TTU Journal of Biomedical Sciences 2024, ***03***:01-04
(RESEARCH ARTICLE) DOI: 10.53901/tjbs.2024.03.art01

Research article

Preliminary Results of a Study Using Dynamic Angiography in Predicting Progression or Regression of Moderate Severity Lesions

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Article history: Manuscript received March 4, 2024; revised manuscript received April 1, 2024; accepted April 9, 2024

ABSTRACT

Background: Many patients with stable angina (SA) having moderate 50% lesions could deteriorate or stay stable for a long time. No present techniques nor test could accurately predict the progression to acute coronary syndrome (ACS) or stabilization of these moderate lesions. Based on the fluid dynamic methodology research, could turbulent flow further damage the plaque and rupture its cap? In contrast, could laminar flow delay the progression of the plaque and keep patients stable for a long period of time?

Methods: Patients with stable angina (SA) were admitted to the intermediate care unit and underwent coronary angiography. Patients were selected if they had a single 50% coronary lesion. The baseline angiographic factors included the flow characteristics: laminar or turbulent, anterograde or retrograde direction, and duration of the turbulent flow across the lesion. The patients were followed up for 2 years. The main clinical endpoints included (A) the development of acute coronary syndrome (ACS), (B) the need for percutaneous coronary interventions (PCI), or (C) persistent stable angina without new clinical or interventional events.

Results: 20 patients with moderate lesions were enrolled and followed up for 2 years. The majority of the lesions (18/20= 90%) were located at the mid-segment of the right coronary artery (RCA) or left anterior descending artery. There were six patients with turbulent flow seen at the lesion. 83% of these patients (5/6) developed ACS regardless of the blood pressure or low-density-lipoprotein (LDL) level. If the patients had laminar flow, with well-controlled HTN (SBP < 130 mmHg) and LDL cholesterol (< 75mg/dL), these patients had NO clinical ACS and event (= 93% 13/14 patients).

Conclusions: The preliminary results of a pilot study with only 20 patients showed that patients with turbulent flow at the location of a moderate lesion progressed to ACS and PCI. The patients with laminar flow across the lesion remained stable without the need for PCI. Larger randomized studies are needed to confirm the above findings.

KEYWORDS Atherosclerosis, dynamic coronary angiography, hemodynamics, fluid mechanics, artificial intelligence, laminar flow, turbulent flow, cavitation, acute coronary syndrome, smoking, lesion progression, lesion regression, coronary artery disease, intensive medical management.

INTRODUCTION

In the care of patients with coronary artery disease (CAD), many patients with moderate 50% coronary lesions could become sicker or stay asymptomatic for a long period of time [1]. No clinical criteria could differentiate the prognosis of these patients. Intravascular ultrasound (IVUS) could predict the rupture of a plaque. However, this technique is time-consuming and costly, and at the same time, it is not affordable nor available everywhere [2]. Doppler flow study and optical coherence tomography (OCT) could not predict whether a moderate lesion would become vulnerable and precipitate acute coronary syndrome (ACS) [3], [4]. Because of the failure of conventional imaging technologies in prognosticating patients with CAD, our team of investigators turns to fluid mechanics (FM) and river engineering (RE) as the main methodology when studying the effect of flow on coronary lesions.

After an extensive search and review of practice by FM or RE engineers were performed, the results were summarized in a fundamental conclusion: Laminar flow protects the lining of pipes, components of pumps, or banks of waterways while turbulent flow damages them [5], [6]. Applying this FM directive to CAD research, our team formulates the strategic question of whether turbulent flow at a coronary lesion further damages the plaque, ruptures its cap, and precipitates the patient into ACS. In contrast, could laminar flow at the lesion preserve the integrity of the endothelial cells layer (or the intima) that line the inside cover of an artery? If so, could the laminar flow also stop the growth of a plaque and perpetuate the stable angina (SA) condition of patients?

In order to identify the detailed images of laminar or turbulent flow, our team redesigned and reprogrammed the current technique of coronary angiography because it could only show the static image of a narrowing on the arterial lumen without identifying the dynamic of the flow proximal or distal to the lesion and interaction of the flow with a narrow luminal diameter at the lesion site [7], [8]. The new recording technique focused on identifying blood flow patterns and analyzing their behaviors by using the same concepts and methodologies of FM or RE when circulating fluid or gas in domestic, industrial pipes or waterways.

In this study, the first goal was to evaluate the efficacy of a new angiographic technique that could identify the characteristics of coronary flow (laminar or turbulent) and quantify the duration of turbulence across the lesion in seconds or milliseconds. The second goal was to correlate the presence of turbulent flow near a lesion with the development of ACS. In contrast, the presence of a laminar flow and no reverse flow were associated with the status quo of the patient's SA.

METHOD

Inclusion and exclusion criteria

Fifty patients who were admitted to the intermediate care unit (IMCU) for stable angina (SA) underwent coronary angiography and were screened for single moderate lesions. The patients were included to the study if their angiogram showed a 50% stenosis in one of the three major coronary arteries. The patients were excluded if they had cigarette smoking, uncontrolled diabetes (HbA1c > 8), or cancer with a life expectancy of < 2 years or the result of the angiogram showed the stenosis less or more than 50% or the lesion in more than one major coronary arteries.

Baseline angiographic risk factor

The baseline angiographic factors to be searched and tabulated were the three flow characteristics proximal, at the middle of and distal to the lesion: structural (laminar or turbulent), directional (antegrade versus retrograde), and temporal (duration of the turbulent flow).

Clinical endpoints

After enrollment, the medical risk factors (hypertension (HTN), diabetes (DM), hyperlipidemia (HLP) were managed optimally with the goals of systolic blood pressure (BP) < 120 mmHg, a fasting low-density lipoprotein (LDL) cholesterol < 75mg/dL and a hemoglobin A1c < 6.4. The patients were followed up every month for the first six months and then every three months for two years at the office to see whether the patients remained stable without the need for percutaneous coronary intervention (PCI) or developed ACS with PCI.

New dynamic angiographic recording technique

At the beginning, the recording started when the contrast was injected until the coronary arteries were completely opacified. As the injection stopped, the camera continued to record the images of the blood in white color moving in. By displacing the contrast in black color, the blood in white could delineate the features of the flow, their structural characteristics, and duration in time. The flow could be either laminar or turbulent, in an anterograde or retrograde direction, short-lived or more prolonged. The coronary angiogram was recorded at 15 images per second, 0.067 seconds (secs) or 67 milliseconds (msecs) per image [7], [8]. Two experienced interventional cardiologists interpreted all the results, and they were blinded by each other while reading the results.

Ethical Standards

All patients signed the informed consent form for participation, and the Institutional Review Board of the University Consortium approved the study.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) for normal distributions or median ± interquartile range (IQR) for non-normal distribution and numbers (percentage) for categorical variables. The *chi*-squared test or Fisher exact test for a small sample size (N < 25) was used to compare the risk of developing ACS/PCI between two turbulent or laminar flow groups. Statistical analysis was performed using the Medcalc software program for

Windows, version 19.9.7. A p value of < 0.05 was considered statistically significant.

RESULT

Twenty of fifty patients admitted to the IMCU met the inclusion criteria and had no follow-up during the two years. These twenty patients were included in the final analysis. Thiry participants were excluded from the study due to mainly either stenosis greater than 60% (N=10) or no stenosis (N=10). At baseline, our participants had an average age of 62 (+/- 14), 30% female, and 60% Caucasian. In terms of comorbidities, 60% had hypertension, 30% had diabetes, and 80% had hyperlipidemia.

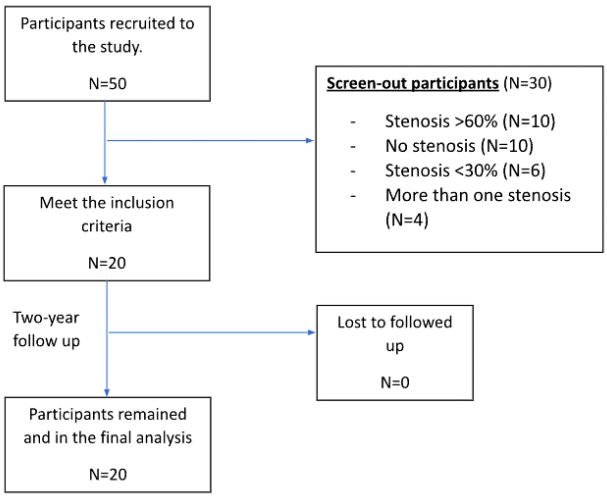

FIGURE 1. Flow chart of the study enrollment.

Regarding the baseline angiographic characteristics, the majority of their lesions (18/20 = 90%) were located at the mid-segment of the right coronary artery (RCA, N = 12) and the end of the proximal segment of the left anterior descending artery (LAD, N = 6) (table 1). There were six patients with turbulent flow due to presence of retrograde flow seen at the lesion site. 83% (5/6) of them developed ACS within six months regardless of the results of blood pressure and LDL cholesterol level. In fourteen patients at baseline with laminar flow at the lesion site, as their blood pressure and LDL cholesterol level were well controlled (SBP < 130 mmHg and LDL < 75mg/dL), at 2 years, these patients remained in SA, had not developed ACS nor required PCI (= 93% 13/14 patients) (table 2). Notably, in this group, only one patient developed ACS during the two-year follow-up (7% vs 83%, p-value = 0.002).

DISCUSSION

The results of this small pilot study of 20 patients with well controlled HTN and HLP showed no progression to ACS if there was laminar flow at the lesion site at baseline. If the flow at the lesion site was turbulent at the beginning of the study, 83% of patients developed ACS regardless of the BP or LDL cholesterol level.

TABLE 1. Baseline Clinical Characteristics.
(RCA: Right coronary artery, LAD: Left anterior descending artery)

	N = 20
Baseline age (mean, SD, year)	36-89 (62 +/- 14)
Gender, Female (N, %)	6 (30%)
Race (N, %)	
- Black	8 (40%)
- White	12 (60%)
Hypertension (N, %)	12 (60%)
Diabetes (N, %)	6 (30%)
Hyperlipidemia (N, %)	18 (90%)
Coronary arteries (N, %)	
- RCA	12 (60%)
- LAD	6 (30%)
Flow structure (N, %)	
- Laminar	14 (70%)
- Turbulent	6 (30%)
+ Anterograde	14 (70%)
+ Retrograde	6 (30%)
Duration of turbulence (Mean, SD, milliseconds)	24.3 (+/- 3.9 msecs)

TABLE 2. Correlation between Flow and Clinical Outcomes.
(ACS: Acute coronary syndrome, PCI: Percutaneous coronary interventions)

		ACS, PCI		
		Yes	No	Total
Flow	Turbulent	5	1	6
	Laminar	1	13	14
Total		6	14	20

Review of Literature

In the literature search, the question written to the search engine was about the correlation between laminar flow and SA or turbulent flow and progression to ACS. The results showed no prior publications on the correlation between laminar or turbulent flow and various clinical presentations of CAD. The absence of publications on laminar or turbulent flow in a clinical context is because this concept is new, and there is no imaging technology to detect the in-vivo laminar or turbulent flow in coronary arteries. Upon further literature search, there were only reviews of wall shear stress (WSS) on atherosclerosis, AND optical coherence tomography (OCT) intravascular ultrasound (IVUS) on coronary plaque [9], [10].

In the first review published by the Journal of the American Heart Association, Stefanadis C et al. re-confirmed that endothelial WSS was the main flow-related factor affecting the distribution of atherosclerosis in a bifurcation. Plaques were more prevalent in low WSS areas and less common in the area with high WSS. This is an important concept of the effect of WSS on atherosclerosis however since its discovery in 1969, WSS did not advance further in solving the mechanism starting and promoting atherosclerosis [11]. The reason is that WSS was measured only in in-vitro or animal studies and the results were translated to human arteries. There is no in vivo test to measure the WSS in patients with CAD so the effect of WSS on the formation and progression of coronary plaque are purely theoretical and speculative.

In the second article on the USC Cardiology, Petrossian G

et al reviewed the role of intracoronary imaging in ACS and highlighted the superior visualization of the culprit plaques by OCT and IVUS compared with conventional coronary angiography. This paper is important in identifying the stable versus unstable plaque [10]. However, the techniques are costly, time consuming and not affordable at every cardiac catheterization laboratory in the world.

Even OCT and IVUS provide a detailed image, both could only provide the static image of a plaque which is a passive interpretation of an arterial phenomenon looking quiescent on its surfaces. In fact, the dynamics of the flow proximal, at the center and distal to the stenotic site is complex and produces various layers of flow which are either laminar, recirculating, turbulent at different speeds based on the Bernoulli principles, by the centrifugal forces or following the Coriolis effects, etc [12]-[14]. OCT or IVUS could not detect none of the above flow movements while the Doppler flow study could only show the basic direction of the flow from one location at a time and not simultaneously at both proximal and distal locations of a coronary artery as the new dynamic coronary angiography could. These are the catastrophic limitations of the current coronary imaging techniques.

What could the new dynamic angiogram show?

Besides a sharp image of a stenosis, the new dynamic angiography could show the various characteristics of a flow from the ostium of the index artery, proximal to the lesion, across the lesion and immediately distal to the lesion. Besides the structural form of the flow (laminar or turbulent) the new angiographic technique could confirm the direction (antegrade and retrograde), and the location where the flow hits the plaque (angle of attack) and the indwelling duration of these flows in secs or msecs (transient or prolonged) [15].

What are the clinical implications and limitations?

In this study, the preliminary results showed that SA patients with turbulent flow at their lesion progressed to ACS with PCI. The SA patients who stayed in status quo without worsening of clinical symptoms had laminar flow in their lesions. These results were preliminary and our pilot study has limited sample size. Therefore, the result could be biased. However, the result could be potentially used to expand the study at a larger size.

CONCLUSION

The preliminary results of pilot study showed turbulent flow at the location of moderate lesion might promote progression to severe stenosis and development of ACS. In contrast, laminar flow might keep the lesion stable and non progressing. Large studies are need to confirm the above findings.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

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