Research on Coronary Artery Stenosis

Restenosis After Coronary Angioplasty
Potential Biologic Determinants and Role of Intimal Hyperplasia

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Restenosis after successful percutaneous transluminal coronary angioplasty (PTCA) remains the major problem limiting the long-term efficacy of the procedure. Despite an extensive number of studies examining the clinical, morphologic, and technical factors associated with an increased risk of restenosis, our understanding of the problem remains incomplete. It is not possible to predict with a high degree of certainty which patients, vessels, or lesions will undergo restenosis. Despite many attempts, no controlled trial has proved successful in establishing an effective technical or pharmacologic solution to the problem. In general, these clinical trials have been flawed by a simplistic approach to what we are coming to appreciate as a very complex process. A remarkable but constant observation has been that despite the unavoidable intimal and medial injury, only the minority of dilated segments (approximately 30%) develop clinically important restenosis. The mechanisms responsible for some dilated lesions undergoing restenosis and for others remaining patent are central to understanding the problem.

This review focuses on the biologic mechanisms involved in the process of lesion restenosis. An attempt is made to relate the many theoretical concepts and observations in laboratory studies to results of clinical investigations and explain these clinical findings from the standpoint of the potential underlying biologic mechanism.

Proposed Mechanisms of Restenosis

Early platelet aggregation and thrombus formation, as well as late myointimal proliferation, probably both affect the development of the recurrent lesions after PTCA. The precise relation between these two processes remains uncertain. Because platelet-derived growth factor is a potent mitogen and because fibrocellular transformation of thrombus is well recognized, mural thrombus at the site of PTCA has been proposed as the primary mechanism. However, evidence fails to support the concept of a significant mass of thrombus being present as the initial lattice frame for most restenotic lesions. First, arteries that are widely patent 2 days after PTCA, free of obstructive thrombus, have exhibited restenosis at catheterization 4–6 months later. Second, because there is no evidence that fibrocellular transformation increases the mass of thrombus, it follows that for the thrombus to be the primary lesion of restenosis, the lesion should become evident early after angioplasty. Careful serial angiographic studies have shown that the peak incidence of restenosis occurs between 2 and 3 months after PTCA. Last, autopsy studies of restenotic lesions have failed to show thrombus as the predominant material.

In only a minority of cases that show restenosis in the first few weeks after PTCA can thrombus or suboptimal initial dilatation or both be considered a primary mechanism. Although some degree of mural thrombus formation after PTCA may be an important initiating or contributing factor, thrombosis per se probably does not determine the final response in most cases.

Direct and indirect evidence strongly supports the concept of intimal hyperplasia or proliferation of smooth muscle cells of medial or possibly of intimal origin as the fundamental process. At least seven autopsy reports have described the histologic status of the coronary arteries in patients who had undergone PTCA within the previous 6 months and developed recurrent lesions. The restenotic lesion in all cases consisted of intimal hyperplasia. In addition, intimal hyperplasia or thickening was consistently observed in all patients after PTCA whether or not restenosis occurred. Direct evidence has come from the study of restenotic lesions in coronary and peripheral atherosclerotic arteries treated with atherectomy. Tissue specimens from these lesions consisted almost entirely of hyperplastic smooth muscle. There is also a large body of indirect and experimental data. Intimal thickening

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induced by balloon injury in normal rat arteries reaches its maximum at 2 months.9 This time course of the intimal growth approximates that observed in humans after PTCA.4 Intimal hyperplasia is also known to be an important component of restenosis in the atherosclerotic rabbit artery.1 Medial smooth muscle cells are the major component of the arterial wall, and the only major reparative or reactive response of the arterial wall to various types of injury, either mechanical or inflammatory, is intimal proliferation from these cells. Two such clinical examples are accelerated left main coronary artery disease due to mechanical injury from guiding catheters10 and coronary arteritis from Takayasu’s disease.11

Although platelet-thrombus accumulation appears to be a contributing factor in restenosis after balloon dilatation3 and has received much attention in recent years, intimal hyperplasia is now emerging as a major mechanism responsible for restenosis after PTCA. Therefore, it is important to understand more about the biology of this process. This review is intended to focus on the mechanism of intimal hyperplasia after angioplasty. The two most important questions are what initiates smooth muscle cell hyperplasia and what determines the degree of hyperplasia because this should ultimately determine the presence or absence of a hemodynamically significant restenotic lesion.

**Growth Regulation of Vascular Smooth Muscle Cells—Growth Control of the Normal Vessel Wall**

Before embarking on discussion of intimal proliferation after balloon injury, it is appropriate to examine the growth regulation of normal vessel walls. In the normal quiescent state, smooth muscle cells proliferate at a very low rate (probably less than 0.1% per day).12 A number of in vitro and in vivo studies have suggested that heparin or its derivatives may have a central role in maintaining the low proliferative activity and normal quiescent state of smooth muscle cells.13 Smooth muscle and endothelial cells in a normal vessel probably are the main source of heparin or heparin sulfate.14,15 Heparin sulfates are known to inhibit smooth muscle cell proliferation and maintain the contractile phenotype.16

Alternatively, endothelial cells, macrophages, and platelets are thought to provide the mitogenic stimulus necessary for the growth of medial smooth muscle cells in normal vessels.14,15 It is therefore reasonable to postulate that smooth muscle cell proliferation is controlled by a complex interaction between the growth stimulatory and inhibitory factors.17 It seems that in the normal quiescent state, the growth inhibiting signal from heparin sulfate is predominant and the proliferative activity is low. We may therefore assume that in situations such as vessel damage from mechanical, inflammatory, or other causes, the release and production of a number of growth stimulating factors overcome the antiproliferative activity of heparin sulfates, smooth muscle cell proliferative activity is greatly increased, and the reparative healing process occurs. These possible growth factors will be discussed later.

In addition to the growth inhibitory and stimulating factors, the proliferative potential of the smooth muscle itself may also have importance in growth regulation. The proliferative activity of individual smooth muscle cells is believed to be heterogenous.18 Whether this heterogeneity is related to the phenotypic difference as a continuous spectrum from contractile phenotypes to synthetic phenotypes when responding to injury,19 or to a selective subpopulation that retains some immature proliferative property20 or just to a difference in the general property of smooth muscle cells is not known. One might assume that this heterogeneity does not influence the reparative or healing process of atherosclerotic arteries in response to balloon injury because as long as the atherosclerotic vessel walls contain some medial smooth muscle cells, the ability to proliferate appears to exist. However, this heterogeneity in proliferative potential may have a role in influencing restenosis after PTCA.

**Biology of Intimal Hyperplasia**

Information about intimal hyperplasia has been largely derived from animal studies, which have attempted to investigate the “response to injury” hypothesis in the investigation of atherosclerosis.21 Some of this information may be applicable to balloon angioplasty. After experimental balloon injury, denudation of endothelial cells is followed by platelet adhesion and aggregation, probably resulting in release of platelet-derived growth factor (PDGF) as well as other growth factors. PDGF is both mitogenic and chemotactic for vascular medial smooth muscle cells. It is thought, therefore, that smooth muscle cells stimulated by PDGF or other growth factors undergo proliferation and migration into the intima resulting in intimal hyperplasia. It has become apparent that at least five basic biologic factors are involved in this process: platelets, growth factors (including PDGF), endothelial cells, smooth muscle cells, and extent of injury, each of which is discussed in more detail below.

**Role of Platelets**

Within 10 minutes of balloon injury to the arterial wall, the platelets that make up the basal adhering layer conform to the highly irregular exposed intimal connective tissue and extend pseudopods into the connective tissue layer.22 Within 30 minutes of balloon injury, platelet factor 4 (PF4), one of the constituents in the α-granules, can be detected throughout the intima and media.23 Because PF4 and other platelet-secreted proteins like PDGF reside in the same granule population and are secreted in response to the same stimuli, it is likely that these proteins, including PDGF, also enter the vessel wall
after removal of the endothelial cells.23 Platelets adhering to the subendothelial surface lose 97% of their α-granules within 40 minutes, whereas most of the platelets that aggregate onto the adherent platelets retain their granules.24 In addition, 80–85% of PDGF which is released into the circulation near the injured site is rapidly inactivated and cleared by plasma protein, that is, α2-macroglobulin.25 The formation of a PDGF-protein complex in vivo may protect against this degradation.25

We may postulate, therefore, that the adherent layer of platelets in direct contact with subendothelial tissue delivers most of the PDGF and other growth factors to the injured vessel wall, whereas the aggregated platelets probably play little role in this process. Aggregated platelets undergo much less degranulation of α-granules, and much of the PDGF that is released undergoes rapid clearance in the circulation. In this manner, PDGF and other growth factors from the platelets are probably delivered locally to the injured tissue (media and intima) to assist in the repair process. The size of the surface area of smooth muscle exposed to platelets caused by denudation, dissection, or fissuring, rather than the intensity of platelet accumulation, may determine the amount of growth factors delivered to the injured site.

**Platelet-Derived Growth Factor and Other Growth Factors**

PDGF is a basic glycoprotein that consists of two polypeptides and is the most potent mitogen found in serum for cells of mesenchymal origin, including smooth muscle cells. It is not only chemotactic for these cells, but also for macrophages and neutrophils. PDGF may be responsible for attracting smooth muscle cells from the media of the artery into the intima as well as for the subsequent intimal proliferation. PDGF stimulates specific target cells by binding to cell surface receptors that mediate a cascade of events leading to DNA synthesis and cell proliferation. However, it is thought that PDGF alone does not optimally stimulate DNA synthesis. PDGF-stimulated cells require a second group of growth factors, termed “progression factors,” to initiate DNA synthesis and cell division.26 PDGF has been termed a “competence” factor in that it makes cells competent to enter the cell cycle by moving the cell from the arrest state (G0) to active cell cycling (G1). Further exposure to progression factors allows cells to enter the DNA synthesis or S phase.28 A number of progression factors are known, and some of them that may be important to intimal proliferation include epidermal growth factors from platelets and somatomedin-C from serum.

Platelets are not only the main source of PDGF in the circulation but are also believed to be the major source of epidermal growth factors and β-transforming growth factors.27 A strong synergistic effect on cellular proliferation among these growth factors has been reported,27 suggesting that their release at the site of injury may be important in wound healing.

In addition, injured smooth muscle and endothelial cells, and activated macrophages, also produce PDGF or PDGF-like molecules.28,29 The relative importance of such different sources of PDGF in stimulating smooth muscle cell proliferation is not known. Other growth factors that may be involved in smooth muscle cell proliferation include a mitogenic factor released from the dead smooth muscle cell, endothelial cell-derived growth factors and macrophage-derived growth factors that are different from PDGF, such as basic fibroblast growth factor (b-FGF) and interleukin-1.30 Although increased PDGF gene expression has been shown in human atherosclerotic arteries,31,32 there is no direct in vivo evidence that growth factors including PDGF are involved in the process of intimal proliferation. However, most investigators consider that these factors are undoubtedly important.14–17 A hypothetical model for considering the relation between these factors and intimal proliferation is shown in Figure 1.

**Role of Endothelial Cells**

Endothelial cells may have a major influence on the degree of intimal hyperplasia.33 This reasoning has come from the observation that when only small areas of endothelial surfaces were denuded and endothelial regrowth was rapid, little or no intimal hyperplasia was observed.34 When large areas of endothelial surfaces were denuded, the area last covered by regenerated endothelium was associated with the greatest degree of intimal thickening.35 These observations were considered consistent with the fact that postconfluent endothelial cells produce heparin sulfates, which inhibit smooth muscle growth. However, additional studies have shown that when large areas of endothelium are denuded, endothelium regeneration remains incomplete. Under these circumstances, endothelial regrowth was arrested 2 weeks after denudation in rabbits and after 6 weeks in rats.36 A relatively large denuded area was left “permanently” uncovered by endothelium.37 If the endothelium had a major role in determining the degree of intimal hyperplasia, then one would have expected to see continuing intimal thickening in chronically denuded areas. In contrast, this has not been observed. In chronically denuded areas, the thickness of intimal hyperplasia has reached its peak at 8 weeks and remained the same without increase in cell numbers or thickness for up to 1 year after injury.37,38 Therefore, at least in the animal models studied, the degree of intimal hyperplasia appears to reach its maximum at 2 months after injury despite the absence of endothelial cells. It thus appears that endothelial cells may have some limiting effects on intimal growth but are not the sole modulators.
Role of Smooth Muscle Cells

Studies examining the proliferative activity of smooth muscle cells have found that most enter the growth cycle between 2 and 3 days after balloon injury and the vast majority of proliferation is completed within 7 days. In addition, the population of nondividing smooth muscle cells remains relatively constant between 7 and 14 days, suggesting that if smooth muscle cells proliferate, they do so soon after injury. Smooth muscle cell proliferation thus appears to be an acute event related to the initial injury. It has also been shown that the total number of smooth muscle cells in the intima peaks at 2 weeks and remains relatively constant up to 1 year after injury despite a slightly increased cell replication rate that is countered by increased cell loss. In animal models, intimal thickening reached its maximum at 8 weeks (possibly 2–3 months in humans). It is therefore reasonable to postulate that the initial intimal thickening 2 weeks after injury is due to increased smooth muscle cell numbers, but that further increases in intimal thickness are due to increased cell volume as well as an important synthesis and accumulation of extracellular matrix and connective tissue.

This view is consistent with the observation that smooth muscle cells migrating into and proliferating within the intima exhibit ultrastructural and functional properties equivalent to synthetic phenotype cells in culture; such cells show increased amounts of synthetic organelles, for example, large amounts of rough endoplasmic reticulum, loss of the capacity to contract, and increased capacity to divide. In contrast, the contractile phenotypic cells possess the opposite properties and make up most smooth muscle cells in normal vessels. Cells of the synthetic phenotype synthesize four to five times the amount of extracellular matrix as that produced by contractile state cells.

Importantly, it has been estimated that about 50% of medial smooth muscle cells activated by balloon injury migrate and undergo approximately 3 rounds of division. These cells constitute eight ninths of the final intimal cell population, whereas the other 50% migrate without further proliferation and make up one ninth of the intimal cell population. The above evidence suggests that the intimal smooth muscle cells come from a large number of medial cells undergoing a very limited number of replications and that further intimal growth comes from the cellular hypertrophy and synthesis of extracellular...
matrix from these cells. One may postulate, therefore, that the population of medial smooth muscle cells activated or recruited for this process determines the degree of hyperplasia. According to this hypothesis, a large population of smooth muscle cells needs to be activated or recruited for restenosis to occur (Figure 1).

**Extent of Injury**

The next question is, “What factors modulate the number of medial smooth cells that are recruited for this process?” As previously noted, exposure to platelets and subsequent release of PDGF and other growth factors from α-granules into the medial smooth muscle has been proposed as the primary stimulus. However, exposure to platelets is neither the only way to initiate smooth muscle cell proliferation nor in itself an adequate stimulus to initiate intimal proliferation.

Animal studies have shown that superficial denudation is carefully carried out in a large area without damaging the media, increased smooth muscle cell replication is observed in the media, but no intimal proliferation occurs despite both platelet adherence on the surface and late recovery of endothelium. When a very narrow but deliberately deeper injury to include the media is performed, intimal proliferation occurs despite the fact that the denuded area is quickly and completely covered by new endothelium within 2 days. Also, intimal thickening has been shown to occur after balloon injury despite absence of platelets. In addition, plastic cuffing around an artery without causing stenosis or significant intimal damage can lead to intimal proliferation. Although small endothelial defects covered by platelets did occur in this situation, evidence suggested that necrosis of the medial muscle cells and leukocyte infiltration were the cause of intimal proliferation.

This evidence suggests that simple denudation and exposure to platelets may not be a strong enough signal to initiate marked intimal proliferation and that direct injury to smooth muscle cells, either mechanical or inflammatory, is essential for this process. It has recently been shown that atherectomy lesions causing damage with removal of smooth muscle layers are more likely to undergo restenosis. If we consider the effect of the commonly used embolectomy balloon catheter in experimental models, in addition to endothelial denudation and platelet aggregation, the balloon injury may also produce the following effects: 1) production of growth factors including PDGF and other mitogenic factors by injured and dead smooth muscle cells; 2) attraction of leukocytes and macrophages by mediators of the inflammatory response including PDGF derived from platelets; it is known that macrophages produce PDGF, basic FGF, and other growth factors and that neutrophils have been implicated in having a role in smooth muscle cell proliferation; 3) mechanical stretching of smooth muscle cells; prolonged or severe tensile stress has been shown to lead to smooth muscle cell proliferation. Although it seems likely that none of these factors alone could induce marked intimal proliferation, one may assume that the intense stimulus produced by the combination of such factors would cause an enhanced response.

Next, the differential effects of balloon catheters on a normal artery and on a stenotic atherosclerotic artery should be considered. Without focal stenosis in the segment to be dilated, it has been noted that the inflated balloon only stretches the artery by approximately 9% of its original diameter. However, in clinical angioplasty, a 0.2-mm stenotic segment, for example, will be dilated to at least 2 mm, a 10-fold increase in diameter. This means that the internal circumference of the arterial wall will be stretched to 10 times its length. In the atherosclerotic stenotic segment, part of the arterial wall is replaced by plaque, which is not usually stretchable, and therefore only the distensible segment that consists mainly of smooth muscle cells is subjected to most of the tensile stress. This may mean that when the stenotic lesion is dilated, the relatively normal wall segment of the lesion may be stretched to many times its original length. One could speculate that such intense injury could evoke an exaggerated reparative intimal proliferative response.

In addition, splitting, fissuring, and dissection of plaque and media are produced after angioplasty of an atherosclerotic lesion, which causes a much more intense thrombotic response than in normal arteries. In addition, a much greater area of smooth muscle cells is directly exposed to platelets, which could increase smooth muscle cell proliferation.

**Anatomic Substrate for Restenosis**

It is reasonable to suggest that if the same number of smooth muscle cells are exposed to injury, the more extensive the injury, the more intense the reparative response and the greater the restenosis. What, then, are the major determinants of the extent of injury?

If we review the literature concerning the structure of coronary stenotic lesions, the following conclusions can be drawn. First, the composition of the stenotic plaques may be quite different, containing varying amounts of fibrous tissue, lipid, calcium, and organized thrombus. Second, the shape of the lesion is noted to be concentric in 30% of all stenotic lesions, eccentric and polymorphous in 40%, and eccentric or “slit-like” in 30%. Third, as the atheroma increases in the vessel wall, the amount of medial smooth muscle decreases and may eventually be replaced almost entirely by plaque tissue. The disease-free wall segment of the coronary stenotic lesions has been noted to vary from 1% to 38% of total wall circumference in autopsy studies. One may therefore postulate that every coronary stenotic lesion has at least two relevant characteristics: 1) different composition of plaque structure
and smooth muscle around the entire circumference of the arterial wall, and 2) distinct morphologic plaque characteristics and thus a unique physical property that determines how it will respond to balloon dilatation. Obviously, during clinical angioplasty, balloon sizes, inflation pressures, and time could also influence the extent and shape of vessel wall injury. However, assuming the balloon is appropriately sized and inflation pressure is adequately applied, balloon inflation probably exerts a relatively uniform tensile stress exerted along the entire circumference of the lesion. The physical structure and property of the lesion may then determine where the stretching, splitting, fissuring, or dissection will occur.51 Much like pulling a string at both ends, the string breaks at its weakest point. In addition, because heterogeneity of individual smooth muscle cell proliferative activity is known18 and arteries of different locations respond differently to the same balloon injury,55 it is unlikely that the same amount of smooth muscle exposed to the same degree and shape of the injury will initiate the same degree of intimal proliferation. Nonetheless, it seems reasonable to hypothesize that the greater the amount of smooth muscle cell in a lesion, the greater the degree of intimal proliferation. The lesion itself may thus determine the amount of smooth muscle that would be exposed to injury. Thus, if this hypothesis is correct, the characteristics of the lesion may importantly predetermine the degree of intimal proliferation and the probability of restenosis. This concept correlates with clinical observations.

Lesion Characteristics and Clinical Predictors of Restenosis

There is some evidence to support the hypothesis that the greater the number of smooth muscle cells exposed to injury, the greater the chance of restenosis. The degree of vasomotor activity of stenotic coronary arteries is proportional to the amount of disease-free wall.56 If this is related to the amount of viable smooth muscle that is available for the recruitment into the process of intimal hyperplasia, we would expect lesions that have higher degrees of vasomotor activity to have a higher incidence of restenosis because of the larger amount of smooth muscle that is available. This is consistent with the clinical finding that restenosis is increased in patients who present with vasospastic, variant angina.37

It has also been suggested that the extent and shape of the injury is related to the restenosis. The tighter the stenosis, the greater the tensile stress that must be applied to the lesion and medial smooth muscle cells. For example, comparing a 0.2 mm lesion dilated to 2 mm with 0.5 mm dilated to 2.5 mm, the circumference of the former lesion is stretched to 10 times its original length compared with the latter lesion whose circumference is stretched to five times. Thus, the former may be expected to have a higher degree of intimal proliferation and restenosis. As noted in many clinical studies, initial stenotic lesions greater than 90% tend to have a higher restenosis rate. As also mentioned above, in eccentric lesions, the plaque-free wall segment is in direct contact with the balloon and subject to greater injury. Eccentric lesions may have a higher incidence of restenosis as noted in at least two clinical studies.58,59

Several studies have suggested that the restenosis rate is increased with increased length of the lesion. In longer lesions, more smooth muscle is possibly exposed to injury and platelet adhesion, which enhances the chance of restenosis. Lesions located in tortuous segments or branch points have been shown to be associated with increased restenosis. Also, these lesions are known to be associated with increased dissection. This type of irregular geometry may promote more extensive injury.

In the above examples, we have attempted to correlate the concept of the anatomic substrate with clinical observations. It must be appreciated, however, that at the same time the quantity and proliferative potential of smooth muscle cells in the lesions, the regional flow characteristics, and other factors may also influence the occurrence of restenosis.

Regional Flow Characteristics

Restenosis is thought to be largely related to the degree of intimal hyperplasia. A significant degree of intimal hyperplasia has been consistently observed to occur in normal arteries after balloon injury, but this intimal thickening is usually not associated with any significant decrease in luminal diameter.60 Other factors must play a role in luminal reduction in atherosclerotic arteries after PTCA in addition to the initial severity of intimal proliferation.

Relation Between Low Wall Shear Stress and Intimal Thickening

Recently, direct assessments of shear stress in animal studies and human cadaver experiments have provided strong evidence that intimal thickening tends to be located in low wall shear stress areas of the arteries, such as in the lateral position of an arterial branch,61 and further correlation revealed that there was an inverse relation between the intimal thickness and the level of wall shear stress, with a positive relation between the intimal thickness and the degree of fluctuation of wall shear stress.61 Several studies in venous bypass grafts in humans as well as in animals also have suggested an inverse relation between blood flow rate and the degree of intimal proliferation.62,63

With regard to fluid dynamics, especially in the case of poststenotic regions, the areas of low wall shear stress are also associated with flow separation, that is, a reversal or disturbance of the flow, and a greater fluctuation of wall shear stress. This may be important because it has been suggested that it is the greater fluctuation of wall shear stress or disturbed flow rather than the absolute value of the time-average mean wall shear stress that leads
to increased endothelial cell turnover and intimal thickening.64 Importantly, a recent in vivo study has shown that the poststenotic region of subcritical stenoses, for example, less than 60%, is associated with increased intimal thickening, and this intimal thickness also correlated inversely with wall shear.65 In addition, in vivo and in vitro studies have suggested that the wall shear stress may influence endothelial recovery after denudation.66-68 Although from these studies, the exact relation between these two factors is not clear. If an extreme deviation of shear stress from normal retards endothelial recovery, this could lessen the inhibitory effect of endothelium and thereby enhance intimal proliferation.

Relation Between Optimal Wall Shear Stress and Arterial Luminal Diameter

In addition to the fact that low wall shear stress promotes intimal thickening, many animal studies have shown an association between wall shear stress and structural changes in the arterial lumen.69,70 The wall shear stress in blood vessels is proportionate to the blood flow velocity and blood viscosity and inversely proportionate to the cube of vessel radius in the state of laminar flow. It has been shown that if the blood flow is increased, for example by arteriovenous shunts that increase wall shear stress, an adaptive increase in arterial luminal size is observed. This increase in luminal size lowers the elevated wall shear stress, and the increase in lumen continues until the shear stress decreases to its original level.69 Alternatively, if the blood flow is decreased, usually by a proximal stenosis that decreases the wall shear stress, there is an adaptive decrease in arterial lumen size. This decrease in luminal size elevates the wall shear stress, and the decrease in lumen continues until the wall shear stress is returned to normal.70 This autoregulatory response of lumen diameter to change in flow rate in order to optimize or normalize the wall shear stress has been shown to be endothelium dependent, and this response may lead to structural modification of the arterial wall as opposed to simply sustained contraction or relaxation of vascular smooth muscle.70 It is believed that this endothelium-dependent phenomenon can be attributed to the endothelial cell’s sensitivity to wall shear stress, and increased wall shear stress may cause first an acute and then a sustained increase in endothelium-derived relaxing factor (EDRF) production or release, which could cause a sustained increase in luminal diameter. An additional mechanism for this vascular response may relate to a sustained increased production of prostacyclin by endothelium in response to increased blood flow. In any case, according to Laplace’s law, one may assume that such a sustained increase in luminal diameter results in an increase in wall tension. The increased wall tension may then trigger a compensatory growth of medial tissues that leads to the final structural changes.71

One interesting study has shown that this flow-luminal diameter relation may be operative in humans; it was noted that aortocoronary venous grafts could respond to increased demand of blood flow through that graft by chronically increasing luminal diameter.72

Wall Shear Stress and Restenosis

In summary, the foregoing evidence suggests that low wall shear stress may enhance intimal proliferation and modify the arterial wall to decrease the lumen (Figure 1). How is this concept of wall shear stress related to restenosis after coronary angioplasty? First, for this mechanism to operate, the stenotic lesions of arteries may need to possess adequate amounts of smooth muscle to respond to balloon injury and endothelial regulatory factors. Although endothelial dysfunction has been noted in atherosclerotic arteries and although regenerated endothelium after denudation may not function normally, indirect evidence suggests atherosclerotic arteries are still able to respond to increased or maintained flow with diameter enlargement.73,74 Recent evidence also suggests the deendothelialized artery can respond to changes in blood flow. Conceivably, because most (70%) of the coronary stenotic lesions are eccentric and possess varying degrees of normal wall segments, the residual normal wall segment may be able to respond according to the flow-diameter relation.

Second, although there are no well-documented studies showing complete endothelial recovery, as a rule, animal studies and human autopsy studies support the concept that complete endothelial recovery is achieved in coronary or peripheral arteries within the first few weeks after denudation.75,76

Third, moderate (e.g., >40-50% cross-sectional area) stenoses in experimental models are associated with significant poststenotic regions exposed to disturbed flow and low wall shear stress.77

If these observations are applied in the setting of coronary angioplasty, we may postulate the following events. After angioplasty of stenotic lesions, the luminal geometry is often drastically changed. There is an immediate active process of intimal proliferation set off by angioplasty injury and an entirely new flow-luminal diameter relation after endothelial recovery. Suppose a significant residual stenosis persists after angioplasty. The exit segment of the stenosis would be associated with a large flow separation area, which would not only enhance intimal proliferation but may also further decrease the lumen by structural wall changes after the endothelium is completely recovered but continues to be exposed to low shear stress. In the entrance segment of the stenosis, however, the flow rate and thus the shear stress is increased due to some degree of luminal narrowing in this segment. After complete endothelial recovery, this increased shear stress may increase the lumen, and this may reduce the flow separation area in the exit segment. How-
ever, if endothelial recovery occurs a few weeks after injury when the process of smooth muscle cell proliferation probably has been mostly completed and if the flow separation area is large and the reparative response is intensive, newly formed intima may increase the flow separation area and the possible beneficial effect of the increased shear stress in the entrance segment may not have an opportunity to exert an influence (Figure 2A). Thus, if a stenotic lesion is less than optimally dilated or located where flow separation inherently occurs, such as at bifurcation or curvature, the resultant increase in luminal diameter may fail to increase the blood flow to correct and optimize low shear stress conditions in the immediate poststenotic segment or the inherently existing flow separation area. The dilated segment, instead of being benefited, may undergo further narrowing because the low shear stress conditions would likely promote intimal growth and in addition cause wall structural changes that would likely decrease the lumen.

With the same basic assumptions, if a mild residual stenosis with relatively small flow separation persists after angioplasty, not only may intimal proliferation be retarded because of small areas associated with low wall shear stress, but also the increased wall shear stress in the entrance segment may increase the lumen and cause the flow separation areas to disappear. The dilated segment of the coronary artery may undergo structural change to maintain or increase the luminal diameter to optimize the shear stress, even if this has been successfully and mechanically opened. Further, if relatively high or normal levels of shear stress are maintained, the intimal thickening may regress after the peak reaction is completed.78,79 (Figure 2B).

**Restenotic Phenomenon From the Viewpoint of Regional Flow Characteristics**

One may reasonably assume, therefore, that the flow-lumen relation may be operative and that flow separation areas may exist in human coronary arteri-
ies following PTCA. In the clinical setting, a less than satisfactory residual lumen after coronary angioplasty or a postdilated residual stenosis greater than 30% is associated with increased restenosis. This is probably not only because given the same degree of intimal growth after angioplasty, the greater the residual stenosis, the greater the chance of recurrence, but also because a larger postdilation residual stenosis tends to be associated with a greater flow separation area; that is, there is a low shear stress area that may promote intimal growth. This hypothesis is supported by another observation. An increased postdilated transstenotic pressure gradient, for example, greater than 15 or 20 mm Hg, is associated with increased restenosis. A high transstenotic pressure gradient usually indicates a greater area of flow separation. Intimal growth may be induced under these conditions, and the chance of restenosis may be increased.

It may be possible, therefore, that a suboptimal hemodynamic result will cause a self-perpetuating cycle. Alternatively, a good result with minimal-to-mild residual stenosis or pressure gradient would break this cycle, and in fact, the new flow-luminal diameter relation may be established and explain the long-lasting effect of coronary angioplasty in most cases. This phenomenon may also explain the frequent observation of late improvement in luminal geometry in a subset of patients after PTCA.

Dilated lesions of the left anterior descending artery are also associated with increased restenosis. Although the mechanism is unclear, one explanation can be offered from the viewpoint of fluid dynamics. It has been estimated in humans that the blood flow velocity in this artery is about 1.5 to 2.5 times that of the right or left circumflex arteries. As noted previously, for the same degree of residual stenosis, a greater blood flow tends to be associated with a greater area of fluid separation and thus neointimal hyperplasia.

The high coronary wedge pressure associated with a high-grade lesion, or dilatation of a chronic total occlusion, has been associated with increased restenosis. Both situations have been shown to be associated with increased incidence of coronary collaterals. It is possible that after PTCA, antegrade coronary flow is relatively decreased because of collaterals. The decreased antegrade flow may be assumed to promote neointimal growth. This is in keeping with the observation that stenosis severity of bypassed coronary lesions accelerates in the first few months after bypass surgery and may be another example of a low-flow state and possibly disturbed flow accelerating neointimal growth.

In addition, it has been noted that at vessel branch points, the shear stress on the wall opposite the flow divider decreases as the branching angle increases. For example, in one study, the wall shear stress decreased by sixfold when the branching angle was greater than 105°. The same may be true for tortuous vessel segments. The wall shear stress tends to be decreased on the side of lesser curvature. Thus, stenotic lesions located at branch points, ostial sites, or tortuous segments are often inherently associated with disturbed flow and low wall shear stress because of the arterial geometry and flow characteristics. Even after successful dilatation, the dilated lesion may still be subject to disturbed flow due to the local luminal geometry. In clinical studies, right ostial lesions, branch points, and segments with marked tortuosity have had higher rates of lesion restenosis. These data further support the hypothesis that abnormalities in flow separation contribute to restenosis.

Complex Biologic Determinants

In the dilated atherosclerotic vessel, it is likely that in addition to flow characteristics, other factors influence restenosis. For example, let us assume that a significant residual stenosis remains after balloon dilatation either because the smooth muscle cell depleted and fibrotic vessel is less stretchable or because a conservative dilatation produces less tensile stress and injury to the existing smooth muscle cells. In either case, it may be postulated that the segment exposed to increased flow separation contains less damage and fewer smooth muscle cells capable of responding. Not only may intimal proliferation not occur, but the entrance segment may further dilate, responding to increased shear stress. Alternatively, it may be postulated that if a mild residual stenosis is achieved because of a relatively more muscular segment, or because a large amount of tensile stress is exerted and smooth muscle cells are damaged, intimal proliferation may occur despite the absence of significant flow separation in the segment. These phenomena may explain the apparent angiographic stability and even improvement of some “suboptimal” dilatations and the marked restenosis observed after some “optimal” initial dilatations.

Restenosis is the final result of the interplay between many biologic determinants. We have postulated that there are two major determinants that may influence the probability of restenosis: first, the lesion characteristics, particularly the amount of existing smooth muscle and the plaque structure, and second, the regional flow characteristics that are determined by the geometry of the dilated lumen of the lesion and blood flow velocity patterns across that lumen. Certainly, there are other determinants. For example, to what extent does proliferative activity of the smooth muscle cell influence this outcome, and how may this activity be influenced by factors such as age, cigarette smoking, and cholesterol levels? What is the role of local thrombus formation? PDGF is a potent vasoconstrictor and it is not known whether this may influence restenosis. It is not difficult to understand why even with all the known clinical predictors of restenosis, it remains difficult to predict restenosis with any precision in a particular case.
Because there are several biologic factors that influence restenosis and because different factors may have different degrees of influence among different individuals in any selected study population or any restenotic lesion, some factors may stand out as important predictors, whereas others may become insignificant. Only the most powerful predictors are likely to be evident from one study to another. This probably explains in part the variability that has been observed among the studies on clinical restenosis.83,84

Future Research Directions

Based on the foregoing discussion, it is possible to speculate on possible approaches to restenosis prevention.

Pharmacologic Approaches

Antiplatelet agents. As noted, most of the currently available antiplatelet agents are antiaggregates, and clinical trials with these agents have failed to show any benefit in reducing restenosis.85 Agents that effectively reduce platelet adhesion will probably be effective in solving the problem. Animal studies have shown that drastically reduced circulating platelet numbers inhibit intimal proliferation;86 however, such a measure carries a great risk of bleeding complications. The ideal agent should inhibit platelet adhesion without increasing the risk of hemorrhage. A number of such agents are currently under investigation, with clinical trials pending.

Antiproliferative agents. Heparin has been shown by numerous in vitro and in vivo studies to be effective in reducing smooth muscle cell proliferation and migration.13-15 Subfragments of heparin that retain antiproliferative properties but have no anticoagulant effect are now available for clinical studies.

Growth factors, especially PDGF, are the main stimulus for smooth muscle cell proliferation and migration. Antagonists of growth factors, especially PDGF, could be useful agents. Several agents have been shown to antagonize PDGF or its receptors in vitro. One agent, triazolopyrimidine, has been shown to be effective in vivo as well as in cell culture studies.87,88 Other agents, such as lovastatin and prostaglandin E2 or I2, have been noted to inhibit smooth muscle cell proliferation.89,90 Cytotoxic agents may be useful if local methods of application can be developed.

Other possible agents. Because smooth muscle cell migration appears to be a major part of the process of intimal proliferation,39 an agent with antimigratory activity could favorably influence the process. Caffeic acid derivatives were shown to be effective antimigrants in vitro.91,92 Certain calcium antagonists also have been suggested to be effective antimigrants.93 In the late stage of intimal proliferation, cellular hypertrophy and accumulation of extracellular material account for the growth of intimal thickness. An agent that could inhibit the production of extracellular material may also be useful in reducing the intimal thickness. Colchicine has been shown to be effective in reducing the secretion of extracellular material.94 These agents may be worthwhile for consideration in preventing restenosis. Steroid hormones have been shown to inhibit smooth muscle proliferation95 and also have a well-known anti-inflammatory activity. Neutrophils and macrophages may be important factors in intimal proliferation. In combination with prolonged heparin administration, steroids have been shown to be effective in the animal model.96 The n-3 fatty acids (fish oil derivatives) also have antiplatelet and anti-inflammatory activity. However, in only one of five clinical trials have fish oil agents been shown to be effective in reducing restenosis. Cyclooxygenase inhibitors, such as aspirin or indomethacin, though possessing anti-inflammatory and antiplatelet activity, have been noted to enhance smooth muscle cell proliferation in vitro.48,89 This may help to explain the failure of these agents to reduce restenosis.

Clinical trials with heparin alone for 12–24 hours and steroids alone for 1 week or less have failed to reduce restenosis. Also, clinical trials with the calcium channel blockers, nifedipine and diltiazem, have failed.98 Two points must be mentioned. The animal studies in which the agents were initially tested have usually used balloon denudation in a normal artery. Clinical balloon angioplasty in stenotic arteries apparently induces a larger and more complicated injury and wider surface areas are exposed to platelets. It is obvious that angioplasty or stenotic lesions induces a more powerful stimulation to smooth muscle cell growth than denudation in normal arteries. This explanation may account for the failure of these agents despite success in animal models. In addition, the process of smooth muscle cell proliferation begins with the onset of injury and continues for at least 1–2 weeks in animal studies. Agents used have to act before or at the time of angioplasty and continue for at least 2 weeks. Therefore, either a very potent agent or a combination of agents started early and continued for a sufficient length of time will be needed to reduce intimal proliferation in angioplasty.

Technical Approaches

Minimizing smooth muscle cell injury. “Atherectomy” devices have been shown to produce smooth luminal surfaces without gross, deep injury to medial tissues. Blood flow characteristics may also be improved. A number of other approaches under current investigation, such as direct laser or ultrasonic ablation of atheroma, may produce similar results. Linear extrusion balloon techniques are an additional approach to limiting vessel wall injury.

 Destruction of anatomic substrate—smooth muscle cells. Elimination of a major portion of smooth muscle cells in the lesion may reduce intimal pro-
liferation. Devices such as “hot-tipped” catheters or “laser balloons” may not only destroy smooth muscle but also may improve lumen geometry. The long-term effect of this approach is not known.

Improvement of blood flow. Providing an optimal luminal size and blood flow could reduce intimal proliferation. Oversizing of PTCA balloons has proved ineffective because of the risk of arterial dissection and the possible influence of increased medial injury. Protracted inflation times may optimize initial luminal results and clinical trials with this approach are pending. Preliminary studies with “stent-like” devices that optimize lumen geometry are currently in progress.100

Restenosis after coronary angioplasty can usually be managed with repeat dilatation or coronary bypass surgery. Any agent or method that is to be considered as an advance in preventing restenosis must be more effective, have a lower risk, and cost less than these procedures. It appears unlikely that a single panacea will exist for all cases of lesion restenosis. It seems more likely that a combination of technical or one or more pharmacologic approaches will be required.

Summary

Restenosis after successful PTCA remains a major problem limiting the efficacy of the procedure. The pathophysiologic mechanism of restenosis has been enigmatic so far, but accumulated evidence strongly suggests that intimal hyperplasia is the major mechanism. Based on current understanding of the process of intimal hyperplasia, one unifying concept may be that there are at least two major local biologic determinants influencing this process, lesion characteristics and regional flow dynamics. Lesion characteristics include the plaque structure and the quantity of smooth muscle. These may provide the anatomic substrate that determines the extent of injury and the degree of smooth muscle cell proliferation. The amount of smooth muscle cells in the stenotic lesion activated by injury to undergo proliferation may determine the eventual bulk of the restenotic lesion. In addition, low wall shear stress could promote intimal hyperplasia and cause structural change of vessels to decrease the lumen, whereas high wall shear stress exerts the opposite effects. Intimal hyperplasia after balloon injury is a complex process involving platelets, growth factors, endothelial cells, smooth muscle cells, mechanical injury, wall shear stress, and probably other unknown factors. Platelets not only contribute growth factors such as PDGF but also cause organized thrombus. Different growth factors may be involved in initiating smooth muscle cell proliferation and may come from many different sources, including smooth muscle cells, endothelial cells, and macrophages. Intact confluent endothelial cells may produce heparin sulfates and inhibit intimal proliferation; however, regenerating endothelial cells may have the opposite effect. Thus, the proliferative potential of smooth muscle cells, endothelial recovery, extent of injury, wall shear stress, and other unknown factors may all influence this process. Based on these concepts concerning the biology of restenosis, some research directions concerning potential forms of therapy are proposed.

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