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Summary

CORONARY artery disease (CAD) is one of the leading causes of mortality and morbidity worldwide. Defined broadly as a pathological systemic process affecting the coronary arteries and other major vessels, it most often refers to atherosclerotic changes in the coronary arteries. A patient with suspected CAD is usually first assessed with a stress electrocardiogram, which has a lower diagnostic accuracy than the conventional coronary angiography (CCA). Although CCA is the reference standard for diagnosing CAD, it is an invasive technique and carries a small risk of complications. Non-invasive techniques such as echocardiography, coronary angiography with computed tomography (CTCA), and myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) and magnetic resonance (MR) are therefore used clinically as gatekeeper tests before CCA. These techniques – especially, CTCA and SPECT/MR- MPI – provide valuable information on both the coronary stenoses and their hemodynamic impact on the myocardial function. However, each of these techniques presents only one aspect of CAD, if used alone. To achieve a higher level of accuracy and precision in CAD assessment, integration of information from different cardiac imaging modalities is essential. The goal of this thesis was therefore to develop techniques to realize this multimodal diagnostic image integration to enhance CAD diagnosis. To this end, we developed novel algorithms for near automated analysis of magnetic resonance based myocardial perfusion images. In addition, we developed and evaluated a new integration framework that allows comprehensive visualization of physiologic information from myocardial perfusion imaging -either with MR or SPECT- and anatomical information from CTCA.

The efficacy of first-pass cardiac MR perfusion (CMRP) imaging in the assessment of CAD has been proven but its clinical use is still limited due to tedious and time consuming manual interaction that is required to quantitatively analyze a large amount of data. In addition, surface coil related inhomogeneities, motion artifacts, and low contrast between the heart and other thorax structures reduce the accuracy of quantitative perfusion assessment. With the advent of semi- and fully automatic image processing methods, not only the challenges posed by these artifacts have been overcome to a large extent, but a significant reduction has also been achieved in analysis time and operator bias. The purpose of **Chapter 2** was to provide an overview of such methods using a categorical study, along with a future perspective on their clinical acceptance. All the reviewed methods were classified into registration, segmentation and fusion/visualization methods. Registration methods are used to correct motion artifacts introduced by respiratory movement. While rigid registration corrects for translations and rotations, elastic or non-rigid registration corrects for the deformation of the heart. Both rigid and non-rigid registration approaches have shown promising results with respect to accuracy, robustness and automation but there is no consensus regarding the optimal approach. Segmentation of the left ventricular myocardium along endo- and epicardial borders is still a very challenging task; in particular, endocardial segmentation is difficult due to trabeculae and papillary muscles, and epicardial segmentation due to image intensity variation in the surrounding structures such as lungs, diaphragm, and epicardial fat. Multi-modality information fusion and visualization techniques allow visual assessment of the perfusion deficits from CMRP images as well as the display of complementary information from different modalities. This chapter concludes that the challenges posed by the rapid developments in CMRP imaging are often difficult to meet with the advancements in image acquisition systems and protocols alone. Therefore, for the CMRP imaging to

become a routinely used modality in the non-invasive assessment of CAD, it is essential that it is augmented by image processing methods, which must continue to evolve, both with respect to functionality, and with respect to evaluation.

Chapter 3 presented an integrated registration and segmentation pipeline that is completely automatic and allows rapid computation of perfusion linked parameters. The complete automation was accomplished by first registering misaligned images using Independent Component Analysis (ICA), and then using the registered data to automatically segment the myocardium with an Active Appearance Model (AAM). In total, 18 perfusion studies (100 images per study) were used for validation, wherein the automatically obtained (AO) contours were compared with expert drawn contours on the basis of point-to-curve error, Dice index, and relative perfusion up-slope in the myocardium. Visual inspection revealed successful segmentation in 15 out of 18 studies. Comparison of the AO contours with expert drawn contours yielded 2.23 ± 0.53 mm and 0.91 ± 0.02 as point-to-curve error and Dice index, respectively. The average difference between manually and automatically obtained relative up-slope parameters was found to be statistically insignificant ($p = 0.37$). Moreover, the analysis time per slice was reduced from 20 minutes (manual) to 1.5 minutes (automatic). The results related to point-to-curve distance and overlap area indicated that our method achieved a high spatial correspondence with the manual gold standard. Furthermore, the analysis based on myocardial time-intensity curve demonstrated that the difference between manually and automatically obtained perfusion parameters was statistically insignificant. With the presented results, we concluded that the proposed method can significantly accelerate the analysis of first-pass CMRP image sequences.

While **Chapter 3** focused only on motion in rest CMRP sequences, emphasis was on motion correction in more challenging stress sequences in **Chapter 4**. As discussed in **Chapter 2**, respiratory motion artifacts are more prominent in stress sequences due to the vasodilatory effects of pharmacological agents. These artifacts lead to unreliable estimates of perfusion linked parameters, such as relative up-slope and myocardial perfusion reserve index (MPRI). Although several methods exist to eliminate such artifacts in rest images, few motion correction methods have been reported for stress images. To this end, we proposed a novel and robust motion correction method that suppresses motion artifacts in the frequency domain and allows fast and near-automated computation of MPRI values. The method was validated for registration accuracy and perfusion parameters on both rest and stress CMRP sequences, and was compared to state-of-the-art registration methods based on independent component analysis (ICA) and normalized cross-correlation (NCC). In contrast to the sub-optimal results from these methods, the proposed method achieved a sub-pixel registration accuracy and a strong agreement with the gold standard perfusion parameters. We concluded that the robustness and fast processing time (20 seconds per slice) of the proposed method makes it potentially viable for the near-automated quantitative analyses of not only rest, but also the more challenging stress MR perfusion sequences in a routine clinical setting.

In **Chapters 5 & 6**, a new multi-modality integration framework, called Synchronized Multimodal heART Visualization (SMARTVis), was presented for a comprehensive assessment of CAD. The framework was designed to integrate information on the extent and severity of coronary stenoses from CTCA images, and on the presence and amount of ischemia from CMRP or SPECT-MPI images. To determine which specific stenosis is associated with which ischemic region, experts use assumptions on coronary perfusion

territories. Due to the high variability between patient's coronary artery anatomies, as well as the uncertain relation between perfusion territories and supplying coronary arteries, patient-specific systems are needed. The proposed patient-specific system consists of the following comprehensive components: (1) two or three-dimensional fusion of anatomical and functional information, (2) automatic detection and ranking of coronary stenoses, (3) estimation of patient-specific coronary perfusion territories. The potential benefits of the SMARTVis tool in assessing CAD were investigated through case-study evaluations (conventional vs. SMARTVis tool). In **Chapter 5**, with CMRP providing functional information, two experts analyzed four cases of patients with suspected multivessel coronary artery disease. When using the SMARTVis tool, a more reliable estimation of the relation between perfusion deficits and stenoses led to a more accurate diagnosis, as well as a better interobserver diagnosis agreement. It was concluded that the SMARTVis comprehensive visualization system can be effectively used to assess disease status in multivessel CAD patients, offering valuable new options for the diagnosis and management of these patients.

A similar but more comprehensive analysis was performed in **Chapter 6**, where the CMRP was replaced by SPECT-MPI for perfusion information. Seventeen symptomatic patients who underwent both CTCA and SPECT-MPI examination within a 90-day period were included in this study; seven of them also underwent CCA. The potential benefits of the SMARTVis system in assessing CAD were investigated through a case-study, involving four experts from two medical centers, where 1) a side-by-side analysis using structured CTCA and SPECT reports, and 2) an integrated analysis using the SMARTVis system in addition to the reports, were performed. The fused interpretation led to 1) a more accurate diagnosis, reflected in an increase of the individual observers' sensitivity and specificity to correctly refer for invasive angiography eventually followed by revascularization, and 2) a better inter-observer diagnosis agreement (increase from 74% to 84%). The improvement was primarily found in those patients who presented CAD in more vessels than the number of reported perfusion defects. We concluded from the results that the integrated analysis of cardiac CTCA and SPECT-MPI using the SMARTVis system results in an improved diagnostic performance.

Future perspectives

Image processing methods

Each cardiac imaging modality has its own advantages and limitations. Moreover, none of the existing modalities can claim to show all aspects of CAD with unequivocal certainty. Therefore, the clinical assessment of CAD and subsequent decision making can be significantly improved by integrating complementary information from two or more imaging techniques. The work described in this thesis showed that such an integration can be effectively achieved by (a) using novel image processing methods (Chapters 3,4) to overcome the challenges in extracting the relevant information from individual modalities, and (b) presenting the extracted information from several modalities in an intuitive and comprehensive visualization framework (Chapters 5,6). However, several possibilities exist to extend the work described in this thesis. In particular, the work presented in Chapter 3 can be further expanded by improving the registration strategy to reduce unusually large and rapid breathing motion that affects the identification and labeling of correct components. In addition, as discussed in Chapter 3, training of an active

appearance model with a larger pool of shapes and images will make the segmentation more robust. Finally, the clinical validation should be extended to multi-vendor datasets and, more importantly, to the images of the patients with pathological conditions in order to demonstrate the true potential of the proposed method. This also holds true for the method presented in Chapter 4. Although the dataset in this chapter included patients suspected of CAD, a more comprehensive validation with a larger pool of data will help in identifying the areas that need further improvements. The Fourier transform based registration method (Chapter 4) can also be extended by (a) incorporating a more robust method to identify the region of interest, and (b) allowing a higher degree of freedom in transformations. With the recent introduction of 3D CMRP imaging[113], it will also be interesting to adapt the method for 3D CMRP datasets.

Based on the trends in past few years, multi parameter visualizations from different imaging techniques and modalities may become more popular in the future. The integrated framework described in Chapters 5 and 6 is a major step in that direction as its modular approach will allow more information to be integrated (e.g., wall motion and thickness from MR) in the already existing set up. In general, the proposed work is more likely to be used by the clinicians if a more extensive validation can show its effectiveness in routine clinical setting. However, with the constraints on the availability of data, it may not be possible to do such a validation unless an open sharing of anonymized data is allowed in the future.

Emerging imaging modalities/techniques

In this thesis, we focused on the fusion of three widely used modalities: CMRP, SPECT and CTCA. Until recently, SPECT has been the most commonly used modality for myocardial perfusion assessment[65, 211] and is still considered the gold standard in many clinics worldwide. Latest developments, however, indicate that CMRP imaging may replace SPECT as the preferred modality as it can perform better not only in terms of cost[107] but also in terms of diagnostic performance [213, 214]. In addition to its non-ionizing property, CMRP imaging offers better resolution than SPECT, or echocardiography, thus permitting a more accurate assessment of regional and global cardiac function and detection of hypoperfusion restricted to the subendocardium [211]. In the future, its inability to assess myocardial perfusion of the entire heart within a very short time period may be overcome by the introduction of 3D CMRP imaging [113]. As shown in [194], cardiac MR may also be used in the future as an alternative to invasive and cumbersome CCA. Further improvements in higher magnetic field imaging (e.g., from 1.5T to 3T) and perfusion analysis methods –including rapid and unsupervised techniques– will allow the establishment of CMRP imaging as a prominent modality for the non-invasive assessment of CAD in the years to come. We expect that the presented CMR analysis methods (Chapters 3,4), and the SMARTVIS framework (Chapters 5,6) can also be applied to these emerging, novel imaging protocols (e.g., 3T MR, 3D CMRP, etc.) with relatively minor adaptations.