Conclusions as to the mechanism of the β-adrenoceptive receptor blocking drugs cannot be exactly determined by the present experiments, since there is no evidence concerning the specificity of the effect of pindolol and propranolol. Provided that all β-receptor blocking agents also act as β-receptor stimulating agents, further experiments, such as the effect of low doses of isoproterenol on ADH-induced kidney alterations etc., are needed. The doses used in the present experiments are proportional to those which have used occasionally in man[3]. Independently of the exact mode of action of pindolol and propranolol, their inhibitory effect against ADH could be taken into consideration.

Zusammenfassung. Intraperitoneal injiziertes Vasopressin (einmal täglich während 3 Tagen) führt bei Ratten besonders im Nierenrindenmark-Grenzgebiet zu ischämischen Veränderungen. Pindolol und Propanolol als sogenannte Blockersubstanz, hemmt, bzw, verhindert diese Veränderungen.

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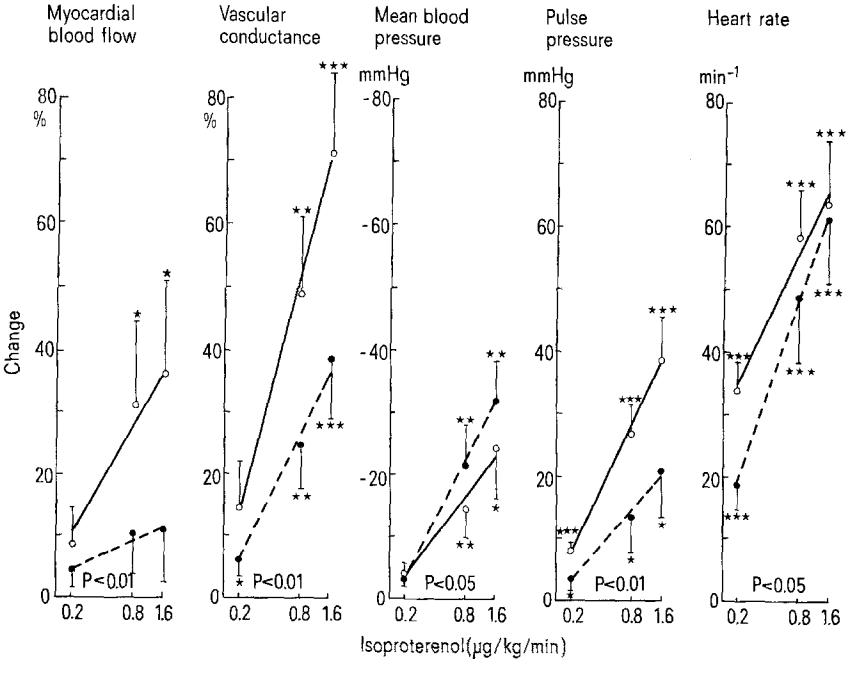
Effect of β-Adrenergic Excitation on Collateral Coronary Blood Flow

Coronary dilatation mediated through β-adrenergic activation may be considered the most important neurohumoral mechanism regulating the blood supply to the normal myocardium. At the same time, little is known of the β-adrenergic effects exerted on the collateral coronary vessels supplying an ischaemic myocardial segment after acute occlusion of its major coronary branch. The present study was designed to elucidate this problem.

Methods. Experiments were performed in 10 open-chest dogs under chloralose (0.11 g/kg body wt.). A myocardial area, amounting to about one-fifth of the total left ventricular mass, was rendered ischaemic by occlusion of the left anterior descending artery (LAD) approximately halfway along its course. Local blood flow of this myocardial segment was measured by means of the heat clearance technique using DC current heated copper-constantan thermal probes. Local flow was continuously registered on a sensitive compensograph. In order to study the collateral flow in a range as wide as possible, the distance of the probe from the supposed centre of the ischaemic zone varied from animal to animal. Local vascular responses to isoproterenol (Isuprel, Winthrop) were registered before and after LAD occlusion, the same myocardial segment serving as its own control. Isoproterenol was infused i.v. in increasing doses of 0.2, 0.8 and 1.6 μg/kg/min. Circulatory parameters were chosen for data analysis during steady state responses. The flow changes were expressed in percentage of the initial control value, by determining zero flow line after having sacrificed the animal. The magnitude of coronary reactions were characterized as local vascular conductance values (%flow/%mean blood pressure) as well, 100% being the normal initial conductance level before LAD occlusion. Thus, vascular changes of a given tissue locus supplied either by the normal or the collateral vessels were defined in the same units. Blood pressure was registered in the carotid artery with the aid of a Statham element; mean pressure was obtained by electrical integration.

Results. LAD occlusion considerably decreased the local myocardial perfusion, while the general circulatory parameters were not modified significantly by this procedure (Table). The effects of β-adrenergic excitation are summed up in the Figure by indicating the linear regression lines of the dose-response relationships. The tissue blood flow of the myocardium increased significantly in the normal state, while it remained fairly constant during the period



Dose-response relationships of the isoproterenol effects. ○—○, normal; ●---●, ischaemic. Vertical bars denote SEM. Symbols refer to the significance of changes from the control values (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). P values above the abscisse refer to the significance of differences between the slopes of regression lines.

Circulatory effects of coronary occlusion ($n = 10$)

	Myocardinal blood flow (%)	Vascular conductance (%)	Mean blood pressure (mmHg)	Pulse pressure (mmHg)	Heart rate (min^{-1})
Initial value	100 ± 0	100 ± 0	112.3 ± 8.7	27.1 ± 3.6	171.0 ± 12.1
Change after occlusion	− 52.9 ± 8.6	− 50.4 ± 10.2	− 2.2 ± 6.7	+ 0.9 ± 1.8	+ 4.6 ± 6.7
p	< 0.001	< 0.001	> 0.5	> 0.5	> 0.5

Mean values ± S.E.M.

of the ishaemia. By contrast, isoproterenol was shown to increase calculated conductance values during both periods, although the slopes of regression lines characterizing the two dilatory responses differed significantly from each other. LAD occlusion potentiated the systemic hypotension elicited by large doses of isoproterenol and reduced the pulse pressure augmenting effect of the drug. The latter modifications are probably associated with a reduced sensitivity of the damaged heart to inotropic stimuli. Moreover, after LAD occlusion somewhat higher concentrations were required to elicit chronotrophic responses than were needed for a similar response in the normal state.

Conclusions. The results indicate that, after coronary occlusion, β-adrenergic activation induces dilatory vascular responses in the ischaemic myocardium. In order to characterize the collateral (ischaemic) vascular response the effects of isoproterenol infusions were measured in the same tissue locus before and after LAD occlusion. It seems that collateral dilatation corresponds to some 50% of the normal response. Since a large amount of vasodilator metabolites are released by the ischaemic myocardium, it may rightly be assumed that collateral channels are delivering blood into a maximally dilated microvasculature, which is insensitive to β-adrenergic stimuli. Thus, β-dilator effects are presumably exerted on the netlike arrangement of small collateral arteries surrounding the ischaemic focus. β-adrenergic excitation, however, is not necessarily beneficial to the ischaemic myocardium, since, during isoproterenol administration, the local oxygen requirement may be expected to increase as well. Indeed, isoproterenol has been reported to augment both active contractile force[1] and the severity of ischaemic damage[2] within a hypoxic myocardial area after experimental coronary occlusion.

Zusammenfassung. Am ischämischen Myokard löst Isoproterenol eine vasodilatatorische Reaktion aus, die qualitativ ähnliche, quantitativ jedoch geringere Werte zeigt als diejenigen, die vor dem Koronar-Verschluss in derselben Myokardzone gemessen wurden.

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18 May 1973.

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A Novel Spasmolytic and CNS Active Agent: 3-(2-benzylmethylamino ethyl) Benzoic Acid Methyl Ester Hydrochloride

In the course of investigations on the influence of structural modifications of related *m*-(aminoalkyl) benzoic acid derivatives[1,2] the title compound (II) was synthesized. Hydrolysis of *N*-benzyl-*N*-methyl-3-trifluoromethyl-phenethyl-amine with conc. sulfuric acid followed by esterification with methyl alcohol yielded (II). The hydrochloride of (II) has a mp 150–151 °C. Analysis for $C_{18}H_{21}NO_2 \cdot HCl$: Calcd: C, 67.60; H, 6.93; found: C, 67.75; H, 6.95. The IR-spectrum recorded on a Beckman IR 8 spectrophotometer is consistent with the assigned structure.

Compound (II) is a potent spasmolytic agent exhibiting approximately three times the activity of papaverine in the rabbit ileum preparation. The spasmogenic effect of 20 mg of $BaCl_2$ is overcome by 0.075–0.1 mg of II.

In the normotensive dog no blood pressure effects are observed following i.v. administration of 1 and 2 mg/kg. Additional doses of 4 and 8 mg/kg cause brief depressor responses. No changes in the heart rate are observed at these levels. In doses up to 16 mg/kg pressor responses to epinephrine and depressor responses to acetylcholine and bradykinin are unaffected. The acute toxicity LD_{50} (p.o.) of II for rats is 700–800 mg/kg. Compound II shows no activity in the motor acitivity test in rats at 100 mg/kg and a slight decrease in activity in mice at 100 mg/kg.

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[2] Hoffmann-La Roche & Cie., Belg. Patent 788, 850 (1973).