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Intracoronary cavitation as a cause of plaque rupture and thrombosis propagation in patients with acute myocardial infarction: A computational study

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ABSTRACT

Background and Objectives: Significant rather than moderate coronary artery stenosis has been postulated to be the main substrate of plaque rupture in acute myocardial infarction (AMI). We evaluate if cavitation could influence the coronary artery plaque rupture contributing to the progression of thrombotic process. **Methods:** We reconstructed a 3D model of the left anterior descending coronary artery (LAD) after reviewing the intravascular ultrasound (IVUS) data of 30 consecutive patients with mild to severe coronary artery disease. **Results:** Turbulent flow or cavitation occurs in both concentric and eccentric coronary artery stenosis (≥ 75% for the former and ≥ 50% for the latter). The analysis of vapor phase demonstrated that cavitation propagated downstream, creating microbubbles, which exploded when the fluid pressure was lower than the vapor pressure at a local thermodynamic state. The relative higher vorticity magnitude (as turbulent flow in vivo angiogram) observed on the distal cap of the atherosclerotic plaque created a higher turbulence, probably able to destabilize the plaque through a micro-erosion process. **Conclusions:** Cavitation seems to be able to promote the thrombotic occlusion within the coronary vessels due the 'constant injuries' created by the micro-explosion of bubbles.

Key words: Atherosclerosis, cavitation, coronary artery disease, plaque

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INTRODUCTION

It is widely believed that acute myocardial infarction (AMI) generally occurs at the site of mild to moderate coronary artery stenosis.[1] Recently, this concept became a matter of speculation because significant rather than moderate coronary artery stenosis has been postulated to be the main substrate of plaque rupture.[2] Unfortunately, the main pathophysiological mechanism underneath the switch from mild to significant stenosis as the main determinant of AMI has not yet been clarified. From a rheological point of view, blood flow turbulences have already been suggested as one of the main causes of plaque formation, growth, rupture and subsequent thrombotic occlusion.[3] However, clinical data in this regard were scant. Conversely, from a physiological point of view, the phenomenon of cavitation, which is well known in the field of ultrasonography, is believed to start the plaque formation, promote its growth, and eventually, trigger its demise by total occlusion of the lumen in experimental models.[4] Cavitation occurs when the pressure in an area of flowing fluid

(blood) decreases to below the level of vapor pressure. This phenomenon could be explained as the result of a large pressure fluctuation seen as and caused by a turbulent flow, which is the essential substrate for the cavitation phenomenon.

The aim of the present study is to demonstrate by computational fluid dynamic (CFD) analysis that cavitation, could influence the coronary artery plaque rupture depending of the degree of local stenosis. The CFD results were validated in-vivo using coronary angiograms in 20 consecutive patients demonstrating the real time turbulent flow across the lesion.

MATERIAL AND METHODS

Patient selection

A virtual 3D model of a coronary artery segment was reconstructed based on the intravascular ultrasound (IVUS) measurements of the left anterior descending coronary artery (LAD) in a series of 30 consecutive patients (19 males, aged 73.8 ± 5.4 years) with mild to severe coronary artery disease (CAD). These patients underwent coronary angiography (CA) and percutaneous coronary interventions (PCI) due to unstable angina within the last 5 years (between January 2013 and December 2017) at our institutions. Subsequently, CA findings of 20 consecutive patients (15 males), observed over 3 months (January 2018–March 2018) with coronary artery lesions ranging from 50% to 75% were reviewed for the in-vivo validation.

All the patients signed the informed consent before the procedure and the local Institutional Boards approved the study.

Demographic data collection

Previous medical history of all the patients was retrospectively reviewed and confirmed by the electronic medical records. Per institution protocol, a fasting venous blood specimen, taken at the registration visit, 7 days before the coronary angiography (CA) was used to determine the serum total cholesterol (TC), triglycerides (TG) and high-density lipoprotein (HDL). LDL-C concentrations were calculated using the Friedewald formula. Body mass index (BMI) was calculated (in kg/m^2) as the ratio of weight to squared height. The subjects were considered to be overweight if the body mass index was between 25 and 29.9 kg/m^2 and obese if ≥ 30 kg/m^2. Patients were labelled as having impaired fasting glucose, if it was between 100 and 125.9 mg/dL, and as diabetic, if it was repeatedly ≥ 126 mg/dL or when having a history of diabetes or treatment with antidiabetic drugs.

Angiography and intra-vascular ultrasound

Quantitative coronary angiographic (QCA) analysis was performed using the edge detection techniques (CAAS II 5.0 version; Pie Medical, Maastricht, Netherlands). Intravascular ultrasound examination (IVUS) was performed following the current guidelines,[5] using the 3 F Opticross coronary IVUS catheter (Boston Scientific, Fremont, CA, USA) and automatic pull-back system. On-line ultrasound assessment was performed in diastole. IVUS images were recorded after administration of 100–200 mg of nitroglycerine. Specifically, the ultrasound catheter was advanced 0.5 mm beyond the lesion and then pulled back to 0.5 mm proximal to the lesion using motorized transducer pullback at 0.5 mm/s. IVUS was performed and interpreted by the treating physician and at least one experienced IVUS technician. QCA and IVUS images were analyzed to obtain the mean diameter and stenosis needed for the reconstruction of the mid-LAD segment.

Review of the dynamic flow in a coronary angiogram.

Each coronary angiogram was reviewed by two investigators. QCA analysis was used to classify lesions as 50% or 75% concentric or eccentric stenosis. The data retrieved included:

Location of the lesion; b) Degree of severity of the lesions (25%, 50%, 75%); c) Types of lesion: concentric or eccentric; d) Types of flow (laminar or turbulent) proximal, at the center of and distal to the lesion; e) Duration of the contrast retention.

Computational fluid analysis

For the computational domain analysis, we considered a hypothetic model of a mid-LAD. Data obtained by QCA and during IVUS were used to build the model using Rhinoceros v. 4.0 Evaluation (McNeel & Associates, Indianapolis, IN). The vessel's size of patients resulted in accordance with the Finnet law in 83.3% of cases (n = 25).

A scale-resolving turbulence model was employed to resolve the turbulent features of the blood flow into the coronary artery. As previously described, blood was modelled as a non-Newtonian, viscous and incompressible fluid. Density was defined as 1060 kg/m^3, according to the standard values cited in the literature. Specifically, the Navier–Stokes equation was adopted to describe the blood flow. Velocity profiles of the blood flow were modelled as previously described to simulate the rheologic conditions of hemodynamically stable patients.[6] Only the diastolic phase, with a mean blood pressure of 80 mmHg (10665 Pa) was considered for the simulation, since the coronary perfusion strictly depends on this part of the cardiac

cycle. A two-phase Euler-Euler flow was simulated with the Volume of Fluid (VoF) method to track the phase's interfaces. Both the equations of conservation of mass and momentum have been solved for the homogeneous mixture of the two continuous phases. Simulation includes an eccentric and a concentric plaque causing an incremental degree of stenosis from 25% to 75% in a straight vessel model.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and were compared with the *t*-test. Categorical variables, presented as percentage, were compared by the Pearson's chi-squared test. A p value of less than 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS statistical software, Version 19.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Patient population

The general characteristics of the patients enrolled to reconstruct the coronary artery model are shown in Table 1. Thirty consecutive patients (19 males, mean age 73.8 ± 5.4 years old) underwent coronary angiogram due unstable angina. A mid-LAD eccentric stenosis of 25%, 50% and 75% were observed in 5, 6 and 5 patients, respectively; while a concentric stenosis of 50% and 75% was detected in 6 and 8 patients, respectively.

The in-vivo group analyzed 20 consecutive patients (15 males, mean age 71.5 ± 3.2) without any significant differences in baseline cardiovascular risk factors with the population used for the CFD analysis. Specifically, 10 patients had a concentric lesion creating a stenosis ranging between 50% to 75%, 5 patients with an eccentric lesion of 50% and 5 patients with an eccentric lesion of 75%.

Table 1: General characteristics of the population

	N = 30
Age (years)	73.8 ± 5.4
Gender (Male) %	19 (63.3)
BMI (kg/m^2)	27.3 ± 5.4
Overweight (%)	12 (40.0)
Obese (%)	11 (36.6)
SBP (mmHg)	138.5 ± 12.4
DBP (mmHg)	74.3 ± 10.8
HR (bpm)	80.2 ± 8.6
TC (mg/dL)	218.4 ± 9.7
TG (mg/dL)	162.3 ± 7.4
HDL (mg/dL)	36.3 ± 15.2
LDL-C	149.6 ± 9.5
IFG (%)	13 (43.3)
Diabetes (%)	8 (26.6)
HT (%)	15 (50.0)
Statins (%)	16 (53.3)
Antiplatelets (%)	8 (26.6)

BMI – Body mass index; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; HR: Heart rate; TC – Total cholesterol; TG – Triglycerides; HDL – High density lipoprotein; LDL – Low density lipoprotein; IGF – Impaired fasting glucose; HT – Arterial hypertension

CFD analysis of eccentric stenosis

The mean value of turbulent kinetic energy (k) at the edge of the plaque with the increase of the stenosis severity from 0.8 ± 0.1 e-01 m^2/s^2, to 1.4 ± 0.2 e-01 m^2/s^2 and 9.10 ± 0.2 e-02 m^2/s^2 for concentric stenosis of 25%, 50% and 75%, respectively, $P < 0.0001$). Similarly, the vorticity magnitude increased with the increase of the stenosis severity ($P < 0.0001$), while the static pressure significantly decreased at the exit edge with the increasing degree severity of the stenosis ($P = 0.001$) (Table 2). Since a pressure decrease and recovery is necessary for the cavitation phenomenon to occur, only in patients with an eccentric stenosis of 75%, this phenomenon was observed. An illustrative example is given in Figure 1.

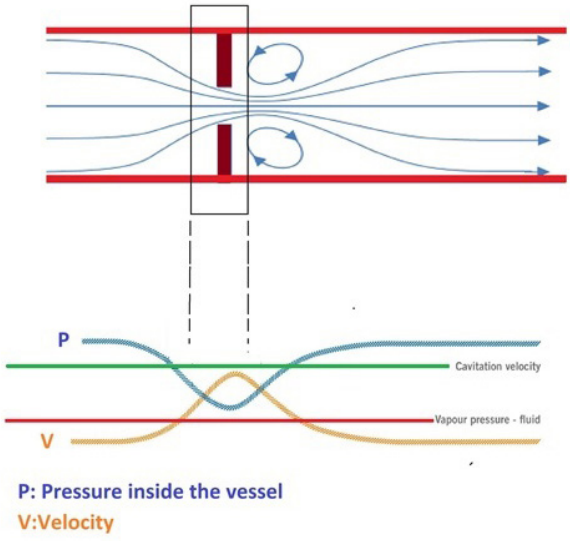

Figure 1: Example of relationship between pressure, velocity and vapor pressure in a hypothetical stenosis of 75% (see text for explanation).

CFD analysis of concentric stenosis

In this type of lesions, the mean value of turbulent kinetic energy (k) at the edge of the plaque was 9.10 ± 0.2 e-02 m^2/s^2 and 16.2 ± 0.1 e-02 m^2/s^2 for concentric stenosis of 50% and 75%, respectively, $P < 0.0001$). Similarly, the vorticity magnitude increased with the increase of the stenosis severity (P for difference 0.0001), while the static pressure decreased significantly as the stenosis became more severe ($P = 0.003$) (Table 3). As expected, from a theoretical point of view, static pressure suddenly dropped at the level of the stenosis, in both cases, and the cavitation occurred (Figure 2). The analysis of the vapor phase demonstrated that cavitation (indicated as phase 2 vapor volume) (Panel

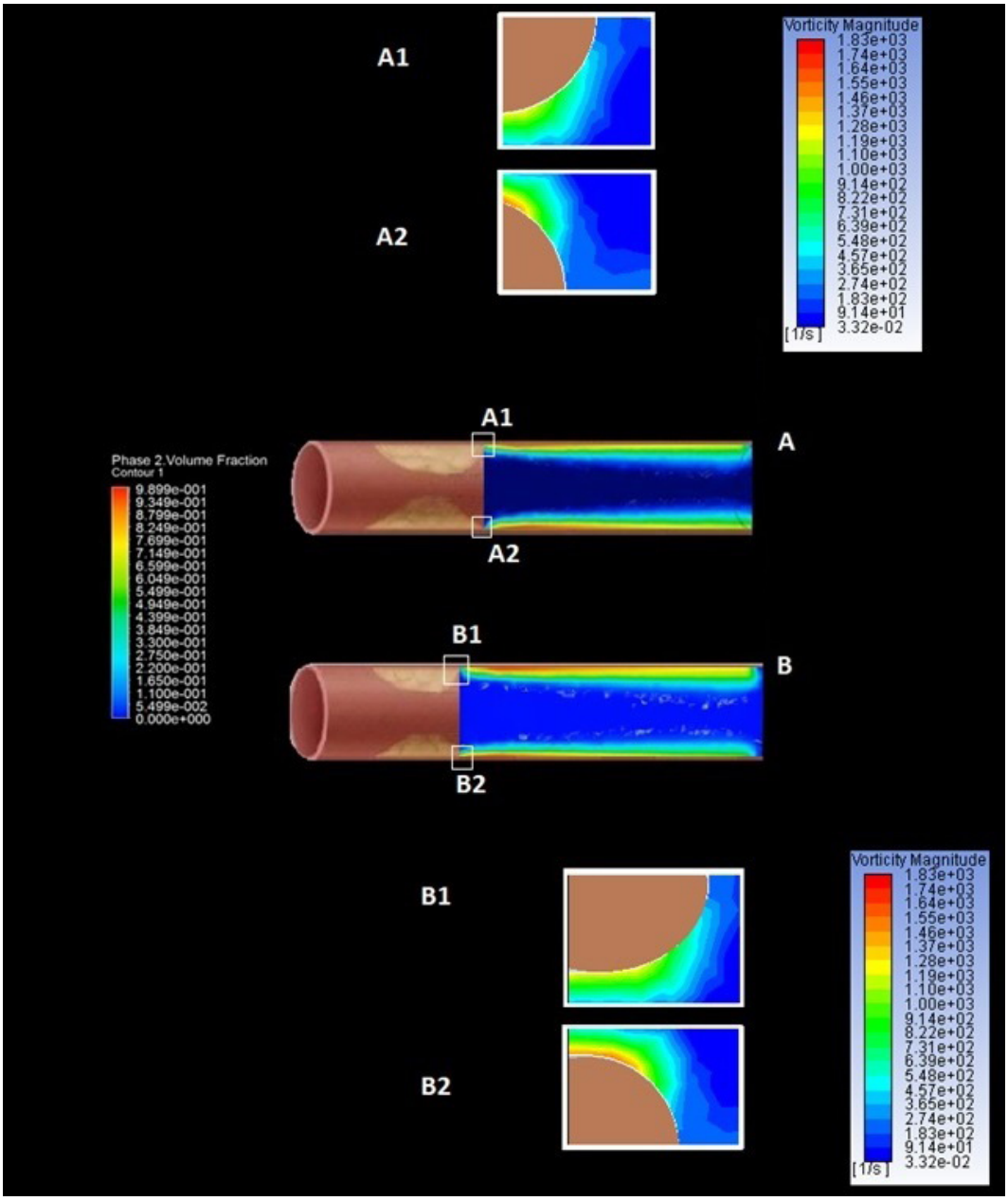

Figure 2: Cavitation and vorticity magnitude (in panels A1-A2 and B1-B2, respectively) in concentric stenosis of 50 and 75%, respectively.

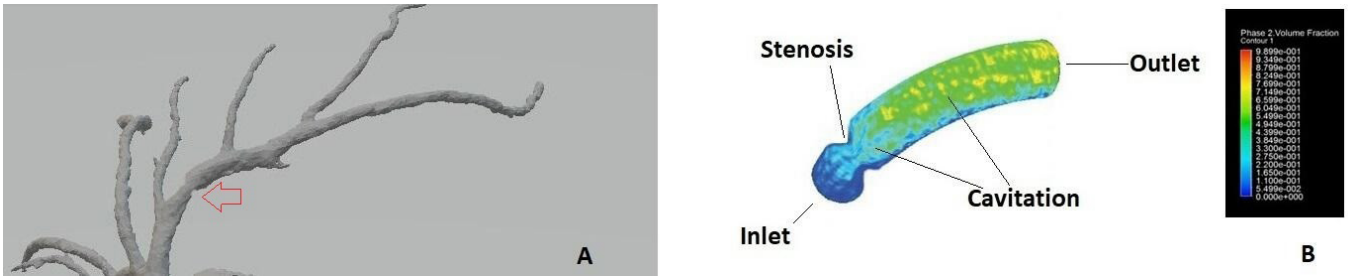

Figure 3: Three-Dimensional reconstruction model of a left coronary artery from a cardiac CT. The stenosis is marked with a red arrow. (B) Demonstration of cavitation in concentric stenosis

Table 2: Rheological properties at the surface of different eccentric stenosis

	25% Eccentric stenosis *N* = 5	50% Eccentric stenosis *N* = 6	75% Eccentric stenosis *N* = 5	*P*
Turbulent kinetic energy (m^2/s^2)	0.8 ± 0.1 e-01	1.4 ± 0.2 e-01	9.10 ± 0.2 e-02	< 0.0001
Vorticity magnitude (1/s)	9.2 ± 0.2 e+01	2.3 ± 0.1 e+02	4.6 ± 0.2 e+02	< 0.0001
Static pressure (Pa)	9.5 ± 0.2 e03	5.3 ± 0.2 e+03	3.1 ± 0.1 e-01	0.001

Pa – Pascal.

Table 3: Rheological properties at the surface of different concentric stenosis

	50% Concentric stenosis *N* = 6	75% Concentric stenosis *N* = 8	*P*
Turbulent kinetic energy (m^2/s^2)	9.10 ± 0.2 e-02	16.2 ± 0.1 e-02	< 0.0001
Vorticity magnitude (1/s)	7.30 ± e+02	9.15 ± e+02	0.0001
Static pressure (Pa)	3.9 ± 0.2 e-01	5.7 ± 0.1 e-01	0.003

Pa – Pascal.

Table 4: Incidence of turbulent flow across the concentric and eccentric lesions

	50% *N* = 5	75% *N* = 5	*P*
Concentric lesion	4 (80%)	5 (100%)	0.32
Eccentric lesion	1 (20%)	5 (100%)	0.03

A and B), propagated downstream, creating microbubbles, which exploded when the fluid pressure was lower than the vapor pressure at a local thermodynamic state. The relative higher vorticity magnitude observed on the distal edge of the atherosclerotic plaque created a higher turbulence, probably destabilized the plaque through a micro-erosion process; while, at the same time, the cavitation phenomenon could propagate the thrombotic process along the vessel (Figure 3).

Analysis of in-vivo hydraulic study

In patients with 50% and 75% concentric stenosis, the flow across the lesion was turbulent in 90% cases (9 out of 10 patients). In patients with 50% eccentric lesions, the flow was mainly laminar, while only 20% of the patients (1 out of 5 patients) showed turbulent flow. If the stenosis was eccentric and of equal or more than 75% stenosis, the flow was turbulent in 100% of cases. (Table 4, Figures 4–5)

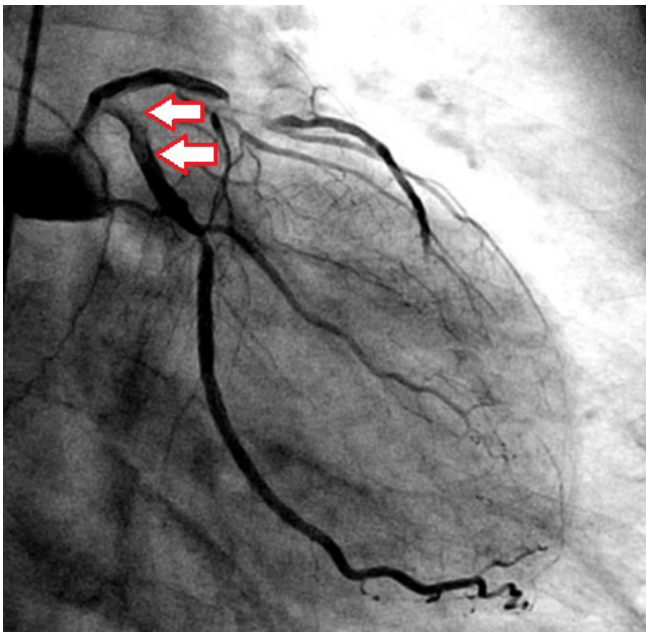

Figure 4: In this right anterior oblique caudal view, the blood moved into the proximal circumflex artery in disorganized fashion (turbulent) with mixing of blood in black contrast and contrast in white (white arrow).

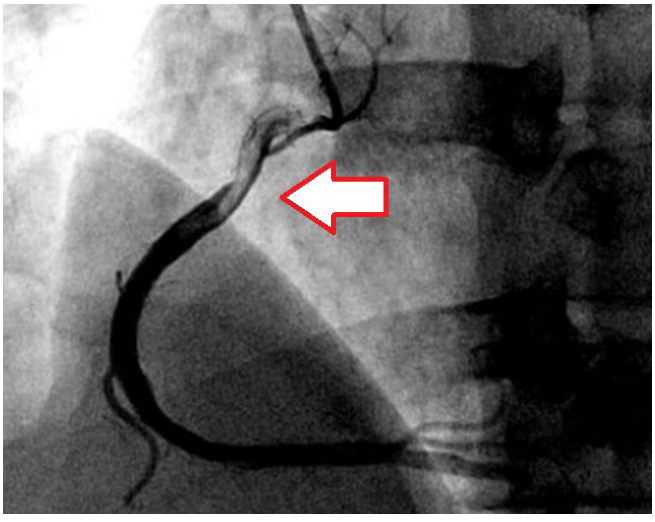

Figure 5: Left anterior oblique caudal view of the coronary artery filled with contrast, the blood moved into the mid right coronary artery in laminar fashion with a pointed tip (arrow).

DISCUSSION

Our computational fluid dynamic study demonstrated that cavitation occurred in coronary artery when a concentric stenosis ranging between 50% to 75% was present. This phenomenon was explained to occur when the fluid pressure was lower than the vapor pressure (to form and grow the bubbles) and recovered to above the vapor pressure inducing a subsequent implosion of bubbles.

In recent years, the interest of cavitation in the field of cardiovascular medicine has grown. Indeed, patients with mechanical heart valves are at higher risk of thromboembolic complications and a possible reason seems to be cavitation.[7] As suggested by our analysis, in vitro studies, using high-speed visualization techniques in transparent fluids, have demonstrated that cavitation occurs only near mechanical valves, but not in biological valves, or native ones. Furthermore, the cavitation bubble implosions can release a significant amount of energy that may impinge on the vessel wall,[8] or the valve, causing potential severe damage to these structures.[9] Moreover, it has been demonstrated in animal models that microbubble due to cavitation are able to cause vessel wall damage in phantom and endothelium lesion of abdominal aorta.[10–11] We believe, based on our results, that this phenomenon could occur also in coronary artery disease having an active role both in the onset and then the progression of thrombotic process in AMI.

In our study, the presence of cavitation, which happened in 75% stenotic lesions, indirectly confirmed the results of recent clinical studies, based on the sophisticated intravascular imaging techniques, that severe stenosis rather than mild or moderate stenosis as the main substrate for triggering plaque rupture and subsequent AMI.[12–13] In addition, this phenomenon could further explain the propagation of thrombotic process along the vessel. A similar concept has been recently suggested by our groups, analyzing coronary artery bifurcation with one or two lesions. In these preliminary reports, cavitation would promote, or even maintain the formation of coronary artery lesions due the 'constant injuries' created by the micro-explosion of bubbles, which break the endothelium, promoting its dysfunction and allowing the infiltration of cholesterol molecules. [14–15]

If confirmed in larger and more sophisticated studies, our findings would suggest that current efforts made in clinical practice to stabilize the atherosclerotic plaque should be revised, especially in those patients with a significant concentric coronary artery lesion. Moreover, cavitation might raise the question about the need of an early stenting approach, also in the presence of a still non-significant lesion, in order to reduce the cavitation and to abolish the local thrombus propagation.

Limitations of the study

Our study has different limitations. Firstly, the design of the study that allowed the enrolment of a relative-small number of patients, which have been used to reconstruct a 3D coronary artery model for the simulation. Secondly, only the diastolic phase, in which the coronary artery perfusion happens, has been considered. The potential presence and role of cavitation in more complex regions, as bifurcation or trifurcation has not been considered and will required future adequate in-vitro analyses. Moreover, the limited period of enrolment of patients of the in-vivo group do not allow the evaluation of concentric stenosis of 25% because no patients with these features were observed over the second study period.

CONCLUSIONS

Cavitation appears to be likely to occur in both concentric and eccentric coronary artery stenosis, 75% for the former and 50% for the latter, respectively. These preliminary in-silico results may link the plaque severity with its rupture. Cavitation seems to be able to promote coronary artery plaque rupture due to the 'constant small injuries' created by the micro-explosion of bubbles. Further studies are needed to confirm our results.

Conflict of Interest

None

Source of Foundation

None

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