Cutaneous and Muscular Vasodilation in the Canine Hindlimb Evoked by Central Stimulation

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SUMMARY Using stereotaxic procedures, we electrically stimulated specific sites in the hypothalamus and midbrain of anesthetized dogs pretreated with guanethidine and atropine methonitrate. A tract in which stimulation caused noncholinergic dilator responses in the hindlimbs was identified. The course of this trace was different from that subserving cholinergic vasodilation in the hindlimb musculature. In a number of experiments we studied the proportional distribution of blood flow to leg and paw. Responses restricted to the paw were regarded as occurring mainly in cutaneous vessels; those restricted to the leg were regarded as occurring mainly in the skeletal muscle vessels. Some dilator responses in both beds were abolished by intra-arterial administration of antihistamines; other dilator responses were abolished by intra-arterial injections of dopamine antagonists. Centrally evoked dilation of leg and paw vessels by noncholinergic pathways suggests physiological roles for these fibers in the regulation of cardiovascular function.

CHOLINERGIC sympathetic vasodilator fibers supplying the vascular bed of the hindlimb musculature in the dog and the cat first were demonstrated by Bülbbring and Burn* and subsequently their central projections through the hypothalamus were described by Eliasson et al. and Abrahams et al. In both species, peripheral stimulation of the sympathetic nervous system when the effects of acetylcholine are abolished by atropine still can produce dilation of the vascular bed of the hindlimb. This dilation occurs in both muscle and skin and is partly sensitive and partly resistant to the action of antihistaminic agents. Studies employing electrical stimulation of the medulla also have provided evidence for dilator responses in the hindlimb that cannot be attributed to activation of sympathetic choliner
gic fibers. In a preliminary report, Bell et al. demonstrated that electrical stimulation at specific loci in the hypothalamus and midbrain of the dog can evoke noncholinergic dilations in the hindlimb. Our present study has extended these findings to investigate the distribution of the nonchol
ergic dilator nerves between leg and paw and to obtain pharmacological evidence for the peripheral transmitters involved.

Methods

Mongrel dogs of either sex and weighing 12-22 kg were anesthetized with chloralose (70 mg/kg, iv) after induction with thiopental (thiopentone) sodium. Supplemental doses of chloralose were administered during the experiment to maintain constant anesthesia, and all dogs were artificially ventilated. Blood flow in one or both femoral arteries was recorded by cuff-type electromagnetic flow probes and a Devices flow meter. Systemic blood pressure was recorded from a branch of the right femoral artery with a Beckman pressure transducer, and heart rate was recorded from standard electrocardiographic limb leads integrated through a cardiotachometer coupler. Results were recorded on a four-channel Beckman R 411 Dynograph recorder. All dogs were treated with guanethidine sulfate (5 mg/kg, sc) 18 and 2 hours prior to the experiment in order to abolish adrenergic vasomotor tone and to prevent peripheral dilator responses due to inhibition of adrenergic discharge. The efficacy of this procedure was checked at the end of each experiment by confirming that systemic administration of hexamethonium bromide (10 mg/kg, iv) had no effect on femoral flow and little (a decrease of less than 10 mm Hg) or no effect on arterial blood pressure.

The dogs were immobilized in a standard stereotaxic apparatus, and coaxial stimulating electrodes (Rhodes Medical Instruments, NE 100) were passed vertically through a window in the skull into the left hypothalamus and midbrain as determined by Horsley-Clarke coordinates. Initially, electrodes were placed 3.5 mm lateral to the stereotaxic midline and stimulation was performed at depths of 25 mm or more from the cortical surface. If no responses were evoked in this plane, electrodes were placed 2 mm and 5 mm lateral to the midline. Stimuli were rectangular pulses provided by a Grass SD9 stimulator at 60 Hz. Pulse duration was 2 msec and current was constant between 0.3 and 1 mA. Each period of stimulation lasted 20-30 seconds.

Occasionally graded dilator responses were produced over a vertical range of 2-4 mm, suggesting some spread of stimulating current. In these cases the correct electrode placement was taken to be that at which the maximum dilator response occurred. Data for maximal dilator responses were pooled to calculate mean increases in flow. Differentiation between dilations in the vasculature of the leg and paw was facilitated by application of a bandage ligature just above the ankle during electrical stimulation. At the conclusion of an experiment the brain was perfused with buffered 10% formaldehyde and the sites of stimulation were determined by macroscopic examination and measurement of the electrode tracts in a parasagittal section through the stimulation plane. In later experiments electrolytic lesions were made at the stimulation sites and histological examination

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of coronal sections was carried out after staining with the cresyl-fast violet method of Keller.12

Drugs used were acetylcholine chloride (Sigma), atropine methonitrate (Sigma), burimamide (Smith, Kline and French), ergometrine maleate (Burroughs Wellcome), glyceryl trinitrate (Anginine, Burroughs Wellcome), guanethidine sulfate (Ciba), haloperidol (Searle), hexamethonium bromide (May and Baker), histamine acid phosphate (David G. Bull), indomethacin (Merck, Sharp and Dohme), isoproterenol (isoprenaline) hydrochloride (Sterling), mepyramine maleate (May and Baker), and propranolol hydrochloride (Imperial Chemical Industries).

The following protocol was used routinely during pharmacological analysis of noncholinergic dilator responses to brain stimulation. Dilations obtained in the presence of atropine first were tested for inhibition by antihistamines. Mepyramine was used in all experiments and was supplemented with burimamide in several. In some experiments any responses resistant to antihistamine treatment were tested further with antagonists to other possible dilator transmitters. In all experiments responses not abolished by one or more of the above treatments were tested for neural origin by ensuring that they were abolished by systemic ganglionic blockade with hexamethonium.

**Results**

**EFFECT ON FEMORAL BLOOD FLOW OF DILATOR AGENTS AND ANTAGONISTS**

Intra-aortic injection of acetylcholine (0.1–1.0 μg), isoproterenol (0.1–1.0 μg), or histamine (2–50 μg) caused femoral vasodilation and increased femoral blood flow. The action of acetylcholine was abolished by atropine methonitrate (0.4 mg/kg, iv) and that of isoproterenol was abolished or considerably attenuated by propranolol (0.1 mg/kg, iv). The dilator responses to histamine were abolished entirely in 22 of 36 dogs by mepyramine (2 mg/kg, ia), but were only reduced in the remaining 14 dogs. In six of these cases administration of the histamine H2-receptor antagonist burimamide13 (2 mg/kg, ia), abolished the mepyramine-resistant response, but in the remaining dogs burimamide had no effect. Burimamide only slightly reduced the response to histamine in two of four dogs in which it was administered alone. None of the above antagonists reduced femoral dilator responses to glyceryl trinitrate (10–50 μg, ia).

**EFFECT OF ELECTRICAL STIMULATION ON FEMORAL BLOOD FLOW**

Electrical stimulation at various sites in the hypothalamus and midbrain produced a variety of cardiovascular responses, including pressor and depressor effects, as well as motor activation. Only increases in femoral blood flow which occurred in the absence of concurrent increases in blood pressure and heart rate and without motor activation were regarded as being true dilator responses.

During initial experiments on 34 dogs, dilator responses to central stimulation were studied prior to the administration of atropine. Cholinergically mediated responses could be elicited in 33 dogs (Fig. 1). In 21 of the 34 dogs other central loci were found at which stimulation caused femoral dilations which were not affected by atropine treatment. In subsequent experiments atropine was injected at the beginning of the experiment. In 21 of these additional dogs loci were found at which electrical stimulation produced noncholinergic dilator responses (Fig. 2).

In this total of 42 dogs, the mean resting flow through the left femoral artery was 9.80 ± 1.52 (mean ± SEM) ml/min per kg. The magnitude of the noncholinergic dilator responses obtained varied among individual dogs and in some dogs responses were obtained at more than one locus of stimulation. The mean magnitude of all such dilator responses was an increase in flow of 1.81 ± 0.19 ml/min per kg (n = 59). These noncholinergic responses were associated with decreases in blood pressure of up to 40 mm Hg but with no changes in heart rate.

**LOCALIZATION AND PHARMACOLOGICAL ANALYSIS OF NONCHOLINERGIC DILATOR RESPONSES EVOKED BY ELECTRICAL STIMULATION**

In 22 dogs we recorded blood flow through both left and right femoral arteries. Central stimulation caused dilator responses in both legs in 12 dogs, but in the remaining dilation was restricted to the left leg (the ipsilateral leg with respect to the site of stimulation). In these dogs right (contralateral) femoral flow sometimes decreased during the period of left femoral dilation (Fig. 2). Contralateral dilator responses never were observed in the absence of ipsilateral dilation.
just above the paw during electrical stimulation. The mean femoral blood flows (ml/min) from anesthetized dogs after treatment with guanethidine and atropine methonitrate, showing responses to electrical stimulation (——). The upper record is from a dog in which the dilation produced in the left leg (L) by electrical stimulation was unaffected during occlusion (occl.) of the paw. The dilator response was unilateral and the femoral flow decreased in the right leg (R) during electrical stimulation. The lower record is from a dog in which the dilator response to electrical stimulation was abolished during occlusion of the paw.

We differentiated dilation of the vasculature of the leg from that of the paw by application of a bandage ligature just above the paw during electrical stimulation. The mean decrease in left femoral blood flow produced by paw occlusion was 1.79 ± 0.38 ml/min per kg (n = 42). In most of the dogs studied stimulation at all active sites elicited dilator responses in only one or the other of these beds. However, in some dogs responses of the paw circulation were obtained after stimulation of some active sites, and responses of the leg circulation followed stimulation of other active sites. In a total of 26 experiments occlusion of the left paw with a ligature prevented the production of atropine-resistant dilation during central stimulation (Fig. 2). In 15 of these experiments mepyramine (2 mg/kg, ia) abolished or reduced the response to central stimulation, whereas in the remainder responses were not affected by mepyramine. Mepyramine-sensitive dilator responses in the paw were reduced from a mean increase in flow of 1.31 ± 0.22 to 0.49 ± 0.09 ml/min per kg (n = 15). In four of the dogs in which mepyramine did not abolish the dilator response completely burimamide (2 mg/kg, ia) also was administered. Reduction of responses to stimulation was observed in only one dog.

In cases in which paw occlusions had no effect on femoral dilator responses to central stimulation (Fig. 2), it was assumed that the dilation occurred in the leg. In two of these dogs the leg was skinned. This procedure did not affect the dilator response to stimulation, and resting flows were not changed (less than 5%). It seems likely, therefore, that the dilator responses in the leg occurred in the vasculature of the skeletal muscle. Mepyramine (2 mg/kg, ia) abolished or greatly reduced these responses in nine of 23 dogs, but had no effect on the remainder. The responses sensitive to mepyramine were reduced from a mean of 1.85 ± 0.25 to 0.61 ± 0.22 ml/min per kg (n = 9). In three dogs in which mepyramine was ineffective the additional administration of burimamide (2 mg/kg, ia) was without effect.

In view of the large number of responses which were resistant to blockade by antihistamines, an attempt was made to gain some insight into the possible mediator involved. We demonstrated in a number of experiments that the mepyramine-resistant dilations were abolished by administration of the ganglion-blocking agent hexamethonium (10 mg/kg, iv) and thus established that the responses were neurogenic. Propranolol (0.1 mg/kg, iv) abolished or greatly reduced femoral responses to intra-arterial isoproterenol (0.05–1 μg), but had no effect on responses to central stimulation, indicating that activation of femoral β-adrenoceptors was not involved. In view of the suggestion that E-type prostaglandins may participate in neurogenic dilator responses of the dog leg to sympathetic chain stimulation, indomethacin (10 mg/kg, iv) was administered to two dogs to prevent synthesis of prostaglandins. One hour after this treatment there was no reduction in responses to central stimulation.

Dopamine is a third substance presently under consideration as a transmitter causing vascular dilation. Evidence has been presented that in the canine femoral bed there are receptors for dopamine that are distinct from adrenoreceptors and that produce vasodilation. It has been shown that, in the dog, haloperidol and ergometrine act as specific blocking agents at vascular dopamine receptors, therefore these drugs were tested the present experiments using doses that in previous studies had selectively antagonized dopamine.

The mepyramine-resistant dilation in the leg was abolished in two dogs after intra-aortic administration of ergometrine, 0.5 mg, but was unaffected in three others. In contrast, this dose of ergometrine abolished the mepyramine-resistant paw dilation in the five dogs tested (Fig. 3). Haloperidol (2 mg, ia) also abolished the dilator response of the paw in one dog tested. Neither ergometrine nor haloperidol antagonized femoral dilator responses to glyceryl trinitrate or isoproterenol.

CENTRAL PROJECTION OF DILATOR PATHWAYS

When composite longitudinal maps were prepared from the series of dog brains, it was found that different pathways...
VASODILATION DUE TO CENTRAL STIMULATION / Lang et al.

Figure 4 Longitudinal sections through hypothalamus and midbrain of the dog. In the upper diagram are shown sites at which electrical stimulation in a series of dogs produced noncholinergic dilator responses restricted to the vasculature of the leg above the paw. In the lower diagram are shown sites at which electrical stimulation in a series of dogs produced noncholinergic dilator responses restricted to the vasculature of the paw. Electrical stimulation at sites shown by ▲ elicited antihistamine-sensitive vasodilation and at sites shown by ● elicited antihistamine-resistant vasodilation, MI = the massa intermedia; P = the pituitary stalk; S = the substantia nigra. Although stimulation was carried out in planes 2-5 mm lateral to the midline, the diagrams are shown as midline sections for convenience.

Figure 5 Sites, in a series of dogs, at which electrical stimulation elicited dilator responses restricted to the vasculature of the leg above the paw. The diagrams show coronal sections of the dog brain at two planes, 10 ± 2 mm and 16 ± 2 mm anterior to stereotaxic zero. The shaded rectangles indicate the area in which electrical stimulation was performed. ■ = dilator responses abolished by antihistamines; ▲ = dilator responses unaffected by antihistamines; and ★ = dilator responses the susceptibility of which was not tested with antihistamines. In the section labeled 10 ± 2 mm, the sites appear to be in the vicinity of the nucleus cuneiformis (1) and more ventrally near the nucleus ruber (2). In the section labeled 16 ± 2 mm the sites are near the region of the fasciculus mamillothalamicus (3) and the columna fornici (4).

Discussion

Electrical stimulation of various sites in the hypothalamus and midbrain produced dilator responses in the hindlimbs of dogs that had been pretreated with guanethidine and atropine. These noncholinergic responses were unaffected by propranolol, and were not associated with any increase in blood pressure or heart rate. Therefore they were not the result of adrenal activation. Administration of hexamethonium caused no appreciable increase in femoral blood flow or reduction of systemic blood pressure, and it is concluded that the dilator responses were not the result of inhibition of any adrenergic vasomotor tone remaining after guanethidine pretreatment.

The noncholinergic dilations produced by electrical stimulation were abolished or reduced by the histamine H1-receptor antagonist mepyramine in many experiments. In only one of several experiments addition of the histamine H2-receptor antagonist burimamide, abolished the dilation still observed after mepyramine. Antihistamine-sensitive dilator responses of this nature were present in the vasculature of both the paw and the leg.

In the most rostral planes the tract responsible for noncholinergic dilator responses was located in the region of the fasciculus mamillothalamicus and the columna fornici. More posteriorly the tract appeared to diverge and pass both in the vicinity of the nucleus ruber and more dorsally near the nucleus cuneiformis. However, it was not possible either with longitudinal or coronal mapping to delineate clearly between active sites associated with antihistamine-sensitive and antihistamine-resistant responses or between those associated with responses localized to the leg or the paw.
Previous studies have suggested the existence of peripheral dilator fibers which are histaminergic. Peripheral sympathetic nerve stimulation after adrenergic neuron blockade has been shown to cause antihistamine-sensitive vasodilation in the skeletal musculature of the dog hindlimb, whereas Brody and Shaffer reported that reflexly produced vasodilation in the leg was attenuated by antihistaminic agents. Liyo and White and Graham and Liyo found that peripheral stimulation of the lumbar ventral spinal cord caused both an antihistamine-sensitive femoral dilation and release of histamine into the circulation. Aoki and Brody reported that noncholinergic dilator responses in the canine hindlimb to electrical stimulation of the medulla were antagonized by antihistamines, whereas Tuttle found that similar responses in the cat were associated with an increase in circulating histamine.

Yeh et al. reported that, within a relatively narrow dose range, intra-arterial injections of haloperidol attenuated dopamine-induced vasodilation in canine renal and mesenteric beds without affecting the vasodilation produced by isoproterenol or bradykinin. We recently have shown that ergometrine, in the dosage used in this paper, is an effective antagonist of dopamine receptors in the canine kidney and hindlimb while having no antagonistic effect on the dilator activities of acetylcholine, histamine, isoprenaline, 5-hydroxytryptamine, or bradykinin. In some of the present experiments the dilator responses to central stimulation that were unaffected by antihistamines were abolished by these dopaminergic antagonists. Haloperidol abolished the dilation in the paw in one experiment. In five additional dogs the paw dilation was abolished by ergometrine. This abolition of centrally evoked femoral dilation by ergometrine therefore might suggest the existence of dopaminergic nerves supplying the vasculature of the paw. Recent results have indicated the presence of dopaminergic innervation of the dog renal vasculature.

In contrast, ergometrine did not consistently affect the antihistamine-resistant dilator responses that occurred in the leg, indicating that its effect on responses in the paw was unlikely to be attributable to a general depressant effect on autonomic function, and suggesting the possible existence of a third population of noncholinergic dilator nerves supplying the leg vessels.

Dopamine injected into the femoral bed activates both vasoconstrictor \( \alpha \)-adrenoceptors and vasodilator dopamine receptors. The dilator effect is, however, often masked by the vasoconstriction unless \( \alpha \)-adrenoceptor antagonists are administered. In the same way, \( \alpha \)-adrenoceptor blockade reveals epinephrine-induced vasodilation due to \( \beta \)-adrenoceptor activation. This raises the question of how dopaminergic nerves could produce the observed femoral vasodilation through the activation of an admixture of \( \alpha \)-adrenoceptors and dopamine receptors. One possibility is that neuronally released dopamine causes vasodilation in a specific region of the femoral bed where dopamine receptors predominate. In addition, it must be remembered that in many blood vessels neurally released dopamine acts as a modulator of vasomotor tone in many of the dogs used.
transmitter probably acts only on receptors situated at the outermost surface of the media.28 Injected antagonists, in contrast, will act primarily on receptors adjacent to the lumen and there is no reason to assume that the two populations of receptors are identical. It is possible, therefore, that even within the same vessel segment a substance released from the vasomotor nerves could affect the vessel differently from the same substance injected intraluminally. An alternative explanation consistent with the results obtained by use of ergometrine and haloperidol is that these compounds may be acting presynaptically to prevent the release of an unknown transmitter substance. Additional biochemical data are needed before the possibility of dopaminergic nerves innervating the femoral vasculature can be confirmed.

Stimulation of some active sites in the hypothalamus and midbrain produced bilateral noncholinergic responses. Eliasson et al.29 reported that the cholinergic vasodilator outflow also has a bilateral representation at this level. In a study in which sites in the medulla were stimulated, Aoki and Brody30 found bilaterality of noncholinergic vasodilatation. It is uncertain why in the present experiments we observed bilaterality of responses only in a minority of dogs. Damage to the central pathways involved in decussation cannot be excluded. On the other hand, our results may merely reflect the neurological data suggesting that most descending autonomic projections from the hypothalamus are uncrossed.30 The course of the tract through the hypothalamus and midbrain responsible for the production of noncholinergic dilator responses in the hindlimb of the dog is different from the tract involved in the production of cholinergic dilator responses. Lindgren et al.31 observed that the latter pathway differed from most of the descending hypothalamic outflow32 in that it rises dorsally into the tectal area, and this characteristic also was noted in our observation on the course of the pathway producing atropine-sensitive responses. From the present results it appears that the tract concerned with noncholinergic vasodilatation may parallel the course of the medial lemniscus but be located more centrally.

In coronal sections the localization of active sites around the fasciculus mamillothalamicus is consistent with the accumulated neurological data on the course of the autonomic pathway through the hypothalamus.33 Furthermore, the sites appear to follow the pathway thought to contain the majority of descending mesencephalic autonomic tracts. These have been reported to be associated with gray matter adjacent to the aqueductus and with the region bordered by the nucleus nervi oculomotorii and nucleus ruber.34 The spread of active sites found in the mesencephalic planes agrees with the findings of Magoun et al.,32 that the ascending autonomic pathways at the midbrain level have wide representation. The apparent grouping of sites in the vicinity of the nucleus ruber and the nucleus centralis may indicate the existence of two tracts, but this can be confirmed only by more extensive mapping into the midbrain and the hindbrain.

The present results do not allow anatomical separation of the noncholinergic tract into different pathways associated with dilator responses which are either sensitive or resistant to antihistamine drugs. Neither do they permit differentiation of the pathways responsible for vasodilatation in the leg or paw. Furthermore, there is at present no known correlation of the responses with behavioral changes. Nevertheless, the demonstration that noncholinergic dilation can be elicited in the hindlimb, not only by brainstem or peripheral nerve stimulation but also by stimulation of specific sites in the forebrain and midbrain, reinforces the idea that such responses serve some role in the central regulation of cardiovascular function.

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Regional Cardiac Prostaglandin Release during Myocardial Ischemia in Anesthetized Dogs

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SUMMARY  Cardiac prostaglandin release was studied in closed-chest dogs during acute coronary occlusion. Aortic and coronary sinus blood was obtained before, and at intervals after, balloon occlusion of the left anterior descending artery in seven dogs. Samples were assayed for prostaglandins F, E, and A by radioimmunoassay. All dogs demonstrated prostaglandin F release. Mean ± se postocclusion aortic levels were 0.26 ± 0.01 ng/ml; coronary sinus levels were 0.67 ± 0.01 ng/ml (P < 0.001). In six dogs, prostaglandin E also was released. Mean postocclusion aortic levels were 0.24 ± 0.01 ng/ml; coronary sinus, 0.44 ± 0.01 ng/ml (P < 0.001). There was no release of prostaglandin A. To examine the site of prostaglandin release, simultaneous samples from the aorta, the coronary sinus, and the great cardiac vein were obtained before and after left circumflex artery occlusion in six additional studies. The great cardiac vein drained effluent from nonischemic myocardium, whereas the coronary sinus drainage included blood from both ischemic and nonischemic zones. All six dogs demonstrated prostaglandin F release from the ischemic region. Mean postocclusion aortic prostaglandin F was 0.32 ± 0.01 ng/ml. Coronary sinus prostaglandin F was 1.69 ± 0.03 ng/ml (P < 0.001), whereas the great cardiac vein level remained at 0.34 ± 0.01 ng/ml (P > 0.05). Prostaglandin E was released from both ischemic and nonischemic regions. Mean aortic prostaglandin E was 0.21 ± 0.01 ng/ml; great cardiac vein, 0.55 ± 0.02 ng/ml (P < 0.001); and coronary sinus, 1.07 ± 0.04 ng/ml (P < 0.001). These results have led us to conclude that the different local availability of prostaglandins E and F may influence the cardiac response to ischemia.

THE RELEASE of prostaglandins from tissues subjected to acute ischemia was first demonstrated by McGiff et al.1 in the canine kidney. Prostaglandin (PG) biosynthesis has been documented in the isolated perfused rabbit heart exposed to hypoxia, mechanical massage, elevated preload, vagal stimulation, and adenosine triphosphate or acetylcholine administration.2-8 Ischemia and anoxia have manifested variable effects on PG biosynthesis,3-5,7,9 whereas acidosis, hyperthermia, hypothermia, hyperosmolality, and hyperkalemia all were without effect.9 Studies utilizing the open-chest dog have shown an increase in prostaglandins in coronary venous blood during postocclusive reactive hyperemia.10,11 The same finding is reported following coronary occlusion in the canine heart-lung preparation.12 These data are significant because of the known vascular actions of these compounds. It generally is agreed that intracoronary administration of prostaglandin E (PGE) produces increased inotropy, chronotropy, and coronary blood flow, whereas intravenous administration produces a marked fall in systemic vascular resistance and arterial pressure.13-14 In contrast, intracoronary administration of prostaglandin F (PGF) has little effect on coronary hemodynamics or ventricular function, but this agent does increase systemic arterial pressure when infused intravenously in large doses.15 It has been suggested that prostaglandins may play a role in the cardiac response to ischemia. In the present study, the cardiac release of PGF, PGE, and PGA was studied in closed-chest dogs during acute coronary occlusion. The identification and quantification of PG release by radioimmunoassay, the time course, and the regional distribution of release were determined.

Methods

Initial experiments (group I) were designed to determine whether prostaglandins are released from the heart following coronary occlusion; and if so, which are released and the time course of release. Subsequent experiments (group II) investigated the site of PG release by selective sampling of venous drainage from ischemic and nonischemic myocardial regions.

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