An automated user-friendly software for fast computation of blood flow velocity from coronary angiographic images

Running Head: Automated measurement of coronary flow velocity

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Author contribution

MC, JPA and CB designed the study, MC, MK, TZ, EE, IHT, XH, ZAA, AHK analyzed the data, VT, RB, NALY, BKK, RR, GVK and CVB acquired the data, MC and CVB drafted the manuscript and AH, PWS AM, AB, RT revised it critically for important intellectual content. All authors approval the revised version to be published.

Abstract

Thrombolysis in myocardial infarction frame count enables assessment of coronary flow but cannot measure coronary flow velocity (CFV), which is needed to examine microvascular function. To overcome this limitation, we introduce a semi-automated software for fast CFV computation using contrast bolus tracking techniques in angiography and compare its performance against experts. The study included patients undergoing coronary angiography. Two experts measured the CFV using the number of frames, segment length, and frame rate. Measurements were repeated for shorter segments and different projections, and their estimations were compared with the software. In total, 123 patients (152 vessels) were included. The software had excellent reproducibility in measuring CFV (intraclass correlation coefficient (ICC)=0.995), which was superior to experts (ICC=0.946) and provided similar estimations irrespective of the segment length (ICC=0.992); conversely, the experts overestimated CFV in short segments. The reproducibility of the experts and the software was moderate when comparing CFV measurements in different projections (1st expert vs. software ICC=0.807, 2nd expert vs. software ICC=0.790, 1st expert vs. 2nd expert ICC=0.885). The software provides reproducible CFV estimations that are close to experts' estimations. Further validation against wire-based functional techniques is needed to examine its potential in assessing microvascular function.

Keywords: Coronary angiography, Coronary flow velocity, TIMI frame count, Quantitative coronary angiography.

1. Introduction

Despite advances in non-invasive coronary imaging, invasive angiography remains the reference standard for assessing the extent and the severity of coronary artery disease (CAD). This modality provides a dynamic evaluation of the coronary artery anatomy, enabling the identification of lesions in the entire coronary tree, quantifying their severity, visualization of coronary motion and the changes in lumen dimensions during the cardiac cycle, and assessment of coronary blood flow. Traditionally, coronary blood flow is quantified using the thrombolysis in myocardial infarction frame count (TFC), which is estimated as the number of frames required for the contrast to reach from the ostium of the vessel to the distal end of the coronary artery when angiography is performed at 30 frames per second (fps). The corrected TFC (CTFC) accounts for the differences in the length of the left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA).[1]

The TFC and CTFC have been extensively used over recent years to identify patients suffering from microvascular angina, predict outcomes in patients with myocardial infarction undergoing percutaneous coronary intervention (PCI), and evaluate the effect of pharmacotherapies on coronary flow.[2] However, this approach has significant limitations as it does not enable accurate measurement of the coronary blood flow but only a qualitative assessment; it has limited inter- and intra-observer variability while its estimations depend on the heart rate and the cardiac phase at the time of the injection.[1] Acknowledging the need to accurately quantify blood flow, several methodologies have been developed over recent years; however, their application in clinical practice is currently limited as most of them have not been extensively validated, are computationally expensive, and require expertise as they operate in a non-user-friendly environment.[3-6]

To overcome these limitations, we have designed a semi-automated, easy-to-use platform for seamless computation of the coronary flow velocity from conventional coronary angiography.

The present study aims to describe this software, evaluate its agreement with the estimations of expert analysts, and assess its reproducibility against the inter- and intra-observer variability of the experts.

2. Methods

2.1. Studied patients

We retrospectively analyzed angiographic data from patients with chronic coronary syndrome (CCS) or acute coronary syndrome (ACS) included in 2 clinical studies conducted at Barts Heart Centre. The 1st study recruited 20 patients with a CCS listed for a coronary angiogram, intravascular imaging, computed tomography, and positron emission tomography imaging with the radiotracer gallium-68 DOTATATE (a PET radiotracer that is believed to be capable of detecting the presence of macrophages in the vessel wall) and aimed to examine the efficacy of hybrid non-invasive imaging in detecting vascular pathology using intravascular imaging as the reference standard (Clinicaltrials.gov ID: NCT04205110). The recruited patients provided written consent before recruitment; the study was approved by the local research Ethics Committee (REC reference number: 19/LO/1086) and was performed in line with the Declaration of Helsinki.

The second study was a retrospective analysis of patients with CCS or ACS who had coronary angiography in four Cardiology Departments (Barts Heart Center, London, UK; Essex Cardiothoracic Center, Basildon, UK; Royal Free Hospital, London, UK; Seoul National University Hospital, Seoul, Korea) demonstrating at least one non-obstructive coronary lesion that was borderline negative on functional assessment (fractional flow reserve (FFR): 0.81-0.85) that aimed to examine the implications of the local hemodynamic forces computed by three-dimensional coronary angiography (3D-QCA) in lesions that will progress and cause events. This study was conducted as part of a local audit that aimed to examine the outcomes

of patients with non-flow limiting lesions and a borderline negative FFR treated conservatively. Since this analysis was part of an audit formal ethical approval was not required.[10]

From these datasets, we identified patients who had an angiogram with a minimum acquisition frame rate of at least 15 fps and vessels with length ≥70 mm that were assessed by at least two angiographic projections. These projections should portray the studied vessel with minimum foreshortening, without overlapping with other vessels, catheters, electrodes, or other objects that affect the accurate delineation of the lumen silhouette and the projections without wire, balloon catheter, or intravascular imaging catheter. Moreover, the angiographic runs in these projections should include at least two frames before contract injection, the guided catheter should be well intubated, and the injection of the contrast should be constant, allowing complete visualization of the studied vessel. Contrast injection during coronary angiography was performed by the operators, by hand injection. Previously revascularized (PCI or coronary artery bypass grafting) vessels were also excluded from the study. Finally, the studied vessel should not have a significant coronary artery stenosis on 3D-QCA (diameter stenosis; DS>70%) or moderate stenoses (40%<DS≤70%) that were flow limiting on functional assessment as in this occasion the TFC is impaired. The flowchart of patient selection and choice of studied vessel projections for analysis is shown in Figure 1.

2.2. 3D Quantitative Coronary Angiography

3D-QCA was performed by an expert analyst using dedicated software (QAngio XA 3D RE, Medis, Leiden, the Netherlands). Two angiographic projections that were at least 25^{o} apart that portrayed the studied vessel with minimum foreshortening or overlapping were selected, and analysis was performed at end-diastole for a segment that was defined by the ostium of the LAD or LCx or the position of the guiding catheter in the RCA and the most distal side branch that was visible in the two projections used for vessel reconstruction (long segment of interest (l-SOI).[7] To examine the effect of the examined segment's length on the blood velocity

calculation, 3D QCA was also performed for short SOI (s-SOI) by identifying a side-branch located at least 20 mm proximal to the distal side-branch of l-SOI.

For each lesion in the reconstructed segment, we estimated the lesion length, the minimum lumen diameter, the reference vessel diameter, and the percent diameter stenosis (%DS).

2.3. Manual measurement of blood velocity by expert analysts

Two interventional cardiologists reviewed the coronary angiograms and estimated in the l-SOI the coronary blood velocity as described by Gibson et al..[1] Knowing the proximal start and distal end of the l-SOI, both cardiologists measured the number of frames required for the contrast to fill this segment. In the LAD and the LCx, the first frame was defined as the frame in which the contrast agent enters the vessel, while in the RCA, the first frame is the frame at which the contrast enters the ostium of the vessel from the catheter.

Then, the coronary blood velocity was computed using the equation:

$$Blood\ velocity = \frac{3D\ Length\ of\ the\ studied\ segment * frame\ rate}{number\ of\ frames}$$

The two cardiologists computed the blood velocity using two projections. Both cardiologists selected the first projection as the best projection that allowed visualization of the studied segment, while the second projection was selected independently by each cardiologist, blindly to the other, as the second-best projection that allowed visualization of the studied segment.

To examine the effect of the length of the studied segment on the computation of the blood velocity, a side-branch located at least 20 mm proximally to the distal side-branch of the l-SOI was detected, and the analysis was repeated for the segment defined by this branch and from the ostium of the LAD or the LCx or the location of the guiding catheter in the RCA (short SOI, s-SOI).

The above analyses were performed twice by the 1st cardiologist in a 2-month interval to compute the intra-observer variability.

2.4. Automated computation of coronary blood flow velocity

Blood flow velocity was computed using a seamless platform named Cardiovascular Angiography Analysis System (CAAS)Workstation 8.5 - Prototype Bolus Tracking, developed by Pie Medical Imaging (Maastricht, Netherlands). Analysis was performed by the operator who also carried out the 3D-QCA, blindly according to the estimations of the two interventional cardiologists.

The bolus tracking software begins by segmenting the coronary artery of interest within a frame where the contrast liquid has fully opacified the artery up to its distal part (l-SOI or s-SOI). From this initial segmentation, the Centerline is extracted, and the contrast bolus is tracked backward in time using a proprietary bolus tracking algorithm.[8] The core concept of this algorithm is to determine the distance from the ostium to the contrast bolus front as it moves through the coronary artery in an angiography image sequence. To track the bolus front, we developed a modified version of a wave propagation algorithm.[9] The distance from the ostium to the bolus front as this moves through the coronary artery in an angiographic sequence over time is computed. From the distances measured along the tracked vessel over time, the slope of a linear fit through the 90th percentiles of the distance set are extracted, representing the coronary blood velocity. The software gives the velocity based on the two-dimensional length resulting from QCA, and this velocity is then calculated based on the 3D length (3D velocity $= 3\text{D length} * \frac{\text{2D velocity}}{\text{2D length}}$).

Automated measurement of coronary flow velocity in l-SOI and s-SOI of a vessel by CAAS Workstation bolus tracking software and calculation of coronary blood flow by TFC for the same vessel by the expert is shown in Figure 2.

The computation of the blood flow velocity was performed in two angiographic projections for the l-SOI. The 1st was the projection that was selected by both cardiologists as the best projection (optimal-fixed projection) that allowed visualization of the studied segment, and the

2nd was a projection selected by the operators independently as the 2nd best projection. The effect of the segment length on the computation of blood velocity analysis was also measured in the 1st projection for the s-SOI. The calculation of the coronary blood velocity was performed twice in the first projection to assess software intra-observer variability.

2.5. Statistics

Continuous variables are presented as median (interquartile range) and categorical as absolute values and percentages. Coronary flow velocity and QCA results were compared by Kruskal-Wallis according to vessel type (LAD, LCX, and RCA). The agreement between the experts and the CAAS Workstation 8.5 - QCA Bolus Tracking was tested using intra-class correlation coefficients (ICC) under a two-way random effects model, considering absolute agreement and average measurements. Pearson correlation coefficient was applied to examine the linear relationship between the estimations of the experts and the CAAS workstation bolus tracking software and Bland-Altman (BA) analysis to assess bias and determine the limits of agreement (LOA) of the measurements. In parametric BA, the bias was calculated as the mean or median difference between the two approaches depending on distribution, while the LOA was defined as a range centered around the mean bias ±1.96 x standard deviation. For non-parametric BA analysis, the median bias and the 2.5th – 97.5th percentiles were computed using quantile regression.

To evaluate the effect of the phase of the cardiac cycle on the agreement between the estimations of the blood flow velocity computed in two different angiographic projections, we identified patients who had an electrocardiogram recording during angiography and used this to split the cardiac cycle into 3 phases; atrial diastole, atrial systole, and ventricular systole. The agreement between the first optimal-fixed projection l-SOI and the second projection was tested using intra-class correlation coefficients (ICC) under a two-way random effects model, considering absolute agreement and average measurements using a linear mixed model. First,

the unadjusted ICC was estimated: subjects and projections (first optimal-fixed projection vs second projection) were included as random effects in the model. Subsequently, to obtain the adjusted ICC, the time of the contrast injection during the cardiac cycle was included as a fixed covariate in the model. The effect of the time of the contrast injection on the agreement of the projections for the coronary flow velocity was considered significant if the confidence intervals of the unadjusted and adjusted ICCs did not overlap.

All statistical tests were two-tailed, and statistical significance was set at $p<0.05$. Analyses were performed by R software v. 4.2.2 (R statistical software, Institute for Statistics and Mathematics, Vienne, Austria) using "psych" and "ggplot2" packages.

3. Results

Studied patients

Out of the 371 patients included in the two studies, 260 patients who had angiograms acquired at 15 fps were considered for inclusion. After reviewing the angiograms of these patients, 123 (152 vessels) had data suitable for analysis and were included in the study; 238 vessels were excluded due to significant stenosis (DS%>70% or DS% 40-70% with significant hemodynamic stenosis), 145 vessels due to previous percutaneous or surgical revascularization, 59 cases due to insufficient information in the DICOM file for 3D QCA analysis, 75 vessels due to extensive foreshortening and overlapping, 60 vessels because the l-SOI was <70 mm, and 51 cases since the contrast injection was started before angiographic image acquisition or because the contrast medium was not injected continuously.

The baseline demographics of the included patients are listed in Table 1. The mean age of the included patients was 63±10 years, and most of them were males (81%) and suffered from hypertension (55%). The incidence of hypercholesterolemia (42%) and diabetes (43%) was high in this cohort, while heart failure was reported in 19% of the cases.

3.1. Studied vessels

The studied vessels, the length of the l-SOI and the s-SOI, and the 3D-QCA analysis results are shown in Table 2. The length of the l-SOI was smaller in the LCx compared with the LAD and RCA, while the length of the s-SOI was similar in the LCx and LAD but larger in the RCA. In total, 170 lesions were detected. There were significant differences in lesion length, minimum lumen diameter, reference vessel diameter, and %DS between studied vessels; however, there were no significant differences in the measured coronary blood velocity in the LAD, LCx, and RCA (Table 2). Other measured coronary flow velocities were given in Table 1S (supplementary material).

3.2. Estimations of the experts and the automated method for blood flow velocity

The estimations of the experts and the CAAS Workstation 8.5 - Bolus Tracking software are shown in Table 2, while Table 3 displays the agreement of the experts and the software for the blood flow velocity. A high correlation, a small bias, and a narrow LOA were noted between the estimations of the two experts for the blood flow velocity when this was measured in the l-SOI or the s-SOI in the optimal-fixed projection. The correlation between the two experts dropped, and the bias and the LOA increased for the blood velocity measured in the 2nd angiographic projection selected by the two experts.

Comparison of the estimations of the CAAS Workstation 8.5 - Bolus Tracking software and the experts revealed a high correlation, a small bias, and LOA that were wider than the LOA noted between the two experts for the blood flow velocity measured in the l-SOI and s-SOI in the optimal-fixed projection. When the analysis focused on the 2nd best projection selected independently by the experts, the correlation was lower, the bias was similar, but the LOA increased between the estimations of the expert analysts. Estimations of the software and the experts found similar reductions. Bland-Altman and correlation graphics between the

estimations of the experts and the automated method for blood flow velocity were shown in Figures 3 and 4.

3.3. Variability of the estimations of the experts and the automated blood flow velocity software

The inter- and intra-observer variability of the experts and CAAS Workstation 8.5 - Bolus Tracking software are shown in Table 4. Comparison of the two estimations of the 1st expert for the blood flow velocity in the l-SOI in the optimal-fixed projection demonstrated a high correlation, a small bias, and a narrow LOA; similar results were noted when the analysis was performed in the s-SOI although the correlations were numerically smaller and the LOA were wider. Although the analyses were reproducible in the l-SOI and s-SOI, the length of the analyzed segment seemed to affect the estimated blood velocity by the experts; the correlation was high between the blood flow velocity measured in the l-SOI and the s-SOI, but there was a large bias – the mean velocity was larger in the s-SOI – and wide LOA between the two measurements. In addition, the selection of the angiographic projection also seemed to affect the expert estimations as there was a moderate correlation, large bias, and wide LOA between the velocities measured in different projections. Results were not different for the estimations of the 2nd expert.

The reproducibility of the CAAS Workstation 8.5 - Bolus Tracking software is shown in Table 4. Comparison of the 1st and 2nd blood flow velocity measurement in the l-SOI in the optimal-fixed projection revealed an ICC and Pearson correlation that were >0.99, a bias that was close to 0 and LOA narrower than the LOA noted for the estimations of the 1st expert. These findings were consistent when the analysis focused on the s-SOI indicating that the software was more reproducible than the expert irrespective of the length of the studied SOI. Furthermore, comparison of the estimations of the software for the blood flow velocity in the l-SOI and s-SOI revealed a high agreement with an excellent ICC and Pearson correlation and a bias close

to 0 – indicating that the length of the SOI did not affect the mean estimation of the blood flow velocity – and LOA that were similar to the LOA noted in the experts. Finally, a comparison of the estimations of the software in two different angiographic projections demonstrated a moderate correlation, small bias, and wide LOA. These findings were also noted by the experts and underscore the angiographic projection's effect on the blood flow velocity computation. Bland-Altman and correlation for the variability of estimations between the experts and the CAAS workstation are shown in Figure 1S and Figure 2S in the supplementary file.

When we examined the effect of the cardiac phase (atrial diastole, atrial systole, and ventricular systole) on the agreement of coronary flow velocity measured by the software between 1st optimal-fixed projection and 2nd best projection in 122 patients that had electrocardiogram recording during angiography, we found no effect of the cardiac phase on the agreement of the measured velocities (unadjusted ICC: 0.72 (95% CI: 0.62-0.80) vs adjusted with cardiac phases ICC: 0.70 (95% CI: 0.58-0.78). This suggests that the cardiac phase does not impact the concordance between the first optimal-fixed projection and second projection methods.

3.4. Analysis time

The time required to estimate coronary blood flow velocity was measured in 50 vessels and was 51±10s/vessel using a desktop PC with an Intel Core i5 processor and 8 GB RAM; this was smaller than the time required by an expert to measure the coronary blood flow velocity in the same vessels (61±9s/vessel, $p<0.001$).

4. Discussion

This study presents a rapid, semi-automated, user-friendly platform named CAAS Workstation 8.5 - QCA Bolus Tracking software for the computation of the blood flow velocity in the coronary arteries. Validation of this approach against the estimations of expert analysts demonstrated that: 1) it is quick as it takes only 50 s to assess coronary blood flow velocity, 2)

it provides estimations for the coronary flow velocity that are similar to those of expert analysts, 3) it is highly reproducible - more reproducible than the experts - when it is applied to assess coronary blood flow velocity in the same angiographic projection irrespective of the length of the SOI, and, 4) the selection of the angiographic projection seems to influence the estimations of the methodology and the experts as there were differences in the measured velocities in different projections.

The assessment of blood flow velocity has been a topic of research for almost 30 years. Gibson introduced in 1996 the TIMI frame count to approximate coronary flow in patients with acute coronary syndrome, which was found to be a predictor of clinical outcomes.[1,10] A limitation of this approach was the fact that the TIMI frame count values relied on the length of the studied vessels. This was partially overcome with the introduction of the corrected TIMI frame count that takes into account vessel type and then with the introduction of the angiographic-based coronary flow velocity that requires measurement of the length of the studied segment – initially with an angiography guidewire – and the time needed for the contrast to fill this segment to derived flow velocity.[11] This approach was used to assess microvascular function and coronary flow reserve (CFR) using the Doppler wire estimations as reference standards, with first studies showing conflicting results; in the study of Magginas et al., there was a correlation between TIMI frame count and Doppler CFR however this was not confirmed in the study of Chugh et al. which showed no association between the estimations of the TIMI frame count and Doppler estimations.[12,13] More recent reports have confirmed the findings of Chugh et al., showing weak performance of the TIMI frame count-based measurement to predict microvascular disease.[14]

Despite these findings, there is currently an increased interest to develop fully automated methodologies that will be able to track contrast motion in the coronary arteries to measure blood velocity as these approaches can be combined with software solutions that enable computation of the pressure drop across lesions and thus estimate in a minimally invasive

fashion both epicardial and microvascular pathophysiology. Moreover, these approaches can be useful in research assessing the implications of the local hemodynamic forces on atherosclerotic disease progression as boundary conditions, and in particular, the inflow velocity in this simulation appears to critically determine flow patterns and shear stress distribution.

Several approaches have been introduced in the literature to assess coronary flow velocity. However, none of them has reached clinical practice as they have significant limitations; some are time-consuming and prone to errors[4], some others cannot operate in unobstructed vessels[5], while others have week reproducibility and agreement with the experts[6] and have not been incorporated in a user-friendly software. Some of these limitations were addressed by the software designed by Zheng et al. that was introduced to facilitate the computation of angiography-based FFR however, the validation study comparing the estimations of the software and experts has shown a large bias and weak agreement – casting doubts about its efficacy to measure coronary blood flow velocity.[15]

The present study introduces a user-friendly semi-automated platform for seamless computation of the blood flow velocity from bolus contrast with the CAAS Workstation 8.5 - Bolus Tracking software. Testing of this module in 152 vessels demonstrated that it is fast and provides highly reproducible estimations of the coronary flow velocity that are similar to the estimations of experts. In contrast to the experts, where the length of the SOI seems to affect the measured blood flow velocity, the CAAS Workstation 8.5 software provides similar estimations irrespective of the SOI. This difference should be attributed to the fact that the expert estimations are based on the number of frames required for the contract to fill the vessel. A minor increase/decrease in the length of the SOI is likely to result in different estimations of the blood velocity as this is determined by the number of angiographic frames needed to fill this segment; the smaller the acquisition frame rate, the larger is expected to be the difference

in the measured velocities. Conversely, the CAAS Workstation estimates a velocity profile using a linear fit slope that connects the velocities computed during contrast injection; therefore, its estimations are expected to be less dependent on the length of the SOI.

When we compared the estimations of the experts and the software in different angiographic projections, we found moderate reproducibility and a large bias and LOA for the measured blood flow velocities. Several studies in the past have examined the factors that can affect TIMI frame count estimations and showed that patient heart rate, the administration of intracoronary nitrates, and the phase of the cardiac cycle where the contrast injection is performed affects blood velocity; conversely, the size of the guiding catheter and the injection rate do not affect the measured velocities.[1,16] In our study, we found that in patients where the electrocardiogram was available, the phase of the cardiac cycle at which the contrast was injected appeared to have no effect on the reproducibility of the experts and the method. This paradox is likely to be due to the effect of the contrast injection on the coronary flow. It has been shown that during contrast injection, there is a mild increase in coronary blood flow, followed by a decrease in the flow, with its minimum value reaching 45% of the baseline flow at 1.9 s, and then there is hyperemia, which reaches its maximum value of 153% between 5-10 s. Normal coronary flow restores to its normal values within 60 s.[17,18] In this retrospective study, there was no delay between sequential angiograms, and this is likely to have affected the reported results. This consideration should be taken into account in the design of future prospective studies evaluating its efficacy in measuring coronary flow velocity and during its applications for retrospective data analysis.

5. Limitations

Several additional limitations of the present study should be acknowledged. Firstly, this analysis compared the output of the CAAS Workstation 8.5 - Prototype Bolus Tracking software using

the estimations of experts as reference standard instead of the absolute flow values measured by continuous thermodilution or a Doppler wire. Secondly, the analysis focused on the measurement of the baseline coronary flow velocity and not during hyperemia, where blood flow computation is more challenging as the flow increases. Future studies should be designed to assess the performance of the Workstation software in this setting and its potential to assess microvascular function. Thirdly, in all the cases included in this analysis, image acquisition was performed at 15 fps; therefore, it is unclear whether our findings would apply to sequences acquired at a higher or lower frame rate.

6. Conclusions

This study describes a rapid, user-friendly platform that relies on the tracking of the bolus contrast to seamlessly compute blood flow velocity. Validation of this platform against experts demonstrated that it is quick, accurate, and provides reproducible estimations irrespective of the length of the segment used for analysis. These features render this module useful in research and support the design of prospective validation studies that examine its potential to assess microvascular function using the estimations of continuous thermodilution or a Doppler wire as the gold standard.

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Figures Legends

Figure 1. Flow-chart of patient selection and analysis protocol. l-SOI, long segment of interest; s-SOI, short segment of interest; 3D QCA, three-dimensional quantitative coronary angiography; CAAS, Cardiovascular Angiography Analysis System

Figure 2. Snapshot of the CAAS Workstation bolus tracking prototype with the estimated coronary blood flow velocity measurement for the s-SOI (A) and l-SOI (B) in a right coronary artery. Panel (C) shows the methodology used by the expert analyst to estimate coronary flow velocity in the same vessel. The first frame at which the contrast opacified both edges of the proximal end of the SOI (frame 1) and the first frame that the contrast opacified the distal branch of the l-SOI (frame 7) and s-SOI (frame 5) were detected, and these were used to estimate the time needed for the contrast to fill the SOIs. The length of the SOIs was then divided by this time to estimate the coronary flow velocity. In this case, the estimated coronary flow velocity was 279 mm/s, for the l-SOI and 275 mm/s for the s-SOI while the corresponding estimations of the expert were: 249 mm/s and 258 mm/s respectively.

l-SOI, long segment of interest; s-SOI, short segment of interest; CAAS, Cardiovascular Angiography Analysis System

Figure 3. Bland-Altman graphics comparing the coronary flow velocity estimations of the experts and the CAAS Workstation bolus tracking software for the l-SOI and s-SOI in the 1st optimal/fixed projection and for the l-SOI in the 2nd projection.

l-SOI, long segment of interest; s-SOI, short segment of interest CAAS, Cardiovascular Angiography Analysis System

Figure 4. Correlation graphics of the estimations of the experts and the CAAS Workstation bolus tracking software for the coronary flow velocity measured in the l-SOI and s-SOI in the 1st optimal/fixed projection and the l-SOI in the 2nd projection.

l-SOI, long segment of interest; s-SOI, short segment of interest; CAAS, Cardiovascular Angiography Analysis System

Table 1. Baseline characteristics and coronary blood velocity of the study population.

Studied patients (n=123)	
Age, (years)	63±10
Gender, (male)	100 (81%)
Co-morbidities	
Hypertension	28 (55%)
Diabetes mellitus	53(43%)
Dyslipidaemia	52 (42%)
Heart failure*	24 (19%)
Chronic renal disease**	34(27%)
Current smoker	22(18%)
Family history of CAD	53 (43%)
History of previous PCI	20 (16%)
History of ACS	38 (30%)
Medications	
Acetylsalicylic acid	100 (81%)
Clopidogrel	51 (41%)
Beta-blockers	52 (42%)
Statin	87 (70%)
Calcium channel blocker	25 (20%)
ACEI/ARB	59 (48%)
Nitrate	14 (11%)

Abbreviations: CAD, coronary artery disease; GFR, Glomerular filtration rate; LVEF, Left ventricular ejection fraction; ACS, Acute coronary syndrome; PCI, percutaneous coronary intervention; ACEI/ARB, Angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers.

* Heart failure was defined as a left ventricular ejection fraction <50%.
**Chronic renal disease was defined glomerular filtration rate <60 mL/min/1.73m^2

Table 2. Angiographic characteristics of the vessels included in the present analysis.

	Studied vessels (n=152)	Left anterior descending (n=46)	Left circumflex (n=49)	Right coronary artery (n=57)	P value
3D Length of l-SOI (mm)	110.9 (93-124.9)	108.4 (95.8-122)	85.7 (81.9-108.9)	124.1 (113.5-136.7)	<0.001
3D Length of the s-SOI (mm)	68.6 (58-87.3)	64.7 (57.4-74)	58.0 (51.1-65.5)	90.1 (78-10.7)	<0.001
3D QCA analysis					
Number of lesions	172 (100%)	54(32%)	58(34%)	58(34%)	0.368
Lesion length (mm)	20.9 (14.6-28.9)	20.3 (13.9-28.4)	18.0 (13.1-25.4)	23.7 (16.1-30.7)	0.044
Minimum lumen diameter (mm)	1.8 (1.5-2.1)	1.7 (1.5-1.9)	1.8 (1.5-2.2)	1.9 (1.6-2.4)	0.003
Reference lumen diameter (mm)	2.8 (2.3-3.3)	2.7 (2.3-2.9)	2.6 (2.2-3.2)	3.0 (2.5-3.4)	0.001
Diameter stenosis (%)	32 (28-38)	34 (29-42)	30.8 (26.5-36.9)	32.8 (28.4-39.4)	0.033
Measured blood flow velocities					
1st expert l-SOI optimal-fixed projection (mm/s)	125 (106 – 164)	135(113-172)	118 (98-144)	139 (111-185)	0.278
2nd expert l-SOI optimal-fixed projection (mm/s)	127 (106 – 169)	135(111-175)	116(98-161)	139(110-184)	0.050
CAAS Workstation l-SOI optimal-fixed projection (mm/s)	132 (107 – 170)	142(108-176)	125(98-155)	133(108-174)	0.060

Abbreviations: l-SOI, long segment of interest; s-SOI, short segment of interest; 3D QCA, Three-dimensional Quantitative Coronary Angiography CAAS, Cardiovascular Angiography Analysis System

Table 3. Agreement of the two experts and the CAAS Workstation bolus tracking software for the blood flow velocity measured in the l-SOI and s-SOI in the two angiographic projections.

		Median Difference (LoA)	ICC	P	Pearson	P
1st expert vs 2nd expert	Optimal-fixed projection l-SOI	-1.3 (-34.1, 31.6)	0.974 (0.964-0.981)	<0.001	0.949	<0.001
	2nd best projection l-SOI	-6.7 (-75.2, 61.9)	0.885 (0.841-0.916)	<0.001	0.794	<0.001
	Optimal-fixed projection s-SOI	-0.9 (-42.8, 40.8)	0.968 (0.956-0.977)	<0.001	0.938	<0.001
1st expert vs CAAS Workstation	Optimal-fixed projection l-SOI	5.1 (-45.2, 55.5)	0.945 (0.924-0.960)	<0.001	0.904	<0.001
	2nd best projection l-SOI	-0.2 (-90.0, 89.6)	0.807 (0.735-0.860)	<0.001	0.676	<0.001
	Optimal-fixed projection s-SOI	-6.4 (-72.8, 59.9)	0.919 (0.889-0.941)	<0.001	0.852	<0.001
2nd expert vs CAAS Workstation	Optimal-fixed projection l-SOI	3.9 (-49.3, 57.1)	0.938 (0.915-0.955)	<0.001	0.892	<0.001
	2nd best projection l-SOI	-6.9 (-97.7, 84.2)	0.790 (0.711-0.848)	<0.001	0.655	<0.001
	Optimal-fixed projection s-SOI	-7.4 (-79.1, 64.4)	0.904 (0.868-0.930)	<0.001	0.826	<0.001

Abbreviations: LoA, limits of agreement; CI, confidence interval; ICC, intraclass correlation coefficient; l-SOI, long segment of interest; s-SOI, short segment of interest; CAAS, Cardiovascular Angiography Analysis System

Table 4. Variability of the experts and the CAAS Workstation bolus tracking methodology in the l-SOI and s-SOI and in different angiographic projections.

		Median Difference (LoA)	ICC	P	Pearson	P
1st expert variability	Optimal-fixed projection 1st vs 2nd estimation l-SOI	0.8 (-45.3, 46.9)	0.946 (0.925-0.961)	<0.001	0.897	<0.001
	Optimal-fixed projection vs 2nd best projection l-SOI	-6.2 (-96.9, 84.4)	0.775 (0.690-0.837)	<0.001	0.634	<0.001
	Optimal-fixed projection l-SOI vs optimal-fixed projection s-SOI	-11.7 (-70.1, 46.6)	0.925 (0.897-0.946)	<0.001	0.870	<0.001
	Optimal-fixed projection 1st vs 2nd estimation s-SOI	-5.7 (-61.4, 50.1)	0.947(0.927-0.962)	<0.001	0.904	<0.001
2nd expert variability	Optimal-fixed projection vs 2nd best projection l-SOI	-11.7 (-110.9, 87.6)	0.700 (0.587-0.782)	<0.001	0.539	<0.001
	Optimal-fixed projection l-SOI vs optimal-fixed projection s-SOI	-11.5 (-72.0, 49.1)	0.919 (0.888-0.941)	<0.001	0.859	<0.001
CAAS Workstation variability	Optimal-fixed projection 1st vs 2nd estimation l-SOI	0.2 (-16.1, 16.5)	0.995 (0.993-0.997)	<0.001	0.991	<0.001
	Optimal-fixed projection vs 2nd best projection l-SOI	-0.9 (-108.9, 107.2)	0.722 (0.618-0.798)	<0.001	0.563	<0.001
	Optimal-fixed projection l-SOI vs optimal-fixed projection s-SOI	-0.2 (-62.3, 61.9)	0.930 (0.903-0.949)	<0.001	0.869	<0.001
	Optimal-fixed projection 1st vs 2nd estimation s-SOI	-0.3 (-22.3, 21.7)	0.992 (0.990-0.995)	<0.001	0.986	<0.001

Abbreviations: LoA, limits of agreement; CI, confidence interval; ICC, intraclass correlation coefficient; l-SOI, long segment of interest; s-SOI, short segment of interest CAAS, Cardiovascular Angiography Analysis System.

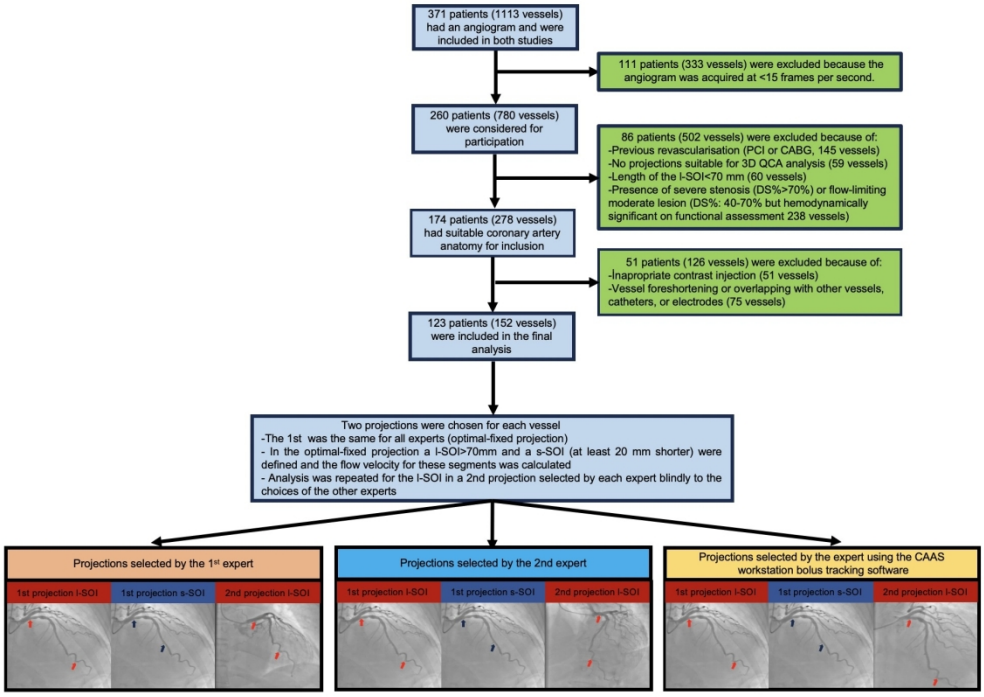

Figure 1

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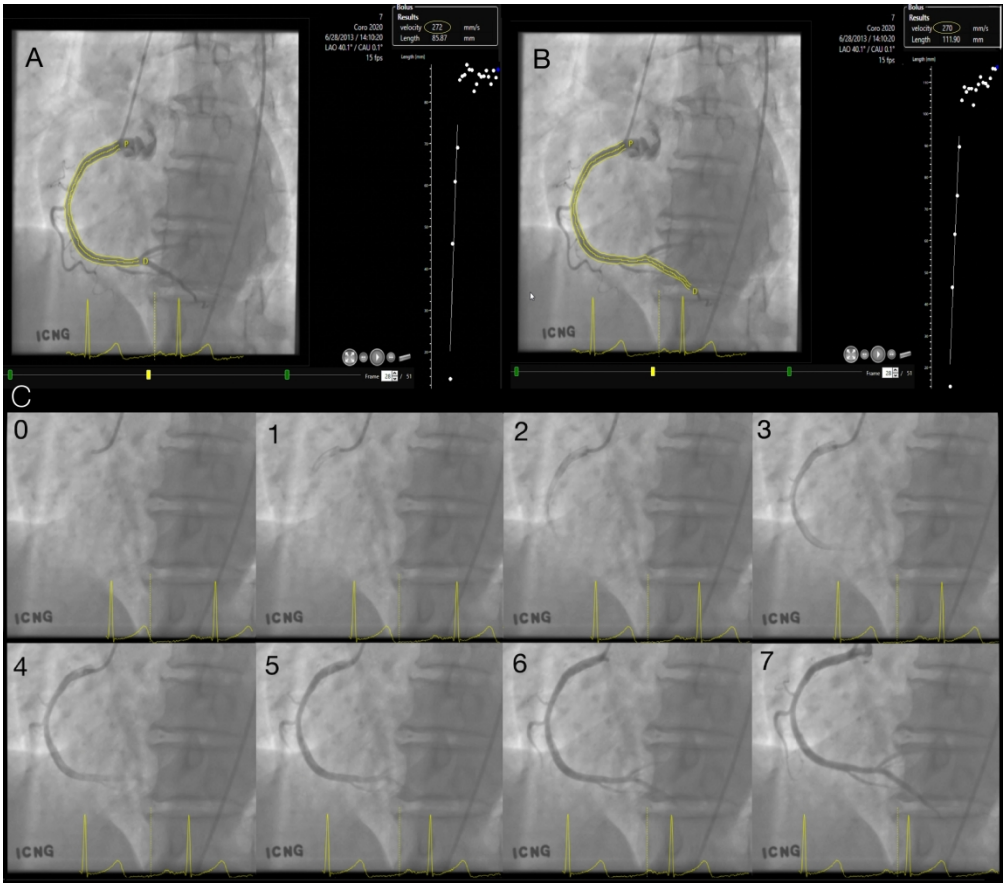

Figure 2

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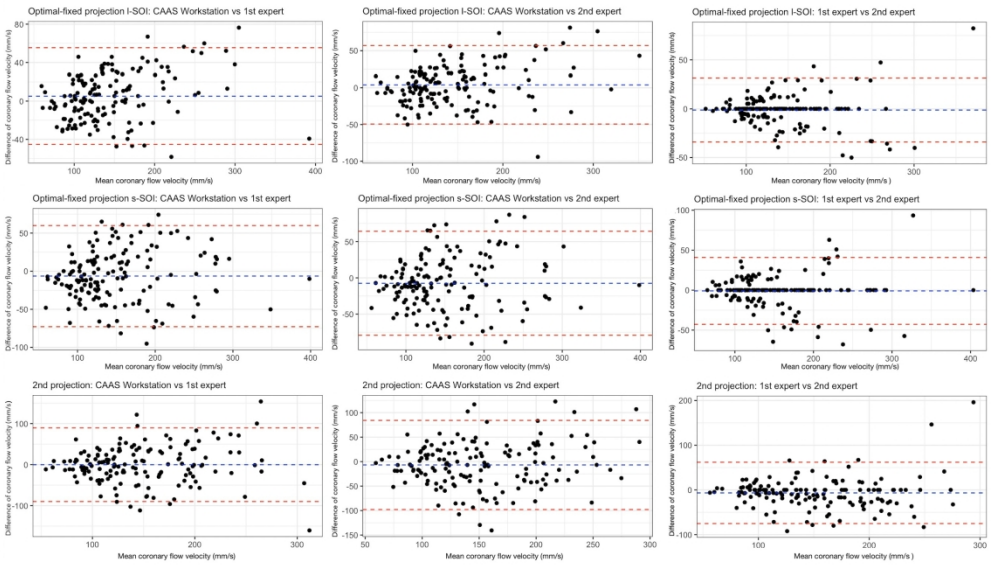

Figure 3

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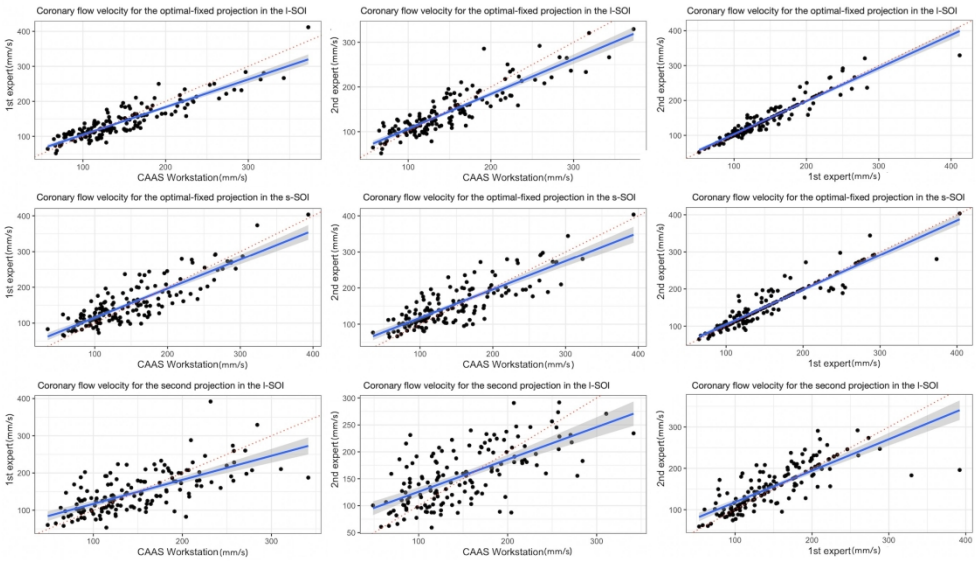

Figure 4

497x290mm (144 x 144 DPI)

An automated user-friendly software for fast computation of blood flow velocity from coronary angiographic images

Supplementary material

Table 1S. Other measured blood flow velocities.

Studied vessels (n=152)	
1st expert 2nd estimation l-SOI optimal-fixed projection (mm/s)	126 (104 - 169)
CAAS Workstation l-SOI 2nd estimation optimal-fixed projection (mm/s)	131 (105 - 170)
1st expert second projection (mm/s)	138 (106 - 181)
2nd expert second projection (mm/s)	150 (109 - 196)
CAAS Workstation second projection (mm/s)	134 (104 - 184)
1st expert 1st estimation s-SOI (mm/s)	136 (112 - 182)
2nd expert optimal-fixed projection s-SOI (mm/s)	138 (110 - 190)
CAAS Workstation 1st estimation optimal-fixed projection s-SOI (mm/s)	129 (102 - 175)
1st expert 2nd estimation optimal-fixed projection s-SOI (mm/s)	139 (112 - 193)
CAAS Workstation 2nd estimation s-SOI (mm/s)	126 (100 - 177)

Footnote: l-SOI, long segment of interest; s-SOI, short segment of interest; CAAS, Cardiovascular Angiography Analysis System

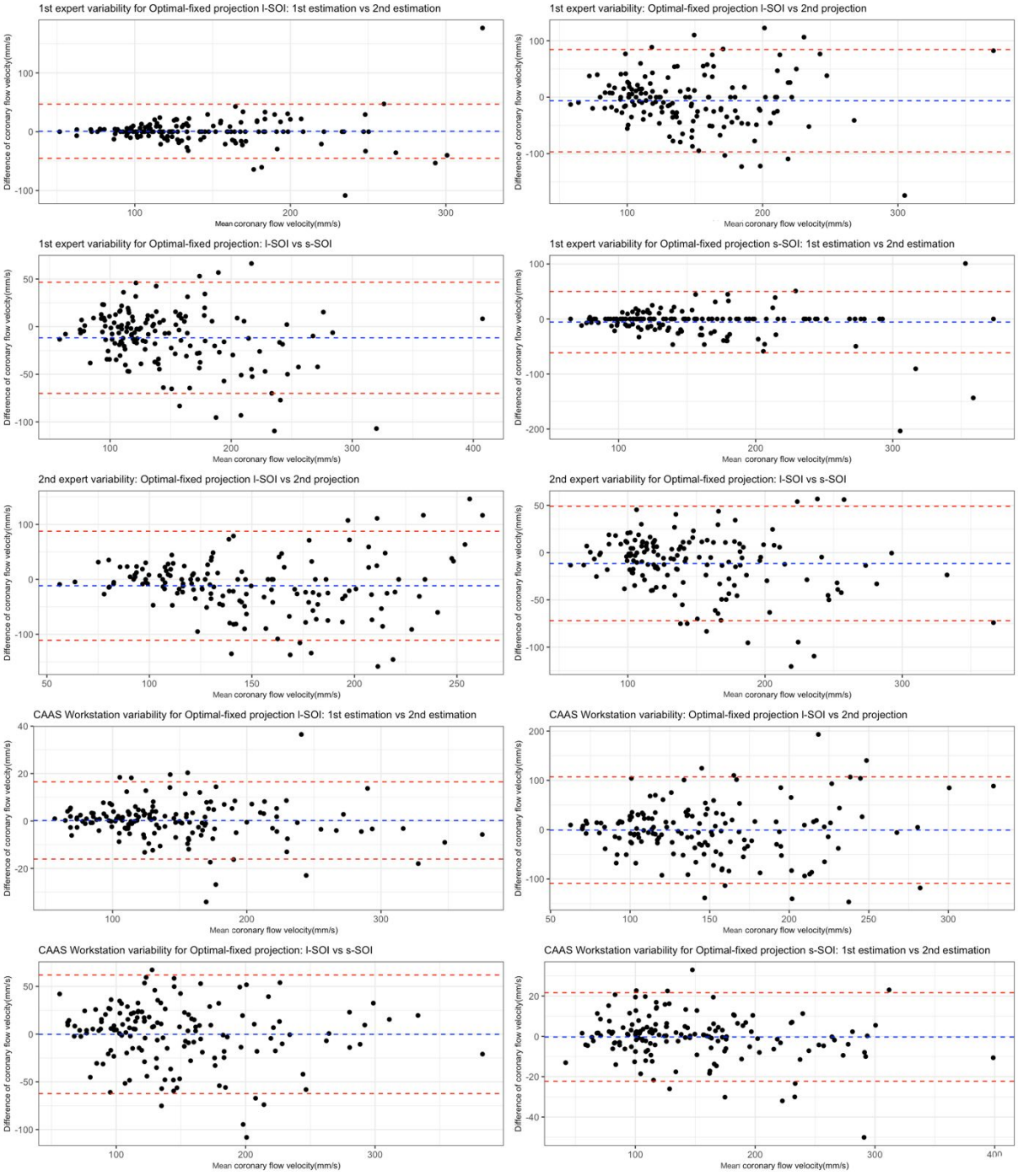

Figure 1S. Bland-Altman graphics displaying the intra-observer agreement of the experts and of the CAAS Workstation bolus tracking software estimations in different SOIs and angiographic projections. l-SOI, long segment of interest; s-SOI, short segment of interest; CAAS, Cardiovascular Angiography Analysis System

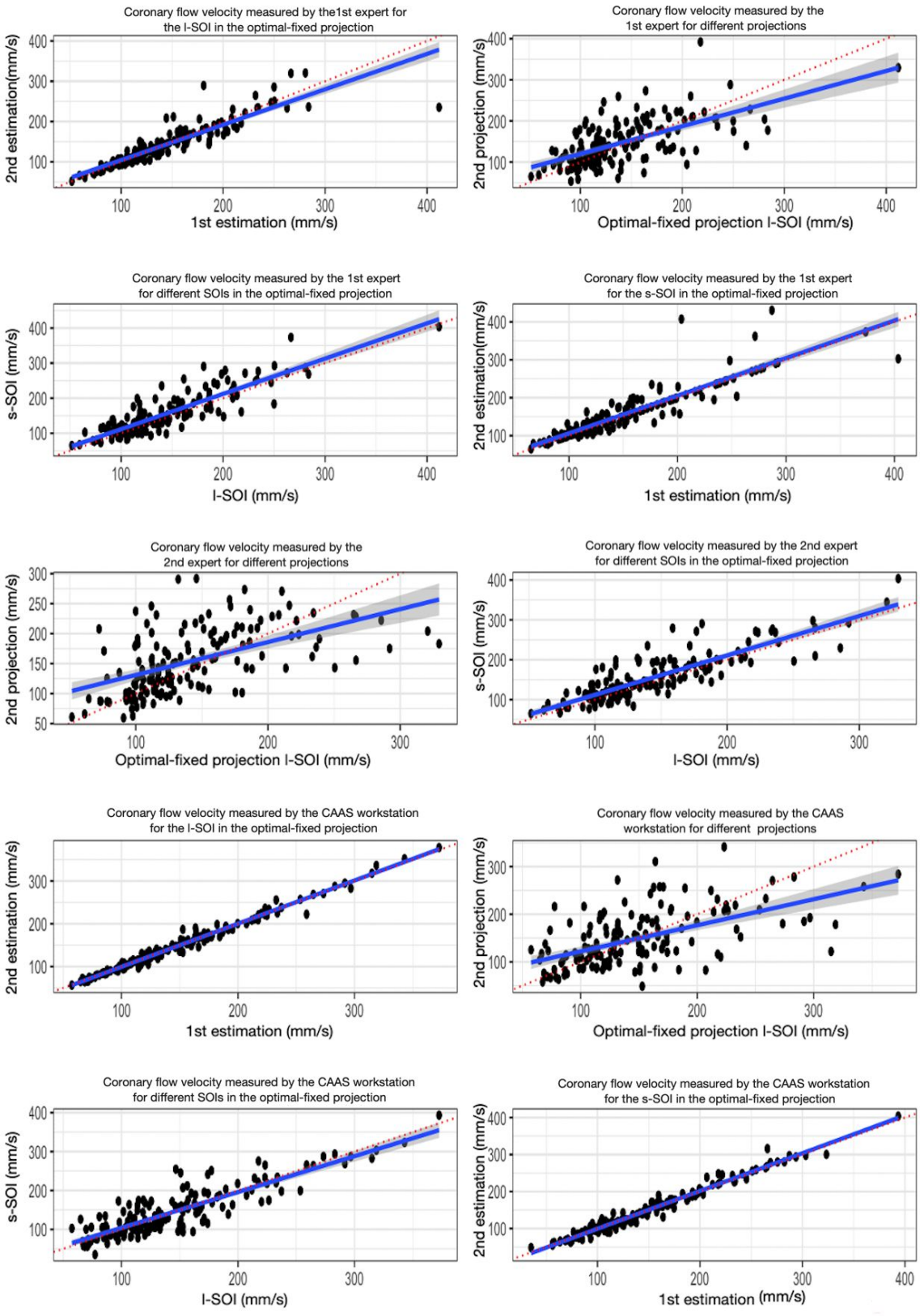

Figure 2S. Correlation graphics showing the intra-observer agreement of the estimations of the experts and of the CAAS Workstation bolus tracking software in different SOIs and angiographic projections. l-SOI, long segment of interest; s-SOI, short segment of interest; CAAS, Cardiovascular Angiography Analysis System