Overview of $\alpha_1$-Adrenoceptor Antagonism and Recent Advances in Hypertensive Therapy

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$\alpha_1$-Receptor antagonists are potent blood pressure lowering drugs, although the use of $\alpha_1$-receptor antagonists by physicians in the treatment of hypertension has been somewhat reserved. The major concern are symptoms of orthostatic dysregulation and synapses. However, reports on a long-acting second generation of $\alpha_1$-adrenoceptor antagonists demonstrate that orthostatic dysregulation is not more frequent in patients treated with these compounds as compared to other antihypertensive drugs. Since blood pressure readings at patients' work sites are of greater prognostic value for the fatal events of cardiovascular disease, the impact of any antihypertensive agent on cardiovascular reactivity during stress becomes most important. Long-acting $\alpha_1$-adrenoceptor antagonists control blood pressure during stressful events, i.e., stimulation of the sympathetic nervous system without altering the physiologic hemodynamic profile. Sustained elevated blood pressure imposes a burden on the cardiovascular system, in particular on arteries, arterial resistance vessels, the cerebrovascular circulation, the kidneys, and the heart. Since the extent of target organ damage is responsible for the impaired prognosis of the hypertensive patient, regression of early hypertensive organ alterations is a most desirable therapeutic goal. In a series of clinical trials we found that $\alpha_1$-receptor antagonists reduced left ventricular hypertrophy (an independent risk factor for cardiovascular mortality and morbidity), lowered total peripheral resistance (related to vascular resistance vessels), improved glomerular filtration rate, and had no effect or improved lipid metabolism, glucose tolerance, and insulin resistance. Hence, $\alpha_1$-adrenoceptor antagonists emerged as attractive agents for antihypertensive therapy.

Evidences has accumulated in recent decades that the sympathetic nervous system is involved in the pathogenesis and maintenance of systemic arterial hypertension. There is increasing evidence that possibly genetic defects are responsible for an exaggerated sympathetic outflow in response to environmental factors like excitatory psychosocial stress and salt intake, with the consequence of an inadequately increased sympathetic tone of peripheral sympathetic nerves. In addition, also the peripheral catecholamine metabolism is considerably altered in hypertension.

Endogenous catecholamines, namely norepinephrine and epinephrine, are involved in the regulation of many organ systems and participate prominently in the regulation of the cardiovascular system. Norepinephrine is a neurotransmitter at sympathetic postganglionic neuroeffector junctions and binds to receptors at certain
sites in the central nervous system highlightening the potential role of the central nervous system in blood pressure regulation. The primarily circulating epinephrine is a hormone produced in chromaffin tissue mainly the adrenal medulla. Norepinephrine can act as a circulating hormone too, since it overflows from sympathetic nerve synapses and is likewise produced by chromaffin tissue. As a matter of fact plasma norepinephrine concentrations exceed those of epinephrine.

The observation that adrenergic agonists followed two patterns in initiating physiological responses led to the principal classification of adrenoceptors in α- and β-subtypes. The subclassification into α1- and α2- and β1- and β2-adrenergic receptors was based on the existence and differential tissue localization of these receptors. Because norepinephrine appeared to be more effective at α1- than at α2-adrenergic receptors and considerably more potent at β1- than at β2-adrenergic receptors, it was concluded that α1- and β1-receptors were located at postsynaptic sympathetic neuroeffector junctions, where they could mediate physiological responses on sympathetic nerve activation, e.g., vasoconstriction. Since α2- and β2-adrenergic receptors exhibited a higher responsiveness to circulating catecholamines, they were thought of as "autoreceptors", which are located on sympathetic nerves that participate in an autofeedback loop regulating the synaptic release of norepinephrine.

Radioligand binding methods that allow receptors in tissue to be identified and quantitated already suggested the existence of subtypes of α1- and α2-adrenergic receptors. Recent methods involving molecular biology and cloning of receptors supported these results and led to the discovery of even more subtypes of adrenergic receptors. At present three subtypes each of α1 (α1A, α1B, and α1D) and α2 (α2A, α2B, and α2C) adrenergic receptors and β-receptors (β1, β2, β3) have been definitely identified and the existence of additional subtypes is being investigated.

The basic principles of intracellular signal transduction due to adrenergic stimulation is by and large well described. Adrenergic receptors link G-proteins to a class of heterotrimeric proteins with α, β, and γ subunits. So far 20 different α, at least five β, and at least six γ subunits have been identified. Although several hundred subunit combinations are theoretically possible, the repertoire of G-proteins used by a particular receptor system is limited. Each type of adrenergic receptors preferentially couples to a different major Gγ-subfamily, e.g., α1-adrenoceptors to Gαq and α2-receptors to Gαi. Each of these Gγ-proteins can link to numerous effector molecules, although most target cells have preferred linkages that in turn lead to changes in intracellular second messenger concentrations. If catecholamines bind to the receptors, the Gγ-unit eventually dissociates from the Gβγ-subunit. Both subunits can regulate the activity of effector molecules and second messengers.

The numbers of activated G-proteins exceeds the number of corresponding receptors and effectors. Hence the activation of G-proteins amplifies signalling by adrenergic receptors.

Alterations in the various adrenergic receptors are very likely to have a role in many clinical settings. Studies using molecular and biochemical techniques will provide new insights into the possible role of the various adrenergic subtypes in health and hypertension, as well as other diseases. How much future antagonists for the various subtypes of adrenergic receptors might affect the management of hypertensive patients is as yet unknown.

CURRENT THERAPEUTIC USE OF ADRENERGIC RECEPTOR BLOCKADE

So far only "classical" α1-adrenoceptor antagonist of the α1A and β1-subgroups are of clinical importance in cardiovascular pharmacology. Nonselective α-receptor antagonists, such as phenoxybenzamine and phenotamine, turned out to be only useful in the management of pheochromocytoma and were not very effective in the management of essential hypertension. α2-Receptor antagonists, such as clonidine, are effective in lowering blood pressure by reducing central sympathetic outflow binding to central α2-receptors and will not be highlighted here due to their specific mode of action.

Although various antagonists of the β-subgroups have been in use for quite a while, only one drug, namely prazosin, was available for a long time as a selective α1-adrenoceptor antagonist. More recently, several other α1-receptors have been used in the management of hypertensive patients: besides prazosin there are terazosin, doxazosin, bunazosin, tiramazosin, indoramin, and urapidil. The increasing awareness that α1-receptor antagonists not only lower blood pressure but also have beneficial effects on lipid and glucose metabolism, has led to the suggestion that α1-receptor antagonists should be recommended for monotherapy of essential hypertension. The beneficial profile of α1-adrenoceptor inhibitors is accompanied by a broad spectrum of applications, because they do not interfere with concomitant diseases, such as obstructive airway disease, peripheral arterial occlusive disease, chronic renal insufficiency, congestive heart failure, and diabetes mellitus. However, to date only the German League for High Blood Pressure Research has listed the new long-acting α1-adrenoceptor antagonists (such as doxazosin or bunazosin) as first-line drugs for antihypertensive therapy, equivalent to diuretics, β-adrenoceptor inhibitors, calcium channel blockers, or angiotensin converting enzyme (ACE) inhibitors.

The α1-receptor antagonists were characterized as nonspecific vasodilators binding competitively to
postsynaptic $\alpha_1$-receptors. Hence neither circulating nor neurally released catecholamines can activate the respective receptors inducing vasoconstriction.\textsuperscript{4,21} Both resistance and capacitance vessels are dilated by $\alpha_1$-adrenoceptor antagonists. Since presynaptic $\alpha_2$-receptors remain open and capable of binding neurotransmitters, they can inhibit the release of additional norepinephrine by a direct negative feedback loop.\textsuperscript{3} Neurally mediated responses to stress and exercise are unaffected and the baroreceptor reflex remains intact.\textsuperscript{21,22} The decrease in preload and the selective blockade of $\alpha_1$-adrenoceptors prevent, to a great extent, the reflex sympathetic activation usually seen with direct vasodilators like hydralazine. Among the undesirable effects, however, is the pooling of blood in the viscera that might explain the first dose hypotension seen with some $\alpha_1$-adrenoceptor antagonists, as described by several authors.\textsuperscript{23,24} Volume retention is common, most likely because the renin-angiotensin-aldosterone system is less suppressed than with other adrenoceptor inhibitors. $\alpha_1$-Adrenoceptor inhibitors are effective in severe arterial hypertension as well as in hypertension associated with chronic renal failure. In the latter situation, the hypotensive action is enhanced and the doses of some drugs (doxazosin, but not bunazosin) have to be adjusted.\textsuperscript{25}

Prospective studies on the final outcome (total and cardiovascular mortality) of hypertensive patients treated with $\alpha_1$-adrenoceptor inhibitors are not yet available.

**ANTIHYPERTENSIVE EFFICACY OF $\alpha_2$-ADRENOCEPTOR ANTAGONISTS**

Since blood pressure readings at patients’ work sites are of greater prognostic value for the fatal events of cardiovascular disease and correlate better with the degree of left ventricular hypertrophy than casual pressure readings, the impact of any antihypertensive agent on cardiovascular reactivity during stress becomes most important.\textsuperscript{26,27} It has been documented that patients with abnormal vascular responses to mental arithmetic, evidenced by an increase in total peripheral resistance with no change or even a decrease in cardiac output, had a high risk of severe cardiovascular disease.\textsuperscript{28} These findings were supported by epidemiological studies revealing that enhanced cardiovascular response to mental arithmetic was a predictor for the development of future hypertension.\textsuperscript{29} As a consequence, for antihypertensive drug regimens an ideal antihypertensive drug should aim to control blood pressure during stress to the same extent as it controls the casual blood pressure at rest. In addition, the hemodynamic profile provoking the rise in blood pressure during stress should not be altered.\textsuperscript{30} In consideration of these issues, the actions of antihypertensive drugs are nowadays examined at rest and under provoked stress conditions in the hemodynamic laboratory. However, the impact of antihypertensive therapy on renal circulation has been less frequently investigated in stressful circumstances.\textsuperscript{31} This is quite astonishing since renal circulation might be prominently involved in the development and maintenance of arterial hypertension.

Two strategies can be used to determine the effects of everyday stress on the cardiovascular system.\textsuperscript{32} Ambulatory blood pressure recordings can be used to reliably determine blood pressure in the natural environment. This method, however, does not allow the assessment of the hemodynamic profile during exposure to mental or physical stress. Furthermore, the level of stress at the time when blood pressure is recorded is not standardized.\textsuperscript{33} Experimental stress testing permits examination of the underlying hemodynamic mechanisms that cause the rise in blood pressure and allows good standardization of stress intensity.\textsuperscript{34} However, only poor correlations between increases in blood pressure during laboratory stress and ambulatory stress readings have been reported.\textsuperscript{35}

Extensive literature is now available on the effects of antihypertensive agents on stress blood pressure.\textsuperscript{36} In clinical trials it turned out that, for example, ACE inhibitors reduce blood pressure during a variety of stressful events without altering the hemodynamic profile and that they may even attenuate vasoconstriction during stress. This response pattern to ACE inhibitors may reduce the impact of recurring stress-induced increases of blood pressure and of exaggerated vasoconstrictive stimuli on the cardiovascular system.\textsuperscript{36} In parallel, blood pressure during daily life stress was also found to be controlled, according to ambulatory blood pressure measurements, by ACE inhibitors. A disparate pattern emerges when one analyzes data for $\beta$-adrenoceptor antagonists and calcium channel blockers. Although $\beta$-adrenoceptor antagonists and calcium channel blockers produced equal control of arterial pressure, $\beta$-adrenoceptor antagonists evoke an abnormal hemodynamic response to mental challenge, whereas calcium channel blockers preserve the physiologic reactivity pattern of the untreated state.\textsuperscript{37} When the ACE inhibitor fosinopril and the calcium channel blocker isradipine were compared, the ACE inhibitor preserved a more physiological hemodynamic response pattern to isometric and orthostatic stress than the calcium channel blocker.\textsuperscript{38} Enhanced sympathetic nervous activation during treatment with the calcium channel blocker isradipine was detected during isometric stress, an unfavorable finding not observed with the ACE inhibitor fosinopril.

With respect to $\alpha_1$-adrenoceptor antagonists, we extensively examined the long-acting $\alpha_1$-adrenoceptor inhibitor bunazosin. In a double-blind randomized trial, bunazosin and nitrendipine lowered systolic and diastolic blood pressure to a similar degree.\textsuperscript{39} Buna-
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\section*{Figure 1. Disparate impact of the \(\alpha\)-adrenoceptor blocker bunazosin and the \(\beta\)-adrenoceptor blocker metoprolol on total peripheral resistance (TPR): left side—absolute values of TPR at rest; right side—change of TPR during mental stress.}

Bunazosin given once a day had a satisfactory antihypertensive effect that was similar to the one with nitrendipine. The response rate and the rate of diastolic normalization were also similar for bunazosin and nitrendipine. The magnitude of diastolic blood pressure reduction in the groups investigated was assessed 24 h after the last drug dose to demonstrate the efficacy of the regimens for a whole day. The decrease of the diastolic blood pressure was about \(-6\) mm Hg, a small reduction that has proven to be relevant in lowering the morbidity rate due to arterial hypertension. It has been pointed out in a metaanalysis study that the reduction of diastolic blood pressure by \(6\) mm Hg over 5 years leads to a reduction of stroke by \(42\%\) and of coronary heart disease by \(14\%).

Ambulatory blood pressure readings revealed that bunazosin effectively controlled awake and sleep blood pressures during long-term therapy in double blind randomized clinical study.\(^{1,4,14}\) Consistently in various lab tests, blood pressure during mental and isometric stress was lowered by bunazosin to the same extent as observed in casual blood pressure readings in control groups treated with the \(\beta\)-adrenoceptor antagonist metoprolol. Moreover, the physiologic hemodynamic response pattern in the systemic circulation provoked by mental stress was sustained during treatment with bunazosin. However, the \(\beta\)-adrenoceptor antagonist metoprolol induced vasoconstriction instead of vasodilation of the peripheral vasculature (Figure 1).\(^{42}\) Similar findings were observed during isometric stress. Thus, long-acting \(\alpha\)-adrenoceptor antagonists, such as bunazosin, control blood pressure during stressful events, ie, stimulation of the sympathetic nervous system, without altering the physiologic hemodynamic profile.

\subsection*{\(\alpha\)-Adrenoceptor Antagonist and Orthostatic Tolerance}

The blood pressure lowering effects of \(\alpha\)-receptor antagonists have been well documented for a long time,\(^{16,4,14}\) but their use by physicians has been somewhat restrained. The major concern has been symptoms of orthostatic dysregulation and syncopes, which have been described after administration of the first dose of prazosin, a short acting compound.\(^{23}\) This led to the development of specific dose regimens in which a small initial dose is titrated to the desired antihypertensive effect in order to minimize the occurrence of hypotensive orthostatic events. \(\alpha\)-Adrenoceptor antagonists have favorable effects on cardiovascular risk factors other than hypertension, such as lipid metabolism\(^{44}\) and insulin resistance,\(^{45}\) and have been documented to reverse early target organ damage.\(^{19}\) The potentially positive properties of \(\alpha\)-adrenoceptor antagonists have stimulated research to answer the question as to what extent orthostastic dysregulation, as observed after administration of prazosin, is a major problem of the whole class of \(\alpha\)-adrenoceptor antagonists, in particular long-term \(\alpha\)-adrenoceptor antagonists. A recent publication by our group has examined the problem of orthostatic dysregulation with respect to the \(\alpha\)-adrenoceptor antagonist bunazosin.\(^{39}\)

Our study\(^{39}\) showed that, if tested for immediately after administration of the first dose, orthostatic dysregulation was a common problem with respect to both the \(\alpha\)-receptor antagonist and the calcium channel blocker. A difference between bunazosin and nitrendipine existed only with respect to the incidence of orthostatic dysregulation, which was slightly higher in patients taking the \(\alpha\)-receptor antagonist. However, no difference was found between bunazosin and nitrendipine concerning the occurrence of orthostatic dysregu-
loration under experimental conditions. After 3 weeks of treatment, the increased susceptibility to orthostatic stress could no longer be detected. This observation was confirmed during tests performed 9 weeks after the initiation of drug therapy with either bunazosin or nitrendipine. The results clearly show that symptoms of orthostatic dysregulation are linked to the first dose of each drug, but are neither a persistent nor a typical feature of the long-acting α₁-adrenoceptor bunazosin alone.

In double-blind randomized studies, symptoms of orthostatic hypotension have been documented more frequently for prazosin and doxazosin than for bunazosin. Hence, the orthostatic potential appeared to be different with respect to various α₁-receptor antagonists. Orthostatic stress is frequently tested in experimental set-ups with the Schellong test. The Schellong test is an intense orthostatic provocation that is not likely to occur under normal conditions in daily life. Indeed, we found a low incidence of orthostatic dysregulation during everyday life. No differences between bunazosin and nitrendipine could be observed in our double blind study. Hence, although a slightly higher incidence of orthostatic dysregulation might be observed in patients taking an α₁-adrenoceptor antagonist such as bunazosin when subjected to provocative maneuvers like the Schellong test, orthostatic dysregulation due to long-acting adrenoceptor antagonists should be much less of a problem in everyday life.

A major problem in the treatment of hypertension is lack of compliance due to the side effects of the drugs used. In addition to the favorable properties of the new generation of α₁-adrenoceptor antagonists, Langenfeld et al. reported that the total rate of adverse effects, as well as the rate of serious events, was significantly lower in patients taking the α₁-adrenoceptor antagonist bunazosin than in those taking the calcium channel blocker nitrendipine. The markedly better tolerability of bunazosin resulted in a lower rate of discontinuation due to drug related side effects. The rate for bunazosin one-tenth of the rate documented for nitrendipine. Frequent side effects in this trial, such as headache and tachycardia, occurred more often with nitrendipine than bunazosin. This was also true for the common side effects of dihydropyridines, such as flushing and leg edema. Dizziness, which is said to be associated with α₁-adrenoceptor inhibitors in some patients, was not seen at a higher rate with bunazosin than with nitrendipine.

In conclusion, the reports on long-acting second generation α₁-adrenoceptor antagonists, such as bunazosin, demonstrate that orthostatic dysregulation is not necessarily more frequent in patients treated with these compounds as compared to other antihypertensive drugs. These drugs are efficient in lowering blood pressure and well tolerated with respect to serious side effects that might influence patient compliance in an adverse manner. If we take into account the favorable effects of α₁-receptor antagonists on other cardiovascular risk factors, this drug class should be considered as an important pharmacological tool in treating patients with arterial hypertension.

Beneficial Metabolic Effects of α₁-Adrenoceptor Antagonists In recent intervention trials, treatment of actual hypertension has proved to be successful in prevention of myocardial infarction and cerebrovascular events. The effect of antihypertensive therapy in these trials on cerebrovascular events seemed to be optimal since the reduction was as high as had been calculated from the evaluation of data from large epidemiological trials. However, with respect to myocardial infarction, the effect of antihypertensive treatment was only half as effective as predicted by the epidemiological studies. This effect was related to the negative effect of the antihypertensive drugs used, especially diuretics and β-blockers, on lipid and glucose metabolism. Hence, it was discussed whether antihypertensive drugs with a metabolically neutral profile might improve the success of antihypertensive treatment with respect to coronary artery disease. Since α₁-receptor antagonists have been found to improve lipid metabolism, these drugs emerged as attractive alternatives for differential therapy in hypertensive patients. As a consequence, especially long-acting α₁-adrenoceptor antagonists of the second generation, such as bunazosin, are now recommended by the German League for High Blood Pressure Research as drugs of first choice for the monotherapy of arterial hypertension. For obese patients with an increased sympathetic tone and probably associated metabolic disorders, α₁-adrenoceptor inhibitors could be particularly effective since they block increased sympathetic tone and improve lipid metabolism.

The favorable effect of α₁-adrenoceptor inhibitors on blood lipid levels has been well established. A decrease in total and LDL cholesterol and triglycerides and a rise in HDL cholesterol were usually observed. In a double blind randomized study, Schmieder et al. observed a decrease of serum LDL cholesterol, an increase of HDL cholesterol, and a decline of serum triglycerides after 6 months of antihypertensive therapy with the α₁-adrenoceptor inhibitor bunazosin, a quite opposite effect to that observed in the control group treated with β-adrenoceptor inhibitors (Figure 2). These pharmacological properties also could not be observed with calcium channel blockers. In a study by Lithell, the α₁-adrenoceptor inhibitor prazosin and the β-adrenoceptor inhibitor metoprolol were compared during a 6 month period: at the end of the trial the group on prazosin exhibited, on average, 15% lower serum cholesterol levels than the group on me-
ropolol. Furthermore, only the α₁-adrenoceptor antagonist doxazosin, but not the β-blocker atenolol, had a positive impact on the fibrinolytic system. In another study, both the ACE inhibitor captopril and the α₁-adrenoceptor inhibitor doxazosin lowered serum cholesterol, but only doxazosin treatment was associated with an increase in HDL cholesterol. The beneficial effects of the α₁-adrenoceptor inhibitor (eg, doxazosin) as compared to β-adrenoceptor inhibitors (eg, atenolol) on lipid metabolism might be of considerable importance for the overall cardiovascular risk.

The physiological and pharmacological mechanisms that are responsible for these beneficial influences on lipid metabolism are not yet fully understood, but may include a decrease in the fractional catabolic rate of HDL cholesterol, an increase in lipoprotein lipase and lecithin-cholesterol acyltransferase activity, and an inhibition of LDL oxidation.

In the last few years attention was paid to the patho- genetic role of insulin resistance and the consequent hyperinsulinism as a pivotal link in the development of primary hypertension. Clinical studies have found that insulin resistance is more pronounced in hypertensive patients than in normotensive individuals and that insulin resistance is correlated to the degree of hypertension, probably a case of secondary induced hyperinsulinemia. Hyperinsulinemia may be partly responsible for increased sympathetic tone, enhanced renal sodium reabsorption, stimulated intracellular free calcium, and enhanced vascular reactivity to vasoconstrictors that is generally observed in patients—especially obese patients suffering from primary hypertension. However, there is also evidence that the pathophysiological alterations are secondary to other genetic and acquired disorders and impaired regulatory mechanisms such as primary increased sympathetic tone or increased free cytosolic calcium in the vascular smooth muscle cell. Regardless of its nature and the reasons for its development, hyperinsulinemia has been found to worsen the course of hypertensive disease.

Antihypertensive therapy should aim to minimize the risk attributed to hyperinsulinemia and antihypertensive drugs should be carefully selected to avoid a further increase in serum insulin concentrations. α₁-Receptor antagonists proved to be very efficient in this respect. This hypothesis could be recently further substantiated by the clinical trial study by Bönner in obese nondiabetic patients (unpublished). Protocols using intravenous glucose tolerance tests and a glucose clamp test could unequivocally demonstrate that treatment with the α₁-adrenoceptor antagonist bunazosin led to an improvement in glucose metabolism. Throughout the study period no body weight gain occurred in any of the obese hypertensive patients. Until now only ACE inhibitors have been found to improve glucose metabolism. Calcium channel blockers seemed to have no effect on glucose metabolism, neither in a positive nor in a negative way, whereas β-adrenoceptor antagonists increased insulin resistance in obese patients.

In conclusion, α₁-adrenoceptor antagonists exert, in addition to their blood pressure lowering effects, a beneficial influence on glucose and lipid metabolism.

Impact of α₁-Adrenoceptor Antagonists on Hypertensive Target Organ Damage. Sustained elevated blood pressure imposes a burden on the cardiovascular system, in particular on arteries, arterial resistance vessels, the cerebrovascular circulation, the kidneys, and the heart. These organ systems are considered hyperten-

**FIGURE 2.** Change in serum lipids after 6 months of therapy with the α₁-adrenoceptor blocker bunazosin and the β-adrenoceptor blocker metoprolol (†P < .05, ‡P < .01).
sive target organs. The extent of target organ damage is responsible for the impaired prognosis of the patient with hypertensive disease.

Left ventricular hypertrophy represents a considerable independent risk factor for cardiovascular mortality and morbidity as well as for death from all causes. It is now clear that left ventricular hypertrophy is not just a compensatory process for offsetting the increased wall stress of the left ventricle, but is an important and blood pressure independent risk factor for congestive heart failure, coronary artery disease, and sudden cardiac death. There is evidence suggesting that reversing left ventricular hypertrophy by antihypertensive therapy is associated with a reduction in cardiovascular complications. Hence, it is of clinical importance that different classes of antihypertensive drugs exhibit variable influences on the prevention or even reversal of left ventricular hypertrophy. Centrally acting sympatholytic agents, like the \( \alpha_1 \)-adrenoceptor antagonist clonidine, and ACE inhibitors have been found to lower the degree of left ventricular hypertrophy in excess of the regression expected according to their blood pressure lowering properties. This suggests that hypertension-associated left ventricular hypertrophy is not solely due to the increase in cardiac work load. It is likely that there are other neuroendocrine factors that influence the development of left ventricular hypertrophy in essential hypertension.

Several in vitro and in vivo studies showed that the sympathetic nervous system, which is activated in hypertensive patients, stimulates myocardial hypertrophy independent of hemodynamic changes. However, these experimental data from animal studies show conflicting results as to what extent the hypertrophic stimulus of the sympathetic nervous system might be transmitted via the \( \alpha \) - or \( \beta \)-adrenoceptors of the myocardium.

Another parameter for target organ damage is the total peripheral resistance, which increases continu-
uously with progressive hypertensive disease. It is therefore often considered to be the hallmark for the severity of changes at the resistance vessel site. In hypertensive disease, renal arteriosclerosis and reduced renal blood flow are determined by the severity of hypertension. Similarly, the reduction of glomerular filtration rate indicates renal and glomerular alterations. Thus, the determination of renal hemodynamics may serve as a marker of hypertensive nephropathy as well as proteinuria.

Nowadays antihypertensive therapy has to aim beyond the lowering of the blood pressure to the reduction or even reversal of hypertensive target organ damage. Various studies have shown that antihypertensive therapy is able to reduce the degree of left ventricular hypertrophy depending on the drug class used and the treatment duration. Reduction of left ventricular hypertrophy has been shown to improve the overall prognosis of primary hypertension.

In a recent study by Schmieder et al, the efficacy of treatment with the α1-receptor antagonist bunazosin and the β1-receptor antagonist metoprolol were assessed with respect to blood pressure reduction over 24 h, the influence on early hypertensive target organ damage, and on the cardiovascular risk profile in a double-blind randomized clinical study using white patients with mild essential hypertension.

This study showed that, during treatment with the α1-receptor antagonist bunazosin, total peripheral resistance (parameter of target organ damage, eg, resistance vessels) was lowered, whereas the administration of the β1-receptor antagonist metoprolol was associated with an increase in total peripheral resistance. The α1-receptor inhibitor causes vasodilation, thereby reducing peripheral resistance and blood pressure. In contrast, the β1-receptor antagonist metoprolol blocks myocardial β-receptors, thereby reducing cardiac output and systemic blood pressure. The blockade of β-receptors by metoprolol might even cause an increase in peripheral resistance by tilting the balance of α- versus β-receptor activity in favor of the α-receptor mediated peripheral vasoconstriction (Figure 1). Reduction of total peripheral resistance, which is the hemodynamic feature of α1-receptor antagonists like bunazosin, might represent a more physiological way of lowering systemic blood pressure than the method of β-receptor antagonists.

Divergent results between bunazosin and metoprolol were also reported with respect to renal hemodynamics in this paper (Figure 3). In spite of similar control of blood pressure, only in the group treated with the α-receptor inhibitor bunazosin were renal plasma and blood flow preserved over the whole

**FIGURE 4.** Cardiac structural changes of the left ventricle after 6 months of treatment with the α1-receptor blocker bunazosin and the β1-receptor blocker metoprolol.
ventricular hypertrophy according to a recent meta-analysis. 

Interestingly, the glomerular filtration rate tended to increase under α-blocking therapy and accordingly serum creatinine concentration dropped significantly in this patient group. These findings are supported by other studies that bunazosin augments the glomerular filtration rate and renal plasma flow in patients with essential hypertension, both those with normal and impaired renal function.

These effects of an α-adrenergic receptor antagonist on renal hemodynamics suggest the as yet unproven hypothesis that treatment with α-adrenoceptors inhibitors may slow down the progression of hypertensive renal vascular impairment independent of the decrease in blood pressure.

In the study by Schmieder et al, α- and β-adrenergic receptor antagonists lowered 24 h blood pressure to a similar extent in the investigated population with mild to moderate hypertension. If one takes into consideration that that 24-h blood pressure correlates more closely with target organ damage than casual blood pressure, it is not amazing that left ventricular hypertrophy was found to be reduced by both α- and β-adrenoceptor blockade (Figure 4). Thus, our report does not support the hypothesis, derived from cell culture experiments, that α-adrenoceptors might be more important than β-adrenoceptors for the cardio-trophic effects on the sympathetic nervous system.

Hence α-adrenoceptors could be part of alternative antihypertensive regimens if, for example, ACE inhibitors (which are most effective in the treatment of left ventricular hypertrophy according to a recent meta-analysis) cannot be used.

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