Patient-specific prediction of coronary plaque growth from CTA angiography: a multiscale model for plaque formation and progression

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Introduction

Atherosclerotic plaque formation and evolution are a complex biological process where biological signaling and fluidodynamic/biomechanical elements are strictly involved. The comprehension of this relationship becomes fundamental to improve the risk stratification of individual early atherosclerotic plaque in order to personalize the therapeutic strategy. ARTreat provides a framework beyond the state-of-the-art, allowing to build patient-specific multi-scale predictive model of coronary and carotid atherogenesis. The methodology integrates several levels involved in the atherogenesis development: a) the anatomical model of the arterial tree; b) the blood flow model and the molecular/cell model of the arterial wall/blood composition; c) the biological mechanism involved in the generation and growth of atherosclerotic plaque. In-vivo assessment of the local wall shear stress (WSS), extent of vascular inflammation and arterial remodeling response, both responsible for individual plaque evolution may all together improve risk stratification of individual early atherosclerotic plaques. The model is focused on use of a patient-specific computational fluid dynamics (CFD) and mass transfer methods. A 3D model of plaque formation and progression has been tested in a group of ten patients who underwent coronary Computed Tomography angiography (CTA) for anginal symptoms. In each patient, blood tests were performed to measure LDL plasma concentrations. The proof of concept of the model effectiveness was assessed by repetition, with a follow-up of six months, of a new biochemical evaluation and morphological analysis of coronary anatomy by CTA or coronary angiography to check the progression of the coronary lesions. The novelty of this work lies in the acquisition of systemic factors related to atherosclerosis evolution (risk profile, LDL levels), measurements of coronary microcirculatory vasodilating capability, and the systematic verification of model prediction by repeated CTA.

Materials and Methods

Patients at intermediate risk for coronary artery disease (CAD) in whom a coronary CTA demonstrated the presence of atherosclerosis lesions, were enrolled; table 1 shows the patient characteristics. Blood samples for determination of LDL were withdrawn. Coronary CTA was performed with a first standard scanning for calcium score computation and a second scanning during contrast medium infusion for coronary arteries visualization. Volume rendering, multiplanar reformatting reconstruction and vessel analysis were used for the evaluation of atherosclerotic lesions of major coronary vessels. Invasive coronary angiography was performed few days after CTA, to assess the functional meaning of the previously detected coronary lesions. Doppler flow measurements and intravascular ultrasound (IVUS) imaging were performed in segments selected by the CTA images: flow velocity and pressure data from IC Doppler velocimetry were applied to the CTA images of the corresponding segment to calculate patient-specific WSS. Fractional flow reserve (FFR) and coronary flow reserve (CFR) were measured for functional assessment of a coronary stenosis and coronary resistance in steady conditions and after systemic adenosine infusion. The IVUS study was performed to obtain detailed information of atherosclerotic plaques. Invasive coronary angiography and IVUS findings (virtual histology) were used to confirm the degree of the lesions and the plaque components. The 3D blood flow was described by the Navier-Stokes equations, together with the continuity equation. Mass transfer within the blood lumen and through the arterial wall was coupled with the blood flow and was modelled by a convection-diffusion equation. The LDL transports in lumen of the vessel and through the vessel tissue (which has a mass consumption term) was coupled by Kedem-Katchalsky equations. The inflammatory process was modelled using three additional reaction-diffusion partial differential equations. A full 3D patient-specific model was created, including blood flow and LDL concentration, as well as plaque formation and progression. Following a follow-up of six months, a new clinical, biochemical and morphological evaluation of coronary anatomy by CTA have been performed to check the progression of the coronary lesions.

Patient	LDL (mg/dL)	Framingham (%)	Vessel	Basal CT Stenosis (%)	F.U. CT Stenosis (%)	IVUS	FFR	CFR
01	118	18	Mid RCA	45.7	48.3	Mixed	0.96	3.0
02	100	10	Mid LAD	60.0	49.6	Mixed	0.96	N.A.
03	166	25	Dist CX	35.8	48.3	Mixed	0.93	2.0
04	87	12	Mid LAD	34.4	34.4	Mixed	0.96	3.2
05	125	23	Dist CX	33.0	67.0	Soft	0.90	2.3
06	83	15	Mid LAD	30.0	40.0	Soft	N.A.	2.0
07	45	8	Apic LAD	60.3	52.4	Mixed/Soft	0.88	3.3
08	88	15	Mid RCA	34.0	39.5	Soft	1.00	3.2
09	168	22	Dist CX	78.0	Patent stent	Mixed	0.68	1.6
10	154	10	Prox LAD	20.0	60.0	Mixed	0.81	2.0

Table 1. Summary of patient characteristics.

Results and Discussion

Plaque progression occurred in the 2 patients (patient 3 and 5) with the highest Framingham risk score (25 and 23) of the enrolled population, both plaques developed at the inner side of curved (myocardial side) distal circumflex artery segments. Interestingly, only these territories showed an impaired CFR indicative of an impaired coronary vasodilating capability. The greatest plaque growth occurred in a non calcified, eccentric plaque (patient 5). At virtual histology the fibro-fatty component was the prevalent content of this plaque, markedly higher than that observed in the other patients. Baseline WSS values in the progressive lesions (patients 3 and 5) were 0.34 Pa and 0.18 Pa, respectively. These values were lower than those calculated immediately before and after the lesions. Conversely, WSS values in patients with stable plaques averaged 0.42 ± 0.04 Pa and were not lower than values calculated in segments immediately adjacent to the stenoses. Location of the lowest WSS (Fig. 1A and B) in the distal portion of the vessel corresponded to the site of plaque growth after 6 months (Fig. 1C and D). CFD data were used as input for a fitting procedure of volume plaque progression. Oxidized LDL distribution at baseline and follow-up study after 6 months in patient 5 is shown in Fig. 2. It can be observed that after 6 months (Fig. 2B and D) there is a significant increase in LDL distribution distal from the most narrowed part of the lumen domain in the site of lower WSS.

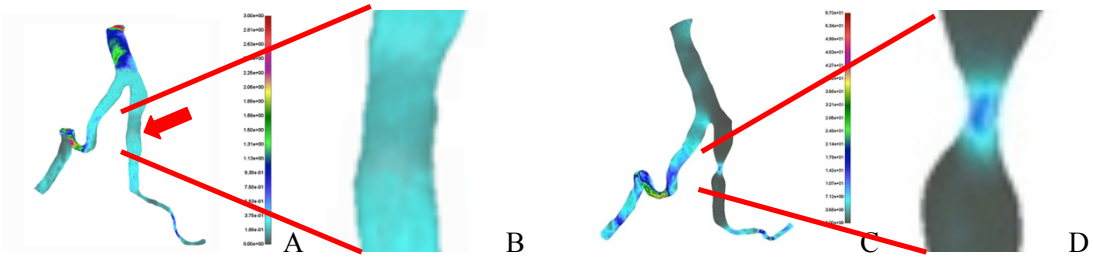

Figure 1. Local shear stress distribution at baseline (A, magnified particular in B) and after 6 months follow-up (C, magnified particular in D) in patient 5. Area with plaque progression at follow-up towards critical stenosis (distal circumflex artery) showed at baseline the lowest shear stress value (red arrow). Wall shear stress values are expressed in [Pa] units.

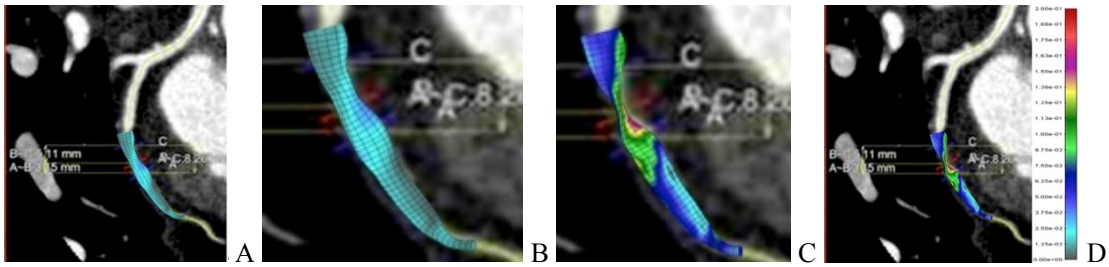

Figure 2. LDL distribution at baseline (A, magnified particular in B) and in the follow-up (C, magnified particular in D) study in the distal circumflex artery with obvious lumen diameter reduction (patient 5). Units for LDL concentration [mg/ml].

Although preliminary, the presented data support the usefulness of CFD and mass transfer approach to 3D reconstructed coronary CTA scans in the evaluation of atherosclerotic plaque burden, potentially shifting the clinical information from morphological assessment towards a functional tool [1]. The worth of this study is the collection of several features (clinical, biological, anatomical, functional) known to be related with coronary plaque formation and progression, that will be tested as predictor of plaque evolution. Impaired CFR, feature not included in plaque models reported in literature, seem interesting features accompanying plaque progression. In particular for CFR, an abnormal value (≤2) was shown to be an independent prognostic indicator of cardiovascular risk. Thus, it is conceivable that coronary vasodilating capability is affecting local WSS values during the daily activity, and that its impact in plaque formation and progression could be much more relevant that baseline flows, usually employed in calculation of WSS by CFD. A main novelty of this work will rely on the existence of a coupling between on the first hand the reaction diffusion equations and age structured model and on the other hand the hemodynamic through the shear stress exerted by the blood flow on the arterial wall. Under a local incompressibility assumption, when foam cells are created, the intima volume is locally increasing [2]. Volume change of the wall affects the fluid lumen domain which means that fully coupling is achieved. This change during plaque progression has a direct influence on the lumen domain and shear stress distribution. Furthermore, the assessment of plaque composition by virtual histology in each patient, providing a degree of accuracy much higher than CTA, allows a better definition of model for plaque progression. Patient-specific local and systemic features, as assessed in this study, can provide insights on the nature of arterial remodeling and, potentially, on plaque vulnerability [3].

Conclusions

Three-dimensional model for plaque formation and growth, coupled with blood flow and LDL concentration in blood has been developed from coronary CTA scans. The model describes the biomolecular process that takes place in the intima during the initiation and the progression of the plaque. Determination of plaque location and composition, and computer simulation of progression in time for a specific patient shows a potential benefit for prediction of disease progression. The proof of validity of 3D reconstructed coronary CTA scans in the evaluation of atherosclerotic plaque burden may shift the clinical information of coronary CTA from morphological assessment towards a functional tool. Although preliminary, this work addresses the relevance of using innovative variables for modeling atherosclerosis, based on “patient-specific” systemic and coronary local determinations, associated to CFD measurements and mass transfer methods merging together macro and micro bioprocesses.

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