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Review article

Annotated Bibliography on the Mechanism Starting and Sustaining Atherosclerosis

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ABSTRACT

Background: In the past 30 years, there has been a significant rise in coronary artery disease (CAD) and atherosclerosis, primarily attributed to dietary changes toward cholesterol-rich fast foods. Traditional research methodologies focusing on molecular biology have been insufficient in fully understanding the initiation mechanisms of these conditions. This paper reviews the literature and defines the knowledge gap for the need for a new dynamic coronary angiographic technique.

Methods: Our approach involved a comprehensive review of fluid mechanics literature to identify gaps in current CAD research. This included analyzing major works from standard physiology textbooks, fluid mechanics reviews, and bioengineering journals. The study also introduced a new technique, "Dynamic Coronary Angiography," aimed at identifying and analyzing blood flow characteristics in coronary arteries using the principles and practices of fluid dynamics.

Results: The literature review highlighted the pulsatile nature of coronary blood flow and the importance of wall shear stress (WSS) in the development of atherosclerosis. However, existing research showed limitations such as reduced applicability of animal model data to human pathophysiology and simplistic experimental designs. The new angiographic technique revealed various flow patterns in cardiac cycle phases, including laminar, turbulent, and retrograde flows, and their possible impacts on the arterial wall.

Conclusions: Our findings suggest that turbulent flow may be critical in initiating atherosclerosis by damaging endothelial cells. This new perspective on the role of blood flow dynamics in CAD provides a promising avenue for understanding plaque formation and growth, potentially leading to significant advancements in cardiovascular medicine.

KEYWORDS Coronary collision, dynamic coronary angiography, laminar flow, turbulent flow, water hammer shock, antegrade coronary flow, retrograde coronary flow.

INTRODUCTION

In the past 30 years, due to the change in dietary consumption from traditional home-cooked meals to cholesterol-packed ready take-out foods, coronary artery disease (CAD) has become the dominant cardiovascular problem in the world [1]. As a result, tremendous resources and manpower were dedicated to the search for the mechanisms that initiate CAD or atherosclerosis and the continuing injuries that sustain them. Even so, up to recently, the majority of outcomes from research protocols that relied on molecular biology and non-invasive imaging were inconclusive [2]. This was why our research team changed tactics and decided to use fluid mechanics (FM) or river engineering (RE) as the first main method when investigating flow in arteries [3].

FM or RE may be the most promising approach for solving or better understanding this problem because the cardiovascular (CV) system is, in reality, a complex network of joining pipes and pumps or natural and man-made waterways. As the CV system seems to function optimally and efficiently by itself, it likely follows the best principles and practices of FM and RE as dictated by the laws of nature. Even so, damage by mechanical erosions or chemically active material deposits could be seen frequently along the river banks or lining the inside cover of pipes or components of pumps [4]. Based on these observations in FM and RE, our investigators hypothesized that the factors triggering and sustaining CAD or atherosclerosis most likely follow the same mechanisms of injuries inflicting damages, stimulating changes, and enforcing corrective measures in pipes, pumps, or waterways.

Before embarking on this new tactical path, our team conducted a feasibility study with a comprehensive review of publications on arterial flows from the FM literature. Within the context of an annotated bibliography, this review aims to identify the relations, contradictions, gaps, and inconsistencies in the current research on the start or growth of CAD or atherosclerosis. Based on the results of this literature search, our team would assess whether a new type of coronary angiographic technique is needed so it could be able to identify the mechanisms of the injuries that trigger and sustain the atherosclerotic cascade.

SELECTION OF REFERENCES

In reviewing current literature on coronary dynamics, the first two major references are the chapter Coronary Circulation and Ischemic Heart Disease by John Hall and Michael Hall, from Guyton and Hall Textbook of Medical Physiology published by Elsevier, Amsterdam, Netherlands. The article "Blood Flow in Arteries" by David Ku was published in the Annual Review of Fluid Mechanics [5], [6]. The Coronary Circulation chapter is selected because Guyton Medical Physiology is currently the standard physiology textbook in medical schools. The chapter's contents, discussions, and references reflect the current understandings, accepted interpretations, and relevant applications on coronary flow by the medical and scientific community [5]. The second major reference, the article "Blood Flow in Arteries", is selected because it is similarly important to assess the relevant bench studies of arterial flow from a fluid dynamic perspective [6].

The second set of selected references includes the three major animal studies that provide the basis of current medical knowledge on the effects of coronary flow or development of CAD [7]-[9]. The third set of references addresses the biomechanical stress in coronary atherosclerosis from computational modeling [10]-[12].

These studies' strengths and weaknesses and methodology will be assessed thoroughly and reported. Then, our team will review a paper introducing a new modified angiographic technique that could show in detail the antegrade, retrograde flow, and collision [13]. This new technique could be most likely a game changer for the investigation of blood flow in arteries, so future research protocols could be planned with a higher probability of success [14].

ANNOTATED BIBLIOGRAPHY

General concept

In reviewing the first reference, J Hall and M Hall summarized all current relevant understandings of coronary circulation in one short paragraph. The coronary blood moves in an antegrade direction with most flow volume in diastole, while two-thirds reduce the flow volume during systole. This flow is pulsatile, meaning that the blood moves intermittently due to a rhythmic increase and decrease of pressure and not on a constant or smooth propagation of a continuous laminar flow [5]. The above observations were extrapolated from major fluid mechanics studies performed in dogs; however, they could not elaborate nor speculate further on the effects of different coronary flow dynamics on human arteries nor their role in developing CAD or atherosclerosis.

In the second reference, Ku's article "Blood Flow in Arteries" analyzed the scientific evidence. It explained the mechanism of antegrade and retrograde flow, the measurement, and the possible effects of wall shear stress (WSS) on atherosclerosis. This review offered the most comprehensive data analysis of all the relevant studies, including the important ones cited in the chapter of Hall et al. [6].

While both groups of authors, Hall and Ku, agree on the large pulsatile antegrade flow volume in diastole and a lesser flow volume during systole, the most surprising detail is what J. and M. Hall failed to mention in their textbook: Retrograde flow and WSS. In contrast, Ku discussed these two subjects extensively. Why was there such a discrepancy? To elucidate this problem, the important contributions and weaknesses of the next two references on WSS and retrograde flow are to be assessed below.

Wall shear stress

In the first publication of the second set of references, Adel Malek et al.'s review "Hemodynamic Shear Stress and Its Role in Atherosclerosis" summarized the possible mechanism of atherosclerosis from a fluid mechanic perspective [7]. WSS is the frictional force exerted on the wall by the flowing blood. WSS is proportional to the viscosity and flow speed and inversely proportional to the third power of the luminal radius. As a result of damage by this frictional force, plaques were found in locations where the WSS was low. This information comes from a study, the fourth reference below [7].

The second paper by John Moore et al. examined the measured WSS in a bench study on a mounted cadaveric human abdominal aorta. It showed that oscillatory WSS behavior and relationship were associated with atherosclerotic plaque in the lower aorta [8]. Based on this study, low WSS is considered the cause of atherosclerosis. However, this study could show only a high statistical association between low WSS and plaques upon further scrutiny. It could not ever prove the cause-effect relationship between WSS and the start of atherosclerotic plaques [8].

The third reference is a paper published by Watts Webb et al., who showed the presence of retrograde flow in coronary arteries [9]. This is a study done on patients during open-chest bypass surgery. Cannulation by plastic catheter through the arteriotomy site distal to the stenosis and connection to a transducer allowed pressure measurement in vivo. This measurement also found the presence of retrograde flow. However, there was no further in-vivo study investigating the causes, changes, or effects of these retrograde flows in patients with all levels of lesion severity [9].

Imaging and Computational Modelling

In a first review by Thondapu V et al. from the third set of references published in the European Heart Journal, the main conclusion is that low wall shear stress (WSS) plays a pivotal role in the initiation and progression of atheroma. This paper highlights the importance of identifying novel markers for plaque vulnerability and the role of advanced computational methods in enhancing the detection of future culprit lesions in cardiovascular disease. There are challenges in using WSS and other imaging-based computational methods to predict plaque progression and identify high-risk plaques. Despite promising correlations, the specificity of WSS measurements for predicting clinically significant plaque progression is limited [10].

The second study by Toth PP in the 3rd set of references explores the dynamic process of atherosclerotic plaque development and its pivotal role in the onset of myocardial infarctions. Noninvasive coronary computed tomography angiography (CTA) scans demonstrated that plaques showing no significant volumetric increase over time seldom precipitate coronary events, irrespective of the degree of luminal narrowing or the presence of high-risk plaque characteristics at the outset. Such findings underscore the concept that plaque progression is an essential precursor to the eventual rupture leading to myocardial infarction [11].

In the third study of the 3rd set of references, Zuin M et al. investigated the relationship between helical flow (HF) and WSS in coronary arteries and their collective influence on atherosclerotic plaque initiation and progression. Computational fluid dynamics (CFD) simulations, informed by pig-specific in vivo Doppler blood flow measurements and reconstructed arterial geometries, quantified HF and WSS descriptors. The findings demonstrated a strong positive correlation between HF intensity and WSS magnitude, with high levels of HF intensity at baseline associated with significantly lower growth of wall thickness (WT) in coronary segments. These results highlight the physiological significance of intravascular hemodynamics by CFD simulations [12].

New Dynamic Coronary Angiography

Currently, conventional coronary angiography focuses on the static image of a narrowing in the arterial channel without identifying the mechanism of the disease nor predicting its progression or regression. To overcome this deficiency, our team took a disruptive approach by modifying the conventional recording technique when filming the coronary artery images. This new dynamic approach identifies flows' various characteristics: movements and changes. As a result, based on the same concepts and experiences by fluid dynamic engineers when investigating the damages in pipes and pumps, our team searches for similar phenomena that may damage the innermost cell layers of a coronary artery and start the atherosclerotic process.

In this first paper of the 4th set of references, the "New Techniques of Recording and Interpretation of Dynamic Coronary Angiography" by Nguyen T. et al. [13], this new technique focuses on the identification of blood flow patterns and analysis of their normal or abnormal dynamics by adapting the same methodologies used by hydraulics engineers when moving fluid or gas through residential or industrial pipes or pumps. During the recording, the camera is positioned at an angle that could record the index artery and vein at full length, with all the images completely visible within the screen. The appropriate views need to be selected so all movements of the blood (and contrast) can be identified accurately on a clean background of the lungs. The selected angles circumvent superimposing the arteriograms or venograms on the bony structures of the spine or the myocardium filled with contrast at the end of the arterial phase and during the venous phase. With this new technique of filming the images of coronary arteries, new flow characteristics may be discovered and help explain the effects of blood flow in arteries [13].

In the second paper of the 4th group of references, the article "Questions on the Genesis and Growth of Coronary Lesions and their Answers Based on Fluid Mechanics Engineering: A New Dynamic Angiography Analysis" of Thach Nguyen et al. published in the TTU Journal of Biomedical Sciences, the authors used a new technique to record and review coronary angiogram. As a result, various types of flows, such as laminar, turbulent, entrance flow, antegrade, and retrograde flow, could be visualized and analyzed in detail during systole, diastole, collision, and recirculation [14].

Strengths and Weaknesses of Studies in Fluid Dynamics

While the studies discussed by Ku and Malek offered valuable information, they were limited because they were primarily done in animals, and the data extrapolated to human pathophysiology. In these experiments, the study animals were either healthy or did not have co-morbidities in lungs, liver, or kidney diseases as in the majority of patients with CAD. As a result, the studies could only allow the extrapolation of data by weak statistical associations.

The second weakness of these studies is that the data could not be repeated in multiple experiments and on a large scale. The reason is due to limited resources as the number of animal studies and the number of animals in each study were limited. This is in contrast to the today's studies with interventional cardiology devices, the data were taken directly from the patients, in multiple instances and at multiple time frames. In these studies, the consistency of the results would guarantee their validity, and the differences in the results would require various interpretations of mechanisms.

The third weakness of these bench studies was their lack of complexities and sophistication in designs and results. The development of atherosclerotic plaques is a complex process that includes multiple pathways that can change based on different anatomical structures and combinations (straight, curved, at bifurcation, etc.) and at different time frames (beginning, at early stage or the end, etc.). The mechanism of atherosclerosis also depends on the composition of the blood (the level of LDL cholesterol molecules) and the level of local and distal blood pressure. Within the complexities of multiple pathological processes, a small number of animal studies could not showcase all the pathways leading to the formation of atherosclerotic plaques in human arteries.

Based on failures from prior studies, as our team continues the use of fluid dynamic methodology in the search for the mechanism of atherosclerosis, our team needs to modify or upgrade the current technique of recording the coronary images so new insights can be reached [15], [16].

CONCLUSION

In the study of CAD or atherosclerosis, plaque formation and development mechanism is still the subject of continuing debate. The new technique of recording and interpreting coronary angiography helps identify different flow patterns in arteries. Applying the FM and RE principles to the coronary system suggests that the mechanism of the first injury is most likely due to repetitive turbulent flow. The recurrent uncontrolled pressure surges inflict injuries to the intima, trigger the birth of a small lesion, and promote its growth. When the lesion grows faster due to the ample amount of available circulating LDL cholesterol molecules in the blood, there is not enough time for its soft cap to harden or become calcified in the event of uncontrolled hypertension, which exaggerates the repetitive pounding by the water hammer; the cap breaks. This is the most likely pathological mechanism precipitating acute coronary syndrome, ST-elevation myocardial infarction, critical limb ischemia, transient ischemic attack, stroke, etc. This new method of recording and reviewing coronary dynamic flows and their clinical corollaries will usher in a new era of crucial insights and applications regarding the diagnosis, medical, surgical, and interventional management of CAD or atherosclerosis.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

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