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# PHARMACOLOGY OF CARDIAC AND VASCULAR REMODELING

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## ABSTRACT

Cardiovascular diseases involve changes in the structure of the heart and blood vessels. Normal structure is maintained by a sophisticated set of mechanical and cellular "checks and balances." A disturbance of these checks and balances induces a remodeling process. The most distinguished features of this process are phenotypic modulation of various cell types in the cardiovascular system; cellular hyperplasia and hypertrophy; and extracellular matrix production, deposition, and degradation. Optimal pharmacotherapy of cardiovascular diseases should be aimed at correcting structural abnormalities in the heart and blood vessels. This goal can be achieved by influencing mechanical stresses on the cardiovascular system or by interfering with the chemical mediators of the remodeling process. Many existing groups of cardiovascular drugs, such as angiotensin-converting enzyme inhibitors, calcium-antagonists, α- and β-adrenoceptor antagonists, and antithrombotic drugs, influence cardiovascular remodeling. New approaches involve the development of drugs acting on peptidergic mediators of cardiovascular remodeling.

## INTRODUCTION

Drugs have had a major impact on life expectancy as well as patterns of mortality and morbidity in this century. Chemotherapy has reduced risks for



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premature death from various types of infections; immunosuppressive drugs have enhanced transplant survival; diabetes, certain forms of cancer, and respiratory diseases can now be effectively treated; cardiovascular drug therapy has reduced the risk of stroke and early death following myocardial infarction. However, there is a reverse side to this development. The effective treatment of major causes of premature death leaves a population more vulnerable to long-term, gradual pathologies of various organ systems. The prevention and treatment of acute myocardial infarction in the last two decades has been parallelled by an increased morbidity and mortality due to heart failure (1). In The Netherlands, more people are now treated in hospitals for heart failure than for acute myocardial infarction (2). Along the same lines, the major problem in therapy and diabetes or asthma is no longer the acute control of plasma glucose levels or bronchoconstriction, but the interference with long-term damage to target organs such as the heart, blood vessels, and kidneys in diabetic patients or the airway walls in asthmatics.

Tissue remodeling is a key event in the shift from acute to chronic pathologies. Under normal conditions, a sophisticated set of cellular "checks and balances" maintains a constant composition of tissues. This balance can be disturbed by perturbations, such as infection, trauma, or ischemia. Such perturbations induce a chain of cellular events that ultimately alters the architecture of the tissues. In comparison to lower animals or plants, mammals have a limited capacity for tissue regeneration (3). Rather than regeneration, the above-mentioned perturbations induce a remodeling process. Although this process may differ for each tissue and type of perturbation, there are several common themes in tissue remodeling: The cellular response usually involves the activation of cytokines or soluble cellular mediators that induce the expression of a variety of genes and affect cell growth as well as cytoskeletal and extracellular matrix structure.

This review focuses on mechanisms of remodeling of the heart and blood vessels in various diseases. Emphasis is on the pharmacology of these processes. Drugs have been important tools in the study of cardiovascular remodeling, but cardiovascular tissue repair (the reversal of remodeling) could also become a primary objective of future drug therapy.

## CARDIOVASCULAR STRUCTURE AND STRUCTURAL CHANGES

Cardiovascular diseases involve changes in the structure of the heart and blood vessels. Consequently, structural alterations of the cardiovascular system and drug effects thereupon have been extensively studied both in experimental animal models and in patients. Until recently, however, the experimental literature remained predominantly descriptive in view of the lack of common

definitions and of a still incomplete knowledge about the mechanisms that govern the genesis of normal cardiovascular structure and its modifications during the pathogenesis of the diverse cardiovascular diseases.

The heart and blood vessels form a continuous system of branching hollow tubes. The basic structural parameters of the system are (*a*) the number of vessels from the branching pattern and (*b*) the mass of the vessel wall. These fundamental parameters are genetically predetermined and can be modulated by local physical and chemical factors. Together they determine the overall volume of the lumen of the system and thus, most aspects of cardiovascular function (cardiac output, large artery compliance, total and local peripheral vascular resistance, venous capacitance). The wall governs these functions on an acute basis by changes in the contractility of the myocytes that populate the tissue. This dynamic regulation acts on top of more static mechanical properties of the wall. The mass and composition of the tissue determine its elastic properties, and thereby its dimension, at any given condition of transmural pressure. Of all cardiovascular wall components, cardiomyocytes and vascular smooth muscle cells (VSMC) have received the most attention in view of both their acute contractile activity and their numeric contribution to mass. However, structure results from the interaction between a tissue and its external mechanical environment, and all tissue components and their interplay must be considered. Thus the description of any tissue, be it a cardiac chamber or a particular vessel segment, cannot be separated from the environmental conditions under which it was described, and it should ideally include all wall components.

The above view on cardiovascular structure has not been followed in most experimental studies, which have instead concentrated on overall tissue volume and on myocyte size and number. The relevance of these observations must now (and in the future) be interpreted in relation to the extracellular matrix in which these cells are imbedded. In the heart, interstitial fibroblasts are now considered as a reactive cell type that contributes, at least under pathological conditions, to overall wall organization by changes in number and by synthesis of matrix material (4). On this basis, Weber and co-workers (4) have developed a cellular two-compartment model to define various aspects of cardiac structural changes in pathological conditions. In this model, the heart consists of a contractile myocyte and a non-myocyte compartment. The non-myocyte compartment comprises fibroblasts, endocardial cells, endothelial and vascular smooth muscle cells of the coronary vasculature, macrophages, and mast cells. The most important non-cellular elements of this compartment are types I and III fibrillar collagen. Expressed by cell volume, approximately 70–75% of the normal heart consists of myocytes. However, in terms of cell numbers, the myocyte compartment represents only 30%. The normal development of the heart, as well as the hypertrophy in response to intense physical exercise, is

based upon a balanced growth of both compartments, thus increasing the performance of the heart. However, the growth response to cardiac pressure or volume overload and ischemia is characterized by an imbalance between the two compartments (4).

Similarly, blood vessel structure is determined by more than one cellular compartment, with each compartment contributing to overall vascular function. For the myocytes themselves, mass and volume are no longer the only structural parameters of interest. Although adult cardiomyocytes and most VSMC may be considered quiescent as regards proliferation, this does not mean that their phenotypic properties are fixed. Especially in VSMC, the once-established view that there are two distinct phenotypes (a contractile and a synthetic) is progressively being replaced by the model of a broad spectrum of interchangeable phenotypes (5). Phenotypic modulation can influence tissue structure by modifying cellular responsiveness to growth promoters and growth inhibitors, and also by changing the synthesis of cytoskeletal proteins and extracellular matrix material. Particularly interesting from a pharmacologist's viewpoint is the concept of differential expression of receptor (sub)types as part of the process of phenotypic modulation of myocytes and other cell types. Besides these alterations of the pre-existing wall structure, more large-scale modifications can develop, such as replacement of infarcted myocardium by scar tissue or extensive formation of intimal structures in the larger arteries during atherogenesis.

Cardiovascular remodeling comprises a multiplicity of structural alterations. Despite this multiplicity, remodeling may rely on a general set of mechanisms that (depending on the local conditions) result in eccentric or concentric wall changes or in the formation of aneurysms and neo-intima. There is no consensus yet on this set of mechanisms, although some elements appear as (*a*) phenotypic modulation of major cell types in the wall of the cardiovascular system and (*b*) differential growth responses of the myocyte and non-myocyte compartments of the wall of the cardiovascular system. We elaborate in the next paragraphs on how cardiovascular structure is altered in major pathologies, then we review the pharmacological approaches towards correction of the structural basis of cardiovascular dysfunction.

## CARDIAC REMODELING IN PATHOLOGICAL CONDITIONS

The normal growth of the heart as occurs during development is controlled by a temporal and spatial pattern of gene expression and subsequent protein synthesis. These genes belong to several groups, such as the homeobox genes (which encode transcription factors regulating body plan formation and cell growth) immediate-early proto-oncogenes, such as c-myc and c-fos (which

control the state of differentiation of heart cells), and genes that encode cytoskeletal and extracellular matrix structural proteins (6, 7). These genes have their highest activity during the embryonic period, and many of them are down-regulated in postnatal life (6). However, cardiac gene expression, and subsequently cardiac structure, can be influenced by certain pathological conditions in the postnatal period. The most important pathological conditions that cause cardiac remodeling are pressure and volume overload to the heart, and ischemia due to obstructions in coronary circulation.

The role of altered gene expression in postnatal cardiac remodeling has recently been reviewed by Schwartz et al (8). These investigators proposed that the genetic reprogramming in cardiac myocytes during mechanical overload produces an enlarged heart that is better adapted to the altered functional demand. The reprogramming involves genes controlling myosin and actin contractile protein isoforms, sarcoplasmic reticulum calcium transport proteins, and atrial natriuretic factor synthesis. Studies on isolated cardiac myocytes have confirmed that mechanical stress alone can induce cardiac gene reprogramming (9, 10).

## *Cardiac Remodeling During Mechanical Overload*

Clinically, the most frequent cause of mechanical overload to the heart is arterial hypertension. Hypertension causes left ventricular hypertrophy (LVH), which further magnifies the risks of complications in hypertensive patients (11). In hypertension, the afterload of the heart increases, leading to enhanced systolic wall stress, and LVH occurs by the addition of sarcomeres parallel to existing sarcomeres along the length of the myofibrils (concentric hypertrophy). This causes thickening of the ventricle, but leaves the chamber volume unchanged or even reduced, which results in normalization of systolic wall stress. Diastolic function, however, usually decreases in patients with hypertension and LVH. This is due to fibrosis of the ventricle and a resultant reduction of its distensibility.

Studies of experimental animal models of hypertension have revealed some aspects of the cellular basis of the cardiac remodeling in hypertension. The myocytes undergo cellular hypertrophy, leading to a significant increase in the cardiac myocyte transverse area (12). The hypertrophic response is paralleled by a transient expression of proto-oncogenes, as well as by shifts in the major expressed isoforms of the contractile proteins myosin and actin (8, 13). Furthermore, the myocytes express increased amounts of growth factors, such as insulin-like growth factor (14). In the non-myocyte compartment, the two most important changes are the increased synthesis of collagen I (4) and the loss of coronary microvessels (15). Thus, whereas the changes in the myocyte compartment may well represent a functionally useful adaptation of the heart to increased pressure, the impairment of cardiac performance is predominantly

caused by events occurring in the non-myocyte compartment: decreased distensibility and reduced oxygen supply to the heart.

Volume overload to the heart, as occurs in aortic regurgitation, induces a different form of LVH. Under these circumstances, LVH occurs by addition of sarcomeres in series to existing ones. As a result, the ventricular cavity enlarges, but ventricular wall thickness does not change, which increases systolic and diastolic wall stress. This process is called eccentric hypertrophy. The enlargement of the ventricular cavity may also contribute to the reduction in coronary reserve by compressing the coronary vascular bed.



## *Cardiac Remodeling During Ischemia*

The major cause of ischemia of the heart is obstruction of the coronary circulation, which ultimately results in myocardial infarction (MI). The initial response to an MI in the infarcted area is myocyte necrosis, inflammation, cellular infiltration, and edema formation. Collagen fibers are broken down by the activation of collagenases and related enzymes. The breakdown of cardiac structure causes slippage of surviving myocytes and expansion of the infarcted area. The contractility of the remaining viable myocardium is augmented due to the activation of the sympathetic nervous system and the renin-angiotensin system.

The initial response to an acute ischemia is followed by long-term changes, which also take place during non-acute forms of cardiac ischemia. In the myocyte compartment, ischemic cardiomyopathy increases DNA synthesis (16). The increased DNA synthesis reflects myocyte hypertrophy in the left ventricle, but is associated with both hypertrophy and hyperplasia in the right ventricle of rats with narrowed coronary arteries (16–18). This surprising result is contrary to the general belief that myocytes are terminally differentiated cells which cannot proliferate. Similar observations were recently made in post-mortem morphometric studies in hearts from humans (19). In this respect, the cellular response differs from that during mechanical overload to the heart, which leads exclusively to myocyte hypertrophy (20).

The non-myocyte response to ischemia involves activation of both fibroblasts and endothelial cells (21). In fact, Van Krimpen et al (21) have shown that more than 99% of the increased DNA synthesis in the ischemic heart is found in the non-myogenic compartment. In animals (21), as well as in humans (22), fibroblast stimulation increases collagen synthesis and causes fibrosis of the infarcted as well as non-infarcted regions of the ventricle. The endothelial cell activation probably represents a process of adaptive angiogenesis as a response to tissue ischemia (23). Again, this form of remodeling shows an important difference from that during mechanical overload to the heart, which causes a loss rather than increase of small blood vessels.

# PHARMACOLOGY OF CARDIAC REMODELING

The above-discussed observations indicate that cardiac remodeling comprises the following processes: (*a*) hypertrophy and hyperplasia of cardiac myocytes, (*b*) dilatation of the left ventricle, (*c*) enhanced synthesis of extracellular matrix components, especially collagen subtypes, and (*d*) altered growth of endothelial cells and coronary small blood vessels. Pharmacological manipulation of cardiac remodeling with the therapeutic aim of cardiac repair should affect one or more of these processes. The overall term *cardiac hypertrophy* used in most pharmacological studies is inadequate to describe cardiac remodeling and its manipulation by drugs. Unfortunately, these studies suffer from a lack of detailed description of which aspect of cardiac remodeling is exactly affected. A second major problem has been the difficulty in distinguishing between the direct effects and the indirect effects of drugs, because of drug-induced hemodynamic (mechanical) changes. For example, a blood pressure–lowering drug may affect the process of cardiac remodeling merely by reducing systolic wall stress of the heart. An alternative for studying direct drug-induced effects is the use of isolated hearts, or cultured cardiomyocytes or other cell types. Apart from their clear advantages, these in vitro approaches pose some problems: (*a*) The phenotype of cardiac cells in vitro may differ from that in an intact organism, and (*b*) in vitro approaches are less suitable for long-term observations in pathological models. Definitive conclusions on the pharmacology of cardiac remodeling can therefore only be drawn on the basis of evidence obtained from a proper combination of in vivo and in vitro studies.

## *Transforming Growth Factor–β Family and Other Polypeptides*

The transforming growth factor–β (TGF-β) family constitutes a series of multifunctional peptides that regulate cell growth and differentiation. TGF-$\beta_1$ acts as a growth inhibitor for many cell types and as a stimulant for other cell types. The effects of TGF-$\beta_1$ are contingent on the precise stage of cell differentiation, cell lineage, and co-existing growth factors, making it extremely difficult to extrapolate cell culture data to in vivo effects (24). Still, the overall evidence suggests a hypertrophic response of myocytes to the administration of TGF-$\beta_1$, both in vitro and in vivo (24). The molecular mechanism of TGF-$\beta_1$–induced myocyte hypertrophy involves the induction of proto-oncogenes, such as c-*fos* and c-*jun* (25). It induces the fetal gene expression program characteristic for cardiac hypertrophy (8, 26).

Apart from its possible role in cardiomyocyte hypertrophy, TGF-$\beta_1$ has an effect on other aspects of cardiac remodeling. It increases the expression of various components of the extracellular matrix of the heart (27). During myocardial ischemia, TGF-$\beta_1$ decreases neutrophil adherence to the endothelium

of coronary microvessels (28) and protects myocytes against the depressant actions of cytokines released upon ischemia-reperfusion (29). The latter action is thought to depend on the ability of TGF-$\beta_1$ to block induction of cellular nitric oxide synthase (30). In summary, TGF-$\beta_1$ has multiple potential sites of interaction with the cardiac-remodeling process. A more definitive understanding of its role will have to await the availability of selective TGF-$\beta$ receptor antagonists.

Other polypeptides with cardiac growth effects are fibroblast growth factor and insulin-like growth factor. Schneider & Parker (31) have reviewed the evidence for a role of these polypeptides in normal cardiac growth and during cardiac remodeling in pathological circumstances. As for TGF-$\beta_1$, the lack of selective receptor antagonists precludes a critical analysis of the effects of these polypeptides on cardiac structure.

## $\alpha$ *Adrenoceptors*

Although most cardiac adrenoceptors belong to one of the $\beta$ subtypes, the most important effects on cardiac structure have been associated with $\alpha_1$ adrenoceptors. $\alpha_1$ Adrenoceptors make up 10–30% of the total cardiac adrenoceptor population (32). The exact density varies between species and location in the heart. Cardiac $\alpha_1$ adrenoceptors are coupled to G-proteins, and increase intracellular protein kinase C activity via an effect on phosphoinositide metabolism (33).

Simpson et al (34, 35) showed that, in cultured neonatal cardiomyocytes, $\alpha_1$ adrenoceptor stimulation causes hypertrophy. The agonist-induced effects were blocked by the nonselective $\alpha_1$ adrenoceptor antagonist prazosin and the $\alpha_{1A}$ selective antagonists WB4101 (35, 36), 5-methylurapidil, and (+)niguldipine (37). The $\alpha_{1B}$ antagonist chlorethylclonidine had no effect (36). Studies in intact animals confirm the potential role of $\alpha_1$ adrenoceptor stimulation in cardiac hypertrophy (38). $\alpha_1$ Adrenoceptors are also involved in normal neonatal cardiac growth in vivo (39).

The molecular mechanisms of cardiomyocyte hypertrophy following $\alpha_1$ adrenoceptor stimulation are similar to those of the peptidergic growth factors. There is an immediate early gene expression of proto-oncogenes within 1 to 2 hours, especially of c-*myc* (40) and c-*fos* and c-*jun* (41). These proto-oncogenes encode transcriptional factors that bind DNA and activate the transcription machinery. Therefore, cardiomyocyte hypertrophy is not only characterized by an enlarged cell size, but also by an up-regulation of a number of constitutively expressed contractile proteins and intracellular calcium transport proteins (42).

Although a role for $\alpha_1$ adrenoceptors in cardiomyocyte hypertrophy now seems well established, very little is known about other aspects of cardiac remodeling. Systematic pharmacological studies on changes of the extracellu-

lar matrix and coronary vessels are needed before more definitive conclusions can be drawn on the overall role of $\alpha_1$ adrenoceptors in cardiac remodeling.

## *Renin-Angiotensin System*

The most comprehensively studied chemical mediator of cardiac remodeling is the renin-angiotensin system. Two factors have contributed to our present understanding of the role of the renin-angiotensin system: (*a*) the availability of multiple drugs to influence this system, and (*b*) the remarkable effects of these drugs on cardiac remodeling in both experimental animal models and human pathologies. It now seems that the renin-angiotensin system plays a role in each of the four elements of the process of cardiac remodeling described above.

The endogenous source of cardiac angiotensin II is a matter of controversy in recent literature. On the one hand, various components of the renin-angiotensin system have been localized in cardiac tissue, which suggests local synthesis and an autocrine or paracrine role for angiotensin II (43). On the other hand, recent biochemical experiments that directly measure angiotensin II synthesis suggest a non-cardiac source and thus a more classical endocrine role for angiotensin II (44, 45). It is beyond the scope of this article to critically review all the evidence pro and con the existence of a cardiac renin-angiotensin system that operates independently of extracardiac factors. More importantly for this article is the presence of angiotensin II receptors in cardiac tissue and the proven effects on cardiac structure following stimulation of these receptors.

Studies on cultured cardiomyocytes show that angiotensin II, in relevant in vivo concentrations, induces cell hypertrophy associated with an induction of immediate-early proto-oncogenes (46, 47). The potential role of angiotensin II in causing cardiac hypertrophy is strengthened by many observations in humans and animal models that ACE-inhibitors reverse hypertrophy, even in the absence of measurable blood pressure–lowering effects (48–53). The nature of the receptor that mediates angiotensin II–induced myocyte hypertrophy has been a matter of recent interest. In vitro, the angiotensin II–mediated hypertrophy could be blocked by the $AT_1$ receptor antagonist losartan, whereas the $AT_2$ receptor antagonist PD 123 319 was ineffective (47). In vivo, infusion of angiotensin II in rats caused cardiac hypertrophy, which could be prevented by losartan (54). Cardiac hypertrophy in experimental hypertension and following myocardial infarction in rats can be prevented by $AT_1$ receptor antagonists (55–57).

In addition to myocyte hypertrophy, ventricular dilatation is an important aspect of cardiac remodeling, especially after MI. In fact, left ventricular dilatation is a major risk factor for post-infarction adverse outcome (50, 58). ACE-inhibition significantly attenuates left ventricular dilatation in both humans (51, 52, 58, 59) and rats after MI (60) as well as in a dog model of

myocardial stunning (61). The structural effects of ACE-inhibition on left ventricular dimension are associated with improvements in ventricular function (49, 50, 58, 59, 62).

Both direct effects on cardiac structure and indirect effects on the basis of hemodynamic changes contribute to the actions of ACE-inhibitors on left ventricular dimension. The hemodynamic changes are based primarily on a reduction of the afterload to the heart. Sharpe and co-workers (63) showed that captopril, but not furosemide, blunts progressive cardiac dilatation in patients after MI. Thus, a drug primarily influencing preload apparently did not alter the course of left ventricular dilatation. The favorable structural effects of ACE-inhibitors on left ventricular dilatation involve effects on collagen metabolism in the cardiac interstitium and reversal of myocyte hypertrophy (52, 61).

The third important structural cardiac effect of the renin-angiotensin system is the angiotensin II–induced increase of extracellular matrix collagen and related glycoproteins. In animal models of hypertension or cardiac volume overload with simultaneous activation of the renin-angiotensin system, cardiac collagen content is increased to a larger degree than could be expected on the basis of the amount of cardiac hypertrophy (21, 64). ACE-inhibitor treatment attenuates this rise in collagen content (21, 65). Conversely, animal models of hypertension or cardiac volume overload without renin-angiotensin system activation do not cause a disproportionate rise in collagen levels (64).

Recent studies assessing ligand binding or mRNA expression have proven the presence of angiotensin II receptors in cultured rat cardiac fibroblasts (67, 68). In cultured fibroblasts, angiotensin II (although at only relatively high concentrations) enhances collagen synthesis (69). Sadoshima and Izumo (47) showed that nanomolar amounts of angiotensin II increase both protein synthesis and thymidine uptake through $AT_1$ receptor stimulation in cultured cardiac fibroblasts. This effect was associated with induction of a number of immediate-early genes. Also in that model, in vivo dissociation between the effects of losartan on collagen deposition, on the one hand, and interstitial cell DNA synthesis after MI, on the other hand, suggests a role for $AT_1$ receptors in collagen deposition (55). Preliminary data indicate that endothelial cell proliferation in the rat MI model is mediated through $AT_2$ rather than $AT_1$ receptors (66).

In addition to its effects on collagen content, angiotensin II influences the expression of fibronectin (68, 70) and $\beta_1$ integrin (67) in cardiac fibroblasts. These proteins play an important role in cell adhesion and migration. Functional roles for these molecules have been implied in embryonic development and wound healing. It seems, therefore, attractive to propose a role in the process of cardiac remodeling.

The final potential target of the renin-angiotensin system in cardiac remod-

eling is the coronary vasculature. Structural changes of coronary arteriolar and capillary vessels contribute to the cardiac abnormalities in patients with arterial hypertension or myocardial ischemia (71). In animal models of these pathologies, hypertrophy of the tunica media of coronary arterioles and rarefaction of cardiac capillaries has been found, associated with augmented coronary resistance (65, 72). Recent observations confirm the significance of these microvascular changes in patients (71). Furthermore, in patients with recent MI, the effectiveness of new coronary microvessel growth is an important prognostic factor (73). Angiotensin II has been implicated both in arteriolar hypertrophy and in capillary growth and rarefaction (see below). However, the degree to which this role also applies to coronary microvessels remains to be determined. Recent data with ACE-inhibitors in various animal models indeed suggest such a role (65, 74).



## *Other Drug-Induced Changes of Cardiac Structure*

Antihypertensive drugs of various classes, e.g. β adrenoceptor blockers, centrally acting sympatholytics, and diuretics and calcium-antagonists, reduce cardiac hypertrophy in hypertensive patients (75). Nonpharmacological reduction of blood pressure with sodium restriction also reduces LVH (76). This suggests that reduction of blood pressure per se, rather than a direct drug-induced effect, is responsible for the regression of cardiac hypertrophy by antihypertensive drugs. Two exceptions are ACE-inhibitors, which influence cardiac remodeling by additional mechanisms besides blood pressure reduction alone (see above), and directly acting vasodilators, such as hydralazine (77) and minoxidil (78), which do not reduce or may even promote cardiac hypertrophy. The pressure-related effects of these latter drugs on cardiac hypertrophy are probably antagonized by opposing trophic effects due to cardiac sympathetic stimulation.

Prolonged nitrate therapy with either nitroglycerin or isosorbide dinitrate prevents left-ventricular remodeling in a dog model of myocardial infarction (79). The effects include prevention of infarct thinning, infarct expansion, ventricular dilatation, and cellular hypertrophy. The mechanism of nitrate action remains to be established, but may be based primarily upon the dilatation of the arterial and venous beds.

Recent observations suggest a possibly favorable effect of adenosine and adenosine-like drugs on cardiac remodeling (80, 81). Adenosine is thought to protect the heart from the damaging effect of ischemia by reducing neutrophil activity, coronary vasodilatation, and inhibition of platelet activation as well as by a still poorly understood phenomenon referred to as "preconditioning" of the heart. The basis of this phenomenon is that short periods of ischemic stress cause adaptive mechanisms in the heart that result in resistance to subsequent ischemic stress. Adenosine-stimulated ATP-dependent $K^+$ channels

are considered to mediate the adaptive mechanisms involved in preconditioning (80, 81).

Another area of research on the pharmacology of cardiac remodeling is the study of antioxidants. Early reperfusion is now a standard procedure in the treatment of acute MI. Apart from the prevention of further damage to the heart, this procedure may by itself cause some injury, which has been attributed to excessive accumulation of reactive oxygen metabolites in reperfused regions through release from invading leucocytes (82). Antioxidants, such as glutathione analogs, sulfhydryl-containing ACE-inhibitors, and α-tocopherol derivatives, could prevent these toxic actions of reactive oxygen metabolites (61, 82, 83). Although the biochemical mechanisms of antioxidant actions in the heart are now well established, there is still considerable controversy about the effects of "reperfusion injury" on long-term cardiac structure and functional behavior in vivo.

## VASCULAR REMODELING IN PATHOLOGICAL CONDITIONS

Like the heart, the vascular system cannot be regarded as a quiescent tissue with fixed structure. Blood vessels are capable of remodeling their architecture chronically in response to specific conditions. This broad approach to vascular remodeling contrasts with the more limited use preferred by some authors (84, 85) to describe the rearrangement of a fixed number of vascular smooth muscle cells around a different diameter. In the more general use of the word, vascular remodeling comprises: (*a*) growth of new vessels (angiogenesis) and disappearance of existing ones (rarefaction), (*b*) change in the number or size of vascular smooth muscle cells (VSMC), and (*c*) an altered composition of the vessel wall extracellular matrix.

The broad interpretation of vascular remodeling is even further complicated by the marked heterogeneity in the vascular system. This heterogeneity exists with respect to both the parallel (various regional vascular beds) and series (various arterial, capillary, or venous segments) organization of the vascular bed. Daemen & De Mey (86) have reviewed the mechanisms and implications of the heterogeneity in vascular remodeling.

The basic rules for vascular development were formulated some 100 years ago by Thoma (87): 1. Vascular branching is determined by the genetic rules and metabolic needs of the tissues; 2. Vascular diameter depends on the flow of blood through its lumen; and 3. Vessel wall thickness is determined by the transmural pressure. Research of the past decade has given insight into the physical and molecular basis of these rules (88–90). Furthermore, it now seems that these rules can also be used in the understanding of vascular remodeling during various pathological conditions.

## *Hypertension*

Elevated blood pressure eventually affects the structure of all segments of the vascular tree. One of the earliest events in both human essential hypertension and animal models of experimental hypertension is rarefaction of arterioles and capillaries (91–94, 95). Some authors observed a parallel increase in the amount of small venules (91, 92). These microvascular changes have been interpreted as a compensatory response to increased tissue blood flow (91, 96). As an alternative explanation, we have suggested that the changed pattern of microvascular growth is the result of genetically controlled differences in the activity of angiogenic molecules (95). More specifically, we have proposed a role for the renin-angiotensin system, acting through a special subset of angiotensin II receptors (97). Other candidate angiogenic mediators include basic FGF and TGF-β (98), vascular endothelial cell growth factor (98, 99), and cytokines, such as tumor necrosis factor–α (98).

The nature of the structural change of small arteries in hypertension has been reviewed recently by several authors (100–102). Histological studies show that, both in human essential hypertension and in genetic animal models of hypertension, the media-to-lumen ratio of small arteries is increased in different stages of development of hypertension. The increased quantity of smooth muscle cells within various small arteries is due to enhanced VSMC DNA synthesis and subsequent hyperplasia (103, 104). In primary models of hypertension, VSMC hyperplasia represents a very early event in the development of hypertension (101–104).

In other small arteries, notably in the cerebral vascular bed of spontaneously hypertensive rats (SHR), the increased media-to-lumen ratio is due to a remodeling of the same number of cells, either circumferentially or longitudinally (84). A similar type of remodeling was found in human intestinal (105) and subcutaneous (106) small arteries. In non-primary models of hypertension, e.g. DOCA salt or renal-clip hypertension, the increased media thickness of small arteries is caused by VSMC hypertrophy rather than hyperplasia (100, 103).

The major growth change at the level of the large arteries in hypertension is VSMC hypertrophy with subsequent increase in wall thickness (102, 103). VSMC hypertrophy in the aorta and several large arteries is generally regarded as an adaptive change, only occurring after hypertension has developed. It may be accompanied by VSMC polyploidy, a process that seems to be absent in the small arteries of SHR and other models of hypertension (103). Unfortunately, very little is known about the nature of the vascular change in large vessels in human hypertension. Both histological (107) and indirect ultrasound studies (108) suggest the existence of wall thickening similar to that in animal models.

The mechanisms underlying VSMC hypertrophy and hyperplasia have been reviewed elsewhere (103, 109). It seems that there is not just a single mechanism that controls VSMC growth. In the past years, the concept of "phenotypic modulation" has been developed to explain growth of VSMC (for an early review, see 110). During fetal and early postnatal life, a significant proportion of VSMC has the phenotype of a synthetic cell with large potential to proliferate and secrete extracellular matrix components. After birth, VSMC phenotype gradually changes into that of a contractile cell. VSMC phenotype can be modulated from a contractile into a synthetic type (and vice versa) by a range of physical and chemical factors. The most important physical factors are flow-associated shear stress and pressure-related tangential wall stress (88–90, 111). The many chemical factors with VSMC growth–affecting potential have been reviewed by Jackson & Schwartz (112), and include catecholamines (113), angiotensin II (114, 115), heparinoids (116, 117), basic FGF, TGF-β, and related peptidergic growth factors (112), low-density lipoproteins (118, 119), endothelium-derived vasoactive substances (120, 121), and extracellular matrix components (122).

Another aspect of vascular remodeling in hypertension is the enhanced synthesis of extracellular matrix components. The extracellular matrix of the arterial wall is an integrated system composed of collagen fibrils, elastic lamellae, proteoglycans, and structural glycoproteins. In hypertension of various etiologies, the synthesis of collagen and elastic fibers is increased. These changes contribute importantly to the decreased distensibility of arteries in hypertension. Additionally, an enhanced stimulation by glycoproteins—such as fibronectin—of integrin cell receptors changes phenotypic characteristics and growth of VSMC in hypertension (122).

## *Atherosclerosis*

Atherosclerosis has long been regarded as the formation of lipid-rich cellular aggregates in the artery wall intima, which ultimately accumulate connective tissue, lipids, and necrotic cellular debris that form a fibrous plaque. In this view, the atherosclerotic lesions would be a response to injury to the vessel wall intima (123). In recent theories on the pathogenesis of atherosclerosis, more emphasis is given to early changes in cellular growth within the intimal layers of the artery wall that are not related to denudation of the endothelium (124, 125). In these theories, atherosclerotic lesions begin as focal accumulations of VSMC in the intima. The following three processes seem to be involved in the remodeling of the arterial wall: (*a*) proliferation of VSMC, macrophages, and (possibly) lymphocytes in the intima; (*b*) the enhanced synthesis by these cells of extracellular matrix proteins, such as collagen and proteoglycans, and (*c*) the accumulation of lipid and cholesterol in the intimal cellular and extracellular matrix structure (125).

Much of the evidence for the hypotheses discussed above was derived from animal models of atherosclerosis and post-mortem material from human arteries. The recent introduction of non-invasive ultrasonographic techniques has allowed the assessment of vessel wall changes in humans at various stages of development of atherosclerosis. Ultrasonographic measurements confirm the importance of intima-media thickening in various arteries in relatively early stages of development of atherosclerosis in humans (126).

The mechanisms underlying the major processes of vascular remodeling in atherosclerosis have been suggested to be similar to those of large artery remodeling in hypertension. The enhanced growth of VSMC in the intima is the result of combined influences exerted by physical and chemical factors. The location of early lesions in atherosclerosis is associated with sites of low shear stress (127). Shear stress is now believed to be a primary physical factor in modulation of vascular cell proliferation (88, 127). Potential chemical mediators of VSMC growth were summarized above in the discussion of hypertension; their role in atherosclerosis has been reviewed by Ross (125). Special attention in recent atherosclerosis research has been given to the roles of low-density lipoproteins (119) and endothelium-derived nitric oxide (128, 129).



## *Restenosis*

Research on arterial remodeling following localized mechanical damage of the arterial lumen has rapidly increased in the past decade, owing to the increase in surgical procedures, such as endarterectomy, percutaneous transluminal angioplasty (PTCA), and bypass grafting. The disappointing results of some of these procedures are probably due to restenosis on the basis of smooth muscle cell accumulation and proliferation, inflammation, and thrombosis. The principal animal model to study this process has been balloon angioplasty of the normal rat carotid artery. Schwartz et al (112) have introduced the "three-wave" model to explain the major events in vascular remodeling following balloon injury. The first wave occurs during the first few days and consists of a dramatic increase in the replication rate of medial VSMC at the injury site. The second wave, starting after some 3–4 days, involves migration of VSMC towards the intima. This is followed by the rapid formation of a neointima by replication of a large percentage of the migrated VSMC. However, this process is followed by a slow and long-acting replication of a small percentage of VSMC, which produces extracellular matrix proteins. Furthermore, in this phase, regenerated or pseudoendothelial cells in the intima express high levels of vascular adhesion molecules (130). The third wave may over a period of months be responsible for most of the restenosis, as observed clinically. The therapeutically most relevant targets are the later two waves (112).

The primary molecules involved in the restenosis process are (*a*) basic FGF

for the first wave of rapid medial VSMC proliferation, (*b*) PDGF for the second wave of VSMC migration, and (*c*) TGF-β, angiotensin II, and noradrenaline for the third wave (112, 131, 132). However, these therapeutic targets have been based upon a still-limited number of studies using appropriate administration of selective antagonist. One important target for future research in the area of molecular modulation of restenosis will be temporal and spatial selective delivery of such antagonists to the area of injury. A limitation of the experimental animal models of arterial injury has been the use of normal arteries. In humans, angioplasty is usually performed in arteries with pre-existing occlusive lesions of atherosclerosis. Recent studies suggest important differences between animal models and clinical studies (133).



## PHARMACOLOGY OF VASCULAR REMODELING

Drugs can influence vascular structure on the basis of a number of potential mechanisms of action: 1. indirectly, by changing physical variables that control the structure of the vascular tree, and/or 2. directly, by influencing (*a*) the growth of new vessels or disappearance of existing ones, (*b*) the adhesion and transvascular migration of various cell types along the vessel wall, (*c*) the number of or size of VSMC, and/or (*d*) the composition of the extracellular matrix. It is often difficult to choose between these potential mechanisms of action when interpreting drug-induced changes in vascular structure. In intact humans or animals, for instance, drugs may simultaneously affect physical factors controlling vascular structure and intraluminal molecular mechanisms of growth. The interpretation of VSMC or endothelial cell culture data may suffer from the phenotypic changes induced by the isolation and culture procedure per se. The interpretation of drug-induced effects in terms of mechanisms of action requires a rigorous set of pharmacological criteria, such as the use of a dose range and appropriate antagonists. These criteria are not always met. Therefore, some caution is needed when trying to draw more general conclusions on the pharmacology of vascular remodeling on the basis of limited sets of studies.

### *Polypeptides*

A number of endogenous polypeptides can act as growth regulatory molecules and induce multiple and, in some instances, apparently divergent effects on vascular structure. These molecules include the family of fibroblast growth factor (FGF), the platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), the TGF-β family, tumor necrosis factor–α, and several interleukins (98, 112, 125).

Some of these factors are general mitogens, whereas others have a certain degree of selectivity for specific cell types. VEGF, for instance, is a specific

vascular endothelial cell mitogen (98, 134). This property makes it a potent angiogenic molecule and a potentially interesting target for the development of drugs influencing angiogenesis.

Other polypeptides have more general growth regulatory properties. Basic FGF, for instance, is a general mitogen (98, 112). In addition, it is a chemoattractant for endothelial cells, and it stimulates extracellular matrix synthesis (125, 135). Recent data suggest hemodynamic effects of basic FGF, possibly through an interaction with endothelial cell nitric oxide metabolism (136). TGF-β has an even more complex mode of action. It is an inhibitor of endothelial cell proliferation but stimulates angiogenesis in vivo (98). Since TGF-β is not an endothelial cell mitogen, it may promote angiogenesis by differentiating endothelial cells after their proliferative phase has ended, possibly by inducing synthesis of matrix (98). In fact, TGF-β is one of the most potent stimulators of connective tissue formation known (125). In addition, TGF-β promotes migration of various cell types along the vessel wall. It influences VSMC phenotype and thus plays a major role in determining whether the response to other growth factors is hypertrophic or hyperplastic (137).

In summary, polypeptides have multiple actions on vascular structure. The pharmacological relevance of these effects remains to be determined and will await the availability of selective antagonists.

## *Endothelium-Derived Vasoactive Substances*

The endothelium has been recognized for some 15 years now as an important source of vasoactive substances. In addition to an effect on vascular tone, some of these substances influence vascular structure (138). The marked influence of the endothelium on vascular structure was first recognized in studies that showed proliferative responses in blood vessels from which the endothelium was mechanically removed (120, 123). Later studies showed that TGF-β, NO, and prostacyclin are the most important candidate mediators of this growth inhibitory effect (139, 140).

The complex effects of TGF-β are discussed above. NO and prostacyclin can exert both direct and indirect effects on vascular structure. The indirect effects involve (*a*) platelet function, causing decreased release of platelet-derived growth factors, as well as decreased platelet adhesion and aggregation (141, 142), and (*b*) hemodynamic effects related to the relaxation of vascular smooth muscle. The direct effects of NO and prostacyclin on vascular structure are still poorly understood. Both substances inhibit the proliferation of VSMC held in culture (139, 142). However, extrapolation of these observations to the intact vasculature is not straightforward. Different findings were reported on the effects of endothelium-derived prostaglandins and NO in isolated VSMC, in arterial organoid culture (140, 143), and in arteries from intact animals (138).

Recent observations in rats with various forms of hypertension do not

support a major role of the endothelium in medial hypertrophy of the arterial wall (121). However, some early intimal growth abnormalities in atherosclerosis or vascular restenosis may be endothelium dependent. A sustained enhancement of vascular NO activity by l-arginine feeding is parallelled by a striking inhibition of intimal lesion formation in hypercholesterolemic rabbits (144) or arterial balloon-injured rabbits (145). Chronic inhibition of NO synthase with nitro-l-arginine methylester (l-NAME) accelerates atherogenesis in hypercholesterolemic rabbits (128, 129).

The molecular mechanism of NO-induced inhibition of neointimal formation remains to be established. Recent studies favor an inhibitory effect of NO on the activation of adhesion molecules and the expression of chemotactic proteins (146). Alternatively, NO may interfere directly as a cytotoxic agent with DNA synthesis via nitrosylation and ADP ribosylation (147).

In addition to growth inhibitors, the endothelium can produce growth activators such as basic FGF, PDGF, and endothelin. The latter substance increases DNA synthesis of VSMC held in culture or contained in intact rat arteries in organoid culture (140). The recent introduction of endothelin receptor antagonists provides useful tools in the further study of the role of this mediator in vascular remodeling.

In conclusion, although the endothelium is a key source of molecular modulators of vascular structure, many aspects of its role need confirmation in appropriate in vivo models. Its best-established effect seems the NO-mediated neointima formation in models of atherosclerosis and restenosis. Other major aspects—such as its role in angiogenesis and rarefaction, extracellular matrix composition, and transvascular cell migration—need further study. The pharmacological tools to perform such studies are now available.

## *Antihypertensive Drugs*

The long-term blood pressure lowering induced by antihypertensive drugs may implicate an effect on vascular structure through a hemodynamic effect, independent of the mode of action of the drug. On the basis of an extensive series of studies using antihypertensives of various classes, Mulvany et al (85, 100) have indeed concluded that resistance artery hypertrophy in experimental hypertension is primarily influenced by the long-term blood pressure–lowering effect of these drugs. There are, however, exceptions to this general rule. On the one hand, there are antihypertensives, such as minoxidil (78) or hydralazine (148), that cause little regression or even an increase of vascular hypertrophy. The more consistent regression of hypertrophy caused by these agents when combined with a sympatholytic agent suggests that, similarly to their effects on the heart, arterial vasodilators increase vascular sympathetic activity (149).

On the other hand, there are antihypertensive drugs, such as calcium antagonists and agents interfering with the renin-angiotensin system, that influence vascular structure by mechanisms independent of blood pressure lowering.

## *Calcium Antagonists*

A variety of growth factors, including PDGF and angiotensin II, stimulate calcium influx, at least partly through voltage operated L-channels in quiescent VSMC (150, 151). The consequent increase in intracellular calcium is believed to play a vital role in VSMC migration and proliferation (152). Calcium antagonists of the L-channel blocker type are potent inhibitors of monocyte infiltration into the vascular intima (153) as well as VSMC migration and proliferation induced by chemical growth factors (reviewed in 112). The effect seems irrespective of the chemical class, i.e. dihydropyridines as well as verapamil and diltiazem inhibit VSMC proliferation and migration (112, 150–152).

In an elegant study done recently, Yang et al (154) showed that VSMC proliferation induced by pulsatile stretch is not inhibited by calcium antagonists. This discrepancy between growth factor or pulsatile stretch-induced VSMC growth may explain some of the divergent effects of calcium antagonists in whole animal models or in patients. On the one hand, calcium antagonists are very effective blockers of myointimal hyperplasia in models of restenosis (152). As was discussed before, myointimal hyperplasia in this situation is primarily dependent upon the effect of VSMC migration and proliferation induced by chemical growth factors. Calcium antagonists have only modest antiatherogenic effects (155) and cause no clear reduction of resistance artery media hypertrophy beyond the level that can be expected on the basis of their blood pressure–lowering effect (100, 156). As an alternative hypothesis, Jackson & Schwartz (112) proposed that calcium influx via L-type channels is necessary for VSMC to achieve a transition from quiescence to active growth. Once VSMC are proliferating, there would be a loss of L-type calcium channels. This "phenotypic modulation" hypothesis of VSMC can be further tested with modern molecular pharmacological tools to quantify calcium channels.

In conclusion, present evidence suggests effects of calcium antagonists on proliferative responses of VSMC and migration of various cell types through the vessel wall. Other effects on vascular remodeling are less evident or have not yet been thoroughly investigated. This is especially the case for the effects of calcium antagonists on extracellular matrix and on angiogenesis. With respect to the latter effect, follow-up studies must be done on the intriguing observation by Hutchins and co-workers (157) that long-term nimodipine treatment increases capillary and arteriolar density of the brain.

## *Drugs Acting on the Renin-Angiotensin System*

Among the chemical mediators of vascular remodeling, angiotensin II is one of the most pluriform factors. In addition to its role as an acute pressor and intrarenally active substance, angiotensin II is involved in angiogenesis and rarefaction, VSMC growth, and vascular extracellular matrix synthesis. It may serve this role as part of an endocrine or paracrine control mechanism that is activated in situations of tissue ischemia or damage.

A role for angiotensin II in angiogenesis was first proposed in studies on the rabbit cornea (158). This was confirmed in the chick embryo chorio-allantois membrane (CAM) (159). We recently showed that angiotensin II–induced angiogenesis in the CAM is mediated by an angiotensin II receptor type, which is different from the previously described $AT_1$ and $AT_2$ receptors (97). Drugs blocking the endogenous activity of angiotensin II, i.e. ACE-inhibitors or AT-receptor antagonists, inhibit the formation of new blood vessels in situations of normal development or ischemia (160–162). The clinical significance of these observations has not yet been assessed, but we can speculate on some adverse effects of inhibitors of the renin-angiotensin system on processes of tissue repair involving the growth of new blood vessels.

The evidence for angiotensin II as a growth factor for VSMC has been reviewed by various authors (112, 163, 164). Briefly, angiotensin II appears to cause hyperplasia of cultured VSMC maintained in growth-supporting concentrations of serum. In contrast, hypertrophic effects are observed in cultures in which cells are rendered quiescent by an absence of sufficient serum (112). It therefore appears that a serum-derived co-factor determines the nature of the cellular growth response to angiotensin II. This would also explain why in vivo observations in rats with balloon-injured arteries show a VSMC proliferation during chronic angiotensin II infusion (115).

The nature of the receptor mediating angiotensin II–induced VSMC growth has not yet been established. Conflicting data were reported, suggesting both the involvement of the $AT_1$ (165) and $AT_2$ or perhaps even another type of AT-receptor (166) in VSMC growth. A lack of clearly defined antagonists for the non-$AT_1$ subtypes of angiotensin receptors precludes definitive studies.

Further, but more indirect, evidence for a role of angiotensin II as a VSMC growth factor comes from studies with ACE-inhibitors. Freslon & Giudicelli (167) were the first to report a decrease in large artery hypertrophy during chronic captopril treatment in SHR. Later studies have confirmed this observation for many other ACE-inhibitors in different models of hypertension (for reviews, see 168, 169). In brief, ACE-inhibitors can attenuate both large- and small-artery hypertrophy during the development of spontaneous or renal forms of hypertension to a greater degree than other antihypertensives, and partly independent of their blood pressure effect. A study by Uehara et al (170)

suggests that ACE-inhibitors diminish VSMC proliferation in cell culture independently of blood pressure–lowering by directly lengthening the $G_2$-M phase of the cell cycle.

Although the effects of ACE-inhibitors on media hypertrophy in hypertension are now well established, there is controversy with regard to their influence on intimal hyperplasia in situations of endothelial damage. In studies on balloon-injured arteries in rats, ACE-inhibitors cause a significant reduction of neointima growth (171). Clinical studies did not confirm this effect of ACE-inhibitors in post-angioplasty restenosis (133, 172). Various reasons could explain the differences between the animal and clinical data: (*a*) the doses applied in animals were usually much higher; (*b*) the timing of the start of drug treatment was different in the animal and clinical studies; (*c*) whereas drugs are administered to experimental animals in a highly reliable manner, human beings have a notoriously poor compliance to their drug regimens; (*d*) in contrast to normal rats, human coronary arteries undergoing angioplasty have a pre-existing intima (in fact, ACE-inhibitors do not prevent intimal hypertrophy in animals with pre-existing intimas) (112); and (*e*) the activity of the endogeneous renin-angiotensin system is different in various experimental models or clinical situations (173).

The final aspect of interactions with vascular structure by drugs acting on the renin-angiotensin system is extracellular matrix synthesis. Angiotensin II promotes the synthesis of various components of the vascular extracellular matrix, such as collagen IV and laminin (174, 175). By doing so, it influences arterial distensibility (176) and also differentiation of VSMC (175). It would be very interesting to investigate the effects of AT-receptor antagonists on the vascular extracellular matrix in view of the marked pharmacology of these drugs in cardiac extracellular matrix modulation (see above).

## *Antithrombotic Drugs*

Among its many biological actions, the mitogenic effect of thrombin has gained increasing support. The recent discovery of a cellular thrombin receptor, the availability of thrombin receptor antagonists, and the detection of mRNA for the thrombin receptor in human atherosclerotic plaques have given impetus to research on thrombin as a VSMC growth stimulant (177). Recent studies indicate that thrombin itself may not be a mitogen but can give rise to a polypeptide growth factor through its proteolytic activity (178). The recent introduction of orally active synthetic low-molecular-weight thrombin inhibitors (177) will probably reveal the exact mechanism of thrombin's mitogenic effect as well as its clinical significance.

A second potential target for drugs to influence vascular remodeling is the urokinase-type plasminogen activator (uPA) and its receptor. uPA inhibitors and receptor antagonists inhibit cell migration through the vessel wall (179).

These effects are probably mediated by other protein factors such as plasmin, which is derived from plasminogen through the action of uPA. Endogenous plasminogen activator inhibitor type-1 (PAI-1) is expressed by endothelial cells and may be a regulator of angiogenesis (179). The major target of clinical development of drugs influencing plasminogen activator is tumor metastasis. However, in view of the pleiotropic potency of the uPA-dependent proteolytic system, a role in cardiovascular remodeling can be anticipated.

Heparin, independent of its anticoagulant properties, inhibits VSMC proliferation in tissue culture as well as in animal models for vascular injury (112). The mechanism whereby heparin inhibits VSMC growth has not been resolved and may involve (*a*) intracellular binding to cell cycle controlling proteins; (*b*) inhibition of intracellular calcium mobilization through an effect on the inositol 1,4,5-tri-phosphate receptor; (*c*) competition for binding to the basic FGF receptor; or (*d*) inhibition of deposition of extracellular matrix components, especially thrombospondin (112).

In contrast to the clear in vitro or animal model results, the clinical effects of heparin on restenosis following vascular injury are controversial (112, 180). The extent of arterial injury as well as the site and means of heparin administration may be decisive factors in the clinical effectiveness of this agent in restenosis (180).

Antiplatelet drugs, especially cyclo-oxygenase inhibitors, have been investigated with respect to their potential to influence neointima formation. The inhibitory effects of these drugs on in vitro VSMC growth has not been systematically confirmed in various animal models or clinical situations of neointima formation (112, 181). A role for antiplatelet drugs in vascular remodeling remains to be established.

## *Other Drugs*

A wide variety of other drugs have been investigated for their capacity to influence VSMC proliferation in vitro or vascular remodeling in animal models. Jackson & Schwartz (112) have summarized the results of these studies. The majority of the investigations were limited to in vitro measurement of VSMC proliferation. Although such studies are useful as a first screening, they do not predict very well whole animal or clinical effectiveness. Data are available for a limited number of drugs in vivo as well. The hypolipidemic agents etofibrate and tradipil reduce neointima formation in animal models of atherosclerosis (182, 183). Drugs in a range of classes, such as the antimycotic terbinafine, the immunosuppressant cyclosporin A, the somatostatin analogue angiopeptin, and the iron chelator desferrioxamine, reduce neointima growth in experimental models of restenosis based on balloon injury of large arteries (184–187). The wide variety of molecular mechanisms of action of these drugs

precludes a conclusion on common pathways in the pharmacology of these drugs in vascular remodeling.

A final candidate with potentially large impact in vascular remodeling is atrial natriuretic peptide (ANP). This hormone has in vitro antiproliferative effects on isolated VSMC (188). In an elegant study in SHR, Mourlon-Le Grand et al (189) recently showed a marked effect of chronic ANP treatment on large artery medial wall thickness and extracellular matrix composition. These effects caused significant improvement of the mechanical behavior of the large arteries (189).



## CONCLUSION AND FUTURE OUTLOOK

The design of pharmacological approaches to influence cardiovascular structure can profit from knowledge of the underlying pathological mechanisms. The development of an "antiproliferative" drug merely to inhibit hypertrophy of the heart or the arteries shows a lack of understanding of these mechanisms. Cardiac and vascular hypertrophy serve, at least to a large degree, an adaptive purpose to cope with increased loads upon these tissues. This implies that a primary target in the pharmacology of cardiovascular remodeling should be the normalization of deranged physical variables modulating cardiovascular structure. Additional targets of pharmacological repair of cardiovascular tissue are those aspects of cardiovascular remodeling that contribute to chronic loss of function. These targets include (*a*) the irreversible loss of small arteries and capillaries or the excessive growth of small venules; (*b*) the unbalanced proliferation of the non-myocyte compartment in the heart or non-VSMC compartment in the vessel wall, with subsequent increased deposition of extracellular matrix material; and (*c*) the migration and phenotypic modulation of VSMC towards the growth-sensitive type in the arterial intima. The key processes to modulate by drug therapy therefore seem to be (*a*) angiogenesis; (*b*) extracellular matrix production, deposition, and degradation; (*c*) phenotypic modulation of various cell types of the cardiovascular system; and (*d*) intimal VSMC migration and proliferation. Some of the molecular targets to modulate these processes were discussed above. However, the major pharmacology of this type of tissue remodeling still must be developed. Classical pharmacology already has many tools available for this research. A fascinating future approach is the cellular phenotypic manipulation by targeted gene transfer (190, 191). The concept of modulation of cellular phenotype includes the differential expression of various receptor (sub)types. A final future approach is the local deposition of drugs or genes to the heart or vessel wall by means of catheters, indwelling stents, drug-containing microparticles, and liposomes, which theoretically will alleviate some of the undesirable side effects of drugs affecting compensatory growth and reorganization of tissues in general.

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