Effects of α -adrenoceptor and of combined sympathetic and parasympathetic blockade on cardiac performance and vascular resistance

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- 1 Cardiac performance and vascular resistance was studied in seven healthy men by radionuclide cardiography and venous plethysmography before and after α -adrenoceptor blockade with phentolamine and after combined α -adrenoceptor, β -adrenoceptor (propranolol) and parasympathetic (atropine) blockade.
- 2 During α -adrenoceptor blockade heart rate and cardiac output increased considerably and left ventricular ejection fraction increased because of increased contractility. Systemic vascular resistance fell both during α -adrenoceptor blockade alone and during combined blockade. The increase in calf blood flow was of the same magnitude after combined blockade and after α -adrenoceptor blockade alone, and was considerably higher than the fall in systemic vascular resistance. Plasma catecholamine concentrations increased after phentolamine, but the changes were blunted when propranolol and atropine were added.
- 3 These results indicate that peripheral vasoconstriction especially that exerted by α -adrenoceptor nervous tone in skeletal muscle restricts left ventricular emptying of the intact heart. During pharmacologic blockade of the sympathetic and parasympathetic nervous system at rest the chronotropic state is augmented, whereas preload and inotropy are unaffected.

Keywords radionuclide cardiography autonomic nervous blockade
phentolamine propranolol atropine

Introduction

The effects of pharmacologic denervation of the heart with combined β -adrenoceptor and parasympathetic nervous blockade has been studied thoroughly (Jose & Taylor, 1969; Bishop & Horwitz, 1971; Kelbæk *et al.*, 1987, 1991). In these studies an elevated heart rate and a reduced stroke volume were found in the intrinsic heart at rest.

Blockade of α -adrenoceptors with phentolamine also results in tachycardia and an increase in cardiac output, probably due to secondary β -adrenoceptor stimulation (Das & Parratt, 1971). However, it is not clear how left ventricular volumes change in response to α -adrenoceptor blockade.

In the present study we examined changes in central haemodynamics including left ventricular volumes induced by α -adrenoceptor blockade with phentolamine.

To evaluate the relative importance of the α - and β -adrenoceptor sympathetic and parasympathetic nervous tone in the innervated heart we also studied haemodynamic changes during combined α -, β - and parasympathetic blockade.

Methods

Subjects

Seven healthy men aged 20 to 34 years, mean 24 years; mean weight 71 kg, range 57 to 78 kg, consented to participate after detailed information. The study protocol was approved by the local ethics committee.

Study protocol

Control experiments and tests with α -adrenoceptor blockade and combined α -, β - and parasympathetic blockade were performed at random in each subject on different days. The subjects were allowed a light breakfast approximately 3 h before they entered the laboratory. Baseline investigations were performed after the subjects had been lying down for at least 1 h, and all measurements were repeated 30 min after induction of pharmacologic blockade with either phentolamine alone or the combination of phentolamine, propranolol and atropine. Control experiments were performed according to the same schedule with isotonic saline.

Investigations

All data were recorded at supine rest. Heart rate was measured by a 3-lead electrocardiogram, blood pressure sphygmomanometrically (the diastolic pressure determined at Korotkoff phase 5).

Left ventricular volumes were determined by radio-nuclide cardiography after *in vitro* labelling of autologous red blood cells with technetium-99m (Kelbæk *et al.*, 1989). A dose of 740 to 1,110 MBq was used for multigated equilibrium imaging in the left anterior oblique projection. Data were acquired using a mobile cardiac gamma camera (Siemens) and a dedicated computer system (Scintiview, Siemens). Left ventricular ejection fraction and volumes, stroke volume and cardiac output were determined as previously described (Kelbæk *et al.*, 1986, 1987). The systemic vascular resistance was calculated by dividing the mean blood pressure (the diastolic pressure plus one third of the pulse pressure) by the cardiac output.

The blood flow of the calf was measured by venous occlusion plethysmography. The strain gauge was placed at the largest girth of the right calf, and a cuff pressure of 50 mm Hg was applied proximal to the strain gauge after calibration. The procedure was repeated four times at each measurement.

Venous blood was drawn from a cubital vein for determination of plasma concentrations of adrenaline and noradrenaline by isotope derivative assay (Christensen *et al.*, 1980).

α -adrenoceptor nervous blockade was induced by intravenous injection of phentolamine as a bolus of 5.0 mg followed by a constant infusion at a rate of 0.5 mg min⁻¹ (Galbo *et al.*, 1977). Combined α -, β - and parasympathetic nervous blockade was induced by intravenous injection and infusion of similar doses of phentolamine, a bolus of 5.0 mg propranolol followed by infusion of 0.08 mg min⁻¹ and a bolus of 0.035 mg kg⁻¹ atropine (Cryer *et al.*, 1980).

Processing of data was performed without knowledge of the investigation sequence.

Nonparametric analysis of variance (Friedman's test modified for multiple comparison) was applied to drug-induced changes on the three occasions (Conover, 1980). The 95% confidence intervals of the differences were calculated according to Gardner & Altman (1986). Changes were considered significant, when the 95% confidence interval of the difference did not encompass zero.

Results

α -adrenoceptor blockade

The systolic blood pressure did not change, while a 19% fall was recorded in the diastolic pressure during α -adrenoceptor blockade (Table 1). The mean left ventricular ejection fraction was increased from 57% to 66% due to a 25% decrease in left ventricular end systolic volume (Figure 1). Stroke volume and heart rate increased causing a 36% increase in cardiac output (Table 1). Thus, the calculated systemic vascular resistance fell by 30%, whereas calf blood flow increased by 78% (Table 1). The plasma concentration of adrenaline did not change significantly, whereas noradrenaline rose by 136% during α -adrenoceptor blockade (Figure 2).

Figure 1 Mean values of left ventricular end diastolic volume (EDV), ejection fraction (EF) and end systolic volume (ESV) during control conditions, after α -adrenoceptor blockade and after combined α -adrenoceptor, β -adrenoceptor and parasympathetic blockade. Bars indicate 95% confidence interval (CI) for the difference, * zero not included in the 95% CI, ** zero not included in the 99% CI.

Figure 2 Mean values of plasma catecholamine concentrations (● noradrenaline, ○ adrenaline) during control conditions, after α -adrenoceptor blockade and after combined α -adrenoceptor, β -adrenoceptor and parasympathetic blockade. Bars indicate 95% confidence interval (CI) for the difference, * zero not included in the 95% CI, *** zero not included in the 99.9% CI.

Table 1 Haemodynamic data before and after α -adrenoceptor blockade and after combined α -adrenoceptor, β -adrenoceptor and parasympathetic blockade. Values are means (s.d.) and 95% confidence intervals (CI) of the differences

	Control		α -adrenoceptor blockade			Combined blockade			Combined vs α -adrenoceptor blockade
	Before	After	Before	After	95% CI	Before	After	95% CI	
Heart rate (beats min ⁻¹)	58 (9)	57 (7)	57 (5)	69 (15)	0.1 to 23.9	55 (5)	86 (7)	27.7 to 34.3	†
Stroke volume (ml)	92 (15)	87 (17)	92 (10)	103 (17)	0 to 23	96 (20)	87 (20)	-22 to 4	†
Cardiac output (l min ⁻¹)	5.42 (1.43)	5.01 (1.40)	5.21 (0.88)	7.06 (1.45)	0.90 to 2.82	5.31 (1.22)	7.44 (1.88)	1.00 to 3.26	§
Systolic blood pressure (mm Hg)	121 (5)	115 (5)	117 (9)	121 (9)	-3 to 11	119 (8)	118 (7)	-5 to 4	§
Diastolic blood pressure (mm Hg)	72 (6)	74 (6)	74 (9)	60 (9)	-22 to -6	74 (9)	82 (8)	0 to 15	†
Calf blood flow (ml min ⁻¹ 100 ml ⁻¹)	2.8 (0.9)	3.0 (1.1)	3.2 (0.9)	5.7 (2.7)	0.3 to 4.9	3.0 (1.0)	5.6 (2.2)	1.3 to 4.0	§
Systemic vascular resistance (dyn $\times$ s/cm ⁵)	1392 (416)	1520 (504)	1386 (209)	966 (194)	-585 to -257	1418 (404)	1046 (274)	-556 to -190	§
Left ventricular end diastolic volume (ml)	160 (27)	153 (28)	160 (18)	155 (15)	-26 to 16	163 (31)	152 (28)	-31 to 9	§
Left ventricular end systolic volume (ml)	68 (17)	67 (15)	69 (15)	52 (6)	-30 to -3	67 (18)	65 (17)	-11 to 7	†
Left ventricular ejection fraction (%)	58 (5)	57 (5)	57 (6)	66 (5)	5.0 to 12.4	59 (7)	57 (7)	-4.1 to 0.3	†

Combined vs α -adrenoceptor blockade: † Zero not included in 95% CI, § zero included in 95% CI.

α -, β - and parasympathetic blockade

Combined blockade with phentolamine, propranolol and atropine only tended to decrease stroke volume when compared with baseline values. However, when compared with the change induced by α -adrenoceptor blockade alone, this difference was significant (Table 1). Because the heart rate increase was more pronounced than during α -adrenoceptor blockade alone, cardiac output was augmented to a similar extent whether or not β -adrenoceptor and parasympathetic blockade was added to the α -adrenoceptor blockade (Table 1). Save a slight increase in diastolic pressure no significant changes were recorded in blood pressures, but the systemic vascular resistance was decreased by more than 25% as with α -adrenoceptor blockade. Left ventricular volumes were unaffected by the combined blockade (Figure 1), and plasma noradrenaline increased by only 35% (Figure 2).

Discussion

The function and clinical significance of the α -adrenoceptor is poorly understood (Insel, 1989). However, certain disorders of the receptor have been proposed of importance in the development of cardiac arrhythmias and essential hypertension (Corr *et al.*, 1989; Michel *et al.*, 1989). In addition, α -adrenoceptor blockade with phentolamine has been shown to produce haemodynamic improvement when administered to patients in congestive heart failure (Gould & Reddy, 1976).

The findings of the present study confirm previously presented evidence suggesting that α -adrenoceptor blockade results in a considerable increase in cardiac output in healthy subjects, mainly brought about by relative tachycardia (Taylor *et al.*, 1965). The study also shows that the elevated cardiac output was withheld, when propranolol and atropine were added to the α -adrenoceptor blockade, because the tendency of these drugs to reduce stroke volume was counterbalanced by the heart rate increase induced by parasympathetic blockade. These results are in accordance with previous findings (Kelbæk *et al.*, 1987, 1991) and suggest that pharmacologic denervation of the heart and vasculature reveals an 'intrinsic' heart working at an unchanged preload and inotropic state albeit at increased chronotropy compared with the heart with intact innervation.

The systemic vascular resistance was reduced to the same extent during α -adrenoceptor blockade alone as during combined sympathetic α - and β - and parasympathetic blockade, although the fall in diastolic blood pressure induced by phentolamine was reversed by propranolol and atropine. The increase in calf blood flow induced both by combined and by α -adrenoceptor blockade alone was considerably larger than the calculated fall in systemic vascular resistance. This finding suggests that α -adrenoceptor blockade induced by phentolamine is most pronounced in skeletal muscle. Addition of β -adrenoceptor parasympathetic blockade did not alter the effects of α -adrenoceptor blockade on either muscle blood flow or vascular resistance. This is in keeping with the results of a previous study of our laboratory (Kelbæk *et al.*, 1987).

It has been postulated that phentolamine has only

little effect on the preload to the heart, and that its effectiveness in the management of cardiac failure is due both to its arteriolar dilatating property and to a mild inotropic effect secondary to cardiac noradrenaline release (Frishman & Charlap, 1988). The findings of our study support these concepts as the left ventricular end diastolic volume was unaffected by α -adrenoceptor blockade. In addition, the ejection fraction was increased and the end systolic volume decreased during α -adrenoceptor blockade, which together with the unchanged systolic blood pressure indicate an increased contractility of the left ventricle (Mahler *et al.*, 1985).

A considerable increase in the plasma concentration of noradrenaline was recorded after α -adrenoceptor blockade. The phentolamine induced rise in plasma noradrenaline is in accordance with the concept that blockade of the presynaptic α -adrenoceptors results in an increased release of noradrenaline (Clarke *et al.*, 1979). However, the dominant cause of this release is probably the fall in vascular resistance. Accordingly, the rise in the plasma level of noradrenaline induced by α -adrenoceptor blockade, was much weaker when

β -adrenoceptor and parasympathetic blockade were added to the α -adrenoceptor blockade. An association between the plasma noradrenaline level and left ventricular volume changes is indicated by the fact that the volume changes were abolished when changes in plasma catecholamines diminished, after induction of β - and parasympathetic blockade was added to the α -adrenoceptor blockade. Still, the primary reason for the increased inotropic state of the heart may be the reduction in vascular resistance and afterload.

The findings of the present study indicate that in healthy subjects the vasoconstricting property of the α -adrenoceptor nervous tone to some extent restricts left ventricular emptying. In addition, the results demonstrate that the heart, disengaged from sympathetic and parasympathetic nervous control works with an increased cardiac output with unaffected preload and no detectable changes in inotropy.

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