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Original Research

The Senescence Process of Internal Thoracic Artery

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Abstract

Objective: The internal thoracic artery (ITA) is the most widely used arterial conduit for coronary artery by-pass, because it is very rarely affected by atherosclerosis. However, the state of its wall at the time of grafting procedure could influence the long-term outcome of coronary artery by-pass.

Methods: We have investigated 20 specimens of distal human ITA, derived from 14 male patients and 6 female patients, aged between 68 and 77 years, operated for atherosclerotic coronary artery disease. The specimens, collected after surgical skeletonization during coronary artery by-pass procedures, were fixed in 10% neutral buffered formalin and then paraffin embedded. In addition to haematoxylin & eosin, histochemistry (Weigert's staining, Van Gieson's staining, Verhoeff's staining) for elastic fibers, and immunohistochemistry for muscle cells (smooth muscle actin, caldesmon, desmin), nerve fibers (S-100 protein), and endothelial cells (CD34) were performed.

Results: A degenerative pathology, most likely due to aging, characterized by the fragmentation of the internal and external elastic membranes and by the consumption of the elastic network of the tunica media has been microscopically observed in a quarter of our patients, without the achievement of classical signs of overt atherosclerosis (cholesterol deposition, fatty infiltration, endothelial ulceration, intimal calcification), which could compromise the long-term patency of the graft.

Conclusions: The degenerative change is followed by a remodelling process, based on the proliferation of unspecialized muscle like cells, able to preserve the architecture and the stability of the arterial wall and consequently its functional long-term behaviour.

INTRODUCTION

The Internal Thoracic Artery (ITA) is the most widely used arterial conduit for coronary artery by-pass; for this reason a large number of researches, concerning with its anatomical, histological and functional aspects, have been performed [1-4]. It is well known that it is very rarely affected by atherosclerosis [5]. Nevertheless, a degenerative process, most likely due to aging, can be observed.

Our aim has been to evaluate if the state of its wall at the time of grafting procedure could influence the long-term outcome of coronary artery by-pass.

MATERIALS AND METHODS

We have histologically investigated 20 specimens of distal human ITA, derived from 14 male patients and 6 female patients, aged between 68 and 77 years, operated for atherosclerotic coronary artery disease. All 20 patients are alive from surgical procedure; only in a quarter of them we have observed a difficult functional recovery with transient heart failure. Our microscopic investigation has been particularly focused on this subgroup of patients. The surgical specimens, collected after surgical skeletonization during coronary artery by-pass procedures, were fixed in 10% neutral buffered

formalin and then paraffin embedded. Autopsy samples were not included in our series because immunohistochemical results were influenced by post-mortem tissue autolysis. All specimens were each other compared to find any histological, histochemical and immunohistochemical changes in the vascular wall, outside the normal structure of a healthy arterial vessel. In addition to Haematoxylin & Eosin, histochemistry (Weigert's staining, Van Gieson's staining, Verhoeff's staining) for elastic fibers and immunohistochemistry for nerve fibers (S-100 protein), muscle cells (smooth muscle actin, caldesmon, desmin) and endothelial cells (CD34) were performed. Tissue sections were submitted to immunostain for S-100 protein, smooth muscle actin (SMA), caldesmon, desmin and CD 34 antibodies. Briefly, after deparaffinization, hydration, endogenous peroxidase blocking, and heat-induced antigen retrieval, the tissue sections were incubated for 30 minutes at room temperature with S-100 protein (clone S100-prediluted; Ventana Medical Systems, Tucson, AZ), SMA (clone 1A4-prediluted; Ventana Medical Systems, Tucson, AZ), caldesmon (clone E89-prediluted; Ventana Medical Systems, Tucson, AZ), desmin (clone DER11-prediluted; Ventana Medical Systems, Tucson, AZ) and CD34 (clone QBEnd10-prediluted; Ventana Medical Systems, Tucson, AZ).. Biotinylated secondary antibody (Ventana) was applied and the staining product detected with avidin-biotin complex (ABC) against a hematoxylin counterstain. Detection of the staining reaction was achieved by an enzyme conjugated polymer complex adapted for automatic stainers from Ventana (Ventana Medical Systems, Tucson, AZ).

RESULTS

In our cases distal ITA displays a prevalent elastic component of the tunica media (Fig. 1A and 1B), while the tunica adventitia is scantly preserved for the surgical technique of skeletonization. In the tunica adventitia the nerve fibers run only around *vasa vasorum*, without generating real plexuses (Fig. 2).

The smooth muscle cells of the tunica media are resulted immunoreactive for smooth muscle actin, desmin and caldesmon. The elastic laminae, normally up to 12 laminae, are well ascertained by histochemical stainings. In all examined specimens, we have not found classical signs of overt atherosclerosis (cholesterol deposition, fatty infiltration, endothelial ulceration, intimal calcification).

In five specimens (25%), fragmentation of internal and external elastic membranes has been observed, together with the disappearance of elastic fibers in the tunica media (Fig. 1C and 1D). We have not found interlamellar spaces, with cystic appearance. On the contrary, elastic fibers have been replaced by a newly formed cell population, immunoreactive for smooth muscle actin and caldesmon, but not reactive for desmin and CD34 (Fig. 3). A parallel alteration has been noticed in the tunica intima, which appeared thickened, but without the achievement of luminal narrowing, for the presence of the same smooth muscle like cells. However, in all cases, CD34 antibody has shown an undamaged endothelium (Fig. 3D).

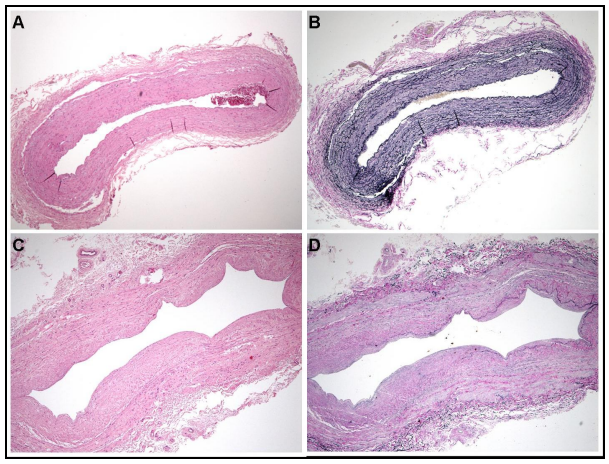

Figure 1. *1A and 1B:* Normal ITA: the tunica media shows a prevalent elastic component (A: Haematoxylin & Eosin, x40; B: Van Gieson staining, x40). *1C and 1D:* ITA in elastic degeneration: the disappearance of elastic fibers of the tunica media and the fragmentation of internal and external elastic membranes are noticeable (C: haematoxylin & eosin, x40; D; Van Gieson staining, x40).

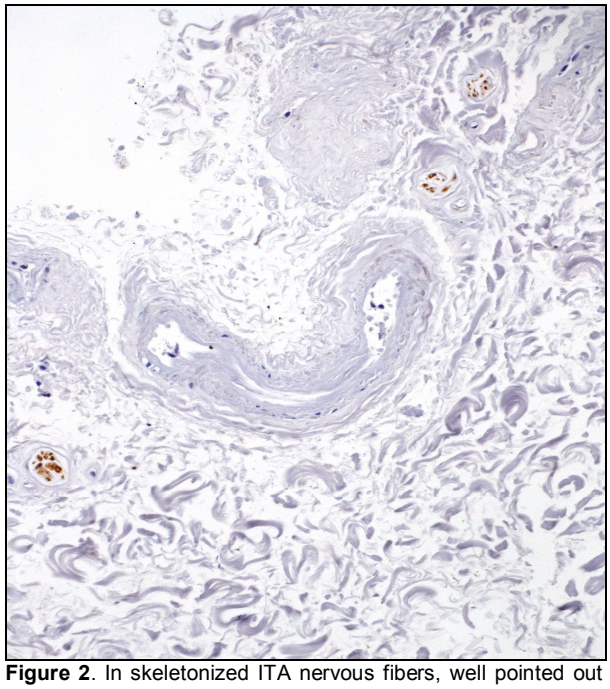

Figure 2. In skeletonized ITA nervous fibers, well pointed out by S100 protein immunostaining, run only around the *vasa*

vasorum of residual tunica adventitia (x200).

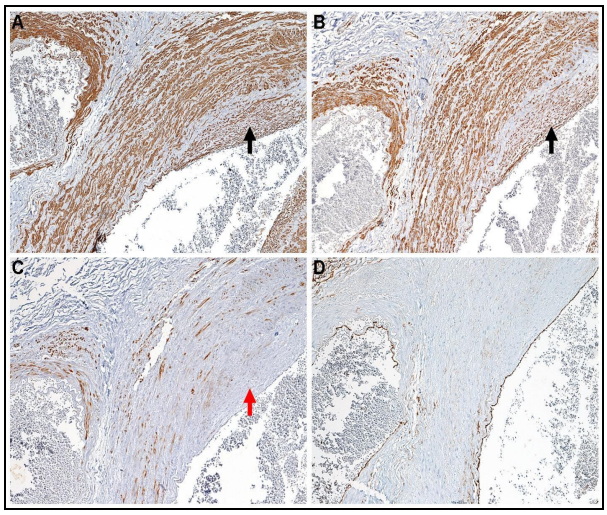

Figure 3. In the subintimal space (arrows) and in the tunica media the degenerated elastic component is replaced by newly formed muscle like cells immunoreactive for smooth muscle actin (A) and caldesmon (B), but not reactive for desmin (C) and CD34 (D). The endothelium above these cells is completely intact, as revealed by CD34 immunostaining (Immunohistochemistry, x100 for all panel).

DISCUSSION

Our histological findings confirm the prevalent elastic component of ITA. The fragmentation of elastic membranes and the disappearance of elastic fibers in the tunica media can be considered a degenerative change, primarily referred to senescence. The replacing cell population presents a muscular immunohistochemical profile, as pointed out by immunolabeling with smooth muscle actin and caldesmon. The absence of desmin expression confers to these newly formed cells only an unspecialized muscle phenotype, while the CD34 negativity allows excluding their 'vascular' origin. The replacement of degenerated elastic fibers by smooth muscle like cells can be as interpreted as the attempt to repair an age-related damage, through the proliferation of mesenchymal cells, in order to preserve the architecture and the stability of the whole arterial wall and consequently its functional behaviour, *in primis* the elastic capacity.

The origin of these cells should be found in the mesenchymal matrix, where a primordial stem cell could evolve towards a smooth muscle like cell, but not towards a more differentiated “vascular muscle” cell [6-8].

Aging is certainly the major factor in the damage of the elastic arterial component. More in particular, an attempt of damage repair is evoked in ITA through a cell proliferation, rather than a deposition of extracellular amorphous material. The function of these cells should be in fact to obviate the age-related disruption of the native elastic laminae and not to create a new smooth muscle like frame, poorly represented in an elastic artery [9]. Other more rudimentary mechanisms, as the deposition of extracellular collagen or the formation of pseudo-cysts, could be inefficient to guarantee the stability and the elasticity of the whole wall.

Moreover, these new cells seem to have the ability to migrate in the sub-intimal space, across fenestrations of the internal elastic membrane, in the attempt of repairing its destruction. The disappearing of the internal elastic membrane has been also observed in the development of atherosclerosis, together with other classical signs of overt atherosclerotic disease, absent in all our investigated cases.

Our observations confirm the ITA special feature of not to be prone to atherosclerosis, making it a suitable vessel for coronary artery bypass grafting. It is the blood vessel of choice for this procedure, also because it is rarely involved by functional spasms, being devoid of efficient nervous innervation after its surgical skeletonization [10, 11]. The conspicuous elastic component of ITA explains its compliance to change blood flow in proportion to coronary demands. The gradual disappearance of elastic component, replaced by smooth muscle like cells, as observed only in some of our cases, can be primarily referred to aging [12].

It has been suggested that the presence of newly formed smooth muscle like cells acts as a protecting mechanism towards atherosclerosis [13]. On the contrary, according to others Authors, the occurrence of these cells in the sub-intimal space can be considered the first step towards the atherosclerotic disease [14-17]. In our opinion the process of senescence should be separated from the onset of atherosclerosis: the disruption of the elastic component of ITA and the proliferation of smooth muscle like cells appear to be the result of aging, followed by a finalized process of remodelling, independent from the development of atherosclerosis [18, 19] and supported by the absence of endothelial damage, the well-known first step towards atherosclerotic disease.

The destructed elastic component of the tunica media is replaced by new smooth muscle like cells and not by collagen fibers, preserving the arterial wall from fibrosis, that instead play an important role in atherosclerosis, as demonstrated in aneurysms of large arteries, where a primary process of elastolysis, with proteolytic degradation and chemical alterations of the elastic fibers, has been observed [20-22].

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