POSSIBLE SIGNIFICANCE OF THE PHARMACOLOGICAL DIFFERENTIATION OF β -BLOCKERS FOR THERAPY OF HYPERTENSION

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1 Cardioselective and non-selective β -blockers affect to a different degree several aspects of the circulatory homeostasis. The evidence available in this regard has been evaluated and the possible clinical importance of these differences has been discussed.

2 Venous return is partly regulated by β -receptors (possibly of the β_2 type) in the venous resistance vessels. Differences in blockade of venous return by the two classes of β -blockers may, therefore, influence the degree of increase in left ventricular size, left ventricular end diastolic BPs and stroke volume during β -blockade.

3 At the first part of the dose-response curve, non-selective β -blockers seem to block more effectively renin release than cardioselective β -blockers.

4 The direction and the extent to which β -blockers 'directly' affect total peripheral resistance (TPR), is determined by the resultant of the degree of decrease in TPR by blockade of renin release and the extent of the increase in TPR by blockade of the β_2 -receptors in the arteriolar wall.

5 The clinical relevance of these differences could be that — especially in the low doses range — non-selective β -blockers may be more 'safe' in patients with compromised cardiac function and may be more appropriate for the therapy of high renin hypertension than cardioselective blockers, whereas the latter may be more appropriate for the majority of hypertensive patients who have low-to normal renin hypertension.

Introduction

Two different β -receptor populations mediate the peripheral cardiovascular actions of the sympathetic nervous systems. β_1 -receptors mainly mediate the positive inotropic and chronotropic actions on the heart, whereas the smooth muscle responses in the arterial and venous vessels and the bronchial tree mainly occur through β_2 -receptors (Lands *et al.*, 1967; Carlsson & Ablad, 1976).

The competitive antagonists of the agonistic action of the catecholamines on the β -receptors, the so-called β -adrenoceptor-blocking agents or β -blockers, have a varying affinity for the two receptor populations. The clinically relevant β -blockers can be divided into the non-selective blockers, affecting both the β_1 - and β_2 -receptors, and the cardioselective blockers, which mainly block β_1 -receptors and to a less extent β_2 -receptors. In patients with asthmatic lung disease these latter drugs have an obvious advantage over the non-selective blockers (for example, Decalmer *et al.*, 1978).

Regarding the therapeutic efficacy of the two classes of β -blockers in hypertension no major differences have yet been found. Theoretically, however, one can expect different cardiovascular

actions of the two classes (Leenen, 1976). Careful analysis of these differences could provide evidence for more specific indications for the two classes of β -blockers in different forms of hypertension. The two classes of β -blockers may have clinically relevant different actions on the following three aspects of the circulatory homeostasis: regulation of venous return; regulation of renin release; and regulation of total peripheral resistance. The influence of the two classes of β -blockers on these three aspects separately will first be evaluated and subsequently the possible clinical importance will be assessed.

β -blockers and venous return

The degree of constriction present in the venous capacitance bed as well as in the venous resistance vessels are important regulatory mechanisms of the venous return and thus of the cardiac output. Recent studies by Green (1975, 1977) using dogs have shown a significant decrease in the venous resistance and increase in venous return after treatment with isoprenaline and the reverse after β -blockade (Green

Figure 1 Changes in cardiac output (a), central venous BP (b), stroke volume (c) and central blood volume (d) induced by hypertonic saline loading before and during treatment with propranolol in ten essential hypertensive patients. (Data derived from Krauss *et al.*, 1972; by permission).

et al., 1975). According to Green, the β -receptors involved are located in the smooth muscle fibres present in the hepatic outflow vessels of the dog, which form a hepatic venous sphincter behind which a major part of the venous capacitance bed is located. The sphincter action of these smooth muscle fibres restricts venous drainage.

Krauss *et al.* (1972) have indicated that also in humans β -blockade can affect venous return. These authors assessed the cardiovascular effects of an intravenous load of hypertonic saline before and during treatment with propranolol in patients with essential hypertension. As shown in Figure 1, propranolol markedly blunted the increases in cardiac output and in stroke volume, but also in central blood volume and central venous BP. It is obvious that depression of myocardial contractility by propranolol cannot explain these findings, because increases in central venous BP and central blood volume should then have remained the same or probably even have become more pronounced. The authors concluded that the blunted cardiovascular response to salt loading during β -blockade was caused by impairment of venous return.

According to the classification of Lands *et al.* (1967), the β -receptor in the smooth muscle of the peripheral vasculature could be classified as β_2 . Although no extensive dose-response curves of different β -blockers are available to confirm that their effect on venous return is a β_2 -mediated action,

if this hypothesis is correct, cardioselective β -blockers should be less effective in decreasing venous return than non-selective β -blockers. Depression of myocardial contractility and heart rate with unopposed venous return will result in a larger increase in left ventricular size and/or end-diastolic (LVED) BP but the same or less decrease in ejection fraction than with opposed venous return. As cardiac output = heart rate $\times$ LVED volume $\times$ ejection fraction, for the same negative inotropic and chronotropic effect cardiac output should then decrease less with a cardioselective β -blocker than with a non-selective β -blocker due to a compensatory increase in stroke volume (= LVED volume $\times$ ejection fraction).

As yet, no within-patient comparisons of the two classes of β -blockers are available in this regard. In two different studies Lund-Johansen (1976a, b) assessed the effect of long-term treatment with the non-selective β -blocker timolol and the cardioselective β -blocker atenolol on the changes in BP and cardiac output during dynamic exercise of essential hypertensive men. The doses used were equipotent in suppressing exercise tachycardia, but differed in their effect on cardiac output and stroke volume: indeed, stroke volume was increased after treatment with atenolol, but showed a tendency to decline after treatment with timolol, resulting in a more significant decrease in cardiac output on timolol than on atenolol.

Figure 2 Relationship between initial PRA and percentage change in mean BP induced by saralasin in patients with different forms of hypertension before (open symbols) and after (solid symbols) marked sodium depletion ($r = -0.82$, $P < 0.01$, $n = 33$). (Data derived from Van Hoogdalem *et al.*, 1978; by permission.)

β -blockers and renin release

It is clear by now that β -blockers can induce a decrease in BP by more mechanisms than only by way of the induced decrease in renin release (for example, Hollifield *et al.*, 1976). However, this does not imply that the effect on the renin-angiotensin system is an unimportant mechanism for the hypotensive action of β -blockers. Several recent studies (Case *et al.*, 1976; Hoogdalem *et al.*, 1978) using competitive antagonists of angiotensin II, such as saralasin, have found a direct relationship between log plasma renin activity (PRA) and the degree of maintenance in BP by the renin-angiotensin system (Figure 2). This relationship implies that whenever (and probably only when) renin is elevated and a drug lowers it, this as such should be an hypotensive mechanism. However, other actions (hypotensive or

Figure 3 Effect of propranolol and saralasin on changes in BP induced by urethane (1.25 g/kg intraperitoneally) anaesthesia in rats. Values represent means $\pm$ s.e.m. of five to seven rats (data derived from Leenen & Provoost, in preparation). *a*: Δ , $t = -5$, 0.9% saline; $t = +60$, saralasin 5 mg/kg s.c. $\bullet$, $t = -5$, saralasin 5 mg/kg s.c.; $t = +60$, saralasin 5 mg/kg s.c. *b*: Δ , 0.9% saline; $\square$, propranolol 0.5 mg/kg s.c. at $t = 0$; $\circ$, propranolol 2.5 mg/kg s.c. at $t = 0$.

even hypertensive) of β -blockers could obscure this relationship. In this regard, one of our own studies in rats is quite relevant: propranolol decreased dose-dependently the urethane-induced increase in PRA in rats (Table 1). This blockade was associated with only a minor decrease in BP, whereas saralasin induced a marked hypotensive response (Figure 3). These data indicate that during urethane anaesthesia propranolol activates an hypotensive mechanism (the decrease in PRA) but at the same time also an hypertensive mechanism, keeping BP at about normal levels during the anaesthesia.

In humans β -blockers have been shown to be quite effective in decreasing renin release in most high-renin and normal renin states. Studies in normal volunteers have shown that propranolol prevents the

Table 1 Effect of propranolol on the increase in PRA induced by urethane anaesthesia in rats

Pretreatment (s.c.) ($t = -30$)	Anaesthetic ($t = 0$)	PRA (Pg A1/ml/h) (+5 min)	PRA (Pg A1/ml/h) (+15 min)
Saline 0.9%	Saline 0.9%	8.9 ± 0.9	9.2 ± 2.5
Propranolol 0.5 mg/kg	Saline 0.9%		7.4 ± 0.9
Propranolol 2.5 mg/kg	Saline 0.9%		6.3 ± 1.3
Saline	Urethane	38.0 ± 4.7	54.2 ± 5.7
Propranolol 0.5 mg/kg	Urethane	16.7 ± 3.3	32.3 ± 2.8
Propranolol 2.5 mg/kg	Urethane	10.4 ± 3.7	13.4 ± 2.3

Figure 4 *a*, Serial changes in PRA induced by intravenous infusion of isoprenaline (left) and methoxamine (right). *b*, Serial changes in PRA after intravenous infusion of propranolol and subsequent administration of isoproterenol or methoxamine. Values represent mean changes $\pm$ s.e.m. of five normal men. (Data derived from Leenen *et al.*, 1975; by permission.)

increase in PRA not only in response to isoprenaline but also to methoxamine (Figure 4). These findings suggest that a β -receptor is involved in the final common pathway of renin release by the juxtaglomerular cells. Most available evidence indicates that the β -receptor involved is probably a β_2 -receptor (see Reid *et al.*, 1978). In a study by Esler (1974) in hypertensive patients practolol 20 mg intravenously did not affect the response of PRA to graded doses of isoprenaline, but did clearly inhibit the increase in pulse rate. In contrast, propranolol 20 mg four times daily for one day and for 2 weeks shifted the dose-response curve of isoprenaline as least as markedly to the right for PRA as for heart rate (Figure 5). However, as usual, dose-response curves assess more accurately the differences between non-selective and cardioselective β -blockers in affecting renin release. Johns & Singer (1974) have shown that atenolol is five times less effective than propranolol in blocking the renin-releasing effects of renal nerve stimulation in cats. Studies in hypertensive patients have shown that at rather low plasma levels propranolol already maximally suppresses PRA, whereas higher concentrations are needed to lower heart rate (Velasco *et al.*, 1974; Zweifler & Esler, 1977). Cardioselective β -blockers behave in the opposite way: most of the hypotensive

action (Figure 6) as well as the blocking effect on exercise tachycardia of atenolol are present at a dose of about 200 mg (Amery *et al.*, 1976; de Plaen *et al.*, 1976). In these hypertensive patients on chronic chlorthalidone therapy, however, this dose of atenolol affected PRA only to a minor degree, and higher doses were needed to obtain more significant decreases in PRA (Figure 7).

These findings suggest that due to the differences in affinity to β_2 -receptors non-selective β -blockers are more potent in suppressing renin release than the cardioselective β -blockers. However, except for full dose-response curves of isoprenaline or endogenously determined high-renin states, this difference probably only becomes apparent at low doses of the two classes of β -blockers.

β -blockers and total peripheral resistance (TPR)

In the context of this paper the importance of differences between β -blockers in direct peripheral arterial β_2 -receptor blockade will be emphasized. Possible differences in the effect on TPR mediated by way of actions within the CNS or the peripheral sympathetic nervous system, or by way of baroreceptors are disregarded.

Figure 5 Effect of propranolol on isoprenaline-induced changes in PRA, BP and heart rate in borderline hypertensive patients. Values represent means $\pm$ s.e.m. ($n=6$). (Data derived from Leenen, Boer and Dorhout Mees in preparation.) Δ , Study 1: 0.9% saline; $\bullet$, study 2: isoproterenol; $\circ$, study 3: propranolol 20 mg four times daily for 1 day; $\circ$ ----- $\circ$, for 2 weeks.

Several studies in humans have shown that β -blockade by propranolol changes the decrease in diastolic BP after administration of adrenaline into a significant increase, without affecting the response to noradrenaline (Harris *et al.*, 1966; Vlachakis *et al.*, 1977). Cardioselective β -blockers such as metoprolol and practolol seem to be less active in reversing the

response of the diastolic BP to adrenaline (Johnsson, 1975). No dose-response curves have yet been published for the two classes of β -blockers.

Based on these pharmacological studies, one could theoretically expect different responses of the diastolic BP to the two classes of β -blockers, especially during increased sympathetic drive resulting in an increase in both plasma noradrenaline and adrenaline levels. However, the resulting effect of peripheral vascular β_2 -receptor blockade on TPR depends on the interaction of several mechanisms:

(1) The degree of maintenance of BP by the vasoconstrictor activity of the renin-angiotensin system determines to what extent the decrease in renin release after β -blockade would result in a decrease in TPR.

(2) Although stimulation of the β_2 -receptors in the arteriolar wall by intravenous isoprenaline results in a dose-dependent decrease in diastolic BP both in normotensive and hypertensive man by at least 20–30 mmHg (Figure 5; Esler, 1974; Leenen *et al.*, 1978), the relative importance of this vasodilatory mechanism in determining TPR both at rest and especially during increased sympathetic drive has not yet been assessed in hypertensive patients.

(3) Administration of a β -blocker also affects the response of the sympathetic nervous system to a given stimulus. Both non-selective and cardioselective β -blockers potentiate the increase in plasma noradrenaline during bicycle exercise, but only non-selective β -blockers potentiate the plasma adrenaline response (Irving *et al.*, 1974); Hansson, 1976; Philipp *et al.*, 1977). The plasma noradrenaline response to insulin-induced hypoglycaemia in non-diabetic patients was not affected by β -blockers, whereas the non-selective β -blocker penbutolol diminished and the cardioselective β -blocker metoprolol potentiated the plasma adrenaline response (Hansson, 1976). It is not known to what extent these different responses of plasma adrenaline reflect effects of peripheral or of central β_2 -receptor blockade.

Even without taking into account possible differences between the two classes of β -blockers in their effect on the baroreceptor response to a decrease in cardiac output or in their capacity to induce TPR by way of actions within the central or peripheral nervous system, it seems obvious that the role of the above mentioned mechanisms in determining the response of the TPR (evident as changes in the diastolic BP) in different forms of hypertension, using only the dose-response curves of the two classes of β -blockers, is not simple to predict. No extensive dose-response curves have been published in this regard. Most within-patient comparisons have been carried out using patients with moderate hypertension, often without concomitant therapy and thus mainly with low or

Figure 6 Antihypertensive effect of increasing doses of atenolol in patients with essential hypertension using chlorthalidone 50 mg daily. Values represent means $\pm$ s.e.m. of six patients. (Data derived from Teeuw *et al.*, 1978; by permission.) O, Standing; ●, lying.

Figure 7 Effect of increasing doses of atenolol on PRA in patients with essential hypertension using chlorthalidone 50 mg daily. Values represent means $\pm$ s.e.m. of six patients. (Data derived from Teeuw *et al.*, 1979; with permission.) * $P < 0.05$; ** $P < 0.01$. Atenolol was administered orally at 09⁰⁰ and 21⁰⁰. Blood samples were taken at 08⁰⁰ recumbent and 08³⁰, 10⁰⁰, 11⁰⁰ and 15⁰⁰ standing on the last day of each 3-d period.

normal PRAs. In such patients cardioselective β -blockers such as metoprolol and atenolol seem to be more effective in decreasing basal diastolic BP than non-selective β -blockers such as propranolol or oxprenolol (Sjöberg, 1978; Turner *et al.*, 1978; Wilcox, 1978). After long-term treatment with the non-selective β -blocker timolol and the cardioselective β -blocker atenolol, Lund-Johansen (1976a, b) observed that in such patients at rest and during dynamic exercise diastolic BP decreased slightly more on atenolol than on timolol and cardiac

output decreased more on timolol than atenolol, whereas — compared with the initial value — TPR increased clearly on timolol but not on atenolol.

In a double-blind, cross-over study, we have assessed the effect of placebo and two doses of propranolol and atenolol on the changes in systolic and diastolic BPs during bicycle exercise until exhaustion in six patients with mild hypertension. As shown in Figure 8, both β -blockers were effective to the same degree in decreasing systolic BP; atenolol was slightly (about 5 mmHg) more effective in

Figure 8 Effect of placebo, propranolol and atenolol on BP at rest and during bicycle exercise until exhaustion in mild hypertensive men. Values represent means $\pm$ s.e.m. ($n=6$). (Data derived from Leenen, Loenen, Zonderland and Maas, in preparation). X, placebo; ■, propranolol 40 mg three times daily; □, propranolol 80 mg three times daily; ●, atenolol 50 mg three times daily; ○, atenolol 100 mg three times daily for 1 week ($n=6$).

decreasing diastolic BP than propranolol, both at rest and during exercise. This difference was mainly related to one patient, in which both doses of propranolol induced a small pressor response, and atenolol an hypotensive response of the diastolic BP (Figure 9). The difference did not become more pronounced during exercise. Any exaggerated sympathetic pressor response after treatment with propranolol as a result of greater peripheral arterial β_2 -blockade compared with atenolol, seems to be

completely overcome by the vasodilatation induced by the metabolic products of the exercising muscles.

Nyberg (1977) assessed the effect of chronic therapy with propranolol and metoprolol on the BP response to isometric exercise (sustained handgrip) in hypertensive patients: metoprolol more effectively attenuated the increase in diastolic BP to handgrip than did propranolol. Nyberg related the difference of 10 mmHg to the vascular β_2 -receptors. In another study (Nyberg *et al.*, 1977) the BP changes induced by

Figure 9 Effect of placebo, propranolol and atenolol on BP at rest and during bicycle exercise until exhaustion in a mild hypertensive patient (data derived from Leenen, Loenen, Zonderland and Maas, in preparation). Heart rate (beats/min) (basal/maximal): X, placebo (92/180); ■, propranolol 40 mg three times daily (75/135); □, propranolol 80 mg three times daily (68/125); ●, atenolol 50 mg three times daily (58/116); ○, atenolol 100 mg three times daily for 1 week (63/124).

mild mental stress (mental arithmetic) were neither attenuated nor enhanced by chronic treatment with metoprolol or propranolol. With more severe hypertensive patients, Guazzi *et al.* (1976) have observed a significant decrease in the BP response to mental arithmetic after chronic treatment with propranolol.

In normal men insulin-induced hypoglycaemia results in a clear decrease in diastolic BP; after treatment with propranolol 10 mg intravenously, however, an increase by about 20 mmHg was observed (Lloyd-Mostyn & Oram, 1975). After chronic treatment with metoprolol in hypertensive patients, insulin-induced hypoglycaemia resulted in an initial increase in only the systolic BP followed by a decrease in both systolic and diastolic BPs (Hansson, 1976). As yet, no within-patient comparisons of dose-response curves of a non-selective and cardioselective β -blocker have been reported; also no data are available regarding the BP responses to hypoglycaemic attacks with and without β -blockers in (hypertensive) diabetics with impaired sympathetic responses.

In conclusion it seems that there is no evidence yet that non-selective and cardioselective β -blockers induce markedly different diastolic BP responses during acute forms of stress (except possibly during hypoglycaemic attacks, prolonged isometric exercise or more severe mental stress). Differences in the effect on basal diastolic BP and TPR may depend on the form of hypertension and/or concomitant therapy.

Possible clinical implications

Assuming that the effects of β -blockers on cardiac output and on renin release are two major determinants of the hypotensive activity of β -blockers, one can hypothesize specific indications for the two classes of β -blockers in different forms of hypertension.

For the same cardiac effects, a non-selective β -blocker may, possibly because of its greater inhibitory action on venous return, induce a smaller increase in LVED volume and LVED pressure than a cardioselective β -blocker. In this regard it is important to stress that the more stiff the left ventricular muscle has become (due to hypertrophy and/or fibrosis from coronary heart disease) the more LVED pressure will increase for a given increase in LVED volume. Therefore, for the same decrease in BP a hypertensive patient with compromised cardiac performance may show less further cardiac impairment (or more improvement) in terms of LVED pressure and volume when using a non-selective β -blocker instead of a cardioselective β -blocker.

Myocardial oxygen requirements are mainly determined by wall tension during systole, the duration of the systolic ejection period and heart rate. Wall tension depends on $(P \times r)/2h$, where P is systolic intraventricular BP, r is ventricular radius, h is wall thickness and r relates to ventricular volume (V) as $V = (4\pi r^3)/3$. Accordingly, any differences in the ventricular volume after using the two classes of β -blockers due to a different influence on venous return will affect r , wall tension and thus myocardial oxygen requirements to a much lesser extent. In this regard, for the same decrease in systolic BP and heart rate a non-selective β -blocker may have a slight advantage over a cardioselective β -blocker in a hypertensive patient with angina pectoris.

In low-renin hypertension (and to some extent also in normal renin hypertension) the role of the renin-angiotensin system in the maintenance of the elevated BP can be assumed to be very limited. The hypotensive action of β -blockers in this form of hypertension may depend therefore mainly on the decrease in cardiac output (disregarding other possible hypotensive mechanisms such as resetting of baroreceptors, and so on). In this form of hypertension peripheral arterial β_2 -receptor blockade has the greatest chance of acting as a pressor mechanism, because it will be less offset by a decrease in PRA. Therefore, in low- or normal renin hypertension (the case in the great majority of the hypertensive patients), a cardioselective β -blocker seems at the lowest dose to have full hypotensive activity with the least β_2 -receptor blockade.

A renin-dependent hypertension is present in only a small percentage of the whole untreated population suffering from hypertension, mainly in patients with more severe forms of hypertension or renovascular hypertension. However, in diuretic- and/or vasodilator-treated hypertension the elevated BP can become largely dependent on the renin-angiotensin system in many patients (for example, Pettinger *et al.* 1973; Gavras *et al.*, 1977; Hoogdalem *et al.*, 1978). Blockade of renin release in these groups of patients offers a major antihypertensive mechanism. The component of the renin release that can be blocked by β -blockers will be blocked by low to moderate doses of non-selective β -blockers, whereas relatively higher doses would be needed when using cardioselective β -blockers. During vasodilator therapy there could be one more reason to use a non-selective β -blocker instead of a cardioselective one. The commonly used vasodilators such as hydralazine, diazoxide and minoxidil induce marked cardiac stimulation, resulting not only in a tachycardia (for several reasons a disadvantage) but also in an increase in cardiac output that offsets the decrease in BP. After administration of a veno-arterial vasodilator (for example, sodium nitroprusside) the venous return will decrease due to an increase in the compliance of

the venous capacitance vessels, and thus the increase in cardiac output will be attenuated. For the same degree of blockade of the increased sympathetic drive on the heart induced by arterial vasodilatation alone, compared with a cardioselective β -blocker, a non-selective β -blocker may have the additional advantage of decreasing venous return. However, even with a non-selective β -blocker cardiac output can remain elevated due to an increase in stroke volume (Klotman *et al.*, 1977), although it could be possible that higher doses would have been more effective.

In conclusions, it seems possible that — especially

at the lower doses — the cardiovascular actions of cardioselective and non-selective β -blockers differ to such an extent that a further improvement in the pharmacotherapy of the different forms of hypertension could be obtained by taking these differences into account. The data suggest that the Lands *et al.* (1967) classification to β_1 - and β_2 -receptors may be unduly restrictive. We may envisage a whole spectrum of β -receptors of different properties, with differing responses to individual drugs corresponding to physiochemical variations in access or stereometric differences of response to drugs.

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Discussion

DR DAVIS (London): A comment about Dr Leenen's paper. He rather threw away the idea that the β -receptor control of renin release is by a β_2 receptor. There is a good deal of evidence which I will briefly mention that suggests it is a β_1 receptor. There are three approaches that I am aware of. A number of groups has found, including myself when I was working with John Laragh in New York, that atenolol will in fact block isoprenaline-provoked renin release in man very effectively indeed. Secondly, we studied across the dose range of propranolol, from 5-40 mg in single doses, and found very similar blockade curves. The third approach that we used was to compare salbutamol and isoprenaline. Salbutamol is a selective β_2 agonist and does not seem to release renin in man.

DR LEENEN (Utrecht): We found a decrease in renin release with atenolol too. However, when you look at the different cardiovascular actions of atenolol in our study as well as of others (for example, Amery *et al.*, 1976), you see a marked blockade of exercise-heart rate and a maximal hypo-

tensive effect at doses of 100-200 mg. At these doses you still get only a small decrease in PRA and you have to go to higher doses before you see a marked decrease in PRA. In comparison, propranolol lowers PRA at low doses, and higher doses are necessary for blockade of exercise-heart rate. Also, Johns & Singer (1974) have shown that you can block the effect of renal nerve stimulation on renin release in cats more effectively with propranolol in low doses than with atenolol. Atenolol is not a pure β_1 -blocking drug, and especially at the higher doses of 400-600 mg you may expect clear β_2 -blocking activity. Thus, when you see an effect of atenolol on PRA, this does not necessarily indicate that a β_1 -receptor is involved. Taken together with the studies on practolol, in my opinion, β -blockers decrease renin release mainly by influencing β_2 -receptors.

DR WILHELMSSEN (Goteborg): You didn't mention anything about the effect on peripheral resistance of β_1 -blocking drugs and β_2 -blocking drugs compared with selective drugs. I think that the effect on the peripheral resistance is markedly different