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Prostaglandins Modulate Baroreflex-Induced Changes in Blood Pressure and Myocardial Function in Anesthetized Dogs[1] (42256)

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Abstract. The purpose of our study was to investigate the role of prostaglandins in the changes in myocardial function and peripheral and coronary vascular resistance which accompany a generalized increase in sympathetic tone caused by carotid baroreflex unloading in the anesthetized dog. Bilateral carotid artery occlusion (BCO) with heart rate held constant by electrical pacing (150 beats/min) resulted in increases in systolic, (33%) diastolic (40%), and mean (35%) arterial pressures, LV systolic pressure (33%) and left ventricular (LV) dP/dt (37%). After blockade of prostaglandin synthesis with indomethacin ($N = 11$) or meclofenamate ($N = 6$) the increases in systolic (41%), diastolic (45%), and mean (41%) arterial pressures, LV systolic pressure (39%), LV dP/dt (52%), and cardiac work caused by BCO were significantly greater, in spite of the initially higher baseline values (11–18%) following the administration of the drugs. In contrast, the changes in circumflex coronary blood flow and coronary vascular resistance to BCO were essentially the same before and after inhibition of prostaglandin synthesis. Systemic prostaglandin synthesis may, therefore, play a significant role in the control of systemic arterial pressure and myocardial function, most probably by modulating the release of norepinephrine from adrenergic nerve terminals, without adversely affecting coronary blood flow regulation.

Previous studies in the isolated perfused hind limb of the dog (1–3) in the isolated rabbit heart (4, 5), and in the isolated spleen (6) have shown that the release of norepinephrine (NE) or the effects of stimulating the efferent adrenergic nerves are greater following the inhibition of prostaglandin (PG) synthesis. Infusion of PGE_1, PGE_2, or PGA_2 blunted the release of NE or the changes in cardiac function associated with adrenergic nerve stimulation (7). Similar results have been obtained in isolated blood vessels (8, 9) and atrial strips (10). These studies imply that the local production of prostaglandins modulates peripheral vascular resistance and myocardial function via the feedback inhibition of NE release from the adrenergic nerve endings. Prostaglandins may, in addition, modulate the actions of NE by affecting vascular muscle reactivity in resistance vessels (11, 12). The regulation of arterial pressure by these mechanisms has, however, never been tested in the whole animal.

Whereas prostaglandins may influence peripheral vascular control, they do not seem to modify the regulation of coronary blood flow (13–15), the coronary vascular response to increased cardiac work, or the response to catecholamine injection into the coronary arteries (16). The purpose of our study was to investigate the effects of systemic inhibition of prostaglandin synthesis on the changes in blood pressure and myocardial function induced by a generalized increase in sympathetic outflow resulting from carotid sinus hypotension. We also evaluated the role of endogenous prostaglandin synthesis and the changes in the control of coronary blood flow following baroreflex unloading.

Methods. *Animal preparation.* Male mongrel dogs ($N = 19$) weighing 19–30 kg (mean 22.0 ± 2) were anesthetized with a 50/50% mixture of Dial urethane (Ciba) and nembutal (Abbott), as previously reported (14), and ventilated with a mixture of room air and 95% O_2, 5% CO_2 at a positive end-expiratory pressure in order to maintain blood gases near normal. The femoral artery and vein were cannulated (PE240) for the injection of sup-

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plemental anesthesia and for blood sampling. The brachial artery was cannulated in the left axilla for the measurement of arterial pressure (P1000A, Narco), and the carotid arteries were isolated in the neck for later clamping.

The dog was then placed on his left side and the right atrium was approached via a right thoracotomy. Since heart rates using this type of surgical procedure are high (14) hearts were paced at a comparable rate. We also found in preliminary experiments that simply tying off the SA node often leads to a high intrinsic rate later in the experiment; therefore, we resorted to excising the node entirely. Accordingly, a cooling probe was used to locate the site of the sinoatrial node (SA), pacing electrodes were sutured to the right atrium, the SA node was crushed, tied off, and excised. Heart rates prior to pacing but after excision of the SA node were generally less than 60 beats/min some as low as 40 beats/min. The pacer (Grass model S44 stimulator attached to an SIU-10 isolation unit) was turned on and the dog paced at 150 beats/min throughout the remainder of the experiment. The pericardium was closed, the right side was closed in layers, and the lung was hyperinflated.

The dog was then turned on its right side, an incision was made in the fifth left intercostal space, and a pericardial cradle was formed. In seven of the experiments, an electromagnetic flow probe (Carolina Medical Electronics) was placed on the descending aorta for the measurement of aortic flow. The left ventricle was cannulated (PE260) via an apical stab wound and a purse string suture for the measurement of left ventricular pressure (P23Db, Statham) and the derivation of LV dP/dt via an electronic differentiator (Narco Biosystems). The left circumflex coronary artery was isolated (N = 10) approximately 2 cm from its origin for the placement of another flow probe (Carolina Medical). A 27-guage needle was inserted directly into the coronary artery for the injection of arachidonic acid to test the extent of PG synthesis inhibition. The heart was kept moist throughout the experiment with saline warmed to 37°C and saline-soaked gauze sponges. Blood flow was recorded using Model 501 electromagnetic flowmeters (Carolina Medical) on a direct writing recorder (Narco).

Experimental design. After surgery the animal was allowed at least 30 min to stabilize before experimentation. With the heart rate held constant the carotid arteries were occluded by clamps bilaterally (BCO) for 2 min while recording blood pressure, left ventricular (LV) pressure, LV dP/dt (N = 17), coronary blood flow (N = 10), and cardiac output (N = 7). The clamps were removed and the animal was allowed 15 min after return to baseline before another occlusion. Occlusions were repeated four times before the infusion of indomethacin (N = 11), meclofenamate (N = 6), or saline (N = 3) and four times after. Prostaglandin synthesis inhibition was assured in every experiment by blockade of the increase in coronary blood flow which resulted from the injection of arachidonic acid (600 μg) as previously reported (14). In one dog BCO was repeated four times after infusion of saline; then indomethacin was given and BCO repeated another four times. This dog was included in the indomethacin group.

Statistical analysis. The steady-state values for blood pressure, coronary blood flow, ventricular pressure, LV dP/dt, and cardiac output during BCO were taken in each case along with the baseline function just prior to BCO. The mean of the four responses prior to PG inhibition was compared to the mean of the responses after indomethacin, meclofenamate or saline along with the changes in baseline function caused by these drugs by analysis of variance. The changes in cardiovascular function in dogs that received indomethacin or meclofenamate were also compared and found not to be different. Therefore, for the final evaluation of the data these dogs were grouped together. Reference in the text to prostaglandin synthesis inhibition will be used to signify the combined data for indomethacin and meclofenamate. In three of the dogs the effects of saline adjusted to pH 8.0 (vehicle) were tested and found to have no effects on the changes in cardiac or peripheral vascular function to BCO. Mean arterial pressure was calculated as the systolic minus the diastolic pressure, divided by 3, plus the diastolic pressure; cardiac work was calculated as the mean arterial pressure times 1.36 gm/cm^2 times the aortic flow in cm^3/min. In Table I, calculations of coronary resistance (N = 10), cardiac work (N = 7), and peripheral resistance (N = 7) are based on only those animals in which pressure and flow were measured simultaneously. Resistance was

calculated as mean arterial pressure divided by flow.

Preparation of drugs. Indomethacin was prepared from the powder (Merck, Sharp and Dohme) by dissolving it in saline buffered to pH 8.0 with bicarbonate. Meclofenamate (Sandoz) was dissolved in 1.0 ml of 100°C NaOH (0.1 *N*) brought to volume with saline and adjusted with HCL (0.1 *N*) to pH 8.0. Arachidonic acid (Nuchek) was prepared in preweighed vials at a concentration of 10 mg/ml as reported previously (14).

Results. Control values before and after prostaglandin synthesis inhibition are shown in Table I along with the changes induced by bilateral occlusion of the carotid arteries. A recording from a single experiment is depicted in Fig. 1. Values are expressed as the means ± the standard error of the mean in the text, Table I, and Fig. 2.

TABLE I. EFFECTS OF BILATERAL CAROTID ARTERY OCCLUSION BEFORE AND AFTER INHIBITION OF PROSTAGLANDIN SYNTHESIS

	Control	*N*	Change from control with carotid occlusion
Left ventricular pressure (mm Hg)			
unblocked[a]	132 ± 4.2	17	44 ± 6.8*
PG-inhibition	147 ± 4.9		57 ± 10*,**
LVdP/dt (mm Hg/sec)			
unblocked	5864 ± 275	17	2062 ± 352*
PG-inhibition	6653 ± 429**		3109 ± 454*,**
Mean arterial pressure (mm Hg)			
unblocked	101 ± 3.0	17	37 ± 7.0*
PG-inhibition	118 ± 4.9**		49 ± 6.0*,**
Arterial systolic pressure (mm Hg)			
unblocked	118 ± 4.2	17	41 ± 7.3*
PG-inhibition	136 ± 4.5**		56 ± 7.3*,**
Arterial diastolic pressure (mm Hg)			
unblocked	93 ± 3.1	17	38 ± 6.6*
PG-inhibition	106 ± 4.3**		47 ± 6.9*,**
Mean coronary blood flow (ml/min)			
unblocked	25.8 ± 2.2	10	22 ± 4.9*
PG-inhibition	23.7 ± 3.0		20 ± 4.2*
Mean coronary resistance (mm Hg/ml/min)			
unblocked	4.39 ± 0.40	10	−0.61 ± 0.34
PG-inhibition	5.49 ± 0.57**		−0.57 ± 0.28
Cardiac output (ml/min)			
unblocked	1489 ± 172	7	179 ± 74
PG-inhibition	1871 ± 303**		25 ± 96
Total peripheral resistance (mm Hg/ml/min)			
unblocked	0.066 ± 0.006	7	0.003 ± 0.002
PG-inhibition	0.077 ± 0.011		0.027 ± 0.001*,**
Cardiac work (kg *M*/min)			
unblocked	1.89 ± 0.24	7	0.57 ± 0.16
PG-inhibition	2.74 ± 0.50**		0.80 ± 0.26*,**

[a] Unblocked = before prostaglandin (PG) synthesis inhibition.

* Significantly different from control ($P < 0.05$), by one-way analysis of variance (32).

** Significantly different from unblocked ($P < 0.05$), by two-way analysis of variance (32).

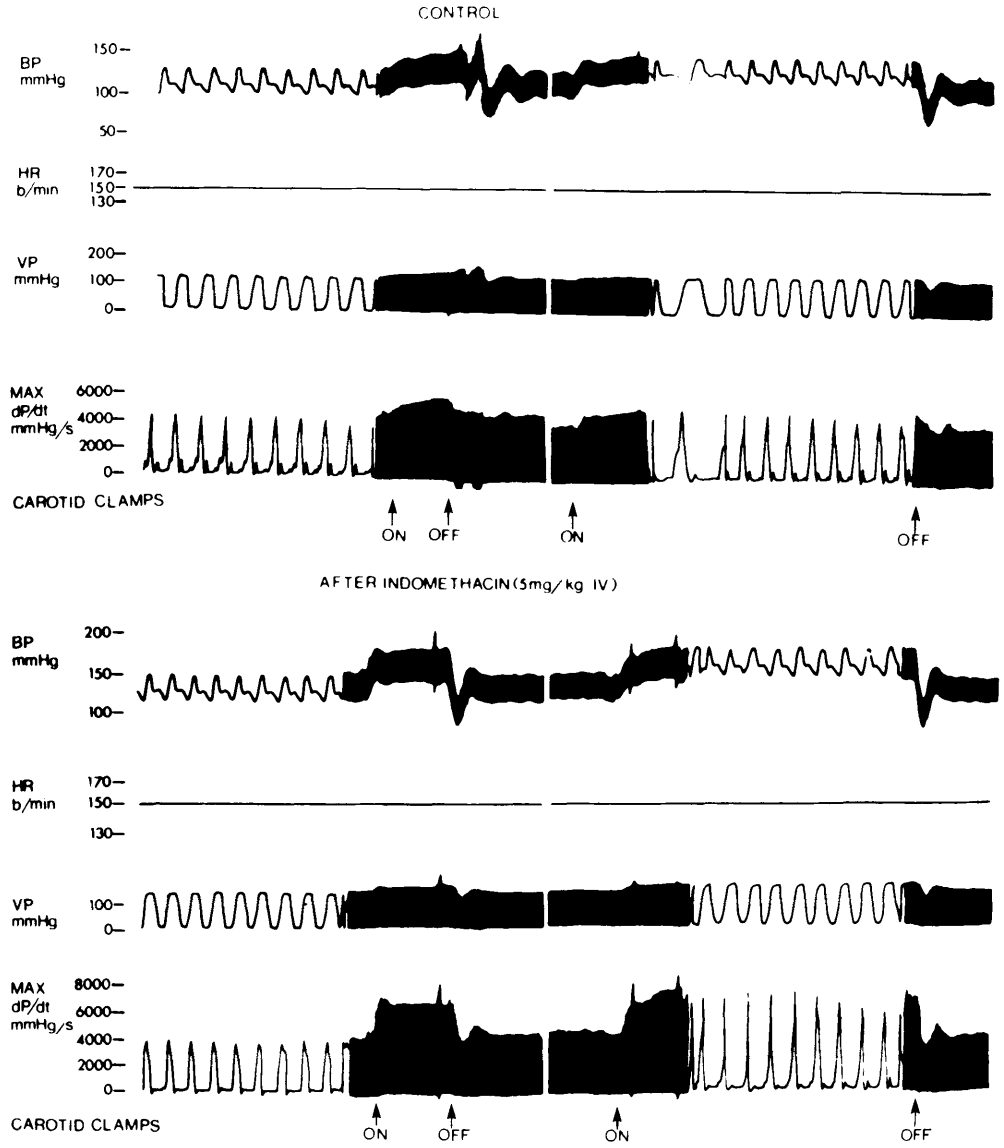

FIG. 1. Clamping the carotid arteries for 2 min (on–off) bilaterally results in increases in systemic arterial blood pressure (BP), left ventricular systolic pressure (VP), and maximum LV dP/dt (upper panel). After prostaglandin synthesis inhibition by indomethacin (lower panel), the changes in BP, VP, and LV dP/dt were significantly greater. Heart rate (HR) was held constant by electrical pacing. These records, showing two different procedures before and after PG synthesis inhibition are from a single dog.

Effects of carotid artery clamping (unblocked). Prior to blockade of prostaglandin synthesis with either indomethacin or meclofenamate bilateral carotid occlusion (Fig. 2) resulted in increases in systolic arterial pressure (33 ± 5.9%), diastolic arterial pressure (40 ± 6.7%), mean arterial pressure (35 ± 6.0%), left ventricular systolic pressure (33 ± 6.0%), and LV dP/dt (37 ± 6.7%). All these changes are significantly different from control (Table I). The change in cardiac work was not significant, however.

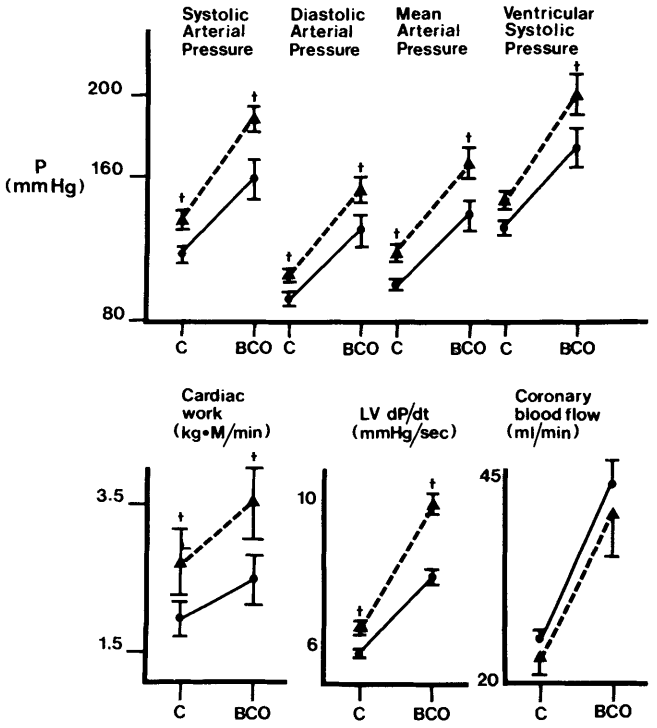

FIG. 2. The actual values of blood pressure, ventricular pressure, cardiac work, LV dP/dt, and coronary blood flow are shown during bilateral carotid occlusion (BCO) before (closed circles and solid lines, unblocked response) and after (triangles, dashed lines) inhibition of prostaglandin (PG) synthesis. PG synthesis inhibition by itself caused significant increases in arterial pressures, cardiac work, and LV dP/dt. With the exception of coronary blood flow, the actual changes after carotid artery clamping were also significantly greater after PG synthesis inhibition than before (+ indicates significant difference from unblocked response, $P < 0.05$; C = control, BCO = bilateral carotid occlusion; unit of LV dP/dt is in 1000 mm Hg/sec).

Effects of prostaglandin synthesis inhibition on baseline cardiovascular function. Prostaglandin synthesis inhibition (Table I) caused significant ($P < 0.05$) increases in systolic arterial pressure (16 ± 2.6%), diastolic arterial pressure (14 ± 3.8%), mean arterial pressure (18 ± 4.4%), LV dP/dt (13 ± 4.4%), cardiac output (26 ± 12%), and cardiac work (44 ± 18%), but not in peripheral resistance (15 ± 12%). Although prostaglandin synthesis inhibition increased coronary vascular resistance significantly (25 ± 7.9%), the decrease in coronary blood flow (−9.7 ± 5.7%) was not significant ($P > 0.10$).

Effects of carotid artery occlusion after prostaglandin synthesis inhibition. After prostaglandin synthesis inhibition carotid artery occlusion (Fig. 2) increased systolic arterial pressure (41 ± 4.9%), diastolic arterial pressure (45 ± 6.6%), mean arterial pressure (41 ± 5.0%), systolic ventricular pressure (39 ± 6.9%), and LV dP/dt (52 ± 8.1%). All these changes were significantly different from control and significantly greater than before prostaglandin synthesis inhibition (Table I) despite the initially higher baseline. The increase in cardiac work which occurred with carotid occlusion after prostaglandin synthesis inhibition was significantly different from control and significantly different from values obtained in the unblocked state.

Coronary blood flow (Table I) increased by similar amounts before (82 ± 15%) and after (78 ± 11%) the inhibition of prostaglandin synthesis during bilateral carotid artery occlusion (Fig. 2). In the same fashion, coronary vascular resistance was reduced to an insignificant degree before (13 ± 6.3%) and after

(11 ± 4.3%) prostaglandin synthesis inhibition during bilateral carotid occlusion. During bilateral carotid occlusion, cardiac output did not change significantly before (11 ± 3.6%) inhibition of prostaglandin synthesis, or after (0.5 ± 5.5%). Peripheral vascular resistance did not increase before prostaglandin synthesis inhibition (3.9 ± 3.0%), however, after prostaglandin inhibition peripheral resistance increased markedly (28 ± 8.3%) during bilateral carotid occlusion.

Changes in dogs following infusion of saline. Prior to prostaglandin synthesis inhibition, bilateral carotid artery clamping increased mean arterial pressure from 115 ± 4.8 to 186 ± 6.4 mm Hg, ventricular systolic pressure from 156 ± 4.0 to 246 ± 6.7 mm Hg, and LV dP/dt from 5152 ± 140 to 9184 ± 224 mm Hg/sec. Following infusion of saline, bilateral carotid artery occlusion increased mean arterial pressure from 117 ± 5.4 to 173 ± 12.1 mm Hg, LV systolic pressure from 160 ± 5.1 to 243 ± 8.8 mm Hg, and LV dP/dt from 5320 ± 140 to 9324 ± 224 mm Hg/sec. None of the changes were different from control, in contrast to the marked changes after infusion of PG synthesis inhibitors (Table I).

Discussion. Baroreflex unloading results in increases in heart rate, myocardial contractility, and peripheral vascular resistance (17) in the anesthetized dog primarily because there is an increase in the release of norepinephrine from sympathetic nerve terminals in the heart and periphery. In our study, bilateral carotid artery occlusion (BCO) resulted in significantly greater increases in LV dP/dt, LV systolic pressure, arterial pressures and peripheral resistance after prostaglandin synthesis inhibition. After prostaglandin synthesis inhibition, the increase in peripheral resistance was primarily due to an increase in peripheral vascular smooth muscle tone since cardiac output did not change significantly.

Inhibition of prostaglandin synthesis by itself, caused an increase in LV dP/dt, arterial and LV pressures, coronary vascular resistance, and aortic flow and work. Some of the vascular effects, i.e., the increases in peripheral and coronary resistances might simply be explained by the absence of vasodilator prostaglandins. Similarly, the increase in dP/dt may reflect the greater afterload (mean arterial pressure), which occurs during BCO following inhibition of PG synthesis. On the other hand, changes in myocardial blood flow both prior to and after prostaglandin synthesis inhibition reflect adjustments in cardiac work, which increased by 27% before and by 38% after inhibition, and changes in myocardial contractility (Table I and Fig. 2).

The role of prostaglandins in the control of coronary blood flow during BCO is unclear. The increase in coronary blood flow that we observed might result from (1) an increase in cardiac metabolism, (2) β-adrenergic vasodilation, and/or (3) coronary blood flow autoregulation due to the increased perfusion pressure. Taken together these mechanisms serve to meet oxygen demand during periods of increased work. The increase in coronary blood flow resulting from an increase in oxygen demand caused by coronary occlusion (13, 14, 18, 19) or by injection of isoproterenol (16) is unchanged by inhibition of PG synthesis. Similarly, based on the present study, prostaglandins do not seem to have an essential role in the regulation of coronary blood flow during baroreflex unloading.

The results of our study imply that prostaglandins modulate the effects of released norepinephrine or the release process itself which is caused by the activation of the carotid baroreflex, to modify blood pressure and myocardial contractility in the dog. Prostaglandins can alter blood pressure (a) by regulation of the release of norepinephrine from adrenergic nerve endings, (b) by opposing the vasoconstrictor actions of locally released or circulating pressor substances, and (c) by direct effects on vascular smooth muscle resulting in either vasodilation or vasoconstriction (4, 5, 20, 21). The relative importance of these three mechanisms depends upon the organ studied.

Previous studies (reviewed in 1, 4, 12), including those in isolated perfused blood vessels (8) and strips of muscle (9, 10), have shown that exogenous prostaglandins (2, 3, 6, 7, 9) and prostaglandins released during sympathetic stimulation of various organs (21–23) may modulate the release of norepinephrine (24–28) and/or the effector response to this neurotransmitter (2, 3, 5–12). This is particularly striking in the heart where the stimulation of sympathetic nerves results in an in-

crease in heart rate and contractility which is inhibited in a dose-dependent fashion by the infusion of prostaglandins (4, 7). In contrast, the inotropic and chronotropic actions of infused norepinephrine are not modified by the administration of E-prostaglandins or the inhibition of prostaglandin synthesis, indicating that the responses to nerve stimulation could only have resulted from presynaptic feedback inhibition (4). Studies by Baum and Shropshire (10) have shown that the inotropic response to field stimulation of isolated guinea pig atrial muscle strips was inhibited by PGE_1, PGE_2, and PGA_2, whereas, according to a study of Hedqvist (4), responses to exogenous norepinephrine or tyramine were not affected. Thus, in the heart, prostaglandins modulate the release rather than the postsynaptic effects of norepinephrine (4). Indomethacin, on the other hand, has been shown to increase the overflow of norepinephrine from nerves in the isolated perfused heart or the isolated sinoatrial node of the rabbit (4) and to increase the inotropic and chronotropic responses observed during nerve stimulation (7, 26). In studies similar to ours, carotid artery clamping or the intracarotid injection of nicotine in dogs resulted in vasoconstriction in the isolated perfused gracilis muscle and an increase in systemic blood pressure. Both of these effects were enhanced by the administration of $PGF_{2\alpha}$ into the perfusion circuit or intravenously (1–3). These results are congruent with our studies in which the changes in peak ventricular pressure and LV dP/dt caused by BCO were markedly enhanced by prostaglandin synthesis inhibition. Since, in order to avoid complication in the interpretation of our data, we used cardiac pacing, we have no direct evidence of an enhanced positive chronotropic effect of inhibition of prostaglandin synthesis.

Unlike in the heart, an organ in which inhibition of prostaglandin synthesis modifies primarily the outflow of norepinephrine, the peripheral actions of prostaglandins or inhibition of prostaglandin results from postjunctional as well as presynaptic effects (1, 11, 12). For instance, in the cutaneous vasculature (27) or the gracilis muscle (1) of the dog, the effects of norepinephrine are mediated both presynaptically and postjunctionally, whereas in the rat cremaster muscle the effects are primarily postjunctional (11, 12). In order for prostaglandins to modulate the effects of norepinephrine *in vivo* they must be either tonically released, as is evident from the effects of indomethacin (and meclofenamate) in our experiments, or they must be released during nerve stimulation (21). The synthesis of prostaglandins during nerve stimulation may be a result of the mechanical distortion of the postjunctional tissues as proposed by Hedqvist (4), and may serve as a negative feedback mechanism in the control of norepinephrine release and/or action.

The direct vasodilator actions of locally released prostaglandins may be evidenced in our study by the increases in blood pressure and vascular resistance which occur following the inhibition of prostaglandin synthesis. Alternatively, the vasodilation may result from the tonic inhibition of norepinephrine release or from an alteration in the response of vascular smooth muscle to norepinephrine.

In our study, inhibition of prostaglandin synthesis increased the effects of reflex stimulation of the adrenergic nervous system on systemic arterial pressure and left ventricular function. Prostaglandins can also affect other types of adrenergic responses. For example, in the rat, cold stress-induced release of norepinephrine and its metabolites into the urine increased significantly following inhibition of prostaglandin synthesis (28). Prostaglandins have also been shown to modulate the activity of the renin–angiotensin system and renal blood flow and function (6, 20, 22–24) and, therefore, may affect the control of blood pressure (20). In a recent study, it has been demonstrated that, in man, indomethacin significantly increased plasma norepinephrine concentration and forearm vascular resistance during sympathetic stimulation by the application of cold, in comparison with control periods (29). Hence, a change in the modulation by prostaglandins of the sympathetic nervous system may play a significant role in the pathogenesis of diseases of the cardiovascular system (30).

In relation to the direct physiologic significance of these experiments, it must be emphasized that as we (14) and others (31) have suggested before, PG synthesis is enhanced due to extensive surgical manipulation and one

must also be cautious in the interpretation of data obtained in anesthetized preparations. Thus, the direct physiologic significance of the modulation of the sympathetic nervous system by prostaglandins is still uncertain. In disease states, where PG synthesis may be acutely or chronically enhanced on the one hand, or, following the chronic administration of PG synthesis inhibitors on the other, the modulation by prostaglandins of sympathetic nervous influence on the cardiovascular system may be much more important.

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