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SYMPATHETIC AND PARASYMPATHETIC COMPONENTS OF REFLEX CARDIOSTIMULATION DURING VASODILATOR TREATMENT OF HYPERTENSION

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1 The alleged importance of cardiac β-adrenoceptors for the baroreceptor induced rise in cardiac output after acute vasodilatation was assessed in 41 patients with essential hypertension.

2 Diazoxide (300 mg i.v.) was given, to patients 1) when untreated ($n=29$), 2) during treatment with propranolol (320 mg/day), ($n=15$), or 3) during propranolol plus atropine (0.04 mg/kg), ($n=12$).

3 Diazoxide-induced reductions in arterial pressure during propranolol, either alone ($-23\pm3\%$) or combined with atropine ($-22\pm3\%$), were not significantly different from those without pretreatment ($-24\pm3\%$, mean $\pm$ s.e. mean.

4 The response of heart rate to diazoxide was somewhat diminished during propranolol ($+14\pm2$ with propranolol v $+21\pm3\%$ without propranolol, 15 paired observations, $P<0.001$).

5 Stroke volume rose more in response to diazoxide after pretreatment with propranolol ($+16\pm11$ with propranolol v $+2\pm5\%$ without propranolol, $P<0.001$) so that the response of cardiac output was not altered by β-adrenoceptor blockade ($+32\pm4$ with propranolol v $+24\pm9\%$ without propranolol, $P>0.05$).

6 The rise in cardiac output was markedly diminished by additional parasympathetic blockade ($+14\pm5\%$ with propranolol plus atropine, $n=12$, v $32\pm4\%$ with propranolol alone, $n=15$, $P<0.01$).

7 Increments in plasma noradrenaline were not significantly different in the three situations, indicating that baroreceptor sensitivity was not altered.

8 We conclude that the baroreflex induced rise in cardiac output during vasodilator treatment of hypertension depends on withdrawal of parasympathetic tone rather than sympathetic stimulation.

Introduction

The major haemodynamic abnormality in long-standing arterial hypertension, whatever its cause, is a raised vascular resistance. Vasodilator drugs will reverse this, but their blood pressure lowering effect is counteracted by a concomittant increase in cardiac output. This response is thought to be mediated through baroreflex-induced stimulation of cardiac β-adrenoceptors. It seems therefore logical to add a β-adrenoceptor blocking agent to vasodilator anti-hypertensive treatment (Frohlich, 1974, Gifford, 1974, Koch-Weser, 1974, 1976, Zacest, Gilmore & Koch-Weser, 1972). Indeed, combinations of this sort are now widely used. However, quantitative data in man on the importance of the β-adrenergic system for the reflex response of cardiac output to baroreceptor hypotension are lacking. Possibly, cardiac output is raised after vasodilatation not so much through sympathetic stimulation, but rather through withdrawal of parasympathetic tone.

We therefore studied the effects of acute vasodilatation on plasma noradrenaline, arterial pressure, heart rate and cardiac output in hypertensive subjects, (1) when they were untreated, (2) during chronic β-adrenoceptor blockade, and (3) after combined β-adrenoceptor and parasympathetic blockade.

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Methods

Patients

Forty-one patients (29 males), age 34–68 years, with benign essential hypertension were investigated. All gave informed consent to the studies. Routine urine-

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analysis, measurements of electrolytes, urea and creatinine in serum, and intravenous urography did not reveal possible causes of their hypertension. In the outpatient clinic blood pressure readings ranged from 160 to 220 mmHg systolic and from 110 to 130 mmHg diastolic, while the patients were untreated for 2–3 weeks.

Study protocol

The patients were in a metabolic ward on a diet containing 50 mmol sodium per day for at least 3 days before studies were started. Haemodynamic measurements and blood sampling were performed with the patient lying in bed after a light breakfast. Diazoxide 300 mg was given as a single rapid intravenous injection. Intra-arterial pressure and heart rate were continuously monitored. Fourteen patients (group 1) were studied without any form of pretreatment. In these patients cardiac output was measured at −5, +20 and +60 min, and venous blood for plasma noradrenaline was sampled at −5, +5, +10, +20, +40 and +60 min. On the basis of the results in this group, the values at −5 and +20 min were chosen for analysing the effects of pretreatment with propranolol and atropine. Fifteen patients (group 2) were studied before and after 2 weeks of treatment with propranolol, 80 mg 4 times a day; diazoxide was given 3 h after the last dose of propranolol. Twelve patients (group 3) were on the same dose of propranolol for 2–3 weeks and received atropine intravenously, 0.04 mg/kg body weight, 3 h after the last dose of propranolol, and 10 min later diazoxide was injected.

Technical procedures

A catheter was inserted into a right antecubital vein and positioned in the subclavian vein for injecting indocyanine green and blood sampling. An indwelling needle was placed in the left brachial artery for pressure measurements and blood withdrawal during determinations of cardiac output. These cannulations were performed at least 30 min before blood sampling was started. Intra-arterial pressure was monitored via a Statham transducer, and heart rate was recorded by ECG. Cardiac output was measured in triplicate by the dye dilution technique, using a dynamic calibration device (Gilford, model 140). Indocyanine green, 5 mg, was injected intravenously as a bolus of 1 ml, and flushed by 10 ml of saline. Plasma noradrenaline was determined by a radio-enzymatic method, using phenylethanolamine-N-methyltransferase and ^{3}H-S-adenosylmethionine as the methylating agent (Henry, Starman, Johnson & Williams, 1975).

Statistical analysis

Values of cardiac output, stroke volume and total peripheral resistance were converted to 1, 73 m^2 body surface area. Data are presented as mean ± s.e. mean, and Student's *t*-tests for paired or unpaired data were used.

Results

Time course of diazoxide-induced changes in arterial pressure, heart rate, cardiac output and plasma noradrenaline

Table 1 shows the results in group 1. The effects of diazoxide on arterial pressure, heart rate and plasma noradrenaline reached their maximum within 5 min. Cardiac output rose but stroke volume did not change significantly. Values for these parameters after 20 min were not significantly different from those after 60 min.

Table 1 Time course of changes (mean ± s.e. mean) after diazoxide in untreated patients (group 1, $n = 14$)

	Time (min)					
	−5	*+5*	*+10*	*+20*	*+40*	*+60*
Mean arterial pressure (mmHg)	145 ± 4	104 ± 2	105 ± 3	106 ± 3	103 ± 5	104 ± 6
Heart rate (beats/min)	71 ± 2	94 ± 4	90 ± 3	90 ± 3	85 ± 5	82 ± 5
Cardiac output (l/min)	5.22 ± 0.30			7.41 ± 0.60		6.53 ± 0.32
Stroke volume (ml)	71 ± 5			81 ± 6		74 ± 5
Total peripheral resistance (dyn s cm^{-5})	2351 ± 172			1319 ± 133		1437 ± 97
Noradrenaline (pg/ml)	296 ± 49	725 ± 172	703 ± 131	614 ± 91	608 ± 101	663 ± 92

Diazoxide (300 mg i.v.) was given at time zero.

Effects of propranolol or combined propranolol/atropine pretreatment on resting values of arterial pressure, heart rate, cardiac output and plasma noradrenaline

After treatment with propranolol for 2 weeks (group 2) mean arterial pressure, heart rate and cardiac output were decreased (Table 2). Stroke volume, total peripheral resistance and plasma noradrenaline were not significantly changed. Atropine (group 3) had no effect on arterial pressure in propranolol pretreated patients (Table 2). Heart rate and cardiac output were higher than with propranolol alone, but stroke volume was smaller. Plasma noradrenaline was unchanged.

Effects of propranolol or combined propranolol/atropine pretreatment on diazoxide-induced changes in arterial pressure, heart rate, cardiac output and plasma noradrenaline

During treatment with propranolol alone, values of arterial pressure, heart rate, cardiac output and plasma noradrenaline in group 2 were not significantly different from those in group 3 (Table 2). Pretreatment with either propranolol alone or propranolol plus atropine had no effect on the reduction of pressure produced by diazoxide (Figure 1). Mean arterial pressure in group 2 fell from 142 ± 4 to 108 ± 4 mmHg without pretreatment, and from 122 ± 4 to 95 ± 5 mmHg during propranolol. In group 3 it fell from 117 ± 4 to 91 ± 6 mmHg during propranolol plus atropine. These reductions of pressure were not significantly different. The response of heart rate to diazoxide was somewhat diminished but still significant during propranolol; heart rate increased from 76 ± 4 to 91 ± 5 beats/min before propranolol, and from 55 ± 2 to 62 ± 2 beats/min during propranolol. Moreover, the diminished response of heart rate was compensated for by larger stroke volume increments (from 81 ± 6 to 80 ± 4 ml before propranolol, and from 83 ± 6 to 96 ± 7 ml during propranolol), so that the effect of diazoxide on cardiac output was not altered by propranolol. Cardiac output rose from 6.03 ± 0.46 to 7.23 ± 0.44 l/min before propranolol, and from 4.55 ± 0.30 to 5.94 ± 0.40 l/min during propranolol.

In contrast, atropine in combination with propranolol completely blocked the response of heart rate to diazoxide (90 ± 5 beats/min before diazoxide, and 90 ± 4 beats/min after this drug), and cardiac output increments were small (from 5.68 ± 0.54 to 6.56 ± 0.49 l/min) as compared with the changes during propranolol alone (from 4.55 ± 0.30 to 5.94 ± 0.40 l/min). Both forms of pretreatment did not affect the diazoxide-induced changes in plasma noradrenaline.

Discussion

Intravenously administered diazoxide is an effective anti-hypertensive agent. In our patients it caused a 24% reduction of mean arterial pressure in the face of a 25% increase in cardiac output, and this compares with other studies (Bhatia & Frohlich, 1973; Hamby, Jankowski, Pouget, Dunea & Gannt, 1968; Rubin, Zitowitz & Hausler, 1963; Wilson & Okun, 1963). The compensatory rise in cardiac output could not be prevented by propranolol. The percentage responses of mean arterial pressure and cardiac output to diazoxide were even not altered by propranolol (Figure 2). The rise in heart rate was somewhat diminished, but definitely not blocked. Mroczek, Lee, Davidov & Finnerty (1976) have found that

Table 2 Effects of propranolol and atropine on resting values (mean ± s.e. mean) of haemodynamic parameters and plasma noradrenaline

	Group 2 (n = 15)			*Group3* (n = 12)		
	Without pretreatment	*Propranolol**	P-*value*	*Propranolol**	*Propranolol** + *atropine***	P-*value*
Mean arterial pressure (mmHg)	142 ± 4	122 ± 4	< 0.001	116 ± 5	117 ± 4	NS
Heart rate (beats/min)	76 ± 4	55 ± 2	< 0.001	58 ± 3	90 ± 5	< 0.001
Cardiac output (l/min)	6.03 ± 0.46	4.55 ± 0.30	< 0.001	4.53 ± 0.20	5.86 ± 0.54	< 0.01
Stroke volume (ml)	81 ± 6	83 ± 6	NS	80 ± 4	65 ± 5	< 0.001
Total peripheral resistance (dyn s cm^{-5})	2029 ± 166	2280 ± 171	NS	2093 ± 131	1736 ± 154	< 0.01
Noradrenaline (pg/ml)	268 ± 41	305 ± 76	NS	310 ± 80	204 ± 49	NS

* = 320 mg/day ** = 0.04 mg/kg i.v.; NS = not significant ($P > 0.05$).

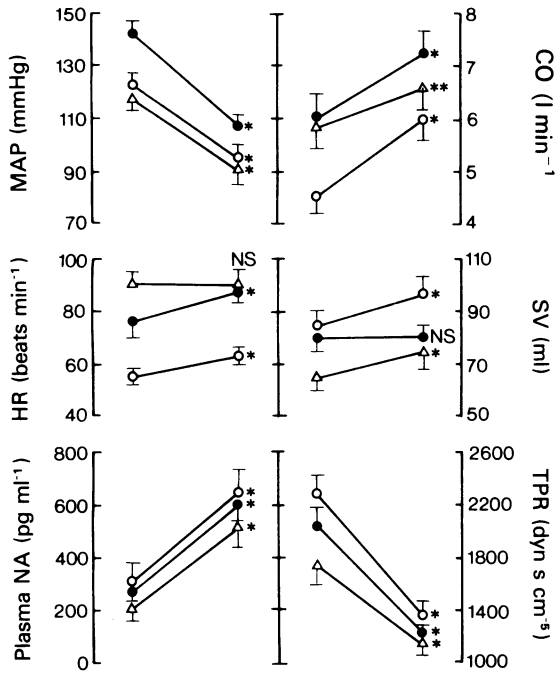

Figure 1 Effects (mean ± s.e. mean) of β-adrenoceptor blockade (propranolol, 320 mg/day) and combined β-adrenoceptor/parasympathetic blockade (atropine, 0.04 mg/kg i.v.) on reflex responses to vasodilatation with diazoxide (300 mg i.v.). Data are based on paired observations in the absence and presence of β-adrenoceptor blockade (n = 15), and on unpaired observations under combined β-adrenoceptor/parasympathetic blockade (n = 12). NS = not significant, $P > 0.05$; * = $P < 0.001$, ** = $P < 0.01$. MAP mean arterial pressure, HR heart rate, NA noradrenaline, CO cardiac output, SV stroke volume, TPR total peripheral resistance. ● without pretreatment, ○ with propranolol, △ with propranolol and atropine

propranolol was not capable of blocking the heart response to diazoxide, and a similar finding has been reported by Sannerstedt, Stenberg, Vedin, Wilhelmson & Werkö (1972) with alprenolol and intravenous dihydralazine. As shown in our study, a diminished response of heart rate to diazoxide with propranolol pretreatment is fully compensated for by a larger stroke volume.

In contrast, the heart rate response to diazoxide was completely blocked, and the rise in cardiac output was markedly inhibited, when atropine had been given in addition to propranolol. This was not related to a smaller drop in arterial pressure during this combined treatment. The pressure drop was not significantly different from that during propranolol alone, both in absolute terms (Figure 1) and in relative terms (Figure 2). Percentage changes in total peripheral resistance were also similar. Furthermore, the pressure level that was ultimately attained with diazoxide was lower during combined propranolol and atropine than during propranolol alone. Thus, it appears that reflex cardiostimulation after acute vasodilator treatment of hypertension does not depend on β-adrenoceptor stimulation alone. The parasympathetic component of this reflex is probably more important. Pickering, Gribbin, Strange Peterson, Cunningham & Sleight (1972) came to a similar conclusion for exercise-induced tachycardia.

It should be noted that cardiac output still rose after diazoxide during pretreatment with propranolol plus atropine. A direct cardiostimulatory effect of diazoxide cannot be ruled out, but experiments in animals have not shown any evidence for this (Rubin *et al.*, 1963). It is possible that reduced left ventricular after-load has contributed to the observed changes in cardiac output.

Theoretically, changes in baroreceptor sensitivity might also have influenced our results. We have no direct information on this, but the response of plasma noradrenaline to the vasodilator-mediated drop in arterial pressure were not modified by propranolol either alone or in combination with atropine. This suggests that sympathetic outflow is not altered by these drugs. The slight increase in plasma noradrenaline after propranolol, as reported by Rahn, Gierlings, Planz, Schols & Staphany (1978) was not statistically significant in the present study.

In conclusion, the effect of acute vasodilatation on arterial pressure is not potentiated by prior β-adrenoceptor blockade, since vasodilator-induced changes in heart rate and cardiac output are related to decreased parasympathetic tone rather than to sympathetic stimulation.

This does not imply there is no case for treating hypertension with combinations of a vasodilator and a β-adrenoceptor blocker. The effects of the two types of drugs on blood pressure are additive. As shown in the present study with acute vasodilatation, and also during chronic vasodilator administration (Zacest *et al.*, 1972), the result of combined treatment is a greater fall in pressure than with a vasodilator alone. The combination may also result in a smaller impact on cardiac reserve, since the β-adrenoceptor blocker lowers both heart rate and cardiac output so that superimposed increments of these variables after vasodilatation do not really lead to a hyperkinetic circulation.

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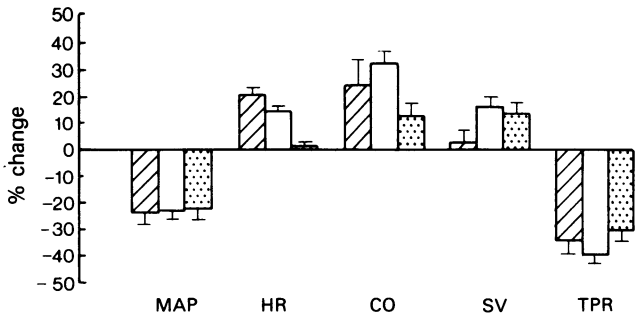

Figure 2 Comparison of the effects of β-adrenoceptor blockade and combined β-adrenoceptor/parasympathetic blockade on reflex responses to vasodilatation. Percentage changes (mean ± s.e. mean) are shown. As in Figure 1, data are based on paired observations in the absence and presence of β-adrenoceptor blockade ($n = 15$), and on unpaired observations under combined β-adrenoceptor/parasympathetic blockade (n = 12). ▨ without pretreatment, □ with propranolol ⊡ with propranolol and atropine. Abbreviations as in Figure 1.

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