Mechanical functional role of non-atherosclerotic intimal thickening

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Abstract—Arteries adjust to alterations in wall shear stress or tensile stress by changes in diameter, wall thickness, structure and composition. The intima participates in these adaptive reactions, particularly when changes in mechanical stresses are imposed after physiologic stress levels have been established during growth. Decreased wall shear stress due to decreased flow, flow separation or complex flow patterns, or increases in tensile stress due to increases in pressure or radius stimulate non-atherosclerotic intimal proliferation. Intimal fibrocellular hypertrophy (IFH), in the form of compact fibrocellular layers resembling the media, stabilizes when the lumen diameter is reduced sufficiently or wall thickness is increased sufficiently to restore baseline wall shear or tensile stress. Reactive-adaptive intimal proliferation is not necessarily self-limiting and may continue in the form of intimal hyperplasia (IH) which is relatively matrix-free and poorly organized. If mural and intimal changes do not result in restoration of baseline wall shear and tensile stress, IH may proceed to further narrowing and stenosis. Identification of the cellular and molecular mechanisms which underly the responses which link flow to diameter, diameter and pressure to mural restructuring, and mural restructuring to intimal thickening should provide new insights into the nature of vessel adaptations in the absence or presence of atherogenesis.

Key words: atherosclerosis; intimal fibrocellular hypertrophy; intimal hyperplasia; artery.

1. INTRODUCTION

The current widespread preoccupation with the nature of non-atherosclerotic intimal thickening stems from observations that an intimal proliferative response is often associated with the failure of surgical revascularization grafts [1] and dialysis access channels [2]. Anastomotic sites have been shown to be particularly prone to develop such local intimal thickenings. Research has been focussed on the possible role of locally released mitogenic factors [3] or local compliance mismatches [4]. Conditions which favor thrombosis have also received attention [5]. The term ‘intimal hyperplasia’ has been applied to the intimal reaction with the implication that the proliferation represents a pathologic state and that therapeutic measures should be directed against the proliferating or migrating cells. Arteries are, however, normally subject to an array of physical forces which may induce adaptive proliferative responses. These mechanical forces include wall shear stress at the lumen surface in relation to blood flow, viscosity and radius, and mural tensile stress in relation to pressure and radius. Mean wall shear stress tends to be maintained at about 15–20 dyne/cm² for mammalian arteries regardless of location [6, 7], while baseline tensile stress varies depending on vessel location [8, 9]. For homologous arteries, however, tensile stress in the media tends to be independent of species [10]. For example, tensile stress is about 2000 dyne/layer
for the aortic media and about 1000 dyne/layer for media of the pulmonary trunk. Imposed deviations from normal or usual mechanical conditions elicit adjustments which tend to preserve the stability and integrity of the artery wall with respect to both wall shear and tensile stress. These adjustments consist of alterations in wall thickness, composition and architecture which tend to restore baseline values and assure flow field characteristics consistent with optimal perfusion of supplied organs.

Findings in human arteries, in prosthetic vessels [11] and in experimental models [12] indicate that non-atherosclerotic intimal thickenings may participate in these reactions and contribute to the re-establishment of baseline shear and tensile stresses [13–16]. Reduction in wall shear stress may, for example, produce intimal widening, thereby narrowing the lumen, and increasing blood flow velocity and wall shear stress. Since wall shear stress is inversely proportional to the third power of the radius, a small change in effective radius is usually sufficient to re-establish baseline values. Conversely, imposition of an abnormal increase of flow rate and shear stress causes arteries to enlarge until the increased lumen radius restores wall shear stress to normal baseline values [6, 7]. The increase in radius results in an increase in tensile stress and may induce compensatory intimal thickening to increase wall thickness and restore tensile stress to baseline values for the particular artery [17]. In straight artery segments of more or less constant radius, these reactive–adaptive intimal thickenings tend to be uniform about the vessel circumference. At bends, bifurcations, branchings, anastomoses and other geometric transitions, the reaction is usually asymmetric and occurs in relation to local effective radii and flow field characteristics. Compensatory intimal proliferative reactions may be expected to be self-limiting and to terminate if and when baseline shear and tensile stresses are re-established. There is, however, evidence that the intimal proliferative response may proceed unabated if baseline conditions are not restored. Distinct morphologic features appear to correspond to the initial response, to the stabilized self-limiting response, to the progressive non-limited response and to transitions among these forms.

We have observed two principal and distinct forms of non-atherosclerotic intimal thickening [18]: (i) intimal fibromuscular hypertrophy (IFH), an orderly, layered widening of the intima including both smooth muscle cells and matrix fibers, echoing but not identical with the architecture of the media, and (ii) intimal hyperplasia (IH), a fairly uniform accumulation of non-oriented cells with smooth muscle and/or myofibroblast features, often in a stroma with few formed matrix fibers and without a well-defined layered architecture. Both of these changes differ from an atherosclerotic plaque (AP), which is usually an eccentric intimal deposit including smooth muscle cells and matrix fibers but also containing macrophages, lipid accumulations and necrotic debris. The components of AP are arranged in a more or less characteristic stratified topography with atrophy of the underlying media and deformation of vessel contour [19]. It is considered that IFH and AP are closely related, because these changes tend to occur in similar locations and lipids may sometimes be identified within IFH thickenings. Regardless of possible relationships to subsequent development of AP, neither IFH or IH contain regions of necrosis, pools of lipid accumulation or necrotic debris. Prominent IFH or IH may be present without evidence of plaque development, and relatively small plaques and fatty streaks may occur with little or no evidence of underlying IFH. Furthermore, the responses to alteration in flow which characterize IFH and IH are also evident in prosthetic grafts and in veins used in arterial revascularization procedures [1] and/or vascular access channels [2]. We submit that each of these forms has different implications with respect to vascular biology and pathology. Examples of IFH and IH are illustrated in Figs 1–3.
Figure 1. (A) The intima (I) of a section of coronary artery is composed of the distinct fibrocellular layers of intimal fibrocellular hypertrophy (IFH) including oriented smooth muscle cells and collagen and elastin fibers. The intima of the vessel was thickened uniformly around the entire circumference of the vessel cross-section and was nearly as wide as the media (M). (B) Intimal hyperplasia in the intima of an artery with a proximal occlusion. The proliferated smooth muscle cells are not oriented and the matrix is devoid of prominent connective tissue fibers.

2. INTIMAL FIBROMUSCULAR HYPERTROPHY (IFH)

At bends, IFH thickenings tend to form on the inner or concave side of the curve. At branch sites and bifurcations, IFH forms at the inflow region proximal to or opposite the flow divider. These are regions of flow separation, complex flow patterns and reduced wall shear stress [8, 9]. Since at geometric transitions these regions tend to be also subjected to increased tangential tension, the media tends to be thicker. The internal elastic lamina is usually preserved. Measurements in human arteries reveal that the width of the well differentiated fibrocellular intimal layers of IFH may be quite uniform [20]. In regions of IFH, such as the lateral wall of the internal carotid artery at the bifurcation, computations of mural tensile stress, which take into account only the width of the media, yield values that are abnormally elevated compared with regions without IFH. If, however, the media and intima are taken as total wall thickness, mural tensile stress approaches normal values in adjacent locations without intimal thickening [13]. In straight artery segments the orderly, stratified layers of intimal cells and formed fibers characteristic of this change (Fig. 1A) may be as thick or thicker than the underlying media, and may occupy the entire circumference of the vessel. IFH corresponds to that change which has usually been described as ‘diffuse intimal thickening’ and occurs as a circumferential or focal enlargement at many locations during growth, maturation and aging, and in relation to modifications in flow, radius or geometric configuration. It appears regularly in coronary arteries (Fig. 1A) and the distribution may be associated with the special and long-term modifications of coronary artery flow, geometric configuration and radius. Figure 2 shows typical IFH reactions in polytetrafluoroethylene (PTFE) grafts which were used in connection with the establishment of access channels for dialysis. These were flow stabilizing reactions which narrowed the lumen somewhat (Fig. 2A) or produced a regular smooth surface over a deformity (Fig. 2B). Thus, on both microarchitectural and functional grounds, it is reasonable to presume that IFH is
Figure 2. PTFE grafts used as access channels for dialysis. (A) Progressive resistance to flow resulted in the formation of well differentiated fibrocellular layers (IFH) which narrow but do not obstruct the lumen, augmenting flow and shear stress at the blood to graft interface. The surface of the graft material is regular (arrows) as is the lumen surface. (B) A site which has been punctured with subsequent scarification has deformed the surface of the graft and produced a deformity (arrows). The intimal fibrocellular reaction has overgrown the irregularity which had created a region of separation and low wall shear stress. IFH has restored a regular smooth blood to tissue interface (arrowheads).

an adaptive-reactive response to mechanical stresses related to local features of flow or wall tension or both, and that it ceases when baseline conditions of shear and tensile stress have been re-established. The absence of disruption, deformity or necrosis within the reaction provides further suggestive evidence that IFH is not, in most instances, a pathologic process. The mechanisms that regulate and limit this response at the cellular and molecular levels and define its limits remain to be illuminated.
Figure 3. (A) Intimal hyperplasia (IH) in a saphenous vein bypass (V). The section was taken distal to an occlusion. The endothelial surface is intact. (B) An intimal reaction which occurred in a PTFE dialysis access channel. An inner dense zone consists of the compact fibrocellular layers of IFH. A superimposed layer has the less differentiated appearance of IH. Conditions presumably changed to reduce flow after the inner region had stabilized as IFH.

3. INTIMAL HYPERPLASIA (IH)

In typical examples, the uniform compact fibromuscular layered structure of IFH is absent. Instead, the cells, although abundant, are distributed within a relatively uniform matrix without prominent fibers (Fig. 1B) or within a matrix containing delicate collagen and/or elastin fibers. IH is located preferentially at anastomotic sites where vessel walls and prostheses differ in compliance, composition and dimensions, where scar tissue replaces or deforms vascular tissue and at abnormal geometric transitions. The close association of IH with graft failure suggests that the completion of the self-limiting adaptive reaction which would restore baseline shear and tensile stress levels may be prevented or inhibited. The presence of abnormal configurations and/or reduced flow velocities continues to stimulate the intimal proliferative response. The reaction cannot stabilize and differentiate into the oriented composite fibrocellular layers of IFH because the proliferative reaction is prevented from altering wall shear or tensile stress sufficiently to restore normal baseline levels. Figure 3(A) shows an IH response in the intima of a saphenous vein used in bypass surgery. Flow rate was reduced below baseline because of stenosis at the anastomotic site. The proliferative response to the persistent stimulus continues, but the persistent reduced flow prevents the establishment of a stable IFH outcome. Low or decreasing distal runoff, progressing proximal stenoses, and geometric configurations and scarifications that create complex flow fields may all engender focal persistent low wall shear stress regions. The changes of IH are identical to those which are noted in progressive lumen obliteration, which occurs distal or proximal to any vessel obstruction or ligation. In contrast to IFH, IH may therefore be
considered to be a dysplastic–hyperplastic response, for it cannot resolve to the stable, layered, fibrocellular, architecturally differentiated IFH which echoes the morphology of the artery media. Like other dysplasias it appears to reflect the lack of formation of a structure consistent with an appropriate equilibrium state.

4. TRANSITIONS AMONG INTIMAL REACTIVE RESPONSES

Transitions between the non-atherosclerotic intimal reactions and in relation to AP would be expected to occur in the event of local temporal modifications of flow and wall tension, and with the imposition or modulation of clinical atherogenic risk factors [16, 21]. Changes in flow or configuration which restore baseline conditions may be expected to result in eventual arrest of IH with conversion to or superimposition of the more structured and stable IFH. This development may be unusual in view of the persistence of the underlying abnormal state at sites predisposed to IH. With progression of underlying disease leading to progressive or sudden decreases in wall shear stress, superimposition of IH on previously stabilized IFH would be expected to occur (Fig. 3B). Progression of AP to stenosis or complications would be expected to modify proximal, distal or local flow field conditions as well as the distribution of wall tension and wall motion. Examples of superimpositions among IFH, IH and AP are readily found, as are the isolated ‘pure’ forms (Figs 1, 2 and 3A) of each reaction.

IFH or IH may also occur in relation to the evolution and complication of APs and probably underlies to some degree the formation of the fibrous cap. IFH and/or IH also develop at focal plaque deformities resulting from ulceration or thrombosis. Conversely, a region of stabilized intimal thickening, which was initially a response to local diminution of wall shear stress or to increased mural tension, can become the site of subsequent atherogenesis with changing exposure to clinical metabolic risk factors or when local mechanical conditions modify near wall residence time of atherogenic particles or augment wall density to reduce transmural transport.

Whether the induced proliferative reactions stabilize and differentiate to form as IFH or progress as the relatively undifferentiated, matrix-poor IH, the initial induction phase is probably indistinguishable from IH. When baseline values of wall shear have been re-established, remodelling in keeping with the new distribution of tensile stress would be expected to lead to IFH as the new intima is integrated into the wall. In the event that the initial proliferative response is a reaction to increased tensile stress, the differentiated layered modelling would be expected to progress more or less in parallel with the proliferative response and in keeping with the magnitude and the rate of imposition of the inducing mechanical stress. Identification of the mechanical, metabolic and biosynthetic factors which regulate and modulate these transitions should permit the development of improved preventive and therapeutic approaches. Clinical and surgical interventions designed to restore normal levels of shear stress and tensile stress may prove more effective than those which suppress the proliferative response. Knowledge of the cellular and molecular mechanisms which govern the responses which link flow to diameter, diameter to mural restructuring, and mural restructuring to intimal thickening should provide new insights into the basis for vessel adaptations in the absence of atherosclerosis and for the factors which govern stability of the atherosclerotic plaque.
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REFERENCES