Impact of Cine Frame Selection on Quantitative Coronary Angiography Results

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ABSTRACT: We evaluated intra- and interobserver variability of quantitative coronary angiography (QCA) due to cine frame selection for 9 coronary stenoses. The projection was selected in advance. Cine frames were selected by 2 blinded experts (blind frame QCA) followed by assignment by supervisor (pre-selected frame QCA). Each expert analyzed 18 frames twice with a 3-month interval. A total of 72 measurements by 2 experts were used for intra- and interobserver variability analysis in calibration factor (CF), minimal lumen diameter (MLD), percent diameter stenosis (%DS), interpolated reference diameter (Int R), and lesion length (LL). Accuracy, precision, and coefficient of variation (CV) were calculated based on 2 measurements. For interobserver variability, intraclass correlation coefficient (ICC) was evaluated. Regarding intraobserver variability, precision (CV) was 0.0026 (1.45), 0.220 (25.1), 0.282 (11.0), 7.626 (11.8), and 4.042 (28.7) for blind frame QCA and 0.0044 (2.46), 0.094 (11.2), 0.225 (8.6), 3.924 (5.9), and 1.941 (12.1) for pre-selected frame QCA and regarding interobserver variability, precision (CV) was 0.0037 (2.09), 0.271 (31.8), 0.307 (11.9), 10.10 (15.4), and 5.121 (39.5) for blind frame QCA and 0.0050 (2.82), 0.098 (11.4), 0.246 (9.5), 5.253 (8.0), and 2.857 (19.0) for pre-selected frame QCA in CF, MLD, Int R, %DS, and LL, respectively. Intraclass correlation coefficient of Int R was almost perfect in blind and pre-selected frame QCA. Intraclass correlation coefficient of MLD, %DS, and LL were substantial/lower by blind frame QCA and improved to almost perfect by pre-selected frame QCA. Blind cine film selection might affect intra- and interobserver variability, especially in MLD and LL. In the multiple linear regression analysis, blind frame QCA was selected as an explanatory factor of QCA variability in MLD, %DS, and LL. The error range due to frame selection must be taken into consideration in clinical use.

KEYWORDS: quantitative coronary angiography, core laboratory, frame selection, cardiac cycle, coronary intervention, minimal lumen diameter, coronary stenosis

Introduction

In the clinical applications of quantitative coronary angiography (QCA),[1] several factors could affect the final QCA results. Although the accuracy and precision of the analytical methods have steadily improved with the increasing complexity of algorithms, there is always a human factor involved in these processes, in terms of image acquisition with adequate contrast infusion, adequate catheter size, projection/frame selection, and segment definition. The users should have a complete understanding of all the possibilities and limitations of the current QCA acquisition and analysis techniques. Selection of optimal image projection[2] and cine frame selection in an assigned projection would be one of the crucial factors. A general guideline for frame selection has been proposed.[3,4] Meanwhile, after agreeing on the general approach for frame selection, there remains a number of important issues that need to be addressed when defining a frame selection strategy for QCA.

Although a frame at the end-diastolic cardiac cycle is recommended,[5–7] this cardiac cycle is sometimes not available due to overlap of vessels or ambiguous vessel border (insufficient contrast in the vessel). In this case, the other cardiac cycle apart from the end-diastolic is preferable to obtain the non-overlapped sharp contour of vessels at stenosis and reference. Cine frame selection finally depends on the assigned analysis experts. Previous studies[5,6,8,9] have showed that variability of QCA parameters due to cine frame selection were small and clinically negligible. However, there has been little data comparing QCA parameters analyzed from an assigned cine frame with those selected blindly in an assigned projection. In this study, we evaluated intra- and interobserver variability of QCA results between blind and pre-selected frames.

Methods

The consecutive patients in whom elective or ad hoc percutaneous coronary intervention (PCI) was planned and written informed consent was obtained between June 1 and July 31 in 2012 at Nagoya City East Medical Center were considered for this study. A total of 9 patients with 9 lesions were included in this study. This study is a sub-analysis of the original study which evaluated the validity of 4F vs 6F catheters for QCA.[10]

Protocol of coronary angiography and QCA

Coronary angiography was performed just prior to PCI using the 6F guide catheter (Mac1, Boston Scientific, USA) and the films

taken were used for calibration and vessel analysis for QCA. All coronary angiographies were performed by a power injector with an injection rate of 2.5 mL after intracoronary injection of an adequate dose of isosorbide dinitrate. The cine film image was acquired with an Allura Xper FD 10/10 biplane system (PHILIPS, Amsterdam, The Netherlands). All angiograms were performed with the same contrast agent, Iopamiron (370 mg iodine/mL; Bauer Healthcare, Berlin, Germany). The image frame rate was 15 per second. The QCA system used was QAngioXA version 7.2 (Medis, The Netherlands). The cine frame used for catheter calibration should include a contrast-filled catheter tip of at least 4 to 5 cm, without contrast dye in the background field and the cine frame and angle/skew used for vessel analysis should be foreshortened minimally without vessel overlap.

Cine frame selection. Before QCA analysis, cine frames for catheter calibration or vessel analysis were selected in a single assigned projection by experienced QCA experts (A.E. and K.K.), who had 2 years of experience at the core laboratory, at the time of study, in a blind fashion and they performed QCA for cine frames selected by themselves (blind frame QCA). Furthermore, a supervisor (S.I.) selected cine frames in advance for QCA in the same assigned projection as blind frame QCA and A.E. and K.K. analyzed them (pre-selected frame QCA). All vessel measurements were performed twice for pre-selected frames and blind frames. All the 3 experts involved in the study have undergone documented training to deal with all the possible difficulties during QCA procedures. Briefly, cine frame selection was conducted based on the standard operating procedures (SOP) which included the selection of frames in maximum opacification, no significant overlapping structures, and occurring as close to end diastole as possible. In the cases where the end-diastolic cardiac portion was unavailable, cine frame with most severe stenosis with sharp edge was selected. This cine film selection process and QCA were undertaken in the original research, but not included in the authors' previously published study.[10]

QCA analysis. The following parameters were automatically calculated during QCA and included for analysis: calibration factor (CF), maximal %DS (percent diameter stenosis), the corresponding minimal lumen diameter (MLD), the interpolated reference diameter (Int R) taken at the site of the obstruction, and lesion length (LL) (shoulder to shoulder). Int R and LL can be automatically measured using the functional curve. %DS is calculated as $(1 - MLD/Int\ R) \times 100$. Quantitative coronary angiography was performed using 6F catheters as a scaling device. The difference in the number of cine frame counts between the 2 separate analyses, by the 2 selected experts in blind frame QCA, was calculated.

Intraobserver reliability in QCA measurements between first and second analyses by 2 experts in the selected and blind frame QCA. The first and second analysis data obtained at a 3-month interval by 2 experts were compared in CF, MLD, Int R, %DS, and LL. Variability in measurements was evaluated using mean and SD of the assigned differences, and coefficient of variation (CV). Data for pre-selected frame and blind frame QCA were analyzed separately.

Interobserver reliability in QCA measurements between 2 analysis experts in the selected and blind frame QCA. Two sequential data analyses were performed at an interval of 3 months by 2 experts, who compared CF, MLD, Int R, %DS, and LL. Variability in measurements was evaluated using mean and SD of the assigned differences, and CV. Interobserver variability between the 2 experts for blind and selected frame QCA measurements was evaluated using CV and intraclass correlation coefficients (ICCs).

Multiple linear regression analysis to explore the potential factors of QCA variability. The procedural and lesion characteristics available in this study were included as potential factors that can be used to explain the variabilities in the QCA parameters.

Statistical analysis

All continuous variables (CF, MLD, Int R, %DS, and LL) were expressed as mean ± SD. Comparison of continuous variables was performed using the non-paired *t* test when applicable. Accuracy (mean differences between the 2 measurements, retaining the direction of the difference), precision (SD of differences), and CV (SD of differences divided by the mean of value of each variable) were calculated using all measurements by both experts, for both blind and selected cine frames, in the first and second analyses. Coefficient of variation was used to compare variability among the parameters. Intraclass correlation coefficient (2, 1) and ICC (2, 2) were used for interobserver reliability assessment and the reliability level was classified as slight (0.0-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), or almost perfect (0.81-1.0).

Bland-Altman plots were given for all comparisons between the blind vs pre-selected and intraobserver vs interobserver analyses of the CF, MLD, Int R, %DS, and LL measurements.

To use a multiple regression analysis to explore the potential factors causing variabilities of CF, MLD, Int R, %DS, and LL, we used a standard deviation between 2 measurements for the same lesion as a dependent variable in a total of 72 repeated measures (8 repeated measures for 9 lesions). As the explanatory variables, cine frame selection mode (blind vs pre-selected), operator mode (intraobserver vs interobserver), target vessel (left anterior descending coronary artery [LAD] vs left circumflex artery [LCx]), lesion location (proximal vs mid), and lesion calcification (non/mild vs moderate/severe) were included.

This study was approved by the institutional review board of the Nagoya City East Medical Center. This study was carried out according to the Declaration of Helsinki. Written informed consent was obtained from all patients for the coronary angiography, PCI, and participation in this study.

Table 1. Clinical and lesion characteristics.

CASE NO.	AGE	SEX	DIAGNOSIS	CORONARY RISK FACTORS	LESION ANGLE/ SKEW	LOCATION OF STENOSIS	CALCIFICATION[a]/ THROMBUS
1	51	Male	Angina pectoris	HT DL	LAD#6 LAO/Caudal	Proximal	None/None
2	74	Male	Angina pectoris	DM HT DL	LAD #6-7, 9 AP/Cranial	Proximal	None/None
3	87	Female	Prior myocardial infarction	DL	LCx #11-13 RAO/Caudal	Proximal	None/None
4	62	Male	Angina pectoris	SAS	LCx#13 RAO/Caudal	Mid	None/None
5	73	Male	Angina pectoris	HT DL	LCx #15 AP/Cranial	Mid	Moderate/None
6	80	Male	Prior myocardial infarction	HT CKD	LAD#7,9 RAO/Cranial	Mid	Moderate/None
7	57	Male	Angina pectoris	DM DL smoking	LAD #7 AP/Cranial	Mid	Severe/None
8	70	Male	Prior myocardial infarction	CKD smoking	LAD #6-7, 9 AP/Cranial	Proximal	Moderate/None
9	66	Male	Unstable angina pectoris	DL smoking	LAD#7 LAO/ Cranial	Mid	None/None

Abbreviations: AP, anterior posterior; CKD, chronic kidney disease; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension; LAD, left anterior descending coronary artery; LAO, left anterior oblique view; LCx, left circumflex artery; RAO, right anterior oblique view; SAS, sleep apnea syndrome.
[a]Calcification includes none/mild, moderate (densities noted only during the cardiac cycle prior to contrast injection), and severe (radio-opacities noted without cardiac motion prior to contrast injection generally involving both sides of the artery wall).

Results

Clinical and lesion characteristics

Data are shown in Table 1. The mean age of the study group was 68.8 years (range, 51-87 years) and 8 subjects were men. The diagnosis was angina pectoris in 5 patients, prior myocardial infarction in 3, and unstable angina pectoris in 1. Diseased vessels were the LAD in 6 patients and the LCx in 3 patients.

Difference in the number of cine frame count

Data are shown in Table 2. Inherently, there was no difference in the pre-selected frame QCA due to its definition. Mean difference was 0.833 in cases that selected a same cardiac cycle in blind frame QCA. Different cardiac cycle (all adjacent cardiac cycle) was used in 6 measurements. In 67% of the analysis, 2 experts selected frame within the same cardiac cycle. In 28% of cases, they selected exactly the same cine frame. In 33% of cases, the 2 selections were in adjacent cardiac cycles, and none of the selection pairs were separated by 2 or more cardiac cycles.

Measurements and variability in CF, MLD, Int R, %DS, and LL between blind and pre-selected frame QCAs

Data are shown in Table 3. A total of 72 measurements performed for 40 frames (9 frames in pre-selected frame QCA and 31 frames (5 frames identical in 2 analysis experts) in blind

frame QCA by 2 experts were included to evaluate intraobserver and interobserver variability. There was no significant difference in measurements in all variables between blind and pre-selected QCAs. Coefficient of variation tended to be larger in MLD and LL than in CF, Int R, and %DS.

Intra- and interobserver variability in the blind and pre-selected frame QCAs

Intra- and interobserver variability are shown in Tables 4 and 5. Mean values were not significant in the intraobserver variability in all variables. There was a significant difference in CF between 2 experts for blind QCA analysis in interobserver variability analysis. There was a significant difference in LL between 2 experts for pre-selected frame QCA in interobserver variability analysis. In the intraobserver variability, CV was higher in MLD and LL than in CF, Int R, and %DS. Coefficient of variation improved in pre-selected frame QCA analysis in all variables besides CF, which was smallest in both blind and pre-selected frame QCA analyses. Similar tendencies were also observed in interobserver variability. Intraclass correlation coefficient data are shown in Tables 6 and 7. The correlation by linear regression analysis was better for Int R than the other variables. Intraclass correlation coefficient (2, 1) and ICC (2, 2) of Int R were almost perfect in blind frame and pre-selected frame QCAs. Intraclass correlation coefficient (2, 1) and ICC (2, 2) were substantial or lower in MLD, %DS, and LL by blind

Table 2. Difference in cine frame number between 2 analysis experts.

CASE NO.	DIFFERENCE IN CINE FRAME NUMBER IN BLIND FRAME QCA ANALYSIS (FIRST ANALYSIS)	DIFFERENCE IN CINE FRAME NUMBER IN BLIND FRAME QCA ANALYSIS (SECOND ANALYSIS)	DIFFERENCE IN CINE FRAME NUMBER IN PRE-SELECTED QCA ANALYSIS
1	2	11 (different cardiac cycle)	0
2	13 (different cardiac cycle)[a]	8 (different cardiac cycle)[a]	0
3	1	1	0
4	0	9 (different cardiac cycle)	0
5	0	0	0
6	1	8 (different cardiac cycle)[a]	0
7	14 (different cardiac cycle)	2	0
8	0	2	0
9	1	0	0

Abbreviation: QCA, quantitative coronary angiography.
[a]One analysis expert selected non-diastolic frame.

frame QCA. They improved to almost perfect when analyzing pre-selected frames in MLD, %DS, and LL.

Bland-Altman plots are shown in Supplement 1: Figures 4a–e. Differences in MLD, Int R, %DS, and LL were larger in the blind frame QCA than in the pre-selected frame QCA, but similar between intraobserver and interobserver analyses.

Multiple linear regression analysis

The mode of cine film selection (Blind) was selected as an explanatory factor of QCA variability in MLD, %DS, and LL (Supplement 2: Tables 8 to 12). The target vessel (LAD) was selected as an explanatory factor of QCA variability in Int R.

Discussion

In both intra- and interobserver variability, the CV was larger in MLD and LL than in CF, Int R, and %DS in independently selected (blind) frame QCA analysis. However, the coefficient improved in pre-selected frame QCA analysis leading to similar CV among all variables. Similarly, ICC between 2 analysis experts in MLD, %DS, and LL using blind cine frames was only fair or moderate but improved to almost perfect after coincidence of the cine frames (pre-selected frames). These results suggested that cine film selection in an assigned projection might influence the QCA analysis. Although the principles for performing QCA analysis accurately are well established, there remains a significant operator-dependent variability in cine frame selection.

Intra- and interobserver variability in QCA practice among analysis experts cannot be overlooked even in the era of sophisticated QCA systems and software. This would be particularly important in the large studies where multiple core laboratories are involved in QCA.[4,11,12]

In the clinical setting, many analyst-dependent factors do exist, until final data reaches the investigators in QCA evaluation. We must remember that cine film selection for catheter calibration and vessel analysis could be an important process in the whole QCA procedure and core laboratory experts should be trained for maintenance of low intra- and interobserver variability.[7,8,13,14]

Figures 1 to 3 show the QCA procedural steps for a lesion in this study comparing the analyses for the blind and pre-selected cine frames. Once the proximal and distal points were determined, an edge detection algorithm and functional line can be used to determine the MLD, Int R, and LL followed by %DS calculation. These steps can be repeated automatically as shown in Figures 2 and 3. However, the most crucial steps in QCA might be obtaining QCA-dedicated cine films for calibration, coronary lesions, and appropriated cine frames (Figure 1).

Herrington and Walford[9] showed the sources of variability in QCA and proposed a general guideline for cine frame selection. Among them, we specifically focused on the influence of cine frame selection in an assigned projection as one of the important QCA procedures in this study. The strength of this study was that we compared QCA results between blind and pre-selected frames, calculated the influence of CF, and evaluated the influence of cine film selection by CV and ICC and multiple linear regression analysis. In contrast to MLD, %DS, and LL, Int R showed almost perfect ICCs in blind frame QCA analysis as well as pre-selected frame QCA. Int R was calculated from the functional line as the reference diameter at the most stenotic site. Similarly, LL was also calculated from functional line (shoulder to shoulder). Intraclass correlation coefficient was substantial in blind frame QCA and improved to almost perfect in pre-selected frame QCA. It is because LL could be strongly influenced by vessel tortuosity change due to

Table 3. Variability of CF, MLD, Int R, %DS, and LL between QCAs for the blind and pre-selected frames.

CF	BLIND	PRE-SELECTED	*P* VALUE
Mean ± SD (range)	0.17783 ± 0.00672 (0.0248)	0.17847 ± 0.00493 (0.0166)	.827
Accuracy (pre-selected-blind)	−0.00026		
Precision (pre-selected-blind)	0.00489		
Coefficient of variation (%)	2.74		
r value (selected: blind)	0.6864		.0017
MLD (MM)	**BLIND**	**PRE-SELECTED**	***P* VALUE**
Mean ± SD (range)	0.877 ± 0.270 (0.880)	0.838 ± 0.244 (0.730)	.4461
Accuracy (pre-selected-blind)	−0.039		
Precision (pre-selected-blind)	0.215		
Coefficient of variation (%)	25.7		
r value (selected: blind)	0.654		.003
INT R (MM)	**BLIND**	**PRE-SELECTED**	***P* VALUE**
Mean ± SD (range)	2.564 ± 0.674 (2.260)	2.607 ± 0.816 (2.710)	.542
Accuracy (pre-selected-blind)	0.043		
Precision (pre-selected-blind)	0.292		
Coefficient of variation (%)	11.2		
r value (selected: blind)	0.961		<.0001
%DS (%)	**BLIND**	**PRE-SELECTED**	***P* VALUE**
Mean ± SD (range)	64.610 ± 11.419 (35.700)	66.383 ± 10.159 (36.300)	.391
Accuracy (pre-selected-blind)	1.773		
Precision (pre-selected-blind)	8.542		
Coefficient of variation (%)	12.9		
r value (selected: blind)	0.585		.011
LL (MM)	**BLIND**	**PRE-SELECTED**	***P* VALUE**
Mean ± SD (range)	14.079 ± 6.600 (21.210)	16.084 ± 6.681 (22.640)	.166
Accuracy (pre-selected-blind)	2.004		
Precision (pre-selected-blind)	5.868		
Coefficient of variation (%)	36.5		
r value (selected: blind)	0.674		.002

Abbreviations: CF, calibration factor; %DS, percent diameter stenosis; Int R, interpolated reference diameter; LL, lesion length; MLD, minimal lumen diameter; QCA, quantitative coronary angiography.

cardiac cycle. Although cine frames for catheter calibration were obtained in blind and pre-selected manner, there was no difference in mean CF between blind and pre-selected cine frame QCA not affecting QCA results. In interobserver variability between 2 experts in blind frame QCA, there was significant difference in CF. The reason was not clear; however, the amount was very limited.

Variability of CF might be one of the causes of variability in QCA results between selected and blind cine frame selection, but has not been clarified. Mean and SD of CF difference were −0.000256 and 0.0048943, respectively. When measuring a 3-mm diameter, 0.0048943 SD of CF difference potentially might correspond to 0.0841 mm. Thus, CF variability might partially explain MLD variability (SD) between blind and

Table 4. Intraobserver variability in 2 analysis experts for blind and pre-selected frame QCA.

	CF	MLD	INT R	%DS	LL
Blind frame QCA					
A and B first	0.1787 ± 0.0067	0.877 ± 0.270	2.564 ± 0.674	64.6 ± 11.4	14.08 ± 6.60
A and B second	0.1779 ± 0.0066	0.854 ± 0.221	2.499 ± 0.626	64.4 ± 11.8	12.31 ± 5.95
P value	.1303	.659	.827	.755	.084
Accuracy	0.0008	0.023	0.064	0.238	1.771
Precision	0.0026	0.220	0.282	7.626	4.042
Coefficient of variation (%)	1.45	25.1	11.0	11.8	28.7
Pre-selected frame QCA					
A and B first	0.1785 ± 0.0049	0.838 ± 0.244	2.607 ± 0.829	66.4 ± 10.2	16.08 ± 6.68
A and B second	0.1773 ± 0.0043	0.872 ± 0.230	2.574 ± 0.738	65.2 ± 8.90	15.65 ± 6.23
P value	.0625	.140	.551	.206	.356
Accuracy	0.0012	−0.034	0.032	1.217	0.434
Precision	0.0044	0.094	0.225	3.924	1.941
Coefficient of variation (%)	2.46	11.2	8.6	5.9	12.1

Abbreviations: CF, calibration factor; %DS, percent diameter stenosis; Int R, interpolated reference diameter; LL, lesion length; MLD, minimal lumen diameter; QCA, quantitative coronary angiography.
Accuracy, precision, and coefficient of variation (%): same as in Table 3.
A and B indicate 2 analysis experts.

Table 5. Interobserver variability between 2 analysis experts for blind and pre-selected frame QCA.

	CF	MLD	INT R	%DS	LL
Blind frame QCA					
A first and second	0.1772 ± 0.0058	0.852 ± 0.258	2.577 ± 0.605	65.7 ± 12.2	12.97 ± 6.573
B first and second	0.1795 ± 0.0072	0.879 ± 0.235	2.487 ± 0.691	63.3 ± 10.9	13.42 ± 6.113
P value	.0209	.682	.231	.333	.717
Accuracy	−0.0022	−0.027	0.090	2.373	−0.446
Precision	0.0037	0.271	0.307	10.10	5.121
Coefficient of variance	2.09	31.8	11.9	15.4	39.5
Pre-selected frame QCA					
A first and second	0.1775 ± 0.0044	0.863 ± 0.246	2.587 ± 0.727	65.5 ± 10.5	15.00 ± 6.18
B first and second	0.1793 ± 0.0063	0.847 ± 0.229	2.594 ± 0.838	66.0 ± 8.5	16.74 ± 6.62
P value	.1498	.482	.910	.682	.019
Accuracy	−0.0018	0.017	−0.007	−0.517	−1.741
Precision	0.0050	0.098	0.246	5.253	2.857
Coefficient of variance	2.82	11.4	9.5	8.0	19.0

Abbreviations: CF, calibration factor; %DS, percent diameter stenosis; Int R, interpolated reference diameter; LL, lesion length; MLD, minimal lumen diameter; QCA, quantitative coronary angiography.
Accuracy, precision, and coefficient of variation (%): same as in Table 3.
A and B same as in Table 4.

Table 6. Interobserver reliability between 2 analysis experts in the average of first and second for blind cine film analysis (N = 18).

VARIABLES	ICC	METHOD	INTRACLASS CORRELATION	95% CI	*P* VALUE F TEST
MLD blind A:B	ICC (2, 1)	Single	0.316	−0.361 to 0.787	.175
	ICC (2, 2)	Average	0.480	−1.132 to 0.881	.175
Int R blind A:B	ICC (2, 1)	Single	0.941	0.778 to 0.986	<.001
	ICC (2, 2)	Average	0.970	0.875 to0.993	<.001
%DS blind A:B	ICC (2, 1)	Single	0.492	−0.162 to 0.855	.065
	ICC (2, 2)	Average	0.660	−0.397 to 0.922	.065
LL blind A:B	ICC (2, 1)	Single	0.643	0.057 to 0.905	.018
	ICC (2, 2)	Average	0.783	0.109 to 0.950	.018

Abbreviations: CI, confidence interval; %DS, percent diameter stenosis; ICC, intraclass correlation; Int R, interpolated reference diameter; LL, lesion length; MLD, minimal lumen diameter.
A and B: same as in Table 4.

Table 7. Interobserver reliability between 2 analysis experts in the average of first and second for selected cine film analysis (N = 18).

VARIABLES	ICC	METHOD	INTRACLASS CORRELATION	95% CI	*P* VALUE F TEST
MLD check A:B	ICC (2, 1)	Single	0.888	0.608 to 0.973	<.001
	ICC (2, 2)	Average	0.941	0.756 to 0.986	<.001
Int R check A:B	ICC (2, 1)	Single	0.941	0.777 to 0.986	<.001
	ICC (2, 2)	Average	0.969	0.874 to 0.993	<.001
%DS check A:B	ICC (2, 1)	Single	0.835	0.462 to 0.960	.001
	ICC (2, 2)	Average	0.910	0.632 to 0.979	.001
LL check A:B	ICC (2, 1)	Single	0.842	0.479 to 0.961	.001
	ICC (2, 2)	Average	0.914	0.647 to 0.980	.001

Abbreviations: CI, confidence interval; %DS, percent diameter stenosis; ICC, intraclass correlation; Int R, interpolated reference diameter; LL, lesion length; MLD, minimal lumen diameter.
A and B: same as in Table 4.

pre-selected cine frame QCAs by about (0.0841/0.215 = SD of MLD difference) 39%.

Herrington and Walford[9] analyzed the coincident rate of selected cine frames in 30 coronary lesions between 2 analysis experts. They selected the optimal frame as close to end diastole according to SOP of each core laboratory. The mean difference in the selected cine frame count was 19.4. In 50% of the 30 lesions, they selected frames from a same cine cardiac cycle, in 35% from adjacent cardiac cycle, and in 15% from 2 separated cardiac cycles. They selected the exactly same frame only in one case. Our study showed better results in the rate of exactly same frame selection. We should recognize that small differences do occur, between analysts, in selecting optimal cine frames despite the use of guideline/SOP. Because cine frame selection would be at the discretion of each analysis experts,

subjective factors might contribute to the final decision when frames for end-diastolic cardiac cycle or sharpest stenosis are not completely acceptable as the optimal frames for QCA in some cases.

Selzer et al[6] showed that frame to frame variation of MLD measured at frames in the end-diastolic portion of the cardiac cycle was very small and smaller than that at frames in the other portion of cardiac cycle. The reason might be related to the least motion artifact, intraluminal mixing of contrast in the end diastole, and least vessel segment straightening. Adjacent frames selected from end diastole had the lowest CV (<5.0%).[6]

Once a portion of the cardiac cycle has been selected, the only remaining question is which frame should be used. Reiber et al[5,15,16] examined the variability of differences between frames that were ±1, ±2, or ±3 frames apart within the same portion of
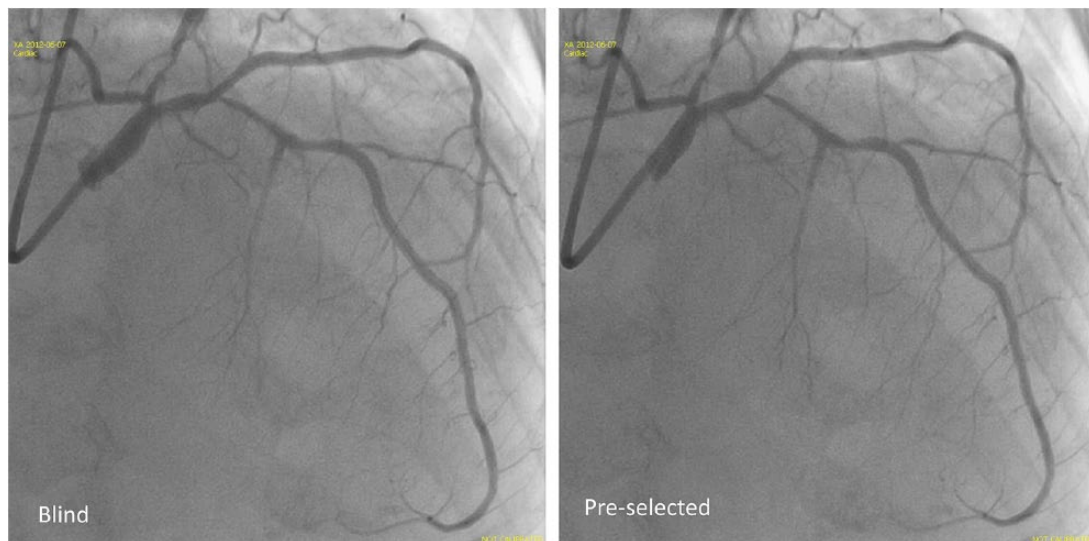
Figure 1. Coronary angiograms for quantitative coronary angiography with a blindly selected and pre-selected cine frames (left and right, respectively).
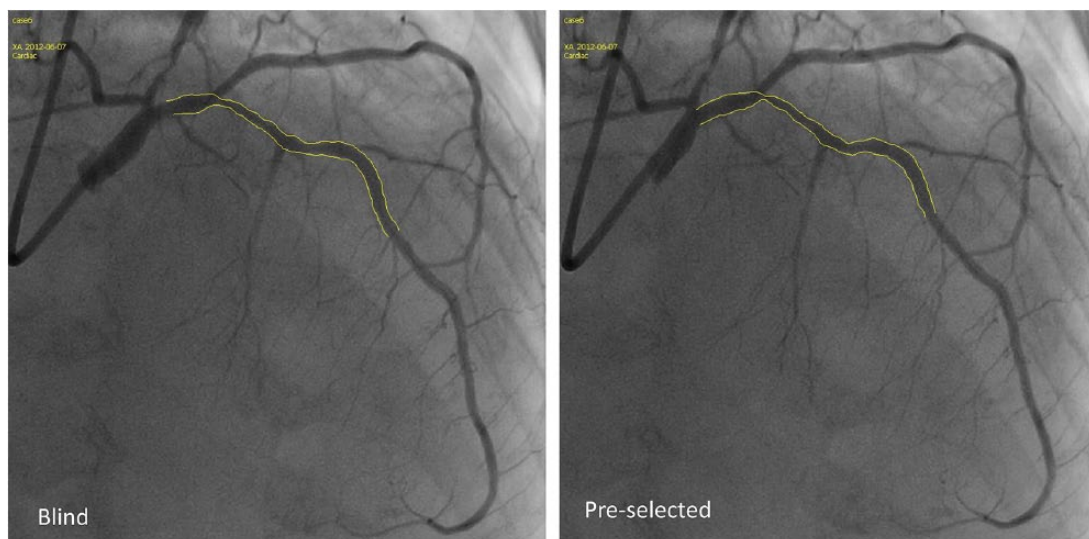
Figure 2. Pictures after borderline determination by the edge detection algorithm.

the cardiac cycle (end-diastolic) and revealed that variability of random error of MLD and %DS measurements was a bit smaller in ±1,2 cardiac frames than in ±3 (MLD; 0.20 vs 0.23, %DS; 6.3 vs 7.0). There was no difference in variability between frames in ±1 cardiac cycle when the selected portion was exactly the same. They concluded that the selection of a cine frame for quantitative analysis in the end-diastolic phase of the cardiac cycle might not be very critical.[5] Sirnes et al[8] also evaluated the reproducibility of QCA assessing variability due to frame selection, different observers, and different digital laboratories. They concluded that the overall variability in the interobserver and interlaboratory comparisons was 11.2% and 10.4%. Precision in MLD ranged from 0.12 to 0.20 mm, which is considered as acceptable in clinical studies. However, this study did not compare QCA results between pre-selected and blind cine frames, as was done in our study.

Meanwhile, Fishcell et al[3] demonstrated a marked variability in the QCA results (%DS immediately post PCI and at

follow-up, restenosis rate, and late luminal loss) in a stent study when operators have the ability to select which frame to analyze (frame bias) using 3 different ways: frame chosen while making the stent appear least narrowed (best), frame chosen while making the stent appear most narrowed (worst), and measurement from the mean value from 3 consecutive end-diastolic frames (core).

Thus, according to the previous studies which evaluated variability of QCA for native coronary stenosis, influence of cine frame selection was not considered as significant.

On evaluation by CV and ICCs, our study revealed that the difference in selected cine frames might affect intra- and inter-observer variability in QCA results in MLD and LL, even when selected end-diastolic phase was used.

In the multiple regression analysis, the blind cine film selection was found to be an explanatory factor of QCA variativity in this study. However, unknown explanatory factors that could
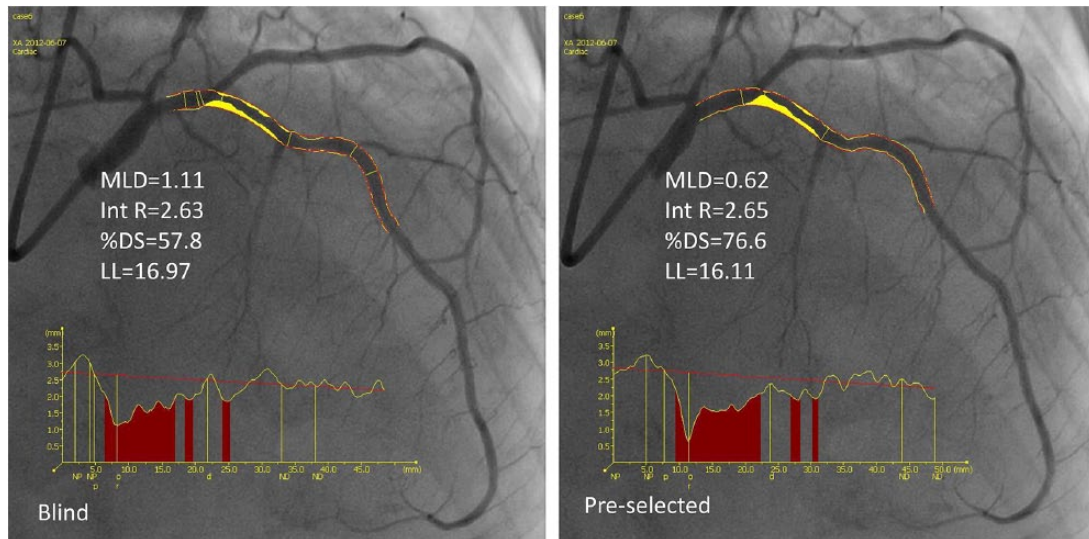
Figure 3. Pictures after final quantitative coronary angiography analysis with functional lines and measured parameters. There were some differences in the values between the blind and pre-selected cine frames. %DS indicates percent diameter stenosis; Int R, interpolated reference diameter; LL, lesion length; MLD, minimal lumen diameter.

not be included in this study might exist according to the small adjusted R^2 value (0.075-0.205). On the other hand, a vessel (LAD) was selected as an explanatory factor in Int R. The reason for this is unknown, however; we suspected that the pre-selected cine frames in some LAD lesions were not appropriate for analyzing Int R. Because the adjusted R^2 was as small as 0.0724 in this model, the influence was limited.

QCA is based on the coronary angiography, which is the most fundamental imaging modality used for diagnosis and intervention. We evaluated the influence of the cine frame selection as one of the crucial QCA procedures for the accuracy and precision of QCA. Meanwhile, the recently developed intravascular ultrasound sonography and fractional flow reserve, which are more invasive than angiography, can provide better accuracy especially in MLD and LL compared with angiography. These modalities should be used differently by taking into the merits and invasiveness.

There are several crucial manual steps besides cine frame selection in performing QCA. In our study, the influence of cine film selection alone was evaluated. This is a novelty of our study in that it comparing blind vs pre-selected cine frames. The influence of every manual step should be eliminated as far as possible. In this respect, we tried to find out how cine film selection affects the QCA results.

Study Limitations

There were several limitations to this study. First, this study was performed on a small number of lesions and by only 2 operators. Furthermore, data on clinical and lesion characteristics were skewed. A larger study with more lesions and operators is warranted to generalize the results of this study. Second, cine films acquired for QCA were at the discretion of the operators. There is a possibility that optimal projections for QCA

might not be selected in some cases. Although coronary evaluation positions should have been standardized, we sometimes could not help selecting an unusual view for QCA due to vessel overlap in the conventionally used views such as in case 5 (anteroposterior cranial view for left circumflex lesion). To overcome this problem, future studies should adopt novel view point planning method to find the optimal C-arm positions for QCA, which has been recently reported by Preuhs et al.[2] Third, the contrast might have affected QCA variability. A future study is warranted to clarify this issue.

Conclusions

Cine film selection might affect QCA results especially in MLD and LL even when following the same selection criteria. Variation of cine frame for CF also partially influence the variability in QCA results. Although the principles for performing QCA analysis accurately are well established, there remains a significant operator-dependent variability partially due to frame selection. The error range of QCA data must be taken into consideration when using QCA to assess individual patients.

Author Contributions

SI: Conceptualization, Design, methodology, data acquisition, analysis and interpretation, writing original draft of the manuscript, and final draft approval. KK and AE: QCA analysis, revising the manuscript, and final draft approval. MN: Supervision, critical revisions, and final draft approval.

Supplemental Material

Supplemental material for this article is available online.

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REFERENCES

1. Garrone P, Biondi-Zoccai G, Salvetti I, et al. Quantitative coronary angiography in the current era: principles and applications. *J Interv Cardiol*. 2009;22:527–536.
2. Preuhs A, Berger M, Bauer S, et al. Viewpoint planning for quantitative coronary angiography. *Int J Comput Assist Radiol Surg*. 2018;13:1159–1167.
3. Fischell TA, Maheshwari A, Mirza RA, Haller S, Carter AJ, Popma JJ. Impact of frame selection on quantitative coronary angiographic analysis after coronary stenting. *Catheter Cardiovasc Interv*. 2005;64:460–467.
4. Beauman GJ, Reiber JHC, Koning G, Vogel RA. Variability of QCA–core laboratory assessments of coronary anatomy. In: Reiber JHC, Serruys PW, eds. *Advances in Quantitative Coronary Arteriography*. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1993:190–218.
5. Reiber JH, van Eldik-Helleman P, Visser-Akkerman N, Kooijman CJ, Serruys PW. Variabilities in measurement of coronary arterial dimensions resulting from variations in cineframe selection. *Cathet Cardiovasc Diagn*. 1988;14:221-228.
6. Selzer RH, Hagerty C, Azen SP, et al. Precision and reproducibility of quantitative coronary angiography with applications to controlled clinical trials. *J Clin Invest*. 1989;83:520–526.
7. Herrington DM, Siebes M, Sokol DK, Siu CO, Walford GD. Variability in measures of coronary lumen dimensions using quantitative coronary angiography. *J Am Coll Cardiol*. 1993;22:1068–1074.
8. Sirnes PA, Myreng Y, Molstad P, Golf S. Reproducibility of quantitative coronary analysis, assessment of variability due to frame selection, different observers, and different cinefilmless laboratories. *Int J Card Imaging*. 1996;12:197–203.
9. Herrington DM, Walford GD. Optimal frame selection for QCA. In: Reiber JHC, Serruys PW, eds. *Advances in Quantitative Coronary Arteriography*. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1993:125–135.
10. Ito S, Kinoshita K, Endo A, Nakamura M, Muramatsu T. Impact of catheter size on reliability of quantitative coronary angiographic measurements (comparison of 4Fr and 6Fr catheters). *Heart Vessels*. 2016;31:1752–1757.
11. Beauman GJ, Reiber JH, Koning G, Vogel RA. Comparisons of angiographic core laboratory analyses of phantom and clinical images: interlaboratory variability. *Cathet Cardiovasc Diagn*. 1996;37:24–31.
12. Tuinenburg JC, Koning G, Hekking E, et al. One core laboratory at two international sites, is that feasible? an inter–core laboratory and intra–observer variability study. *Catheter Cardiovasc Interv*. 2002;56:333–340.
13. Herrington DM, Siebes M, Walford GD. Sources of error in quantitative coronary angiography. *Cathet Cardiovasc Diagn*. 1993;29:314–321.
14. Reiber JH, Goedhart B, Brand GJ, et al. Quantitative coronary arteriography: current status and future the influence of image enhancement and reconstruction on quantitative coronary arteriography issues of QCA validation a new approach for the quantification of complex lesion morphology: the gradient field transform; basic principles and validation results accuracy and precision of quantitative digital coronary arteriography: observer-, short-, and medium-term variabilities angiographic assessment of dimensions of 6f and 7f Mallinckrodt softouch coronary contrast catheters from digital and cine arteriograms. *Heart Vessels*. 1997;12:209–211.
15. Reiber JH, Serruys PW, Kooijman CJ, et al. Assessment of short-, medium-, and long-term variations in arterial dimensions from computer-assisted quantitation of coronary cineangiograms. *Circulation*. 1985;71:280–288.
16. Reiber JH, van Eldik-Helleman P, Kooijman CJ, Tijssen JG, Serruys PW, Visser Akkerman N. How critical is frame selection in quantitative coronary angiographic studies? variabilities in measurement of coronary arterial dimensions resulting from variations in cineframe selection. *Eur Heart J*. 1989;10:54–59.