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Alpha- and beta-blocking agents: pharmacology and properties

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■ Adrenergic receptors have been separated into alpha and beta groups, which have then been further subdivided. Agents have been developed that block each type of receptor with varying degrees of specificity between the sub-types, leading to differences in pharmacodynamic profile. A more recent innovation has been the development of multiple action beta-blocking drugs, ie, those not only blocking the beta receptors but also possessing a peripheral vasodilator effect that may be due to alpha blockade, beta-2 stimulation, or a vasodilator action independent of either alpha or beta receptors.

□ INDEX TERMS: ALPHA BLOCKERS; BETA BLOCKERS; HYPERTENSION □ CLEVE CLIN J MED 1991; 58:337-350

THE CONCEPT that binding of catecholamines to receptors leads to differing responses was first described by Langley, who in 1905 noted that a cell may make motor or inhibitory substances or both, and that "the effect of a nerve impulse depends upon the proportion of the two kinds of receptive substance which is affected by the impulse."¹ In 1906, Dale reported that ergot blocked the excitatory but not the inhibitory actions of adrenaline.² In 1933, Cannon and

Rosenblueth suggested that a transmitter released at sympathetic nerve endings produced either inhibitory or excitatory responses as a result of combination with sympathin I or sympathin E at the receptor.³

The current classification of alpha and beta responses is based on the classic work of Ahlquist,⁴ who studied six sympathomimetic amines and found two patterns of reactivity. One group of actions, mediated by what were termed "alpha receptors," were principally excitatory. The excitatory actions included vasoconstriction, as well as contraction of the uterus, ureter, and nictitating membrane. But alpha actions also included inhibitory actions, such as dilator pupillae and intestinal relaxation. The most potent agent at these receptors was adrenaline, followed by noradrenaline.

In the second group, mediated by what were termed "beta receptors," inhibitory actions predominated. These inhibitory actions included vasodilation; and relaxation of the uterus and bronchial smooth muscle. There was also an important beta-excitatory action,

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TABLE 1
EFFECTS OF RECEPTOR STIMULATION AND BLOCKADE

Organ/Tissue	Receptor	Stimulation causes	Blockade causes
Blood vessels (resistance vessels)	α_1 α_2 β_2	Constriction Constriction Dilatation	Dilatation Dilatation Constriction
Heart	α_1 $\beta_1 > \beta_2$	Contractile force \uparrow Heart rate \uparrow AV conduction \uparrow Contractile force \uparrow	? Bradycardia AV conduction \downarrow Contractile force \downarrow
Spleen	α_1	Contraction	Relaxation
M sphincter pupillae	α_2	Dilatation	Contraction
Thrombocytes	α_2	Aggregation	—
Adenylcyclase	$\beta_1 + \beta_2$	Hyperglycemia Free fatty acid \uparrow	Hypoglycemia Free fatty acid \downarrow
Intestine	$\beta_1 + \beta_2$	Relaxation	—
Bronchi	$\beta_2 > \beta_1$	Relaxation	Constriction
Uterus	β_2	Relaxation	Constriction
Skeletal muscle	β_2	Tremor	Anti-tremor

From van Zweiten.¹¹ AV, atrioventricular; \uparrow , increase; \downarrow , decrease

TABLE 2
ALPHA AGONIST AND ANTAGONIST SELECTIVITY

Agents	Receptor stimulated or blocked	Application
Agonists		
Noradrenaline (neurotransmitter)	$\alpha_1 + \alpha_2 + \beta_1 + \beta_2$	Vasoconstrictor ($\alpha_1 + \alpha_2$)
Adrenaline (neurotransmitter)	$\alpha_1 + \alpha_2 + \beta_1 + \beta_2$	Vasoconstrictor ($\alpha_1 + \alpha_2$)
Phenylephrine	$\alpha_1 > \alpha_2$	Vasoconstrictor (α_1), decongestant (α_2)
Clonidine	$\alpha_2 > \alpha_1$	Antihypertensive (central α_2)
Guanfacine	$\alpha_2 > \alpha_1$	" "
Azepexole (B-HT 933)	α_2	" "
B-HT 920	α_2	Antiglaucomatous (experimental)
UK-14, 304	α_2	Experimental pharmacology
Antagonists		
Phentolamine	$\alpha_1 + \alpha_2$	Pheochromocytoma preoperative phase ($\alpha_1 + \alpha_2$)
Tolazoline	$\alpha_2 > \alpha_1$	Vasodilator ($\alpha_1 + \alpha_2$)
Prazosin	α_1	Antihypertensive (peripheral α_1)
Doxazosin	α_1	" "
Terazosin	α_1	" "
Trimazosin	α_1	" "
Labetalol	$\alpha_1 + \beta_1 + \beta_2$	Antihypertensive (peripheral $\alpha_1 + \beta_1$ & β_2)
Corynanthine	α_1	Experimental pharmacology
Rauwolscine	α_2	" "
Yohimbine	α_2	" "
Idazoxan	α_2	" "

From van Zweiten.¹¹

cardiac stimulation (Table 1). Isoprenaline was the most potent stimulant at the beta receptor; adrenaline was also effective.

Subsequently, the alpha and beta receptors were further delineated. The alpha receptors were subdivided into alpha-1 and alpha-2 receptors. Both alpha-1 and alpha-2 receptors are found on the postsynaptic membrane, where vasoconstriction is mediated. The nerve endings that function as a negative feedback mecha-

nism, inhibiting noradrenaline release, contain presynaptic receptors of the alpha-2 subtype.⁵ More recently, investigations using animals have identified further subtypes of alpha receptors, as well as alpha-1a, alpha-1b, alpha-2a, and alpha-2b receptors.⁶

The distribution of receptors is not the same in all species or all organs. For example, in some vascular beds, such as the cerebral arteries of the dog, alpha-2 receptors are more numerous than alpha-1 receptors.⁷ By comparison, the human forearm has both alpha-1 and alpha-2 receptors.⁸

Receptors also vary in their tissue and synaptic locations. The receptors in vascular smooth muscle that mediate the nerve impulses are postsynaptic receptors of the alpha-1 subtype, whereas the receptors that mediate contraction in response to hormonal stimulation are extrasynaptic alpha-2 receptors.⁵ In vascular smooth muscle, the alpha-1 receptors are located in the adventitial layer; the alpha-2 receptors are found closer to the interior, where they respond to circulating catecholamines.⁹

In the central nervous system, different functions

have been identified for alpha-1 and alpha-2 receptors. The adrenergic postsynaptic receptors in the central nervous system are predominantly alpha-2. Stimulation of these receptors produces a fall in blood pressure and bradycardia. Central alpha-1 receptors, demonstrated by receptor-binding techniques,⁸ may mediate baroreceptor reflex function. Alpha-1 blockade of these central receptors may be the reason that the alpha-1 blocker prazosin does not produce reflex tachycardia.¹⁰

Agents that are active at adrenergic receptors may be classified by their alpha activity. Methoxamine and phenylephrine are alpha-1 stimulants; clonidine and its analogues are alpha-2 stimulants; noradrenaline and adrenaline stimulate both alpha-1 and alpha-2 receptors. Prazosin, doxazosin, terazosin, and urapidil are alpha-1-blocking agents; yohimbine and rauwolscine are alpha-2-blocking drugs; phentolamine blocks both alpha-1 and alpha-2 receptors (Table 2).^{5,6,11}

The beta receptors have also been divided into beta-1 and beta-2 receptors. More recently, beta-3 receptors have been described in animal studies.⁶

As with alpha receptors, beta receptors also differ in their distribution and function. Beta-1 receptors predominate in the human heart. However, beta-2 receptors are also present, constituting 35% of the beta receptors in the right atrium. For example, beta receptors mediate increase in heart rate and force of contraction and increase in conductivity. Among the many responses mediated by beta-2 receptors are relaxation of vascular and bronchial smooth muscle.

Adrenergic agonists and antagonists can be distinguished by their beta reactivity (Table 3). The agonist dobutamine is relatively beta-1-selective, although it also stimulates the beta-2 and alpha-1 receptors. Xamoterol is a specific but partial agonist for the beta-1 receptor. Noradrenaline is much more effective on the beta-1 receptor, whereas adrenaline stimulates both types of beta receptor. The antagonist propranolol is the most widely evaluated nonselective (beta-1, beta-2) blocking drug and atenolol, the most studied of the beta-1 inhibitory drugs. No beta-2-blocking drug is clinically available.

ALPHA-1 RECEPTOR-BLOCKING DRUGS

Classification

The alpha-receptor inhibitory drugs can be classified into the noncompetitive (eg, phenoxybenzamine) and the competitive blocking drugs. The competitive agents may be further divided into nonselective (alpha-1, alpha-2) and alpha-1-selective drugs, such as prazosin, which are currently used in hypertension.

In noncompetitive alpha-1 blockade, the drug is irreversibly bound to the receptor.¹² Therefore, in physiological conditions where increased alpha-1-mediated vasoconstriction is required, as in standing, the noncompetitive alpha-receptor-blocking drugs, alone or in combination, result in a fall in blood pressure. This fall occurs because the increased vasocon-

TABLE 3
BETA AGONIST AND ANTAGONIST SELECTIVITY

Agent	Receptors stimulated or blocked
Agonists	
Noradrenaline (norepinephrine, neurotransmitter)	$\beta_1 + \alpha_1 + \alpha_2$
Adrenaline (epinephrine, neurotransmitter)	$\beta_1 + \beta_2 + \alpha_1 + \alpha_2$
Dobutamine	$\beta_1 > \beta_2 + \alpha_1$
Isoprenaline (isoproterenol)	$\beta_1 + \beta_2$
Orciprenaline (metoprolol)	"
Fenoterol	$\beta_2 > \beta_1$
Pirbuterol	"
Rimiterol	"
Ritodrine	"
Salbutamol	"
Terbutaline	"
Antagonists	
Propranolol	} and other nonselective beta blockers
Alprenolol	
Pindolol	
Oxprenolol	
Timolol	
Sotalol	
Practolol	$\beta_1 > \beta_2$
Atenolol	"
Metoprolol	"
Acebutolol	$\beta_1 > \beta_2$

From van Zweiten.¹¹

strictor impulses needed in the erect posture to maintain blood pressure are blocked by the irreversible binding of the inhibitor to the receptor.

On the other hand, if the block is competitive and the dosage is appropriate, the increased sympathetic activity associated with standing is likely to result in sufficient reversal of the alpha-receptor inhibition so that a postural fall of blood pressure does not occur. At high drug dosage, however, even the competitive block may be sufficient to prevent adequate compensatory vasoconstriction and, therefore, a fall in blood pressure occurs on standing.¹³

Several alpha-1-blocking drugs have been evaluated for use in hypertension: prazosin,^{14,15} terazosin,¹⁶ doxazosin,¹⁷ and indoramin.¹⁸ Another alpha-1-blocking drug, urapidil, may lower blood pressure by an additional effect, stimulation of central serotonin (5-HT_{1a}) receptors.¹⁹

Mode of action

Alpha-1 blockade lowers the blood pressure because the vasoconstrictive action of noradrenaline, released by the nerve impulse, is blocked at the postsynaptic alpha-1 receptor.¹⁴⁻¹⁷ The alpha-1 receptors also mediate the influence of centrally generated sympathetic tone responsible for the control of blood pressure.

The alpha-blocking drugs used in hypertension are

alpha-1-selective;²⁰ they do not block the alpha-2 receptor. Because the prejunctional alpha-2 receptor is not blocked, the alpha-2 receptor-mediated inhibition of noradrenaline release (a negative feedback mechanism) can occur. Tachycardia and renin release are not produced, as noradrenaline is not increased.

By contrast, if a nonspecific drug (with alpha-1- and alpha-2-blocking effects) is used, alpha-2 blockade results, with an increase in noradrenaline output that antagonizes the postjunctional alpha-1-blockade. Noradrenaline produces increased beta-receptor stimulation, resulting in tachycardia, and an increase in renin release occurs.^{14,16,17}

Some studies suggest that acute and chronic effects of alpha-1 blockade may differ. An increase in heart rate has been demonstrated after the acute administration of an alpha-1-blocking drug.¹⁴ In acute single-dose studies with alpha-1 blockade, some increase in renin and noradrenaline have also been noted. This finding is in contrast to the absence of these effects with prolonged administration of such drugs as terazosin.¹⁶ Chronic administration of doxazosin also has little effect on renin levels.¹⁷

Hemodynamic effects

The alpha-1-receptor inhibitory drugs lower blood pressure by reducing peripheral resistance.²¹ These drugs have both arterial and venous effects. The arteriolar dilatation produced by alpha-1 receptor inhibitory drugs increases tissue perfusion and tends to increase cardiac output. On the other hand, the reduction in venous tone causes venous dilatation, which results in venous pooling and decreased venous return and tends to reduce cardiac output. Overall, cardiac output is usually unchanged acutely with alpha blockade, but cardiac output is raised in the long term with such treatment,²¹ whether with prazosin,²² terazosin,¹⁶ or doxazosin.¹⁷ These alpha-1-blocking drugs do not generally lead to tachycardia, as there is no presynaptic alpha-2 blockade.^{14,17}

Regional blood flow

Alpha blockade can affect regional blood flow. Alpha-1 blockade would be expected to increase peripheral blood flow. Although evidence is lacking with prazosin,¹⁴ data for indoramin demonstrate increased blood flow in the skin of the legs and in the calf itself.¹⁸

Renal hemodynamics may also be altered by alpha blockade. Some reports have held that oral prazosin has no effect on renal hemodynamics or glomerular filtration,¹⁴ but others found a small increase in renal

blood flow.²³ All alpha-blocking drugs might be expected to behave similarly. Experiments with intra-arterial doxazosin, given at the time of renal angiography, revealed an increase in renal blood flow.²⁴ Although oral indoramin reduced blood pressure, the accompanying decrease in renal vascular resistance was more than enough to compensate for the fall in blood pressure, producing an increase in effective renal plasma flow and glomerular filtration.^{18,23}

Cardiovascular reflexes

Alpha-1-mediated vasoconstriction is needed for the reflex increase in tone necessary to maintain blood pressure in the erect position. Because alpha-1-receptor-blocking drugs act by inhibiting this alpha-1-mediated vasoconstrictor tone, it is possible that, even with competitive agents (in larger doses), alpha-1 blockade cannot be overcome and the increase in sympathetic tone may be inhibited enough so that a postural fall in blood pressure results. This may be seen in particular with the first-dose phenomenon, in which time the circulation is especially sensitive to alpha-1 blockade.

While a postural drop of blood pressure is not often a clinical problem, the standing pressure tends to be lower than the supine pressure with use of alpha-1 inhibitors, as has been reported with prazosin^{25,26} and doxazosin.¹⁷ Symptoms of postural hypotension, such as dizziness, can result in discontinuation of treatment with prazosin,¹⁴ terazosin,¹⁶ or doxazosin.¹⁷

First-dose phenomenon

If commencement of alpha-1-receptor inhibition is too rapid, a first-dose phenomenon may occur. Because the circulation is especially sensitive to alpha-1 blockade at initiation of therapy, the necessary reflex increase in sympathetic tone may be sufficiently blocked to produce a postural decrease in blood pressure. This phenomenon was a considerable problem in the early stages of prazosin use when, after the first dose, symptoms of severe postural hypotension occurred.²⁷⁻²⁹ In several instances, loss of consciousness occurred, suggesting a specific effect on cerebral blood flow. In a later study, however, prazosin did not appear to alter cerebral blood flow.³⁰

The first-dose phenomenon is dose-dependent.^{28,29} A low starting dose of 0.5 mg, particularly if given at bedtime, is likely to cause minimal (if any) dizziness. When prazosin is administered chronically, an increase in systemic blood volume probably occurs,³¹ and excessive sensitivity to the alpha blockade declines.

Other factors in addition to the commencing dose influence the first-dose phenomenon. A low-sodium diet provokes the effect, whereas a high-sodium diet abolishes the phenomenon.²⁹ Also, the prior administration of a beta-adrenoceptor-blocking drug may increase the fall in blood pressure associated with the initial dose of prazosin.³²

Effect on lipids

Alpha-1-blocking drugs favorably affect the lipid profile, an important cardiovascular disease risk factor.¹⁷ In general, these drugs decrease total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and triglycerides, and raise the ratio of high-density lipoprotein (HDL) to total cholesterol.

Prazosin produces a fall in total serum cholesterol³³ and in LDL and VLDL, as well as an increase in cholesterol ratio (Figure 1).³³⁻³⁷ It probably reduces triglycerides, but some studies have reported no effect.^{33,34,36,38} In a 1-year study of prazosin in postmenopausal women, Lithell and associates³⁹ found no change in the lipids. But, prazosin, like propranolol, was shown to decrease lipid deposition in the aorta of cholesterol-fed rabbits.⁴⁰

Another alpha-1-blocking drug, terazosin, significantly decreases cholesterol and the LDL and VLDL lipoprotein fractions and increases the HDL/cholesterol ratio.^{37,41} Likewise, doxazosin increases HDL and the HDL/cholesterol ratio and decreases total cholesterol and triglyceride levels.¹⁷

BETA-ADRENERGIC-BLOCKING DRUGS

Classification

The currently available beta-adrenoceptor-blocking drugs are all competitive inhibitors. They can be classified on the basis of differing pharmacological properties: beta selectivity; presence or absence of intrinsic sympathomimetic activity (ISA) or partial agonist activity (PAA) and membrane-stabilizing activity (MSA); and vasodilator activity (due to alpha-receptor blocking, beta-2 partial agonist, or direct vasodilator effects) (Table 4).^{42,43}

Nonselective agents block both beta-1 and beta-2 receptors, while other drugs have a selective action on the beta-1 receptors. Beta-1-selective drugs were previously termed "cardioselective," reflecting their preferential effect on the heart in contrast to certain other tissues, such as bronchial smooth muscle. However, as both beta-1 and beta-2 receptors are found in the heart,

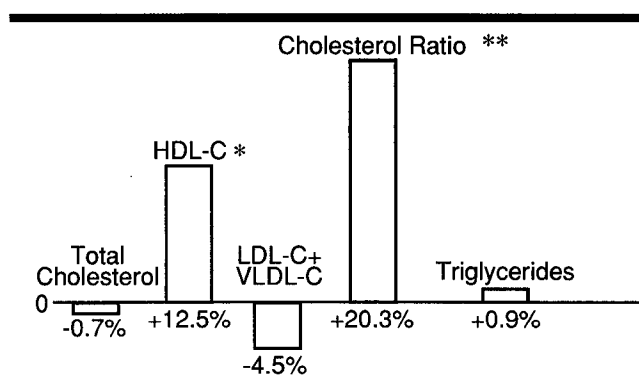


FIGURE 1. Percent changes in baseline levels after 12 weeks of therapy with prazosin. Total cholesterol and triglycerides were essentially unchanged and LDL and VLDL decreased. HDL and the cholesterol ratio increased significantly. From Kokubu et al.³⁵ (* $P < 0.05$, ** $P < 0.01$)

TABLE 4
CLASSIFICATION OF BETA-ADRENOCEPTOR
BLOCKING DRUGS

- I. Nonselective beta blockade
 1. Non PAA, eg, propranolol, sotalol, timolol
 2. PAA, eg, oxprenolol, pindolol, carteolol
- II. Beta-1 Blockade
 1. Non PAA, eg, metoprolol, atenolol, bisoprolol
 2. PAA, eg, practolol
- III. Nonspecific Vasodilation
 1. Vasodilation by alpha blockade, eg, carvedilol, labetalol
 2. Vasodilation by partial beta-2 agonism stimulation, eg, dilevalol (withdrawn) celiprolol
 3. Vasodilation independent of alpha or beta receptors, eg, prizidolol (withdrawn)

PAA, partial agonist activity

the term "cardioselective" is now considered obsolete.

The property of membrane-stabilizing activity (also termed quinidine-like or local anesthetic effect) does not appear to be important, except when beta blockers are used as eye drops and MSA should be avoided. For example, the d-isomer of propranolol possesses the same MSA but not the beta-blocking effect of racemic (ordinary) propranolol. It lacks the antihypertensive effect and anti-anginal action seen with racemic propranolol.⁴³

Competitive inhibition

For competitive antagonists like the beta-adrenoreceptor blockers, the degree of inhibition or blockade depends on the receptor occupancy, which in turn depends on the ratio of the concentration of

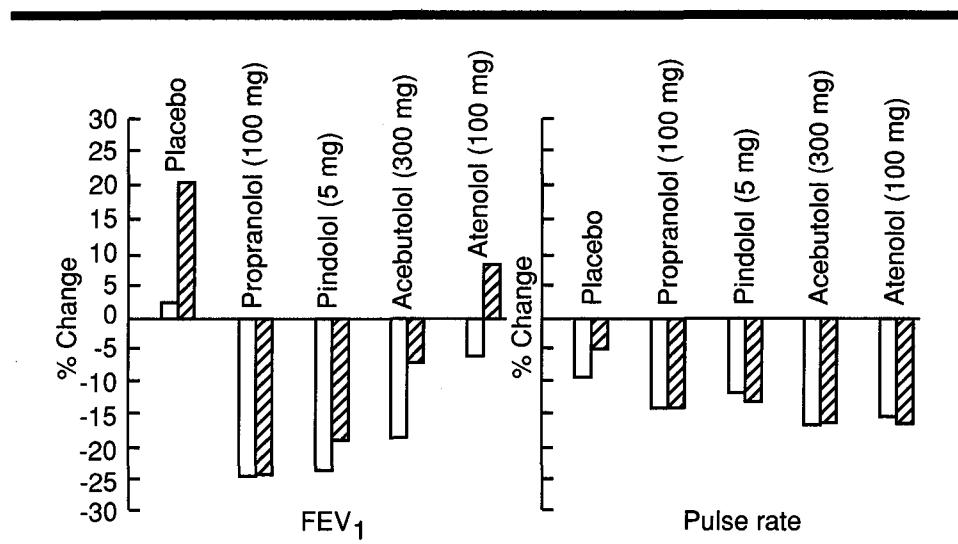


FIGURE 2. Mean changes in FEV₁ (left) and pulse rate (right) in five "responders" following a beta-adrenoceptor blocking drug and subsequent response to isoprenaline. Open bars, 2 hours post-beta-adrenoceptor blocking drug; hatched bars, 2.25 hours post-isoprenaline. From Benson et al.⁴⁶

agonist to antagonist. A series of dose-response curves to the beta-agonist isoprenaline in the presence of increasing doses of a beta-adrenoceptor antagonist (eg, labetalol) can therefore be constructed. The curves show a parallel shift to the right, with the same maximum response being obtained after the various doses of antagonist by increasing the dose of the agonist.⁴⁴ That is, as the dose of antagonist is increased, the same degree of blockade can be maintained by increasing the amount of the agonist. No dose is completely beta-blocking in terms of exogenous stimuli, as an increase in agonist overcomes the blockade.

Besides inhibition of exogenous stimuli (agonist), beta-blocking drugs also inhibit endogenous stimuli. This is most clearly shown by inhibition of the beta-1-adrenergic effect, exercise tachycardia, and the rise of systolic blood pressure on exercise.⁴³

Beta-1 selectivity

Beta-1-selective agents produce different effects than nonselective beta blockers. Beta-1-blocking drugs produce little or no beta-2 inhibition. Beta-1 selectivity is important because the increase in airway resistance is less than with nonselective blockade and inhibition of beta-2-mediated bronchial dilatation is markedly reduced (Figure 2).⁴⁵⁻⁴⁷ However, it should be emphasized that even beta-1-selective drugs must be regarded as potentially dangerous in asthmatic patients.⁴⁷

Beta blockade opposes the beta-1 cardiac effects of the beta-agonist isoprenaline, such as exercise tachycardia. For equivalent inhibition of exercise tachycardia, the beta-1-selective drugs show far less antagonism of the cardiac effects of isoprenaline than do the nonselective agents, either with or without ISA.⁴⁸⁻⁵² The reason for this difference is that beta-2 receptors, present in the atria along with beta-1 receptors, are not blocked by the beta-1-selective agent.^{51,53,54}

This difference in the effects of beta-1-selective and beta-nonselective antagonists does not appear to be due to unopposed

beta-2 vasodilator activity from isoprenaline following beta-1-selective blockade. Such a fall in blood pressure could indeed produce vagal de-inhibition from beta-1 blockade, leading to vagally induced cardiac acceleration and minimizing any antagonist cardiac blockade of isoprenaline. However, this explanation appears unlikely as the difference persists, unaffected by prior administration of atropine to block the vagus⁵⁵ or by angiotensin to prevent any fall of blood pressure.⁵¹

Pressor reactions that involve the liberation of adrenaline (beta-1, beta-2), such as smoking⁵⁶ or insulin hypoglycemia, are increased when the beta-2-mediated vasodilator action of adrenaline is antagonized, leaving unopposed adrenaline beta-1 vasoconstriction and a more marked increase in blood pressure (Figure 3). Nonselective beta blockade antagonizes the beta-2-mediated vasodilator of adrenaline, in effect converting the action into that of noradrenaline (beta-1).⁵⁷

As might be expected, these pressor responses involving the liberation of adrenaline are affected differently by beta-1-selective blockade.⁵⁸ The pressor responses to a combination of coffee and cigarettes have been reported to be attenuated by atenolol, which does not block the beta-2 vasodilatory effect of adrenaline, whereas neither of the nonselective blockers oxprenolol or propranolol had any effect.⁵⁹

Beta selectivity also has metabolic consequences.

Whereas alpha-blocking drugs favorably affect serum lipids, beta blockade can adversely alter these cardiovascular risk parameters. Beta-1-selective drugs lead to less of an increase in LDL and less of a fall in HDL than do non-selective agents.⁴² Beta-1-selective agents do not appear to prolong insulin hypoglycemia, whereas some prolongation occurs with nonselective drugs.^{42,60} Lastly, beta-1-selective agents do not impair the metabolic changes in muscles associated with exercise to the same degree as seen with nonselective drugs.⁴²

PAA or ISA

Beta blockade produces decreased heart rate and cardiac output. The addition of intrinsic sympathomimetic activity (ISA) or partial agonist activity (PAA) would be expected to oppose the beta blockade. It has been shown that, when a beta-adrenoceptor blocker has intrinsic sympathomimetic activity or partial agonist activity, a number of different pharmacological phenomena result, most notably modification of hemodynamic effects.⁶¹ A drug with a significant degree of ISA ameliorates the effects of beta blockade, resulting in a lesser fall in resting heart rate^{62,63} and cardiac output^{64,65} and, at least partly because of this, a lesser reduction in peripheral blood flow.⁶⁶⁻⁶⁸

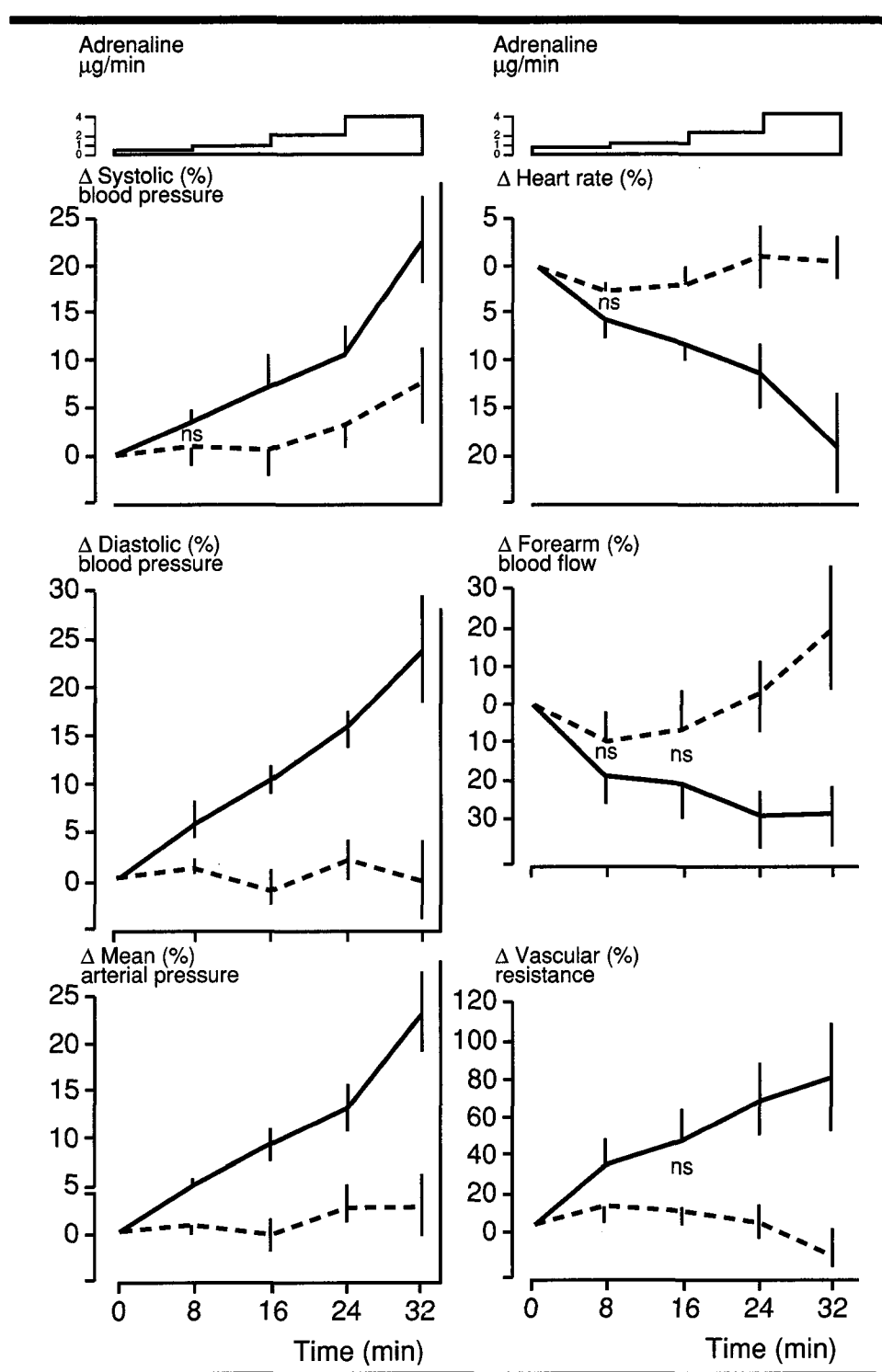


FIGURE 3. Percent changes in blood pressure, heart rate, forearm blood flow, and forearm vascular resistance induced by stepwise increases in epinephrine infusion after long-term treatment with propranolol (solid line) and metoprolol (dashed line) in five hypertensive patients. From Houben et al.⁵⁸ (ns = not significant; otherwise $P < 0.05$)

The reduction of blood flow with a non-ISA drug, whether beta-1-selective or nonselective, is largely a compensatory response to the fall in cardiac output. However, a drug possessing beta-2 ISA will also exhibit peripheral vasodilation action from stimulation of beta-2 vasodilator receptors.⁶⁹ An ISA-possessing drug may even increase heart rate if the level of sympathetic tone is low enough, as during sleep. With high levels of exercise and full doses of the drugs, a beta-blocking drug with ISA reduces exercising heart rate less than a non-ISA drug.^{52,61}

The presence of ISA also has nonhemodynamic effects. In asthmatic subjects, the modest beta-stimulant action on bronchial smooth muscle is not important in this context as these patients are potentially sensitive to any receptor blockade.⁷⁰ However, when an ISA beta blocker is stopped, no post-beta-blocking drug hypersensitivity is seen, in contrast to non-ISA agents.^{71,72} This difference is due to the fact that a drug which possesses ISA "down-regulates" (decreases) beta receptors, whereas non-ISA drugs increase receptor populations. Lastly, evidence exists that the possession of ISA results in less of a disturbance in certain metabolic processes, such as the metabolism of liver-metabolized drugs.⁷³ In particular, lipid metabolism is less altered, with less increase in VDL or decrease in HDL.⁴²

MULTIPLE-ACTION BETA-ADRENOCEPTOR BLOCKERS

More recently, a group of beta-adrenoceptor blockers has been developed which, in addition to beta blockade, possesses significant peripheral vasodilator activity. The initial drug of this group, labetalol, was first reported in the early 1970s.^{74,75} Prizidilol, which followed next and was widely studied, was withdrawn because of animal toxicity. This agent has been followed by a number of other multiple action beta blockers,⁴³ including bucindolol, and medroxalol and the more widely studied carvedilol, celiprolol, and dilevalol (the latter was withdrawn recently because of its association with liver toxicity).

Hemodynamic effects

These multiple action drugs show hemodynamic properties that might be expected from the combination of beta-adrenoceptor blockade and peripheral vasodilator action.^{21,76} Administration of a beta-blocking drug without partial agonist activity leads to a fall in heart rate and cardiac output and an increase in peripheral resistance at rest or during exercise.

Vasodilatation from alpha-1 blockade with prazosin produces a fall in peripheral resistance at rest or during exercise and may increase the cardiac output. The hemodynamic effects of the combination of beta blockade plus prazosin are similar to those caused by labetalol (beta blockade plus peripheral vasodilatation from alpha-1 blockade): less of a fall in heart rate or cardiac output than that seen after beta blockade alone and, instead of an increase in peripheral resistance, a reduction.^{21,76,77}

While effects vary with the dose, the physiological conditions under which measurements are made, and the ratio of beta-blocking to vasodilating properties of the drug, research indicates that the hemodynamic effects of various beta-blocking vasodilator drugs show a similar pattern. In animal studies, the nonselective beta antagonist propranolol increased peripheral resistance and reduced cardiac output, whereas the multiple-action agent carvedilol showed a reduction of peripheral resistance, accounting for the fall in blood pressure, while cardiac output was affected little.⁷⁸ In hypertensive patients, propranolol resulted in increased peripheral resistance and a fall in cardiac output, and carvedilol has been shown to produce a fall in forearm vascular resistance.⁷⁹

Unlike the situation with beta-adrenoceptor-blocking drugs without vasodilatory properties, the fall in blood pressure from carvedilol was not associated with a fall in renal blood flow. A decline in renal vascular resistance compensated for the reduction in blood pressure, maintaining renal blood flow.⁸⁰ Investigation in patients with angina showed a tendency for vascular resistance to fall at rest and to be affected only a little on exercise with carvedilol, in contrast to the increased resistance with propranolol. Carvedilol also had little effect on cardiac output, either at rest or during exercise, whereas it was reduced by propranolol.⁸¹

Celiprolol also caused reduced peripheral resistance and no reduction in cardiac contractility in animals.^{82,83} Likewise, hemodynamic studies in man revealed that celiprolol did not reduce cardiac output at rest and it led to a fall in peripheral resistance.⁸⁴⁻⁸⁷ In an investigation of patients with ischemic heart disease, doses of celiprolol that caused a small fall in exercise tachycardia of eight beats per minute were associated with a 7% reduction in cardiac output and a small (9%) increase in vascular resistance. The beta-1 antagonist atenolol, at a dose resulting in a 10 beats-per-minute fall in exercising heart rate, caused a 16% fall in cardiac output and an 18% increase in systemic

vascular resistance.⁸⁸ Celiprolol reduced forearm vascular resistance and increased blood flow.⁸⁹ Despite the fall in blood pressure, renal blood flow was maintained due to the reduction in renal vascular resistance.⁹⁰

Another multiple action beta-adrenoceptor drug, dilevalol, reduced peripheral resistance in conscious dogs, with a marginal effect on heart rate. Intermediate doses gave a small increase in cardiac output, but larger doses had no effect.⁹¹ The hemodynamic effects of dilevalol were found to be similar to carvedilol (Figure 4).^{92,93} Similar to carvedilol, dilevalol maintained glomerular filtration rate, unlike the pattern observed after beta-blocking drugs without any vasodilator component.⁹⁴ The other multiple-action drugs have been less widely studied. However, the hemodynamic changes produced in animals after medroxalol⁹⁵ or in hypertensive patients after bucindolol⁹⁶ appear similar to those reported for carvedilol.

Mechanism of peripheral vasodilation

Three mechanisms may be responsible for peripheral vasodilation: alpha-receptor-blocking action that interferes with alpha-receptor-mediated vasoconstrictor tone; beta-2 agonism that results in a beta-2-mediated vasodilation; and, lastly, dilator action that is independent of either the alpha or beta receptors. Most evidence concerning the mechanisms of dilatation for the various agents comes from animal investigations, but human studies have provided some evidence.

Alpha-blocking activity

These agents exhibit an alpha blockade-type effect, but less than that seen with alpha blockers; and different drugs show different amounts of alpha blockade.

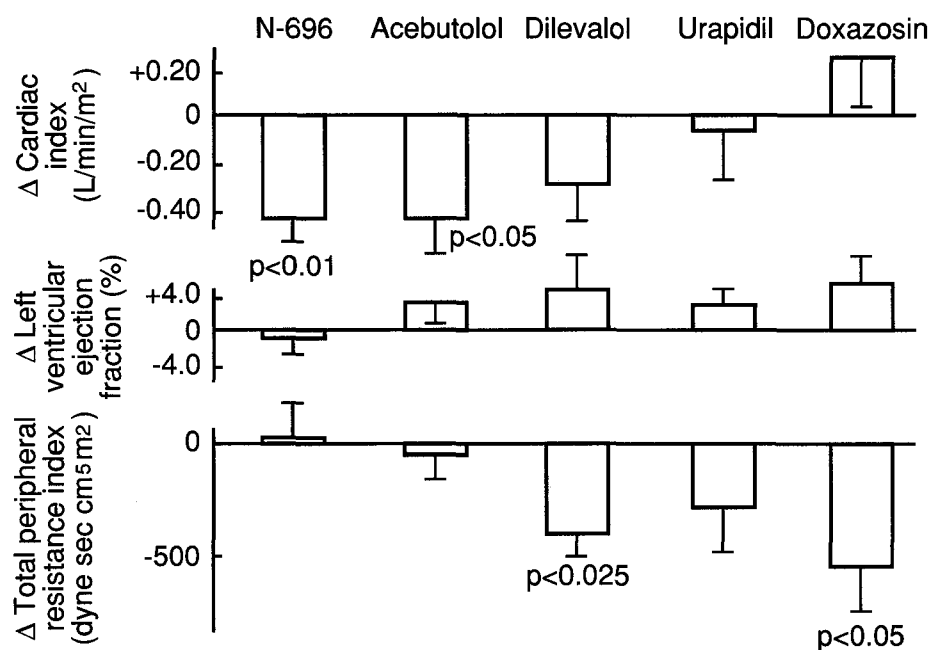


FIGURE 4. Effects of N-696, acebutolol, dilevalol, urapidil, and doxazosin on cardiac index, left ventricular ejection fraction (LVEF), and total peripheral resistance index (TPR) in essential hypertension. From Tsukiyama et al.⁹³

In the rat aortic strip assay, noradrenaline was used to produce contraction. Carvedilol relaxed the rat aortic strip that had been precontracted by noradrenaline. But this effect appeared to be at least partly a nonspecific one, as it resembled the effect seen with glyceryl trinitrate and was much less than the effect observed with the alpha-1 blocker prazosin.⁹⁷ Likewise, using strips precontracted by noradrenaline or potassium chloride, inhibition of both was achieved by similar concentrations of carvedilol; in contrast, there was a separation of the dose-response curves with labetalol, with lower doses required for noradrenaline-contracted strips compared to potassium chloride.⁹⁸ When doses were used which gave similar antihypertensive effect in the pithed rat, carvedilol caused much less inhibition of the dose-response curve to alpha-1 stimulation with methoxamine (an alpha-1 agonist) compared to phen-tolamine (alpha-1, alpha-2 antagonist).⁹⁸

Bartsch and associates⁹⁹ studied inhibition of endogenous sympathetic activity in the conscious rabbit.

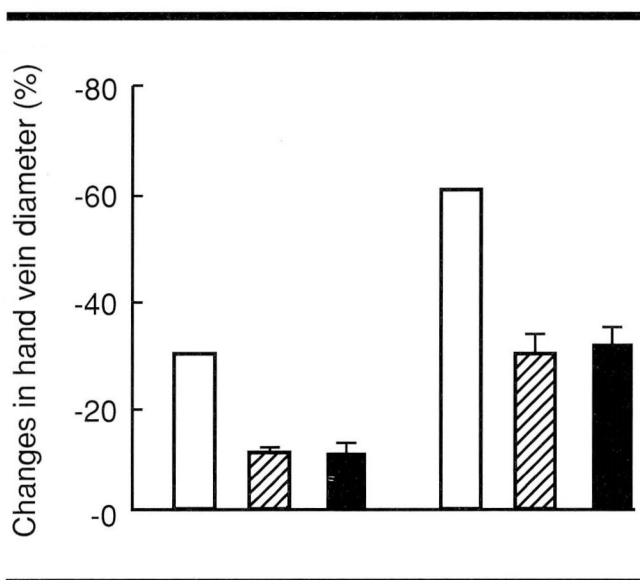


Figure 5. Reduction of hand vein diameter by noradrenaline before (open bar) and 1 hour (hatched bar) and 3.5 hours (solid bar) after oral administration of carvedilol, 50 mg. From Belz et al.¹⁰²

They used equivalent antihypertensive doses and measured the postural hypotensive effects of alpha-1 inhibition. Intravenous prazosin (alpha-1 blockade), labetalol (combination of alpha and beta effects), and guanethidine (inhibition of neuronal release of noradrenaline) each resulted in a more marked postural effect than seen with carvedilol.

Notwithstanding these animal observations, evidence of alpha₁-receptor inhibition in man has been seen. Studies of single doses of the alpha-1 agonist phenylephrine in normal volunteers revealed an inhibition of the pressor effect by intravenous carvedilol, while responses to single doses of angiotensin were not affected.¹⁰⁰ Similarly, when dose-response studies to phenylephrine were performed, oral carvedilol inhibited responses, but did not alter the pressor effect of angiotensin.¹⁰¹ Carvedilol also inhibited the constriction alpha effect of noradrenaline on veins (Figure 5).¹⁰²

Other multiple-action drugs also exhibited some alpha-1-blocking activity. Medroxalol inhibited the pressor responses to phenylephrine in animals⁹⁵ and man.^{103,104} Weak alpha-2-blocking activity has also been suggested for celiprolol on the basis of animal experiments.^{82,85}

Beta-2 agonism

Beta-2 agonism is not part of the vasodilating

mechanism of carvedilol: the relaxation it produced in the rat aortic strip preparation was not inhibited by incubation with the beta-2-blocking agent ICI 118551.⁹⁸ Some evidence exists, however, that beta-2 agonism contributes to the vasodilator effects of celiprolol, dilevalol, labetalol, medroxalol, and pindolol. Relaxation of isolated guinea pig trachea (beta effect) by dilevalol and labetalol was inhibited by the nonselective beta-blocker propranolol.¹⁰⁵ Baum and Sybertz¹⁰⁶ found that pretreatment with the beta-agonist propranolol in ganglion-blocked anesthetized dogs inhibited the fall of blood pressure from pindolol and dilevalol, suggesting a beta-2 dilator component. However, propranolol did not affect the fall in blood pressure from the direct vasodilator hydralazine or the beta blocker vasodilator prazosin.

Similarly, propranolol was observed to block the fall in blood pressure from pindolol in the spontaneously hypertensive rat (SHR) and to reduce the effect of labetalol and dilevalol.¹⁰⁶ The dilator action of dilevalol in the vascular bed of the dog was completely blocked by propranolol.¹⁰⁶ More recently, it has been found that dilevalol increased aortic compliance (beta-2 action), and this effect was inhibited by propranolol.¹⁰⁷

In animals, medroxalol was not affected by beta-1 blockade from practolol, but its blood pressure-lowering effect was partly inhibited by propranolol, with its beta-1- and beta-2-blocking activity.^{95,108} Celiprolol possesses weak beta-1-stimulant activity but predominantly has a beta-2-stimulant action.⁸⁵ It has been shown to down-regulate beta-2 receptors of human lymphocytes, typical of a beta-2-stimulant effect.¹⁰⁹ The relaxant beta-2-type effect of celiprolol and pindolol on human arteries and veins was reduced, though not completely abolished, by both sotalol and propranolol (beta-1, beta-2 antagonists).¹⁰⁸

PERIPHERAL VASODILATION

Although multiple action drugs may exhibit evidence of an alpha-blocking or beta-2-mediated vasodilator action in animals or man, the peripheral vasodilation is not necessarily fully explained by this property. Doses that produce an equal blood pressure-lowering action in the pithed rat were used to construct a series of dose-response curves. The alpha-1 antagonist prazosin (0.15 mg/kg) resulted in a 23.3-fold shift of the alpha-1 agonist methoxamine dose-response curve and a 9.9-fold shift to noradrenaline; with the alpha-1, alpha-2 antagonist phentolamine

(2.8 mg/kg) the shifts were 30.6 and 44.8, respectively; with carvedilol (0.37 mg/kg) the shifts were only 4.27 and 2.78, like the effects of the direct vasodilator dihydralazine (1.1 mg/kg), which resulted in a 2.85 and a 2.81 shift.⁹⁸ Dihydralazine produced a 10.2-fold shift, with a flattening of the curve to angiotensin II; the other agents were without effect.

Further evidence supports the existence of vasodilation independent of alpha blockade or beta-2 stimulation. Other animal investigations performed by Strein and associates⁹⁷ and by Bartsch and colleagues,⁹⁹ discussed above, confirm some dissociation of the antihypertensive activity of carvedilol and alpha-1 blockade. Research data also support a direct smooth muscle-relaxing effect for celiprolol. As noted previously, its relaxant effect on isolated human arteries and veins is not completely inhibited by beta blockade.¹⁰⁸ Evidence of a bronchodilator effect independent of beta receptors has also been found.⁸⁵

BETA BLOCKADE IN HYPERTENSION

Although beta-blocking drugs have been in use for over 20 years, their antihypertensive mode of action is not completely clear. Blood pressure is lowered regardless of the presence or absence of the associated properties (beta-1 selectivity, ISA, and membrane activity), although a high level of beta-1 agonism reduces the antihypertensive effect. Moreover, the membrane-active non-beta-blocking isomers are without antihypertensive effect.

It seems clear that beta-adrenoceptor-blocking drugs lower the blood pressure because of their beta-1-receptor-blocking action. Several explanations have been suggested for the hypotensive effect of beta-adrenergic blockers, including the following: direct action on the central nervous system; adrenergic neuron blocking, possibly via presynaptic beta-2 receptors; anti-renin activity; increased vasodilator prostaglandins; effects secondary to reduced cardiac output; and resetting of baroreceptors. Resetting of baroreceptors may occur because beta blockade produces reduced cardiac activity and therefore reduced pressor peaks in response to various pressor stimuli. However, the exact mode of action remains unclear.¹¹⁰ It may be that in some patients a particular effect may be more important than

in other patients.

A possible correlation of the effect of beta-adrenoceptor blockers on the blood pressure with renin levels has received most attention. Buhler and associates¹¹¹ found that patients with high-renin levels responded best to propranolol, normal-renin patients less well, and low-renin patients had a poor response. Hollifield and associates¹¹² also found that propranolol, at a relatively low dose of 160 mg a day, readily lowered the blood pressure in high-renin patients, while higher doses of propranolol (320 to 960 mg/day) lowered the blood pressure in low-renin patients, independent of effects on renin level. Some investigators have found a good correlation between renin levels and response of blood pressure to a variety of beta-adrenoceptor-blocking drugs,¹¹⁰ whereas others have not found such a correlation.⁴³ Leonetti and associates¹¹³ found that a relatively small dose of propranolol fully suppressed renin but had little effect on the blood pressure, whereas only a larger dose (above 40 mg/day) caused a significant fall in diastolic blood pressure. Similar findings were obtained when propranolol was given to patients already on the diuretic chlorthalidone.^{114,115} It was noted by Man in't Veld and Schalekamp⁶⁶ that, while beta-adrenoceptor-blocking drugs with no intrinsic sympathomimetic activity lowered blood pressure and renin levels, those with ISA, like pindolol, also lowered blood pressure but had little effect on renin activity. Finally, some have observed in patients not fully responding to the angiotensin-converting enzyme inhibitor captopril (which suppresses the renin system), that the addition of propranolol lowered blood pressure.¹¹⁶

Those beta-adrenoceptor-blocking drugs that have a peripheral vasodilatory effect have this additional mechanism to lower the blood pressure. The vasodilator action lowers peripheral resistance, in contrast to the effect seen with beta blockade alone. The presence of beta blockade inhibits the tachycardia often seen when a direct vasodilating drug is used alone.

The antihypertensive effects of beta-blocking agents are complex. These effects have yet to be fully clarified, but obviously a variety of interactions are involved. Opposing alpha and beta effects and compensatory cardiovascular mechanisms, including the renin-angiotensin system, need further investigation.

REFERENCES

1. Langley JN. On the reaction of cells and of nerve endings to certain

poisons, chiefly the reaction of striated muscles to nicotine and to curare. *J Physiol* 1905; 33:374-413.

2. Dale HH. On some physiological actions of ergot. *J Physiol (London)* 1906; 34:160-206.

3. Cannon WB, Rosenbleuth A. Studies on conditions of activity in endocrine organs; Sympathin E and Sympathin I. *Am J Physiology* 1933; **104**:557-574.
4. Ahlquist RP. A study of the adrenotropic receptors. *Amer J Physiol* 1948; **153**:586-600.
5. Langer SZ, Duval N, Massingham R. Pharmacological and therapeutic significance of alpha-adrenoceptor subtypes. *J Cardiovasc Pharmacol* 1985; **7**(Suppl 8):S1-S8.
6. Graham RM. Adrenergic receptors: physiology and pharmacology. *Cleve Clin J Med* 1990; **57**:481-491.
7. Langer SZ, Hicks PE. Alpha-adrenoceptor subtypes in blood vessels: physiology and pharmacology. *J Cardiovasc Pharmacol* 1984; **6**:S547-S558.
8. van Zwieten PA, Jie K, Van Brummelen P. Postsynaptic α_1 - and α_2 -adrenoceptor changes in hypertension. *J Cardiovasc Pharmacol* 1987; **10**(Suppl 4):S68-75.
9. Langer SZ, Shepperson NB. Recent developments in vascular and smooth muscle pharmacology: the postsynaptic α_2 adrenoceptor. *Trends Pharmacol Sci* 1982; **3**:440-444.
10. Huchet AM, Doursout MF, Chelly J, Schmitt H. Possible role of central α_1 -adrenoceptors in the control of the autonomic nervous system in normotensive and spontaneously hypertensive rats. *Eur J Pharmacol* 1982; **85**:239-242.
11. van Zwieten PA. Antihypertensive drugs interacting with α - and β -adrenoceptors. A review of basic pharmacology. *Drugs* 1988; **35**(Suppl 6):6-19.
12. Beilin LJ, Juel-Jensen BE. Alpha and beta-adrenergic blockade in hypertension. *Lancet* 1972; **1**:979-982.
13. Prichard BNC, Boakes AJ. Labetalol in long-term treatment of hypertension. *British Journal of Clinical Pharmacology* 1976; **3**:743-750.
14. Stanaszek WF, Kellerman D, Brogden RN, Romankiewicz JA. Prazosin update. A review of its pharmacological properties and therapeutic use in hypertension and congestive heart failure. *Drugs* 1983; **25**:339-384.
15. Stokes GS. Prazosin and new α -blocking drugs. [In] Doyle AE (ed): *Handbook of Hypertension. Clinical Pharmacology of Antihypertensive Drugs*. Elsevier Science Publishers B.V., 1988.
16. Titmarsh S, Monk JP. Terazosin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in essential hypertension. *Drugs* 1987; **33**:461-477.
17. Young RA, Brogden RN. Doxazosin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in mild or moderate hypertension. *Drugs* 1988; **35**:525-541.
18. Holmes B, Sorkin EM. Indoramin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and related vascular, cardiovascular and airway diseases. *Drugs* 1986; **31**:467-499.
19. Prichard BNC, Tomlinson B, Renondin J-C. Urapidil, a multiple action α -blocking drug. A Symposium: pharmacologic and therapeutic aspects of urapidil. *Am J Cardiol* 1989; **64**:11D-15D.
20. Graham RM. Selective α_1 -adrenergic antagonists: therapeutically relevant antihypertensive agents. *Am J Cardiol* 1984; **53**:16A-20A.
21. Lund-Johansen P. Haemodynamics of the α - and/or β -blocking agents. Effects on heart, blood vessels and regional circulation. *Cleve Clin J Med* (in press).
22. Lund-Johansen P, Omvik P, Haugland H. Acute and chronic haemodynamic effects of doxazosin in hypertension at rest and during exercise. *Br J Clin Pharmacol* 1986; **21**(Suppl 1):45S-54S.
23. Bauer JH, Jones LB, Gaddy P. Effects of prazosin therapy on BP, renal function, and body fluid composition. *Arch Intern Med* 1984; **144**:1196.
24. de Leeuw PW, van Es PN, De Bos R, Birkenhager WH. Acute renal effects of doxazosin in man. *Br J Clin Pharmacol* 1986; **21**(Suppl 1):41S-43S.
25. Stokes GA, Gain JM, Mahony JF, Raftos J, Stewart JH. Long-term use of prazosin in combination or alone for treating hypertension. *Med J Austr (Special Supplement)* 1977; **2**:13-16.
26. MacCarthy EP, Thornell IR, Stokes GS. Prazosin: long-term therapy of hypertension. *J Cardiovasc Med* 1981; **6**(Suppl):70-76.
27. Bendall MJ, Baloch KH, Wilson PR. Side effects due to treatment of hypertension with prazosin. *Br Med J* 1975; **2**:727-728.
28. Rosendorff C. Prazosin: severe side effects are dose dependent. *Br Med J* 1976; **2**:508.
29. Stokes GS, Graham RM, Gain JM, Davis PR. Influence of dosage and dietary sodium on the first-dose effects of prazosin. *Br Med J* 1977; **1**:1507-1508.
30. Rutland MD, Nimmon CC, Lee TY, Granowska M, Britton KE. Measurement of the effects of a single dose of prazosin on the cerebral blood flow of hypertensive patients. *Post Med J* 1980; **56**:818-822.
31. Falch DK, Quist Paulsen A, Odegaard AE, Norman N. Central and renal circulation, renin and aldosterone in plasma during prazosin treatment in essential hypertension. *Acta Medica Scandinavica* 1979; **206**:489-494.
32. Seideman P, Grahnen A, Haglund K. Prazosin first-dose phenomenon during combined treatment with a β -adrenoceptor blocker in hypertensive patients. *Br J Clin Pharmacol* 1982; **13**(6):865-870.
33. Velasco M, Silva H, Feldstein E, et al. Effects of prazosin and α -phamethyl dopa on blood lipids and lipoproteins in hypertensive patients. *Eur J Clin Pharmacol* 1985; **28**:513-516.
34. Leren P, Eide I, Foss OP, et al. Antihypertensive drugs and blood lipids: the Oslo study. *J Cardiovasc Pharmacol* 1982; **4**(Suppl 2):S222-224.
35. Kobuku T, Itoh I, Kurita H, Ochi T, Murata K, Yuba I. Effect of prazosin on serum lipids. *J Cardiovasc Pharmacol* 1982; **4**(Suppl 2):S228-S232.
36. Velasco M, Silva H, Morilla J, Pellicer R, Urbina-Quintana A, Hernandez-Pieretti O. Effects of prazosin on blood lipids and on thyroid function in hypertensive patients. *J Cardiovasc Pharmacol* 1982; **4**(Suppl 2):S225-S227.
37. Deger G. Effect of terazosin on serum lipids. *Am J Med* 1986; **80**(Suppl 5B):82-85.
38. Goto Y, Tanabe T, Ogasawara Y, et al. The effects of prazosin and propranolol in combination with thiazide diuretics on blood pressure and serum lipids: a multicentre study. *Eur J Clin Pharmacol* 1987; **33**:339-344.
39. Lithell H, Waern U, and Vessby B. Effect of prazosin on lipoprotein metabolism in premenopausal, hypertensive women. *J Cardiovasc Pharmacol* 1982; **4**(Suppl 2):S242-S244.
40. Blau A, Neusy AJ, Lowenstein J. The effects of propranolol and prazosin on plasma lipids and aortic atherosclerosis in cholesterol-fed rabbits. *J Hypertension* 1986; **4**(Suppl 5):S485-S487.
41. Holtzmann JL, Kaihlanen PM, Rider JA, Lewin AJ, Spindler JS, Oberlin JA. Concomitant administration of terazosin and atenolol for the treatment of essential hypertension. *Arch Intern Med* 1988; **148**:539-543.
42. Prichard BNC, Tomlinson B. The additional properties of β -adrenoceptor blocking drugs. *J Cardiovasc Pharmacol* 1986; **8**(Suppl 4):S1-S15.
43. Cruickshank JM, Prichard BNC. *Beta-blockers in Clinical Practice*. Churchill Livingstone, Edinburgh. 1988 pp. 1-1003.
44. Richards DA, Prichard BNC, Boakes AJ, Tuckman, Knight EJ. Pharmacological basis for antihypertensive effects of intravenous labetalol. *Br Heart J* 1977; **1**:99-106.
45. Tattersfield AE, Harrison RN. Effect of β -blocker therapy on airway function. *Drugs* 1983; **25**(Suppl 2):227-231.
46. Benson MK, Berrill WT, Cruickshank JM, Sterling GS. A comparison of four β -adrenoceptor antagonists in patients with asthma. *Br J Clin Pharmacol* 1978; **5**:415-419.
47. McDevitt DG. Pharmacologic aspects of cardioselectivity in a β -blocking drug. *Am J Cardiol* 1987; **59**:10F-12F.
48. Briant RH, Dollery CT, Fenyvesi T, George CF. Assessment of selective β_1 -adrenoceptor blockade in man. *Br J Pharmacol* 1973; **49**:106-114.
49. Graham BR, Littlejohns DW, Prichard BNC, Scales B, Southorn P. Preliminary observations on the human pharmacology of ICI 66082 in normal volunteers. *Br J Pharmacol* 1973; **49**:154P-155P.

50. Walden RJ, Bhattacharjee P, Tomlinson B, Cashin J, Graham BR, Prichard BNC. The effect of intrinsic sympathomimetic activity on beta-receptor responsiveness after beta-adrenoceptor blockade withdrawal. *Br J Clin Pharmacol* 1982; 13:359S-364S.
51. McGibney D, Singleton W, Silke B, Taylor SH. Observations on the mechanism underlying the differences in exercise and isoprenaline tachycardia after cardioselective and nonselective-adrenoceptor antagonists. *Br J Clin Pharmacol* 1983; 15:15-19.
52. Tomlinson B, Bhattacharjee P, Graham BR, Hill JM, Raeburn J, Prichard BNC. A comparison of penbutolol with atenolol and long-acting propranolol. (abstract) *Br J Clin Pharmacol* 1984; 17:186p.
53. Andersen GS. Antihypertensive treatment of elderly patients in general practice (preliminary results). *Acta Med Scand Suppl* 1982; 676:151-160.
54. Zerkowski H-R, Ikezono K, Rohm N, Reidemeister J Chr, Brodde O-E. Human myocardial beta-adrenoceptors: demonstration of both beta1- and beta2-adrenoceptors mediating contractile responses to beta agonists on the isolated right atrium. *Naunyn-Schmiedeberg's Arch Pharmacol* 1986; 332:142-147.
55. Arnold JMO, McDevitt DG. Interpretation of isoprenaline dose-response curves in the presence of selective and nonselective beta-adrenoceptor blocking drugs. *Br J Clin Pharmacol* 1982; 13:585P.
56. Trap-Jensen J, Carlsen JE, Lysbo-Svendsen T, Christensen NJ. Cardiovascular and adrenergic effects of cigarette smoking during immediate nonselective and selective beta-adrenoceptor blockade in humans. *Eur J Clin Invest* 1979; 9:181-183.
57. Prichard BNC, Ross EJ. Use of propranolol in conjunction with alpha-receptor blocking drugs in pheochromocytoma. *Am J Cardiol* 1966; 18:394-398.
58. Houben H, Thien T, van 't Laar. Effect of low dose epinephrine infusion on hemodynamics after selective and nonselective beta-blockade in hypertension. *Clin Pharmacol & Ther* 1982; 31:685-690.
59. Freestone S, Ramsay LE. Effect of beta blockade on the pressor response to coffee plus smoking in patients with mild hypertension. *Drugs* 1983; 25(Suppl 2):141-145.
60. Kendall MJ. Impact of beta1 selectivity and intrinsic sympathomimetic activity on potential unwanted noncardiovascular effects of beta blockers. *Am J Cardiol* 1987; 59:44F-47F.
61. Prichard BNC. Pharmacologic aspects of intrinsic sympathomimetic activity in beta-blocking drugs. *Am J Cardiol* 1987; 59:13F-17F.
62. Prichard BNC. Aspects of the evaluation of antihypertensive drugs. [In] *Proceedings of the International Symposium on Clinical Pharmacology*, Royal Academies of Medicine of Belgium, Brussels, 1970, pp 193-208.
63. Kostis JB, Frishman W, Hosler MH, Thorsen NL, Gonasun L, Weinstein J. Treatment of angina pectoris with pindolol: the significance of intrinsic sympathomimetic activity of beta blockers. *Am Heart J* 1982; 104:496-504.
64. Svendsen TL, Hartling O, Trap-Jensen J. Immediate haemodynamic effects of propranolol, practolol, pindolol, atenolol and ICI 89406 in healthy volunteers. *Eur J Clin Pharmacol* 1979; 15:223-228.
65. Taylor SH. Alpha-adrenoceptor antagonists in hypertension. [In] *Amery A, ed. Hypertensive Cardiovascular Disease: Pathophysiology and Treatment*. 1982, The Hague: Martinus Nijhoff Publishers, pp. 755-782.
66. Man in't Veld AJ, Schalekamp MADH. How intrinsic sympathomimetic activity modulates the haemodynamic responses to beta-adrenoceptor antagonists. A clue to the nature of their antihypertensive mechanism. *Br J Clin Pharmacol* 1982; 13(Suppl. 2):245S-257S.
67. Svensson A, Gudbrandsson T, Sivertsson R, Hansson L. Haemodynamic effects of metoprolol and pindolol: a comparison in hypertensive patients. *Br J Clin Pharmacol* 1982; 13:259S-267S.
68. Man in't Veld AJ. Effect of beta blockers on vascular resistance systemic hypertension. *Am J Cardiol* 1987; 50:21F-25F.
69. Chang PC, Blauw GJ, van Brummelen P. Pindolol: a beta blocker with vasodilating properties due to stimulation of vascular b2 adrenoceptors. *J Hypertension* 1983; 1(Suppl 2):338-339.
70. McDevitt DG. The assessment of beta-adrenoceptor antagonists and respiratory function. *Br J Clin Pharmacol* 1978; 5:97-99.
71. Prichard BNC, Walden RJ, Tomlinson B, Liu J-B. The cardiovascular effect of withdrawal of beta-adrenoceptor blocking drugs. *Current Opinion in Cardiology* 1988; 3(Suppl 2):S19-S29.
72. Frishman WH. Clinical significance of beta1 selectivity and intrinsic sympathomimetic activity in a beta-adrenergic blocking drug. *Am J Cardiol* 1987; 59:33F-37F.
73. Lysbo Svendsen T, Tango M, Waldorff S, Steiness E, Trap-Jensen J. Effects of propranolol and pindolol on plasma lignocaine clearance in man. *Br J Clin Pharmacol* 1982; 13:223S-226S.
74. Louis WJ, McNeil JJ, Drummer OH. Pharmacology of combined alpha- beta-Blockade I. *Drugs* 1984; 28(Suppl 2):16-34.
75. Prichard BNC. Combined alpha- and beta-receptor inhibition in the treatment of hypertension. *Drugs* 1984; 28(Suppl. 2):51-68.
76. Lund-Johansen P. Comparative haemodynamic effects of labetalol, timolol, prazosin and the combination of tolamolol and prazosin. *Br J Clin Pharmacol* 1979; 8(Suppl 2):107S-111S.
77. Lund-Johansen P. The pharmacology of combined alpha- beta-blockade II. *Drugs* 1984; 28(Suppl 2):35-50.
78. Tanaka M, Masumura H, Tanaka S, Akashi A. Studies on the antihypertensive properties of carvedilol, a compound with beta-blocking and vasodilating effects. *J Cardiovasc Pharmacol* 1987; 10(Suppl 11):S52-S57.
79. Eggertsen R, Silvertsson R, Andren L, Hansson L. Hemodynamic effects of carvedilol, a new beta-adrenoceptor blocker and precapillary vasodilator in essential hypertension. *J Hypertension* 1984; 2:529-534.
80. DuPont AG, Van der Niepen P, Taeymans Y, et al. Effect of carvedilol on ambulatory blood pressure, renal hemodynamics and cardiac function in essential hypertension. *J Cardiovasc Pharmacol* 1987; 10(Suppl 11):S130-S136.
81. Wendt Th, van der Does R, Schrader R, Landgraf H, Kober G. Acute haemodynamic effects of the vasodilating and beta-blocking agent carvedilol in comparison to propranolol. *J Cardiovasc Pharmacol* 1987; 10(Suppl 11):S142-S151.
82. Riddell JG, Shanks RG, Brogden RN. Celiprolol: a preliminary review of its pharmacodynamic and pharmacokinetic properties and its therapeutic use in hypertension and angina pectoris. *Drugs* 1987; 34:438-458.
83. Pruss TP, Khandwala A, Wolf PS, Grebow P, Wong L. Celiprolol: a new beta-adrenoceptor antagonist with novel ancillary properties. *J Cardiovasc Pharmacol* 1986; 8(Suppl 4):S29-S32.
84. Gensini G, Dator C, Esente P, Caruso FS, Solomon T. Comparison of the acute hemodynamic effects of intravenous celiprolol and propranolol in patients with suspected coronary disease. *J Cardiovasc Pharmacol* 1986; 8(Suppl 4):S83-S85.
85. Norris RJ. Antihypertensive therapy with celiprolol: a new cardioselective beta blocker. *Am J Cardiol* 1988; 61:14C-22C.
86. Trimarco B, Lembo G, DeLuca N, et al. Long-term reduction of peripheral resistance with celiprolol and effects on left ventricular mass. *J of Intl Med Res* 1988; 16(Suppl 1):62A-72A.
87. Taylor SH. Pharmacological and therapeutic properties of an ideal beta-blocker. *J Intl Med Res* 1988; 16(Suppl 1):8A-16A.
88. Silke B, Verma SP, Frais MA, Reynolds G, Taylor SH. Differential actions of atenolol and celiprolol on cardiac performance in ischemic heart disease. *J Cardiovasc Pharmacol* 1986; 8(Suppl 4):S138-S144.
89. Mancia G, Grassi G, Parati G et al. Effects of celiprolol on reflex control of the cardiovascular system in essential hypertension. *J Cardiovasc Pharmacol* 1986; 8(Suppl 4):S67-S74.
90. Lucarini AR, Salvetti A. Systemic and renal hemodynamic effects of celiprolol in essential hypertensives. *Am J Cardiol* 1988; 61:45C-48C.
91. Baum T, Watkins RW, Sybertz EJ, et al. Antihypertensive and hemodynamic action of SCH 19927, the R, R-isomer of labetalol. *J Pharmacol Exp Ther* 1981; 218:444-452.
92. Bugni WJ, Ayers CW, Ashby R, Bittle PA, Ramirez G. Effects of dilevalol on rest and supine exercise. Hemodynamics in mild to moderate systemic hypertension. *Am J Cardiol* 1989; 63:452-456.
93. Tsukiyama H, Otsuka K, Takasaki I, Horii M. Haemodynamic effects of dilevalol and N-696, new beta-blocking agents with vasodilating properties and doxazosin and urapidil, new alpha-blocking agents, in essential hypertension. *J Cardiovasc Pharmacol* 1988; 11(Suppl 2):S32-S35.

94. Wallin JD, Clifton G, Cook E, Poland M, Cubbon J. Effects of oral dilevalol treatment on renal function. Dilevalol—The Beta-Blocking Vasodilator: Satellite Symposium to the Third European Meeting on Hypertension, Milan, 19 June 1987, 26 (abstract).
95. Dage RC, Cheng HC, Woodward JK. Cardiovascular properties of medroxalol, a new antihypertensive drug. *J Cardiovasc Pharmacol* 1981; 3:299–315.
96. Kimura S, DeQuattro V, Edmiston WA, et al. Efficacy of bucindolol in systemic hypertension. *Am J Cardiol* 1987; 60:1083–1086.
97. Strein K, Sponer G, Muller-Beckmann G, Bartsch W. Pharmacological profile of carvedilol, a compound with beta-blocking and vasodilating properties. *J Cardiovasc Pharmacol* 1987; 10(Suppl 11):S33–S41.
98. Sponer G, Strein K, Muller-Beckmann B, Bartsch W. Studies on the mode of vasodilating action of carvedilol. *J Cardiovasc Pharmacol* 1987; 10(Suppl 11):S42–S48.
99. Bartsch W, Sponer G, Strein K, Bohm E, Hooper RG. Evaluation of the risk for drug induced postural hypotension in an experimental model: investigations with Carvedilol, prazosin, labetalol and guanethidine. *J Cardiovasc Pharmacol* 1987; 10(Suppl 11):S49–S51.
100. Cubeddu LX, Fuenmayor N, Varin F, Villagra VG, Colindres RE, Powell JR. Mechanism of the vasodilatory effect of carvedilol in normal volunteers: a comparison with labetalol. *J Cardiovasc Pharmacol* 1987; 10(Suppl 11):S81–S84.
101. Tomlinson B, Bompert F, Graham BR, Liu JB, Prichard BNC. Vasodilating mechanism and response to physiological pressor stimuli of acute doses of carvedilol compared with labetalol, propranolol and hydralazine. *Drugs* 1988; 36(Suppl 6):37–47.
102. Belz GG, Beermann C, Schloos J, Neugebauer. Influence of carvedilol on the responsiveness of human hand veins to noradrenaline and dinoprost. *Drugs* 1988; 36(Suppl 6):69–74.
103. Elliott HL, McLean K, Meredith PA, Sumner DJ, Reid JL. Comparison of medroxalol and labetalol, drugs with combined alpha- and beta-adrenoceptor antagonist properties. *Br J Clin Pharmacol* 1984; 17:565–572.
104. Jaillon P, Weissenburger J, Biour M, et al. Beta- and alpha-adrenoceptor antagonism by medroxalol in healthy volunteers: relationship to dose and plasma concentration. *J Cardiovasc Pharmacol* 1982; 4:705–713.
105. Matsunaga K, Nakamura K, Ueda M. Intrinsic beta-sympathomimetic activity of dilevalol, R,R-isomer of labetalol. *J Pharmacobiodyn* 1985; 8:785–787.
106. Baum T, Sybertz EJ. Antihypertensive actions of an isomer of labetalol and other vasodilator beta-adrenoceptor blockers. *Federation Proceed* 1983; 42:176–181.
107. Watkins RW, Sybertz EJ, Antonellis A, Pula K, Rivelli M. Effects of the antihypertensive dilevalol on large artery compliance in anesthetized dogs. *J Cardiovasc Pharmacol* 1987; 10(Suppl 11):S58–S63.
108. Thulesius O, Gjores JE, Berlin E. Vasodilating properties of beta-adrenoceptor blockers with intrinsic sympathomimetic activity. *Br J Clin Pharmacol* 1982; 13:229S–230S.
109. Daul A, Wang XL, Borchard U, Bock KD, Brodde O-E. Differential changes in lymphocyte b2-adrenoceptor density by beta-blocker administration: role of intrinsic sympathomimetic activity. *J Cardiovasc Pharmacol* 1986; 8(Suppl 4):S93–S96.
110. Prichard BNC, Owens CW1. Beta-adrenoceptor blocking drugs. [In] Doyle AE (Ed.) *Handbook of Hypertension 11. Clinical Pharmacology of Antihypertensive Drugs*. Amsterdam: Elsevier Science Publishers. 1988 pp. 187–243.
111. Buhler FR, Burkart F, Lutold BE, Kung M, Marbet G, Pfisterer M. Antihypertensive beta-blocking action as related to renin and age: a pharmacologic tool to identify pathogenic mechanisms in essential hypertension. *Am J Cardiol* 1975; 36:653–669.
112. Hollifield JW, Sherman K, Vander Zwaag R, Shand DG. Proposed mechanisms of propranolol's antihypertensive effect in essential hypertension. *New Engl J Med* 1976; 295(2):68–73.
113. Leonetti G, Mayer G, Morganti A, et al. Hypotensive and renin suppressing activities of propranolol in hypertensive patients. *Clin Sci Mol Med* 1975; 48:491–499.
114. Morganti AA, Terzoli L, Sala C, Bianchini C, Leonetti G, Zanchetti AS. Interactions between diuretics and propranolol in treatment of arterial hypertension. *Cardiovasc Med* 1979; 4:43–52.
115. Zanchetti A, Leonetti G, Terzoli L, Sala C. Beta blockers and renin. *Drugs (Symposium on beta blockers in the 1980's)* 1983; 25(Suppl 2):58–63.
116. Staessen J, Fagard R, Lijnen P, Verschueren LJ, Amery A. Double-blind comparison between propranolol and bendroflumethiazide in captopril-treated resistant hypertensive patients. *Am Heart J* 1983; 106(2):321–328.