## Hemodynamic and Pharmacological Aspects of the Biphasic Pressor Response to Acetylcholine in Atropinized Dogs

Large intravenous doses of acetylcholine (100–300 µg/kg) provoke a biphasic pressor response in anesthetized dogs, pretreated with atropine and physostigmine. There is general agreement that the second phase is due to catecholamine release from the adrenal medulla, whereas the immediate pressor effect variously has been attributed to stimulation of the sympathetic ganglia[1,2], to adrenal medullary stimulation[3,4], or to chemoreceptor stimulation[5]. The relative contributions of cardiac output or vasoconstriction towards these pressor reactions also remain a matter of controversy[2,4]. The aim of our experiments was to get some further insight into the mechanism and the hemodynamic features of this biphasic hypertension. At the same occasion we have studied the effect of beta-adrenergic blockade using pronethalol and propranolol. These drugs have been reported to reduce or to reverse the first pressor phase and to enhance the second one[2,6,7].

*Material and methods.* Anesthetized dogs (sodium pentobarbital, 30 mg/kg, i.p.) were treated with atropine (5 mg/kg, i.v.) and physostigmine (1 mg/kg, i.v.). The femoral arterial blood pressure was recorded in 30 dogs and the influence of pronethalol and propranolol on the nicotinic pressor reaction has been evaluated.

In 8 additional experiments, the animals were ventilated by a Palmer pump, median sternotomy was performed and the following parameters were continuously recorded: arterial blood pressure and left ventricular pressure (lvp); dp/dt of lvp was taken as an indication of the inotropic activity; heart rate was derived from the R-R interval of the electrocardiogram; arterial blood flows were measured via electromagnetic perivascular flow probes (Medicon) placed around the descending aorta, the femoral artery, the cranial mesenteric artery and around the left subclavian artery after ligation of the costo-cervical trunk and of the left axillary artery. The latter flow probe informs about the cerebral blood flow and the aortic probe allows an approximative evaluation of the changes in cardiac output. In these conditions, the nicotinic effects have been studied before and after pronethalol or propranolol, 1 mg/kg.

*Results.* Blood pressure measurements were performed in groups of 5 dogs which received pronethalol, respectively, 0.25, 1 or 4 mg/kg, or propranolol, 0.25, 0.5 or 1 mg/kg, i.v. The primary pressor action of acetylcholine was not uniformly affected by pronethalol, 0.25 or 1 mg/kg, but was unvariably decreased and in most cases reversed after pronethalol, 4 mg/kg, and in all propranolol experiments.

The secondary hypertensive phase was slightly potentiated after 0.25 mg/kg of either drug. This potentiation was more important after pronethalol 1 or 4 mg/kg, but failed to occur after propranolol 0.5 or 1 mg/kg. The mean results are illustrated in Figure 1, where the secondary hypertensive phase is described in three different ways. The upper tracings represent the surface area of the pressor reactions and the middle tracings indicate the maximal amplitude of blood pressure increase. The lower curves illustrate the duration of the second pressor phase, by means of the time interval between the onset and the end of the reaction, measured at a level of 20% of the maximal amplitude. In this way major disturbance of the time estimation due to minor variations of the blood pressure level before and after the nicotinic reaction, is avoided.

These results reveal that the duration of the reaction is slightly prolonged after both drugs, but that the peak effect of blood pressure increase is markedly diminished after propranolol, 1 mg/kg. The hemodynamic features of the cardiovascular function during the biphasic acetylcholine-hypertension are illustrated in Figure 2. The

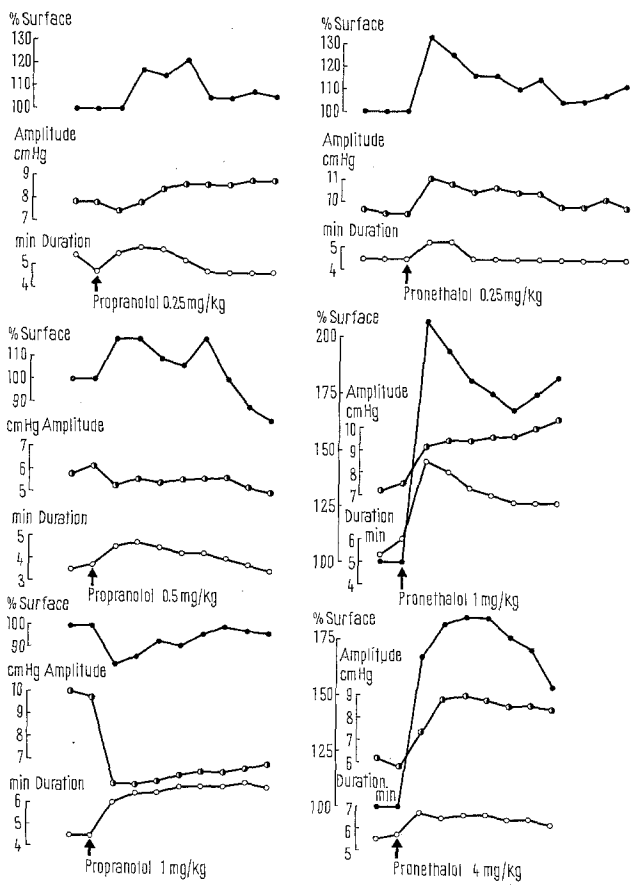


Fig. 1. Influence of different doses of pronethalol and propranolol on the secondary pressor effect of acetylcholine, 0.1 mg/kg, i.v. Time interval between successive acetylcholine injections: approximately 7 min. 2 or 3 control reactions were performed before, and 7 to 10 reactions after the administration of β-adrenergic blocking agents. All curves represent the mean results of 5 experiments. ●—●, surface, calculated as % of control reactions; ▲—▲, amplitude of maximal blood pressure increase; ▼—▼, duration of the secondary pressor phase.

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early hypertension is accompanied by a marked respiratory stimulation as has been previously described[5]. Each pressor phase is characterized by an increase of the myocardial contractility (dlvp/dt) and by a decrease of the blood flow through the cranial mesenteric artery. However, the second intestinal vasoconstrictor effect was much shorter than the second pressor phase.

The fall of dlvp/dt between both pressor phases at the moment of maximal cardio-acceleration was less prominent in most other experiments. Nevertheless, a transitory relative fall of inotropic activity, together with a marked intestinal vasodilation between two constrictory phases, are the two major phenomena which may explain the dip of the blood pressure between both hypertensive phases.

After pronethalol, 1 mg/kg, the first pressor phase is diminished. The hemodynamic basis for this attenuation includes a smaller increase of dlvp/dt and some initial bradycardia. During this period the cardiac output remains at a lower level than before treatment. The second pressor phase was potentiated in the four pronethalol experiments, although the increase of the cardiac output remained smaller. On the other hand, a more important secondary vasoconstriction was observed in the femoral circulation.

After propranolol, 1 mg/kg, the first pressor phase of the nicotinic effect was abolished in all experiments and the second pressor phase was markedly reduced (2 cases) or completely inhibited (2 cases). Propranolol itself provoked an important depression of dlvp/dt and it antagonized almost completely the myocardial stimulation of the subsequent acetylcholine-injections.

*Discussion.* The early pressor reaction, provoked by acetylcholine injection, results at least partly from myocardial stimulation and intestinal vasoconstriction. The question remains open whether this occurs through stimulation of sympathetic ganglia or through chemoreceptor activation. The respiratory reactions indicate that the latter phenomenon may be important. Hypertension and myocardial stimulation are antagonized by pronethalol and propranolol, whereas intestinal vasoconstriction is hardly affected. The mechanism of the reduction of the pressor response is therefore largely due to inhibition of the myocardial reactivity. Through a similar hemodynamic pattern, propranolol was found to antagonize the pressor effects of injected norepinephrine[8] and of carotid occlusion reactions[9]. This antagonism was attributed to beta-adrenergic blockade. Inhibition of the early pressor reaction via local anesthesia of the chemoreceptors is improbable in our experiments, since the intestinal vasoconstriction is maintained after pronethalol and propranolol.

The secondary pressor effect of acetylcholine is attributed to a release of adrenal medullary catecholamines. Moderate $\beta$-adrenergic blockade, induced by pronethalol, 1 mg/kg, greatly inhibits the cardioaccelerator action of acetylcholine, whereas its positive inotropic effect is largely maintained and its vasoconstrictor effect increased as demonstrated in the femoral circulation. It is conceivable that the overall result leads to a potentiation of the secondary pressor phase in spite of a less pronounced elevation of the cardiac output. Extensive $\beta$-adrenergic blockade, induced by propranolol, 1 mg/kg, inhibits the the positive chromotropic and inotropic effects as well as the elevation of the cardiac output. This largely impairs the secondary pressor phase of acetylcholine.

*Conclusion.* It was confirmed that the primary pressor effect of large acetylcholine doses in atropinized dogs is reduced by pronethalol and propranolol. This reduction is partly due to an antagonism of acetylcholine-induced myocardial stimulation. It was found that the secondary pressor phase of the nicotinic action was potentiated after pronethalol and after the smallest dose of propranolol (0.25 mg/kg). Larger doses of propranolol, however, antagonized the secondary pressor phase. Potentiation may be due to vascular $\beta$-adrenergic blockade, whereas inhibition may be attributed to myocardial $\beta$-adrenergic blockade of the larger propranolol doses. An important mesenteric vasoconstriction was observed during both pressor phases of the nicotinic reaction, but this vasoconstriction was not inhibited by pronethalol nor by propranolol.

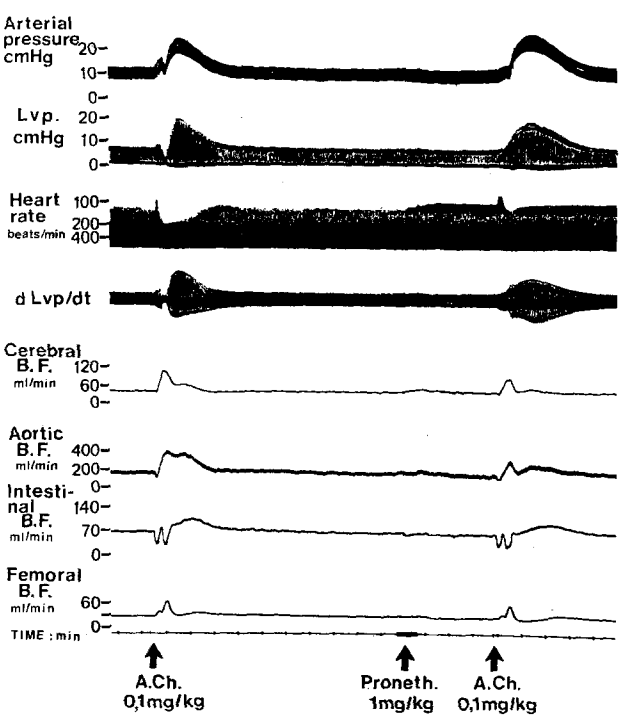


Fig. 2. Hemodynamic aspects of the pressor effects of acetylcholine in the atropinized dog. Influence of pronethalol.

*Zusammenfassung.* Es wird der Blutdruckanstieg nach Acetylcholin bei Atropin- und Physostigmin-vorbehandelten Hunden untersucht und unter Benützung von $\beta$-Blockern analysiert. Es ergibt sich ein komplexes Bild, an dem offenbar mehrere Faktoren beteiligt sind.

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