EFFECT OF CAFFEINE ALONE AND IN COMBINATION WITH STROPHANTHIN ON COLLATERAL BLOOD FLOW AFTER ACUTE OCCLUSION OF THE CORONARY ARTERY

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By recording the retrograde blood flow and presence in the zone of distribution of the ligated anterior descending branch of the left coronary artery in acute experiments on dogs, it was shown that caffeine, in a dose of 10 mg/kg, increases the collateral blood flow without producing significant changes in the systemic arterial pressure or pressure in the ligated vessel. The intensity of the positive effect of caffeine was reduced against the background of action of octadine and atropine. In experiments on isolated cats' hearts with a ligated coronary artery caffeine clearly dilated the coronary anastomoses. Simultaneous administration of strophanthin (0.2 cat unit/kg) reduced the intensity of the positive action of caffeine on the inflow of blood into the ischemic myocardium.

The object of this investigation was to study the effect of caffeine and strophanthin, which are commonly used for the clinical treatment of acute coronary failure [2], on the collateral coronary blood flow.

EXPERIMENTAL METHOD

Experiments were carried out on mongrel dogs weighing 7-24 kg anesthetized with nembutal (40 mg/kg, intraperitoneally). The state of the collateral circulation in the heart was assessed from the retrograde blood flow and the pressure in the peripheral segment of the ligated anterior descending branch of the left coronary artery [8]. The systemic arterial pressure was recorded in the left carotid artery by a mercury manometer. The electrocardiogram was taken in chest (GP-4) and epicardial (boundary zone of ischemia) leads. Heparin (1500 units/kg, intravenously) was injected to prevent clotting of the blood.

The effect of caffeine on the inflow of blood into the ischemic myocardium was investigated after exhaustion of the catecholamine reserves with octadine [9], blocking of muscarine-like cholinergic structures with atropine, and pituitrin spasm of the coronary vessels [7]. The drugs were injected intravenously: octadine in a dose of 5 mg/kg 12-16 h before the experiment (8 experiments), atropine in a dose of 0.05 mg/kg 10 min before injection of caffeine (8 experiments), and pituitrin in a dose of 0.5 unit/kg 1 min before injection of caffeine (8 experiments). The myotropic action of caffeine was studied on isolated cats' hearts with simultaneous measurement of the total coronary outflow and the outflow of perfusion fluid from the area supplied by the ligated anterior descending branch of the left coronary artery [3].

Caffeine was injected intravenously in single doses of 10 mg/kg (8 experiments) and 20 mg/kg (9 experiments). The effect of a combination of caffeine (10 mg/kg) and strophanthin (0.2 cat unit/kg) also was investigated. The compounds were injected simultaneously at a constant speed from 2 syringes. The results were analyzed by statistical methods [6].

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EXPERIMENTAL RESULTS AND DISCUSSION

Caffeine, in a dose of 10 mg/kg, produced a steady increase (by 45.2 ± 3.6%; $P < 0.001$) in the retrograde blood flow (during the first 25 min) against the background of a very small (by 4 ± 1.9%) and transient elevation of the arterial pressure.

Injection of caffeine in a dose of 20 mg/kg in 4 of 9 experiments caused an increase in the collateral blood flow with simultaneous elevation of the arterial pressure. In the remaining experiments these indices were reduced, so that no general statistically significant tendency could be discovered. The heart rate was slightly increased, just as in the preceding series of experiments.

Preliminary injection of octadine sharply reduced the effect of caffeine (10 mg/kg) on the inflow of blood into the ischemic myocardium (increase in inflow of blood only 16.9 ± 2.5%), although the duration of this effect was the same as in the main experiments. The general arterial pressure was virtually unchanged, but the pressure in the peripheral end of the coronary artery rose by 10.1 ± 3.7% ($P < 0.05$) in the space of 35 min. Changes in the heart rate were inconsistent in direction and not statistically significant.

The increase in retrograde blood flow following administration of caffeine against the background of the action of atropine was smaller still (11.2 ± 4.3%; $P < 0.05$) and shorter in duration (10 min). The arterial pressure fell gradually during the experiments. Similar changes affected the peripheral coronary pressure. The heart rate rose very slightly.

The writer's earlier experiments [7] showed that pituitrin (0.5 unit/kg) sharply reduces the retrograde coronary blood flow and significantly increases the pressure in the ligated vessel 20-30 sec after its injection. Slowing of the heart rate and even an initial fall in the arterial pressure were observed at the same time. Caffeine, in a dose of 10 mg/kg, either prevented or reduced the degree of the fall in the retrograde blood flow produced by pituitrin.

In experiments on the isolated heart, injection of caffeine into the perfusion fluid (in concentrations of 1:50,000 and 1:10,000) increased the total outflow of fluid by 24.0 ± 10.7% ($P < 0.05$) and the outflow of perfusion fluid from the area supplied by the ligated artery by 14.6 ± 2.2% ($P < 0.001$).

Injection of caffeine with strophanthin was followed by a transient (15-20 min) increase (by 27.3 ± 6.2%; $P < 0.01$) in the collateral blood flow in only 8 of the 13 experiments against the background of elevation of the arterial pressure but a simultaneous fall in pressure in the ligated vessel. In the remaining 5 experiments both these indices fell progressively. In most experiments the heart rate increased very slightly.

Ligation of the coronary artery was reflected on the EKG by a sharp displacement of the S-T segment above the isoelectric line, by an increase in amplitude of the Q and T waves, and by arrhythmia. Injection of caffeine did not prevent the changes in the EKG produced by myocardial ischemia. Against the background of the action of atropine and octadine, arrhythmia was observed less commonly after injection of caffeine. Conversely, injection of caffeine in combination with strophanthin was accompanied by the appearance of grouped ventricular extrasystoles.

The ability of caffeine, in a dose of 10 mg/kg, to increase the retrograde coronary blood flow without significant changes in the arterial pressure and in the pressure in the peripheral segment of the coronary artery can be interpreted as the result of its dilator effect on interarterial anastomoses, as was confirmed by experiments with pituitrin spasm of the coronary vessels and on isolated cats' hearts. Meanwhile the myotropic action of caffeine on the coronary anastomoses obviously made a comparatively unimportant contribution to the development of its coronary-dilator effect, as shown by experiments with preliminary injection of octadine and atropine. There are reports in the literature that the stimulant effect of caffeine on the heart is associated with the liberation of endogenous catecholamines [10, 12-14]. Possibly the exhaustion of their reserves by octadine reduces the dilator effect of caffeine on interarterial anastomoses. The possibility is not ruled out that this action is effected through β-adrenergic structures of the heart [5]. It must be emphasized that caffeine, against the background of the action of octadine, caused an increase in the pressure in the ligated vessel, and this probably prevented the inflow of blood into the ischemic myocardium. Evidently blocking of the muscarine-like cholinergic structures of the heart by atropine creates conditions favoring the inhibitory action of caffeine on the coronary anastomoses and the heart, as manifested by a smaller increase in retrograde blood flow, accompanied by a progressive decrease in the arterial pressure.

Earlier investigations [1] showed that strophanthin, in a dose of 0.2 cat unit/kg, increases the retrograde coronary blood flow against the background of the pressor reaction of the arterial pressure, but when the arterial pressure was stabilized, it produced slight constriction of the anastomoses. Caffeine evidently potentiates the constrictor action of strophanthin, as revealed by the relatively smaller increase, or even a decrease in the retrograde blood flow produced by it. At the same time, marked disturbances of the cardiac rhythm were observed, and after an initial increase, the arterial pressure showed a progressive decrease, probably resulting from the toxic action of the combination of these drugs [2]. Depression of the coronary-dilator effect of methylxanthines when combined with strophanthin, with an increase in toxicity, has also been observed by other investigators [11].

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