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Introduction
1.1 Background

The human circulatory system consists of an intricate network of vessels that transport blood to and from the different organs of the body. The heart (Figure 1.1) forms the core of this complex distribution system. Anatomically, it consists of four chambers- two atria and two ventricles- and has an auto-excitabile musculature thanks to the sino-atrial node (SAN), which sets the pace of cardiac (heart related) activities. A disorder in the cardiac function can be generally detected by analyzing the electrical activity of the heart that is recorded from the body surface by using electrocardiograph; the recording itself is called electrocardiogram (ECG).

In addition to the systemic circulation system that supplies blood to other organs of the body, a dedicated network of coronary arteries (Figure 1.1 (b)) exists exclusively for the circulation of blood to and from the cardiac musculature. The major coronary arteries are: right coronary artery (RCA), left anterior descending artery (LAD), and left circumflex artery (LCX).

1.2 Coronary artery disease (CAD)

An abnormal narrowing (Figure 1.2), called stenosis, in one of the coronary arteries compromises its function and leads to coronary artery disease (CAD). A stenosis occurs due to the accumulation of atheromatous plaques in the vessel wall and may lead to a significant reduction in the blood flow through the affected vessel. These plaques often consist of lipids, such as cholesterol, and fibrous tissue with or without calcium deposition [97, 140]. Although not all stenotic lesions may themselves be fatal at the onset, they are more likely to predispose a patient to other cardiovascular complications in the future. In advanced atherosclerosis, however, there is a higher risk of rupture and thrombus formation that may result in an abrupt obstruction of a coronary artery [72]).

The progression of CAD begins with an interruption of myocardial perfusion and leads to a sequence of events called cascade of ischemia [165] (Figure 1.3), where ischemia is defined as a disbalance between supply and demand of oxygen. As shown in Figure 1.3, an immediate decrease of myocardial contractility occurs next in the hypo-perfused area. Subsequently, irreversible tissue necrosis occurs primarily in subendocardial regions followed by its spread towards the subepicardial space. Such a spread of necrotic tissue results in a transmural myocardial infarction. To prevent an irreversible necrosis, it is therefore essential that not only the location and extent of coronary stenosis but also its effect on cardiac musculature are detected at an early stage.

1.3 Non-invasive cardiac imaging for the detection of CAD

Various events (Figure 1.3) including myocardial hypoperfusion, dysfunction and cell death can be tracked by either directly imaging the cardiac anatomy at high resolution or by imaging the circulation of radiolabeled and paramagnetic contrast agents through the coronary blood vessels. By non-invasive monitoring of otherwise asymptomatic ischemic events (Figure 1.3), the diagnostic imaging techniques allow risk stratification and treatment planning for patients with an intermediate likelihood of CAD. Among the most prominent are computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI) and echocardiography (Echo). Each of them can assess one or more different manifestations of myocardial ischemia (Table 1.1).
The detection of CAD by a non-invasive imaging technique is based on an assessment of the hemodynamic significance of a stenoses through visualization of inducible ischemia. For this purpose, myocardial perfusion imaging with gated SPECT and MRI has been used most extensively as they allow the detection of impaired myocardial blood supply caused by atherosclerotic lesions in the epicardial arteries. In recent years, X-ray based computed tomography has been proposed as an alternative for evaluation of patients with suspected CAD. However, because it visualizes coronary artery stenoses directly, rather than the hemodynamic significance of the lesions, it identifies atherosclerosis instead of ischemia [209].

1.3.1 Myocardial perfusion imaging

Myocardial perfusion imaging is commonly conducted using single photon emission computed tomography (SPECT) with radionuclide tracers that allow perfusion to be imaged directly [96]. Among the most commonly used tracers are thallium-201, technetium-99m MIBI, tetrofosmin, etc. [243]. With ECG-gating, SPECT myocardial perfusion imaging can also be used to assess myocardial motion, thickening, and global function. Although the relatively low resolution of the images makes it difficult to detect small areas of infarction such as endocardial defects[16, 211], SPECT is still the most widely used imaging modality for myocardial perfusion imaging due to its ability to directly assess the myocardial viability.
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Figure 1.2: The schematic depiction of a stenotic lesion in a coronary artery

Figure 1.3: Cascade of ischemia: myocardial dysfunction occurs in a predictable sequence which is detectable prior to clinical symptoms
In contrast to SPECT, MRI offers higher spatial resolution and moderate temporal resolution. The superiority of MRI in ischemia detection was also shown by a multi-centre randomised trial comparing SPECT and MRI techniques [213]. Not surprisingly, it has become an increasingly important tool for the clinical evaluation of patients with CAD and has, in theory, similar capability to echocardiography in suspected acute infarction [239]. Myocardial perfusion imaging with MR requires paramagnetic contrast agents such as Gd-DTPA (Gadolinium-Diethylene Triamine Pentaacetic Acid) to assess myocardial perfusion [13, 39, 153] and the increase in extracellular space associated with the fibrosis of chronic infarction [239]. Furthermore, MR can also be used as a one-stop-shop for cardiovascular imaging in the future as it allows the identification of not only CAD but other diseases (e.g., congenital heart diseases) as well.

Myocardial perfusion imaging with both SPECT and MR is performed under conditions of rest and hyperemic stress to estimate the ischemic burden. Regions of high tracer/contrast agent uptake are assumed to be normally perfused, while regions with relatively low uptake (perfusion defects) typically reflect stenosis of the upstream arteries. If a stress perfusion defect normalizes at rest, they are identified as the regions of reversible myocardial ischemia.

1.3.2 Computed tomography based imaging

Coronary lumen visualization is vital for the reliable assessment of atherosclerosis and invasive catheter-based X-ray coronary angiography (CCA) has been used as the gold standard for this examination [41]. However, its routine clinical application suffers from two disadvantages: (i) there exists a risk of procedure related complications [271] due to its invasive nature, and (ii) only coronary lumen can be visualized due to the two-dimensional nature of CCA images. A non-invasive three-dimensional modality such as CT avoids these problems and can be used as a potential alternative to CCA [158].

Multi-slice CT (MSCT) without contrast (henceforth referred to as MSCT) allows the detection and visualization of calcified coronary plaques. It has been demonstrated that the amount of calcium quantified with CT has a prognostic value for future cardiac events [173]. CT with contrast or CT based coronary angiography (CTCA) employs a contrast agent (generally, iodine-based) to highlight the coronary lumen and assess its morphology, which helps in evaluating the presence, extent, and type (non-calcified or calcified) of coronary plaque [208].

1.4 Motivation and objectives

It follows from the preceding discussion that a comprehensive detection and assessment of CAD requires information on both, myocardial perfusion and coronary anatomy. While the presence and amount of ischemia can be identified using MR or SPECT based myocardial perfusion imaging, the extent and severity of a coronary stenosis can be determined by using CT imaging. Currently, such complementary information is presented separately that makes it not only difficult to relate function to anatomy, but also prone to inter- and intra-observer variability. Furthermore, different imaging techniques—especially, MR based myocardial perfusion imaging—pose a few problems of their own before the relevant information can be obtained from the corresponding images. Following are, therefore, the two major challenges that need to be addressed for a comprehensive assessment of CAD.

a. To obtain diagnostically relevant information from MR based myocardial perfusion
images, certain semi-quantitative parameters need to be estimated. However, due to the presence of motion artifacts (Chapter 2) and a huge amount of data to be processed, automated registration and segmentation strategies are required for a reliable estimation of clinically relevant perfusion parameters (e.g., relative upslope).

b. To find the correct association of a specific stenosis with an ischemic region, experts have to use assumptions on coronary perfusion territories. However, the high variability between coronary artery anatomies, combined with uncertain relation between perfusion territories and supplying coronary arteries, make the CAD detection extremely challenging.

This thesis aims to provide novel solutions to overcome these challenges and thus its major goals can be defined as follows:

a. to develop novel registration and segmentation algorithms for near automated analysis of MR based myocardial perfusion images acquired both at rest and during stress.

b. to integrate the functional information from myocardial perfusion imaging -either with MR or SPECT- and anatomical information from CT for a simultaneous analysis of not only the location but also the hemodynamic significance of the stenoses.

1.5 Thesis overview

The remainder of the thesis is organized as follows:

Chapter 2 focuses on the various aspects of cardiac MR perfusion (CMRP) image acquisition and processing. A comprehensive survey of all the existing methods for CMRP image processing is provided with a broad categorization of all such methods on the basis of two major image processing components: registration and segmentation. The methods for multimodality information fusion and visualization are also discussed within a distinct category.

Chapter 3 describes an automatic registration and segmentation method for the derivation of perfusion linked parameters from CMRP images. The proposed method is based on independent component analysis for registration and active appearance modeling for segmentation. A validation of this method on 15 rest CMRP datasets shows its potential for rapid clinical analysis of myocardial perfusion at rest.

Chapter 4 introduces a novel method for motion correction especially in stress CMRP images that is fast, robust and utilizes frequency domain properties of the motion artifacts. The method is validated using rest and stress perfusion datasets of 20 patients and is compared to state-of-the-art registration methods based on independent component analysis and normalized cross-correlation.

Chapter 5 introduces a novel framework for the integrated analysis of functional information from CMRP images and anatomical information from MSCT and CTCA images. The potential benefits of the proposed framework in assessing CAD were investigated through case-study evaluations, wherein two experts analyzed four cases of patients with suspected multivessel CAD.
Chapter 6 extends the applicability of the integrated framework proposed in Chapter 5 for the integrated analysis of functional information from SPECT perfusion images and anatomical information from MSCT and CTCA images. In addition, calcium scores from non-contrast CT images were integrated. The aim of this study is to show the potential of this tool as one-stop-shop for the analysis of multimodality cardiac images. Validation of this method is performed on datasets from 17 patients with an intermediate likelihood of CAD and findings from the tool are compared to the observations in invasive coronary angiography images, which serve as the gold standard.

Chapter 7 summarizes the results and conclusions of the work described in different chapters of this thesis. This chapter concludes with the future perspectives on image processing methods and imaging modalities with respect to the non-invasive assessment of coronary artery disease.

The work described in this thesis was performed as a part of multicenter *Heart in 3D* project. The goal of this project was to develop novel algorithms and quantitative analysis tools to connect complementary diagnostic information on myocardial perfusion and coronary anatomy from multimodality imaging studies.