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CHAPTER 8

Clinical validation of the new T- and Y-shaped models for the quantitative analysis of coronary bifurcations: An inter-observer variability study

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Abstract

Objectives: This paper presents the results of an inter-observer validation study of our new T- and Y-shape bifurcation models including their edge segment analyses.
Background: Over the last years, the coronary artery intervention procedures have been developed more and more towards bifurcation stenting. Since traditional straight vessel QCA is not sufficient for these measurements, the need has grown for new bifurcation analysis methods.
Methods: In this paper, our two new bifurcation analysis models are presented, the Y-shape and T-shape model. These models were designed for the accurate measurement of the clinically relevant parameters of a coronary bifurcation, for different morphologies and intervention strategies and include an edge segment analysis, to accurately measure (drug-eluting) stent, stent edge and ostial segment parameters.
Results: The results of an inter-observer validation study of our T-shape and Y-shape analyses are presented, both containing the pre- and post-intervention analyses of each 10 cases. These results are associated with only small systematic and random errors, in the majority of the cases compliant with the QCA guidelines for straight analyses. The results for the edge segment analyses are also very good, with almost all the values within the margins that have been set by our brachytherapy directive.
Conclusions: Our new bifurcation approaches including their edge segment analyses are very robust and reproducible, and therefore a great extension to the field of quantitative coronary angiography.

8.1 Introduction

Since the late 1970s, Quantitative Coronary Arteriography (QCA) has become the standard method for hospitals and core laboratories to quantify the effects of pharmacological agents and interventional devices on the regression and progression of coronary artery disease [133]. In the past, the emphasis has always been on the so-called straight vessel, for which conventional QCA has demonstrated to be a robust technique for the accurate and reliable assessment of the arterial dimensions (lesions and other clinically relevant parameters). However, in the last decade the interventional armaments for coronary and peripheral artery lesions have expanded significantly (e.g., with drug-eluting stents and bifurcation stents). Especially with the increasing interest in the quantification of bifurcating arterial vessels and their lesions, it became clear that conventional QCA did not meet the requirements anymore for a standardized and accurate quantification of the bifurcating vessel. In particular issues regarding the determination of the correct reference diameter per vessel segment, the resulting over- and underestimations of the percentage diameter stenosis of the bifurcation lesion, and the bifurcation lesion length became apparent [120]. To overcome these problems, a special bifurcation analysis option needed to be developed. The first approach that we developed was the so-called three-section bifurcation analysis model, which became commercially available with the release of QVA-CMS® V6.0 in 2005 and its successor QAngio XA V7.0® in 2006 (both Medis medical imaging systems BV, Leiden, The Netherlands). The particular advantage of this three-section model was that it combined the proximal and two distal artery segments (fragments) with the central fragment of the bifurcation, resulting in three separate analyses (sections) each with its own set of parameters, all derived in one analysis procedure. The accuracy and precision of the bifurcation analysis results for each of the three sections was conform or better than the conventional straight QCA analysis results [134, 135, 121], so that useful information about the bifurcating vessel and the extent and severity of the bifurcation lesion was provided for the various clinical studies in which this technique was employed [136, 137, 122, 138].

However, based on further discussions with key opinion leaders and practical experiences regarding the optimal derivation of clinically relevant parameters, a new QAngio XA software package (Version 7.2, Medis medical imaging systems BV, Leiden, The Netherlands) was developed with two new models for the bifurcation analysis option. These two new models were developed in order to provide optimal bifurcation data for the specific bifurcation morphology at hand, and such that these models follow the widely accepted Medina classification [120, 139, 140]. As a result, there is now a two-section model for the T-shaped bifurcation (a main vessel being a proximal vessel that continues in the same direction into a distal vessel, and a side branch at an acute angle) and a three-section model for the Y-shaped bifurcation (a proximal vessel with two distal branches that are approximately equal in size and split off at similar angles). Both new models are based upon a typical combination of the proximal and two distal vessel segments with the bifurcation core, but now resulting in two or three sections (depending on the model type), respectively, such that each of these sections has its own diameter function and associated parameter set.

The advantages (including decreased analysis time) and accuracy of the bifurcation analysis mentioned in previous studies on its comparison with conventional straight analyses [2,3], holds for the new bifurcation models as well [17,18] due to the fact that the models are based on the same principles, composed of similar building blocks, and use the same underlying algorithm for the straight parts.

The two bifurcation models are mainly based upon vessel anatomy, which can be automatically determined by the software. However, practice shows that the applied intervention (e.g. provisional T-stenting or skirt stenting) mainly defines the bifurcation model type, due to the available model type specific parameter set (see further on). Therefore, for a selected stent study, the model type can be fixed in advance by the user, to allow simple comparison of the study data.

Similar to the QCA developments for straight vessel stenting, the bifurcation analysis required the ability to deal with drug-eluting stent (DES) analysis as well. Therefore, both bifurcation analysis models are extended (optional) with an edge segments analysis. The segment numbering (see below) is achieved in collaboration with and based upon the methodology proposed by Lansky et al. [120]. The goal of this paper is to present the two new bifurcation models, the edge segments analysis and their accompanying inter-observer variability data. With these validation data we want to prove that the two new bifurcation analysis models are very reproducible in use.

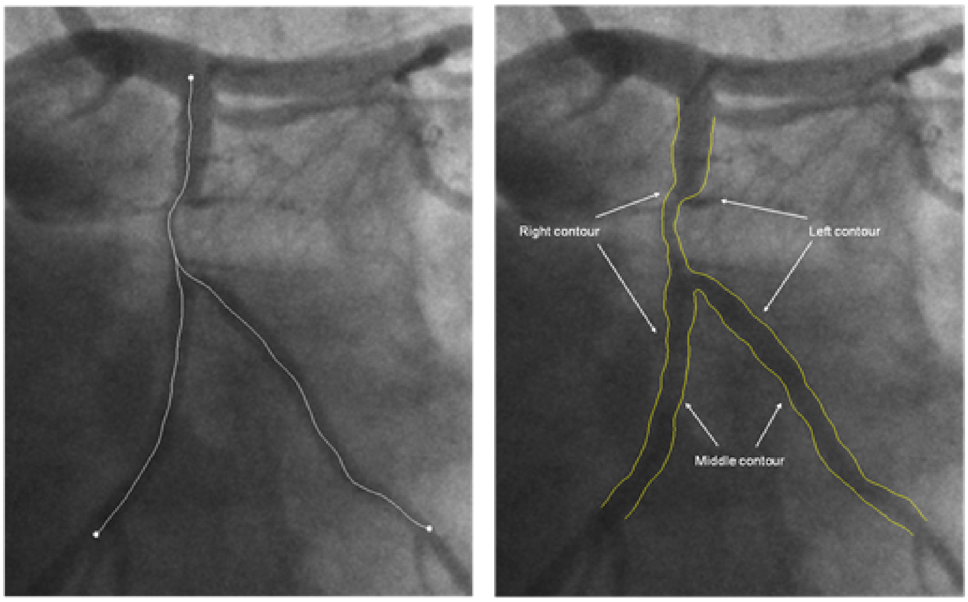
8.2 Material and Methods

8.2.1 Methods

The basic principles of the coronary bifurcation analyses of the T-shape and Y-shape models can be summarized as follows: As a first step, the user places three pathline points to define the bifurcating vessel segment of analysis: a start point in the proximal vessel and one end point in each of the two distal vessels. Subsequently, independent of the model type, two wavepath pathlines are detected (Figure 8.1(a)) [84, 102] followed by the automated detection of the arterial contours of all three vessel segments at once using the minimum cost algorithm (MCA) (Figure 8.1(b)) [39, 129]. When the QCA operator does not agree with one or more specific parts of the initially detected contours, the operator can edit the contours by choosing the automatic (attraction point) or manual contour correction option, similar to the conventional and established QCA approach for straight vessels [129, 141, 115].

In addition to the arterial contours, the initial position of the carinal point (split point of the two distal vessels) on the arterial middle contour is automatically determined as well. In case the operator finds the local arterial middle contour at the carinal point or the position of the carinal point itself being improperly detected, the position of the carinal point can be edited by manually dragging the carinal point to a different position. Subsequently, the MCA algorithm searches again for the contours, based on the available image information and the modified carinal point (that serves as a support point).

In the next step, the position of the proximal delimiter of the bifurcation core is automatically determined. This position is independent of the presence of lesions, with the advantage of having a similar position throughout Pre, Post and FU analyses. The positions of the proximal delimiter and the carinal point serve to define the four building blocks of the two bifurcation models. In the following paragraphs, the differences between the two models will be described.



(a) (b)

Figure 8.1: An example of a bifurcation analysis with: a) the three pathline points and the two detected bifurcation pathlines which are coinciding in the proximal segment; and b) the three detected arterial contours.

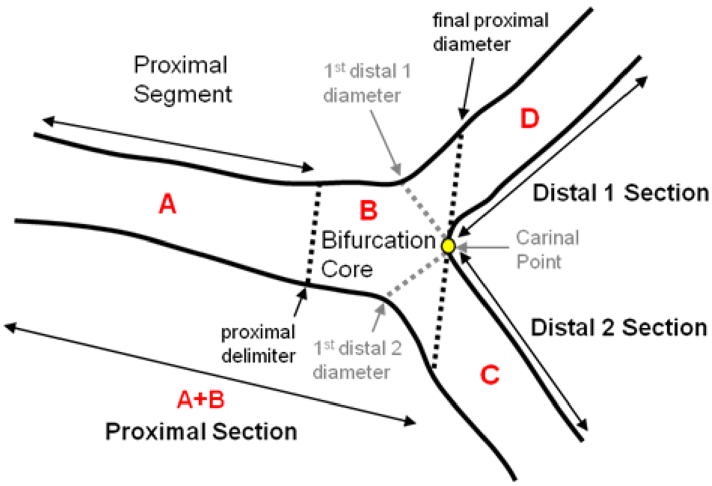


Figure 8.2: Scheme of the Y-shape model, explaining the segments, proximal delimiter and sections terminology. The partitioning of the bifurcation segment is into three sections: the proximal section, the distal 1 section and the distal 2 section. Using this model, the arterial and reference diameters up to the carina point and the distal 1 and 2 sections can be determined accurately.

The Y-shape model

The bifurcation core of the Y-shape model is defined as the area between the automatically determined proximal delimiter and the carinal point. Based on the arterial contours and the carinal point, three sections are defined (the proximal section, the distal 1 section and the distal 2 section: Figure 8.2) and their corresponding arterial diameter functions are calculated following the conventional straight analysis approach [115]. This method guarantees that within the bifurcation core the arterial diameters are measured to their fullest extent.

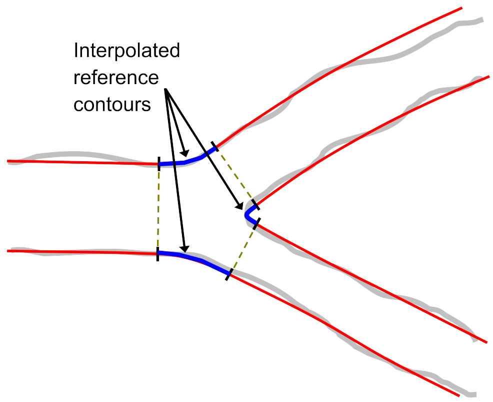


Figure 8.3: The interpolation of the reference contours in the bifurcation core.

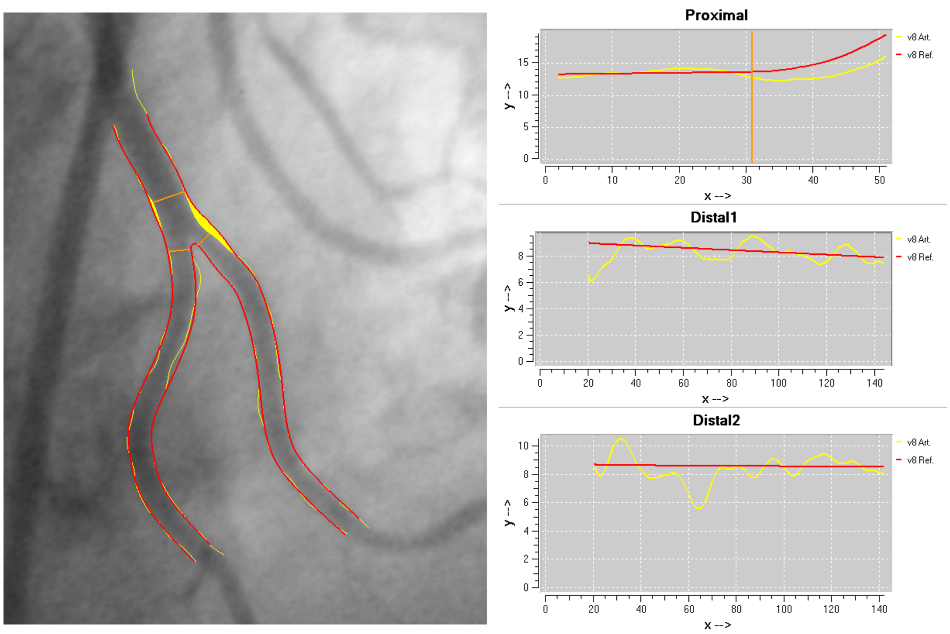


Figure 8.4: An example of a bifurcation analysis using the Y-shape model, showing the final arterial and reference contours, plaque filling and the three separate diameter functions of the three sections.

It is well known, that it is not a simple task to obtain an appropriate reference diameter function for the entire bifurcating vessel segment, due to the "step down" phenomenon [120]. To obtain a suitable and automatically derived reference diameter function for each section, the calculation of the reference diameter function is based on each of the vessel segments separately (so excluding the bifurcation core). In practice this means that from the arterial diameter functions of the proximal and two distal vessel segments the corresponding interpolated reference diameter functions are derived separately by an iterative regression technique [115]. In this way, it is assured that these reference diameter functions are only based on the arterial diameters outside of the bifurcation core. The reference diameter function of the bifurcation core itself is mainly based on two interpolated reference contours (spline-based), reconstructing a smooth transition between the reference diameters of the proximal and the two distal vessel segments [132] (Figure 8.3). As a result, the reference diameter function graph of the proximal section will be displayed as one function, which is straight for the proximal segment and curved in the bifurcation core (Figure 8.4). The two reference diameter functions of the distal sections are straight and will each be displayed as one function (Figure 8.4).

The T-shape model

The bifurcation core of the T-shape model is defined as the area between the proximal delimiter and the carinal point, delimited at one side by the first diameter of the distal main subsection and at the other side by a virtual contour between the proximal segment and the distal main subsection (Figure 8.5). This virtual contour, which separates the side branch from the main vessel, is created by making use of the interpolated reference contours (see text above) and the linearly interpolated reference diameters of the bifurcation core (see text below) [132]. Based on the arterial contours and the virtual contour, two sections are defined: the combination of the proximal segment, distal main subsection and the bifurcation core defines the first section (i.e. main section), while the side branch forms the second section (Figure 8.5). For the entire main section the arterial diameter function is continuously calculated following the conventional Medis straight analysis approach, while the Medis ostial analysis approach is followed for the side branch section, to assure that the arterial diameters at the ostium of the side branch are measured properly [115, 132].

Similar to the Y-shape model, the T-shape model deals with the "step down" phenomenon in a partly comparable manner. This means that from the arterial diameter functions of the proximal segment and distal main subsection, the corresponding interpolated reference diameter functions are derived separately. In the bifurcation core, the reference diameters are linearly interpolated (by means of a straight reference diameter function; red line [see Figure 8.6(a)]), reconstructing a transition between the proximal and distal main reference diameters. By using the interpolated reference contour opposite to the side branch ostium and the linearly interpolated reference diameters, a virtual contour is created (see Figure 8.6(b)).

It should be noted that besides being the virtual contour for the reference diameters, this contour is used to delimit the arterial diameters in the bifurcation core as well. Note that the arterial diameters inside the virtual reference contour are left unchanged, so only the diameters at the actual side branch crossing are clipped. By keeping the virtual contour equal for the arterial and reference diameters crossing the actual side branch ostium, means that in essence

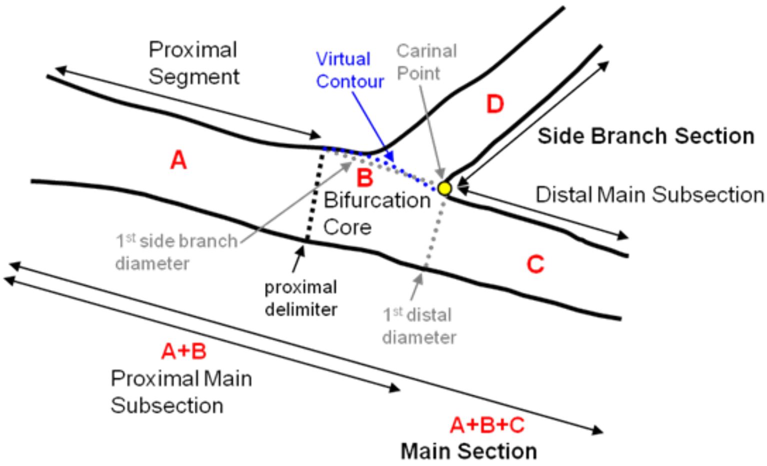
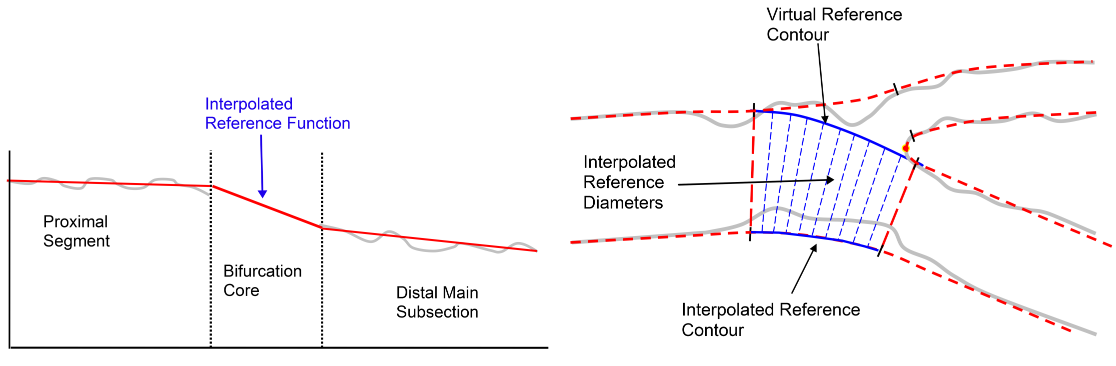


Figure 8.5: Scheme of the T-shape model, explaining the segments, proximal delimiter, virtual contour and sections terminology. The partitioning of the bifurcation into two sections: the main section and the side branch section. Using this model, the arterial and reference diameters of the ostium of the side branch and the whole main section can be accurately determined.



(a)

(b)

Figure 8.6: a) The virtual reference contour that bridges the sidebranch and b) the reference diameters in the T-shape analysis.

any obstruction of the main section at the location of the side branch is found opposite to the side branch [132]. As a final result, the reference diameter function graph of the entire main section will be displayed as one continuous function, which is composed of three different straight reference lines that are linked together (Figure 8.7). One additional advantage of this continuous diameter function for the main section is the possibility to detect and calculate parameters of a so-called "combined lesion" (i.e. the total main section lesion). This is a bifurcation lesion that starts in the proximal main subsection and extents into the distal main subsection. Previously, such a lesion was: 1) split up into two separate straight analyses (a proximal and distal segment of analysis), with each having its own lesion and leaving to the user to determine what the

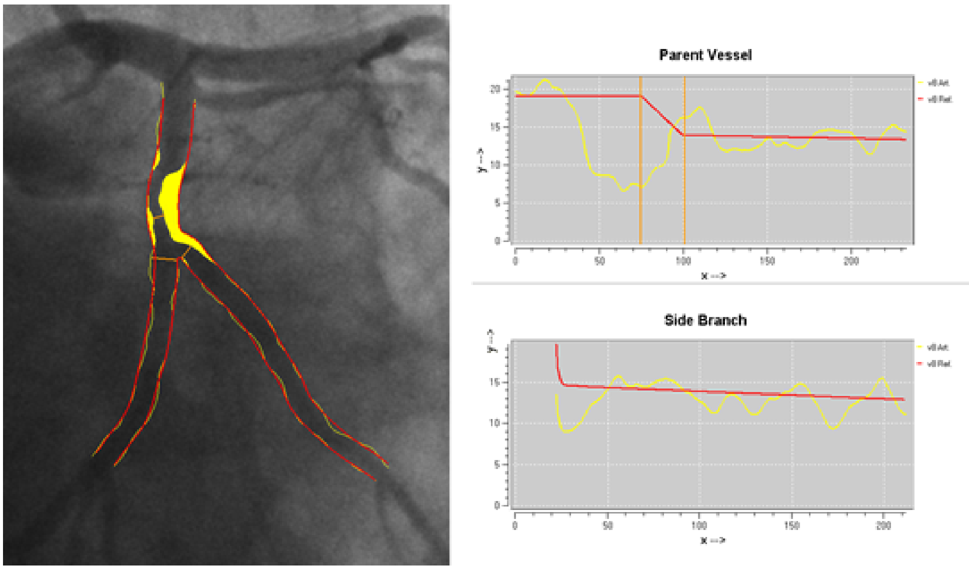


Figure 8.7: An example of a bifurcation analysis using the T-shape model, showing the final arterial and reference contours, plaque filling and the two separate diameter functions of the two sections.

actual obstruction diameter and total lesion length is; or 2) detected as one lesion, with an over- or under-estimations of the %DS and lesion length, in case of a single straight analysis "over the bifurcation core". However, the "combined lesion" does take into account the "step down" phenomenon [120] and provides the accurate lesion parameters for one single lesion. For the side branch section an "ostial" reference diameter function calculation is used [115, 132]. This will result in a reference diameter graph of the side branch section that will be displayed as one function, which is straight for the most part and slightly curved proximally (Figure 8.7).

Edge segments

For the assessment of (drug eluting) stent segments, an edge segment analysis option was created, providing a set of 9 suitable parameters for each of the segments as defined in Figure 8.8 (for Y-shape) and Figure 8.9 (for T-shape). This edge segment analysis allows studying the regression and progression of the bifurcation lesion more accurate, by including some extra parameters; the MLD position relative to the stent boundary (in stent edge segments) and the (sub-) segment start positions.

It should be noted that segment 14 of the T-shape edge segments (stented segment from proximal - over the bifurcation core - into the side branch) and segments 12 and 14 of the Y-shape edge segments (stented segments from proximal - over the bifurcation core - into the either distal branches) are not continuous in the bifurcation core (i.e., this trajectory consists of two separate diameter functions) and therefore the full parameter set cannot be calculated. The segment length (in this case representing the stented length) is the only value that can be calculated for these segments.

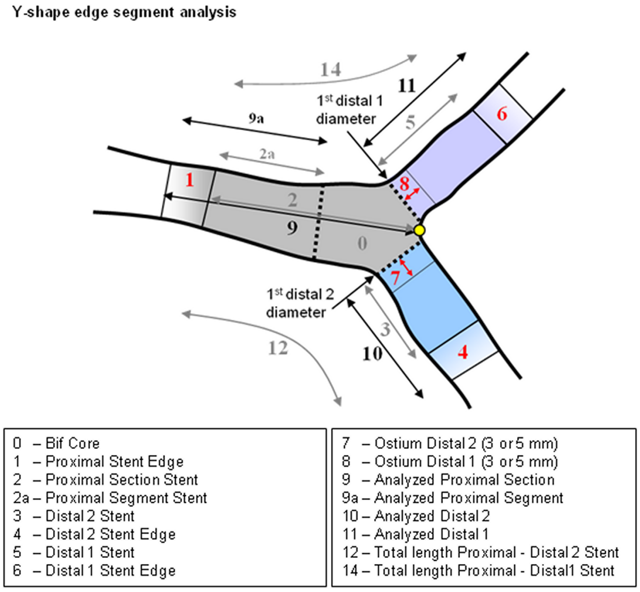


Figure 8.8: A schematic overview of the segments of the Y-shape bifurcation analysis with edge segments.

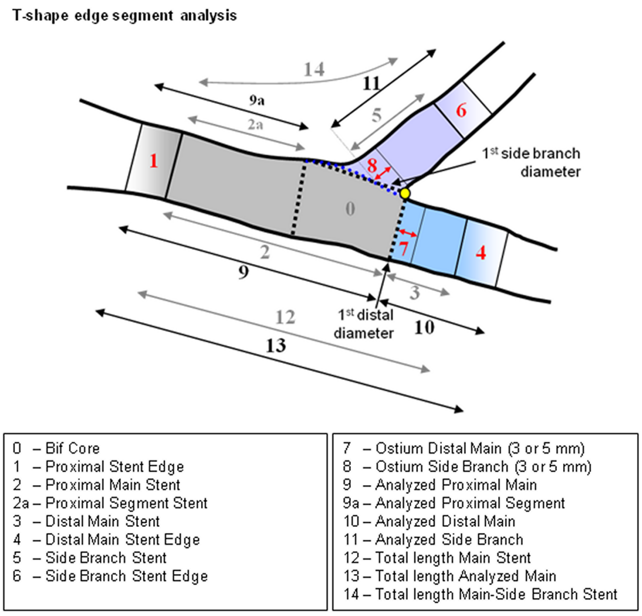


Figure 8.9: A schematic overview of the segments of the T-shape bifurcation analysis with edge segments.

8.3 Material

For this validation study 20 patient cases were selected at the Cardiovascular Research Foundation (CRF, New York, NY, USA). Ten cases were randomly selected from the cohort of the Diverge trial. This study is making use of the self-expanding DEVAX stent, which is a carinal skirt stent. These cases were analyzed with the Y-shape bifurcation model, specifically designed for the optimal stent length and diameter measurements up to the carinal point. Another 10 cases were randomly selected from the TriReme medical TOP study. This study is making use of main branch stenting (so, crossing the bifurcation core) with side branch preservation. In consequence of expansion of the stent body, an ostial crown (designed of ca. 2 mm long struts) automatically deploys into the ostium of the side branch. These cases were analyzed with the T-shape bifurcation model, specifically designed for the optimal (total) stent length and diameter measurements, while crossing the bifurcation core and optimal diameter measurement of the side branch ostium.

For each of these 20 patient cases the pre- and post-intervention analyses (n=40) were carried out with the two bifurcation analysis models of QAngio XA V7.2. The analyses were performed by two different QCA analysts, and according to QCA standard operating procedures (SOPs) [48]. Some specifics of the used analysis SOPs were: 1) bifurcation analyses started with the post-intervention case to define the bifurcation segment of analysis; 2) the bifurcation segment of analysis was defined by the length of the implemented stent(s) plus at least an additional 5 mm or a nearby landmark (e.g. side branch); 3) in case the initial interpolated reference diameter function was wrongly or too much tapered, flagging was primarily used for editing; 4) for pre-intervention analysis the same bifurcation segment of analysis was used as in the post-intervention analysis; and 5) in case a user-defined reference diameter was needed for the analysis, it was positioned in an approximately normal region of the vessel segment (or when applicable outside the stent).

8.3.1 Statistics

The four most relevant parameters for the bifurcation analysis that were studied are: the obstruction diameter (mm), reference diameter (mm), diameter stenosis (%), and obstruction length (mm). These parameters were studied per section and are expressed in terms of systematic and random errors (inter-observer variability).

For the bifurcation analysis with edge segments, the following three relevant parameters were studied: the mean diameter (mm), obstruction diameter (mm) and the diameter stenosis (%). These parameters were studied per segment (i.e., segment 1 to 11, see Figure 8.8 and 8.9) and are expressed in terms of systematic and random errors. Additionally, the stented length (mm) for segment 12 to 14 was studied in a similar manner. The systematic error is defined by the average value of the signed differences between measurement 1 and 2. The random error is defined by the standard deviation of the signed differences between measurement 1 and 2. The student's paired t-test was used to determine the significance of the differences (which hypothetically are equal to zero) between the repeated measurements. Level of significance $\alpha = 0.05$.

8.4 Results

The guidelines and results from previous publications presenting straight QCA inter-observer variability values are used to evaluate the performance of the two bifurcation models. This is done in the first place because of the lack of suitable bifurcation analysis references, and secondly because the bifurcation and straight analyses quality should be very similar.

The standard bifurcation analysis is compared to the QCA guidelines for straight analyses [115, 132, 48, 118] and study data of a previous publication [39], showing an inter-observer variability range of 0.10-0.15mm for the obstruction and reference diameter, 5.64% for the diameter stenosis and 1.46mm for the lesion length.

The bifurcation analysis with edge segments results is compared with the data of a straight brachytherapy analysis study [142]. The inter-observer variability data of the brachytherapy's injured segment (based on balloon and stent markers) was used for comparison with the bifurcation's stented segment (both determined by manually positioned markers). The brachytherapy inter-observer variability results (further on called the brachytherapy directive) show a slightly larger inter-observer difference (0.08 ± 0.17mm for the obstruction diameter) than conventional straight QCA (see above), due to the manual positioning of the markers (additional user variability).

Table 8.1: Inter-observer variability data of the Y-shaped bifurcation analysis model. The 10 pre- and 10 post-intervention cases used, were selected from the Diverge Trial.

	Proximal Section		Distal 1 Section		Distal 2 Section	
n=20 (pre + post cases)	sys err	rand err	sys err	rand err	sys err	rand err
Obstruction Diameter (mm)	0.06	± 0.16	-0.05	± 0.08*	-0.03	± 0.07
Reference Diameter (mm)	-0.05	± 0.24	0.00	± 0.10*	-0.01	± 0.09
Diameter Stenosis (%)	-1.9	± 4.6	2.1	± 4.2	0.8	± 3.3
Lesion Length (mm)	-0.49	± 1.44	0.63	± 1.02*	-0.37	± 1.12

* statistically significant difference

In Table 8.1, the inter-observer differences of the 10 pre and 10 post intervention cases analyzed with the Y-shape analysis model are presented for the four most relevant parameters.

Most values are well within the boundaries defined by the QCA guidelines for straight vessel analyses. Only the random errors of the obstruction and reference diameters in the proximal section are a bit larger and all the differences (except for the reference diameter) in the distal 1 section are statistically significant (although within the boundaries of the QCA guidelines). The inter-observer differences for the analyses using the T-shape analysis model (10 pre and 10 post intervention cases as well) are presented in Table 8.2. Again, all values are within the boundaries of the QCA guidelines, except for the side branch section, where the difference of the obstruction diameter is a bit larger (statistically significant) and the percentage diameter stenosis shows a statistically significant difference (although within the boundaries of the QCA guidelines).

In Table 8.3, the inter-observer differences of the edge segment analysis using the Y-shape model (10 post intervention cases) are presented. In the segments 0, 2 and 9, an absolute positioning of the MLD is used instead of the relative one. The reason for this is that all the data for

Table 8.2: Inter-observer variability data of the T-shaped bifurcation analysis model. The 10 pre- and 10 post-intervention cases used, were selected from the TriReme Study.

	Proximal Section			Distal Main Section			Side Section		
n=20 (pre + post cases)	sys err		rand err	sys err		rand err	sys err		rand err
Obstruction Diameter (mm)	0.01	±	0.11	0.04	±	0.15	0.09	±	0.12*
Reference Diameter (mm)	-0.01	±	0.13	0.01	±	0.14	0.01	±	0.15
Diameter Stenosis (%)	-0.4	±	4.3	-1.1	±	5.3	-3.0	±	4.2*
Lesion Length (mm)	-0.53	±	1.70	0.13	±	0.87	-0.28	±	0.93

* statistically significant difference

the edge segment analyses come from POST analyses, which do not really have lesions (percentage diameter stenosis smaller than 24%). This means that the obstruction position is influenced heavily by noise, since there is no obvious obstruction. Especially in the bifurcation core, which is a transition area that widens severely, a small difference in the percentage diameter stenosis can result in a large shift of the obstruction position due to the relative MLD calculation. Considering the tapering of the bifurcation core this can result in very different obstruction diameters. Therefore, the obstruction diameter found in a relative way is not a representative measure. This holds mainly for segment 0, 2 and 9 (all containing the bifurcation core) in the Y-shape edge segment analysis. Therefore, for these three segments, the absolute obstruction position was studied.

Table 8.3: Inter-observer variability data of the Y-shaped bifurcation's edge segment analysis. The 10 post-intervention cases used, were selected from the Diverge trial.

	n=10 POST	Mean diam (mm)			Obstr diam (mm)			Diam stenosis (%)			Stenth length(mm)		
	Segment	sys err		rand err	sys err		rand err	sys err		rand err	sys err		rand err
0	Bifurcation Core	-0.08	±	0.12	-0.05	±	0.15	2.4	±	5.5			
1	Edge Prox	0.07	±	0.10	-0.07	±	0.13	3.5	±	3.9*			
2	Stented Prox	-0.02	±	0.06	-0.07	±	0.10	1.3	±	5.0			
2a	Stented Prox	-0.01	±	0.06	-0.06	±	0.10	3.0	±	4.6			
3	Stented D2	-0.01	±	0.04	0.05	±	0.17	-1.0	±	1.8			
4	Edge D2	-0.06	±	0.11	0.02	±	0.10	-0.3	±	3.8			
5	Stented D1	0.01	±	0.02	0.03	±	0.06	1.3	±	2.4			
6	Edge D1	0.02	±	0.11	0.04	±	0.14	-0.1	±	4.8			
7	Ostium D2	0.01	±	0.04	0.03	±	0.09	0.0	±	2.5			
8	Ostium D1	-0.02	±	0.06	0.00	±	0.05	0.7	±	2.9			
9	Analyzed Prox	-0.04	±	0.05	-0.10	±	0.10*	2.5	±	4.5			
9a	Analyzed Prox	-0.03	±	0.06	-0.08	±	0.11*	3.7	±	4.1*			
10	Analyzed D2	-0.01	±	0.04	0.05	±	0.17	-0.8	±	3.6			
11	Analyzed D1	0.02	±	0.05	0.04	±	0.12	-0.1	±	4.9			
12	Stented Prox-D2										0.30	±	0.51
14	Stented Prox-D1										0.28	±	0.28

* statistically significant difference

Most of the inter-observer values are smaller than the values specified by the brachytherapy directive. We see, however, some deviations in the proximal segments; a slightly larger obstruction diameter error in segment 9 and significant differences in the obstruction diameters of segments 9 and 9a and in the percentage diameter stenosis of segments 1 and 9a.

Finally, the results of the inter-observer validation of the edge segment analysis using the

T-shape model (10 post intervention cases) are presented in Table 8.4. The majority of the measured inter-observer variabilities are smaller than the values specified by the brachytherapy directive. In the proximal section, the mean diameter of segment 2a is statistically significantly different (although within the boundaries of the guideline). In the distal main section, somewhat larger random errors can be seen for the lesion diameter (segment 3, 7, 10, 12) and percentage diameter stenosis (segment 3 and 7). In the side branch section, a slightly larger systematic error for the obstruction diameters of segment 5 and 8 (in segment 8 statistically significant), and for the mean diameter of segment 8 are found.

Table 8.4: Inter-observer variability data of the T-shaped bifurcation's edge segment analysis. The 10 post-intervention cases used, were selected from the TriReme Study.

	n=10 POST	Mean diam (mm)			Obstr diam (mm)			Diam stenosis (%)			Stenth length(mm)		
	Segment	sys err		rand err	sys err		rand err	sys err		rand err	sys err		rand err
0	Bifurcation Core	-0.07	±	0.18	-0.05	±	0.14	-0.1	±	5.2			
1	Edge Prox	0.02	±	0.06	-0.01	±	0.06	-0.5	±	2.1			
2	Stented Prox	-0.02	±	0.05	-0.02	±	0.05	-0.6	±	2.1			
2a	Stented Prox	-0.01	±	0.02*	-0.01	±	0.07	-0.8	±	2.3			
3	Stented Dist	-0.01	±	0.10	0.05	±	0.23	-1.2	±	7.0			
4	Edge Dist	-0.01	±	0.06	0.02	±	0.15	-0.9	±	3.8			
5	Stented Side	-0.06	±	0.06	-0.10	±	0.11	3.4	±	5.7			
6	Edge Side	0.07	±	0.12	0.05	±	0.10	-2.6	±	4.9			
7	Ostium Dist	-0.01	±	0.14	0.01	±	0.28	-0.2	±	9.5			
8	Ostium Side	-0.11	±	0.15	-0.10	±	0.12*	3.5	±	5.5			
9	Analyzed Prox	-0.01	±	0.04	-0.02	±	0.05	-0.5	±	2.0			
9a	Analyzed Prox	0.00	±	0.02	-0.01	±	0.07	-0.7	±	2.2			
10	Analyzed Dist	-0.01	±	0.06	-0.05	±	0.22	0.7	±	4.3			
11	Analyzed Side	-0.04	±	0.05	-0.02	±	0.09	3.5	±	3.8			
12	Stented Main	-0.02	±	0.05	0.01	±	0.25	-0.2	±	2.4	-0.23	±	0.64
13	Analyzed Main	-0.01	±	0.04	-0.04	±	0.17	0.0	±	3.2	-0.23	±	0.64
14	Stented Prox-Side										-0.29	±	0.26

* statistically significant difference

8.5 Discussion

In this article we describe the results of an inter-observer variability study performed with the new Y- and T-shape bifurcation analysis models of QAngio XA V7.2. A validation study like this is essential to determine whether the bifurcation analyses performed are reproducible, given the fact that the analyses are performed at different moments in time (without previous obtained knowledge), by two QCA analysts (introducing a subjectivity level), and by using the same analysis SOPs.

Looking at the inter-observer analysis data of the Y-shape analysis model, the results are very good and comparable to the values known from previous publications and the QCA guidelines for straight analyses [39, 115, 118], which are very precise. Only in a few cases the random error shows a slightly larger value. The first very slightly diverging value is the variability in the proximal section's obstruction diameter (0.16 mm vs. 0.15 mm of the QCA guidelines). It turned out that this is caused by the minor variations in the arterial contours, caused by manual edits of the two analysts. When this is the case at the lesion site, this greatly influences the value of the obstruction diameter. Therefore, we strongly recommend not to edit the lesion sites. Nevertheless, sometimes one cannot fully avoid it, for example, when: a) using the automatic correction points, which might have a slight influence further along the contour; b) the lesion is very irregular due to complexity or poor edges and requires manual editing, or c) because of a small vessel that overlaps or a side branch crossover that requires correction. Unfortunately, all these situations were present in our study cases, which is a random sample of practice.

Furthermore, the variability in the reference diameter in the proximal section is a bit larger as well (0.24 mm), which is indirectly caused by the variation in arterial contours between the two analysts, as discussed above. Differences in arterial contours can lead to different automatic reference diameter functions and because of that slightly different (relative) obstruction positions (based upon the maximum percentage diameter stenosis), which in turn has its influence on the corresponding reference diameter value. Besides that, a second cause might have been the editing of the reference diameter function itself. Of course an analysis SOP was used to do this, but small difference in the proximal or distal sections can have an influence on the reference diameter function of the bifurcation core as well, mainly due to the significant tapering in this area. Besides these random errors, we see some statistical differences (p-value <0.05) for the obstruction, diameter stenosis and lesion length of the distal1 section (see Table 8.1). However, looking at the corresponding systematic and random errors, these values are not large at all. The random errors are much smaller than mentioned in the QCA guidelines and literature, which causes the found differences to be significant. Besides that, clinically speaking, systematic error values of this magnitude do not have any influence on the clinical decision making process or meaning for study outcomes, in other words: they're clinically not relevant [143, 144, 145].

The validation data of the T-shape analysis model looks very good as well; the random errors of the obstruction and reference diameter are similar to the inter-observer variability data previously published [39] and the percentage diameter stenosis is even smaller than these published values. Only the systematic error of the obstruction diameter in the side branch is a bit large (0.09 mm) and statistically significant. Splitting up the side branch data in lesions in the straight part and ostial part of the side branch section, it turned out that the ostial lesions are the cause of this systematic difference (n=10; 0.13 ± 0.15 mm, p-value 0.004 compared to n=10; 0.04 ± 0.07 mm, p-value 0.09). This significant difference is probably caused by small differences in the manual editing of the carinal point by the two analysts. As a result of this, the middle arterial contour can shift slightly, causing differences in arterial diameters that are positioned proximally in the distal branches. In that perspective, both branches are oppositely influenced. In combination with an ostial lesion this might slightly influence the size of the obstruction diameter. In these cases, the main reason for editing the carinal point was poor contrast and poor edges in that region of the image, resulting in slightly subjective editing differences. Therefore, we recommend not to edit the carinal point too easily. Furthermore, only the diameter stenosis of the side branch section shows a statistical significant difference. Again the relatively small random errors are the cause for this. Clinically these differences are not relevant [143, 144].

Finally, the random error for the obstruction length of the proximal section is somewhat larger than published before (1.70mm vs. 1.46mm) [39]. This is mainly due to small differences in the arterial contours, causing a small shift in the positioning of the proximal and/or distal lesion markers. Nevertheless, the inter-observer variability value remains so small that it will not have any influence on the clinical decision making process. As can be expected, these small shifts in the proximal and distal lesion marker positions have a comparable (slightly enlarging) influence on the random errors of the "combined lesion" length (2.21 mm, p >0.05; n=6!) as well. The inter-observer variability for the percentage diameter stenosis of the "combined lesion" (5.22%, p >0.05) is very comparable to the value mentioned before (5.64%) [39]. Given the fact that these variations have clinically no relevance, it does indicate that the "combined lesion" data can be used very well.

8.5.1 Edge segments

In general, the inter-observer data for the bifurcation analysis with edge segments of both models are good and consistent with the results that were previously published [142]. In fact, most of the data is even within the ranges defined by the QCA guidelines for straight analyses and a previous publication [39, 115, 118].

For the Y-shape edge segments, Table 8.3 shows that only a few diverging values are present in the proximal segments, which is similar to the conventional Y-shape bifurcation analysis. The segment results for the two distal sections are considered to be similar. The statistically significant differences found are due to the relatively small random errors, and are considering the size of the systematic error not clinically relevant [143, 144, 145]. The only exception is segment 9, the obstruction diameter, for which the systematic error is a bit large (-0.10 mm) as well. According to the conventional bifurcation analysis this can be traced back to the differences in manual edits of the analysts (see size mean diameter segment 0 and 1 as well). Because segment 9 is composed of segment 0, 1 and 2a, differences are accumulated here the most.

As can be seen in Table 8.4, the T-shape edge segments show very good inter-observer values in the proximal segments, only segment 2a shows a statistically significant difference (due to the very small random error), which has clinically no relevant meaning (-0.01 mm) [144, 145]. Similar to the conventional T-shape bifurcation analysis is the influence of the manual repositioning of the carina point, which has caused slightly larger systematic and random errors for the obstruction diameter and percentage diameter stenosis in (particularly) the ostial segments (7 and 8) and the segments (3, 5, 10 and 12) containing these ostial segments.

For both models, the systematic errors of the stent lengths of segment 12, 13 (only T-shape) and 14 are very comparable to the values in the brachytherapy directive, but the random errors are very small compared to the brachytherapy directive. As a result, the manual positioning of the stent markers and with that the definition of the edge segments are very reproducible. One should however notice that this accuracy will be influenced by the visibility of the stent struts or stent markers and the preciseness of the analyst when placing the stent markers.

In general, the results of this bifurcation analysis (with edge segments) inter-observer variability study are very good, although one must recognize the influence of the manual contour edits. Probably due to the fact that this type of analysis has become very complex, the edits, especially the ones around the bifurcation core (the most complex part) have a slightly larger influence on the results than one is used to for straight analysis. Looking at the results of the intra-observer variability study, performed on exactly the same dataset [146], it will be noticed that for the T- and Y-shape model the systematic- and random errors of the obstruction and reference diameter are very low (random errors $\leq$ 0.11 mm!). This demonstrates the possibility of a high reproducibility of the bifurcation analysis with both models and the influence of the subjective differences caused by the manual contour edits. In other words, it is possible to obtain even better inter-observer variability data when: 1) less contour edits are needed (clear vessel edges, optimal bifurcation viewing angle, etc), and/or 2) the analysts are editing more alike. Because the arterial contours are the basis of every type of QCA analysis, we want to emphasize (once more) the importance of highly precisely and unambiguously written Standard Operating Procedures (SOPs) for the analyses, which will help the analysts to accomplish good and reproducible analysis results.

8.6 Conclusion

The inter-observer variability data of the T- and Y-shape bifurcation analysis models show a robust and very good reproducibility for both models. The data for the bifurcation analysis with edge segments (both models) is very good as well, although in some segments a slightly larger random error might be evident. In general, the inter-observer variability data shows that the T- and Y-shape models of the bifurcation analysis (with edge segments) is a great improvement in the field of quantitative coronary angiography.