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Journal of Cardiovascular Emergencies 2017;3(1):5-8
DOI: 10.1515/jce-2017-0001

EDITORIAL

Atherosclerosis-Triggered Hypertension or Hypertension-Triggered Atherosclerosis? A Challenging Hypothesis

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Despite the significant progress encountered in recent years in the field of diagnostic techniques, key aspects involved in the development and progression of atherosclerosis are not fully understood. Based on clinical observations of acute coronary syndromes in young patients with angiographically normal coronary arteries, a new premise can be proposed to explain some of the mechanisms involved in atheromatous plaque formation. This hypothesis is that, even in the oscillating phase, hypertension is a trigger for the development of atherosclerotic disease due to mechanical stress.

This premise represents the starting point of a chicken and egg argument: does atherosclerosis lead to hypertension, or do repeated episodes of hypertension lead to atherosclerosis?

ACUTE CORONARY SYNDROMES WITH SLOW-FLOW PATTERN IN NON-OBSTRUCTED CORONARY ARTERIES. CLINICAL OBSERVATIONS GENERATING THE HYPOTHESIS

The hypothesis is based on data recorded in several patients aged between 23 and 44 years, presenting in the emergency department of our institution with typical angina, electrocardiographic (ECG) changes highly suggestive of ischemia, and positive cardiac enzymes.

In these patients, coronary angiography showed the absence of any obstructions or significant stenosis in the coronary arteries and an abnormal non-laminar coronary flow located in the middle segment of the left anterior descending coronary artery (Figure 1A). Optical coherence tomography (OCT) showed the presence of a dissection in the subendothelial layer of the coronary wall at the level of the turbulent flow (Figure 1B). In all these patients, repeated episodes of hypertension preceded an angina attack.

In the proposed hypothesis, the following are proposed as characteristics associated with a new pattern of acute cardiac patient seen in an emergency setting:

- repeated episodes of hypertension;
- presenting with chest pain;
- ECG changes and positive cardiac enzymes;
- coronary angiography indicating slow flow in at least one coronary artery;
- OCT revealing the presence of subendothelial dissection.

FROM HYPERTENSION TO ATHEROGENESIS DUE TO MECHANICAL STRESS

Repeated episodes of a sudden increase in the blood pressure can cause the abrupt dilatation of the coronary wall, which becomes wrinkled on returning to its original shape. This wrinkled surface can lead to the alteration of shear stress and, at the same time, of the circumferential stress inside the coronary lumen, contributing to endothelial dysfunction and the development of turbulent coronary flow at this level.

The endothelium that usually protects the coronary wall is exposed to altered luminal forces caused by the in-

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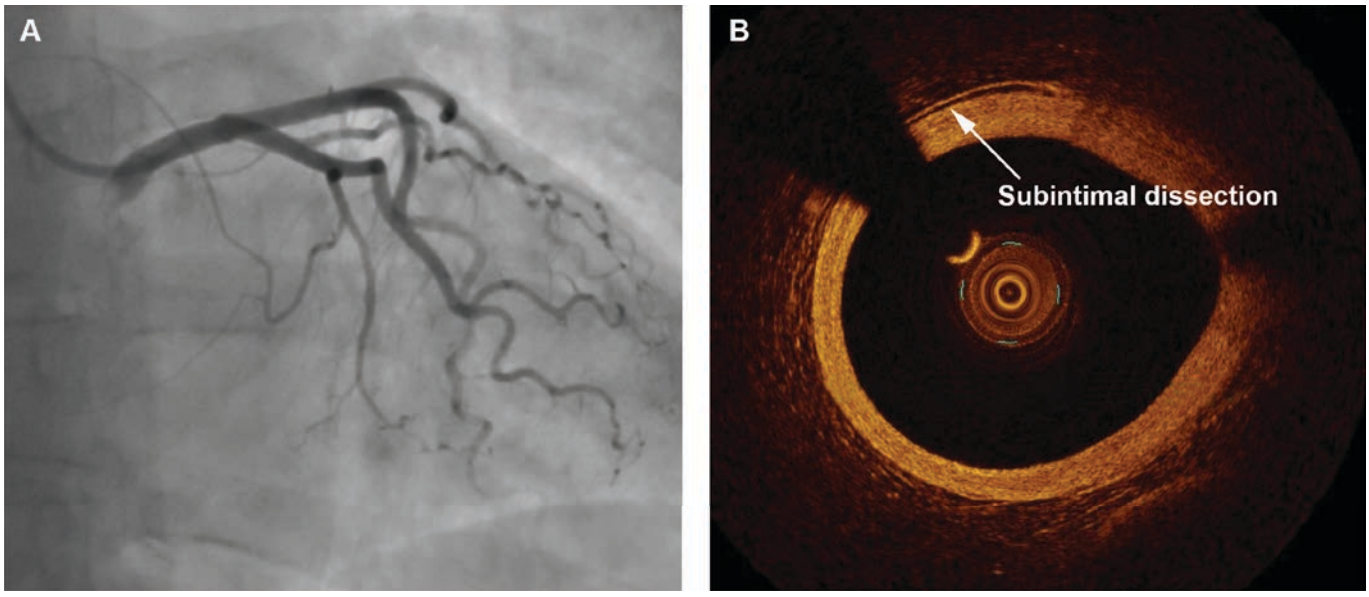

FIGURE 1. Invasive assessment of coronary arteries in a young patient with typical chest pain. A – Coronary angiography indicating absence of any obstructions or any significant stenosis in the coronary arteries and an abnormal non-laminar coronary flow located in the middle segment of the left anterior descending coronary artery. B – Optical coherence tomography (OCT) indicating the presence of a dissection in the sub-endothelial layer of the coronary wall at the level of the turbulent flow.

crease in wall stress during repeated episodes of hypertension, leading to a dilatation of the coronary wall. Once dilated, the coronary wall becomes "wrinkled" when it returns to its original shape, on the return of blood pressure to normal values. This "wrinkled" contour leads to modifications of the typical structure of the arterial wall in the region adjacent to the endothelium, increase in circumferential stress, and alteration of the shear stress. As a result, the endothelium will lose its elastic properties, generating a turbulent laminar coronary flow.

At the same time, during these repeated episodes of coronary wall dilation and contraction the vasa vasorum are compressed, causing alterations of the nutrition of the coronary wall, temporary modifications of the fibroblasts, alteration of endothelial integrity, and dissection. The endothelial structures lose their contact with internal structures, and the process is continued by fibroblast deposition, proliferation, and mastocyte migration. The recurrence of subsequent episodes of hypertension leads to the augmentation of these processes, finally resulting in atherosclerosis (Figure 2).

PATHOPHYSIOLOGICAL SUBSTRATE OF SUBCLINICAL ATHEROSCLEROSIS — A CONTINUING MYSTERY?

In spite of recent progress in understanding the physiopathology of acute coronary syndromes, many key aspects involved in the development of this disease remain unclear. For instance, many patients presenting at an emergency department with typical chest pain, an electrocardiographic pattern characteristic for acute myocardial infarction, and a significant raise in cardiac enzymes have normal coronary arteries as shown by routine coronary angiography. According to reported studies, acute coronary syndromes in patients with normal coronary arteries, as indicated by angiography, have a prevalence of 10 to 20%.[1,2] This distinct pathophysiological entity is termed "acute coronary syndromes with angiographically normal coronary arteries". Different theories have been proposed to explain the cause of this odd clinical presentation, such as coronary vasospasm, coronary embolism, myocardial bridging, or coronary artery dissection.[1–3] When no possible cause can be identified, this clinical presentation is termed "coronary X syndrome", an expression suggestive of the fact that the etiology remains a mistery, and though attempts have been made to associate this atypical presentation with a possible etiological factor, as yet no direct relation has been proven.[3,4]

ENDOTHELIAL DYSFUNCTION — THE PATHWAY FROM HYPERTENSION TO ATHEROSCLEROSIS

The role of endothelial dysfunction (ED) in the pathogenesis of atherosclerosis and in the initiation and progression

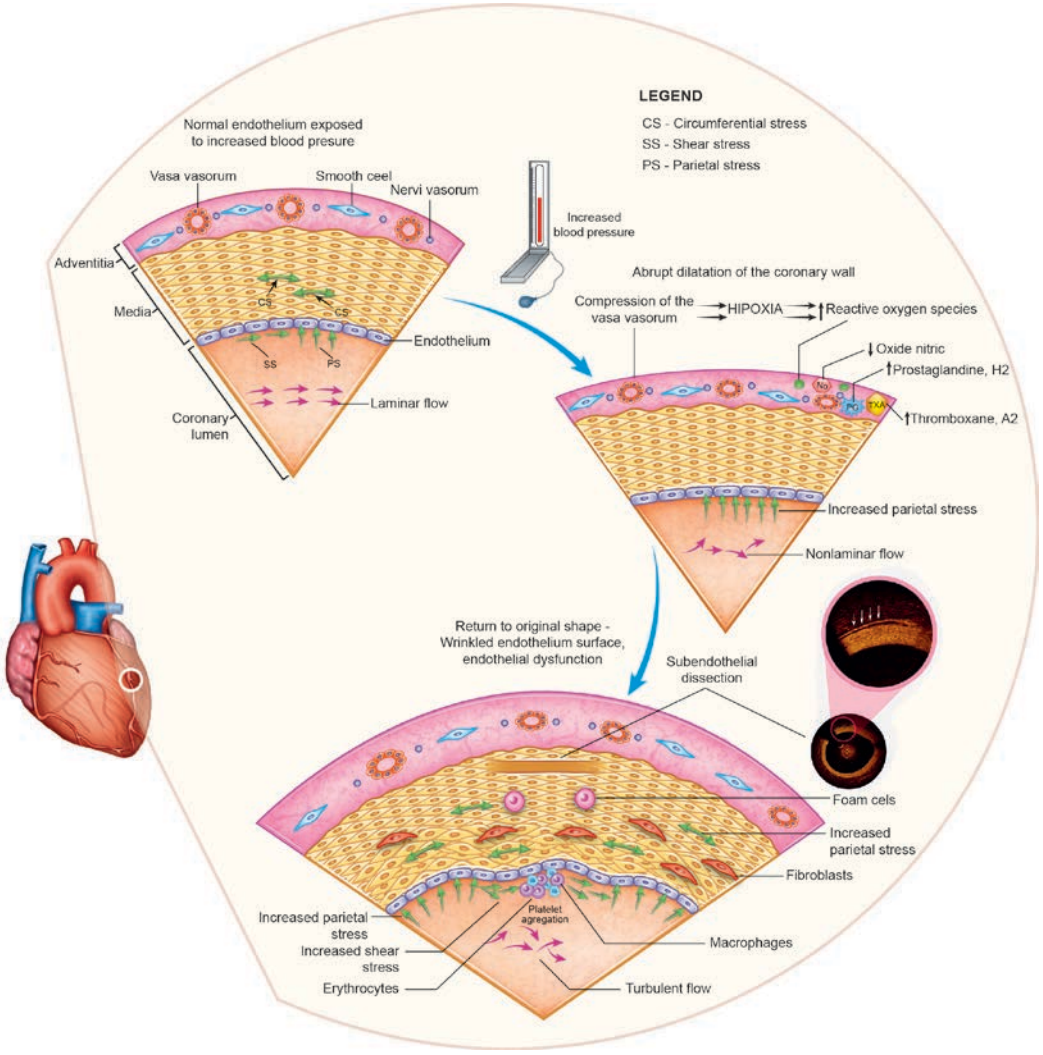

FIGURE 2. From hypertension to atherogenesis via mechanical stress

of coronary artery disease has been described and demonstrated.[5–7] When ED occurs, the endothelium loses its protective role and becomes a pro-atherosclerotic player, releasing pro-atherogen and vasoconstrictor substances and mediators, such as endothelin ET-1, thromboxane A2, prostaglandin H2, and reactive oxygen species.[7]

The increased parietal stress caused by arterial hypertension leads to a reduction in the nitric oxide (NO) production at the level of the vessel intima, and, subsequently, to an increase in the production of free radicals. The augmented oxidative stress associated with ED promotes vascular lesions, platelet aggregation, smooth muscle fiber proliferation, increased macrophage migration, and an overall promotion of inflammation.[4,5,8] This is probably the key pathophysiologic link between hypertension and typical atherosclerosis.

Different types of pressure are exerted on the arterial wall. The normal stress caused by blood pressure acts perpendicularly to the arterial wall, while the so-called "shear stress", or fluid-wall shear stress, acts parallel to the wall. At the same time, cells within the arterial wall are exposed to circumferential wall stress, which varies according to the elastic properties of the vessel.[9]

A low arterial shear stress, below 4 dyne/cm^2, has been demonstrated to be frequently encountered at the level of atherosclerotic plaques, being associated with an atherogenic phenotype and plaque vulnerability.[9]

SUBENDOTHELIAL CORONARY DISSECTION — A NOVEL FINDING IN ACUTE CORONARY SYNDROMES WITH ANGIOGRAPHICALLY NORMAL CORONARY ARTERIES

Vascular remodeling, arterial stiffness, increased and altered parietal, circumferential and shear stress caused by hypertension, along with the inflammatory process, in-

creased oxidative stress, and endothelial dysfunction, may contribute to the development of lesions in the vascular wall.

An increased intracoronary pressure may also lead to rupture of the vasa vasorum, resulting in a subintimal hemorrhage and an intramural hematoma, a condition associated with acute chest pain, though the coronary lumen retains a typical appearance on the coronary angiography.[10]

These alterations of the coronary wall structure are, in most cases, difficult to diagnose using coronary angiography, as this technique allows visualization of the coronary lumen and detection of the luminal narrowing without providing any information about the vessel wall.[11] This can explain the angiographically normal aspect of coronary arteries in patients with acute coronary syndromes and a slow-flow pattern. The assessment of coronary wall structure has become possible in recent years, following the introduction of optical coherence tomography, which has become the golden standard technique for visualization of ruptures in the coronary endothelium.[1] The techniqur allows the identification of zones with even minimal subendothelial dislocation of the coronary vessel layers, the so-called subendothelial dissection, which is another form of separation between the media and adventitia, distinct from the intramural hematoma and the classical endothelial dissection. This subendothelial dissection could be a starting point for the advancement of the atherosclerotic process. Repeated episodes of a sudden raise in blood pressure are present in the history of almost all patients with coronary artery atheromatous plaques and may represent the key element that triggers the destructuration of the endothelium leading to subendothelial dissection. In severe cases, this subendothelial dissection becomes manifest immediately, and the patient presents at an ER with typical chest pain, without any significant luminal narrowing as shown by coronary angiography. In less severe cases this remains clinically silent but may still trigger the future development of an atheromatous process via a complex mechanism involving endothelial dysfunction, alteration of wall nutrition due to compression of vasa vasorum, macrophage accumulation, and increase of the parietal stress leading to non-laminar flow.

CONFLICT OF INTEREST

Nothing to disclose.

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