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Summary, Conclusions and Future Perspectives
Cardiovascular Disease

Cardiovascular disease remains one of the leading health care issues these days, even though considerable advances in diagnosis, therapeutic options and prognostication of patients with cardiovascular disease have been made in the last couple of decades.1-3

Novel insights into cardiac imaging and post-processing techniques can be used to further improve currently applied diagnostic, therapeutic and prognostic algorithms for patients with cardiovascular disease.

The general introduction of the thesis (chapter 1) describes novel insights into cardiac imaging for evaluation of patients with cardiovascular disease, predominantly in the setting of coronary artery disease (CAD) and chronic heart failure.

The aim of the thesis was to evaluate the role of novel insights into cardiac imaging for diagnosis (Part I), treatment (Part II) and risk stratification (Part III) of patients with cardiovascular disease.

Part I: Dedicated Automated Quantitative Computed Tomography in Patients with Coronary Artery Disease

Chapter 2 provides an overview of the currently available approaches for cardiac computed tomography (CT) to quantify coronary atherosclerosis. In addition, it reviews the potential value of quantitative cardiac CT to guide percutaneous coronary intervention procedures.

The study described in chapter 3 was designed to demonstrate the feasibility of a novel dedicated algorithm for automated quantification of stenosis severity on cardiac CT in a direct comparison to quantitative coronary angiography (QCA). In 100 patients (53 men, 59.8±8.0 yrs), cardiac CT and QCA showed good correlations for percentage diameter stenosis on a vessel-basis (n=282, r=0.83, p<0.01) and a patient-basis (n=93, r=0.86, p<0.01). Furthermore, a good agreement was observed between cardiac CT and QCA for semi-quantitative assessment of diameter stenosis (accuracy of 95%). Moreover, quantitative CT showed a significantly higher positive predictive value (100% vs. 78%, p<0.05) and higher diagnostic accuracy (95% vs. 87%, p=0.08) for assessment of ≥50% diameter stenosis when compared to visual analysis. In summary, quantitative CT was well-correlated to QCA for assessment of stenosis severity. Importantly, the study showed an improved diagnostic accuracy and positive predictive value of quantitative CT when compared to visual analysis of CT images.

Chapter 4 describes the feasibility of automated coronary plaque quantification on cardiac CT using dedicated software with a novel 3D coregistration algorithm of CT and intravascular ultrasound (IVUS). A total of 51 patients (40 men, 58±11 yrs, 103 coronary arteries) with 146 lesions were evaluated. Quantitative CT and IVUS showed good correlation for minimal lumen area (MLA) (n=146, r=0.75, p<0.001). Both quantitative techniques were well-correlated for lumen area stenosis (n=146, r=0.79, p<0.001) and plaque burden (n=146, r=0.70, p<0.001) at the level of the MLA. Finally, mean plaque burden (n=146,
r=0.64, p<0.001) and remodeling index (n=146, r=0.56, p<0.001) showed significant correlations between QCT and IVUS. In conclusion, automated quantification of coronary plaque using CT with a dedicated quantitative software and a novel 3D registration algorithm is feasible.

In chapter 5, the value of cardiac CT for assessment of diastolic function in comparison with 2D echocardiography using tissue Doppler imaging (TDI) is evaluated. A total of 70 patients (46 men, mean age 55±11 yrs) who had undergone both cardiac CT and 2D echocardiography with TDI were included. Cardiac CT and 2D echocardiography were well-correlated for early transmirtal peak velocity (E) (r=0.73, p<0.01), E/A (r=0.87, p<0.01), peak mitral septal tissue velocity (Ea) (r=0.82, p<0.01) and E/Ea (r=0.81, p<0.01). Furthermore, a good agreement was observed between cardiac CT and 2D echocardiography with TDI for assessment of diastolic function (agreement of 79%). Accordingly, cardiac CT can be used to provide information on LV diastolic dysfunction in addition to coronary atherosclerosis.

Part II: Myocardial Perfusion SPECT for Selection of Heart Failure Patients Referred for Cardiac Resynchronization Therapy

The potentials of nuclear imaging with gated myocardial perfusion single photon emission computed tomography (SPECT) (GMPS) in heart failure patients referred for cardiac resynchronization therapy (CRT) are evaluated in chapter 6. The review concluded that GMPS with phase analysis allows detailed assessment of myocardial ischemia, infarct tissue and viability along with left ventricular (LV) mechanical dyssynchrony using a single SPECT data set. A comprehensive evaluation of heart failure patients referred for CRT with the use of GMPS and phase analysis can improve the selection of patients who will benefit from CRT.

In chapter 7, the QGS algorithm for phase analysis on GMPS is validated in a direct comparison with echocardiography using TDI for assessment of LV systolic dyssynchrony. Additionally, the prediction of response to CRT using GMPS with phase analysis is evaluated in chapter 7. In 40 heart failure patients (32 men, mean age 63±8 yrs), phase analysis on GMPS was significantly correlated with TDI for assessment of LV systolic dyssynchrony (histogram bandwidth (HBW) (r=0.69, p<0.01) and phase standard deviation (SD) (r=0.65, p<0.01). Moreover, phase analysis on GMPS allowed prediction of CRT response, in which the optimal cutoff value for HBW was defined at 72.5°, yielding a sensitivity of 83% and a specificity of 81%. The area under the curve for HBW was 0.83. The optimal cutoff value for phase SD was set at 19.6°, which yielded a sensitivity of 83% and a specificity of 81%. The area under the curve for phase SD was 0.85.

Chapter 8 evaluates the relation between the site of latest mechanical activation on GMPS, LV lead position and response to CRT. A total of 90 heart failure patients (72% men, mean age 67±10 yrs) were included, of which 52 (58%) patients showed a concordant LV lead position and 38 (42%) patients showed a discordant LV lead position. GMPS and 2D speckle tracking radial strain analysis agreed well for assessment of the site of latest
mechanical activation (total agreement of 86%, $k$ value=0.79). Furthermore, the study has demonstrated that response to CRT was significantly more often documented in patients with concordant LV lead position as compared to patients with discordant LV lead position (79% vs. 26%, $p<0.01$). Moreover, patients with concordant LV lead position showed significant improvement in LV volumes and LV systolic function ($p<0.05$) at 6 months follow-up, whereas patients with discordant LV lead position showed no significant improvement in LV volumes and LV systolic function. In conclusion, GMPS with phase analysis can be used to assess the site of latest mechanical activation. Importantly, a concordant LV lead position was associated with significant improvement in LV volumes and LV systolic function.

The study in chapter 9 has evaluated the feasibility of phase analysis on GMPS for assessment of LV diastolic dyssynchrony in comparison with TDI. In 150 heart failure patients (114 men, mean age 66.0±10.4 yrs), diastolic HBW ($r=0.75$, $p<0.01$) and diastolic phase SD ($r=0.81$, $p<0.01$) showed good correlations with LV diastolic dyssynchrony on TDI. In addition, patients with LV diastolic dyssynchrony on TDI (>55 ms) showed significantly larger diastolic phase SD (68.1±13.4° vs. 40.7±14.0°, $p<0.01$) and diastolic HBW (230.6±54.3° vs. 129.0±55.6°, $p<0.01$) as compared to patients without LV diastolic dyssynchrony on TDI (≤55 ms). Accordingly, phase analysis on GMPS allows assessment of LV diastolic dyssynchrony.

Finally, chapter 10 describes whether LV diastolic dyssynchrony on GMPS allows prediction of response to CRT. A total of 50 moderate-to-severe heart failure patients (36 men, mean age 66.5±9.9 yrs) with depressed LV systolic function (LV ejection fraction (LVEF) ≤35%) were included. Thirty-four (68%) patients showed response to CRT, while 16 (32%) patients were non-responders. CRT responders showed a significant improvement in New York Heart Association (NYHA) functional class, quality-of-life score, 6-minute walk distance, LV volumes and LVEF at 6 months follow-up ($p<0.05$). Multivariate analyses showed that LV diastolic dyssynchrony along with LV systolic dyssynchrony and myocardial scar were independent predictors of CRT response ($p<0.05$).

**Part III: Cardiac Sympathetic Nerve Scintigraphy with 123-I Metaiodobenzylguanidine for Risk Stratification of Patients with Cardiovascular Disease**

The role of cardiac sympathetic nerve imaging with 123-iodine metaiodobenzylguanidine (123-I MIBG) scintigraphy for risk stratification of patients with cardiovascular disease is described in chapter 11. The review concludes that cardiac innervation imaging with 123-I MIBG holds great potential for risk stratification and prognostification of heart failure patients. Cardiac 123-I MIBG imaging can be used to identify patients with heart failure at risk for (cardiac) death, worsening heart failure as well as ventricular arrhythmias or sudden cardiac death.
The potentials of 123-I MIBG scintigraphy for prediction of ventricular arrhythmias are evaluated in chapter 12. In total, 116 heart failure patients (80 men, mean age 65±9 yrs) referred for implantable cardioverter-defibrillator (ICD) therapy were included. During a mean follow-up of 23±15 months, appropriate ICD therapy was documented in 24 (21%) patients and appropriate ICD therapy or cardiac death in 32 (28%) patients. The study showed that late 123-I MIBG SPECT defect score was an independent predictor for appropriate ICD therapy and the combined endpoint of appropriate ICD therapy or cardiac death. More specifically, patients with a large late 123-I MIBG SPECT defect (summed score >26) showed significantly more appropriate ICD therapy (52% vs. 5%, p<0.01) and appropriate ICD therapy or cardiac death (57% vs. 10%, p<0.01) when compared to patients with a small late 123-I MIBG SPECT defect (summed score ≤26) at 3-year follow-up. Thus, cardiac sympathetic denervation allowed prediction of ventricular arrhythmias causing appropriate ICD therapy.

Chapter 13 describes the relation between contrast-enhanced magnetic resonance imaging (MRI) and 123-I MIBG/perfusion scintigraphy for assessment of myocardial infarct size and infarct border zone, referred to as myocardium at risk for ventricular arrhythmias. In 40 patients with ischemic heart failure (29 men, mean age 66±10 yrs), contrast-enhanced MRI and myocardial perfusion scintigraphy showed good correlations for infarct size (r=0.72, p<0.01). Moreover, the 123-I MIBG SPECT defect score (48.2±12.5% vs. 32.1±9.5%, p<0.05) and innervation/perfusion mismatch score (13.9±11.0% vs. 6.8±6.0%, p<0.05), which were used as markers of myocardium at risk for ventricular arrhythmias, were significantly larger in patients with an infarct border zone on contrast-enhanced MRI (≤16.7 grams of infarct border zone) than in patients without an (≤16.7 grams of infarct border zone) infarct border zone on contrast-enhanced MRI. In conclusion, the study has demonstrated that contrast-enhanced MRI and 123-I MIBG/perfusion scintigraphy correlated for assessment of infarct size and infarct border zone, which are commonly referred to as myocardium at risk for ventricular arrhythmias.

Conclusions and Future Perspectives

The purpose of the thesis was to explore the role of novel insights into cardiac imaging for diagnosis (Part I), treatment (Part II) and risk stratification (Part III) of patients with cardiovascular disease. Rapid developments in cardiac imaging techniques have already contributed significantly in the evaluation of patients with a broad spectrum of cardiovascular disease, predominantly in the setting of coronary artery disease and chronic heart failure.4-7

New insights in cardiac imaging and post-processing technologies can further refine currently applied diagnostic, therapeutic and prognostic algorithms for patients with cardiovascular disease. Moreover, further developments in cardiac imaging can help to generate a patient-tailored health care system, which in turn should result in an improved cost-effectiveness as patients are more appropriately selected for diagnostic procedures and
therapeutic interventions, such as (percutaneous) coronary intervention procedures and
dedicated cardiac device therapies.

At first, the value of automated quantitative CT for evaluation of coronary atherosclerosis
has been demonstrated in this thesis. As the feasibility of quantitative CT has been shown in
several studies presented in this thesis, new developments in quantitative software should
further improve its diagnostic accuracy for quantification of coronary plaque, particularly
for coronary lesions with severe calcifications. Additionally, refinements in quantitative
algorithms for cardiac CT may help to solve difficulties regarding quantification of in-stent
stenosis and bifurcation lesions. Consecutively, the value of quantitative CT to guide coro-
nary intervention procedures as well as to monitor progression of coronary atherosclerosis
(e.g. once pharmacologic treatment has been started) can be prospectively validated in
future studies. Moreover, further improvements in quantitative CT algorithms should reduce
the amount of post-processing time required for evaluation of CAD.

Secondly, the thesis has shown that GMPS with phase analysis provides important infor-
mation in heart failure patients referred for CRT. GMPS with phase analysis allows integrated
assessment of myocardial infarction, viability and ischemia along with LV mechanical
dyssynchrony and site of latest mechanical activation, which altogether play an important
role in response to CRT. Accordingly, phase analysis on GMPS provides information that
can be used to improve the currently applied algorithm for selection of patients who will
benefit from CRT. As the value of GMPS with phase analysis has been demonstrated in
patients referred for CRT, additional studies are needed that prospectively validate selection
algorithms including GMPS with phase analysis for identification of responders to CRT.
Ultimately, one should demonstrate the improved cost-effectiveness of these comprehensive
algorithms for selection of heart failure patients for CRT.

Finally, the thesis has demonstrated that cardiac 123-I MIBG scintigraphy can be used for
selection of patients prone for ventricular arrhythmias or sudden cardiac death. Although
the benefits of cardiac 123-I MIBG scintigraphy have been demonstrated in patients at risk
for ventricular arrhythmias, the incremental value of cardiac 123-I MIBG scintigraphy in
relation to other non-invasive risk markers for ventricular arrhythmias or sudden cardiac
death should be addressed more thoroughly in future studies. Implementation of cardiac
123-I MIBG scintigraphy in currently applied risk models for ventricular arrhythmias
would provide important information on the incremental value of 123-I MIBG imaging
over already existing risk markers for ventricular arrhythmias or sudden cardiac death. In
addition, the role of cardiac 123-I MIBG scintigraphy for prediction of clinical outcome in
patients with unstable clinical conditions, such as acute coronary syndromes, needs to be
further elucidated. Currently, cardiac 123-I MIBG imaging has only been used in patients
with prior myocardial infarction or acute coronary syndrome for assessment of sympathetic
denervation patterns. In this subset of patients, regions with deprived sympathetic innerva-
tion may be present which reach beyond the peripheral border of myocardial necrosis,
indicating the presence of viable but denervation myocardium.\textsuperscript{8-10} Accordingly, beyond the setting of chronic heart failure, cardiac 123-I MIBG scintigraphy may provide incremental information to risk stratify patients with ischemic heart disease.