Mechanisms Underlying Systemic Hemodynamic Responses to Experimental Coronary Artery Occlusion

A Preliminary Study with Hexamethonium

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SUMMARY

The hemodynamic changes induced by coronary occlusion were investigated in anesthetized dogs. Coronary occlusion elicited an immediate but transient increase in the systemic blood pressure and in the vascular resistance of the hind limb perfused at constant flow. Thereafter, systemic hypotension and vasodilatation in the perfused region were observed. Vagotomy abolished the initial increase of the systemic and perfusion pressure and reduced significantly the late vasodilator response both systemically and in the perfused hind limb. After the subsequent administration of hexamethonium the vasodilatation in the hind limb was no longer manifest but the fall in blood pressure was unmodified.

These results seem to suggest that multiple mechanisms are involved in the hemodynamic response to coronary occlusion.

Additional Indexing Words:

Vagotomy Perfusion pressure Perfused hind limb

IT is well documented that coronary occlusion produces a fall in peripheral vascular resistance and systemic hypotension.^{2),4),6)} The mechanism of this phenomenon is somewhat controversial. The observation that vagotomy reduces the magnitude of the response indicates the participation of vagal afferents in the mediation of this reflex. On the other hand, the factors responsible for the residual vasodilatation which is still demonstrable after vagotomy, have not been identified. The findings that coronary occlusion is followed by the activation of sympathetic nerves to skeletal muscle and that the electrical stimulation of the sympathetic nerves to the perfused paw is as-

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sociated with the release of a vasodilator substance,¹⁾ have prompted the hypothesis that the residual vasodilatation induced by coronary occlusion in vagotomized animals could be due to an unknown vasodilating agent.¹⁾ More recently, Bishop and Peterson,²⁾ while confirming the role of vagal afferents, suggested that part of the response could be related to the fall in cardiac output due to a direct depressant effect of myocardial ischemia on cardiac function. In view of the uncertainty still present in this subject we thought it would be of interest to further investigate the mechanisms underlying the hemodynamic changes induced by coronary occlusion in the dog.

MATERIALS AND METHODS

The experiments were performed on mongrel dogs of both sexes weighing 15–20 Kg. Anesthesia was induced with sodium thiopental (Farmotal, Farmitalia) (30 mg/Kg of body weight i.v.). A stable level of anesthesia was maintained throughout the experiment with additional doses of 30–40 mg of the same drug. The trachea was intubated and artificial ventilation was performed at a rate of 13–16 cycles per min after skeletal muscle relaxation induced by succinylcholine (Midarine, Wellcome) (0.2 mg/Kg i.v.) and maintained by repeated i.v. injections of 0.05 mg of the same drug.

Body temperature was periodically measured and maintained at 37–37.5°C by using a heated operating table. The arterial pO_2 was maintained above 90 mmHg and pCO_2 below 35 mmHg. Arterial pH was kept between 7.35–7.40 by i.v. administration of appropriate doses of disodium bicarbonate (90 mM in 0.9% saline). Arterial pO_2 , pCO_2 , and pH were evaluated by a hemogasanalyzer (Corning EEL 165).

The whole limb was prepared as previously described by Hanley et al.⁶⁾ After heparin i.v. administration (Liquemin, Roche) (500 U/Kg), the femoral artery to the hind limb was cannulated and perfused at constant flow with a Sigmamotor T8S peristaltic pump with blood from the same animal obtained through a polyethylene catheter introduced via the external iliac artery into abdominal aorta. In these conditions, changes in vascular tone of the perfused region were reflected by proportional changes in perfusion pressure. Blood flow rate was adjusted to give perfusion pressure slightly above systemic blood pressure, due to the resistance of the tubing system, and was left unchanged throughout the experiment. Perfusion pressure was measured from a T connection on the outflow side of the pump. Arterial blood pressure was continuously monitored through a catheter placed in the thoracic aorta via the contralateral femoral artery. A Battaglia-Rangoni multi-channel polygraph and pressure transducers were used. A thermoregulated delay loop (120 sec) was introduced in the perfusion system so that any substances which might be released into the blood stream would arrive at the artificially perfused area well after the end of the hemodynamic response.

Left thoracotomy was performed through the fifth intercostal space. The pericardium was opened with an incision parallel to the phrenic nerve. The main segment of the anterior descending coronary artery was dissected free along a longi-

tudinal incision made in the overstanding tissues in order to minimize injury to nerves accompanying the vessel. A loose ligature was then placed around the artery. The two ends of the ligature were then passed through a plastic sleeve so that artery could be reversibly occluded. During the coronary occlusion care was taken to avoid touching other parts of the heart or the lungs. Thus it was possible to exclude the possibility that the response could arise from mechanically stimulated adjacent thoracic structures.

A midline cervical incision was made and both the right and the left vagosympathetic trunks were exposed and dissected free from the common carotid artery. Loose ligatures were then placed around the carotid arteries. A femoral vein was cannulated for intravenous administration of drugs.

Statistical analysis was performed by Student's *t* test for paired observations.

Experimental protocol:

After the surgical procedures were completed the hemodynamic response to a 30-sec coronary occlusion was evaluated under control conditions in 7 dogs. Then the vagi nerves were cut and after systemic blood pressure stabilized, a second response to coronary occlusion was evaluated. Then, after injection of sodium nitrite (0.75 mg) and norepinephrine (0.5 μ g) into the perfused hind limb, hexamethonium was administered at the dose of 10 mg/Kg i.v. that has been demonstrated to induce ganglionic blockade⁷⁾ and the responsiveness of the hind limb vessels was tested by evaluating a second hemodynamic response to sodium nitrite and norepinephrine. In these conditions a third coronary occlusion was performed.

RESULTS

Fig. 1A illustrates the changes in mean systemic blood pressure (BP) and mean perfusion pressure (PP) of the hind limb induced by coronary occlusion.

Fig. 1. Changes in systemic blood pressure (B.P.) and hind limb perfusion pressure (P.P.) induced by coronary occlusion in the basal state (A), after vagotomy (B) and vagotomy plus i.v. administration of hexamethonium (C). Each point represents mean $\pm$ 1 S.E. of seven experiments. Statistical analysis was performed comparing each value to the corresponding time zero by the *t* test for paired observations. One or two asterisks indicate $p < 0.05$ and $p < 0.01$, respectively. Arrows indicate the duration of coronary occlusion.

BP rapidly rose from the basal value of 162 ± 5 mmHg to 169 ± 5 mmHg ($p < 0.05$) at 4 sec and then fell progressively reaching the nadir of 135 ± 9 mmHg ($p < 0.05$) at the termination of the coronary occlusion. Thereafter, BP returned slowly to the baseline. Similarly, PP transiently increased at 4 sec (from 175 ± 7 mmHg to 184 ± 8 mmHg, $p < 0.05$), fell significantly to 154 ± 8 mmHg ($p < 0.005$) by the end of the coronary occlusion, and then returned to values not different from baseline. Heart rate (105 ± 6 beats/min in the basal state) increased significantly to 116 ± 4 ($p < 0.05$) at 4 sec, but later fell to 82 ± 9 ($p < 0.01$) 28 sec after the beginning of coronary occlusion.

The transient increase in BP and PP observed in the control experiments was completely abolished by vagotomy (Fig. 1B). Both BP and PP fell significantly following coronary occlusion ($p < 0.05$ and $p < 0.05$). However, the absolute decrement in BP after vagotomy (12 ± 8 mmHg) was significantly smaller ($p < 0.05$) than that observed in the control experiments (29 ± 10 mmHg). In a like manner, the fall in PP induced by coronary occlusion in vagotomized dogs (18 ± 3 mmHg) was significantly smaller ($p < 0.05$) than in control studies (23 ± 3 mmHg). Hexamethonium treatment abolished completely the vasodilatation in the perfused hind limb but was without any effect on BP which fell from 100 ± 5 mmHg to 78 ± 7 mmHg ($p < 0.01$) 28 sec after the beginning of the coronary occlusion (Fig. 1C). The absolute decrement in BP observed in vagotomized dogs after hexamethonium treatment was not statistically different from that induced by coronary occlusion after vagotomy alone (Fig. 2). Heart rate did not show any statistically significant change during coronary occlusion both after vagotomy alone (from 125 ± 7 beats/min

Fig. 2. Maximum change in mean systemic blood pressure (Δ B.P.) and perfusion pressure (Δ P.P.) induced by a 30 sec coronary occlusion in the basal state (A), after vagotomy (B) and vagotomy plus i.v. administration of hexamethonium (C). * indicates $p < 0.05$ when statistical comparison is made between A and B or A and C; ▲ indicates $p < 0.05$ when statistical analysis is performed between B and C.

to 137 ± 4 beats/min, n.s.), and after vagotomy plus hexamethonium administration (from 97 ± 10 beats/min to 109 ± 8 beats/min, n.s.).

DISCUSSION

The current data that vagotomy reduces significantly the fall in blood pressure following coronary occlusion are in agreement with previous reports underscoring the role of vagal afferents in the genesis of this hemodynamic response. In this respect, it has also been reported that the increased activity of the vagal afferents coincides with the systolic bulging of the ischemic myocardium thereby suggesting that the stimulus is mechanical in nature rather than chemical.⁵⁾ Furthermore, the observation that hexamethonium abolishes the vasodilatation in the perfused hind limb could be explained by the hypotheses that the vasodilatation in the perfused hind limb would be mediated by a vasodilating substance released during sympathetic overactivity¹⁾ or by the sympathetic cholinergic vasodilator fibers.⁷⁾ The failure of hexamethonium to prevent the systemic hypotension suggests that factors other than a nervous reflex may be involved in the hemodynamic response to coronary occlusion. In this regard, it has been reported that coronary occlusion is followed by a fall in cardiac output due to a direct depressant effect of myocardial ischemia on cardiac function,²⁾ which, obviously, is not influenced by hexamethonium. On the other hand, the observation that hexamethonium leaves the systemic hypotensive response unchanged could be due to the simultaneous abolition of two different mechanisms which tend to antagonize each other, that is, the baroreceptor reflex and the above-mentioned release of a vasodilating substance.

A small but significant increase in systemic blood pressure was observed soon after the beginning of coronary occlusion and preceded the fall in peripheral resistances. This phenomenon which disappears after vagotomy might be explained by the stimulation of stretch receptors in the occluded coronary artery which generates afferent impulses running in the vagi nerves. The existence of such mechanoreceptors, characterized by a discharge frequency directly related to coronary perfusion pressure, is well documented.³⁾

Our results do not allow any conclusion to be drawn as to the mediators of the decrease in resistance in the hind limb which occurs on coronary artery occlusion but indirectly support the hypothesis that the fall in cardiac output induced by myocardial ischemia mediates, at least partially, the fall in systemic blood pressure observed during coronary occlusion in vagotomized dogs. Furthermore, the small increase in systemic blood pressure which immediately follows coronary occlusion seems to suggest that the coronary mechanorecep-

tors act as a baroreceptorial area. This observation is in agreement with the findings of Zelis et al⁸⁾ who reported the occurrence of a reflex vasodilatation during coronary angiography probably due to the activation of coronary mechanoreceptors evoked by the injection of the contrast into the coronary artery.

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