Summary and Conclusions

Coronary artery disease remains one of the major health problems in 2016, with high morbidity and mortality numbers. Different cardiac imaging techniques can be used for the diagnostic and prognostic evaluation of patients with coronary artery disease. Due to the large number of techniques, it can be challenging for the practicing cardiologists to take full advantage of the different imaging modalities for the therapeutic management of these patients. This thesis highlights the importance of using all information provided by the different imaging techniques, because seemly less relevant information may assist in risk estimation of patients with suspected or known coronary artery disease. Moreover, this thesis demonstrated that the specific advantages of different imaging modalities can be of particular added value in specific patient groups, such as adult patients with congenital heart disease and/or heart failure.

The aim of this thesis was to improve the clinical usefulness of cardiac imaging in different patient categories encountered in the daily cardiology practice, with the purpose of improving risk estimation in patients with suspected coronary artery disease, patients who suffered from STEMI and heart failure patients.

In the first part of this thesis (**Part I**), the presence of a left dominant coronary artery system was shown to be of prognostic importance in patients with suspected coronary artery disease and in patients with recent STEMI. Furthermore, the first part showed that there is a significant association between the risk of coronary artery stenosis and the presence of variant coronary anatomy in adult patients after correcting surgery for congenital heart disease.

The second part (**Part II**) describes how the use of cardiac ^{123}I-MIBG imaging could be improved and therewith assist in heart failure care.

Part I: Importance of coronary arterial dominance in patients with suspected and known coronary artery disease

In the first part of this thesis, the clinical relevance of variations in coronary anatomy is evaluated in patients with suspected and known coronary artery disease. More specifically, the presence of a left dominant coronary artery system is shown to be of negative prognostic influence in these patients. Moreover, the presence of a variant coronary anatomy in patients after correcting surgery for the transposition of the great arteries is associated with a higher incidence of abnormal coronary findings on CTCA.

Chapter 2 evaluates the prognostic value of coronary arterial dominance in relation to significant coronary artery disease in 1425 patients referred for CTCA. During a median follow-up period of 2 years after CTCA, patients were followed for the occurrence of non-fatal myocardial infarction and all-cause mortality. The presence of a left dominant coronary artery system was found to be an important and significant predictor for the occurrence of non-fatal myocardial infarction and all-cause mortality during follow-up. Moreover, a left dominant coronary artery system had incremental prognostic value over

the traditional cardiovascular risk factors and severity of coronary artery disease on CTCA. When evaluating a subgroup of patients with significant coronary artery disease on CTCA, patients with a left dominant coronary artery system had a significantly higher cumulative event rate of 35% at 3 years follow-up after CTCA, compared to 9.5% in patients with a right dominant coronary artery system (P<0.001). Therefore, taking into account coronary arterial dominance, next to the severity and extent coronary artery disease on CTCA, may improve risk assessment of patients with suspected coronary artery disease.

The aim of **Chapter 3** was to assess influence of coronary arterial dominance on the short- and long-term outcome after STEMI. Coronary angiographic images of consecutive patients presenting with first STEMI were retrospectively reviewed to assess coronary arterial dominance. Of the 1131 STEMI patients, 971 (86%) patients had a right dominant, 102 (9%) a left dominant and 58 (5%) a balanced system. After 5 years of follow-up, the cumulative incidence of all-cause mortality was significantly higher in patients with a left dominant system, compared with a right dominant and balanced system (log-rank P=0.013). Importantly, patients with a left dominant system had a more than two-fold increased risk of mortality within the first 30 days post-STEMI (OR of 2.51, 95% CI 1.11–5.67, P=0.027). In addition, a left dominant system was also associated with a higher risk of reinfarction and cardiac death within 30-days after STEMI (OR 2.25, 95% CI 1.09–4.61, P=0.028). On the other hand, in patients surviving the first 30 days post-STEMI, coronary arterial dominance was not of influence on long-term outcome. Up till present, the awareness of the prognostic relevance of coronary arterial dominance seemed limited. This chapter provides novel information on the relation between coronary circulation and clinical outcome after STEMI.

While these previous two chapters showed that the presence of a left dominant coronary artery system was associated with worse outcome after STEMI, the association between coronary vessel dominance and LV function at follow-up after STEMI remained unclear. **Chapter 4 e**valuated the relationship between coronary vessel dominance and LV function on echocardiography shortly and at one year post-STEMI. A total of 741 STEMI patients were evaluated with 2D-echocardiography within 48 hours of admission and at 12 months follow-up post-STEMI. A right, left and balanced dominant coronary artery system was noted in 640 (86%), 58 (8%) and 43 (6%) patients, respectively. At baseline, patients with a left dominant coronary artery system had lower left ventricular ejection fraction (LVEF) early after STEMI compared with patients with a right dominant or balanced coronary artery system, with a mean LVEF of 45±8% in patients with a left dominant versus 48±9% and 50±9% in patients with a right dominant and balanced coronary artery system, respectively (P=0.03). During the first year after STEMI, an overall improvement of LV function was observed, independent of coronary vessel dominance. At 12 months follow-up after STEMI, LV function was comparable between the three coronary vessel dominance groups.

As the previous chapters describe the importance of coronary artery anatomy in patients with suspected coronary artery disease and post-STEMI patients, **Chapter 5** demonstrated the influence of coronary artery anatomy on the prevalence of abnormal coronary findings on CTCA in a specific group of adult patients with congenital heart disease. Patients with congenital heart disease have a higher prevalence of coronary anomalies or variant coronary anatomy. In Chapter 5 the coronary anatomy in adult patients with a transposition of the great arteries corrected by arterial switch operation was evaluated. In 30 adult patients, late after arterial switch operation (22 men, 22 ± 3 years), CTCA was performed to assess variations in coronary anatomy patterns and the presence of abnormal coronary findings on CTCA. Abnormal coronary findings were defined as the presence of a significant coronary artery stenosis, an interarterial coronary course, and an acute angled coronary origin. Additionally, neo-aortic root dimensions and coronary takeoff height were also assessed. A variant anatomy patterns was observed in 20% of patients (6/30). All patients with variant coronary pattern showed to have abnormal coronary findings on CTCA. Therewith the prevalence of abnormal coronary findings was significantly higher in these patients as compared with patients with common coronary pattern (100% and 29%, respectively; p=0.003). In particular, an acute angle of the coronary origin was frequently observed. Patients with an acutely angled coronary origin showed to have significantly larger neoaortic root dimensions and a higher coronary artery takeoff. The observations presented in this study may help explain the pathophysiology of the ostial coronary lesions that are frequently encountered in patients after arterial switch operation.

Part II: Use of cardiac 123-iodine metaiodobenzylguanide imaging in patients with chronic heart failure (PART II)

In Part II of this thesis the clinical usefulness of cardiac sympathetic nerve imaging with cardiac ^{123}I-MIBG imaging for the clinical management of heart failure patients is evaluated. Despite the proven prognostic value of ^{123}I-MIBG myocardial scintigraphy in patients with heart failure, there are still several limitations that prevent this technique from being implemented as a clinical management tool in patients with heart failure. The lack of validation and standardization of cardiac ^{123}I-MIBG imaging was one of the factors hampering clinical implementation. Therefore, **Chapter 6** investigates the reproducibility of planar MIBG imaging in patients with heart failure. Planar myocardial MIBG images of 70 heart failure patients were analyzed by two experienced and one inexperienced observer. The impact of the level of post-processing experience on the reproducibility of planar MIBG images was investigated, as well as the effect of cardiac ROI size and position on the assessment of the H/M ratio. Moreover, the influence on the reproducibility of two different methods to assess the WR was evaluated. In addition, because of the known difficulty of accurate assessment of the cardiac ROI in patients with very low H/M ratios (delayed H/M ratio <1.4), a subanalysis was performed in these patients. The intra- and interobserver

analyses, as well as the experienced versus inexperienced observer analysis showed excellent agreement for the measured early and delayed H/M ratios and WR on planar MIBG images. Furthermore, we found that a fixed size cardiac ROI could be used for the assessment of delayed H/M ratios, with good reliability of the measurement. In addition, for the calculation of the WR, the method without background correction resulted in higher reliability than calculation of the WR with background correction. Finally, the delayed H/M ratio measurements remained reliable in a subgroup of patients with a very low delayed H/M ratio. In conclusion this chapter showed excellent reproducibility of cardiac ^{123}I-MIBG imaging in heart failure patients, confirming this technique could easily be implemented in daily cardiology practice.

CONCLUSIONS

Over the last decade, there has been an exponential development in cardiac imaging technology. Currently, cardiac imaging plays a central role in clinical management and decision making in the diverse and growing population of patients encountered in daily cardiology practice. Important outcome-related parameters can be derived from these techniques, allowing better risk stratification of patients with ischemic heart disease. Still, the large amount of information provided by the different imaging modalities can be overwhelming and it can be challenging for the cardiologist to make optimal use of all information that is provided by the different modalities. The purpose of this thesis was to optimize the clinical usefulness of specific cardiac imaging modalities for particular patient categories, with the purpose of improving risk estimation in patients with suspected coronary artery disease, patients who suffered from STEMI and heart failure patients.

Part I of this thesis shows that information about coronary artery anatomy on CTCA or conventional angiography holds important prognostic information, predominantly in patients with suspected or known coronary artery disease. Several studies presented in this thesis showed that the presence of a left dominant coronary artery system was associated with worse outcome during follow-up, as compared to patients with a right dominant or balanced coronary artery system. In patients with suspected coronary artery disease referred for CTCA a higher incidence of all-cause mortality and myocardial infarction was observed in patients with a left dominant coronary artery system. Moreover, when those patients develop a ST-elevation myocardial infarction, the risk of early death and refarction after first STEMI seems to be increased. This thesis showed that first STEMI patients with a left dominant system had a more than two-fold increased risk of mortality within the first 30 days post-STEMI. Furthermore, this thesis demonstrated that patients with a left dominant coronary artery system had lower LVEF on echocardiography early after STEMI. On the other hand, long-term outcome post-STEMI was not influenced by coronary arte-

rial dominance and after one year post-STEMI left ventricular function was comparable between the three coronary arterial dominance groups. Up till present, the value of this anatomical information may have been underestimated. There are multiple 'risk models' available estimating the future risk for adverse events in patients after STEMI, with the purpose of optimizing secondary prevention. In these risk models known risk factors, such as age, gender, blood pressure and heart rate are incorporated. However, coronary anatomy is not taken into account in these risk scores. The incorporation of coronary anatomy in clinical risk scores would possibly improve the risk stratification in post-STEMI patients. Still, future prognostic analyses in patients with STEMI are necessary to give an answer to this question.

Secondly, the first part of this thesis showed that information about coronary artery anatomy on CTCA can be of particular added value in a specific group of adult patients with congenital heart disease. Because CTCA has the advantage of three-dimensional imaging of the coronary artery tree in relation to the great vessels, it allows better visualization of the coronary ostia. This thesis showed that in patient with a transposition of the great arteries corrected by arterial switch operation the presence of a variant coronary artery anatomy pattern is relatively frequently observed. Patients with a variant pattern showed to have a higher incidence of potential harmful abnormal coronary findings on CTCA, such as an acute angle of the coronary origin. Additionally, the presence of an acutely angled coronary origin was associated with larger neo-aortic root dimensions in these patients, possibly explaining part of the pathophysiology of the frequently encountered ostial coronary artery lesions in patients late after arterial switch operation.

Finally, Part II of this thesis demonstrated the usefulness of ^{123}I-MIBG myocardial scintigraphy in patients with heart failure. Despite the large number of studies on cardiac ^{123}I-MIBG imaging, methodological and analytical limitations hampered large scale implementation of this technique in daily cardiology practice. This thesis showed that cardiac ^{123}I-MIBG imaging has excellent reproducibility and the evaluation of the planar MIBG images is easily performed. In addition, when using the right calculations for the assessment of the WR and proper cardiac ROI shape and position for the assessment of the H/M ratio, the image analysis can become more standardized. These data represent an important step to improved utility of cardiac ^{123}I-MIBG imaging in clinical cardiology practice.

Finally, this thesis demonstrated that making optimal use of different cardiac imaging modalities in specific patient categories, by using all information that is provided, allows better risk estimation of patients with ischemic heart disease.