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ORIGINAL PAPER

Impact of two formulas to calculate percentage diameter stenosis of coronary lesions: from stenosis models (phantom lesion model) to actual clinical lesions

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Abstract

Percentage diameter stenosis (%DS) by angiography is still commonly used to determine luminal obstruction of coronary artery disease (CAD) lesions. While visual estimation of %DS is widespread, because of high inter-operator variability, quantitative coronary arteriography (QCA) analysis is the gold standard. There are two %DS formulas: %DS1 averages the proximal and distal reference vessel diameter (RVD); %DS2 interpolates the RVD. This study aims to evaluate the difference between %DS assessed by QCA in two datasets, phantom lesion models and CAD patients. Ten phantom lesion models (PLMs) and 354 CAD lesions from the FIRST trial were assessed by QCA. In the latter, two scenarios were assessed: Scenario A (worst view), the most common approach in the clinical setting; and Scenario B (average of two complementary views), the standard core-laboratory analysis. In the PLMs, %DS1 and %DS2 mean ± standard deviation (median) was 58.5 ± 21.7 (61.6) and 58.7 ± 21.6 (61.8), respectively, with a signed difference of − 0.2% ± 0.3% (− 0.1%). In Scenario A, the mean %DS1 was 43.8 ± 9.1 (43.3) and 44.0 ± 9.1 (42 .9) in %DS2. In Scenario B, the mean %DS1 was 45.3 ± 8.8 (45.1) and 45.5 ± 9.0 (45.1) in %DS2. The signed difference was − 0.2% ± 2.4% (0.0%) and − 0.2% ± 2.1% (0.0%) in Scenario A and B, respectively. These differences between formulas ranged from − 1.2 to 0.5% for the phantom cases compared to − 17.7% to 7.7% in Scenario A and to − 15.5% to 7.1% in Scenario B. Although the overall means of the formulas provide similar results, significant lesion-level differences are observed. The use of the worst view versus the average of two views provided similar results.

Keywords QCA · %DS · Phantom models · CAD

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Introduction

Coronary angiography remains the "gold standard" for assessing and grading coronary artery disease (CAD) lesion stenosis [1]. Current American guidelines recommends revascularization of CAD lesions based on visual assessment percentage diameter stenosis (%DS) observed in the available angiographic view with the highest degree of luminal obstruction (i.e. worst available view) for acute coronary syndrome (ACS) and stable CAD patients [2, 3]. In the later, an additional, invasive or non-invasive, positive ischemic test is also required [3]. However, the accuracy of cardiac catheterization to visually assess percentage diameter stenosis (%DS) has been the subject of debate, as it can overestimate severe lesions and underestimate mildly diseased segments [4, 5]. Furthermore, visual estimation of %DS has an inter-observer variability is as high as 50% [6, 7]. In the International Survey on Interventional Strategy study, 71% of interventionalists relied solely on the visual angiographic appearance of the vessel to make a diagnosis and did not pursue any further imaging modalities that were available to them if needed [8]. Of this, 47% of the diagnoses made were discordant with the correct degree of stenosis as determined by fractional flow reserve (FFR), showing that inaccuracies in visual estimation of coronary lesions affect patient management [8].

Quantitative coronary arteriography (QCA) has been applied to reduce these limitations [9, 10]. In QCA software, there are two distinct formulas to determine %DS, which differ in their calculation of the reference vessel diameter (RVD). Both formulas are widely applied, but the difference in the %DS between each formula remains unknown. The aim of this paper is to evaluate the magnitude of the difference between the %DS1 and %DS2 formulas when applied to a controlled ideal scenario (i.e., phantom lesion model) and in actual CAD cases.

Methods

The QCA analysis was performed using the Coronary Angiography Analysis System—CAAS—v7.3 (Pie Medical Imaging, Maastricht, The Netherlands) in the phantom lesion models and CAAS v5.9.2 (Pie Medical Imaging, Maastricht, The Netherlands) in FIRST trial [11, 12]. The quantitative analysis started with the determination of the target segment by the analyst in two complimentary views using only end-diastolic frames. Followed by the catheter size calibration (pixels/mm), luminal tracing and automatic obstruction detection. From the QCA analysis, were extract Minimum lumen diameter (MLD), proximal RVD, distal RVD, and interpolated RVD of each case, PLMs and CAD lesions, and used to calculate the %DS1, %DS2, and signed difference between %DS1 and %DS2 (Fig. 1a, b) [11].

This study analysis consisted of two parts. In the first part, 5 core laboratory (Corelab) analysts independently assessed ten phantom lesion models (PLMs) as the ideal controlled scenario (Supplement Fig. 1). Notably, given that the phantom models are assumed to be perfectly cylindrical (i.e., concentric lesions only) from all projections, no complementary images were taken. In the second part, actual CAD lesions (i.e., DS of 40–80%) from FIRST trial were assessed by QCA [12]. Only lesions with two complementary views were included in the analysis, and the %DS1 and %DS2 for each view were averaged to provide a bi-dimensional assessment of the lesions. In the actual cases, the lesions were also assessed in two different scenarios: the worst available view (Scenario A) and the average of two complementary views (Scenario B). The flow diagram of the study is presented in Fig. 2. The QCA analysis was performed using Core Laboratory Standards at Medstar Health Research Institute's Invasive Coronary Imaging Core Laboratory (Washington, DC, USA).

Percentage of diameter stenosis formulas and definitions

There are several formulas to assess %DS by QCA [4, 5, 13–15]. However, in the field, the two most used formulas differ in the adopted reference to estimate the RVD. The first formula (%DS1) averages the proximal and distal normal RVD in the lesion segment, whereas the RVD of the second formula (%DS2) is estimated by acquiring the interpolation point within the segment of interest. Each equation is listed below:

- %DS1 = {1 – [minimum lumen diameter/(average of proximal and distal reference vessel diameter)]} × 100
- %DS2 = [1 – (minimum lumen diameter/interpolated mean reference vessel diameter)] × 100

Clinical Scenario B assessment required the average of the two complementary views (i.e. projections A and B) MLDs and RVDs, before evaluating the *signed differences* between %DS1 and %DS2 formulas. So, the formulas utilized in this analysis are fully presented below:

- %DS1 for Scenario B = {1 – [average of (minimum lumen diameter projection A and projection B)/average of (average of (proximal reference vessel diameter projection A and proximal reference vessel diameter projection B) and average of (distal reference vessel diameter A and distal reference vessel diameter B))]} × 100
- %DS2 for Scenario B = {1 - [average of (minimum lumen diameter projection A and projection B)/average of (interpolated mean reference vessel diameter projection A and interpolated mean vessel reference diameter projection B)]} × 100

Phantom lesion models (PLMs) were a group of ten carved Plexiglass models with fixed diameters simulating coronary artery stenotic lesions [i.e. proximal and distal reference vessel diameter (RVD), minimum lumen diameter (MLD) and narrow segment length] divided in two Plexiglass models. The PLMs were filled with undiluted contrast dye and positioned directly on top of the fluoroscopy machine table. A Plexiglass block was placed under the PLMs in order to achieve the corresponding height of the midchest-level, approximately 12 cm from the table top [16]. The fluoroscopy machine table was positioned in the zero-set level, and the still images were acquired using a Flat Panel X-ray detector at the pure posterior-anterior angulation. The actual %DS of each PLMs 1 to 10 were 16%, 20%, 32%, 40%, 30%, 40%, 50%, 60%, 80% and 71%, respectively.

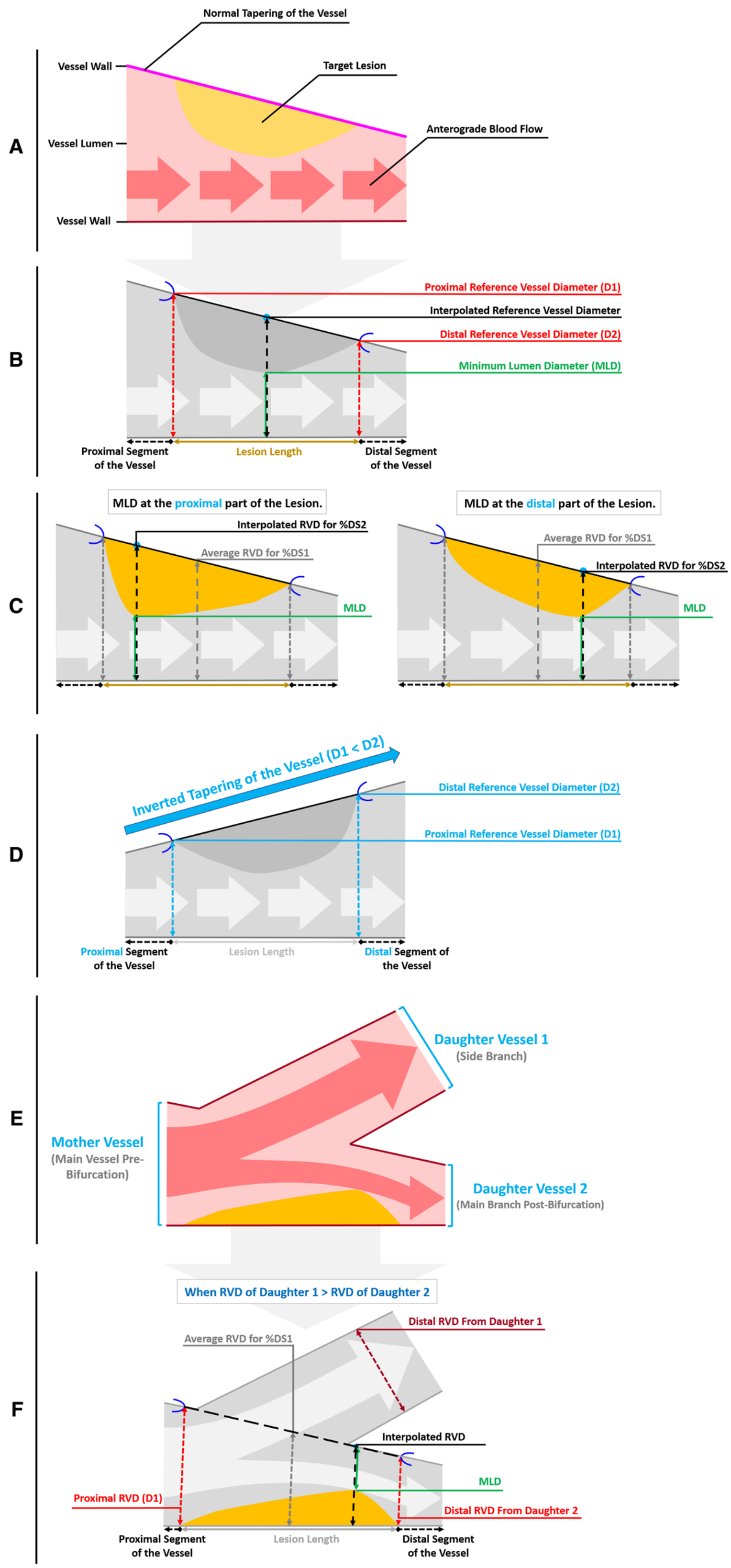
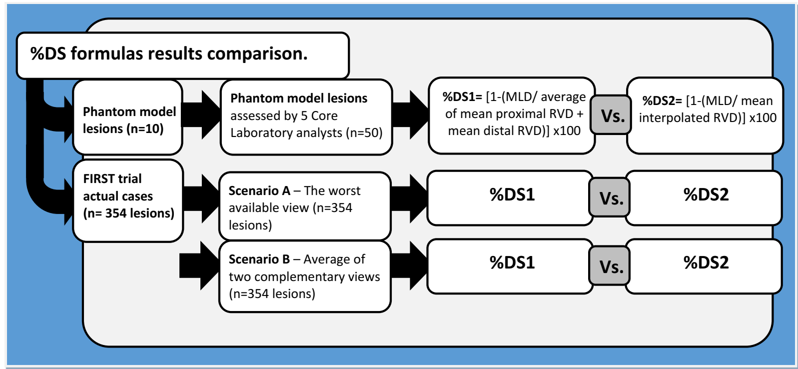


Fig. 1 Schematic representation of a coronary artery segment showing a diseased segment and the quantitative variables used to calculate the percentage diameter stenosis formulas (%DS1 and 2) and the situations that may present differences in the %DS1 and 2 results. **a** Target lesion (i.e. diseased) within physiologic tapering segment of a coronary vessel (pink line). **b** Illustrates the proximal reference vessel diameter (RVD), distal RVD, interpolated RVD, minimum lumen diameter (MLD), lesion length and the blue semi-circles delimitates the diseased segment. **c** The changes in the %DS assessment between formula 1 and formula 2 if the MLD is presented in different segments within the lesion. **d** A situation where there is an inverted tapering of the vessel, when the proximal RVD is smaller than the distal RVD, resulting in unpredictable MLD to RVDs ratio due to the distribution of the plaque and MLD postion within the lesion. **e** A bifurcated segment and the distribution of the subsequent branches (daughters 1 and 2) with an obstructive plaque. **f** A bifurcated segment with a desproportion between branches (daughter 1 > daughter 2) where the narrowest point of the lesion is at the smallest branch

Fig. 2 Flow diagram of the study



Abbreviations: %DS = percentage of diameter stenosis; MLD = minimum lumen diameter; QCA = quantitative coronary arteriography; RVD = reference vessel diameter. FIRST trial = Fractional Flow Reserve and Intravascular Ultrasound Relationship Study.

A *Complementary View* was defined as the difference of ≥ 30º apart in the left–right or cranial-caudal axis. *Worst Available view* was defined as the view with highest %DS (i.e., narrower lesion) between the two available complementary views, representing the approach most commonly used in clinical setting at the Catheterization Laboratory. The *average of* two *complementary views* is the %DS assessment frequently adopted by a Core Laboratory in clinical trials' QCA analysis in order to properly analyze the lesion without overlooking its severity (e.g., eccentric lesions). The *Signed Differences* between the formulas was determined by subtracting the result of %DS2 from %DS1.

Statistical analysis

Means and standard deviations were used to report continuous variables and frequencies and percentages for categorical variables. In the phantom lesion model analysis, the findings were reported first as overall data (average of all lesions) and per lesion analysis (average of all analysts). The results of the actual cases were reported according to the specific Scenarios A or B. The relationship between %DS1 and %DS2 was performed using Pearson's coefficient of correlation (R) presented in Fig. 3a, c, e. Bland–Altman plot was used to determine the level of agreement between the formulas was set in 95%, mean bias of ± 1.96 times standard deviation (Fig. 3b, d, f). The p value between the %DS formulas was considered significant < 0.05. The QCA inter- and intra-observer reproducibility were provided in the Supplement Material Table 1.

Results

In total, ten phantom lesion models were assessed by five CoreLab analysts (n = 50), and 354 actual coronary artery lesions from FIRST trial cohort were included in this analysis. The baseline patient characteristics are summarized in Table 1. Overall, the mean age of the patients was 61 ± 10 years, 74% of whom were male, 55% with stable angina, and 85% of type A or B1 lesions.

Phantom lesion model

In the phantom lesion models, the overall %DS1 mean value was 58.5 ± 21.7% and 58.7 ± 21.6% for %DS2, and the signed difference was − 0.2 ± 0.2% (Table 2). The signed difference between %DS1 and %DS2 ranged from − 1.2% to 0.5%. The coefficient of correlation between %DS1 and %DS2 formulas was 99.9% ($p < 0.001$) (Fig. 3a), with 95% limits of agreement ranging from − 0.68 to 0.37 and bias of − 0.156 ± 0.267 (Fig. 3b).

Actual coronary artery lesions

In the actual Scenario A cases, the mean %DS1 value was 43.8 ± 9.1% and mean %DS2 value was 44.0 ± 9.1%, the signed difference was − 0.2 ± 2.4% (Table 2). With a correlation of 96.6% ($p < 0.001$) (Fig. 3c), 95% limits of agreement ranged from − 4.88 to 4.43 and bias of − 0.221 ± 2.375 (Fig. 3d).

In Scenario B, the mean %DS1 value was 45.3 ± 8.8% and mean %DS2 value was 45.5 ± 9.0%, and the signed difference was − 0.2 ± 2.1% (Table 2). The %DS1 and %DS2 correlation was 97.3% ($p < 0.001$) (Fig. 3e), 95% limits of agreement from − 4.26 to 3.90 and bias of − 0.181 ± 2.080 (Fig. 3f).

For Scenarios A and B, the %DS signed difference, between %DS1 and %DS2, ranged from − 17.7% to 7.7% and − 15.5% to 7.1%, respectively.

Discussion

There were three main findings in this study. First, in the controlled ideal scenarios (i.e., phantom lesion model), the mean difference between %DS1 and %DS2 was

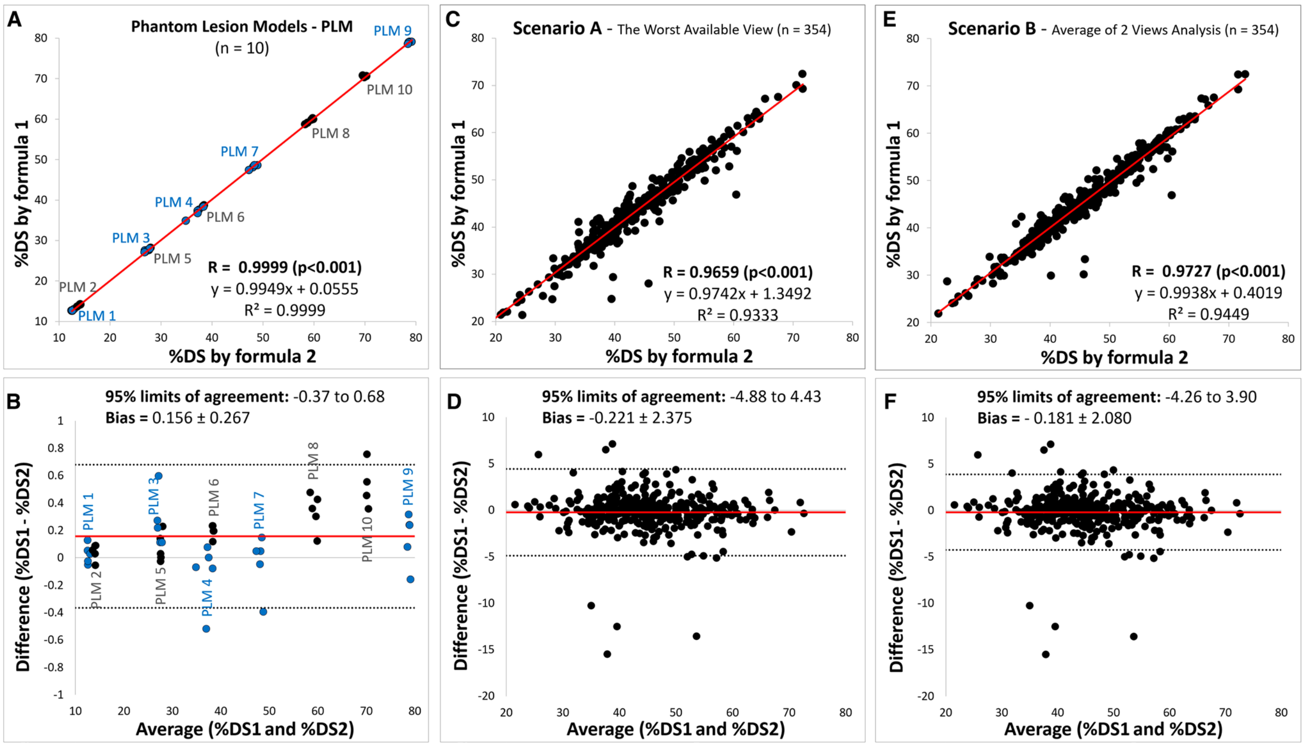


Fig. 3 Pearson's coefficient of correlation scattered plots (**a**, **c**, **e**) and Bland–Altman plots (**b**, **d**, **e**) showing the signed difference between percentage of diameter stenosis (%DS) formulas 1 and 2, for phantom lesion model (PLM), Scenario A (Worst available view) and Scenario B (Average of two complementary views). *%DS* percentage of diameter stenosis

− 0.2 ± 0.2%. Second, in the actual Scenario A and B cases, the differences between %DS1 and %DS2 were − 0.2 ± 2.4% and − 0.2 ± 2.1%, respectively. Lastly, the maximum %DS difference between the actual Scenarios A and B cases was up to 15%.

While multiple technical issues have been ameliorated with enhanced acquisition technology, image magnification, automatic edge-detection, standardization with ideal phantom lesions, and video-densitometry application (thus increasing the accuracy of QCA and reducing its variability), this paper establishes that the %DS equations themselves are another source of diameter stenosis variability. %DS1 is calculated by taking the average vessel diameter from two complementary views of the 5 mm proximal to the lesion and the 5 mm distal to the lesion, and then taking the average of these two numbers to produce the RVD of the vessel between them. However, in order for this formula to produce the proper RVD at the MLD and therefore the correct %DS, there must be a perfectly linear rate of vessel tapering in the in-segment vessel length without any changes in caliber throughout it, and the MLD must be at the mid-point of the in-segment vessel length, as that is the point where the RVD average is mathematically calculated given the %DS1 formula.

Regarding the former point, if there is not perfectly linear tapering throughout the vessel and the proximal and distal reference segments are affected, incorporating their measurements into the calculation for the RVD will skew the result and produce an incorrect %DS. There is a variety of uncommon in coronary arteries given the multitude of conditions that can affect vessel diameter, including: MLD in the proximal or distal segments of the lesion segment (Fig. 1c); tandem or long lesions (≥ 20 mm) (Fig. 1c); pathologic dilation in the distal segment of leading to inverted tapering of the vessel (i.e., aneurysm, ectasia) (Fig. 1d); and bifurcations (Fig. 1e, f). In the later, the particularity comes from the distribution of the subsequent branches (daughters 1 and 2), particularly when the target lesion is in the smallest one. The common pattern found in all these situations was the change in the position of the RVD and MLD within the target segment (Fig. 1b, c). Since in %DS1 formula, the RVD is determined by the average the proximal and distal normal references of the lesion segment, this equation fixes the denominator (i.e. RVD) at the mid-point of the target lesion segment (in a normal tapering vessel). Meaning that regardless of the position of the MLD (i.e. numerator) does not impact the result of the %DS1 (Supplement Fig. 1). While in the %DS2 formula the denominator is *the* interpolated RVD, which varies according to the position of the MLD within the lesion segment, as seen in the Supplement Table 1. This last observation was also demonstrated in our dataset, by

Table 1 Patient and lesion characteristics

	N	%[a]
Per patient, n		
Age, years	61.5	± 10.9
Male	260	74.3
Clinical presentation		
Stable angina	192	54.9
Unstable angina	130	37.1
NSTEMI	18	5.1
Silent ischemia	115	32.9
Multivessel disease	22	6.3
1—vessel disease	328	93.7
2—vessel disease	20	5.7
3—vessel disease	2	0.6
Per lesion, n		
Target vessel		
LMCA	2	0.5
LAD	214	57.2
LCx	89	23.8
RCA	68	18.2
ACC/AHA lesion classification		
Type A	135	36.1
Type B1	184	49.2
Type B2	51	13.6
Type C	4	1.1
Eccentric lesions	56	15.0
True bifurcation lesions[b]	29	8.2
Lesion length, mm (mean ± SD)	14.67	± 7.53
RVD (mean ± SD), mm[c]	2.59	± 0.48
Interpolated RVD (mean ± SD), mm	3.00	± 0.59
MLD (mean ± SD), mm	1.62	± 0.44

LAD left anterior descending artery, *LCx* left circumflex artery, *LMCA* left main coronary artery, *MLD* minimum lumen diameter, *NSTEMI* non ST elevation myocardial infarction, *RCA* right coronary artery, *RVD* reference vessel diameter; *SD* standard deviation

[a]Percentages otherwise indicated

[b]Medina classification: 1.1.1; 0.1.1; 1.0.1

[c]Average of the proximal and the distal references

standard deviation in the signed differences between the %DS formulas in the PLMs compared to Scenarios A and B. In the Phantom Lesion Models, standard deviation of the signed difference was very small (overall ± 0.2%) since there is no difference between proximal and distal normal references of the lesion segment. Whilst, in the actual cases the standard deviation of the signed difference around ± 2.4%, representing the variability in the difference between %DS1 and %DS2 when the MLD is at the proximal or distal part of the lesion due to the unpredictability of the biological effect.

Regarding the second point of ensuring that the MLD is at the mid-point of the in-segment length, the RVD is calculated at the mid-point of the in-segment vessel length because implicit in the %DS1 equation is the assumption that an average of the averages of two normally distributed datasets results in the value halfway between them. This means that when the 5 mm proximal segment diameter average and the 5 mm distal segment diameter average are themselves averaged together, the result is the average vessel diameter between those averages, which is itself equidistant between the two initial averages. In an ideal lesion that is well-demarcated with the appropriate proximal and distal segment lengths on either side and has perfectly linear tapering, the appropriate MLD/RVD fraction in the equation can be found by placing the MLD at the RVD to calculate the proper %DS1 at that site. Otherwise, there is a discordance between the position of the MLD and RVD, and that will result in an incorrect %DS. To illustrate this, consider a lesion proximal enough to the ostium such that the full proximal 5 mm of the inter-segment length would have stretched into the aorta. This has three effects. First, the datasets on either side of the lesion (i.e., the proximal and distal in-segment lengths) are no longer equal and averaging the two will skew the resulting RVD more distally on Fig. 1 and not at the anatomic MLD, resulting in an incorrect %DS unless properly adjusted. Second, the RVD value itself will be decreased, as D1 is less than it otherwise would be because the assumingly larger caliber part of the vessel was omitted, resulting in a greater %DS1. Third, more variability is introduced into the dataset as a smaller sample is taken. These three effects also would be the case if, for some reason, part of the proximal or distal segment was disregarded because the user recognized an abnormality in vessel diameter that would affect the RVD. However, in an effort to correct this abnormality in caliber change by disregarding the lesioned part, the user unknowingly introduces the error described above.

There are a number of benefits regarding %DS2 over %DS1. The primary advantage is that %DS2 is calculated using the interpolation of the RVD from non-diseased or "known" vessel diameters taken from data points along the length of the vessel. This means that the parts of a vessel the formula assumes to be non-diseased are used as references. %DS2 also has the advantage of producing RVDs at every point along the in-stent vessel length, which means that a %DS can be calculated wherever the MLD may lie in this range. This may make %DS2 slightly more useful for calculating RVDs in ostial lesions, as a full 5 mm proximal segment diameter does not need to be used to calculate the RVD. However, as with %DS1, %DS2 cannot properly incorporate diffuse atherosclerosis, or some changes to vessel diameter caliber, such as inverse tapering, may produce inaccurate results.

In short, these equations are too simplistic to accurately model complex coronary vasculature. The %DS1 and %DS2 formulas aim to calculate the same %DS but use different

Table 2 Percent diameter stenosis (%DS) as assessed by %DS1 and %DS2 formulas in phantom lesion models and in actual cases in 2 different scenarios: the worst view *(Scenario A)*; or the average of two complementary views *(Scenario B)*

	%DS1		%DS2		Signed difference (%)		Lesions analyzed, no.
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	
Phantom lesion models							
Overall[a]	58.5 ± 21.7	61.6	58.7 ± 21.6	61.8	− 0.2 ± 0.2	− 0.1	50
Phantom lesion model 1	87.3 ± 0.2	87.4	87.3 ± 0.2	87.3	0.0 ± 0.1	0.0	5
Phantom lesion model 2	85.9 ± 0.2	85.9	86.0 ± 0.3	85.9	0.0 ± 0.1	− 0.1	5
Phantom lesion model 3	72.6 ± 0.3	72.5	72.8 ± 0.4	73.1	− 0.3 ± 0.2	− 0.2	5
Phantom lesion model 4	63.1 ± 1.3	62.7	62.9 ± 1.3	62.8	0.1 ± 0.2	0.1	5
Phantom lesion model 5	72.2 ± 0.2	72.4	72.3 ± 0.2	72.4	− 0.1 ± 0.1	0.0	5
Phantom lesion model 6	61.5 ± 0.1	61.5	61.7 ± 0.1	61.6	− 0.2 ± 0.0	− 0.2	5
Phantom lesion model 7	51.8 ± 0.5	51.8	51.8 ± 0.6	51.8	0.0 ± 0.2	0.0	5
Phantom lesion model 8	40.4 ± 0.6	40.2	40.8 ± 0.7	40.5	− 0.3 ± 0.1	− 0.4	5
Phantom lesion model 9	21.1 ± 0.2	21.0	21.2 ± 0.3	21.2	− 0.1 ± 0.2	− 0.2	5
Phantom lesion model 10	29.4 ± 0.2	29.4	30.1 ± 0.3	30.1	− 0.7 ± 0.3	− 0.6	5
Actual cases							
Scenario A—the worst available view	43.8 ± 9.1	43.3	44.0 ± 9.1	42.9	− 0.2 ± 2.4	0.0	354
Scenario B—average of two complementary views	45.3 ± 8.8	45.1	45.5 ± 9.0	45.1	− 0.2 ± 2.1	0.0	354

%DS percentage of diameter stenosis, *QCA* quantitative coronary arteriography; SD = standard deviation

%DS1 = {%DS1 = [1-(minimum lumen diameter/average of (mean proximal reference vessel diameter + mean distal reference vessel diameter))] × 100}

%DS2 = {%DS2 = [1-(minimum lumen diameter/Interpolated mean vessel reference)] × 100}

[a]The fixed %DS on the models were from 20 to 87% of stenosis

inputs to do so. In ideal settings, meaning normal tapering of the vessel, the calculated %DS is similar. But the variability of the results is maximized in non-ideal scenarios, including situations where is not possible to determine one of the references or inverted tapering (i.e. proximal reference is smaller than the distal) may compromise the %DS formula result. When performing coronary angiography and QCA, it is important to be mindful of the lesion as well as the proximal and distal lengths, especially depending on which DS formula is used. %DS2 appears to be more useful overall; however, neither formulas take into account diffuse disease. The researcher or physician must make a proper judgment as to which formula may be most useful in a particular situation, but more research needs to be done to incorporate these unaccounted variables. It also may be possible to design entirely different equations or methods to establish proper RVDs, which would then lead to more accurate %DS.

Conclusion

The variability of the signed differences between the two %DS formulas reveals a very narrow range in the phantom lesion models, while the opposite was observed regarding the actual coronary lesions. These findings may affect clinicians and researchers' patient management, since depending on the case, the magnitude of coronary stenosis may be affected by which formula is used to calculate diameter stenosis.

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Compliance with ethical standards

Conflict of interest Ron Waksman—Advisory Board: Abbott Vascular, Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips Volcano, Pi-Cardia Ltd.; Consultant: Abbott Vascular, Amgen, Biosensors, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips Volcano, Pi-Cardia Ltd.; Grant Support: Abbott Vascular, AstraZeneca, Biosensors, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance. All other authors—none.

Ethical approval In FIRST study (NCT01153555 - J Am Coll Cardiol 2013;61:917–23) all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the original FIRST study (NCT01153555 - J Am Coll Cardiol 2013;61:917–23).

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