JACC Vol. 25, No. 2
February 1995:516–20

EDITORIAL REVIEW

Restenosis After Percutaneous Transluminal Coronary Angioplasty: Have We Been Aiming at the Wrong Target?

JESSE W. CURRIER, MD, FACC, DAVID P. FAXON, MD, FACC

Los Angeles, California

Restenosis after percutaneous coronary balloon angioplasty remains a significant problem. Despite success with a variety of agents in animal models, no agent has proved clearly successful in reducing restenosis in humans. There are many potential reasons for this, but one possibility is that because of our incomplete understanding of the restenotic process, therapy has been directed at the wrong target. Arterial remodeling (changes in total vessel area or changes in area circumscribed by the internal elastic lamina) is well described in de novo atherosclerosis, and there is increasing evidence that this process occurs after angioplasty. Thus, restenosis can be thought of not merely as neointimal formation in response to balloon injury, but as arterial remodeling in response to balloon injury and neointimal formation. Arterial remodeling may consist of actual constriction of the artery, as has been described in some animal models and in preliminary fashion in humans, or of compensatory enlargement as has been described in de novo atherosclerosis and in the hypercholesterolemic rabbit iliac artery model. Arterial constriction can result in restenosis with minimal neointimal formation. Compensatory enlargement accommodates significant amounts of neointimal formation, with preservation of lumen area despite an increase in neointimal area adequate to cause restenosis in a noncompensated artery. This expanded paradigm of arterial remodeling and intimal formation may in part account for the lack of success in clinical trials to date, and therapy directed at arterial remodeling as well as intimal formation may be required to reduce restenosis after coronary interventions.

(J Am Coll Cardiol 1995;25:516–20)

Percutaneous transluminal coronary angioplasty has gained universal acceptance as a revascularization procedure despite important limitations. One of the major limitations is the chronic renarrowing of the dilated vessel in response to the balloon (or other interventional device) injury that typically occurs over 3 to 6 months after the procedure (1). The pathophysiology of restenosis is complex and incompletely understood. Early events in restenosis are thought to consist of immediate elastic recoil, platelet deposition and thrombus formation, followed by smooth muscle cell proliferation and matrix formation (2). It has been suggested that restenosis is analogous to wound healing (3), and the commonly accepted paradigm is a process of neointimal hyperplasia in response to balloon injury (4,5). As understanding of the various components of this pathophysiologic paradigm has advanced over the past decade, attempts have been made to attack restenosis at many points along the process, with impressive success in multiple animal models. In collaboration with colleagues in molecular biology, newer, more potent agents have been utilized, particularly against platelet deposition (6) and smooth muscle cell proliferation (7). Despite >50 published major clinical trials randomizing >12,000 patients and attempting to limit restenosis by pharmacologic means, there is no agent that has clearly been shown to be effective in humans (8).

There are many potential reasons why the clinical trials have been negative (9). First, perhaps the process in humans is different from that occurring in currently available animal models. Second, many clinical trials (10,11) have used agents shown to be effective in animal models (12,13), but often the positive effect in the animal model was achieved only at very high doses that would not be tolerated in humans. Some of the clinical trials did not pretreat patients (14), even when the animal data suggested a much greater benefit with pretreatment (15). Finally, many clinical trials were underpowered to detect a significant difference, suffered from significant withdrawal bias, or had incomplete angiographic follow-up for angiographically defined restenosis (9).

In addition to these possible explanations for our failure to reduce restenosis, we believe that another explanation must be considered. The recent study by O'Brien et al. (16) has raised questions as to the validity of the classical paradigm of intimal hyperplasia as the etiology of restenosis. Using proliferating cell nuclear antigen (PCNA) immunohistochemical labeling of human directional atherectomy specimens, these investigators showed that proliferation in primary and restenotic coronary artery lesions occurs infrequently with no obvious temporal peak. On the basis of experimental data from our laboratory and others as well as preliminary data in humans, it appears that differences in arterial remodeling after angioplasty, as measured in changes in total vessel area or area circumscribed by the internal elastic lamina, has a more significant impact on

From the Division of Cardiology, Department of Medicine, University of Southern California School of Medicine, Los Angeles, California.

Manuscript received March 4, 1994; revised manuscript received August 12, 1994, accepted August 29, 1994.

Address for correspondence: Dr. Jesse W. Currier, Division of Cardiology, University of Southern California, Room 117, Ambulatory Care Building, 1355 San Pablo Street, Los Angeles, California 90033.

0735-1097/95/$9.50
0735-1097(94)00372-W

chronic lumen diameter after angioplasty than differences in intimal formation. Thus, rather than considering restenosis a process of neointimal formation in response to balloon injury, these studies suggest that restenosis is a process of arterial remodeling in response to balloon injury and neointimal formation. Arterial remodeling may consist of compensatory enlargement with an increase in total vessel cross-sectional area, or constriction with a decrease in total vessel area. This editorial review discusses the background of arterial remodeling, reviews the preliminary evidence that it occurs after angioplasty in animal models and humans, shows the magnitude of the effect and discusses possible mechanisms.

Arterial Remoding in De Novo Atherosclerosis

Arterial remodeling is well described in de novo atherosclerosis. Glagov et al. (17) observed that in human necropsy specimens, the left main coronary artery undergoes adaptive vessel enlargement in response to progressive plaque expansion and maintains the lumen area until the plaque lesion occupies 40% of the area circumscribed by the internal elastic lamina or external elastic lamina, a process they termed compensatory enlargement. Intravascular and epicardial ultrasound studies have shown that this process is not limited to the left main coronary artery; individual coronary arteries undergo compensatory enlargement that maintains lumen area as atherosclerosis develops (18,19). Zarins et al (20) showed that the arterial enlargement in response to increases in intimal plaque varies by location, with significant segmental differences in compensatory enlargement in the left anterior descending coronary artery. Thus, arterial remodeling occurs in de novo coronary atherosclerosis and may limit the effect of plaque development on lumen narrowing.

Arterial Remodeling After Angioplasty

There is increasing experimental evidence that arterial remodeling also occurs after angioplasty. We examined the quantitative histologic results from animals killed immediately after angioplasty in the hypercholesterolemic rabbit model and compared them with the same areas from animals killed 4 weeks after the procedure, when restenosis occurs in this model (21). Quantitative angiography was performed to ensure that the acute and chronic groups were comparable in minimal and reference lumen diameters at the time of angioplasty as well as in the immediate angiographic result of angioplasty. The area circumscribed by the internal elastic lamina increased by 20% from immediately after to 4-week follow-up after angioplasty. The compensatory enlargement of the vessel, as seen in the increase in internal elastic lamina area, was able to accommodate nearly 60% of the neointimal formation in response to the balloon injury and limit lumen narrowing. When the chronic group was divided into restenotic and nonrestenotic subgroups, surprisingly, the intimal areas in the two subgroups were virtually identical. The difference in the lumen area between restenotic and nonrestenotic vessels resulted from the significantly greater internal elastic lamina area in the nonrestenotic subgroup.

In both restenotic and nonrestenotic vessels, the internal elastic lamina area was highly correlated with intimal area. In the restenotic arteries, the slope of this correlation was <1; hence, for a given increase in intimal area, there was smaller increase in internal elastic lamina area, suggesting inadequate compensatory enlargement for intimal formation in this group. In the nonrestenotic vessels, conversely, the slope was >1, such that a given increase in intimal area was associated with a greater increase in internal elastic lamina area, with preservation of the lumen area. These data show that vascular remodeling is able to limit the effects of intimal formation on chronic lumen diameter and that differences in vascular remodeling, not differences in intimal formation, account for restenosis in this model.

Data from other laboratories have also demonstrated the effects of vascular remodeling. Post et al. (22,23) showed that in normal rabbit femoral arteries subjected to primary balloon injury, intimal thickening accounted for only 23% of late loss in angiographic lumen diameter. In normal or hypercholesterolemic Yucatan micropig with iliac lesions induced by balloon deendothelialization, these investigators found that intimal thickening following subsequent balloon angioplasty accounted for only 11% or 49%, respectively, of the late lumen loss, and the major contribution to late loss was chronic constriction. Lafont et al. (24) have recently shown in an atherosclerotic rabbit femoral artery model that at the time of restenosis there was only a 33% increase in intimal plus medial area but a 52% reduction in lumen area compared with the reference site as a result of a reduction in internal elastic lamina area at the lesion site.

There is also preliminary intracoronary ultrasound evidence that vascular remodeling occurs after angioplasty in humans. Kovach et al. (25) showed that intimal formation accounted for only 32% of late lumen loss and that a mean 7.5% decrease in total vessel area (corresponding to external elastic lamina area) was more important. These findings were confirmed in a larger series of patients by the same investigators (26), where arterial remodeling with constriction accounted for 60% of late lumen loss.

Potential Magnitude of Effect of Arterial Remodeling

The magnitude of the effect of vascular remodeling on restenosis is potentially great. To illustrate this, the following derivation shows the relation, assuming a circular lumen, between chronic radius in an artery without compensation (r_{NC}) and one with compensatory enlargement (r_C). If no compensatory enlargement occurs, the lumen area would be πr_{NC}^2, and plaque area in the noncompensated artery would be defined by the area circumscribed by the internal elastic

JACC Vol. 25, No. 2
February 1995:516–20

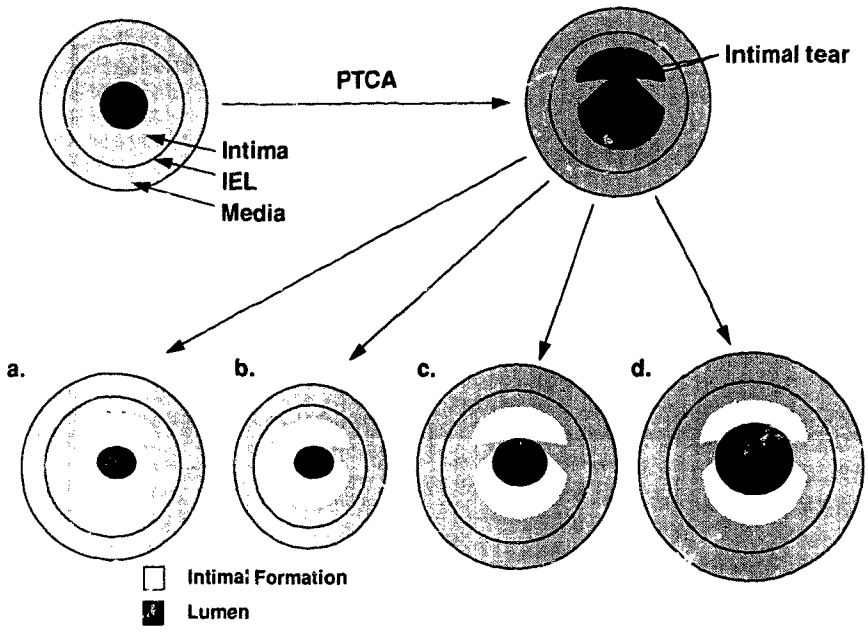

Figure 1. Expanded paradigm of restenosis after angioplasty. Several possible responses to balloon injury are illustrated. The classical paradigm (**a**) is intimal formation with no remodeling. If vascular constriction occurs (**b**), even minimal amounts of neointima may result in restenosis. A moderate amount of compensatory enlargement (**c**) may accommodate neointima with less lumen narrowing. Augmented compensatory enlargement (**d**) may result in a widely patent artery despite significant intimal formation. IEL = internal elastic lamina; PTCA = percutaneous transluminal coronary angioplasty.

lamina minus the lumen area, or $\pi r_{IEL}^2 - \pi r_{NC}^2$. If one extrapolates the results from our animal studies, one would expect a 20% compensatory increase in internal elastic lamina area, or a 10% increase in internal elastic lamina radius ($1.1r_{IEL}$) from immediately after angioplasty to the time of restenosis. Thus, in an artery with compensatory enlargement, plaque area would be $\pi(1.1r_{IEL})^2 - \pi r_C^2$. If the same amount of intimal formation occurs in arteries with and without compensatory enlargement, $\pi r_{IEL}^2 - \pi r_{NC}^2 = \pi(1.1r_{IEL})^2 - \pi r_C^2$. Solving this equation for the compensated lumen radius gives $r_C^2 = r_{NC}^2 + 0.21r_{IEL}^2$, or $r_C = (r_{NC}^2 + 0.21r_{IEL}^2)^{1/2}$.

If this equation is applied in a human coronary artery of 3-mm reference diameter, and the reference segment has no intimal plaque, then lumen area is the same as the area circumscribed by the internal elastic lamina (πr_{IEL}^2), so r_{IEL} = 1.5 mm. If there is a 75% angiographic stenosis at the lesion and no change in the reference at follow-up in an artery with no compensatory enlargement, r_{NC} = 0.375 mm. From the equation derived in the previous paragraph, the radius of an artery subjected to the same degree of injury that did undergo compensatory enlargement can be calculated: $r_C = [0.375^2 + 0.21(1.5^2)]^{1/2}$, or r_C = 0.78 mm. Thus, a 10% compensatory increase in internal elastic lamina radius at the lesion site increases the chronic lumen radius from 0.375 to 0.78 mm, or a 108% increase in final lumen diameter. Similar calculations can be performed showing the magnitude of the effect of vascular constriction on final lumen diameter. It is only in arteries with significant stenoses that the large effects of vascular remodeling are apparent.

Mechanisms of Arterial Remodeling

A number of possible mechanisms of arterial remodeling have been proposed for de novo atherosclerosis. Increased flow with a concomitant increase in shear stress may lead to adaptive enlargement in nonatherosclerotic arteries, as is seen in arteriovenous fistulae (27,28). In stenotic arteries, increased shear stress at the lesion site because of increased velocity of flow could initiate compensatory enlargement (28–31). Another possibility is that as atherosclerotic plaque develops, it may destroy or compress the underlying vascular supply of the artery and damage the extracellular matrix support structure, with protrusion of the lesion outside the original contour of the artery (32), which has been described in pathologic specimens (33,34).

The mechanism of arterial remodeling after balloon injury remains to be determined. After balloon angioplasty in the atherosclerotic rabbit model, as in humans, dissections extending into the intima and media are common (35). These dissections may weaken segments of the arterial wall and allow enlargement in response to increased shear stress as intimal formation occurs. Alternatively, the inflammatory response to balloon injury could initiate the remodeling process through the release of proteolytic enzymes. Thus, either of the mechanisms described above for remodeling in de novo atherosclerosis may occur in restenosis. If only chronic constriction were seen after angioplasty, one would also have to consider other possible etiologies, such as elastic recoil or vessel spasm. The fact that internal elastic lamina area increased in both restenotic and nonrestenotic arteries, compared with arteries examined immediately after angioplasty in the atherosclerotic rabbit model (21), suggests that at least in this model it is a true process of arterial remodeling rather than recoil or spasm.

If the analogy of wound healing applies to vascular injury, one might expect a similar sequence of events: initial nonspecific inflammation followed by specific degradation of the preexisting collagen matrix by increased collagenase activity; extracellular fibronectin deposition, activated cell invasion, type III collagen deposition, increased type I collagen deposi-

tion, and finally, typical cross-linked collagen fiber appearance (3,36–39). Arterial remodeling may occur during this process of degrading preexisting matrix and depositing new matrix components. Concomitant with collagen deposition in generalized wound healing, the phenomenon of wound contracture occurs. The end result of wound contraction is to reduce the size of the granulation tissue volume by reorganizing the collagen fibrils (40). This phenomenon in the vessel wall could result in chronic constriction.

The contribution of remodeling to restenosis after nonballoon coronary intervention is unclear. It is possible that debulking devices, such as directional coronary atherectomy, may result in increased remodeling by removing structural components of the vessel wall. Coronary stenting may result in a larger acute lumen, but if the stent diameter remains constant, any component of arterial remodeling, either enlargement or constriction, may be eliminated. It is premature to speculate about the pharmacologic manipulation of remodeling after angioplasty until more is known about its mechanism. However, preliminary data using vitamins C and E in the swine balloon injury model suggest a beneficial effect on chronic lumen diameter arising from alterations in arterial remodeling (41).

Conclusions

Future studies of arterial remodeling after angioplasty will require newer imaging modalities such as intravascular ultrasound. Angiography is not helpful in distinguishing between arterial remodeling and intimal formation because only the lumen is visualized. Serial intravascular ultrasound studies after angioplasty in the hypercholesterolemic rabbit are in progress in our laboratory. The use of serial intravascular ultrasound in human coronaries is also possible, but meticulous technique is required to ensure that images at exactly the same site are compared (25,26).

We believe that restenosis after angioplasty can best be thought of as a balance between intimal formation and arterial remodeling (Fig. 1), not intimal formation alone as in the current paradigm. The studies of Post et al. (22,23) and LaFont et al. (24) as well as the human ultrasound experience (25,26) suggest that in some cases actual arterial constriction may occur, which, with or without intimal formation, may result in restenosis. In the rabbit iliac model (21), compensatory arterial enlargement occurred after angioplasty and limited the effect of intimal formation on lumen narrowing; restenotic arteries had less arterial enlargement than nonrestenotic arteries. Compensatory enlargement and chronic constriction may represent two ends of the spectrum of arterial remodeling in response to balloon angioplasty. This expanded paradigm of arterial remodeling and intimal formation may in part account for the paucity of success in clinical trials to date, and therapeutic strategies to alter arterial remodeling in conjunction with altering intimal formation may be required to reduce restenosis after coronary interventions.

References

1. Holmes DR, Vlietstra RE, Smith HC, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA registry of the National Heart, Lung, and Blood Institute. Am J Cardiol 1984;53: 77C–81C.
2. Haudenschild CC. Pathogenesis of restenosis. Z Kardiol 1989;78(3):28–34.
3. Forrester JS, Fishbein M, Helfant R, Fagin J. A paradigm for restenosis based on cell biology: clues for the development of new preventive therapies. J Am Coll Cardiol 1991;17:758–69.
4. Liu MW, Roubin GS, King SB III. Restenosis after coronary angioplasty: potential biologic determinants and role of intimal hyperplasia. Circulation 1989;79:1374–87.
5. Ip JH, Fuster V, Badimon L, Badimon J, Taubman MB, Chesebro JH. Syndromes of accelerated atherosclerosis: role of vascular injury and intimal proliferation. J Am Coll Cardiol 1990;15:1667–87.
6. Ellis SB, Bates ER, Schaible T, et al. From basic studies to clinical trials: prospects for the use of antagonists to the platelet glycoprotein IIb/IIIa receptor to prevent postangioplasty restenosis and thrombosis. J Am Coll Cardiol 1991;17:89B–95B.
7. Simons M, Edelman E, DeKeyser J, Langer R, Rosenberg RD. Antisense *c-myb* oligonucleotides inhibit intimal smooth muscle cell accumulation in vivo. Nature 1992;359:67–70.
8. Franklin SM, Faxon DP. Pharmacologic prevention of restenosis after coronary angioplasty: review of the randomized clinical trials. Coronary Art Dis 1993;4:232–42.
9. Hillegass AB, Ohman EM, Califf RM. Restenosis: the clinical issues In: Topol EJ, editor. Textbook of Interventional Cardiology. 2nd ed. Philadelphia: Saunders, 1994:415–35.
10. Keefe JH, McCallister BD, Bateman TM, Kuhnlein DL, Ligon RW, Hartzler GO. Ineffectiveness of colchicine for the prevention of restenosis after coronary angioplasty. J Am Coll Cardiol 1992;19:1597–1600.
11. Faxon DP, Spiro T, Minor S, et al. Enoxaparin, a low molecular weight heparin, in the prevention of restenosis after angioplasty: results of a double blind randomized trial [abstract]. J Am Coll Cardiol 1992;19:258A.
12. Currier JW, Faxon DP. Animal models of restenosis. In: Schwartz R, editor. Coronary Restenosis. Cambridge (MA): Blackwell Scientific, 1993:293–324.
13. Currier JW, Pow TK, Haudenschild CC, Minihan AC, Faxon DP. Low molecular weight heparin (Enoxaparin) reduces restenosis after iliac angioplasty in the hypercholesterolemic rabbit. J Am Coll Cardiol 1991;17:118B–25B.
14. MERCATOR study group. Does the new angiotensin converting enzyme inhibitor Cilazapril prevent restenosis after percutaneous transluminal angioplasty? Results of the MERCATOR study. A randomized, double-blind placebo-controlled trial. Circulation 1992;86:100–10.
15. Powell JS, Clozel JP, Muller RK, et al. Inhibitors of angiotensin-converting enzyme prevent myointimal proliferation after vascular injury. Science 1989;245:186–8.
16. O'Brien ER, Alpers CE, Stewart DK, et al. Proliferation in primary and restenotic coronary atherectomy tissue: implications for antiproliferative therapy. Circ Res 1993;73:223–231.
17. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371–5.
18. Hermiller JB, Tenaglia AN, Kisslo KB, et al. In vivo validation of compensatory enlargement of atherosclerotic coronary arteries. Am J Cardiol 1993;71:665–8.
19. McPherson DD, Sirna SJ, Hiratzka LF, et al. Coronary arterial remodeling studied by high-frequency epicardial echocardiography: an early compensatory mechanism in patients with obstructive coronary atherosclerosis. J Am Coll Cardiol 1991;17:79–86.
20. Zarins CK, Weisenberg E, Kolettis G, Stankunavicius R, Glagov S. Differential enlargement of artery segments in response to enlarging atherosclerotic plaques. J Vasc Surg 1988;7:386–94.
21. Kakuta T, Currier JW, Haudenschild CC, Ryan TJ, Faxon DP. Differences in compensatory vessel enlargement, not neointimal formation, account for restenosis following angioplasty in the hypercholesterolemic rabbit model. Circulation 1994;89:2809–15.
22. Post M, van Erven L, Velema E, Bentala M, Borst C. Which part of the angiographic diameter reduction after balloon dilation is due to intimal hyperplasia? [abstract]. J Am Coll Cardiol 1993;21: Suppl A:36A.
23. Post M, Borst C, Kuntz RE. The relative importance of arterial remodeling

compared with intimal hyperplasia in lumen renarrowing after balloon angioplasty: a study in the normal rabbit and the hypercholesterolemic Yucatan micropig. Circulation 1994;89:2816–21.

24. Lafont AM, Chisolm GM, Whitlow PL, Goormastic M, Cornhill JF. Post angioplasty restenosis in the atherosclerotic rabbit: proliferative response or chronic constriction? [abstract]. Circulation 1993;88: Suppl I:I-521.
25. Kovach JA, Mintz GS, Kent KM, et al. Serial intravascular ultrasound studies indicate that chronic recoil is an important mechanism of restenosis following transcatheter therapy [abstract]. J Am Coll Cardiol 1993;21: Suppl A:484A.
26. Mintz GS, Kovach JA, Saturnino PJ, Diirano CD, Leon MB. Geometric remodeling is the predominant mechanism of late lumen loss after coronary angioplasty [abstract]. Circulation 1993;8: Suppl I:I-654.
27. Kamiya A, Togawa T. Adaptive regulation of wall shear stress to flow change in the canine carotid artery. Am J Physiol 1980;239:H14–H21.
28. Zarins CK, Zatina MA, Giddens DP, Ku DN, Glagov S. Shear stress regulation of artery lumen diameter in experimental atherogenesis. J Vasc Surg 1987;5:413–20.
29. Langille BL, O'Donnell F. Reductions in arterial diameter produced by chronic decreases in blood flow are endothelium dependent. Science 1986; 231:405–7.
30. Furchgott RF. Role of endothelium in responses of vascular smooth muscle. Circ Res 1983;53:557–73.
31. Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. N Engl J Med 1990;323:27–36.
32. Bond MG, Adams MR, Bullock BC. Complicating factors in evaluating coronary artery atherosclerosis. Artery 1981;9:21.
33. Glagov S, Zarins CK. Quantitating atherosclerosis: problems of definition. In: Bond MG, Insull W Jr, Glagov S, Chandler AB, Cornhill JF, eds. Clinical diagnosis of atherosclerosis, quantitative methods of evaluation. New York: Springer-Verlag, 1983:11–35.
34. Crawford T, Levene CI. Medial thinning in atheroma. J Pathol 1953;66:19–23.
35. Faxon DP, Weber VJ, Haudenschild CC, Gottsman SB, McGovern WA, Ryan TJ. Acute effects of transluminal angioplasty in three experimental models of atherosclerosis. Atherosclerosis 1982;2:125–33.
36. Clark RA, Colvin RB. Wound repair. In: McDonagh J, editor. Plasma Fibronectin. New York: Marcel Dekker, 1985:197–262.
37. Clark RA. Potential roles for fibronectin in cutaneous wound repair. Arch Dermatol 1988;124:201–6.
38. Colvin RB. Fibronectin in wound healing. In: Mosher DF, editor. Fibronectin. San Diego: Academic Press, 1989:213–54.
39. Alverez O, Goslen J, Eaglestein W, Welgus H, Striclin G. Wound healing. In: Fitzpatrick T, Eisen A, Wolff K, Freedberg I, Austin K, editors. Dermatology in General Medicine 3rd ed. New York: McGraw-Hill, 1986:321–36.
40. Erlich HP, Griswold RT, Rajaratnam J. Studies of vascular smooth muscle cells and dermal fibroblasts in collagen matrixes: effect of heparin. Exp Cell Res 1986;164:154–63.
41. Nunes GL, Sgoutas DS, Sigman SR, et al. Vitamins C and E improve the response to coronary balloon injury in the pig: effect of vascular remodeling [abstract]. Circulation 1993;88: Suppl I:I-372.