

Vascular Protection: Paradigm for the Treatment of Patients at High Cardiovascular Risk

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ABSTRACT

Endothelial dysfunction, an early feature of atherosclerosis, contributes to atherogenesis by promoting abnormal vasomotility, a procoagulant state, and excessive infiltration of inflammatory cells into the vessel. Although the exact mechanisms remain unclear, alterations in the redoxstate and inactivation of nitric oxide seem to play a pivotal role. There is a great and growing interest in endothelial dysfunction as a possible cause of disease and potential target of medications that can protect against the structural vessel alterations that are the first step toward target organ damage.

INTRODUCTION

Until 20 years ago, the endothelium was simply regarded as a protective barrier separating the bloodstream from the muscular component of the vascular wall. However, since the fundamental observations of Furchgott and Zawadzki¹ in the early 1980s, it has been extensively reassessed and is now considered to be an organ with autocrine/paracrine activities, the dys-

function of which plays a primary role in promoting atherosclerosis and vessel wall remodeling.

The endothelium plays a key role in regulating the contraction of smooth muscle cells located on the tunica media by means of a delicate balance of substances with vasodilating and vasoconstricting activity.² The integrity of the endothelium is necessary to ensure a vasodilating response to different stimuli, as was first demonstrated by the observation of acetylcholine-induced aortic relaxation in rabbits, and has since been confirmed by observations of other mediators in many different arteries (and some veins) in all of the studied animal species,^{3,4} including some evolutionarily very primitive species.⁴ These findings support the ancestral nature and physiological importance of this kind of peripheral vasomotor regulation.

From a structural point of view, the most important and widely studied vasodilating substance produced by the endothelium is endothelium-derived relaxing factor (EDRF), which was subsequently identified as nitric oxide² (NO), but there are other active vasodilating substances such as prostacyclin (PGI₂) and endothelium-derived hyper-

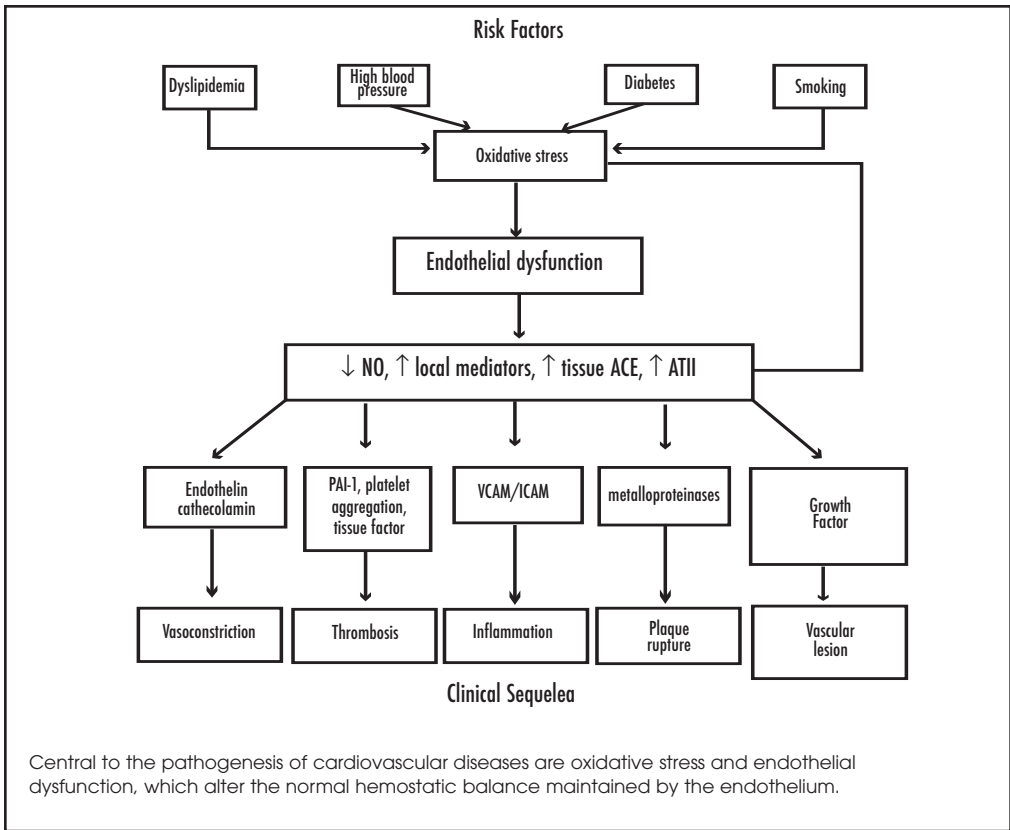


Figure 1. Proposed model integrating the role of angiotensin II in the complex pathologic processes occurring in the development and progression of vascular disease.

polarizing factor (EDHF),⁵ both of which have an antiplatelet effect.

Inside endothelial cells, EDRF-NO is produced from L-arginine by a key-stone enzyme, NO synthetase (NOS), the activity of which can be stimulated by various agonists, such as bradykinin, acetylcholine, and thrombin, which, by interacting with specific receptors, activate NOS and thus increase EDRF-NO synthesis.

The complex function of EDRF-NO in peripheral district regulation is due to the fact that it inhibits many processes, including the contraction of tunica media myocytes, the proliferation of smooth muscle cells, platelet aggregation, LDL oxidative processes, the expression of adhesion molecules, the adhesion of monocytes and platelets,

and the production of vasoconstricting and vasodilating substances.⁶⁻⁸ Among these substances, a pre-eminent role is played by factors that are dependent on cyclo-oxygenase, including endoperoxides such as thromboxane A₂ (TxA₂) and prostaglandin H₂ (PGH₂),⁹ and oxygen free radicals.¹⁰ Endothelin-1 (ET-1) must also be mentioned because it interacts with specific AT_A receptors located in the smooth muscle cells of the tunica media, thus causing their contraction. In the absence of EDRF-NO production, ET-1 interacts with other (ET_B) receptors located in the endothelial cell membrane, the stimulation of which induces EDRF-NO and EDHF production as a result of interactions with various receptors. Endothelin can therefore induce both vasoconstriction (which usually

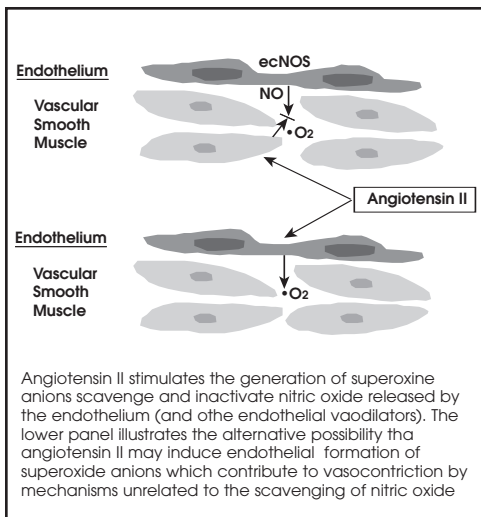


Figure 2. Simplified schematic drawing of possible endothelium-dependent effects of superoxide anions induced by angiotensin II.

prevails), and vasodilation, particularly when EDRF-NO is not produced.

ENDOTHELIAL DYSFUNCTION AND CARDIOVASCULAR RISK

Under specific circumstances such as old age and menopause, or in a variety of pathological conditions such as hypertension, diabetes mellitus, dyslipidemia, atherosclerosis, and reperfusion damage, the activation of endothelial cells may lead to the production and release of the above-mentioned vasoconstricting factors, which can counterbalance and overcome the vasodilating effects of EDRF-NO, and thus cause inappropriate vasoconstriction and prothrombotic effects.

This alteration in vessel wall function (or endothelial dysfunction) can be caused by a failure to produce EDRF-NO or, if EDRF-NO synthesis is preserved, by an imbalance in favor of vasoconstricting factors.

A number of clinical observations have shown that endothelial dysfunction is a constant feature of hypertensive patients,^{11,12} in whom it is caused by reduced EDRF-NO availability due to

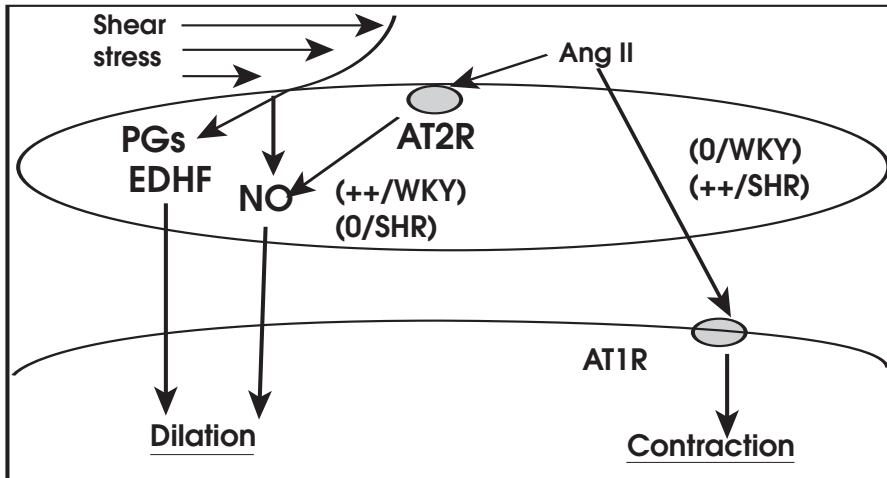
the inactivation induced by the oxidative stress associated with hypertension.¹³ In this pathological condition, EDRF-NO is destroyed by the binding of superoxide anions. This leads to the production of peroxynitrites, which have multiple negative effects on blood vessel wall function and structure. Endothelium-mediated vasodilation seems to be less effective when little EDRF-NO is available because it can only be achieved by vicarious mechanisms such as hyperpolarization.¹⁴

The endothelial dysfunction in hypertensive patients may also be due to an interaction between the EDRF-NO and ET_1 systems. Although the blood levels of ET_1 are not increased, its constricting activity is, and the availability of EDRF-NO is reduced. The limited availability of EDRF-NO may reduce its inhibitory effect on ET_1 production via ET_B receptors, thus leading to an imbalance between the two systems with an increase in ET_1 vasoconstricting and proliferative effects.¹⁵

Although endothelial function is always altered in hypertension, it is not specific to it because it is common to all cardiovascular risk factors, including age, menopause, hypercholesterolemia, smoking, diabetes mellitus, and hyperhomocysteinemia.

Combinations of risk factors increase the severity of endothelial dysfunction, which is why it is included among the mechanisms leading an exponential increase in risk in patients with a number of predisposing factors.¹⁶

It is therefore reasonable to assume that endothelial dysfunction may be a common pathogenetic mechanism that can promote the onset and progression of atherosclerosis. This hypothesis is supported by experimental evidence showing that, in addition to having opposite hemodynamic effects, EDRF-NO and vasoconstricting substances respectively inhibit and activate a number of the



In normotensive Wistar-Kyoto rats, flow-induced dilation involves AT-2R-dependent dilation through NO the pathway. In spontaneously hypertensive rats (SHR), shear stress-induced AT-2R-dependent dilation is absent and AT-1R-dependent contraction antagonizes flow-dependent dilation.

Figure 3. Possible role of AT-1Rs and AT-2Rs in the response of mesenteric resistance arteries to flow (shear stress).

mechanisms involved in the development of atheromatic plaques and the pathogenesis of thrombotic events, including platelet aggregation, reduced fibrinolytic properties, the migration of smooth muscle cells, the expression of adhesion molecules, and the adhesion of monocytes.¹⁷

Furthermore, a close relationship between endothelial dysfunction, cardiovascular risk markers, and clinical events has been demonstrated in patients with hypertension or atherosclerosis.

In hypertensive patients, the altered vascular bed forearm response due to the lack of EDRF-NO is related to the media-intimal thickness of the carotid, an important marker of atherosclerosis.¹⁸ The response of epicardial coronary arteries to acetylcholine is inversely related to the presence of wall plaques detected using intravascular ultrasound. Furthermore, in the epicardial coronary arteries of patients who have undergone heart transplantation, endothelial dysfunction predicts the further development of atherosclerosis¹⁹ and the onset

of clinical events.²⁰ The association between endothelial dysfunction and cardiovascular events has also been confirmed by longitudinal clinical trials involving patients with coronary artery disease. One of these²¹ evaluated the outcome of patients with moderate coronary artery disease (CAD) on the basis of endothelial function at the time of randomization, and found that only the patients with severe endothelial dysfunction (as assessed by means of a coronary infusion of acetylcholine) experienced clinical events during the 28-day follow-up. In patients with CAD, the incidence of clinical events during the subsequent 7 years has been significantly related to coronary endothelial dysfunction assessed by means of a variety of stimuli, including acetylcholine infusion, sympathetic activation (cold pressor test), or flow-mediated activation (papaverine infusion).²² Endothelial dysfunction has also been detected in the peripheral arteries of CAD patients (e.g., the brachial artery), and has been found to be related to more frequent

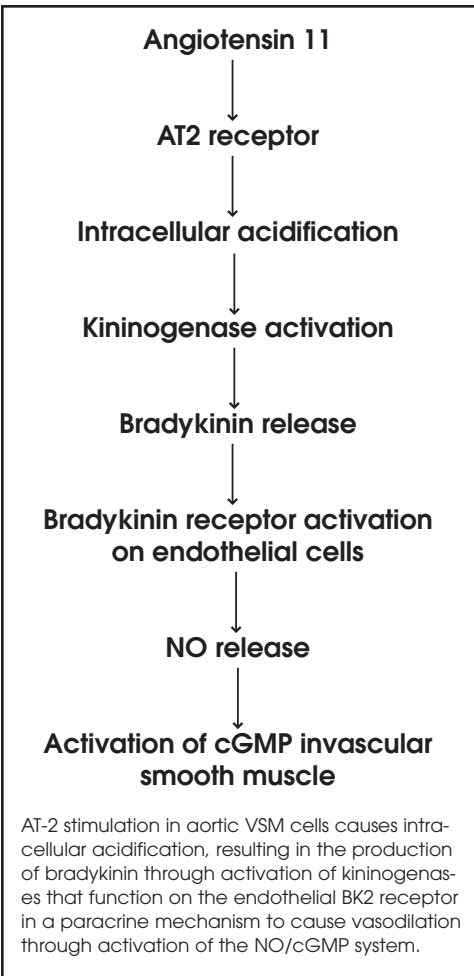
ENDOTHELIUM AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The balance between vasoconstricting and vasodilating factors (mainly EDRF-NO) is closely related to the oxidative state of endothelial cells.²⁵ Cardiovascular risk factors increase oxidative stress,²⁶ and the correlation between the various risk factors and increased endothelial oxidative stress depends on the activation of a number of regulatory systems, one of the most important of which is angiotensin II (Ang II).²⁷

There is a complex interaction between Ang II and the mediators produced by endothelial cells.²⁸ Risk factors increase oxidative stress via a common mechanism, and consequently increase endothelial dysfunction, vessel wall inflammation, coagulation activation, and vascular remodeling (Figure 1). Local inflammatory processes increase Ang II production: a positive feedback mechanism then takes place and is responsible for increasing Ang II levels and reducing EDRF-NO availability.

For example, in hypertension, experimental evidence shows that the hypertensive condition itself does not stimulate superoxide anion production, whereas the presence of Ang II does.²⁹ Superoxide anion production is mediated by the interaction between Ang II and AT₁ receptors, whereas the interaction with AT₂ receptors has opposite effects. Both tissue and circulating Ang³⁰ induce the production of superoxide anion by all of the cells in the vessel wall, including adventitial fibroblasts, tunica media smooth muscle cells, and endothelial cells.³¹ Ang II not only has a local effect on the oxidative state of the vessel wall, but also a systemic effect.

The superoxide anion produced by the smooth muscle cells of the tunica media inactivates the EDRF-NO produced by endothelial cells (Figure 2, upper part), which then produce super-



AT-2 stimulation in aortic VSM cells causes intracellular acidification, resulting in the production of bradykinin through activation of kininogenases that function on the endothelial BK2 receptor in a paracrine mechanism to cause vasodilation through activation of the NO/cGMP system.

Figure 4. Proposed pathway responsible for AT-2-mediated cGMP synthesis in vascular smooth muscle (VSM) cells.

coronary events.²³

These data indicate that the presence of endothelial dysfunction in the coronary and large peripheral arteries of CAD patients is associated with an increased frequency of cardiovascular events. Endothelial dysfunction, assessed by means of the response to a forearm acetylcholine infusion, has also proved to be a good predictor of cardiovascular events in patients with hypertension,²⁴ and is therefore related to an increase in the frequency of cardiovascular events in both CAD and arterial hypertension.

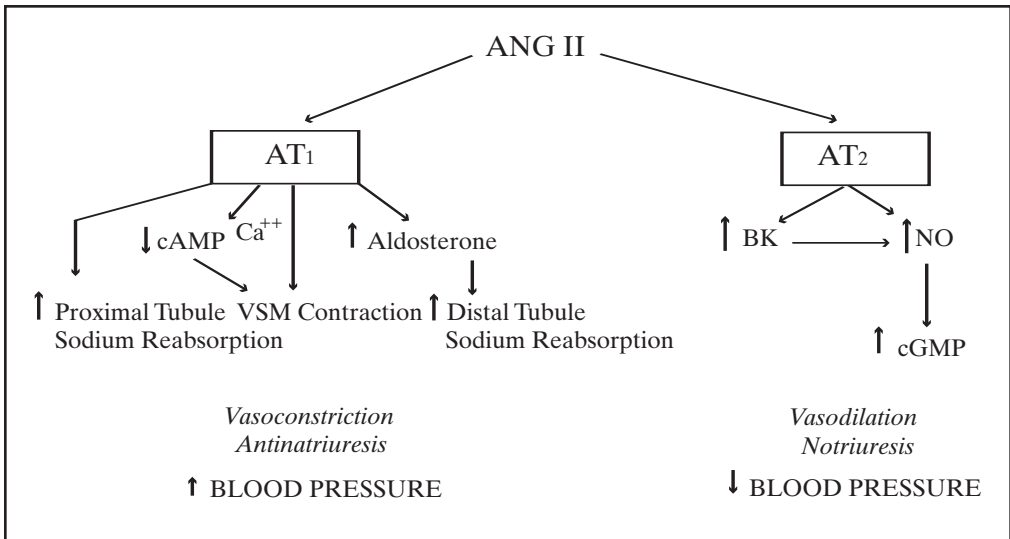


Figure 5. Role of AT-1 and AT-2 receptors in blood pressure regulation.

oxide anion (Figure 2, lower part) and subsequent vasoconstriction, regardless of the inactivation of EDRF-NO.³²

In conclusion, in the presence of one or more risk factors, the renin-angiotensin system (RAS) acts as a link between the mechanical insults occurring in arterial hypertension, metabolic damage in dyslipidemia and diabetes mellitus, and the functional and structural alterations in the blood vessel wall that lead to target organ damage and clinical events.

ENDOTHELIUM AND THE KININ SYSTEM

The biologically active kinins—bradykinin and kallidin—arise from the metabolic transformation of precursor molecules, such as high- and low-molecular weight kininogens. These precursor molecules are the substrate for a number of proteolytic enzymes, including the kallikreins that give rise to bradykinin. Only tissue kallikreins have kininogenic activity and form active kinins. Kallidin is a decapeptide, whereas bradykinin has nine amino acids and differs from kallidin insofar as it lacks a lysinic terminal in position 1. Both substances are

biologically active and have a half-life of 15 seconds, about 80%-90% being catabolized in the pulmonary vascular bed.

The principal kinin-catabolizing enzyme is kininase II, better known as angiotensin converting enzyme (ACE), which represents a biological link between the RAS and the kinin system. ACE is a proteolytic enzyme that activates the RAS by converting biologically inactive angiotensin I into Ang II; however, it inactivates the kinin system because transforms active bradykinin and kallidin into biologically inactive fragments.

At least two distinct kinin receptors have been identified: B1 and B2. The B2 receptor interacts with both bradykinin and kallidin, and mediates most kinin effects in the absence of inflammation, whereas the B1 receptor undergoes up-regulation only as a result of trauma or inflammation. B2 receptor stimulation activates the G-protein system, phospholipase C (PLC) and phospholipase A₂ (PLA₂). PLC activation increases the intracellular concentration of diacylglycerol and phospho-inositol-3 (IP₃), which induces the synthesis and release of EDRF-NO.

PLA₂ activation causes arachidonic acid release by membrane phospholipids and may promote the formation of various inflammation mediators, such as PGI₂, which has a potent vasodilating effect.

By stimulating the B2 receptors located on endothelial cells, bradykinin and kallidin can therefore induce the synthesis of two potent vasodilating factors: EDRF-NO and PGI₂. In terms of cardiovascular effects, bradykinin is one of the main regulators of the endothelium-mediated vasodilating response because its stimulation of B2 receptors induces the synthesis and release of both EDRF-NO and PGI₂. Bradykinin has other protective effects on cardiac and vascular structures: it contributes to the myocardial ischemic preconditioning mechanism, prevents vascular smooth muscle cell growth and proliferation, and stimulates the production of plasminogen tissue activator (tPA) by endothelial cells.

In conclusion, normal kinin system function is crucial for the maintenance of normal endothelial function. Increased bradykinin synthesis can have not only a vasodilating action, but also protective effects on the structure of the myocardium and vessel walls.

ENDOTHELIUM AND COAGULATION

The endothelium is an important component of the coagulation system. Under normal resting conditions, endothelial cells express thrombomodulin, activated protein C, heparin cofactor II, and plasminogen activator, leading to potent anticoagulant action. Ang II increases the circulating levels of plasminogen activator inhibitor-1 by increasing its synthesis and release in endothelial cells.^{33,34} This increase may be blunted by antagonists of angiotensin 1 (AT-1) receptors.³⁵ Accumulating data suggest that high type-1 plasminogen activator inhibitor (PAI-1) levels are risk factor for recurrent myocardial infarction.³⁶

THE AT-2 RECEPTOR: A BIOLOGICAL LINK

As discussed above, Ang II causes vasoconstriction by modifying the oxidative state of vessel wall smooth muscle cells, which leads to an increase in superoxide anion production and progressive EDRF-NO inactivation. These effects, which contribute to the onset and progression of endothelial dysfunction, are mediated by the stimulation of AT-1 receptors on the smooth muscle cells of the tunica media. However, recent observations have shown that Ang II is potentially capable of promoting vasodilation by interacting with AT-2 receptors.³⁷ and so it can affect vasomotor response in either direction. The mechanism that induces vasodilation and reduces blood pressure by stimulating AT-2 receptors has recently been investigated: studies have highlighted the role that bradykinin and EDRF-NO play in this vasodilating response in the aorta,³⁸ coronary arteries,³⁹ and myocardium.⁴⁰ In particular, a study of rats⁴¹ has shown that in the presence of AT-1 receptor blockade, the stimulation of AT-2 receptors causes significant vasodilation of the mesentery resistance arteries that is mediated by the local formation of bradykinin and its interactions with B2 receptors. The bradykinin-dependent vasodilation induced by Ang II is flow dependent as it increases proportionally to blood flow. It is worth noting that perfusion with Ang II in the absence of an AT-1 receptor blockade induces vasoconstriction in the same model. Removal of the endothelium eliminates the vasodilating response completely, which demonstrates that the AT-2 receptors responsible for bradykinin-mediated vasodilation are located in endothelial cells (Figure 3). In contrast, in the absence of AT-1 blockade, endothelium removal exacerbates vasoconstriction. This indicates that the AT-1 receptors responsible for vasocon-

striction are located on the smooth muscle cells of the tunica media (Figure 3), and that stimulation of AT-2 receptors also occurs in the absence of AT-1 blockade and attenuates the AT-1-mediated vasoconstricting response. In this model, bradykinin is the main mediator of AT-2-mediated vasodilation because the administration of a selective B2 receptor blocker reduces vasodilation by more than 70%.

The complete abolition of the vasoconstricting and hypertensive response to Ang II has been observed in transgenic mice with induced aortic AT-2 receptor overexpression.⁴⁰ This effect, together with the predominance of AT-2 over AT-1 stimulation, is due to an increase in smooth muscle cell kininogenase activity, associated with an increase in bradykinin production and release. This stimulates the B2 receptors in endothelial cells and consequently increases the production of vasodilating EDRF-NO. The possible sequence of events linking the vasodilating effect mediated by AT-2 receptors to the kinin system is summarized in Figure 4.

These data show that Ang II has varying activities on the regulation of blood pressure as a result of the predominance of AT-1 over AT-2 receptor stimulation (Figure 5).⁴¹ When AT-2 stimulation prevails, because of its up-regulation or a pharmacological blockade of AT-1 receptors, instead of promoting vasoconstriction, Ang II potentiates the EDRF-NO system and has protective vasodilating effects.

ANGIOTENSIN II ANTAGONISTS AND ENDOTHELIAL FUNCTION

By stimulating AT-1 receptors, Ang II modifies the oxidative state of the vessel wall, causes vasoconstriction, promotes cell proliferation, and has an antidiuretic effect.⁴¹ In the presence of one or more risk factors, all of these actions (which are essential for the maintenance of

physiological cardiovascular homeostasis) may represent the link between hemodynamic or metabolic overload, and the onset of functional and structural vascular alterations that ultimately lead to organ damage and clinical events. Consequently, the prevention of events should not only involve controlling individual risk factors, but should also act on the regulation systems linking hemodynamic and metabolic overload and vascular damage in order to interrupt the descent down the “risk slope” from endothelial dysfunction to organ damage, clinical events, and death. Among the mechanisms that cause the progression of the cardiovascular continuum, the Ang II AT-1-mediated effects of Ang II play an important role and, for this reason, the pharmacological blockade of AT-1 receptors may offer protection against vascular and cardiac damage.^{42,43}

AT-1 receptor blockade increases the production of Ang II,⁴⁴ which stimulates the AT-2 receptors available to interact with the agonist depending on the selectivity of the AT-1 receptor blockade. AT-2 stimulation triggers the bradykinin-mediated mechanism described earlier, which leads to the release of EDRF-NO and its associated vascular and myocardial protective effects.⁴⁵

In conclusion, these findings show that Ang II AT-1 receptor blockade plays an important protective role in the presence of risk factors and myocardial and vascular damage. This protection depends on the blockade of AT-1-mediated vasoconstricting effects and the potentiation of the local protective effect related to bradykinin-EDRF-NO system activation by the stimulation of the AT-2 receptors.

SELECTIVITY OF INHIBITION AND VASCULAR PROTECTION

The particular mode of action of Ang II

antagonists consists of inhibiting the adverse effects of AT-1 receptor stimulation, and indirectly stimulating the AT-2 receptors that promote the peripheral vasodilating system activation related to EDRF-NO production.

This dual action therefore depends on the selectivity of the receptor blockade: the more selective the blockade, the more favorable the modification of the relationship between the effects that are dependent on the two receptor isoforms, with the predominance of AT-2-mediated activity. It must be pointed out that the degree of selectivity of the various Ang II antagonists currently available for clinical use depends on their relative affinity for the two receptor isoforms, with valsartan (Diovan) being the most selective—that is, at least three times more selective than the other drugs in the same class.⁴⁶

This high degree of selectivity allows valsartan to stimulate AT-2 receptors more intensely than losartan (Cozaar). This has been demonstrated in a comparative study of the two drugs in rats, which estimated cyclic guanosine monophosphate (GMPc) concentrations in renal interstitial fluid, a variable that depends on AT-2 stimulation.⁴⁷ *In vivo* studies have demonstrated that AT-2 receptor stimulation increases the concentration of GMPc in renal interstitial fluid by means of a bradykinin-dependent mechanism that leads to EDRF-NO release.⁴⁸ For this reason, the concentration of GMPc was measured using microdialysis techniques after the administration of doses of valsartan and losartan that are equivalent in terms of their antihypertensive potency in order to verify whether their specific AT-2 effects were different. Furthermore, to check that the variations in GMPc concentrations depended on AT-2 receptor stimulation, the effects of the two drugs were also measured in the presence of PD123319 (PD), a selective AT-2 recep-

tor blocker. Siragy et al. showed that valsartan significantly increased the concentration of GMPc in the interstitium, not only in comparison with baseline, but also in comparison with losartan. The increase disappeared completely in the presence of PD, demonstrating that the effect was specifically mediated by AT-2 stimulation.⁴⁹ Using the same experimental model, the authors also demonstrated that valsartan-induced stimulation of AT-2 receptors increases GMPc in interstitial fluid by activating the kinin system.⁴⁹ This mechanism was confirmed by the increased interstitial fluid concentration of bradykinin after the administration of valsartan, which induces a higher EDRF-NO production. Valsartan therefore activates the EDRF-NO system to a greater degree than losartan by means of indirect AT-2 receptor stimulation.

In the presence of risk factors such as hypertension and dyslipidemias, selective AT-1 blockade may have a dual protective effect: (1) it can attenuate the negative vessel wall oxidative modifications induced by Ang II; and (2) it can potentiate peripheral EDRF-NO release. These theoretical effects have been confirmed in a study of normotensive rabbits fed a cholesterol-enriched diet⁵⁰ with the aim of evaluating whether the administration of valsartan protects vessels from the endothelial dysfunction and structural alterations (such as intimal thickening) associated with the development of organ damage. To this end, the rabbits were divided into six groups: a control group fed a normocholesterolemic diet without pharmacological treatment; a group fed a hypercholesterolemic diet without pharmacological treatment; two groups fed a normocholesterolemic diet and treated with two different valsartan doses (3 mg/kg/d and 10 mg/kg/d); and two groups fed a hypercholesterolemic diet and treated with the same two doses of

valsartan for 10 weeks. In comparison with the control group, the groups treated with the cholesterol-enriched diet showed a significant increase in blood cholesterol; neither of the valsartan doses induced any variation in blood cholesterol levels or systolic blood pressure, but they did have a protective effect against functional and structural alterations in the aortic walls. The animals fed a cholesterol-enriched diet developed endothelial dysfunction, demonstrated by the inability to respond to the acetylcholine vasodilating stimulus in the presence of phenylephrine-induced contracture. The treatments with valsartan 3 mg/kg/d and 10 mg/kg/d almost completely preserved the physiological ability to respond to the vasodilating stimulus, as the response was not significantly different from that of the animals fed a normocholesterolemic diet. In terms of structural alterations, the animals fed a cholesterol-enriched diet and not treated with valsartan developed significant intimal thickening, whereas, even in the presence of a hypercholesterolemic diet, valsartan treatment induced a dose-dependent protective effect that was already evident at the dose of 3 mg/kg/d, and was complete at the dose of 10 mg/kg/d.⁵⁰

The results of this interesting study show that the metabolic overload correlated with hypercholesterolemia, just as the hemodynamic overload related to hypertension produces the progressive onset of functional and structural vascular alterations that are closely dependent on Ang II action. Treatment with high doses of selective blockers of AT-1 contributes to maintaining normal endothelial function, and protects against the onset and progression of vessel wall structural alterations. A similar protective effect was found in mouse heart during a hemodynamic overload induced by 6 weeks' aortic banding.⁵¹ The study analyzed AT-2 receptor-null

and wild-type control mice, and found that the aortic banding induced an increase in cardiac mass and intimal hypertrophy in the coronary arteries of the wild-type controls, whereas valsartan 1 mg/kg/d (which does not affect systolic blood pressure) significantly reduced ventricular hypertrophy in a similar way in both the controls and the genetically modified animals. In mice with aortic banding, treatment with valsartan favorably affected intimal thickening of the coronary wall in comparison with untreated animals. However, this protective effect was considerably greater in the control animals than in the AT-2 receptor-null animals. The drug had no effect on the animals that did not undergo aortic banding. In the presence of a pressure overload, the favorable effect of valsartan on the heart and coronary arteries is mediated by a local protective mechanism that depends on the stimulation of AT-2 receptors, thus leading to the activation of the bradykinin-EDRF-NO system.

The fact that valsartan's protective effect on the heart depends on EDRF-NO system stimulation was confirmed by a study in which control and genetically modified mice with an induced lack of endothelial NO synthetase (eNOS) were subjected to a myocardial infarction (MI) induced by ligating the left coronary artery, and experienced subsequent heart failure.⁵² One group of mice was treated with enalapril (Vasotec), an ACE inhibitor, 20 mg/kg/d, and a second group was treated for 5 months with valsartan 50 mg/kg/d. In this model, valsartan had a protective effect on left ventricular function, leading to a smaller decrease in ejection fraction and ventricular wall remodeling, with less interstitial fibrosis. The fact that this protective effect was observed only in the wild-type controls (and not in the mice without eNOS) demonstrates that treatment with valsartan affords significant protec-

tion in post-infarction heart disease—a protection that implies the integrity of the bradykinin-EDRF-NO system, as it comes from a local increase in EDRF-NO production.

The protective effect of valsartan on vascular function has also been observed in human studies.⁵³ Carotid-femoral pulse wave velocity (PWC), which is an index of arterial stiffness (an increase in velocity indicates a reduction in wall compliance), was studied in healthy volunteers. The infusion of Ang II at a dose of 5 ng/kg/min for 30 minutes significantly increased the propagation rate of the pulse pressure wave, whereas the administration of valsartan at a dose of 80 mg/d for 3 days abolished this negative effect. Valsartan is therefore capable of reducing the negative effect of Ang II on the compliance of large conductance vessels starting from the first days of treatment. With reference to the available experimental data, the authors concluded that the protective effect may be linked to the blockade of AT-1-mediated Ang II negative activity, and the protective peripheral effect mediated by bradykinin-EDRF-NO system stimulation.

CONCLUSION

The experimental data show that because it is much more selective than the other drugs belonging to the same class, valsartan has a dual mechanism of action that combines the blockade of negative AT-1-mediated effects with the protective stimulation of AT-2 receptors. This potentiates the bradykinin-EDRF-NO system in the vessel wall, which is essential to ensure correct endothelial function and protection against the structural vessel wall alterations that are the necessary first step toward target organ damage.

This dual-protective mechanism is effective in the presence of the metabolic overload associated with hypercholes-

terolemia and the hemodynamic overload associated with arterial hypertension, and encompasses both functional and structural aspects by maintaining normal endothelial function and antagonizing vessel wall remodeling.

The favorable actions of a selective AT-1 blockade highlighted by experimental studies obviously need clinical confirmation in patients with hypertension and/or post-infarction ischemic heart disease. For this reason, two large-scale clinical trials are being or have been carried out: the VALUE study of hypertensive patients, and the VALIANT⁵⁴ study of patients with myocardial infarction.

The VALUE study is comparing the effects of antihypertensive-equivalent doses of valsartan and amlodipine (Norvasc) on total mortality and cardiac events in more than 14,000 high-risk hypertensive patients, and its results are expected in 2004. Any significant difference in the event rate between the two treatment groups would support the hypothesis that reducing blood pressure is not sufficient to normalize cardiovascular risk, and that hypertensive patients should be treated with drugs such as valsartan that are capable of modulating the RAS, a regulatory system that plays a crucial role in the development of organ damage.

VALIANT⁵⁴ was a multicenter, double-blind, randomized, active drug-controlled, parallel group study comparing the efficacy and safety of long-term treatment with valsartan, captopril, and their combination in high-risk post-MI patients. It tested the hypothesis that treatment with valsartan alone (n = 4,909) or in combination with captopril (n = 4,885) would lead to similar or better survival than treatment with a proven ACE inhibitor (n = 4,909 patients) in MI patients receiving treatment soon after hospital admission and followed up for 2 years. During a medi-

an follow-up of 24.7 months, death occurred in 979 patients in the valsartan group, 941 in the valsartan plus captopril group, and 958 in the captopril group (valsartan versus captopril hazard ratio: 1.00; 97.5% confidence interval: 0.89-1.09; $P = 0.73$). The upper limit of the one-sided 97.5% confidence interval was within the prespecified margin for non-inferiority in terms of mortality ($P = 0.004$) and the composite endpoint of fatal and nonfatal cardiovascular events ($P < 0.001$). Valsartan was thus found to be non-inferior to captopril and better tolerated. Consequently, selective adrenergic receptor blockers can be considered a clinically effective alternative to captopril in the early phase of myocardial infarction, and even the first-line choice in subgroups of patients such as hypertensives and diabetics, in whom endothelial dysfunction has been clearly demonstrated.

The results of ongoing clinical trials will be crucial in order to verify whether the favorable results of previous experimental and clinical studies of valsartan in patients with hypertension and ischemic heart disease can be exploited in clinical practice to treat these diseases, the epidemiological impact of which is increasing.

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