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Challenges of the 21st Century: Part 4 - Interventional Anatomy: a case-based discussion

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SUMMARY

Dynamic coronary angiography applies the principles of hydraulics to blood flow and examines the relationship between anatomical structure of the artery and fluid mechanics. Both normal anatomy and anatomic variation in the coronary arteries change blood flow, and can produce an environment favorable for cavitation phenomenon and the development of coronary lesions. Thus, the anatomy of the coronary arteries in a patient can be used as a predicative factor (i.e., predictive anatomy) of where lesion formation will occur. Anatomical preservation by medicine, or restoration of natural anatomy by advance anatomical intervention, restores laminar flow patterns and lessens the chances for vessel injury. This novel model presented in this manuscript symposium represents a new and provocative way of thinking for anatomists and cardiologists, and demonstrates how anatomy research continues to be important in the modern era.

Key words: Anatomy – Anatomical preservation – Anatomical restoration – Coronary artery

ABBREVIATIONS

Acute Myocardial Infarction (AMI)

Aspirin (ASA)

Beta-blockers (BB)

Blood Pressure (BP)

Cerebral Vascular Accident (CVA)

Coronary Angiogram(s) (CAG/CAGs)

Coronary Artery Bypass Surgery (CABG)

Coronary artery Disease (CAD)

Diabetes Mellitus (DM)

Hypertension (HTN)

Left Anterior Descending Artery (LAD)

Left Circumflex Artery (LCX)

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Left Main Coronary Artery (LM)

Low Density Lipoprotein (LDL)

Percutaneous Coronary Intervention (PCI)

Peripheral Arterial Disease (PAD)

INTRODUCTION

Thus far in this manuscript symposium, the authors have (1) discussed the challenges of diagnostic, prognostic and interventional anatomy in the modern era; (2) presented a novel and groundbreaking approach to examine coronary lesions based on the relationship between anatomical structure and fluid mechanics; and (3) correlated injuries caused by flow anomalies with formation of lesions and then used principles of fluid mechanics to explain the anatomical/structural cause-effect mechanism and future risks.

From an anatomical perspective, there are many patterns of variation in the coronary arteries (Moore et al., 2018; Anbumani, et al., 2016; Bhimalli et al., 2011; Ortale et al., 2005; Fazliogullari et al., 2010; Nguyen and Talarico, 2018; Ballesteros et al., 2011; Kalpana, 2003; Ortale et al., 2004; Nguyen and Talarico, 2019). In cardiology, the coronary arteries are considered normal or of normal variations if they are long, short, curved, or straight, etc. If the arteries are within the 90% of these extremes, then the artery is considered to be normal or normal variations. However, anatomical variations coronary arteries could lead to pathological problems. Results in Part 3 of this symposium showed how the anatomy/geometry of coronary arteries affects flow dynamics and could be used to predict where lesions would form (i.e., predictive anatomy). Even further, it was suggested that these results applied not only to the coronary arterial system, but to the peripheral arteries, as well. This leads anatomists and cardiologist to an intriguing question: Does restoration of the *anatomy* restore the function? This is the question that will be examined in this, the final article, of this symposium. The approach taken herein is a case-based format, where each situation (or condition) is illustrated with a real-life problem.

What is the ultimate goal of guideline directed medical therapy (GDMT) or mechanical interventions in coronary and peripheral arterial disease? The ultimate goal is to preserve or restore the original anatomy in order to maintain optimal function. For example, in a specific situation, what does Aspirin (ASA) do to the coronary artery? ASA helps to keep the lumen of the artery constantly open, without encroachment of the lumen by the platelet rich white thrombus. Thus, the blood flow is "controlled" secondary to the principles of fluid dynamics because the lumen (i.e., the anatomy) is restored to normal as possible. In another example, it can be asked, "What does a statin do to the coronary artery?" Statins, also known as HMG-CoA reductase inhibitors, are a class of lipid-lowering medications that reduce illness and mortality in those who are at high risk of coronary artery disease (CAD). By lowering cholesterol levels in the blood, statins prevent enlargement of a plaque encroaching the lumen of the artery. Similarly, what does a stenting procedure do to a patient? A stent is a tiny tube that is inserted into a blocked passageway and expanded in order to keep it open. The stent restores the flow of blood where it is placed. Thus, stenting restores the natural anatomy of a coronary lumen in order for the artery to fulfill its function of channeling blood to the distal myocardium.

Image Research Depository. The complete database of images used in the development of this novel model and in this research investigation has been established at DIGITAL ACCESS to SCHOLARSHIP at Harvard Library, Office for Scholarly Communication (https://dash.harvard.edu/). Readers are invited to explore, and to comment and discuss.

ANATOMICAL PRESERVATION BY MEDICINE

In the care of patients with confirmed CAD, three important medications are included in the GDMT: ASA, statin and beta blockers (BB). The role of ASA is to block the formation of thromboxane which is responsible for the aggregation of platelets. Its main role in all patients with proven CAD (secondary prevention) is to prevent the formation of a platelet rich white thrombus in the first phase

of the coagulation cascade. Is there a role of ASA in primary prevention based on the new discoveries on turbulent flow or boundary or separation layers discussed in this symposium? What is the indication of ASA in asymptomatic patients with aneurysmal coronary arteries? For betablockers and statin, what are their interference in turbulent flow, collision line, reversed flow and laminar flow? The answers to the above questions will be discussed in this article.

Antiplatelet Therapy in Coronary Artery Disease

Physicians and scientists do not question the efficacy of ASA in patients with proven CAD, after percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). However, in asymptomatic patients without any history of CAD, peripheral arterial disease (PAD), or stroke, is ASA effective in primary prevention?

Based on the incidence of turbulent flow and presence of boundary layers at the borders, it is reasonable to suggest that ASA may help to prevent the aggregation of platelet without changing the disease process. In patients with hypertension (HTN), if the blood pressure (BP) is well controlled, the chance of acute myocardial infarction (AMI) and cerebral vascular accident (CVA) will be much lower. The benefits come from a lower BP and rate of rise (which is defined as the change of pressure over time, or dp/dt) creating an attenuated collision due to a weaker reversed systolic flow. If the collision was weaker in a coronary artery, then there is lower incidence of AMI. If the collision is weaker in the carotid or mid-cerebral artery, then there is lower incidence of CVA. If weaker collision happens in the iliac or femoral artery, then the incidence of PAD would be lower. ASA would not change the profile of AMI, CVA, PAD if blood pressure is elevated. HTN puts an extra strain on all the blood vessels in the body. This can make a AMI, CVA and PAD more likely, because HTN damages blood vessels and makes them become stiffer and more narrow (Hörnsten et al., 2016; Gaciong et al., 2013).

In case of smoking, uncontrolled diabetes (DM), old age, infection, or recent surgery, the patients may have thick boundary layer due to high viscosity. These thick boundary layers caused mild damage to the intima, mostly as a weaker version of cavitation. The coronary angiograms (CAGs) of these patients showed multiple minimal to mild diffuse lesions along the arterial wall (Fig. 1). The reason for no severe lesion is speculated because of the absence of repeated shock waves from cavitation. Thus, with the presence of multiple diffuse minimal to mild lesions, the use of ASA may be beneficial for this high risk group of patients.

ASA for Aneurysmal Artery

In a huge artery, the flow could be turbulent and creates intertwining areas of high or low

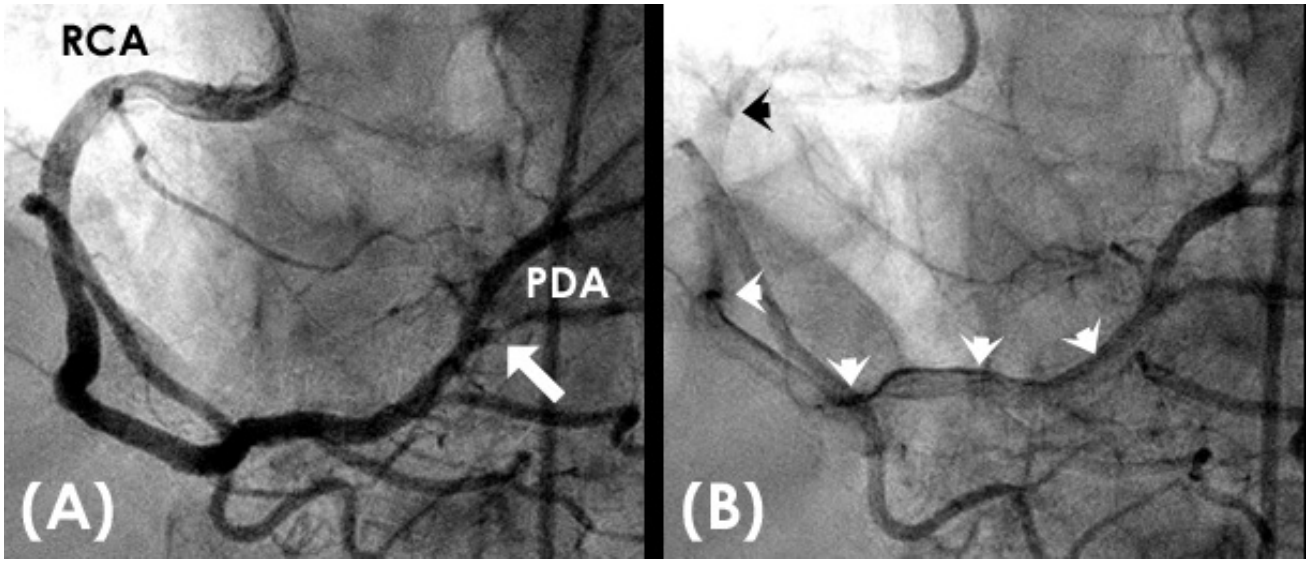

Fig. 1.- Right Coronary Artery Angiogram. **(A)** This was the right coronary artery (RCA) CAG of a patient with uncontrolled diabetes, smoking and high level of low-density lipoprotein (LDL)-cholesterol. Her troponin level was high. There was a severe lesion in a posterior descending artery (PDA) branch (arrow). **(B)** There was a moderately thick boundary layer along the inner curve due to high viscosity of the blood (short arrows).

pressure favorable for the bubbles to rupture if they venture between these areas (i.e., the cavitation phenomenon) (Fig. 2). Because of many areas with recirculation and stagnant flow, the probability of thrombotic formation is high, ASA is used to prevent the formation of the thrombi. If the patient developed recurrent chest pain and elevated cardiac enzyme level, in spite of ASA, full dose of anticoagulation with new oral anticoagulant drugs is suggested (Su et al., 2014).

Preservation of the Natural Lumen by Statin

In patients with CAD, statins lower the low density lipoprotein (LDL) cholesterol level and prevent more acute myocardial infarction than PCI (Boden et al., 2007). Statin prevents the growth of the cholesterol plaques which encroach the arterial lumen. Consider the case of a 70-year-old, male patient having PCI of the proximal LAD. CAG documented that the distal RCA had a fairly significant lesion (Fig. 3). Because the patient was asymptomatic, he declined any intervention. The patient was on statin, BB and ASA. A recent echocardiography showed normal function of the inferior wall in the 2-chamber view. Statin and ASA preserved the arterial lumen (i.e., the anatomy), and this is why the patient was asymptomatic.

The Effects of Betablockade

In general, betablockade was associated with lower mortality in patients with anterior wall infarction (3.9% vs 13.4%, $p < 0.0001$) whereas nonsignificant benefits were observed in nonanterior wall infarct location (2.0% vs 3.3%, p = NS) (De Luca et al. 2005). Applying the novel model of this symposium, some interesting questions arise. What was the exact mechanism of this benefit? Could bradycardia caused by BB offer the protection to the coronary arteries? Was the speed in the coronary arteries slower with BB so that the BB offered protection from plaque rupture? Below, selections of images are reviewed showing the size of the artery, the speed of the coronary flow and the extent of the recirculation flow after a bifurcation are presented in patients after treatment with BB.

Vasoconstriction. In 2011, a patient with PCI of the LAD, the LAD showed a diameter >2 mm in the left anterior oblique cranial view, after PCI. In 2019, the same patient now on BB underwent PCI of the left circumflex (LCX), and a diagnostic CAG of the LAD was performed (Fig. 4). Compared with the angiogram of 2011, the diameter of the LAD was smaller. Because BB caused distal vasoconstriction, BB could provide an anatomy

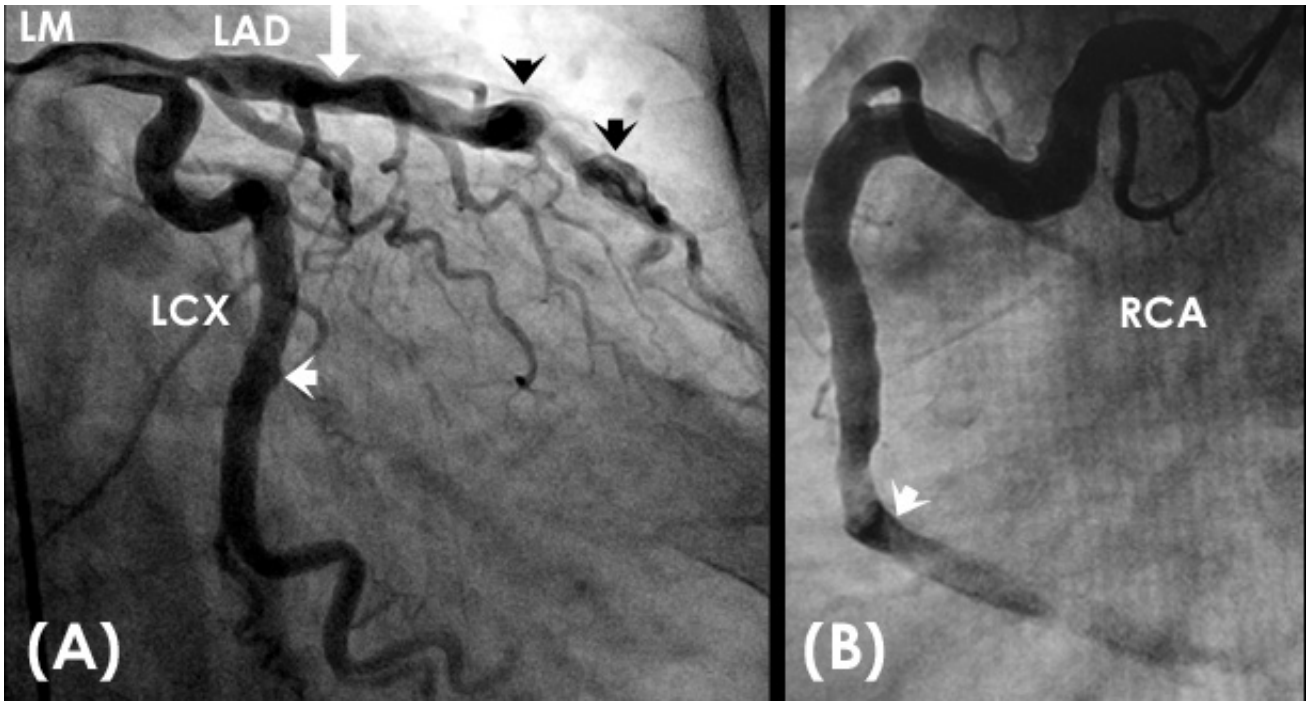

Fig. 2.- Coronary Angiograms and Aneurysmal Arteries. **(A)** In this CAG of the left coronary artery, there was diffuse no-critical lesion in the left main (LM) left anterior descending (LAD) and the left circumflex arteries (arrow heads). The LAD had a mild to moderate ostial lesion (white arrow) and has been stable for the last 5 years. The fractional flow reserve was negative. **(B)** CAG of the right coronary artery (RCA) showed diffuse mild lesions.

suitable for laminar flow to be developed distally and so offer protection from new plaque formation and rupture of current plaques (Nguyen et al., 2021a; 2021b; Billinger et al., 2001).

Speed of the Coronary Flow. In the hemodynamics of coronary flow, fast speed was correlated with cavitation phenomenon so more lesion could develop during fast speed in diastole. Beta blockers slowed the speed in general as seen (Fig. 5). By slowing the speed, less turbulence occurs and so less chance for cavitation and lesion formation (Nguyen et al., 2021a; 2021b).

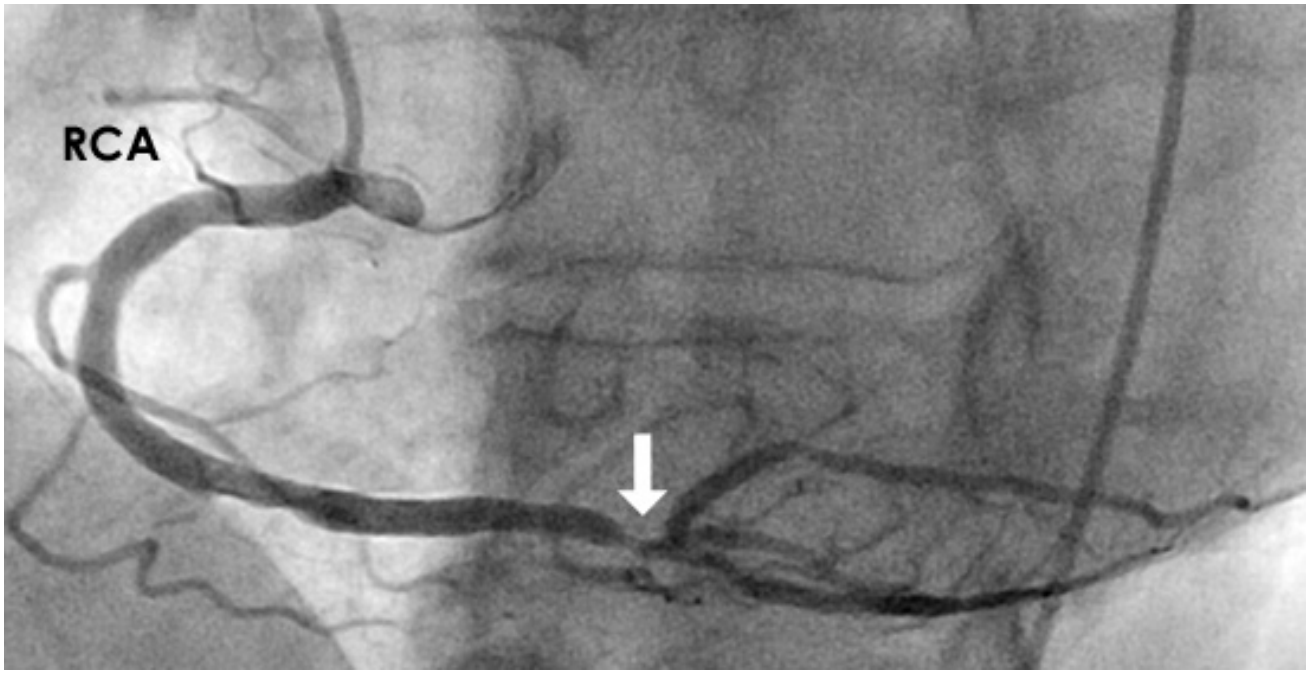

Fig. 3.- Right Coronary Angiogram. This is the CAG of the right coronary artery (RCA) of an elderly patient who came for stenting of the proximal left anterior descending artery. A significant lesion was observed in the distal RCA. The patient refused further stenting of the distal posterior descending artery and was treated successfully with statin, beta blockers and aspirin.

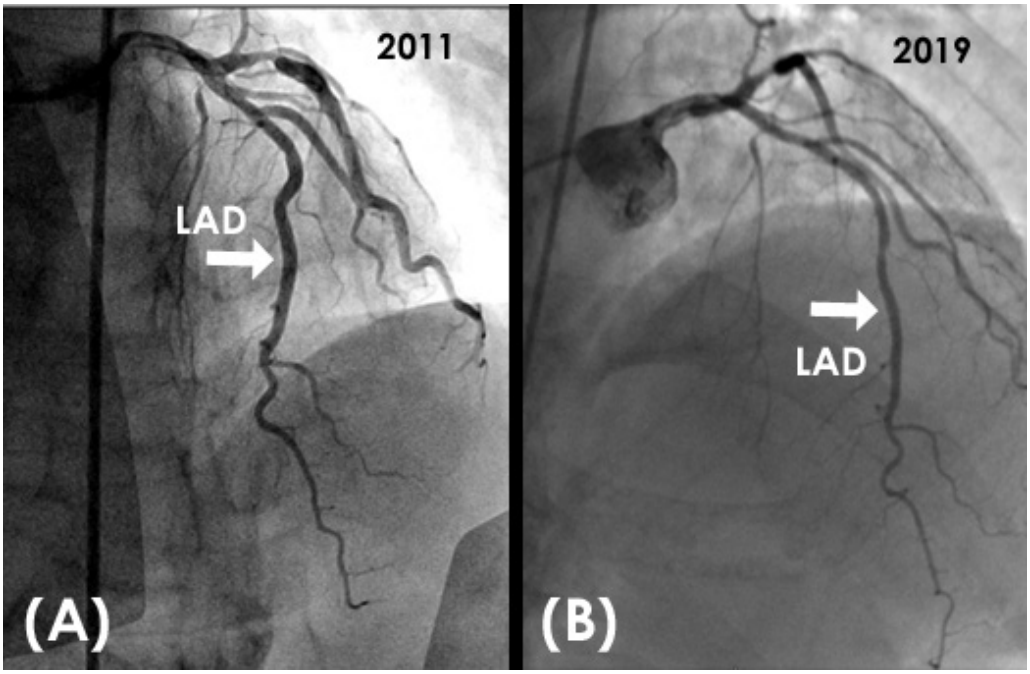

Fig. 4.- Left Coronary Angiograms before and after Beta Blockers. **(A)** In 2011 after undergoing stenting; with the 6 French guide of diameter = 2.03 mm, so the diameter of the mid-segment of the left anterior descending (LAD) artery was >2.5 mm (arrow). At discharge, beta blockers were prescribed **(B)** In 2019 the left CAG showed the size of the mid-LAD while patient was on beta blockers. The diameter of the 5 French diagnostic catheter was equal = 1.67 mm, so the diameter of the mid-to-distal segment of the LAD was a little below 2 mm (arrow). Beta blockers caused distal vasoconstriction and provided an environment for development of laminar flows which caused no new coronary lesion. This is the beneficial mechanism of beta blockers (i.e., restorative anatomy).

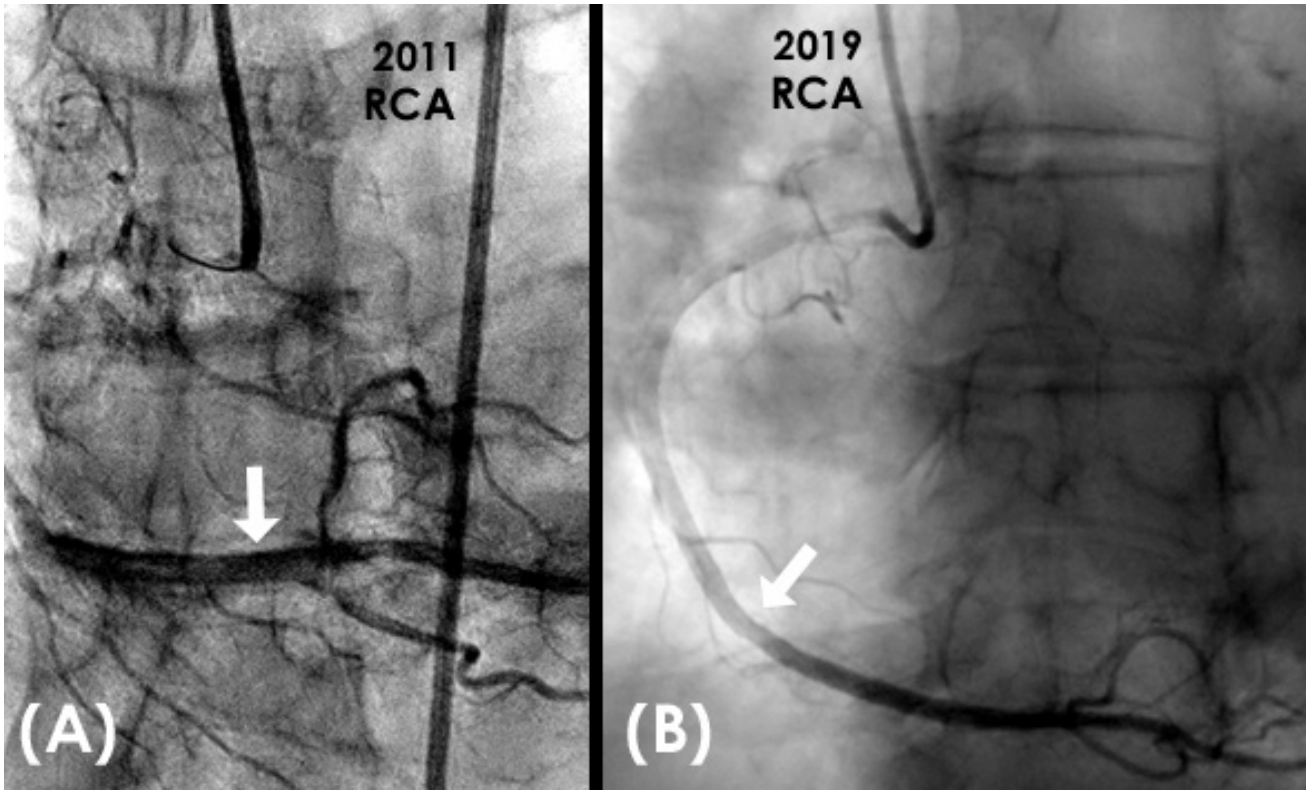

Fig. 5.- Right Coronary Angiography, Beta Blockers and Flow. **(A)** In 2011 after stenting, after 10 images or 0.6second, the blood arrived to the distal segment of the right coronary artery (RCA) (arrow). At that time, the patient was not on beta blockers. **(B)** in 2019 with the patient on beta blockers, the blood arrived after 0.6 second at the beginning of the distal segment (arrow). The blood moved more slowly and had less turbulence. This is the secondary protective effect of beta blockers.

ADVANCED ANATOMICAL INTERVENTION

Restoration of the Natural Anatomy by Stenting

In coronary arteries, at the end of diastole and beginning of systole, there was a strong collision between the antegrade and retrograde flow, seen on CAGs as mixing of blood in white and contrast in black. In many cases, there was a sharp horizontal demarcation line suggestive of the high intensity of collision. This location was called the collision line and was where the majority of lesions were found (Fig. 6). This event could happen to every person even before birth; however in patients (i.e., years after birth) with high LDL cholesterol level, the injured area had enough material available to build up a plaque. The anatomy of the artery provided a favorable environment at a specific location - the collision line - for plaque development.

In the management of CAD, how does the interventional cardiologist (i.e., interventional anatomist) restore the natural anatomy of a coronary segment? The answer is the placement of a small wire mesh tube, or stent. The role of a stent is to crush the lesion and prop the artery open, thus restoring the anatomy of the original lumen in its radial axis. What happened to the flow after stenting of the mid RCA in patient show in Fig. 6? CAG documented restoration of the arterial lumen and laminar flow with a minimal boundary layer (Fig. 7). Thus, restoration of the natural anatomy removed the environment favorable for collision and cavitation.

In summary, stenting restored the anatomy and changed the flow pattern by: (1) moving the collision line distally, (2) creating less turbulent flow, (3) favoring less flow reversal, (4) producing more laminar flow. All of these 4 factors provide a less favorable environment for turbulence and jet waves and prevent formation of new plaques and the rupture of current plaques. The above effects were reinforced further with beta blockers and statin. This is the protective mechanism created by restoring the original *anatomy* by stenting, antiplatelet and anti-inflammatory medications.

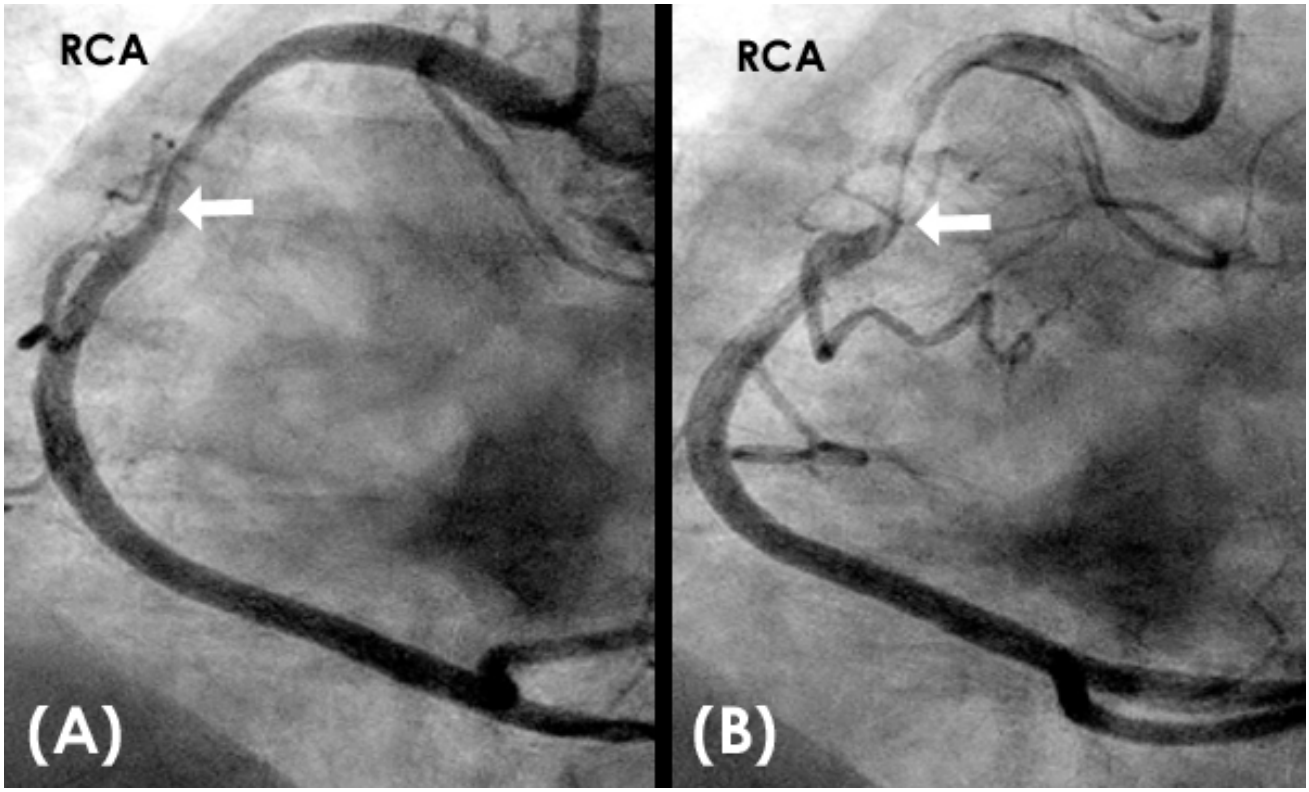

Fig. 6.- Right Coronary Angiogram and Collision Line. **(A)** There was a severe lesion (white arrow) in the mid-right coronary artery (RCA). Why did the lesion happen here, and not more proximally or more distally? **(B)** The reason was because the antegrade flow arrived at the mid RCA at the end of diastole and beginning of systole. There both antegrade and retrograde flows collided, causing shock wave and triggering the cavitation phenomenon. This location was called the collision line (arrow).

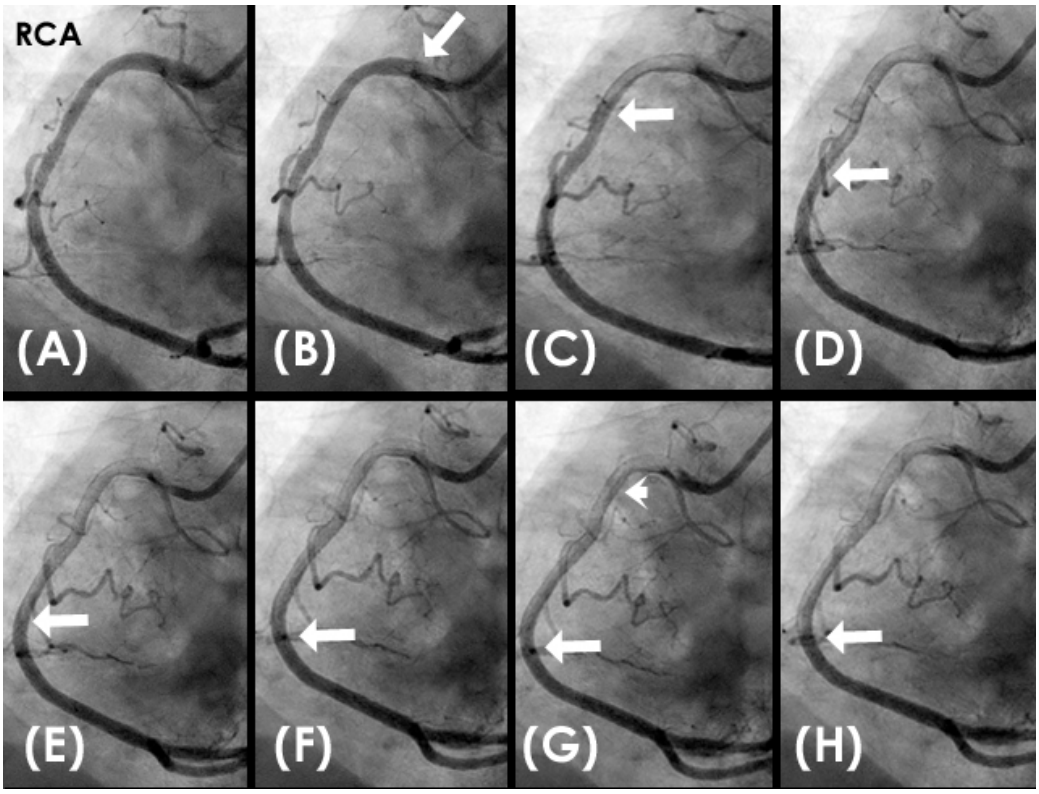

Fig. 7.- Right Coronary Angiogram after Stent Procedure. These images are continuously sequenced. **(A)** The right coronary artery (RCA) was completely filled with contrast (black) after stenting. **(B)** The blood (white) moved in at the ostial proximal segment of the RCA (arrow). **(C)** The blood now covered the proximal part of the mid-segment. The flow was laminar with a minimal boundary layer (arrow). **(D)** The blood (white) passed the collision line and reached the distal part of the mid-segment (arrow). **(E)** The blood in laminar flow almost reached the junction between the mid and the distal segment (arrow). **(F)** The blood could only advance minimally. This is the beginning of systole and the location of the collision line (arrow). **(G)** The blood (white) stayed in one place and there was some reversal of the flow (i.e., with more black contrast in the inner curve; arrowhead). **(H)** The blood now reached the junction of the mid and distal segment of the RCA with a sharp demarcation line. After stenting, the location where the antegrade and retrograde flow collided, was moved further distally (arrow).

ADVANCED INTERVENTIONS

Does Restoration of the Anatomy Restore Function?

In the care of patients with CAD, restoration of the natural ideal anatomy of the patient is the goal of interventional anatomy or cardiology. If the original anatomy is tortuous, because the metallic stent is somewhat straight and difficult to be bent, PCI may not perfectly restore the original curve (Fig. 8). This raises an interesting question for the cardiac patient. Does this new anatomy correct the ischemic problem and prevent future angina? In the case of a middle-aged patient (Fig. 8), the question of the correction of the lesion was that it changed the original anatomy. Was this correction acceptable and beneficial to patients? Based on the characteristics of flow dynamics and the extended time post-stenting (Fig. 8D), the answer is yes.

Does Intervention to Restore the Anatomy Correct the Functional Problem? The Detrimental Effect of Stenting.

In the spring of 2011, a young woman was seen because of recurrent angina. Her risk factor was smoking. CAG showed severe lesion in the mid left circumflex artery (LCX) and mild lesion in the right coronary artery (RCA) (Fig. 9). Her left main was special with a distal trifurcation to the left

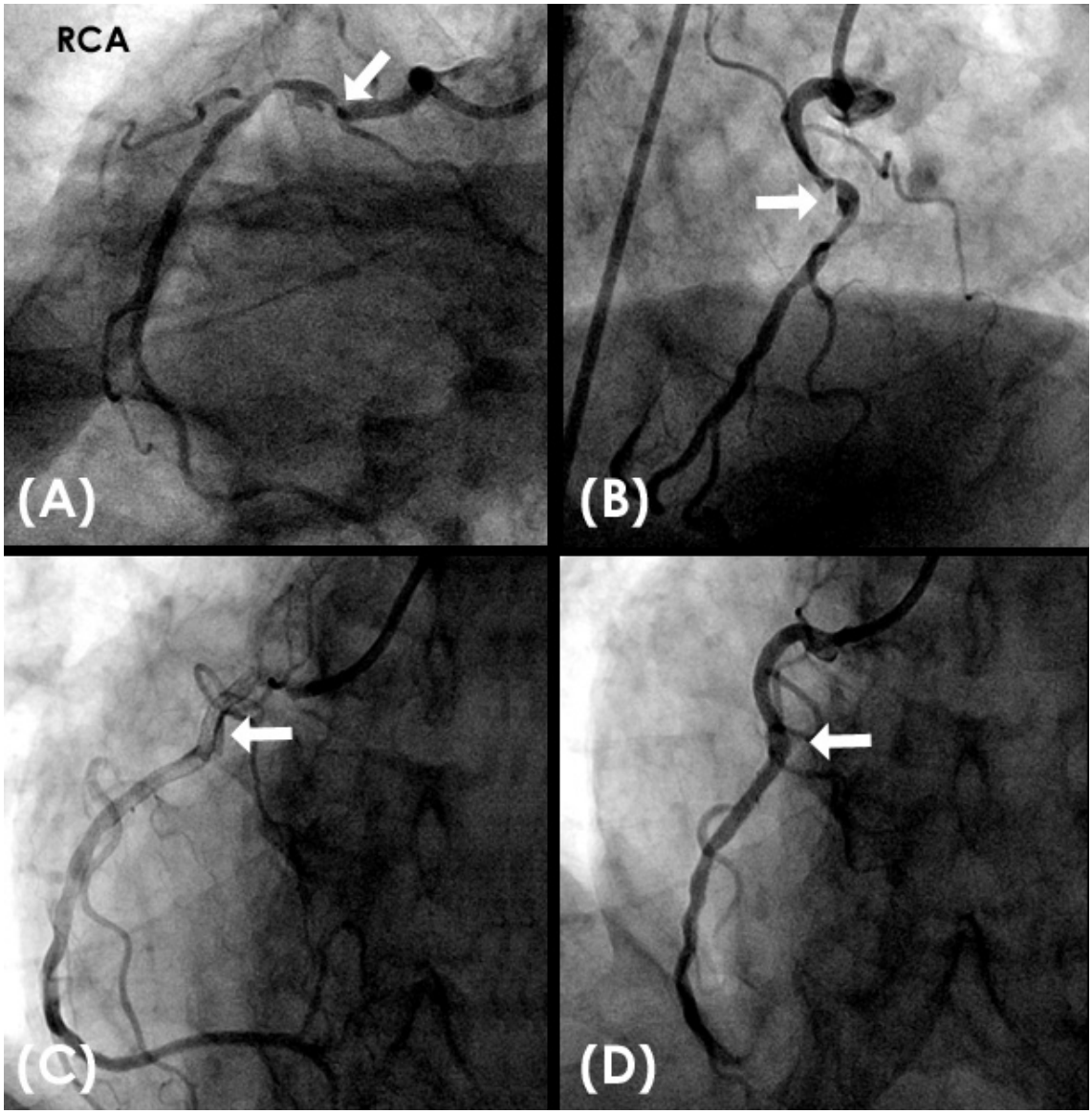

Fig. 8.- Right Coronary Angiogram before and after Stenting. **(A)** This is the right CAG (left anterior oblique caudal view) of a middle-aged man. There was a severe lesion in the proximal right coronary artery (RCA) (arrow). The segment was very tortuous. **(B)** The RCA in the right anterior oblique view. **(C)** After stenting, the curve of the angles was not as stiff. Blood (white) entered the RCA in laminar fashion (arrow). **(D)** This CAG is from the same patient 10 years after stenting. The patient did well; without recurrent chest pain.

anterior descending artery (LAD), a large ramus intermedius and the LCX (Fig. 9A, arrow). She successfully underwent stenting of the mid LCX. In 2020, the patient came back because of recurrent chest pain. She underwent a new CAG which showed severe disease in the ramus intermedius (Fig. 9C). Why did this occur if stenting restored the anatomy? The reason for this observation has not yet been well explained.

Extent of the Recirculation Flow

In the hemodynamics of coronary flow, after a bifurcation, specifically at the distal end of the left main (LM) artery, where the LM divided into the left anterior descending (LAD) and left circumflex arteries (LCX), blood tends to course through the larger branch with fewer curves.

Because the LAD was frequently the primary branch, less blood was available for the LCX. When the blood moved through the ostium of the LCX, the layers at the centerline would continue go forwards while the layers at the borders would for recirculation flow. This condition created turbulence and mixing between layers and formed a favorable environment for cavitation and plaque formation. Because beta blockers (BB) slowed the speed of the coronary flow, did BB decrease the incidence and the extent of recirculation flow? When evaluating the CAG in Fig. 10, the answer is yes.

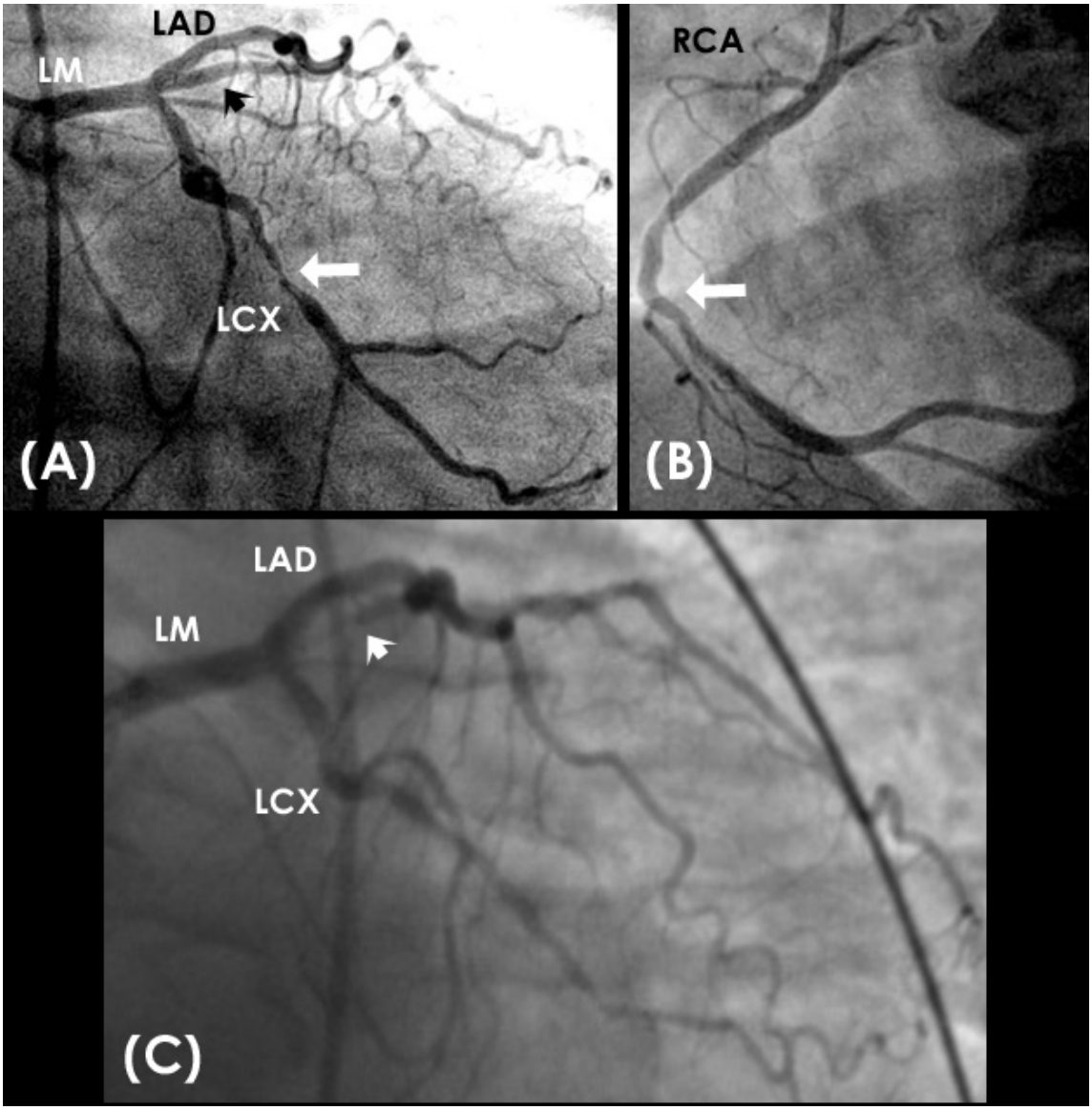

Fig. 9.- Coronary Angiograms. **(A)** The CAG of the left system in 2011 - left main (LM) left circumflex artery (LCX), left anterior descending artery and the ramus intermedius (t black arrow head) - before stenting of the LCX (arrow). **(B)** The CAG of the same patient of the right coronary artery (RCA) with 2 lesions (arrow). **(C)** CAG of the left system in March 2020. Besides the in-stent restenosis in the distal LCX, there was another important abnormality in the angiogram. The ramus intermedius had severe proximal disease (arrow head).

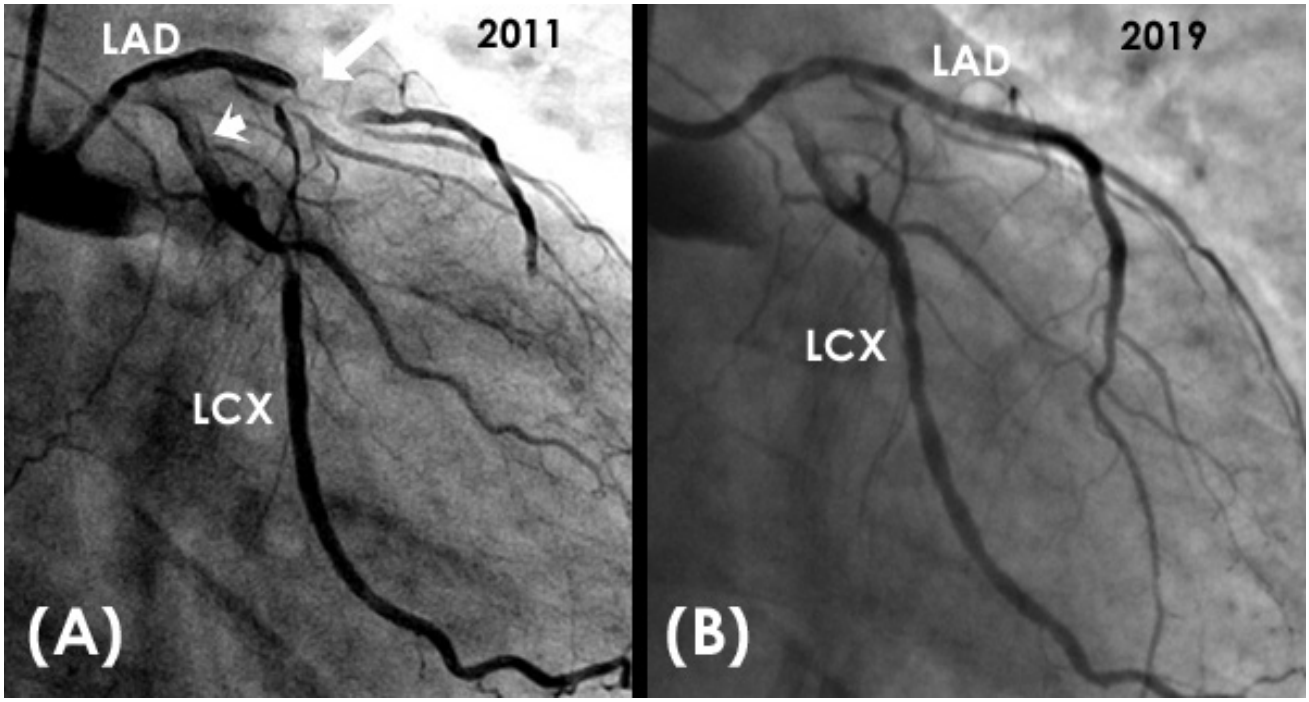

Fig. 10.- Restoration of Anatomy and Recirculation of Flow. **(A)** In 2011, a patient underwent stenting of the left anterior descending artery (LAD) (arrow). The flow to the left circumflex artery (LCX) showed the usual thick separation layer at the outer curve of the LCX, opposite to the carina (arrow head). Since the CAG of 2011, patient was treated with aspirin, statin and beta blockers. **(B)** In 2019, because of recurrent chest pain, the patient underwent stenting of the mid LCX. The stent in the LAD was patent. The separation layer in the proximal LCX was thinner and shorter, because the flow from the left main to the LCX was more organized. This is the benefit of beta blockers and anti-inflammatory drugs. In this case, the correct anatomy helps to keep patients healthy.

CONCLUSIONS

The application of hydraulic principles of fluid dynamics to blood flow in the coronary arterial system shows that the normal anatomy and anatomical variation of the arteries affect blood flow and that changes in the anatomy can result in the development of coronary lesions. The anatomy can be used to predict where lesions will form. Restoration of the natural anatomy of the coronary arteries results in blood flow that is more laminar, and less turbulent, and thus less likely to produce the cavitation phenomenon. This model extends beyond the coronary system to the peripheral arterial system.

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