart failure). In addition, RV strain provided incremental value to clinical information, infarct characteristics, LV function and RVFAC. This study highlights that RV function provides strong prognostic information in STEMI patients treated with primary PCI.

Chapter 10 evaluates the value of calibrated backscatter imaging for the characterization of LV fibrosis. The pathophysiologic processes underlying LV remodeling are complex and have not been fully elucidated. Changes in the extracellular matrix with deposition of collagen may change the ultrasound properties of the myocardium. Overall, myocardial ultrasound reflectivity was higher at the infarct zone as compared to the remote zone. Interestingly, compared to patients without LV remodeling, patients with LV remodeling showed an increased myocardial ultrasound reflectivity in the infarct zone and remote zone at 3 months follow-up. In addition, no changes over time were observed in myocardial reflectivity in patients without LV remodeling, whereas patients with LV remodeling showed a further increase in myocardial reflectivity at the infarct zone and remote zone.

This study demonstrates that postinfarction LV remodeling is associated with an increase in myocardial reflectivity in the infarcted and non-infarcted myocardium as assessed with calibrated integrated backscatter echocardiography.

Part III Diastolic Function after Acute Myocardial Infarction

In **Chapter 11** the different aspects of left atrial function during baseline and 12 months follow-up are assessed. Left atrial maximal volume increased from 25±8 to 28±8 ml/m^2 from baseline to 1-year. Echocardiographic assessment at 1-year follow-up demonstrated that 81 patients (22%) developed left atrial remodeling (defined as an increase of ≥9 ml/m^2 in left atrial maximal volume). At multivariate analysis, only left atrial maximal volume and left atrial strain were independent predictors of left atrial remodeling. Interestingly in patients without left atrial remodeling, no changes were observed in left atrial function during follow-up. However, in patients with left atrial remodeling, left atrial function significantly worsened during follow-up. In line, left atrial strain and strain rate were significantly lower at 12 months compared to baseline. The study shows that left atrial remodeling occurs in 22% of the patients with concomitant deterioration of left atrial function.

In **Chapter 12** a novel technique for the noninvasive assessment of total atrial conduction time (PA-TDI duration) in relation to the development of new-onset atrial fibrillation is evaluated. Consecutive patients underwent echocardiography within 48 hours of admission and were followed at the outpatient clinic. During follow-up, 12-lead electrocardiograms and Holter recordings were performed regularly and the development of new-onset atrial fibrillation was noted. Left atrial maximal volume, total left atrial ejection fraction and PA-TDI duration were univariate predictors of new-onset atrial fibrillation. After multivariate analysis, left atrial maximal volume and PA-TDI duration independently predicted new-onset atrial fibrillation. Furthermore, PA-TDI duration provided incremental prognostic value to traditional clinical and echocardiographic parameters for the prediction of new-onset atrial fibrillation. This study shows that PA-TDI duration is a simple measurement which can identify patients at risk for the development of new-onset atrial fibrillation.

Chapter 13 focuses on the role of left atrial performance as assessed with volumes, mechanical function and strain in relation to clinical outcome. A total of 320 patients were followed for 27±14 months. During follow-up, 48 patients (15%) reached the composite endpoint. After adjustment for clinical and echocardiographic parameters, left atrial maximal volume and left atrial strain were independently associated with adverse outcome. In addition, left atrial strain provided incremental value to left atrial maximal volume for the prediction of adverse outcome. The study demonstrates that left atrial strain provides additional prognostic value beyond left atrial maximal volume.

Part IV Chronic Ischemic Heart Disease

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. A total of 1060 patients were followed for a median duration of 31 months. Compared to survivors, patients who died (270 patients, 25%) had larger LV volumes, lower LV ejection fraction, higher wall motion score index and greater impairment of LV strain. On multivariate analysis, age, diabetes, hemoglobin, renal function and LV strain were independently associated to all-cause mortality. The study shows that assessment of global strain in patients with chronic ischemic cardiomyopathy is strongly associated with long-term mortality.

Chapter 15 evaluates the prevalence of LV dyssynchrony early after STEMI and the relation with long-term outcome including the development of heart failure. Within 48 hours of admission for the index infarction, mean LV dyssynchrony was 61±79 ms and 14% of the patients demonstrated ≥130 ms time difference defined as significant LV dyssynchrony. During a mean follow-up of 40±17 months, 82 patients (8%) reached the primary endpoint. In addition, 36 patients (4%) were hospitalized for heart failure. The presence of LV dyssynchrony was associated with an increased risk of all-cause mortality and hospitalization for heart failure during long-term follow-up. Moreover, LV dyssynchrony provided incremental value over known clinical and echocardiographic risk factors for the prediction of adverse outcome. This study shows that LV dyssynchrony is a strong predictor of long-term mortality and hospitalization for heart failure in the contemporary population of patients admitted with STEMI treated with primary percutaneous coronary intervention.

Chapter 16 investigates the effect of CRT on diastolic function quantified with myocardial deformation imaging. A total of 188 end-stage heart failure patients undergoing CRT implantation were evaluated. Extensive echocardiographic assessment using speckle-tracking imaging was performed before and 6 months after the implantation to evaluate the effect of biventricular pacing on LV diastolic function. In particular diastolic strain rate parameters were measured during the isovolumic relaxation period (SR_{IVR}) and early diastole. At 6 months follow-up, 59 patients could be classified as responders (defined as ≥15% decrease in LV end-systolic volume). Conventional parameters of diastolic function showed an increase in deceleration time in both responders and non-responders. Interestingly, SR_{IVR} only improved in the responders to CRT. In addition, when dividing patients into ischemic and non-ischemic etiology, SR_{IVR} only improved in the patients with non-ischemic cardiomyopathy. The study demonstrates that novel diastolic strain rate indices may be useful for evaluation of changes in both LV filling and myocardial relaxation after CRT. In addition, improvement in diastolic function was only observed in the responders to CRT and patients with non-ischemic etiology. Therefore, the effect of CRT on diastolic function may be closely related to the improvement in systolic function and the presence of viable myocardium.

Finally, **Chapter 17** describes the role of echocardiography in the evaluation of the effect of intramyocardial bone marrow cell therapy. In a total of 50 patients, diastolic function was evaluated before and 3 months after bone marrow cell injection using standard echocardiography and strain analysis. LV ejection fraction increased from 50± 5% to 54± 7% in the bone marrow cell group, which was a significant improvement as compared to the placebo group. E/E' ratio improved from 14± 5at baseline to 12± 4 at 3 months in the bone marrow cell group, whereas no improvement was observed in the placebo group. Furthermore, E/A ratio showed a significant increase in the bone marrow cell group as compared to the placebo, which was mainly related to an increase in the early (E) peak flow rate in the bone marrow cell group. This study demonstrates that intramyocardial bone marrow cell injection is associated with a beneficial effect on myocardial relaxation and filling pressures in patients with chronic myocardial ischemia.

Conclusions and future perspectives

In the past decades, primary percutaneous coronary intervention has improved the outcome of STEMI patients significantly. However, despite aggressive therapy, mortality rates after STEMI are still substantial. On the other hand, the improved survival has caused a growing number of patients with chronic ischemic heart disease and therefore, secondary prevention of cardiovascular events including heart failure currently plays an important role in the risk stratification of these patients.

The current thesis evaluated traditional and novel parameters which may be useful in identifying STEMI patients treated with primary PCI at risk for adverse outcome. First, clinical parameters were evaluated to provide more insight in the characteristics of the contemporary population of STEMI patients. In addition, the value of well-known risk factors from the thrombolytic era was re-assessed in patients treated with primary PCI. Secondly, the present thesis focused on the role of echocardiography in the risk stratification after STEMI. The results show that echocardiographic evaluation is useful both at baseline as during the follow-up. Furthermore, besides solely evaluating LV systolic function, more comprehensive assessment of global myocardial function including LV diastolic function, RV function and left atrial function seems to be useful for the identification of patients at risk for adverse outcome. Finally, the recently introduced novel echocardiographic techniques are very promising. Deformation imaging with speckle-tracking imaging allows accurate assessment of myocardial function and may detect impaired function earlier than conventional echocardiographic measurements. Moreover, the semi-automated assessment of myocardial function has potential to improve the application of echocardiography in clinical practice. Currently, the subjective assessment in echocardiography is the main limitation. If the variability between different observations can be reduced by automated function imaging, the interpretation by less experienced users may be more feasible which will extend the application of echocardiography in daily practice.