



# Myocardial infarction as a consequence of atherosclerosis

## *Infarto de miocardio como consecuencia de aterosclerosis*

Rafael Moguel-Ancheita, MD\* Virginia Samaniego, MD‡

### INTRODUCTION

Atherosclerosis is a main cause of myocardial infarction (MI), establishing a vicious circle that increases atherosclerosis and risk of more infarctions.<sup>1</sup> There are many ancient descriptions and recent discoveries of myocardial infarction and coronary calcification on ancient mummies. One of the first findings on sudden death, came from the Danish sculptor's autopsy Bertel Thorvaldsen in 1844, where an ulcerated coronary atherosclerotic plaque exposing subendothelial components was shown.<sup>1</sup>

The current knowledge about atherothrombosis causing myocardial infarction evolved through the last three centuries. The present chapter describes the atheroma events causing MI and the process of myocardial necrosis.

### THE VULNERABLE PLAQUE

The atherosclerotic plaque starts very early in life, and later progresses towards a lesion which is a potential cause of ischemic heart syndromes: angina or equivalent, myocardial infarction, and sudden death. In 1858, Rudolf Virchow published a book containing his lectures in the Pathological Institute of Berlin. Lecture XVI described the pathology and histology of «fatty metamorphosis». He described the atheromatous process in arteries, as it is currently explained, stating that the plaque contained a fat core with muscular layer's involvement, identifying fat granules

containing cells, and evidence of inflammation. Virchow interprets the atheroma as a dermal cyst,<sup>2</sup> similarly to an abscess contained into its capsule, that could eventually break.

The plaque involves several anatomic, histological, mechanical, and chemical properties that interact with other environmental factors that include several physical forces. The plaque becomes vulnerable when it is prone to rupture and causing thrombosis.<sup>3</sup> However, a significant proportion (40%) of complicated plaques do not provoke thrombosis,<sup>4</sup> and half of them do not cause severe stenosis. The vulnerability is expressed when the cover atheromatous cap is less than 65  $\mu\text{m}$  –the thin fibrous cap–,<sup>5</sup> there is loss of smooth muscle cells, increased components of extracellular matrix, inflammatory infiltrate, high-volume necrotic core, intra-plaque hemorrhage, calcification, and numerous vasa vasora.<sup>6,7</sup>

Rupture or erosion may be the main vulnerable plaque complication. The first one consists of the loss of continuity of an area of the fibrous cap covering a large necrotic core plaque, macrophage and lymphocytic infiltration, and thrombi. The ruptured plaque is a major cause for sudden death in men under 50 and women over 50 years old, with a significant correlation with high total cholesterol/HDL-cholesterol ratio and major thrombosis particularly in smokers.<sup>8,9</sup> Nonetheless, the ruptured plaque is not always associated with sudden death. Farb et al., found proteoglycan and smooth muscle cell-enrich plaques denuded from the endothelium,

\* Colegio Mexicano de Cardiología Intervencionista y Terapia Endovascular (COMECITE), México.  
‡ The Clinics of the Heart, Cozumel, Q. Roo, Mexico.

Received:  
28/06/2021  
Accepted:  
08/07/2021

**How to cite:** Moguel-Ancheita R, Samaniego V. Myocardial infarction as a consequence of atherosclerosis. Cardiovasc Metab Sci. 2021; 32 (s3): s247-s252. <https://dx.doi.org/10.35366/100806>

without rupture, in 44% of autopsy specimens, with several differences between ruptured and eroded plaques. The latter were more frequent in younger subjects and women, originating less stenosis, with less macrophages and T cells infiltration, more frequent smooth muscle cells clusters adjacent to thrombi, and less expression of human leukocyte antigen-DR isotype (HLA-DR).<sup>5</sup>

In both rupture and erosion, the presence of macrophages, T cells, and HLA-DR antigens on these cells and on adjacent smooth myocytes is consistent with the concept of inflammation, destabilizing the fibrous cap and enhancing the risk of coronary thrombosis.<sup>4</sup>

On the other hand, almost half of cases of sudden death result from plaque's erosion characterized by endothelium absence with exposure of smooth muscle and proteoglycans, less necrotic core and inflammatory cells than ruptured plaques. This event is more frequent in 50 years old or younger men and women. Plaque rupture and erosion may coexist in a single event.<sup>10</sup>

Calcified nodules may complicate plaques causing disruption and thrombosis. These complications may result from the action of torsion forces and mechanical lesion of the plaque by the hard calcified nodule, especially in the mid-segment of the right coronary artery.<sup>11</sup> Interestingly, approximately one-fourth of sudden death cases may show intact plaques, but significant stenosis and myocardial scars from old infarctions. Other cases present plaque fissuring with hemorrhage and fibrin inside the necrotic core. These fissures possibly result from vasa vasora rupture and are possible precursors of ruptures. Fissures may be incidental findings in non-cardiovascular deaths.<sup>11</sup> The complicated plaque sometimes heals when new synthesis of type-III collagen cover the disrupted fibrous, with a matrix composed of proteoglycan-enrich mass or collagen-enrich scar. These healed events may contribute towards more lumen occlusive plaques.<sup>12</sup>

Another significant component for plaque's vulnerability is the vasa vasorum developed from the adventitia, which is a stem cell reservoir. The vessel wall injury stimulates angiogenesis and immature vessels penetrate the plaque favoring plaque growth and

hemorrhage. The vasa vasora may be the conduit of inflammatory cells arriving into the plaque, and the initial factor for instability.<sup>13,14</sup>

Inflammation is involved in atherogenesis, atheroma development, and partly responsible for plaque complications. The phagocytes, mainly macrophages, produce proteolytic enzymes, particularly collagenases, members of the matrix metalloproteinases family, that could damage the biomechanical stability of the fibrous plaque.<sup>15</sup>

Several substances activate focal and global inflammation and may constitute clinical markers for major cardiovascular events prediction and prognosis. The C-reactive protein is the current dominant marker. It participates in plaque formation, stimulates monocytes and macrophages to synthesize interleukins 6 and 1 $\beta$ , tumor necrosis factor- $\alpha$ , vascular cell adhesion molecule 1, and intercellular adhesion molecule 1, and opsonizes the low-density lipoprotein, favoring macrophage's uptake. Other inflammation related substances present are pregnancy associated plasma protein, soluble P-selectin.<sup>16</sup>

Inflammation may involve infections and immunity, increasing local thermal activity, energy production uncoupling, exothermic chemical reactions, blood friction over the wall, turbulent flow, blood viscosity and red cell aggregation.

Oxidized low-density lipoprotein and lipoprotein (a) not only produce plaque growth but induce more inflammation, necroptosis, thrombosis, cholesterol delivery to atheroma, and smooth muscle cell proliferation and together with the formation of cholesterol crystals may damage the plaque from inside, establishing a continuous event that weakens the plaque's fibrous cap and extracellular matrix.<sup>17</sup>

The plaque stability or instability relate to external mechanical and hydraulic forces

1. The Laplace's stress, which is directly proportional to the vessel's ratio and the blood pressure and indirectly proportional to the wall thickness, is higher in the plaque edges because of the major ratio and thinner wall.

2. Shear, which is the blood's force over the vessel wall as it flows over it.
3. The turbulent flow that causes areas with less shear and continuous particle interaction with the wall.
4. The torsion of the vessel during the heart movement.

Unstable plaque presence can be associated with acute coronary syndromes, although controversy exists due to the coexistence of unstable and stable plaques and because the relationship of either one to specific events is not linear.<sup>18</sup>

Several diagnostic tools, aimed to visualize the anatomical aspects of the atherosclerotic plaque *in vivo*, such as the optical coherence tomography (OCT) obtained during cardiac catheterization have been recently developed. This imaging tool can distinguish the coronary arteries' layers with high resolution, well beyond the intravascular ultrasound. The sensitivity and specificity may reach over 90% for detecting fibrous plaque, fibroatheroma, and fibrocalcific plaque. It may detect very small processes such as microthrombi, erosion, ulcers, macrophage aggregates, calcific nodules, lipid core, thin cap, vasa vasora, microdissections, and intra-plaque hemorrhage.<sup>19</sup> Some examples of images obtained in our catheterization laboratory show some of the aspects described above (*Figure 1*).

Apart from the vulnerable plaque, we must consider the relevant role of blood in the process. The thrombogenic blood status can be established by the presence of several markers of hypercoagulability (fibrinogen, D-dimer, factor V Leiden), increased platelet aggregation, increased coagulation factors, decreased anticoagulation factors, decreased endogenous fibrinolysis, prothrombin mutation, increased viscosity, and transient hypercoagulability.

The possibility of an acute coronary syndrome and its magnitude is also related to factors beyond the vulnerable plaque and blood, yielding to the concept of the vulnerable patient and vulnerable myocardium. This includes metabolic syndrome, inflammation, gut microbiome, smoking, diet, physical activity, psychosocial stress, and socioeconomic status. The vulnerable myocardium includes sympathetic activity, autonomic reactivity,

hypertrophy, cardiomyopathy, valvulopathy, commotio cordis, anomalous coronary origin, myocarditis, myocardial bridging, and electrophysiological disorders.<sup>20,21</sup>

## THROMBOSIS

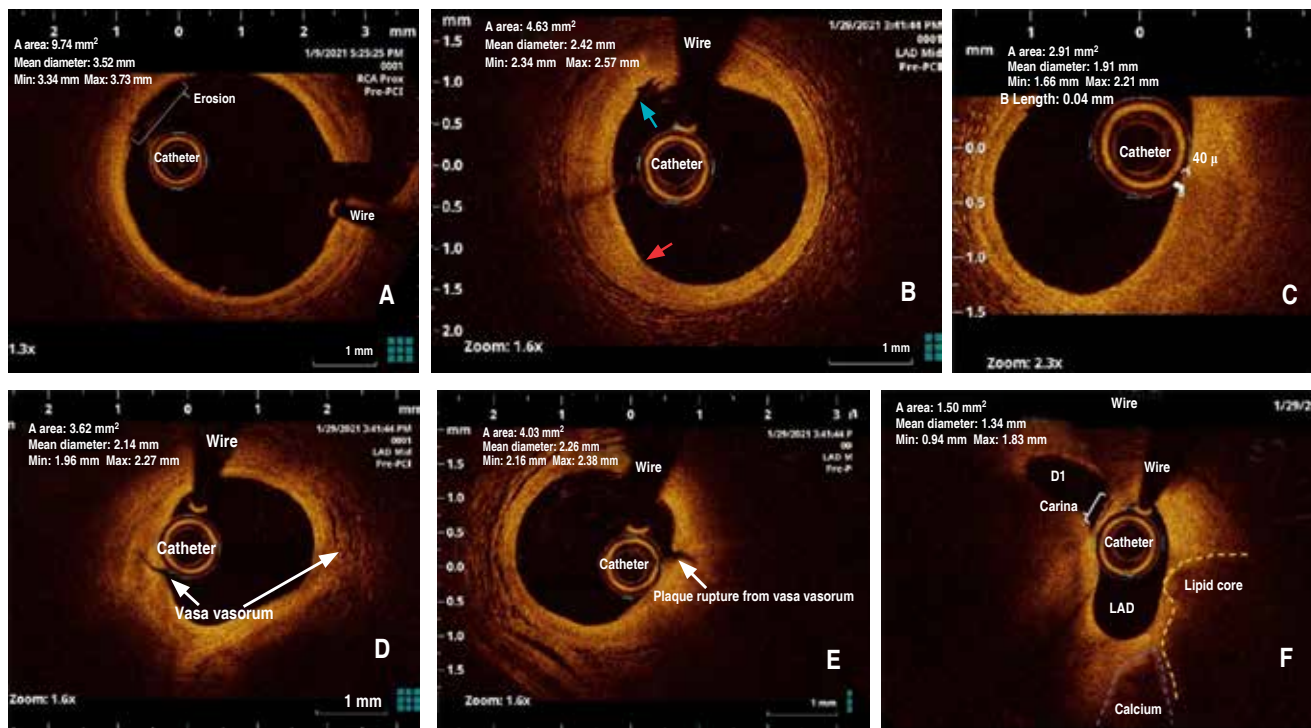
Virchow, in 1848, coined the terms thrombosis and embolus that meant the same as today. In the same year, he described the triad of vascular lumen irregularity, damaged blood flow, and increased coagulability. Virchow's work in the vascular area was continued and crowned by his remarkable student Julius Cohnheim who injected wax emboli into the frog's tongue and demonstrated the lesions that a hundred years later would be called ischemic necrosis and hemorrhagic infarction.<sup>2</sup>

The coronary thrombosis is finally a continuum of the complicated plaque. Either rupture or erosion, going from microthrombi to complete thrombotic occlusion, related to the same plaque, blood, and patient's risk factors. It is a major cause of death in developed and developing countries.<sup>22</sup>

The endothelial layer is composed by a unique cell type compatible with blood without causing coagulation activation. When the endothelium loses its integrity, subendothelial components contact circulating platelets that activate and aggregate them, later releasing serotonin, adenosine diphosphate, thromboxane A<sub>2</sub>, endothelin, and other vasoconstrictors.

The subendothelial matrix releases tissue factor and activates the extrinsic coagulation cascade leading to fibrin accumulation, thrombus formation, acute occlusion, interruption of blood flow, and further ischemic complications. The thrombus composition includes platelets conglomerates, erythrocytes, vasoconstrictors, thrombin, and other procoagulants in a net of two different fibrin fibers, thin and thick; the first ones resistant to mechanical forces and fibrinolysis.<sup>23</sup>

Other fact that participates in atherosclerotic-related processes is the ectopic fat (visceral, intrahepatic, pericardial, and perivascular) since it causes direct lipotoxicity, local and systemic pro-inflammatory effects, dysregulating cytokines and adipokines, finally



**Figure 1:** **A)** Shows endothelial denudation, microdissection, microthrombi, and macrophage aggregates. **B)** Shows an ulcer and microthrombi. **C)** Shows a typical thin cap fibroatheroma with a large lipid core and macrophage aggregates. **D)** Shows vasa vasorum with a dissection. **E)** Shows a ruptured plaque from the vasa vasorum. **F)** Shows mixed plaque containing a large necrotic core and a calcific nodule. The carina between the left anterior descending coronary (LAD) and the first diagonal (D1) branch is free from atheroma.

causing inflammation, endothelial dysfunction, atherogenesis progression, and pro-thrombotic milieu. The thrombus formation results from the interaction of blood cells, complement, myeloid cell tissue factor, and coagulation proteases.<sup>24</sup> The early detection of risk factors, including ectopic fat and inflammation markers, raises the possibility for opportune secondary prevention.<sup>25,26</sup>

Interestingly, if thrombosis develops, the color of the thrombus, white or red, is important not only for the histological (more fibrin and fewer cells in the white) differences but several features that finally give the latter a better prognosis and response to treatment. The white thrombus is smaller than the red, occurs in smaller vessels, and associates with smaller thrombus burden, lower creatine kinase-MB and troponin, higher post-procedural TIMI-3 flow and blush grade, and lower ischemic time. One-third of myocardial infarctions display white thrombi.<sup>27</sup> The OCT detects very small

thrombi and can differentiate white from red. The white one is low-backscattering projections within the lumen, and the red is a high-backscattering mass protruding into the artery lumen, with signal-free shadowing (Figure 2).<sup>28</sup>

## MYOCARDIAL INFARCTION AND SUDDEN DEATH

Unfortunately, the myocardial infarction and sudden death are dramatic events present in history for thousands of years, from the Ebers papyrus, dating more than three thousand years, the sudden death of Horemkenesi, priest of Ammon, and the Hippocratic descriptions. Later, da Vinci's first necropsy performance after a coronary death in 1506, Lancisi's book «De subitaneis mortibus», Dr. John Hunter's sudden death 1793, and the case of the sculptor Bertel Thorvaldsen, already described above.<sup>2</sup>

Irreversible myocardial injury takes place after more than 20 minutes from coronary

occlusion. The lesion size depends on the occlusion characteristics, the extent of collateral circulation, myocardial preconditioning, and reperfusion.

During the first day of the non-reperfused infarction, early signs of coagulation necrosis start, with sarcoplasmic hypereosinophilia and initial nuclei chromatin condensation, followed by neutrophil infiltration in the ischemic edges and complete coagulation necrosis with sarcomere elongation. During the first week, the infarction center reveals loss of myocyte nuclei and striations with later inflammatory cellular infiltrations that decline giving place to granulation, neocapillarity, and appearance of lymphocytes and plasma cells. After two weeks, there is a prominent fibroblast activity, removing necrotic myocytes, and healing process with collagen production and angiogenesis leading to a chronic scar after one to two months.

If reperfusion was possible, a different histological behavior is present, with in-infarction hemorrhage in the first four to six hours, followed by neutrophil infiltration and necrosis interdigitation with normal myocardium. The next five days show macrophages, stromal cells, neutrophil debris, and fibroblasts. After one week, the tissue shows collagen deposition,

macrophages containing ingested myocytes, lymphocytes, and angiogenesis, for a complete heal after two to three weeks.<sup>29</sup>

The topography of the infarction is frequently regional along with the distribution of the occluded coronary artery, but the early reperfusion can interrupt the wave front of necrosis, limiting the irreversible damage to the subendocardium. The presence of collaterals can cause a less defined section of infarction. Hypotension on the multivessel coronary disease can cause a circumferential infarction usually involving the entire subendocardium (be aware of rapid blood pressure reduction in the hypertensive patient). Other topographic localizations include regional subendocardial and diffuse multifocal infarctions. The myocardial infarction may complicate with pulmonary edema causing a 20-40% 30-day death rate. Heart rupture is rare after reperfusion, but it can involve left ventricle free-wall, interventricular septum, and papillary muscle.<sup>30</sup>

Other anatomical complications are left ventricular aneurysms and pseudoaneurysms, mitral valve insufficiency, and pericarditis.<sup>31</sup>

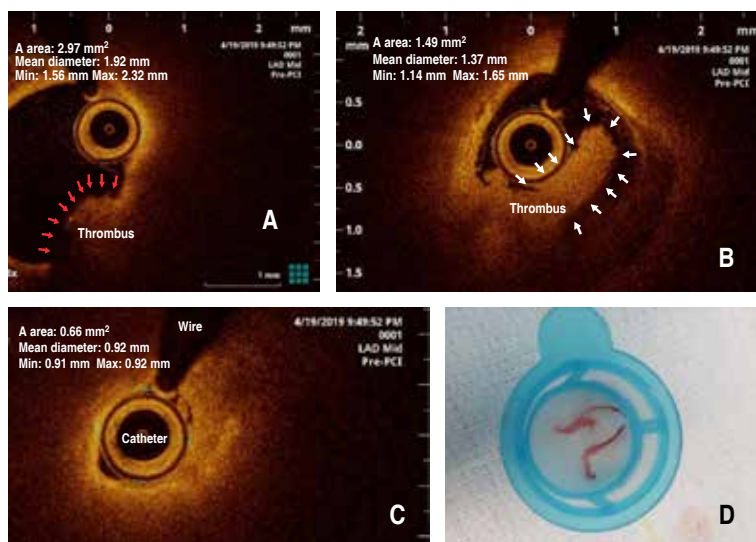
## CONCLUSIONS

This chapter stresses the importance of the knowledge of the process that finally leads to myocardial infarction. Understanding the characteristics of the unstable plaque interaction with hydraulic and mechanic forces and other susceptibility factors in the blood, the patient, and the myocardium should contribute towards a more efficient diagnosis and treatment.

The present approach allows for distinguishing patients prone to myocardial infarction, using non-invasive and invasive diagnostic tools, favoring more effective secondary prevention.

## REFERENCES

1. Moguel R, Cabrera C. A minimal tour towards the history of the myocardial infarction. *Cardiovasc Metab Sci.* 2020; 31 (3): 104-108.
2. Virchow R, Chance F. Cellular pathology as based upon physiological and pathological histology: twenty lectures delivered in the Pathological Institute of Berlin during the months of February, March, and April, 1858. London: John Churchill; 1860.



**Figure 2:** OCT from our catheterization laboratory. (A) Shows a ruptured plaque with subendothelial exposure and red thrombus, (B) shows a large white thrombus, completely occluding the coronary artery in (C); (D) shows the retrieved white thrombus.

3. Yonetsu T, Jang IK. Advances in intravascular imaging: new insights into the vulnerable plaque from imaging studies. *Korean Circ J*. 2018; 48 (1): 1-15.
4. Van der Wal AC, Becker AE, Van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. *Circulation*. 1994; 89: 36-44.
5. Farb A, Burke AP, Tang AL, Liang TY, Mannan P, Smialek J et al. Coronary plaque erosion without rupture into a lipid core: a frequent cause of coronary thrombosis in sudden coronary death. *Circulation*. 1996; 93: 1354-1363.
6. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med*. 1997; 336: 1276-1282.
7. Davies MJ, Woolf N, Rowles PM, Pepper J. Morphology of the endothelium over atherosclerotic plaques in human coronary arteries. *Br Heart J*. 1988; 60 (6): 459-464.
8. Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med*. 1997; 336: 1276-1282.
9. Virmani R. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. *Circulation*. 1998; 97: 2110-2116.
10. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000; 20: 1262-1275.
11. Davies MJ. Anatomic features in victims of sudden coronary death: coronary artery pathology. *Circulation*. 1992; 85: 119-124.
12. Davies MJ. Stability and instability: two faces of coronary atherosclerosis: the Paul Dudley White Lecture, 1995. *Circulation*. 1996; 94: 2013-2020.
13. Kawabe J, Hasebe N. Role of the vasa vasorum and vascular resident stem cells in atherosclerosis. *Biomed Res Int*. 2014; 2014: 701571.
14. Ito H, Wakatsuki T, Yamaguchi K, Fukuda D, Kawabata Y, Matsuura T et al. Atherosclerotic coronary plaque is associated with adventitial vasa vasorum and local inflammation in adjacent epicardial adipose tissue in fresh cadavers. *Circ J*. 2020; 84 (5): 769-775.
15. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2012; 32 (9): 2045-2051.
16. Schwartz RS, Bayes-Genis A, Lesser JR, Sangiorgi M, Henry TD, Conover CA. Detecting vulnerable plaque using peripheral blood: inflammatory and cellular markers. *J Interv Cardiol*. 2003; 16 (3): 231-242.
17. Stefanadis C, Antoniou CK, Tsiachris D, Pietri P. Coronary atherosclerotic vulnerable plaque: current perspectives. *J Am Heart Assoc*. 2017; 6 (3): e005543.
18. Libby P, Pasterkamp G. Requiem for the 'vulnerable plaque'. *Eur Heart J*. 2015; 36 (43): 2984-2987.
19. Toutouzas K, Karanasos A, Tousoulis D. Optical coherence tomography for the detection of the vulnerable plaque. *ECR*. 2016; 11 (2): 90-95.
20. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. *Circulation*. 2003; 108 (15): 1772-1778.
21. Tomaniak M, Katagiri Y, Modolo R, De-Silva R. Vulnerable plaques and patients: state-of-the-art. *Eur Heart J*. 2020; 41 (31): 2997-3004.
22. Mahajan K, Negi PC, Merwaha R, Mahajan N, Chauhan V, Asotra S. Gender differences in the management of acute coronary syndrome patients: One year results from HPIAR (HP-India ACS Registry). *Int J Cardiol*. 2017; 248: 1-6.
23. Adnan G, Singh DP, Mahajan K. Coronary artery thrombus [Updated 2020 Oct 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. Available in: <https://www.ncbi.nlm.nih.gov/books/NBK534808/>
24. Spronk HMH, Padro T, Siland JE, Prochaska JH, Winters J, van der Wal AC et al. Atherothrombosis and thromboembolism: position paper from the second maastricht consensus conference on thrombosis. *Thromb Haemost*. 2018; 118 (2): 229-250.
25. Libby P, Loscalzo J, Ridker PM, Farkouh ME, Hsue PY, Fuster V et al. Inflammation, immunity, and infection in atherothrombosis: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2018; 72 (17): 2071-2081.
26. Olie RH, van der Meijden PEJ, Ten Cate H. The coagulation system in atherothrombosis: Implications for new therapeutic strategies. *Res Pract Thromb Haemost*. 2018; 2 (2): 188-198.
27. Quadros AS, Cambuzzi E, Sebben J, David RB, Abelin A, Welter D et al. Red versus white thrombi in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: clinical and angiographic outcomes. *Am Heart J*. 2012; 164 (4): 553-560.
28. Kubo T, Yamano T, Masyo T, Takarada S, Imanishi T, Tomobuchi Y et al. Abstract 3060: assessment of coronary red and white thrombus by optical coherence tomography. *Circulation*. 2006; 114: II\_645.
29. Romero ME, Fernández-Jiménez R, Ladich E, Fuster V et al. Chapter 37: Pathology of myocardial infarction and sudden death. In: Fuster V, Harrington RA, Narula J, Eapen ZJ, eds. *Hurst's the heart*. 14 edition. New York, NY: McGraw-Hill Education; 2017.
30. Michaud K, Basso C, d'Amati G, Giordano C, Kholová I, Preston SD et al. Diagnosis of myocardial infarction at autopsy: AECVP reappraisal in the light of the current clinical classification. *Virchows Arch*. 2020; 476 (2): 179-194.
31. Pasotti M, Prati F, Arbustini E. The pathology of myocardial infarction in the pre- and post-interventional era. *Heart*. 2006; 92 (11): 1552-1556.

**Correspondence:****Rafael Moguel-Ancheita, MD****E-mail:** [cathboss@gmail.com](mailto:cathboss@gmail.com)