Br. J. clin. Pharmac. (1984), **18**, 573–579

Unchanged peripheral sympathetic activity following withdrawal of chronic metoprolol treatment. A study of noradrenaline concentrations and kinetics in plasma

G. OLSSON[1], MAUD DALESKOG[2], P. HJEMDAHL[2,3] & NINA REHNQVIST[1]
[1]Department of Medicine, Danderyd Hospital, S-182 88 Danderyd, Sweden, [2]Department of Pharmacology, Karolinska Institutet, S-104 01 Stockholm, Sweden and [3]Department of Clinical Pharmacology, Karolinska Hospital, S-104 01 Stockholm, Sweden

1 Noradrenaline plasma kinetics were assessed in 17 male patients, who had been treated with metoprolol 100–200 mg daily ($n = 8$) or placebo for 3 years after an acute myocardial infarction, before and 1 week after gradual withdrawal (during 1 week) of the study treatment. Endogenous noradrenaline concentrations in plasma were measured by high performance liquid chromatography. Noradrenaline spillover rate, plasma clearance and the $t_{1/2}$ for the rapid removal from plasma were determined by radio-tracer methodology.

2 During treatment the plasma noradrenaline concentrations and noradrenaline plasma kinetic variables were similar in the two groups.

3 Venous plasma noradrenaline concentrations were more closely correlated to the spillover rates of noradrenaline to plasma than to the clearance of noradrenaline from plasma, but the spillover rates were correlated to the clearance rates.

4 Following the withdrawal of metoprolol noradrenaline clearance from plasma increased slightly (by 18 ± 5%, $P < 0.05$), but the plasma concentrations and spillover rates of noradrenaline were unchanged. In the placebo group withdrawal did not result in any significant changes.

5 Our results indicate that a generalised increase in sympathetic nerve activity is not the cause of so-called rebound phenomena following withdrawal of chronic β-adrenoceptor blockade.

Keywords noradrenaline kinetics chronic β-adrenoceptor blockade metoprolol

Introduction

β-adrenoceptor antagonists are widely used in the treatment of various cardiovascular disorders. Although the efficacy of these drugs is undisputed, their exact mechanisms of action and their influence on sympatho-adrenal activity are not entirely understood. Plasma levels of noradrenaline have frequently been used to assess sympathetic outflow, as reviewed by e.g. Goldstein (1981) and Man In't Veld & Schalekamp (1982). β-adrenoceptor blocking agents have been found to elevate plasma noradrenaline levels at rest in some studies (Rahn *et al.*, 1978; Fischer Hansen *et al.*, 1978; Morganti *et al.*, 1979; Lijnen *et al.*, 1979; Vlachakis, 1979), whereas other studies have shown no such effect (de Leeuw *et al.*, 1977; Watson *et al.*, 1980; Vandongen *et al.*, 1981; Planz & Planz 1981; Olsson *et al.*, 1984). However, caution must be exercised when noradrenaline concentrations in peripheral

venous plasma are used to assess sympathetic nerve activity, since these concentrations to a large extent represent noradrenaline released from sympathetic nerves supplying skeletal muscle and sympathetic activity in other organs seems to be underestimated (Folkow *et al.*, 1983; Hjemdahl *et al.*, 1984). Furthermore, the concentrations of noradrenaline are determined both by the release of the amine into plasma and its clearance from plasma. During treatment with propranolol (Esler *et al.*, 1981) and oxprenolol (Esler, 1982) the clearance of noradrenaline from plasma is reduced, which may explain why β-adrenoceptor blockade frequently is found to elevate plasma noradrenaline concentrations. We have previously shown significant and transient increases of resting heart rates and increased ischaemic symptoms following the withdrawal of chronic metoprolol treatment (Olsson *et al.*, 1984). In that study plasma noradrenaline levels were unchanged at rest and reduced during exercise following withdrawal (Olsson *et al.*, 1984). However, it has been suggested that withdrawal of β-adrenoceptor blockade may be associated with increased sympathetic activity (Nattel *et al.*, 1979). The primary aim of this study was to clarify whether sympathetic activity is increased in the withdrawal phase, and thus if increased noradrenaline release to plasma is masked by β-adrenoceptor blockade induced changes in noradrenaline plasma kinetics. Thus, we have studied noradrenaline kinetics in plasma during and after withdrawal of chronic metoprolol treatment.

Methods

Patients

Seventeen randomly chosen patients from the Stockholm metoprolol postinfarction study (Olsson *et al.*, 1981) were investigated. The patients were all non-smoking men who had been on double-blind treatment with metoprolol 100–200 mg daily ($n = 8$) or placebo ($n = 9$) for 3 years following a myocardial infarction. None had suffered a reinfarction during the year preceding the investigations. The mean ages of the patients in the placebo and metoprolol groups were 60 ± 9 and 61 ± 4 years, respectively. Three patients were taking digoxin and five were taking diuretics in the placebo group. The corresponding figures were one and four in the metoprolol group.

Procedures

Noradrenaline plasma kinetics were studied while the patients were on the full dose of metoprolol or placebo (= day 0). Treatment was then gradually withdrawn during 1 week and the study was repeated on day 14. We could not repeat the study after a longer wash-out period, when absolutely basal conditions were established, as ethical doubts were raised against a third exposure of the patients to radioactive isotopes. The study was performed in a double-blind fashion. All medication, except the study drug, was kept constant. The tests were performed at the same time of day for each individual patient. The subjects were in the supine position in a quiet single-bedroom. The patients were asked to avoid coffee and tea during 12 h prior to investigations. All patients gave their informed consent to participate in the study, which was approved by the Ethical Committee at the Karolinska Hospital and the local Isotope Committee.

Technique for determination of noradrenaline kinetics

[^{3}H]-(−)-noradrenaline with a specific activity of 30–45 Ci/mmol (TRK584, The Radiochemical Centre, Amersham) and a radiochemical purity between 96 and 98% was prepared for administration to humans. Radiochemical purity, sterility and freedom from pyrogens were checked in each preparation of [^{3}H]-noradrenaline.

The radio-tracer infusion studies were carried out according to the procedure of Esler and coworkers (1979). Following an intravenous bolus injection of 15 $\mu Ci/m^2$, a constant infusion of 0.35 $\mu Ci/m^2 \times min^{-1}$ was administered during 90 min. This corresponds to 7.8–11.7 $pmol/m^2 \times min^{-1}$ (1.3–2.0 $ng/m^2 \times min^{-1}$) of (−)-noradrenaline, which is a physiologically inactive dose. Venous blood was sampled from an indwelling cannula in an antecubital vein on the contralateral arm after 70, 80 and 90 min of infusion and 1, 2, 3, 6, 9, 15, 20, 30 and 40 min after cessation of infusion. The blood samples (10 ml) were collected in ice-cooled plastic tubes containing EGTA and reduced glutathione (final concentrations 2.5 mmol/l and 2.0 mmol/l, respectively). After centrifugation for 10 min at 4°C the plasma was removed and stored at −70°C until analyzed.

Labelled and unlabelled noradrenaline were extracted from plasma on to alumina, which was carefully rinsed before eluting the catechols in 0.1 M perchloric acid. Aliquots of the same eluate were used to determine endogenous noradrenaline concentrations by high performance cation exchange liquid chromatography with electrochemical detection (Hjemdahl *et*

al., 1979) and to measure [^{3}H]-noradrenaline (i.e. alumina-extracted radioactivity), which was determined in a Packard 300C Liquid Scintillation Counter using the scintillation cocktail Pico Fluor 30 (Packard Instrument Co) and conventional methods of compensation for quenching. Since the same alumina eluate was used to assay endogenous and [^{3}H]-noradrenaline, corrections for incomplete recovery in the alumina extraction step could be made for both compounds by the internal standard (α-methyldopamine). The alumina extracted radioactivity represents virtually only [^{3}H]-noradrenaline with negligible amounts of dihydroxylated ^{3}H-labelled noradrenaline metabolites (Esler *et al.*, 1979; Esler, personal communication). The inter- and intra-assay coefficients of variation for measurements of endogenous noradrenaline (at plasma concentrations of 1–2 nmol/l) are 2–3% in our laboratory.

The spillover rate of noradrenaline (NA) to plasma and the clearance of [^{3}H]-noradrenaline from plasma at steady state were calculated by the following equations (Esler *et al.*, 1979):

$$\text{NA spillover rate} = \frac{\text{[}^3\text{H]-NA infusion rate}}{\text{Plasma NA specific activity}}$$

$$\text{NA plasma clearance} = \frac{\text{[}^3\text{H]-NA infusion rate}}{\text{Plasma [}^3\text{H]-NA concentration}}$$

$t_{½}$ was calculated from the slope of rapid removal of [^{3}H]-noradrenaline following the cessation of infusion using a computerized pharmacokinetic analysis (Statistical Analysis Systems, SAS Institute Inc., N.C., USA).

Statistical analysis

Student's *t*-test for unpaired samples was used for comparisons between the two groups. When comparing results from the two different investigations within a group Student's paired *t*-test was used. Analysis of variance was used in the comparison of the two groups with regard to intra-group changes between the two different investigations. Sequential multiple linear regression analysis and analysis of variance were used to determine and compare correlations between the different parameters of noradrenaline kinetics. A *P*-value < 0.05 was regarded as indicative of a significant difference. In the text mean values and standard errors of the mean (s.e. mean) are given.

Results

Resting heart rate did not change significantly in the placebo group (64 ± 3 beats/min before and 68 ± 4 beats/min after withdrawal) whereas a significant increase from 55 ± 2 beats/min on day 0 to 66 ± 3 beats/min ($P < 0.01$) was seen after the withdrawal of metoprolol. Blood pressures did not change in either group (136 ± 7/84 ± 2 mm Hg *vs* 131 ± 5/82 ± 4 mm Hg and 128 ± 4/78 ± 2 mm Hg *vs* 136 ± 6/84 ± 3 mm Hg in the placebo and metoprolol groups, respectively).

Data on the plasma concentrations of noradrenaline, spillover rates to plasma, noradrenaline clearance and $t_{½}$ are shown in Table 1. Endogenous venous plasma noradrenaline concentrations at rest were similar in connection with the two investigations in both groups and there were no significant differences between the two groups on either occasion. Similarly, no significant changes in noradrenaline spillover rate to plasma or in $t_{½}$ were found in either group and the two groups displayed similar values for these variables on both occasions. Values for $t_{½}$ were not obtained from one patient in each group due to difficulties with rapid blood sampling following the cessation of the [^{3}H]-noradrenaline infusion.

Table 1 Venous plasma NA concentrations, NA spillover rates to plasma, NA clearance from plasma and $t_{½}$ for the rapid removal of [^{3}H]-NA from plasma following cessation of infusion in the two study groups day 0 (on drug) and day 14 (off drug, i.e. 1 week after gradual withdrawal of the study treatment). For numbers see Table 2. * $P < 0.05$.

	Placebo group		*Metoprolol group*	
	On drug	*Off drug*	*On drug*	*Off drug*
Plasma NA (nmol/l)	2.27 ± 0.16	2.50 ± 0.18	2.82 ± 0.37	2.24 ± 0.37
NA spillover rate ($\mu g\ min^{-1}\ m^{-2}$)	0.59 ± 0.07	0.71 ± 0.10	0.68 ± 0.12	0.77 ± 0.23
NA clearance ($l\ min^{-1}\ m^{-2}$)	1.53 ± 0.13	1.64 ± 0.14	1.46 ± 0.21	1.72 ± 0.26*
$t_{½}$ (min)	2.14 ± 0.25	2.15 ± 0.30	2.11 ± 0.37	1.95 ± 0.35

The clearance of [^{3}H]-noradrenaline from plasma during infusion was constant in the placebo group. In the metoprolol group, on the other hand, a significant ($P < 0.05$ as estimated by Student's *t*-test) increase of the noradrenaline plasma clearance rate amounting to 18 ± 5% was found after withdrawal of treatment. However, analysis of variance revealed no significant difference with regard to withdrawal induced changes in noradrenaline concentrations between the two groups. Furthermore, no significant difference between the two groups was found on either occasion. The individual values for endogenous noradrenaline concentrations, spillover rates and noradrenaline clearance are shown in Figure 1.

Correlations between the different parameters of noradrenaline kinetics are shown in Table 2.

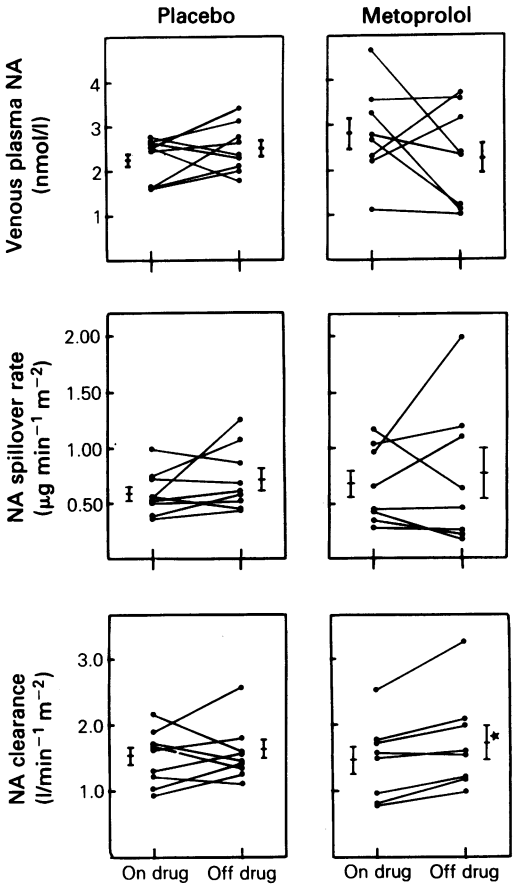

Figure 1 Noradrenaline concentrations in venous plasma (top), spillover rates (middle) and clearance rates (bottom) during resting conditions before and after withdrawal of placebo and metoprolol. Values for individual patients are shown. The mean values and s.e. mean are indicated by the vertical bars. * = $P < 0.05$.

Statistically significant correlations were found between noradrenaline spillover rates and clearance rates in both groups. Noradrenaline plasma concentrations and spillover rates tended to be correlated in both groups. In the metoprolol group there was a significant correlation between plasma concentrations and clearance rates for noradrenaline from plasma after the withdrawal of metoprolol. This correlation was not found during metoprolol treatment or in the placebo group.

The relationships between noradrenaline spillover rates and clearance rates, as well as noradrenaline spillover rates and venous plasma noradrenaline concentrations in the metoprolol group are shown in Figure 2. The former showed a slight but significant parallel shift of the curve ($P < 0.05$) after the withdrawal of metoprolol, due to the 18% increase in noradrenaline plasma clearance. A significant change in the slope of the relation between noradrenaline spillover rates and venous plasma concentrations ($P < 0.05$) following the withdrawal of metoprolol was also found (Figure 2). In the placebo group the positions and slopes of these regression lines were unchanged following the withdrawal.

The different parameters concerning noradrenaline plasma kinetics were also tested in a sequential multiple linear regression analysis in order to elucidate the relative degree of explanation offered by the various parameters determined (Table 3).

Discussion

In the present study, the plasma concentrations and spillover rates of noradrenaline to plasma and the $t_{1/2}$ for the rapid removal of noradrenaline from plasma were unchanged after the withdrawal of metoprolol treatment. The clearance of noradrenaline from plasma was slightly increased one week following gradual withdrawal of chronic metoprolol treatment, although analysis of variance revealed no significant difference when compared to the placebo group. In previous non-placebo controlled reports similar reductions of the clearance of plasma noradrenaline have been shown during treatment with propranolol (Esler *et al.*, 1981) and oxprenolol (Esler, 1982). The patients in the studies of Esler and co-workers (1981, 1982) were investigated in the reverse sequence as compared to our patients. The change in noradrenaline clearance from plasma observed by us following withdrawal of metoprolol therefore probably does not represent transient rebound phenomenon, but rather a return to

Table 2 Correlation matrix for variables concerned with NA kinetics in plasma in the placebo group (n = 9, except for $t_{½}$ when n = 8) and the metoprolol group (n = 8, except for $t_{½}$ when n = 7) before and after withdrawal of study treatment.

	Placebo group		*Metoprolol group*	
	On drug	*Off drug*	*On drug*	*Off drug*
NA *vs* SO	0.56	0.81**	0.65†	0.91**
NA *vs* CL	–0.08	0.47	–0.19	0.79*
NA *vs* $t_{½}$	–0.50	0.09	0.44	0.37
SO *vs* CL	0.77*	0.90***	0.61	0.97***
SO *vs* $t_{½}$	0.23	–0.16	0.03	0.59
CL *vs* $t_{½}$	0.67†	–0.23	0.61	0.60

SO = NA spillover rate to venous plasma; CL = clearance of [^{3}H]-NA from plasma; $t_{½}$ = half life for the rapid removal of [^{3}H]-NA from plasma upon cessation of [^{3}H]-NA infusion. †$P < 0.1$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

normal values. Neither of the two studies involving β-adrenoceptor antagonists lacking intrinsic sympathomimetic activity, i.e. propranolol (Esler, 1981) and metoprolol (present study), showed any significant changes in spillover rates or venous plasma concentrations of noradrenaline, indicating that peripheral sympathetic nerve activity at rest is not significantly altered by chronic β-adrenoceptor blockade.

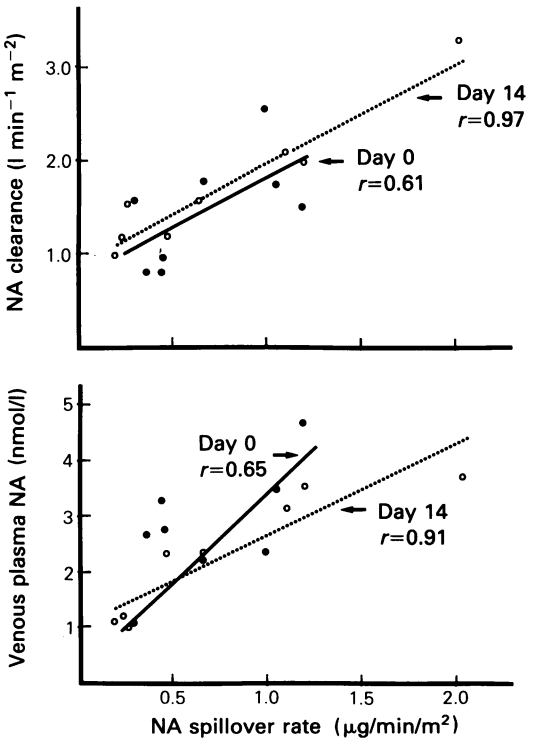

Figure 2 Correlations between noradrenaline spillover and clearance values (top) and venous plasma noradrenaline concentrations (bottom) in the metoprolol group while on treatment (= day 0, filled circles and solid line) and off treatment (= day 14, open circles and dotted line).

Results obtained by the sequential multiple linear regression analysis suggest that the clearance of noradrenaline from plasma is not the main determinant of plasma noradrenaline levels at rest. Thus, the spillover rates were more closely correlated to the plasma concentrations of noradrenaline than were the clearance rates. $t_{½}$ for the rapid removal of the infused [^{3}H]-noradrenaline contributed little to the 'explanation' of inter-individual variability of endogenous noradrenaline concentrations.

Noradrenaline spillover rates to and clearance rates from plasma were correlated. After metoprolol withdrawal the regression line for noradrenaline clearance *vs* spillover rate showed a significant shift. The parallelism of these regression lines (Figure 2) indicates that the metoprolol induced reduction of noradrenaline clearance from plasma is constant and independent of the spillover rate.

The relationship between noradrenaline spillover rates and venous plasma concentrations was altered by metoprolol treatment in such a way that the plasma concentrations of noradrenaline showed a steeper increase with increasing spillover rates of noradrenaline. This might explain why the plasma concentrations of noradrenaline may be unchanged at rest, but significantly increased in connection with exercise during chronic β-adrenoceptor blockade (Watson *et al.*, 1980; Planz & Planz, 1981; Olsson *et al.*, 1984). Similarly, metoprolol and propranolol administration elevates plasma levels of noradrenaline when the spillover rate is 'artificially' increased, such as during intravenous infusions of noradrenaline (Hjemdahl *et al.*, 1983). The latter study showed similar effects of the two β-adrenoceptor blockers on

Table 3 Explained variance of venous plasma NA levels in a sequential multiple linear regression analysis. Symbols etc. as in Table 2.

	Placebo group		*Metoprolol group*	
	On drug	*Off drug*	*On drug*	*Off drug*
NA *vs* SO	0.312	0.653	0.428	0.822
NA *vs* (SO + CL)	0.950	0.989	0.986	0.928
NA *vs* (SO + CL + $t_{½}$)	0.949	0.993	0.995	0.966

noradrenaline concentrations during intravenous infusions.

In a previous study we found reduced plasma noradrenaline concentrations during exercise 1 week after the complete withdrawal of chronic metoprolol treatment, the reduction being 48% at 100 W (Olsson *et al.*, 1984). Part of this reduction of noradrenaline concentrations in plasma may be explained by the change in clearance. However, the exact importance of variations in noradrenaline clearance during exercise cannot be evaluated, since so far only data concerning noradrenaline kinetics at rest have been reported. It is possible that reduced sympathetic nerve activity may have contributed to the findings, since there are indications that β-adrenoceptor sensitivity is increased after withdrawal of β-adrenoceptor blockade (Boudoulas *et al.*, 1977; Rangno *et al.*, 1982 a, b). This may result in a reduced need for sympathetic nerve activity during exercise. The present findings of unchanged plasma levels and spillover rates for noradrenaline were obtained during the period when patients have transient increases of heart rate at rest (Olsson *et al.*, 1984). Increased sensitivity to isoprenaline after withdrawal of β-adrenoceptor blockade has been demonstrated (Boudoulas *et al.*, 1977; Rangno *et al.*, 1982 a,b). Taken together, the results of these various studies support the concept of increased β-adrenoceptor sensitivity rather than increases in sympathetic nerve activity following withdrawal of chronic β-adrenoceptor blockade.

In conclusion, chronic metoprolol treatment reduces the clearance of noradrenaline from plasma slightly without changing the noradrenaline spillover rates or plasma concentrations at rest. Following withdrawal of treatment we observed a slight increase in noradrenaline clearance from plasma but no signs of altered noradrenaline release at rest indicative of any major change in peripheral sympathetic nerve activity. Our findings are compatible with increased β-adrenoceptor sensitivity as an explanation for the clinical and laboratory findings followed withdrawal of chronic treatment with β-adrenoceptor blockade. The kinetic determinants of noradrenaline concentrations in venous plasma seem to be (in order of importance): spillover rate and clearance, but probably not $t_{½}$ for the rapid removal of [^{3}H]-noradrenaline following the cessation of infusion.

This study was supported by grants from the National Association against Heart and Lung Diseases, the Swedish Medical Research Council (5930), AB Hässle (Mölndal, Sweden) and Roussel Laboratories Ltd (Stockholm, Sweden).

References

Boudoulas, J., Lewis, R. P., Kates, R. E. & Dalamangas, G. (1977). Hypersensitivity to adrenergic stimulation after propranolol withdrawal in normal subjects. *Ann. Intern. Med.*, **87**, 433–436.

de Leeuw, P. W., Falke, H. E., Kho, T. L., Vandongen, R., Wester, A. & Birkenhäger, W. H. (1977). Effects of beta-adrenergic blockade on diurnal variability of blood pressure and plasma noradrenaline levels. *Acta med. Scand.*, **202**, 389–392.

Esler, M. (1982). Assessment of sympathetic nervous function in humans from noradrenaline plasma kinetics. *Clin. Sci.*, **62**, 247–254.

Esler, M., Jackman, G., Bobik, A., Kelleher, D., Jennings, G., Leonard, P., Skews, H. & Korner, P. (1979). Determination of norepinephrine apparent release rates and clearance in humans. *Life Sci.*, **25**, 1461–1470.

Esler, M., Jackman, G., Leonard, P., Skews, H., Bobik, A. & Jennings, G. (1981). Effect of propranolol on noradrenaline kinetics in patients with essential hypertension. *Br. J. clin. Pharmac.*, **12**, 375–380.

Fischer Hansen, J., Hesse, B. & Christensen, N. J. (1978). Enhanced sympathetic nevous activity after intravenous propranolol in ischaemic heart disease: plasma noradrenaline splanchnic blood flow and mixed venous oxygen saturation at rest during exercise. *Eur. J. clin. Invest.*, **8**, 31–36.

Folkow, B., Di Bona, G. F., Hjemdahl, P., Thorén,

P. H. & Wallin, G. B. (1983). Measurements of plasma norepinephrine concentrations in human primary hypertension: A word of caution on their applicability for assessing neurogenic contributions. *Hypertension*, **5**, 399–402.

Goldstein, D. S. (1981). Plasma norepinephrine as an indicator of sympathetic neural activity in clinical cardiology. *Am. J. Cardiol.*, **48**, 1147–1154.

Hansson, B-G., Dymling, J-F., Manhem, P. & Hökfelt, B. (1977). Long term treatment of moderate hypertension with the $beta_1$-receptor blocking agent metoprolol. *Eur. J. clin. Pharmac.*, **11**, 247–254.

Hjemdahl, P., Daleskog, M. & Kahan, T. (1979). Determination of plasma catecholamines by high performance liquid chromatography with electrochemical detection: comparison with a radioenzymatic method. *Life Sci.*, **25**, 131–138.

Hjemdahl, P., Freyschuss, U., Juhlin-Dannfelt, A. & Linde, B. (1984). Differentiated sympathetic activation during mental stress. *Acta Physiol. Scand.*, Suppl. 527, 25–29.

Hjemdahl, P., Pollare, T., Gillberg, M. & Åkerstedt, T. (1983). Influence of beta-adrenoceptor blockade by metoprolol and propranolol on plasma concentrations and effects of noradrenaline and adrenaline during i.v. infusion. *Acta Physiol. Scand.* Suppl. 515, 45–53.

Lijnen, P. J., Amery, A. K., Fagard, R. H., Reybrouck, T. M., Moerman, E. J. & de Schaepdryver, A. F. (1979). The effects of beta-adrenoceptor blockade on renin, angiotensin, aldosterone and catecholamines at rest and during exercise. *Br. J. clin. Pharmac.*, **7**, 175–181.

Man In't Veld, A. J. & Schalekamp, M. A. D. H. (1982). How intrinsic sympathomimetic activity modulates the haemodynamic responses to beta-adrenoceptor antagonists, a clue to the nature of their antihypertensive mechanism. *Br. J. clin. Pharmac.*, **13**, 245S–257S.

Morganti, A., Pickering, T. G., Lopez-Ovejero, J. A. & Laragh, J. H. (1979). Contrasting effects of acute beta-blockade with propranolol on plasma catecholamines and renin in essential hypertension: a possible basis for the delayed antihypertensive response. *Am. Heart J.*, **98**, 490–494.

Nattel, S., Rangno, R. E. & van Loon, G. (1979). Mechanism of propranolol withdrawal phenomena. *Circulation*, **59**, 1158–1164.

Olsson, G., Hjemdahl, P. & Rehnqvist, N. (1984). Rebound phenomena following gradual withdrawal of chronic metoprolol treatment in patients with ischemic heart disease. *Am. Heart J.* (in press).

Olsson, G., Rehnqvist, N., Lundman, T. & Melcher, A. (1981). Metoprolol treatment after acute myocardial infarction: Effects on ventricular arrhythmias and exercise tests during 6 months. *Acta. med. Scand.*, **210**, 59–65.

Planz, G. & Planz, R. (1981). Dissociation between duration of plasma catecholamine and blood pressure responses to beta-adrenergic blockade in normotensive subjects during physical exercise. *Eur. J. clin. Pharmac.*, **19**, 83–88.

Rahn, K. H., Gierlichs, H. W., Planz, G., Planz, R., Schols, M. & Stephany, W. (1978). Studies on the effects of propranolol on plasma catecholamine levels in patients with essential hypertension. *Eur. J. clin. Invest.*, **8**, 143–148.

Rangno, R. E., Langlois, S. & Stewart, J. (1982). Cardiac hyper- and hyporesponsiveness after pindolol withdrawal. *Clin. Pharmac. Ther.*, **31**, 564–571.

Rangno, R. E., Langlois, S. & Lutterodt, A. (1982). Metoprolol withdrawal phenomenon: Mechanism and prevention. *Clin. Pharmac. Ther.*, **31**, 8–15.

Ross, P. J., Lewis, M. J., Sheridan, D. J. & Henderson, A. H. (1981). Adrenergic hypersensitivity after beta-blocker withdrawal. *Br. Heart J.*, **45**, 637–642.

Vandongen, R., Davidson, L., Beilin, L. J. & Barden, A. E. (1981). Effect of beta-adrenergic receptor blockade with propranolol on the response of plasma catecholamines and renin activity to upright tilting in normal subjects. *Br. J. clin. Pharmac.*, **12**, 369–374.

Vlachakis, N. D. (1979). Blood pressure variability and plasma catecholamines in man. Effect of propranolol therapy. *Biochem. Med.*, **21**, 253–261.

Watson, R. D. S., Eriksson, B-M., Hamilton, C. A., Reid, J. L., Stallard, T. J. & Littler, W. A. (1980). Effects of chronic beta-adrenoceptor antagonism on plasma catecholamines and blood pressure in hypertension. *J. cardiovasc. Pharmac.*, **2**, 725–738.

(Received February 22, 1984, accepted June 23, 1984)