

## Histological Characterization of the Internal Thoracic Artery as Preferred Conduit for Coronary Bypass

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### Abstract

#### Background

The Internal thoracic artery is today the preferred conduit for coronary bypass. This correlates with the histological characteristics of this artery. This particular topic was considered worthy of morphological researches, by the modern immune-histo-chemical techniques.

#### Methods

Histological researches, performed also with immune-histo-chemical techniques were performed on surgical specimens of internal thoracic artery of patients submitted to coronary surgery.

#### Results

Internal thoracic artery is a small-medium vessel with prevalent characteristics of elastic vessel, especially in its proximal part. It demonstrates a particular resistance to atherosclerosis, also in elderly. A possible elastotic degeneration, often secondary to age, can interest the elastic fibers of the internal membrane and of the tunica media. These degenerative lesions are repaired through a remodeling process. In this way, new smooth muscle-like cells are formed, which appear morphologically and functionally different from the vascular smooth muscle cells.

#### Conclusions

The internal thoracic artery, also when remodeled preserves its elastic capacity and resistance to atherosclerosis, ensuring good functional characteristics with a reactivity normal to vasodilators, but decreased to vasoconstrictors.

**Keywords:** Internal thoracic artery; Pathological fragmentation; Elastic vessel; Vascular endothelial

**Abbreviation:** ITA: Internal Thoracic Artery

### Introduction

Today the internal thoracic artery (ITA) is the preferred conduit for coronary artery bypass. It has been clinically demonstrated that an arterial conduit fits better with the hemodynamic conditions of an arterial system, where a systemic arterial pressure is present. The recent surgical improvements allow to use a single pedicle of ITA for multiple bypasses. They can be also constructed sequentially, implanting in a T fashion an adequately long segment of ITA on the contralateral pedicle, which acts as unique arterial vascular conduit [1,2]. Being an artery of medium-small caliber, ITA should be expected to be involved by atherosclerotic lesions, especially in elderly patients, that often present other localizations of this disease. However, ITA seems to enjoy of a privileged preservation toward atherosclerosis.

### Clinical Correlations

The arteries can be subdivided, according to their microscopic structure, into large elastic conducting arteries and medium-sized muscular distributing arteries. From a clinical point of view, three different types of arterial grafts have been proposed: type I - somatic arteries; type II - splanchnic arteries; type III - limb arteries. Type I arteries, such as ITA, are equipped of enhanced endothelial functions and release a significant amount of nitric oxide. Type II arteries, such as gastro-epiploic artery, and type III arteries, such as radial artery, show higher reactivity to vasoconstrictors and are prone to spasms, requiring more active pharmacological interventions [3]. Clinical

correlations disclose the elastic behavior of ITA, despite of its size. First, early angiographic controls after coronary artery bypass, performed with ITAs, have demonstrated a prompt and evident dilatation of these arterial conduits that adapt their caliber to the increased blood necessity of the new periphery. This can be explained considering the prevalent elastic component of ITA media, particularly in its first part (Figure 1). Second, in coronary surgery, the use of catecholamines at the end of cardio-pulmonary bypass is not contraindicated, not demonstrating a particular negative effects on ITA grafts. This fact further confirms the prevalent elastic component of ITA wall. Third, the difference between the caliber of a single native ITA and the multiple bypassed coronary branches is often evident at surgery. However, the excellent clinical results, also in early stages, support the good elastic compliance of ITA, able to supply an enlarged periphery. Fourth, according to the new surgical techniques, the ITAs are singularly skeletonized, and not with their entire pedicle, which includes artery, veins, autonomic nervous fibers, and interstitial connective tissue. In this way, many peri-arterial

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**Received** November 11, 2013; **Accepted** January 18, 2016; **Published** January 23, 2016

**Citation:** Manenti A, Roncati L, Caprili L, Fedeli C (2016) Histological Characterization of the Internal Thoracic Artery as Preferred Conduit for Coronary Bypass. J Mol Histol Med Physiol 1: 103

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**Figure 1:** The abundant elastic component of ITA wall (insert) is highlighted by histochemistry for elastic fibres (Weigert stain, x 2.5).

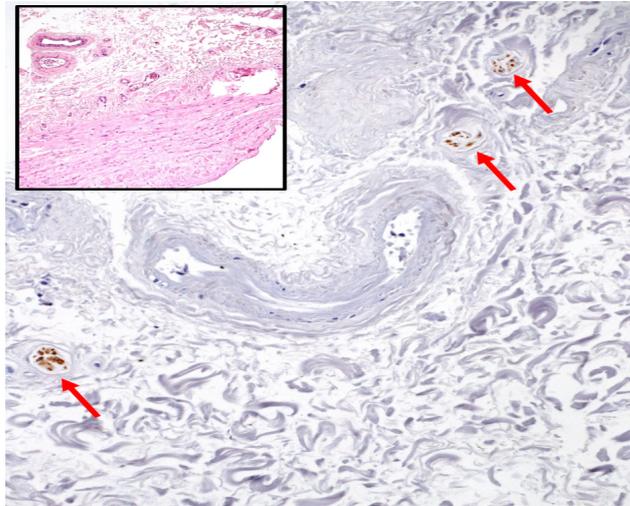
autonomic fibers are interrupted from their afferent connections, and the ITA wall is deprived of a complete innervation (Figure 2). This agrees with a reduced answer of skeletonized ITA to adrenergic stimuli [4-7].

### Histological Observations

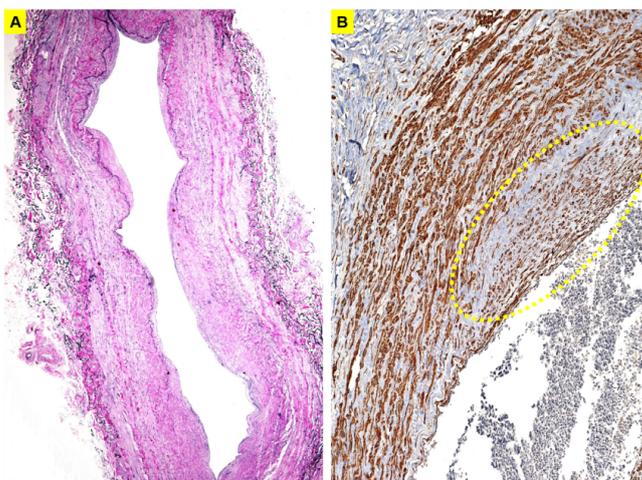
We have performed histological researches using fresh surgical specimens, instead of autolytic material, not suitable for immunohistochemical studies. Obviously, we have used the discharged segments of ITA grafts, usually corresponding to their distal part, but upstream to its bifurcation in musculophrenic and superior epigastric artery. In a series of 20 specimens collected from as many patients, aged between 68 and 77 years, operated for atherosclerotic coronary diseases, we have not found signs of overt atherosclerosis in ITAs, as intimal calcification, fatty infiltration, cholesterol deposition, etc. This agrees with analogous results of other studies [1,2]. Interestingly, in five specimens (25%) we have noted a pathological fragmentation of the elastic component of the arterial wall (elastotic degeneration), mainly involving the proper elastic fibers of the media and the internal elastic membrane. More in detail, we have observed the elastic fibers replaced by newly formed smooth muscle-like cells. These cells have been resulted immunoreactive for smooth muscle actin and caldesmon, but not for desmin (Figure 3). They have been also detected in the sub-intimal space, where they are prone to repair the fenestrations of the internal elastic membrane, preserving at the same time the endothelial integrity. We have considered this finding as secondary to senescence and not to atherosclerosis, interpreting this exuberant proliferation of new smooth muscle-like cells a sort of compensation mechanism to the elastotic degeneration [8-13]. The above mentioned cells, replacing the elastic fibers, have showed an immunohistochemical profile coherent with smooth muscular elements. The absence of desmin expression has indicated an unspecialized muscle phenotype, while the CD34 negativity has excluded their vascular origin.

### Discussion

We have interpreted our histological observations as the result of



**Figure 2:** All around ITA wall (insert) a nervous network is well noticeable by immunohistochemistry for nervous fibres, pointed by arrows (S100 protein, polyclonal, Ventana, x 20).



**Figure 3:** ITA wall diffusely involved by elastotic degeneration (A, Weigert stain, x 2.5): the elastic fibres are replaced by newly formed muscle-like cells (circle), revealed by immunohistochemistry (B, smooth muscle actin, clone 1A4, Ventana, x 20).

a remodeling process, able to repair the age-related damages of the elastic fibers, so preserving the elastic capacity, the architecture and the peculiar stability of ITA wall. The source of these muscle-like cells can be found in primordial mesenchymal stem elements located in the connective tissue of the adventitia, present also in skeletonized ITA [14,15]. They can evolve toward smooth muscle-like cells under the action of different growth factors (GF), such as the epidermal (EGF), the platelet-derived (PDGF), and the vascular endothelial (VEGF). These growth factors act as potent mitogens, stimulating the smooth muscle-like cells and opposing their apoptosis. The absence of a relevant number of inflammatory cells in the remodeled ITA wall has allowed to exclude a concomitant action of cytokines or chemokines [16,17].

Two aspects of this remodeling appear particularly interesting. The first regards to the development of these cells towards a smooth muscle-like, and not a true smooth muscle, phenotype, provided

with an intrinsic elasticity. This represents a providential process of remodeling, instead of deposition of extracellular amorphous material with generation of pseudo-cysts that could impair the elasticity and stability of the arterial wall. The new cells well integrate into ITA wall, demonstrate a long life, and an increased resistance to atherosclerosis [18-20]. These characteristics have been also confirmed by clinical studies [1,2]. Their reactivity to vasoconstrictors, such as  $\alpha$ -adrenergic agents, endothelin and angiotensin, is decreased or abolished, while the action of nitrous oxide and other vasodilators is preserved and more pronounced than in muscular arteries [11,21].

We have considered ITAs as elastic arteries, mainly on the basis of their functional behavior and histological characteristics, in particular after remodeling. However, this histological aspect is more appreciable in their upper tract. They in fact origin from the subclavian arteries, which embryologically derivate from the fourth arch as part of the thoracic aorta [11,12].

Complications related to possible ischemia of skeletonized ITAs have not been reported [1,2]. The absence of a real network of vasa vasorum invites to consider essential the mechanism of diffusion of oxygen and nutrients through the endothelium towards the other components of the arterial wall. Noteworthy, the coronary subclavian steal syndrome, sometimes observed in hemodialyzed patients with upper extremity arterio-venous fistulas, is caused by a reversed blood flow in ITA, which persists notwithstanding an increased infusion of catecholamines, while disappears after external compression of the brachial artery. This further proves a preserved double-way permeability of the coronary bypass performed by ITA, resisting to adrenergic stimuli [22]. On the other hand, when a coronary bypass is followed by an early and acute cardiac ischemia, in absence of signs of anastomotic malfunction of ITA, the cause of this complication can be researched in the subclavian artery, narrowed at its origin and inadequate to supply an increased peripheral arterial network. The integrity of ITA endothelium has been remarked by our histological observations. In particular, we underline the absence of fibrin deposition, extracellular connective tissue matrix and recruitment of leucocytes. Besides, immunohistochemistry has successfully revealed the difference between smooth muscle-like cells and true smooth muscle cells. The cytological features of these smooth muscle-like cells do not correlate with telomere or other chromosomal dysfunction during their replication process [11,14,15]. Telomere pathology has been found associated with senescence and atherosclerosis, through its action on vascular smooth muscle and endothelial cells [23-27]. The newly formed smooth muscle-like cells follow not an atherosclerotic, but a remodeling process of the arterial wall, that justifies the good clinical results, also at long-term, of ITA as conduit for coronary bypass [1,2].

## Conclusions

The contribution of histology to clarify the peculiar hemodynamic properties of ITA is evident. ITA senescence is usually followed by remodeling, while atherosclerosis is absolutely rare, notwithstanding these two processes are often connected each other [20]. Interestingly, the new smooth muscle-like cells, that actively participate to the remodeling process, do not behave as senescent elements, nor cause dysfunction, and demonstrate a long expectation of life [1,2].

Contrariwise, venous grafts used for coronary bypasses undergo a phenomenon of arterialization, characterized by intimal hyperplasia and fibrosis of the media, resulting in thickened wall with possible lumen narrowing. They can complicate with thrombosis, aneurysmal dilatations and also atherosclerosis. This is mainly due to the systemic

arterial pressure, to which the new venous conduits are exposed, and to the limited compliance of the venous walls to this new function. In conclusion, the clinical relevance of the present study has been to explain the good results of ITA as arterial conduit in coronary surgery, through its systematical histological examinations. In the light of our findings, we can confirm that today ITA is the preferred choice among the conduits for coronary bypass.

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