An automated software for real-time quantification of wall shear stress distribution in quantitative coronary angiography data

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ABSTRACT

Background: Wall shear stress (WSS) estimated in 3D-quantitative coronary angiography (QCA) models appears to provide useful prognostic information and identifies high-risk patients and lesions. However, conventional computational fluid dynamics (CFD) analysis is cumbersome limiting its application in the clinical arena. This report introduces a user-friendly software that allows real-time WSS computation and examines its reproducibility and accuracy in assessing WSS distribution against conventional CFD analysis.

Methods: From a registry of 414 patients with borderline negative fractional flow reserve (0.81-0.85), 100 lesions were randomly selected; 3D-QCA and CFD analysis were performed using the conventional approach and the novel (CAAS Workstation WSS) software, and the QCA and WSS estimations of the two approaches were compared. The reproducibility of the two methodologies was evaluated in a subgroup of 50 lesions.

Results: A good agreement was noted between the conventional approach and the novel software for the 3D-QCA metrics (ICC range: 0.73-0-93) and the maximum WSS at the lesion site (ICC: 0.88). Both methodologies had a high reproducibility in assessing lesion severity (ICC range: 0.83-0.97 for the conventional approach; 0.84-0.96 for the CAAS Workstation WSS software) and WSS distribution (ICC: 0.85-0.89 and 0.83-0.87, respectively). Simulation time was significantly shorter using the CAAS Workstation WSS software compared to the conventional approach (4.13±0.59min vs 23.14±2.56min, $p<0.001$).

Conclusion: CAAS Workstation WSS software is fast, reproducible, and accurate in assessing WSS distribution. Therefore, this software is expected to enable the broad use of WSS metrics in the clinical arena to identify high-risk lesions and vulnerable patients.

INTRODUCTION

Wall shear stress (WSS) is an established instigator of atherosclerotic disease progression and has a role in plaque destabilisation and rupture through the activation of mechano-transduction pathways that regulate plaque pathobiology. [1, 2] Several studies have demonstrated that WSS provides incremental prognostic information to plaque composition and burden allowing identification of high-risk lesions and patients. [3-5] Despite the undoubted value of WSS metrics in vulnerable plaque detection their clinical applications are limited. This should be partially attributed to the fact that accurate estimation of WSS requires reliable reconstruction of lumen geometry that is mainly obtained from the fusion of intravascular imaging data with coronary angiography. This process involves vessel interrogation with an intravascular imaging catheter, image segmentation and fusion followed by computational fluid dynamic (CFD) analysis; thus, it is time-consuming and cannot be performed in real-time while the patient is on the catheterisation table. [6, 7]

We have demonstrated that three-dimensional quantitative coronary angiography (3D-QCA) offers an effective alternative for reliable quantification of flow patterns and WSS distribution [8], while several reports have shown that 3D-QCA derived-WSS provides useful prognostic information allowing identification of non-flow limiting lesions causing major adverse cardiovascular events (MACE). [9-11] Although vessel reconstruction from 3D-QCA is fast, CFD analysis of the obtained geometries and data post-processing are tedious processes that require expertise. To overcome this limitation, we introduce a novel user-friendly software for real-time computation of WSS. The aim of this report is to describe the developed software and assess its accuracy and reproducibility in evaluating WSS using conventional CFD analysis as reference standard.

METHODS

Studied patients

We analysed data from a registry of 414 patients created to investigate the value of 3D-QCA-derived WSS in detecting vulnerable plaques and predicting events. This registry included patients who underwent coronary angiography between January 2012 and June 2017 at four cardiac centres (Barts Heart Centre, London, UK; Essex Cardiothoracic Centre, Basildon, UK; Royal Free Hospital, London,

UK; Seoul National University Hospital, Seoul, South Korea) and had at least a non-flow limiting lesion with borderline negative fractional flow reserve (FFR: 0.81-0.85) that was left untreated. Exclusion criteria were described in the Supplementary Material.

From this dataset we randomly selected 100 lesions that had ≤1 major side branch (≥1mm in diameter); these were reconstructed using 3D-QCA software and processed with CFD techniques using a previously described and well-established methodology [8-10] - "conventional approach" - and a newly developed software named "CAAS Workstation WSS" (Pie Medical Imaging, Maastricht, the Netherlands) (Figure 1).

This study was conducted as part of a local audit to assess the outcome of patients with borderline negative FFR lesions treated conservatively in line with the international guidelines. [12] All patient identifiable information were removed prior merging of the datasets. The local ethics committee advised that formal ethical approval was not required for this retrospective study. [10]

3D-QCA reconstruction and WSS computation

Conventional approach

Angiographic reconstructions and CFD analysis were performed at the Barts Heart Centre by experienced analysts blinded to baseline demographics, coronary angiography, and pressure wire study report. QAngio XA 3D RE software (Medis Medical Imaging Systems, Leiden, The Netherlands) was used for 3D-QCA analysis of the coronary segment with borderline negative FFR lesion by using two end-diastolic angiographic views at least 25° apart (Supplementary Material). Fusion of the segment of interest and its major side branch, if this was present, was performed using the QAngio CT 3D Workbench 1.5.0.2 software (Medis Medical Imaging Systems bv, Leiden, the Netherlands) to generate a single 3D surface of the lumen geometry.

CFD analysis was performed in the reconstructed geometries using commercially validated software. The Simpleware P-2019.09 (Synopsys, Inc. CA, USA) software was used to mesh the 3D vessel geometry and it generated a tetrahedral hybrid mesh with a global mesh size of 0.1 mm. Near the wall boundary (at the surface of the body), the mesh had 6 layers of prismatic elements, with the minimum element thickness of 0.02 mm nearest to the wall and total layer thickness close to the global mesh size.

The meshed geometry was then imported to Ansys CFX 19.0 (Ansys Inc., PA, USA) software for blood flow simulation (Supplementary Material). To expedite these steps, we developed a program in MATLAB R2020b (MathWorks, Natick, Massachusetts, USA) that integrates the functionalities of the two software in a user-friendly platform allowing the operator to use them in a timely manner. This in-house tool was also used for the post-processing and WSS data extraction. [9, 10] The segment of interest was split in 3mm segments and for each segment the mean WSS value across the circumference and length of the segment was computed. In addition, the location of the lesion was identified in the model and the highest mean WSS value of the 3mm segments was recorded and corresponded to the "maximum" WSS of the lesion.

CAAS Workstation WSS

3D-QCA reconstruction of each segment of interest was generated using two end-diastolic angiographic projections at least 30° apart (Supplementary Material). The meshing of 3D models was performed using a curvature-based approach, the elements had tetrahedral shape with a minimum size of 0.05mm and near the wall boundary the mesh had 3-layer tetrahedral elements. The curvature-based approach resulted in a dynamic change in the size of the elements that increase in size in regions where the coronary artery is straight. The reduced number of near wall layers and the increased element size led to the generation of a less dense mesh enabling the CAAS Workstation WSS software to run this step quicker than the conventional approach. The governing equations of fluid motion were solved in their discretized form under transient-state conditions by applying the finite element code Kratos [13] that was incorporated in the CAAS Workstation WSS using the same assumptions of the conventional approach in blood flow simulation (Supplementary Material). However, the blood flow simulation was faster in this software because the Kratos solver was specially designed to perform CFD analysis in the coronary arteries and thus it included only the processing steps that were necessary for this purpose. Conversely, the analysis performed by ANSYS CFX, which is a commercial package, involved additional computational steps that were not required for the assessment of WSS distribution in 3D-QCA models resulting in a longer computational time in the conventional approach.

The WSS was computed by the first derivate of the velocity's perpendicular to the coronary vessel wall multiplied with the blood viscosity. Post-processing was performed as described in the conventional approach.

Comparison of the conventional approach with the CAAS Workstation WSS software

In a recent study, 3D-QCA-derived WSS and lesion characteristics estimated by 3D-QCA provided useful prognostic information in patients with borderline negative FFR lesions enabling not only identification of the non-flow liming plaques that progressed and caused events, but also detection of high-risk patients who had an event at 4-year follow-up. [10]

To examine the potential value of the developed software in stratifying cardiovascular risk, we compared the following variables estimated by the CAAS Workstation WSS software and the conventional approach for each lesion:

- 3D-QCA-metrics including lesion length, mean reference lumen area, minimum lumen area (MLA) and % area stenosis (AS; computed by the equation: 100 x (1-MLA/reference lumen area at the MLA site estimated from the proximal and distal reference lumen area using a linear interpolation approach).
- Maximum WSS value.
- Mean WSS values in 3mm segments.

Finally, for the above variables we examined the intra- and inter-observer variability of the conventional approach and the CAAS Workstation WSS in 50 vessels that were randomly selected. An expert analyst performed twice, within 2-month interval, 3D-QCA and CFD analysis using the conventional approach and the novel software and the estimations of each approach at these two time points were compared. To examine the inter-observer variability, a 2nd analyst analysed the same dataset using the conventional method and the CAAS Workstation WSS and the estimations were compared with the first analyst.

Statistical analysis

Continuous variables were presented as mean±SD, while categorical variables as absolute numbers and percentages. Intraclass correlation coefficient (ICC) and Bland-Altman analysis were used to investigate

the agreement between the estimations of the conventional method and the CAAS Workstation WSS and examine the inter- and intra-observer variability of the two approaches.

In a recent study, AS ≥58.6% and maximum WSS ≥7.69Pa estimated using the conventional approach were independent predictors of MACE in borderline negative FFR lesions. [10]

To examine the efficacy of the CAAS Workstation WSS in detecting lesions that had AS ≥58.6% or maximum WSS ≥7.69Pa with the conventional approach, receiver operating characteristic (ROC) curve analysis was performed and the Youden's index was calculated to define the best cut-offs that predicted these values when using the novel WSS software. In addition to the area under the curve (AUC), the sensitivity, specificity, the positive and negative predictive value and the accuracy of the CAAS Workstation WSS software in identifying an unfavourable haemodynamic environment (WSS ≥7.69 Pa) and coronary anatomy (AS ≥58.6%) were presented. Statistical analysis was performed using SPSS Statistics 25 (IBM, Chicago, Ill., USA); a p-value <0.05 was considered statistically significant.

RESULTS

100 lesions (99 patients) were included in the current analysis. The mean age of the patients was 63.3±10.2 years, more than a half suffered from hypertension (59.6%) and hypercholesterolemia (53.5%) and most of them underwent a coronary angiogram because of chronic coronary syndrome (90.9%; Supplementary Table 1). The studied lesions were mainly located in the left anterior descending artery (75%) and 30% of them included a side branch with a diameter ≥1mm.

Conventional approach vs CAAS Workstation WSS

An excellent ICC was noted between the estimations of the QAngioXA 3D RE software and the CAAS Workstation WSS for lesion length, mean reference lumen area and MLA, whereas the ICC for the AS was moderate. The ICC was high for maximum WSS values at the lesion site and good for the mean WSS values in 3mm segments across the reconstructed segment (Table 1).

The mean±SD of the differences between the estimations of the two approaches for the 3D-QCA metrics and WSS distribution are shown in Table 1, while the Bland-Altman analyses for the MLA, AS and WSS distribution in Figure 2. The mean±SD of the differences for the estimations of the two approaches

for the maximum WSS at the lesion site and the WSS across the entire lesion were similar (0.79±2.52Pa and 0.51±2.34, respectively).

ROC curve analysis showed that the novel software had a very good AUC and accuracy in detecting lesions with AS ≥58.6% (Supplementary Figure 1, panel A) and maximum WSS ≥7.69Pa (Supplementary Figure 1, panel B) according to the conventional approach. The best AS and WSS cut-off for detecting these lesions on the CAAS Workstation WSS software were 61.3% and 8.24Pa, respectively.

The time required to reconstruct the coronary segments and perform blood flow simulation in 25 cases that were randomly selected – including 8 cases with side branch – was 23.14±2.56min for the conventional approach and 4.13±0.59min for CAAS Workstation WSS on a standard computer with processor Intel(R) Xeon(R) W-2255 CPU, 3.70GHz, RAM 128Gb.

Reproducibility of the conventional approach and of the CAAS Workstation WSS software

The 1st analyst used the same angiographic projections to perform the 3D-QCA reconstruction and blood flow simulation in 94% of the cases. A high agreement for the selected angiographic projections that were used for 3D-QCA analysis was noted between the 1st and 2nd analyst (90% of the cases).

The intra-observer variability was excellent for both methodologies with regards to 3D-QCA and WSS metrics. Similarly, a high agreement was observed between the estimations of the two experts for 3D-QCA and WSS metrics derived by the conventional approach and CAAS Workstation WSS (Supplementary Table 2-3 and Supplementary Figure 2-3).

DISCUSSION

In this study, we introduced a novel user-friendly software for fast WSS computation and examined its reproducibility and efficacy in assessing WSS distribution. We found that 1) CAAS Workstation WSS software enables 3D-QCA reconstruction and WSS computation within ≈4min allowing its real-time use while the patient is on the catheterisation laboratory, 2) WSS estimations of the CAAS Workstation WSS are in close agreement with the conventional approach, 3) the novel software has good accuracy in identifying lesions that are exposed to an unfavourable haemodynamic environment carrying promise

for detection of vulnerable plaques and high-risk patients and 4) both the conventional approach and novel software are highly reproducible.

Experimental and clinical studies have provided unique insights about the implications of WSS distribution on atherosclerotic disease progression. Low WSS contributes to the formation of vulnerable lesions through mechano-transduction pathways that promote endothelial dysfunction and vascular inflammation [1, 14, 15], while high WSS appear to contribute to plaque destabilization as it induces degradation of the fibrous cap over necrotic core. [16] The clinical implications of these findings have been confirmed by several clinical studies providing convincing evidence that local haemodynamic forces estimated in models reconstructed from fusion of coronary angiography with intravascular imaging data [4, 5, 17], 3D-QCA [9-11] or CTCA [18, 19] can predict plaque progression and future adverse events. Despite these findings, the application of WSS in the clinical arena is limited mainly because of the long time required for vessel reconstruction and blood flow simulation.

The CAAS Workstation WSS software may overcome the above limitation enabling coronary modelling and assessment of WSS distribution in ≈4min which is shorter than the time needed for an FFR study and similar to the time required for computational assessment of FFR using emerging software. [20] This is feasible because of the seamless platform designed for 3D-QCA and CFD analysis, the generation of a less dense and complex computational mesh in the 3D models and the inclusion of the Kratos solver – a package specially developed for blood flow simulation in coronary arteries. These developments constitute a step forward in the field carrying promise for the broad applications of WSS metrics in clinical arena for vulnerable plaque detection and risk stratification.

Validation of this novel software against a conventional approach that has been proven effective in accurately predicting lesions that are likely to progress and cause events [9-11] showed a high agreement between the two approaches for the 3D-QCA metrics and maximum WSS at the lesion site. The moderate ICC (0.73) noted for the AS should be attributed to the different edge detection algorithm and reconstruction methodologies used for 3D-QCA reconstruction, and to the fact that the AS depends not only on the MLA but also on the reference lumen area and the location of MLA within the lesion. Moreover, the included lesions were moderate in severity and thus the range of the measured AS was narrow (30.8-71.3%). Since ICC is a dimensionless value, the outcome changes in agreement with the

dependent variables; a wide range of values generates a high ICC value, whereas a narrow range of values will result in a low ICC. [21, 22] It is reassuring that in this study the CAAS Workstation WSS had good accuracy (78%) in detecting lesions with AS ≥58.6%. Despite the moderate ICC for the AS and the differences in the meshing parameters used in the two approaches, it is promising that the estimations of the CAAS Workstation WSS for the maximum WSS at the lesion site and WSS distribution along the segment of interest were highly correlated to those derived by the conventional approach. More importantly, the novel software had good accuracy in detecting lesions exposed to an unfavourable haemodynamic environment indicating that this approach may be used to identify high-risk lesions and patients. The reported SD of the differences between the estimations of the two approaches was 2.52Pa for the maximum WSS at the lesion site and 2.34Pa across the 3mm segments (Table 1 and Figure 2), and it was similar to the inter-observer variability of the conventional approach for the maximum WSS at the lesion site (2.42Pa) (Supplementary Table 2 and Supplementary Figure 2). When we examined the reproducibility of 3D-QCA and blood flow simulation analyses, we found that the two analysts consistently selected the same views for coronary artery reconstruction. This resulted in a high intra- and inter-observer agreement between the 3D-QCA metrics derived by the QAngio XA 3D RE and the CAAS Workstation WSS, and in a good agreement for the WSS estimations. With regards to the reproducibility of WSS, it should be considered that this variable is highly sensitive to the vessel geometry as it is inversely related to the cube of the radius; therefore, minor changes in lumen dimensions have a significant effect on WSS values. Acknowledging the importance of vessel geometry on WSS estimations and considering the limited efficacy of 3D-QCA in assessing lumen morphology – as it assumes that the lumen has an elliptic shape – we studied the agreement between the two approaches and the reproducibility of the mean WSS in 3mm segments; conversely, we did not investigate other haemodynamic variables used in previous intravascular imaging-based studies such as maximum or minimum predominant WSS [4, 5] or multidirectional indices [23, 24] that may also affect lumen pathobiology, but are very sensitive to minor changes in lumen architecture.

However, despite the limited resolution and the approximations made in the reconstruction of vessel geometry from angiographic data, the mean WSS values in 3-5mm segments seems to provide useful prognostic information in severely stenotic lesions [11], in lesions with vulnerable phenotype assessed

by intravascular imaging [9], and in lesions with borderline negative FFR [10] enabling more accurate identification of high-risk plaques and patients. Therefore, software solutions such as the CAAS Workstation WSS which are fast, user-friendly, accurate, reproducible and can be combined with tools for computational quantification of lesion severity – i.e., the vFFR software [25] – have the potential to allow complete evaluation of lesion physiology with accurate assessment of plaque vulnerability and prediction of future events. Clinical studies are needed to prove this hypothesis before advocating the broad use of such software in clinical practice for risk stratification.

Limitations

A major limitation of the present analysis is the assumptions in blood flow simulation because the blood was assumed to be a Newtonian fluid, the flow was assumed to be steady and the vessel wall to be rigid. These simplifications, however, enabled fast WSS computation in a few minutes rendering this analysis clinically feasible. Conversely, complex simulations requiring detailed reconstructions of vessel architecture can be achieved only with the use of intravascular imaging data.

Moreover, this study examined the agreement of the two approaches for the 3D-QCA indices and the mean WSS in 3mm segments and did not investigate their agreement in assessing multidirectional WSS indices or WSS distribution across the circumference and length of 3D-models. Previous intravascular imaging studies have demonstrated a weak reproducibility of the WSS values in a point-by-point comparison and reports have shown that focal flow patterns are unable to predict plaque evolution. [26, 27] Therefore, the present report focused on a clinically relevant metric – the mean WSS values in 3mm segment – that appears to provide important prognostic information [9, 10].

In addition, this study is a retrospective analysis that included patients with borderline negative FFR lesions. These inclusion criteria are likely to underestimate the reproducibility and agreement of the two approaches, whereas a prospective study is expected to result in optimal angiographic image quality and thus more reproducible delineation of lumen borders. Finally, the inclusion of lesions with a wide range of AS values – and consequently of maximum WSS at the lesion site – is anticipated to result in a higher ICC. [21, 22]

Conclusions

The CAAS Workstation WSS software enables fast, reproducible, and accurate evaluation of WSS distribution and identification of lesions exposed to an unfavourable haemodynamic milieu. Hence, this tool carries the potential to expand the application of WSS metrics in the clinical arena and enable more accurate detection of vulnerable plaques and high-risk patients. Prospective studies are needed to confirm this hypothesis and examine the value of this software in detecting lesions and patients who will benefit from pre-emptive focal or systemic therapies targeting plaque evolution.

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TABLES

Table 1. Intraclass correlation coefficient and mean differences of the estimations of the conventional approach and the CAAS Workstation WSS software.

	Conventional approach	CAAS Workstation WSS	ICC (95%CI)	P value	Mean difference ± SD
Lesion length (mm)	28.8±13.1	32.6±12.8	0.93 (0.90, 0.95)	<0.001	-3.86±4.73
Mean reference lumen area (mm^2)	5.96±2.10	6.20±2.09	0.91 (0.87, 0.94)	<0.001	-0.24±0.88
MLA (mm^2)	2.48±0.90	2.36±0.88	0.93 (0.89, 0.95)	<0.001	0.11±0.34
AS (%)	55.1±11.1	59.7±10.7	0.73 (0.62, 0.81)	<0.001	-4.56±8.42
Maximum WSS (Pa)	10.38±5.49	9.59±4.96	0.88 (0.83, 0.92)	<0.001	0.79±2.52
WSS distribution across the segment of interest (Pa)	5.06±3.93	4.55±3.65	0.81 (0.79, 0.83)	<0.001	0.51±2.34

Table footnote: AS, area stenosis; CI, confidence interval; ICC, intraclass correlation coefficient; MLA, minimum lumen area; SD, standard deviation; WSS, wall shear stress.

FIGURE LEGENDS

Figure 1. CAAS Workstation WSS software allowing real-time 3D-QCA analysis and WSS computation.

Figure 2. Bland-Altman plots comparing the estimations of the conventional approach and the CAAS Workstation WSS software for the MLA (A), AS (B), the maximum WSS at the lesion site (C) and the WSS distribution in 3mm segments (D).

AS, area stenosis; MLA, minimum lumen area; maxWSS, maximum wall shear stress.