Advances in quantitative coronary and vascular angiography

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CHAPTER 1

General Introduction

1.1 Coronary heart disease

Cardiovascular disease (CVD) is the leading cause of death and disability among adults in the developed countries today. As the burden of heart disease and stroke continues to grow, it is expecting to be the leading cause of death worldwide within 10 years. It causes half of the total number of deaths in the western world and the overall worldwide death rate for cardiovascular disease is 355 per 100,000 people.

The American Heart Association estimated that in 2006 about 1.2 million Americans would have a first or recurrent coronary attack and about 479,000 of these people would die. Coronary heart disease is American's single leading cause of death [1], with 831000 deaths in 2006 followed by cancer with 560000 deaths in the same year. According to the European Heart Network, CVD causes over 4.35 million deaths in Europe, nearly half of the total number of deaths (49%). CVD is the main cause of years of life lost from early death in Europe - around a third of years of life lost from early death are due to CVD. Overall CVD is estimated to cost the EU economy 169 billion a year [2]. From data of the World Health Organization, it is estimated that worldwide 17 million people die of CVDs, particularly heart attacks and strokes, every year [3].

The major cause of cardiovascular disease is atherosclerosis, the forming of plaque in the coronary arteries. These coronary arteries are the arteries that supply blood to the muscle of the heart itself (Fig. 1.1). This plaque mostly consists of fatty substances, cholesterol, cellular waste products and calcium, and can lead to a severe narrowing of the vessel lumen, called stenosis, which can disturb the blood flow dramatically and even totally occlude the vessel (Fig. 1.2). In case of an occlusion a part of the heart muscle is exempt from oxygen carried by the blood flow, which usually leads to a myocardial infarction. Furthermore, when a plaque ruptures, embolies (blood clots) can travel through the vascular system and get stuck elsewhere, causing a blockage of an artery and/or vein (embolism), which can lead to a myocardial infarction if one of the coronaries is blocked, stroke when one of the cranial arteries is occluded, or pulmonary embolism when one of the lung vessels is blocked.

1.2 Imaging techniques: X-ray

Over the years, cardiologists have been looking for ways to detect these atherosclerotic lesions at an early stage and assess the progression of the disease over time [4]. This monitoring of the progression of coronary atherosclerosis was made possible by making use of the much earlier discovery of X-rays by Röntgen [5, 6] and their ability to penetrate the human body. The first introduction of "selective" coronary X-ray arteriograms was done by Sones in 1958 [7]. X-ray angiography is a technique that uses an X-ray system (X-ray source at one side of the patient and a detector at the other side, Fig. 1.3) and a contrast agent that is administered into the artery, which absorbs a substantial amount of the X-ray beam that is passing through. This results in an image that shows the projection of the lumen of the arteries under study as can be seen in Figure 1.4.

Much earlier, already in the 30's, the concept of coronary X-ray arteriograms was introduced by Castellanos [8]. However, the quality of the images was very poor, due to weak radiographic generators that required long exposure times and therefore resulted in motion artifacts. Further-

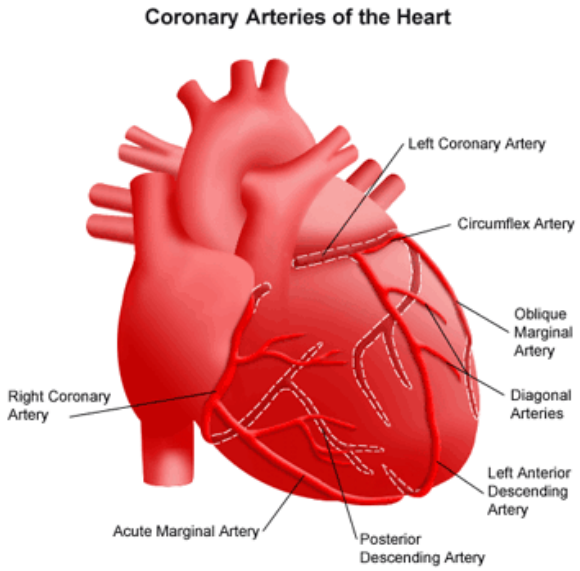


Figure 1.1: Schematic representation of the heart and its coronary arteries. (image from www.yalemedicalgroup.org)

more, the injection of the contrast medium was too slow causing a poor filling of the coronary arteries. In 1945, it was Radner who published the first attempt to visualize coronary arteriograms in living humans. In 1956, Arnulf developed a method to visualize the coronary arteries much better by inducing a cardiac arrest and to administer the contrast by direct needle punc-

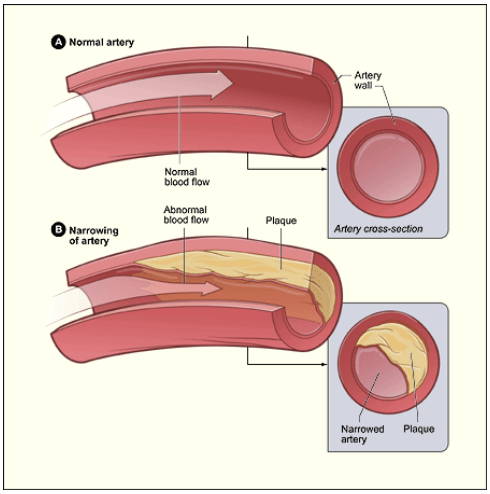


Figure 1.2: Atherosclerosis: the forming of plaque inside an artery. (image from wikimediafoundation.org)

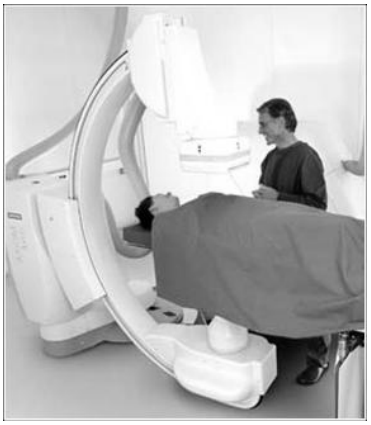
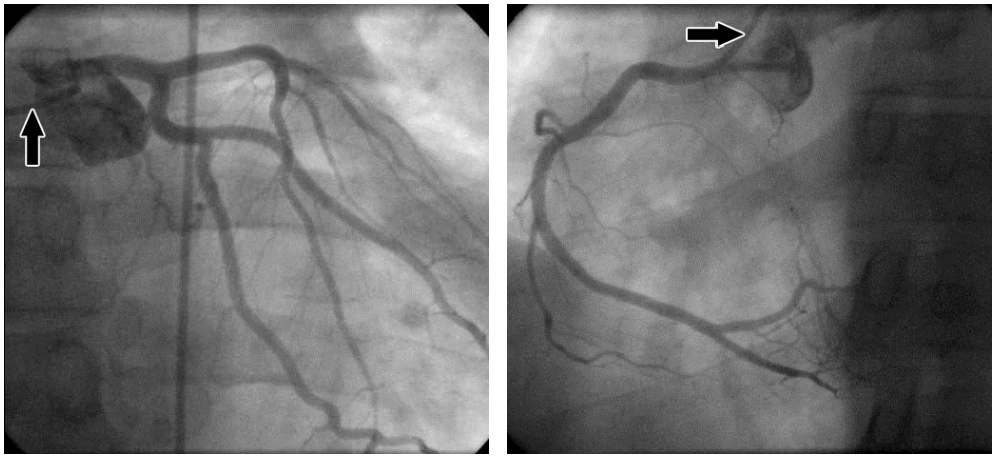


Figure 1.3: Modern X-ray system with a source on one side and a detector on the other side of the patient, both mounted on a so-called c-arm.

ture in the aortic arch [9]. Then, in 1958, Sones managed to achieve the first selective angiogram, that was really usable in clinical practice; the technique was not published until 1962 [7]. He developed a method that uses only small amounts of the contrast agent and delivers it directly into the coronary arteries. In the 60's, the procedure was further improved by Judkins [10] and Amplatz [11], resulting in transfemoral catheter techniques (injection of contrast agent via the femoral artery) using pre-bent catheters, quite similar to the techniques used today. Later on, the imaging equipment was developed further and further for example by the introduction of rotating gantries and linking the image intensifiers to TV screens. Systems that allow caudo-cranial recordings were developed, as described by Ludwig and Bruschke [12]. A problem with this technique in relation to the atherosclerosis, is that the vessel wall cannot be seen in an X-ray image, and therefore the earliest stage of the coronary artery disease cannot be detected. In this stage, the forming of plaque doesn't cause a narrowing of the lumen yet, but results in a thickening of the vessel wall. This is called arterial remodeling as described by Glagov et al [13]. Only when the disease continues and the outer vessel wall cannot be stretched further, the lumen becomes affected and this can be detected by means of the X-ray angiograms as can be seen in Fig. 1.5.

1.3 Other imaging techniques

In order to image the coronary vessel wall itself, another technique has been developed, namely Intravascular Ultrasound (IVUS). This technique provides real-time cross-sectional images using ultrasound that is transmitted and received by the tip of the catheter which is inserted in the artery under study. An advantage of this technique is that the early stage of atherosclerosis can be detected. However, there are also significant disadvantages associated with the technique, such as: the catheter cannot be inserted in the smallest coronary vessels, only one vessel can be imaged at a time, but most seriously, the catheter manipulation can damage the arterial wall, resulting in a puncture of the wall, or even worse small pieces of plaque could become



(a) (b)

Figure 1.4: Example of a typical coronary angiogram. At the left hand side, the left coronary system is depicted, on the right hand side the right coronary system. The arrow depicts the catheter that is positioned in the ostium of the artery and through which the contrast medium is administered. This is an example of a normal angiogram without any narrowings in the vessels.

loose, resulting in embolization of the distal vessels. Although such serious events do not happen very often, the interventional cardiologists in general do not wish to manipulate the catheter in the coronary artery more than is absolutely necessary. Another technique that images the vessel wall from the inside has been developed in the last decade: Optical Coherence Tomography (OCT). This technique uses interferometric imaging typically with near-infrared light to produce cross-sectional images of micrometer resolution. The relatively long wavelength allows the light to penetrate into the surrounding tissue. Similar to IVUS, OCT is an invasive, catheter-based technique that can image only one vessel at a time, making it perfect for studying complex lesions and the malapposition of stent struts, but less suitable for diagnostic purposes. The advantage of OCT with respect to IVUS is its much higher axial resolution, whereas its disadvantage is the limited penetration in the vessel wall. OCT is perfectly suitable to study the thin fibrous cap and the positions of the stent struts, but does not allow the assessment of the plaque composition. In that sense, OCT and IVUS are complementary imaging techniques; intravascular imaging companies are therefore also developing new catheters with both IVUS and OCT elements on the same tip.

In the last decades, a new noninvasive technique for imaging vessels has been developed, namely CTA (Computer Tomographic Angiography). This technique provides a three-dimensional image of the vessels under study, allowing the analyst to select the view in which the lesion is best visible. The problem of overlapping vessels doesn't occur when using this new modality. Over the years, this technique has been improved and the resolution has been increased making it now possible to image the coronary arteries.

As described by Achenbach [14] and Schuijf [15], the quality of coronary CT angiography is increasing rapidly nowadays. The spatial and temporal resolution of the modern multi-slice-CT

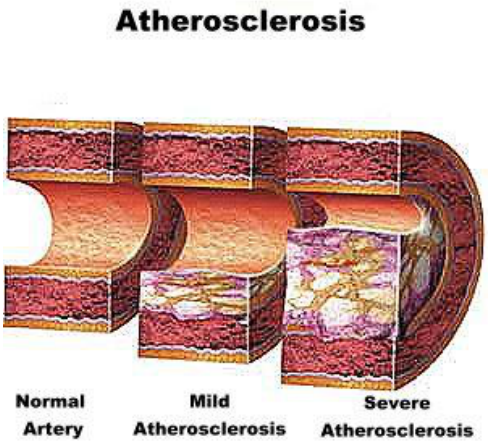


Figure 1.5: Progression of atherosclerosis: left a healthy vessel, in the middle the early stage of atherosclerosis: arterial remodeling and at the right a severely diseased vessel. (image from www.fitnessavenue.net)

scanners (MSCT) however, is still limited compared to the X-ray angiography, which makes accurate stenosis quantification more difficult [16, 17]. Furthermore, the reproducibility of the measurements is not optimal [18]. However, the development of more automatic methods reduced the variability in the outcomes and therefore improved the precision of the methods, as shown by [19, 20]. Moreover, the dose of radiation remains a big concern in CT-imaging.

On the other hand, a big advantage of MSCT is that the same images that were used for stenosis quantification can hopefully also be used for plaque characterization [21, 22, 23]. When a multi-frame CT is recorded (a 3-dimensional image for a number of phases in the heart beat), also the left ventricular function [24, 25, 26] and even mitral and aortic valve anatomy [27, 28, 29] can be assessed, making it a very efficient and versatile imaging technique.

Another new noninvasive vessel imaging technique that has been developed in the last decades is MRA (Magnetic Resonance Angiography), which is also a three-dimensional technique. Similarly to CTA, there are lots of developments currently going on in MRA and its quality has increased substantively. Quantitative methods have been developed to assess the degree of stenosis in diseased vessel segments [30, 31]. Furthermore, MRA can be extended with Vessel Wall Imaging (VWI), allowing visualization of the arterial wall, and even of the composition of the plaque components [32, 33]. Most of this research is performed on the carotid arteries and only very little is done on the coronary arteries [34] since the limited spatial resolution makes it very hard to image the vessel wall in the (smaller) and rapidly moving coronary arteries. Fusion of the MRA and VWI data will provide a better accuracy of the luminal dimensions and the wall visualization and quantization as was demonstrated by Adame et al [35]. This will work even better with the new 3T MRI systems.

CTA is used more and more for diagnostic purposes since it is still being improved and image quality is getting better and better due to newer scanners and better reconstruction algorithms. However, it is not to be expected to replace traditional invasive coronary angiography on a wide

scale yet. Not only because the spatial resolution is still not as high as in the X-ray angiographic images, but mainly because this technique (and the same holds for MRA) cannot be used during an intervention. X-ray, on the other hand, is the only available technique that is applicable during an intervention. Physicians use the X-ray projection images during a catheterization to steer the catheter towards the vessel of interest, while injecting contrast agent from time to time to see the artery tree in which the guide wire and imaging catheter is positioned. Since X-ray is the only technique that makes this possible, it is still the most commonly used technique in the catheterization laboratories for the visualization of the coronary arteries.

1.4 QCA

Currently, three different methods are used to assess the presence and extent of possible narrowings from X-ray arteriograms. The first method is the purely visual interpretation of the images to estimate the percentage diameter stenosis, which is generally seen as the most important parameter when assessing the severity of the lesion and the need for an intervention. Despite the relatively low accuracy and reproducibility and the strong observer dependence, this is still the most widely used method in routine clinical practice. The second method of assessing parameters from X-ray arteriograms is measuring the obstruction diameter using a caliper, a single line piece drawn by the observer, but this is of course very inaccurate and poorly reproducible. The last method, the one we have focused our research on, is the Quantitative Coronary and Vascular Angiography (QCA/QVA) [36, 37, 38, 39, 40].

Apart from the methods that rely on X-ray arteriograms, there are other ways of assessing the severity of a stenosis, for example by determining the functional significance in terms of blood flow, using pressure catheters. Several different methods have been developed to measure flow and flow reserve [41]. Nevertheless, they all suffer from the same problem: there is too much variation in normal values to distinguish between normal and pathological cases [42]. As a solution for this problem, the Fractional Flow Reserve (FFR) can be determined, as introduced by Pijls et al [43, 44, 45, 46]. This FFR is defined as the maximum achievable blood flow in the presence of a stenosis divided by the maximum blood flow in case the vessel had not been diseased. These values are derived from the mean arterial pressure, the central venous pressure and the pressure measurement distal to the stenosis in the diseased vessel. As a result, FFR appears to be a good indicator for the severity of the lesion; it has been demonstrated that an FFR <0.75 means that the obstruction is functionally significant and therefore should be treated by the interventional cardiologist. The advantage of this method is that not the geometric dimensions of the stenosis are measured, but its functional severity in terms of reduction in blood flow. The disadvantage is that a pressure catheter is needed for the measurement and there are problems assessing very severe stenoses and total occlusions.

QCA is a quantitative tool that provides objective and reproducible data about the narrowings in the vessels. Over the past 30 years, many developments have taken place, from using manual calipers, drawing the vessel contours on projected cinefilm images, to automated edge detection techniques. QCA requires user-interaction by selecting the segment that is under study and performing a calibration, usually on the catheter that is inserted into the ostium of the vessel to administer the contrast agent. The QCA-tool detects the segment and the lumen contours of

this segment and calculates the diameters of the lumen over the entire length of the segment. From these diameter measurements and an estimation of the lumen in a healthy situation, the stenosis parameters are calculated.

Over the last several decades, QCA has been generally accepted as the proper method for accurate and reproducible assessment of coronary artery disease from X-ray angiograms and the quantification of the severity of coronary artery lesions. Its precision and accuracy have been widely proven in several studies, using phantom data as well as clinical patient data [39]. QCA facilitates the choice of the proper recanalization devices during interventional cardiology as well as the evaluation of the development of a disease over time, by extracting clinically relevant parameters such as diameter stenosis, minimal lesion diameter and estimated reference diameter, as well as lesion length. Furthermore, QCA is used by core laboratories for the evaluation of the outcomes of clinical and pharmaceutical research trials, for example to determine the effects of statins, and stent trials, to assess the effect of new types of (drug-eluting) stents.

Since the early times of QCA, technical developments have proven their importance in the catheterization laboratories, facilitating the use of QCA and improving the analysis results. The 35mm cinefilm has been replaced by digital images in DICOM-format, stored on CD or in a PACS-system. This not only facilitates copying the original images and transferring these copied images to other physicians or core labs for further analysis, but also preserves the quality of the images. Furthermore, the introduction of the flat-panel systems as a replacement for the conventional image intensifier and CCD camera has removed a large amount of the spatial distortions from the X-ray system and preserved more of the X-ray signals, making the angiograms better and therefore the QCA analysis more accurate and more suitable for measurements or other post processing applications. The automated software packages that were developed in our group over the last decades provide reliable results and are generally seen as one of the leading applications in QCA [39, 40]. This application that was originally called QCA-CMS and later changed into QAngio XA, achieves a precise and accurate measurement of a stenosis in the coronary arteries. The system is applicable in online situations, during an intervention, as well as in offline situations, in both hospital and core laboratory environments. Its accuracy and precision were demonstrated by several extensive validation studies using both phantom and clinical data [39]. Furthermore, the system was validated by measuring the inter- and intra-observer variabilities and even inter- and intra-core lab variabilities [39, 47, 48].

Although the measurements are very fast and accurate, it is still not a fully automatic method, which means that there is still some user interaction required to perform the analysis. Therefore, there is still some variation in the results of a lesion quantification when a single segment is measured repeatedly by different analysts (inter-observer) or even by the same analyst (intra-observer). Besides this variation, there are still some difficulties when analyzing complex lesion morphologies and strongly curved vessels, which can lead to less accurate measurements. Furthermore, the interventional approaches that were originally designed for cardiac applications, are no longer restricted to the coronary arteries nowadays, but extended to the peripheral vessels as well, for example the aorta, the renal, iliac, femoral and carotid arteries. This extension of the intervention methods implies the inclusion of a whole new range of vessel sizes, much larger than the size of the coronary arteries. In addition to that, the analysis method had to be extended to be able to cope with new vessel morphologies, namely ostial segments and bifurcation segments, which cannot be measured properly with the conventional "straight"

segment analysis method.

The developments of these new intervention techniques have led to additional requirements for the automatic analysis software, such as measuring the exact location and quantifying the severity of vascular lesions at the position of the ostium of a sidebranch and at the position of an arterial bifurcation. These new requirements combined with the variation in the existing analysis results are the basis of our research towards new algorithms for the improvement of quantitative coronary and vascular analyses.

From our point of view, a quantitative coronary or vascular analysis consists of four steps that are performed subsequently: First, the rough position of the vessel is detected and usually this is done by finding a pathline or centerline through the vessel from a user-defined startpoint to endpoint, see Figure 1.6(a). The second step is finding the exact outlines of the vessel, using the already detected pathline as a definition of the segment under study, see Figure 1.6(b). This contour detection is a very important part of the analysis since the accuracy of the contours determines to a large extend the accuracy of the measurements. The third step is measuring the luminal diameters and estimating the diameters as they would have been in a healthy case, which we call the reference diameters, see Figure 1.6(c). The fourth and last step consists of measuring the stenosis parameters such as minimal lumen diameter (MLD), percentage diameter stenosis and obstruction length. In order to achieve a correct, reliable and reproducible lesion measurement, it is essential that all steps in this analysis perform equally well: the system is as precise and as robust as its weakest link in the chain of the analysis. Therefore, the overall goal of this research is to find new algorithms and improve all steps of the quantitative analysis to achieve a better overall result. Furthermore, the new algorithms should make it possible to extend the current analysis in order to cope with peripheral vessels and different vessel morphologies, such as sidebranches and bifurcations.

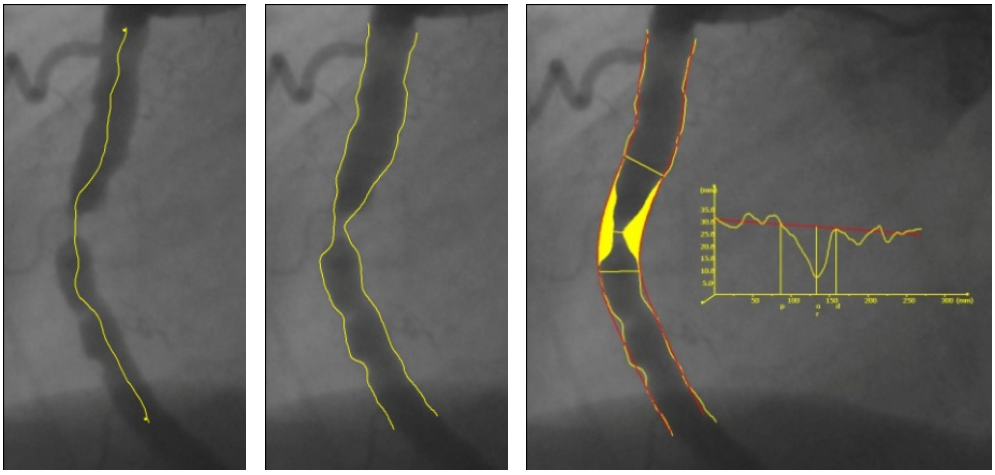
1.5 Outline of the thesis

The structure of the remaining part of this thesis is as follows:

In chapter 2, a general overview is presented of the main contour detection techniques that exist within the medical applications. Many methods are listed here and the most important advantages and disadvantages are discussed. This overview was the starting point of our contour detection research and led to the overall choice of the most promising technique for our application.

In chapter 3, our novel method for detecting pathlines in digital coronary angiograms is introduced. This new method that we denote Wavepath is based on the wavefront propagation method (fastmarching levelset-method). Wavepath was developed to reduce the influence of the user-defined start- and endpoint and results in a more stable, reproducible pathline, as demonstrated in the validation study that was performed on coronary angiograms. Furthermore, this method expands the possibilities of the pathline, making it suitable for different morphologies required for the new ostial segment and bifurcation segment analyses.

Chapter 4 describes the application of the Wavepath in peripheral applications, analyzing vessels with various sizes and morphologies. The extended validation was performed on a large variety of images, showing various vessels and morphologies. This validation proves the robust-



(a) (b) (c)

Figure 1.6: Example of a typical coronary angiogram. At the left hand side, the left coronary system is depicted, on the right hand side the right coronary system. The arrow depicts the catheter that is positioned in the ostium of the artery and through which the contrast medium is administered. This is an example of a normal angiogram without any narrowings in the vessels.

ness of the Wavepath, since the resulting pathline has proven to be virtually independent of the user-variation in placing the start- and endpoints.

Chapter 5 discusses our novel approach for the contour detection in X-ray angiograms, that we denote the Wavecontour. As the name already suggests, this method is also based on the wavefront propagation principle and performs the detection in a two-stage approach. The method was developed with the major goal to improve the robustness and reproducibility of the contour detection and to be a solution for the problems the other contour detection techniques suffer from, such as the detection of the contour in sharp corners (for example the contour between the two distal branches in a bifurcation segment) and at the position of complex lesions and side-branches. In addition to the description of the methods that we use in this approach, we also discuss the validation study that was performed to demonstrate the precision and accuracy of this new method. In this validation study, both in-vivo patient data and phantom data were used to show the improvement in accuracy and reproducibility that was achieved with the Wavecontour.

Chapter 6 describes the new approach for the measurement of the diameters and the estimation of the reference diameters of the blood vessels. This new approach was developed to overcome the problems that were encountered with the direction of the measurements in strongly curved vessels or strange vessel morphologies. Furthermore, this new approach optimizes the diameter measurement of the proximal part of an ostial lesion, as well as the estimation of the vessel as it would have been without disease. This diameter calculation method improves the accuracy of the lesion measurement substantially. Besides that, we also discuss the new analysis methods that were designed to analyze a bifurcation segment and measure all its diameters and stenosis parameters at the same time. We introduce two different models, the Y-shape and T-

shape model, which together cover the whole range of different bifurcation morphologies. These analyses provide data for the proximal segment and the two distal segments as well as data for the central part of the bifurcation, which was previously not possible to measure. In a phantom validation study, the accuracy and the precision of this new analysis method is calculated and discussed.

In chapter 7, the total bifurcation analysis is discussed, including our two new bifurcation models and the newly introduced edge segment analysis that provides data for stent segments and the corresponding stent- and ostial edge segments. This can be done for both the Y-shape and the T-shape model, representing the different intervention techniques. Furthermore, the results of the first validation study on clinical material are presented, which shows the intra-observer variability, proving the good reproducibility of our new bifurcation analysis.

Chapter 8 describes an extended validation study that was performed on clinical data using both the Y-shape and the T-shape model. This validation study assesses the inter- and intra-observer variability on pre- and post-intervention data showing the robustness of our newly developed bifurcation analysis methods.

Chapter 9 provides discussions for each of the previous chapters and an overall conclusion. For each of the newly developed methods, it is discussed to what extend our research goals have been met and which issues are still left for further research and improvement. Finally, the goals of the whole research are considered and overall conclusions are drawn.