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EXPERIMENTAL STUDIES

Platelet-Mediated Thrombosis in Stenosed Canine Coronary Arteries: Inhibition by Nicergoline, a Platelet-Active Alpha-Adrenergic Antagonist

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The effects of nicergoline, a new agent that blocks alpha-adrenergic receptors and inhibits platelet phospholipase, were evaluated in a canine model of platelet-mediated coronary thrombosis. In 48 open chest dogs, the circumflex coronary artery was stenosed by plicating the artery wall with a suture. Thirty-four of the 48 dogs exhibited cyclic reductions in flow in the stenotic vessel, followed by a sudden return to control levels. The reductions in flow were unabated in all but two dogs after heparin administration (1,000 U/kg per h), unaffected by large doses of nitroglycerin and nifedipine and associated with platelet aggregates in the stenotic segment (demonstrated by histologic and electron microscopic examination). These observations support the conclusion that the flow reductions were caused by platelet aggregation rather than by fibrin deposition or vasospasm.

Twenty dogs were monitored for 1 hour after heparin administration and then assigned to a control (n = 7) or nicergoline-treated (n = 13; 1 mg/kg intravenously) group. In control dogs, cyclic reductions in flow continued unchanged for another hour, whereas in the treated group they were markedly decreased in 1 dog and completely abolished in the other 12 dogs. Aspirin (30 mg/kg intravenously) suppressed flow reductions in all control dogs, confirming the primary role of platelet aggregation in the phenomenon.

This study provides a modified model of platelet-mediated thrombosis in stenosed coronary arteries. Furthermore, the results indicate that nicergoline can effectively interfere with platelet function in vivo. The potent antithrombotic activity exhibited by nicergoline might enhance the therapeutic usefulness of this vasodilator.

Coronary artery thrombosis has a major impact on morbidity and mortality among patients with coronary artery disease. Recent intraoperative (1) and angiographic (2–4) observations have demonstrated that a thrombus superimposed on a stenotic lesion is usually responsible for obstruction of the infarct-related vessel early in the course of acute myocardial infarction. Furthermore, some cases of sudden death may result from occlusive thrombosis of a large coronary artery (5,6) or from lysis of a proximal coronary thrombus and distal embolization of platelet aggregates (7,8).

Folts et al. (9–12) have recently developed a canine model of coronary thrombosis. They have demonstrated that a critical coronary stenosis can induce a gradual decrease of coronary blood flow that is often followed by a spontaneous, sudden return to the initial levels. They have also provided compelling evidence that the transitory reductions in flow are mediated by platelet aggregation rather than by vasospasm or fibrin deposition. For example, the reductions in flow are abolished by platelet inhibitors, including aspirin, sulfinpyrazone, prostacyclin, ibuprofen and indomethacin, but not by heparin, nitroglycerin or papaverine (9,10,12). Furthermore, they have documented histologically the presence of a platelet thrombus in the stenotic vessel (9,10). Similar models have been used by others (13–17). The ability of a drug to suppress platelet-mediated thrombosis in these experimental models might have important clinical implications, because the role of platelets in the genesis of human arterial thrombi is crucial (18,19).

Nicergoline is a new potent alpha-adrenergic antagonist (20,21) relatively selective for postsynaptic alpha$_1$-receptors (21,22). It has been used clinically as an antihypertensive agent and a peripheral and cerebrovascular vasodilator (23).

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In addition to its vasodilator properties, nicergoline interferes with platelet function (24–29). Because coronary artery disease is frequently associated with hypertension or peripheral vascular disease, or both, the demonstration that nicergoline can prevent coronary thrombosis might be of considerable clinical interest. Our study was undertaken to evaluate the effect of nicergoline on spontaneous coronary thrombosis in a modified canine model derived from that of Folts et al. (9). Preliminary experiments were performed to ascertain that the observed cyclic reductions in coronary flow were caused primarily by platelet aggregates.

Methods

Experimental Preparation

Forty-eight mongrel dogs of either sex, weighing 16 to 30 kg, were sedated with sodium thiamylal (10 mg/kg intravenously) and anesthetized 10 minutes later with alpha-chloralose (70 mg/kg intravenously). Additional doses of alpha-chloralose were administered during the experiment as necessary to abolish the corneal reflex. The dogs were intubated and ventilated with room air. The chest was opened through the left fifth intercostal space and the heart was suspended in a pericardial cradle. The proximal left circumflex coronary artery was isolated from the surrounding tissues. The site of dissection was chosen to provide a long segment (approximately 3 cm) free of ramifications; small branches were tied whenever necessary.

Instrumentation. A Doppler ultrasonic flow probe was placed around the artery at the proximal end of the isolated segment (Fig. 1). A 2-0 silk ligature was placed around the vessel at the distal end of the dissected segment; because of its distance from the flow probe, the ligature could be used to produce temporary complete occlusions for measurement of reactive hyperemia without altering the position of the probe (Fig. 1). Polyethylene catheters for pressure measurement were inserted into the left atrium through the left atrial appendage and into the aorta through the left carotid artery. Both catheters were connected to Statham P23Db pressure transducers. A solid state pressure transducer (Konigsberg, model P-20) was positioned in the left ventricular cavity through an incision in the left ventricular apex. The first derivative of left ventricular pressure (dP/dt) was obtained by electronic differentiation. Aortic pressure, left ventricular pressure, dP/dt, left atrial pressure, left circumflex coronary artery flow velocity and lead II of the electrocardiogram were recorded continuously throughout the study on an eight channel direct writing oscillograph (Gould Brush System 200).

Production of coronary stenosis. After baseline recordings, a stenosis was produced in the left circumflex coronary artery in the following manner. The vessel was plicated by passing a series of stitches (6-0 Prolene with

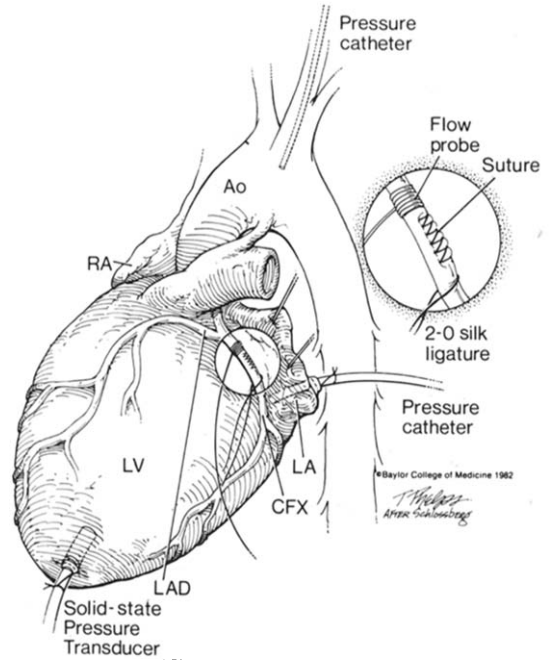

Figure 1. Schematic representation of the experimental preparation. Ao = aorta; CFX = left circumflex coronary artery; LA = left atrium; LAD = left anterior descending coronary artery; LV = left ventricle; RA = right atrium.

nontraumatic needle) through its wall in the segment between the flow probe and the ligature, starting at the level of the ligature (Fig. 1 and 2). The plication produced a 50 to 70% reduction of the vessel diameter. After each stitch, the coronary artery was completely occluded for 20 seconds to measure reactive hyperemia. The plication was extended proximally until the hyperemic response to these occlusions was completely abolished. This was usually achieved with plications 3 to 5 mm long. Of the 48 dogs instrumented, 34 showed cyclic reductions in left circumflex coronary artery flow. All of these animals were given heparin (1,000 U/kg per h intravenously) to prevent deposition of fibrin at the stenotic site. The cyclic reductions in flow were abolished by heparin in 2 dogs and unaffected in the remaining 32. Twelve of these 32 dogs were used to validate the model and 20 entered the nicergoline protocol.

Validation of the Model

Studies were carried out in 12 dogs to confirm that the cyclic reductions in flow were caused primarily by platelet aggregation rather than by fibrin deposition or coronary spasm.

Histologic and ultrastructural studies. In seven dogs, the thrombus was obtained for histologic and electron microscopic observation. The left circumflex coronary artery flow was observed carefully and, when it reached a low point, the artery was ligated distally and then proximally. The vessel was immediately excised and immersed in either

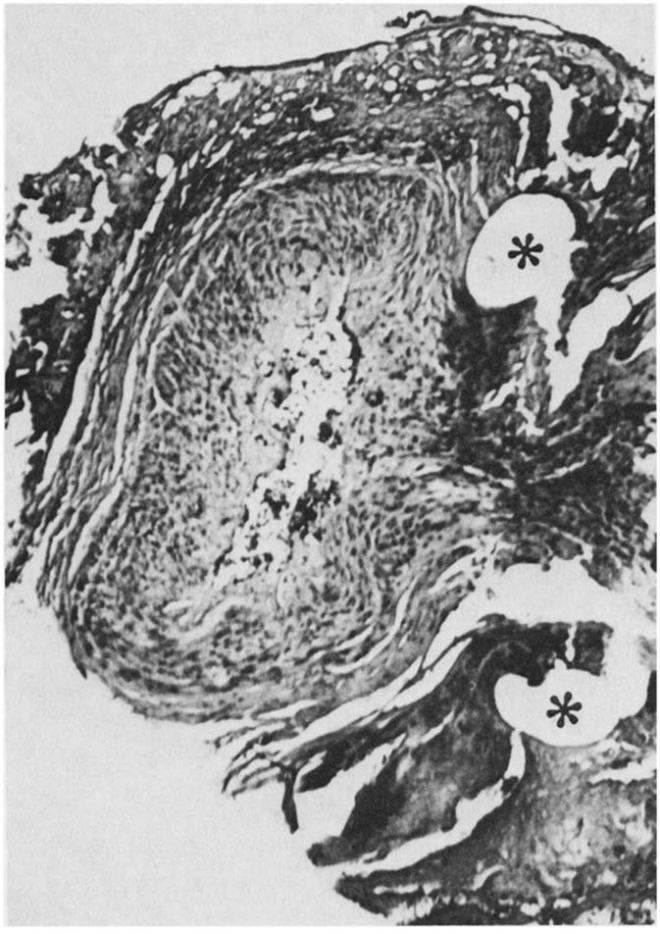

Figure 2. Low power view (hematoxylin-eosin ×180, reduced by 23%) of a plicated circumflex coronary artery demonstrating the spaces occupied by the suture material in vivo (**asterisks**). (The stitches were removed after fixation to facilitate sectioning.) Note that the suture material was not exposed in the stenotic lumen. The lumen of the plicated portion of the vessel (**right**) is completely obliterated.

buffered 10% formalin or buffered 3% glutaraldehyde, pH 7.3. The fixed tissue was cut into 5 mm segments and embedded in paraffin. Serial sections of the entire segment were stained with hematoxylin-eosin, Movat, periodic acid-Schiff, phosphotungstic acid-hematoxylin and Verhoeff-van Gieson stains.

Specimens for scanning electron microscopy were fixed in buffered 3% glutaraldehyde, dehydrated through a graded series up to absolute acetone, critical point dried in liquid carbon dioxide and sputter-coated with gold-palladium 60/40 ratio. Samples for transmission electron microscopy were fixed in buffered 3% glutaraldehyde, postfixed in osmium tetroxide, dehydrated and embedded in Spurr's medium according to conventional procedures. All samples were examined on a JEOL 100C electron microscope equipped with scanning attachment.

To determine whether platelet aggregates form in the stenotic vessel in the absence of variations in flow, histologic and ultrastructural studies were also carried out in 3 of the 13 dogs that failed to exhibit cyclic flow reductions after production of the stenosis and in 2 of the 7 control dogs after flow reductions had been eliminated by aspirin (see later).

Experiments with vasodilators. A second group of five dogs was observed for 1 hour and then treated with nitroglycerin (300 μg intravenous bolus followed by an infusion of 6 μg/kg per min, n = 3) or nifedipine (100 μg/kg intravenously over 5 minutes followed by an infusion of 3 μg/kg per min, n = 2). All measured variables were monitored for 1 hour after the start of treatment.

Nicergoline Protocol

Twenty dogs were used for the nicergoline protocol, which consisted of two parts. The first part was a 1 hour observation period during which hemodynamic variables and the electrocardiogram were continuously recorded to define a baseline. Dogs were then assigned either to the control group (n = 7), which received no intervention, or to the treated group (n = 13), which was given nicergoline (1 mg/kg intravenously over 5 minutes). Nicergoline was dissolved in water (concentration 10 mg/ml) with tartaric acid (3 mg/ml). Tartaric acid has no known action on platelets. The dogs were continuously monitored thoughout the subsequent hour (the second part of the protocol). At the end of the second part, the seven control dogs received acetylsalicylic acid intravenously (30 mg/kg dissolved in 150 ml of normal saline solution) and were observed for a third hour. At the end of the experiment, the alpha-adrenergic blocking action of nicergoline was assessed by determining the arterial pressure response to intravenous injections of various doses of phenylephrine in five control and eight nicergoline-treated dogs. In the remaining two control dogs, the stenotic artery was examined by light and electron micrograph as just described.

Data analysis. The frequency of cyclic reductions in flow in the stenotic artery was expressed as the number of reductions per hour. The magnitude of cyclic reductions in flow was defined as the average of all the sudden increments in circumflex coronary artery flow during the observation period. To minimize intra- and interobserver variability, each increment was measured from the level immediately preceding to the level immediately following the sudden flow increase (Fig. 3).

All measured variables are reported as mean ± standard error. Comparisons of means were performed with the two-tailed Student's *t* test for paired or unpaired data as appropriate.

Results

Cyclic reductions in flow in the stenosed coronary artery were characterized by a slowly decreasing flow followed by a sudden return to control levels (Fig. 3 and 4). The sudden

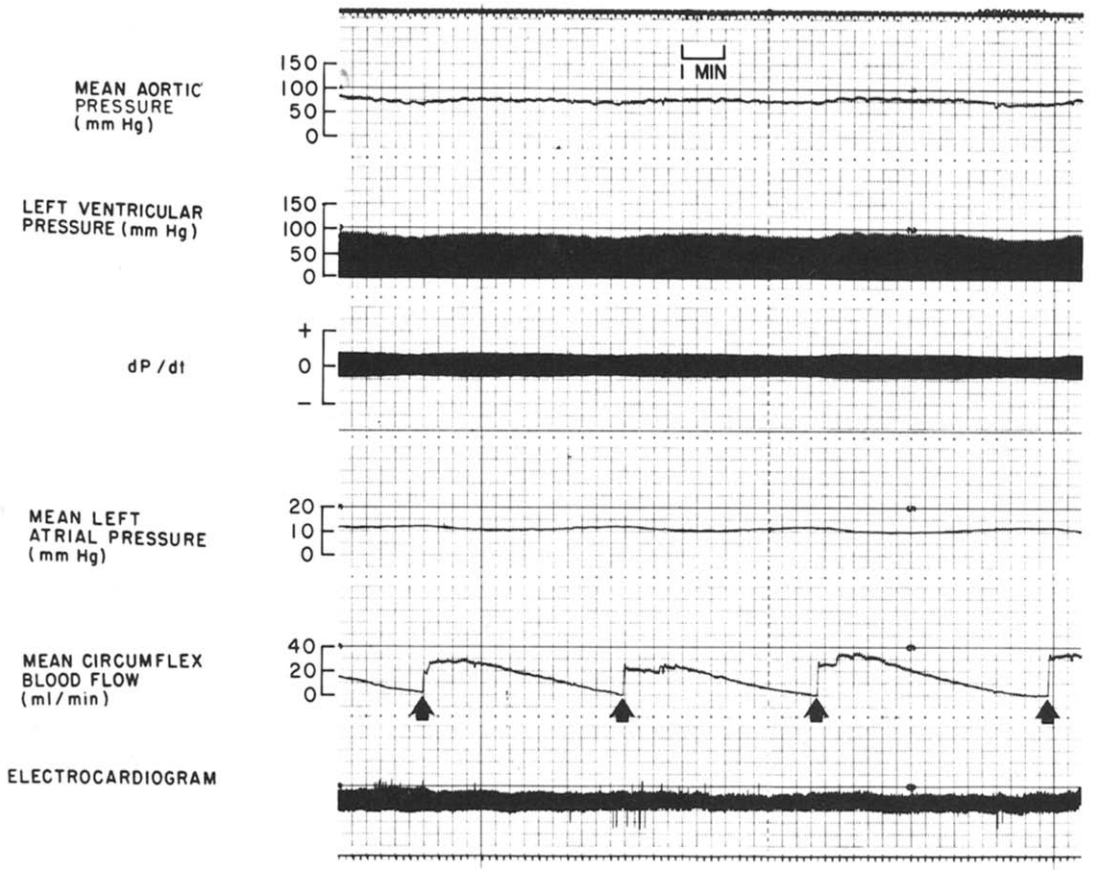

Figure 3. Cyclic reductions in flow in the stenosed circumflex artery. The reductions in flow are associated with hemodynamic changes suggestive of myocardial ischemia: decrease in left ventricular systolic pressure, decrease in positive and negative first derivative of left ventricular pressure (dP/dt) and increase in left atrial pressure. For example, during the last reduction in flow (**right**), left ventricular pressure decreases from 90 to 79 mm Hg, peak positive dP/dt from 1,661 to 1,411 mm Hg/s and peak negative dP/dt from 1,161 to 936 mm Hg/s, whereas mean left atrial pressure increases from 10.0 to 11.8 mm Hg. **Arrows** indicate spontaneous restoration of blood flow after each reduction.

restorations of flow occurred either spontaneously or, if flow declined to zero, after gentle shaking of the vessel. Marked reductions in flow were associated with ST segment shifts on the electrocardiogram (Fig. 4) and with hemodynamic changes suggestive of myocardial ischemia (decrease in left ventricular systolic pressure, decrease in positive and negative left ventricular dP/dt and increase in left atrial pressure [Fig. 3]).

Validation of the Model

Histologic and ultrastructural studies. Histologic examination of the excised vessels showed the suture material to be outside of the stenotic lumen, due to the fact that the portion of the artery penetrated by the stitches was plicated and, therefore, completely obliterated (Fig. 2). Consequently, thrombus formation in this model cannot be ascribed to exposure of suture material in the lumen. Histologic evidence of endothelial damage in the stenosed vessel (for example, discontinuity of the internal elastical lamina) was observed in 4 of the 12 dogs examined.

In all seven dogs that exhibited cyclic flow reductions, histologic examination of the vessels that were ligated during a episode of flow reduction revealed a luminal thrombus in the stenotic segment (Fig. 5 and 6). Scanning and transmission electron micrograph demonstrated the thrombus to be made up mostly of platelet aggregates with small amounts of fibrin and occasional white and red blood cells (Fig. 7). In contrast, no platelet aggregates were observed in those vessels that were excised from control dogs (n = 2) after aspirin had abolished cyclic reductions in flow. Likewise, no platelet thrombus was found in the stenosed artery of dogs (n = 3) that failed to exhibit reductions in flow.

Effects of vasodilators on cyclic reductions in flow. The vasodilators nitroglycerin and nifedipine were administered to evaluate the possibility that the cyclic reductions in flow were caused by vasospasm. Neither nitroglycerin (n = 3) nor nifedipine (n = 2) affected the frequency or the magnitude of reductions in flow in the stenosed coronary artery, despite administration of doses sufficient to decrease mean

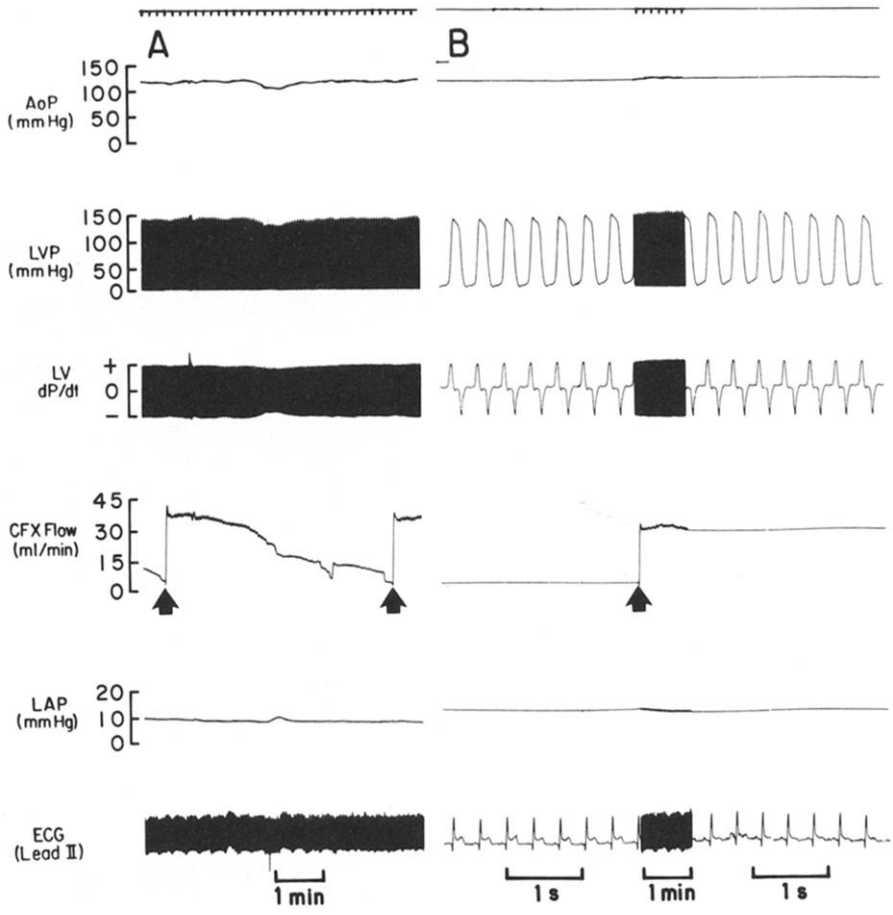

Figure 4. Cyclic reductions in flow in the stenosed circumflex artery recorded at low (**A**) and high (**B**) paper speed during the same experiment. The two recordings are not continuous. The ST segment is elevated in lead II of the electrocardiogram (ECG) during the phase of low flow (**B**), suggesting ischemia in the circumflex artery (CFX) territory; 1 minute later, after the thrombus is dislodged and control flow restored (**arrow**), the ST segment returns to normal levels. AoP = mean aortic pressure; LAP = mean left atrial pressure; LV = left ventricular; LVP = left ventricular pressure.

arterial pressure by 22 ± 3 mm Hg (nitroglycerin) and by 30 ± 5 mm Hg (nifedipine).

Nicergoline Protocol

Hemodynamics (Table 1). In control dogs, heart rate, mean arterial blood pressure and mean left atrial pressure did not change significantly throughout the study. Although mean circumflex coronary artery blood flow decreased slightly after the stenosis was produced, the decrease did not achieve statistical significance.

In nicergoline-treated dogs, none of the hemodynamic variables changed significantly after the coronary artery was stenosed. Treatment with nicergoline significantly lowered heart rate (−51 ± 3 beats/min), mean arterial blood pressure (−32 ± 1 mm Hg) and mean circumflex coronary artery blood flow (−13.4 ± 2.9 ml/min).

Cyclic reductions in flow. *Control group (Table 2).* During the first part of the protocol, the frequency of cyclic reductions in circumflex coronary artery flow in control dogs averaged 16/h; the magnitude of these reductions averaged 14.5 ± 2.6 ml/min (corresponding to an average 33% decrease in blood flow from the levels observed between reductions). Both the frequency and magnitude of cyclic reductions in flow remained essentially unchanged during the second part of the protocol. At the end of this part, cyclic reductions in flow were completely abolished by aspirin in every dog, indicating that they were caused primarily by platelet aggregation.

Nicergoline-treated group (Fig. 8). Before treatment, the frequency and magnitude of cyclic reductions in flow were similar to those observed in the control group. Nicergoline completely abolished cyclic reductions in flow in all but one dog within a few minutes after its administration ($p < 0.001$ versus pretreatment frequency). In those dogs in which nicergoline was administered during the phase of decrease in flow, the flow reduction was promptly reversed. In one dog, cyclic reductions in flow were not totally suppressed; however, the frequency decreased by 68% and the magnitude by 63%.

Alpha-agonist dose-response studies. Nicergoline exhibited a potent alpha-adrenergic blocking activity. In the five control dogs, the increase in mean arterial pressure in response to 0.25, 3.2, 16.0 and 32.0 μg/kg of phenylephrine averaged 4.7 ± 1.8, 25.6 ± 4.1, 72.8 ± 8.9 and 86.1 ± 13.2 mm Hg, respectively. In the eight treated animals that were tested, no appreciable change in blood pressure was observed with phenylephrine doses of 8 μg/kg or less; doses of 16 and 64 μg/kg produced an increase in mean arterial pressure of 5.7 ± 1.1 and 23.2 ± 5.0 mm Hg, respectively ($p < 0.01$ versus corresponding values in control dogs).

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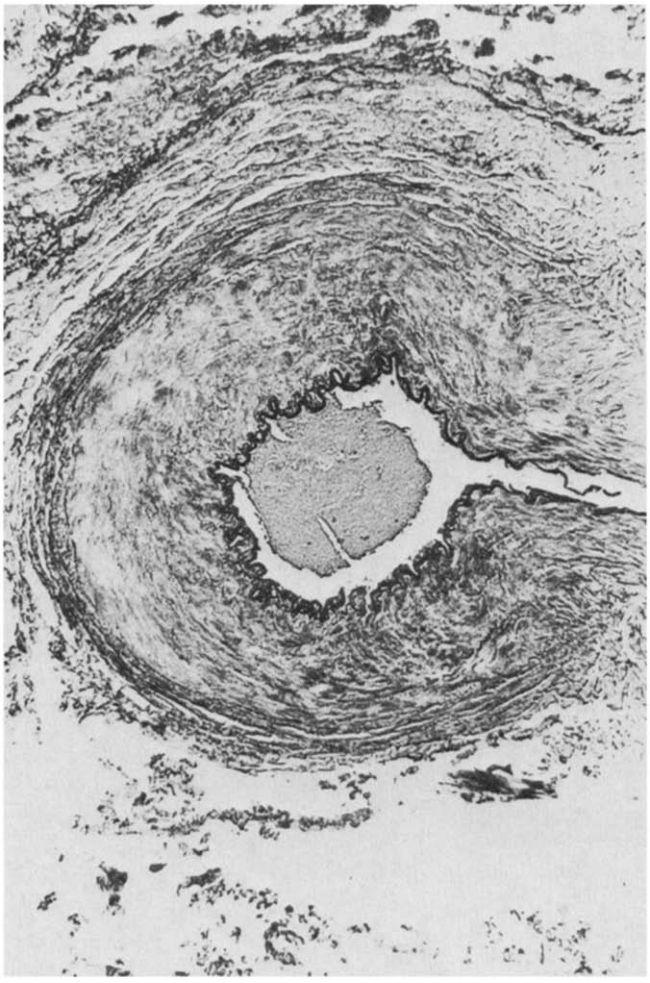


Figure 5. Low power view (Verhoeff-van Gieson stain ×100, reduced by 25%) of the stenotic segment of a coronary artery excised during a reduction in flow. The lumen is almost entirely occupied by a thrombus loosely attached to the intima (the internal elastic lamina is the **dark wavy line** in the intima). The plication of the vessel by the suture is visible on the right. The apparent presence of a residual lumen in the plicated part is a postmortem artifact due to retraction of tissues during fixation and to removal of the stitches to facilitate sectioning of the specimen.

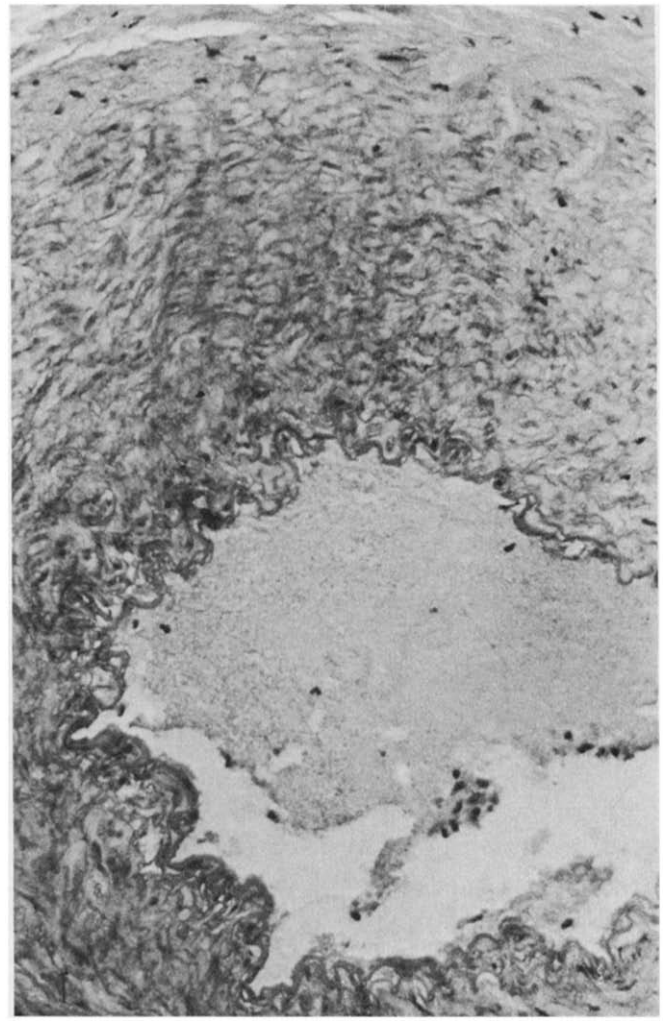


Figure 6. Higher power view (periodic acid-Schiff stain ×250, reduced by 26%) of a different area of the thrombus shown in Figure 5. Note the fine granularity of the thrombus, which is suggestive of platelet aggregates. Some white blood cells are present at the periphery of the thrombus.

Discussion

Modeling considerations. The model of coronary thrombosis used in this study is a modification of that originally described by Folts et al. (9) and employed by others (15–17). Common to both models is the presence of a critical coronary stenosis that does not restrict basal flow, but completely prevents the hyperemic response to total occlusion. The main difference between the two models is that Folts and coworkers produced the stenosis by encircling the vessel with a plastic cylinder, whereas we plicated the arterial wall with a suture. This technique was selected because it affords fine control of the severity of the stenosis, as stitches can be added until the desired degree of obstruction is achieved. The suture also ensures a stable narrowing of the lumen, which cannot be modified by the movements of the heart or by manipulations of the vessel (particularly when transient complete occlusions are produced or the thrombus is manually dislodged). Another difference from previous models is that our animals were treated with heparin. The rationale for this was to reduce fibrin deposition and, thus, to maximize the contribution of platelets to thrombus formation. This, in turn, might enhance the sensitivity of the model to drugs that solely affect platelet function.

Role of endothelial damage. Although unequivocal histologic evidence of endothelial damage was observed only in 4 of the 12 dogs examined, the plication was probably associated with some endothelial injury in all the dogs. This, however, does not represent a drawback of the method. Endothelial damage is invariably present even when coronary stenosis is produced by an external constrictor, as in

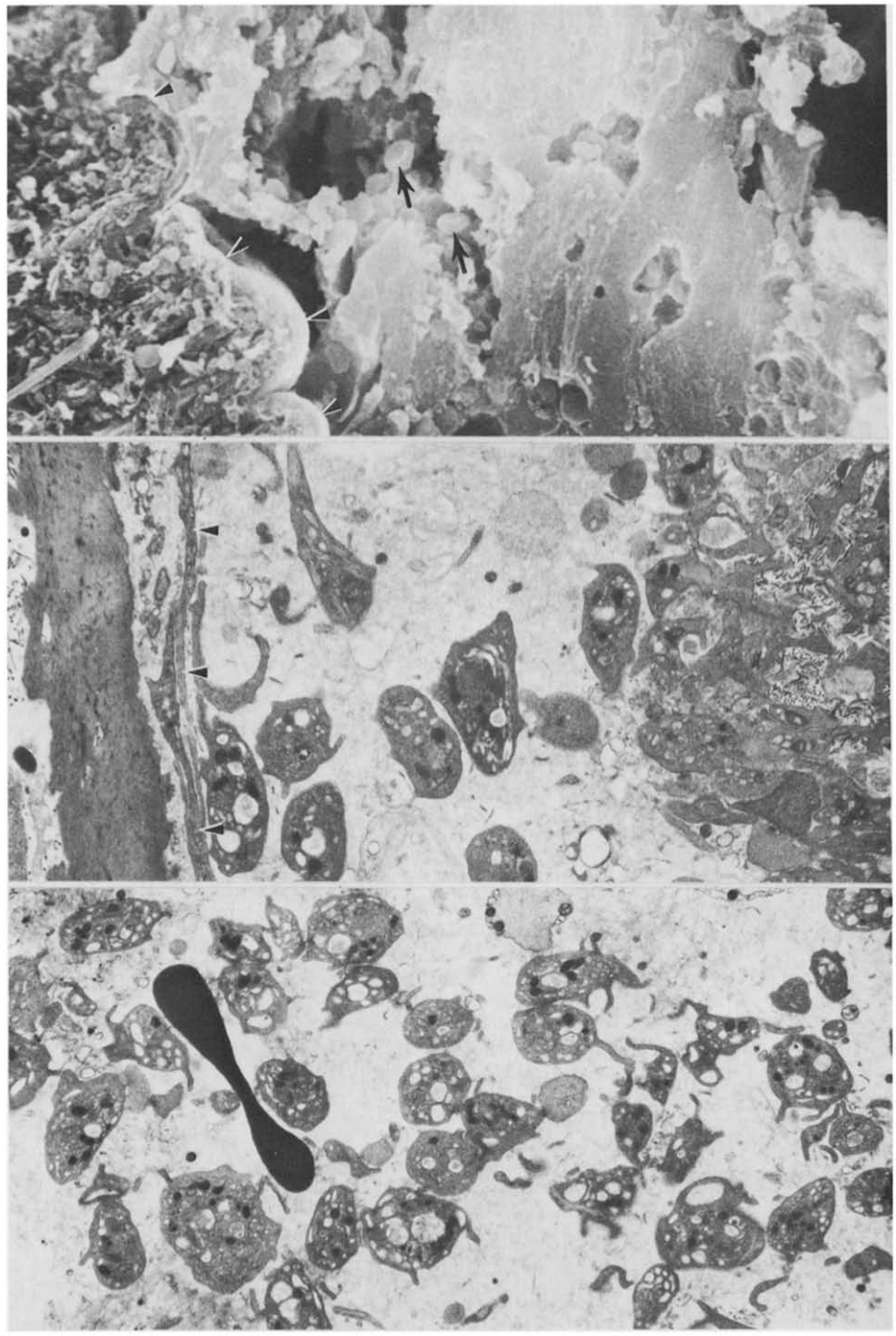


Figure 7. Ultrastructural examination of the stenotic segment of circumflex coronary artery excised during an episode of reduction in flow. **Upper panel**, Scanning electron micrograph (× 1,000). An intraluminal thrombus is attached to the endothelium (**pointers**). **Arrows** indicate red blood cells within the thrombus. **Middle panel**, Transmission electron micrograph (× 7,000). A mass of coalesced platelets (**right**) is adjacent to the endothelial surface (**pointers**). A smooth muscle cell is visible below the endothelium. **Lower panel**, Transmission electron micrograph (× 7,000) of a different area of the same thrombus. A red blood cell is surrounded by activated platelets. All panels reduced by 34%.

the models of Folts et al. (10,11) and Aiken et al. (15,16). Such damage may be important in inducing platelet aggregation (9–11) and appears to be necessary for thrombi to form in a reproducible fashion (15,16). Furthermore, endothelial lesions are common in human atherosclerotic plaques (30).

Platelet aggregation and cyclic flow reductions. Theoretically, the cyclic reductions in flow observed in our model might have been produced by platelet aggregation, fibrin deposition, vasospasm or a combination of these factors. Several lines of evidence identify platelet aggregates as the primary cause of the phenomenon. First, the cyclic reductions in flow were consistently abolished by aspirin, but not by massive doses of heparin, or doses of nitroglycerin and nifedipine sufficient to produce marked hypotension. Second, the histologic and ultrastructural examination of vessels ligated at a time when flow was at a low point demonstrated that the cyclic reductions in flow were associated with platelet plugs. The primary role of platelet aggregates is further supported by their absence in vessels with

Table 1. Hemodynamic Variables in Control and Nicergoline-Treated Dogs

	Heart Rate (beats/min)		Mean ABP (mm Hg)		Mean LAP (mm Hg)		Mean LCx Flow (ml/min)	
	C	N	C	N	C	N	C	N
Before stenosis	160.1 ± 8.0	163.5 ± 9.1	94.1 ± 7.0	90.7 ± 6.2	5.1 ± 0.7	5.3 ± 0.6	50.3 ± 6.2	48.1 ± 5.8
After stenosis, 5 minutes before treatment	162.9 ± 7.8	168.8 ± 8.0	90.2 ± 6.5	91.3 ± 5.4	6.0 ± 0.9	6.2 ± 1.0	43.5 ± 7.8	39.9 ± 6.1
30 minutes after treatment	161.5 ± 7.9	117.8 ± 4.1*	88.1 ± 6.7	59.2 ± 4.7*	6.2 ± 1.1	5.6 ± 1.1	40.1 ± 7.1	26.5 ± 4.0*

*$p < 0.001$ versus control subjects.
ABP = arterial blood pressure; C = control subjects; LAP = left atrial pressure; LCx = left circumflex coronary artery; N = nicergoline-treated.

similar stenoses but obtained from dogs in which reductions in flow either failed to occur or were abolished by aspirin.

Platelet aggregation in the stenotic segment might result from the trauma to the endothelium, which exposes collagen fibers, as well as from the turbulence of blood flow, which damages platelets and red blood cells, causing release of adenosine diphosphate (11). The lack of cyclic reductions in flow in 14 of the 48 animals in which coronary stenosis was produced may reflect an insufficient degree of endothelial damage or a defect in platelet function that is present in some dogs (31).

Platelet-inhibitory activity of nicergoline. Nicergoline is a new semisynthetic ergoline derivative with potent alpha-adrenergic blocking activity (20,21). This was confirmed in our study, in which a marked degree of alpha-adrenergic blockade was observed in treated animals. The potency of nicergoline's alpha-adrenergic blocking activity is similar to that of phentolamine (32). In contrast to phentolamine, however, nicergoline is relatively selective for postsynaptic $alpha_1$-adrenergic receptors (21,22). Unlike other ergot alkaloids, it has no intrinsic alpha-adrenergic agonist activity (20,21). The negative chronotropic action observed in our treated group represents a unique feature of this alpha-adrenergic antagonist and appears to be mediated by an effect on the central nervous system (21,33,34).

Previous reports (25,27–29) documented a potent platelet inhibitory activity of nicergoline in vitro. The drug completely inhibits aggregation of human platelets by epinephrine, adenosine diphosphate and collagen (25,27,28). If added after platelets have been exposed to the aggregating agent, nicergoline arrests the process of aggregation and causes disaggregation (25,27). In vitro inhibition of platelets has also been observed after oral administration of nicergoline to patients with atherosclerosis (25,26). However, evidence of efficacy of this drug in vivo is still lacking. Such evidence is necessary because tests of platelet function in vitro may not reflect the events occurring in the physiologic environment (35).

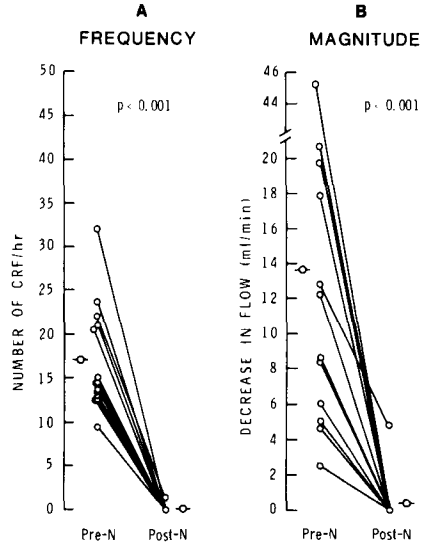
Our study demonstrates that nicergoline markedly interferes with platelet function in vivo. The suppression of cyclic reductions in flow documents inhibition of platelet aggregation in the stenotic vessel. Furthermore, our observation that nicergoline promptly reversed the decrease in flow occurring at the time when treatment was started suggests that the drug acted to disaggregate recently formed thrombi. This finding might be the in vivo equivalent of the disaggregating properties observed in vitro (25,27).

Table 2. Frequency and Magnitude of Cyclic Reductions in Flow in the Stenosed Artery in the Control Group

	Frequency (CRF/h)	Magnitude (ml/min)
First part of protocol (first hour)	16.0 ± 2.1	14.5 ± 2.6
Second part of protocol (second hour)	14.5 ± 1.5	13.1 ± 1.9
After aspirin (third hour)	0	0

CRF = cyclic reductions in flow.

Figure 8. Effect of nicergoline (N) on frequency (**A**) and magnitude (**B**) of cyclic reductions in flow (CRF) in the stenosed circumflex coronary artery.



The mechanism by which nicergoline inhibits thrombosis may be related to the alpha-adrenergic blocking activity of the drug. Alpha-adrenergic receptors have been identified in platelet membranes (36,37) and have been shown to mediate the aggregating response to epinephrine in vitro (38,39). A role of these receptors in vivo is suggested by the recent report (11) that the alpha-adrenergic antagonist phentolamine reduces cyclic reductions in flow in a model similar to that employed in the present study. The effect of nicergoline on thrombosis could also reflect extra-adrenergic actions. Nicergoline induces platelet ultrastructural changes (such as depolymerization of microtubules [27]) and inhibition of platelet phospholipase (28). This latter action prevents liberation of arachidonic acid from membrane phospholipids and, thus, production of thromboxane A_2 (28).

Clinical implications. *Value of experimental model.* In this study, we present a canine model of platelet-mediated thrombosis in stenotic coronary arteries. Extrapolation of our experimental data to human beings must be made with caution, because the events leading to thrombosis in an atherosclerotic vessel may differ from those taking place in a traumatized, previously normal artery. Nevertheless, because platelets play a critical role in the formation of occlusive coronary thrombi in human beings (18,19,40), the basic mechanism causing coronary obstruction appears to be similar in the experimental and clinical settings. Accordingly, this canine model might be useful for the study of the mechanisms that lead to thrombus formation at the site of an atherosclerotic lesion, as well as for the assessment of platelet-active agents of potential therapeutic value.

Role of nicergoline. Our investigation also demonstrates that nicergoline completely prevents thrombosis in stenosed canine cronary arteries. Clinical studies are obviously necessary before these results can be applied to human beings; for example, it is difficult to correlate the dosage of nicergoline in our canine model with that used in patients. Clinical trials have employed doses ranging from 30 to 60 mg orally (25) and from 5 to 20 mg intravenously (33). Although in relation to body weight these doses are lower than ours (1 mg/kg intravenously), the pharmacokinetics of nicergoline have not been defined in human subjects or in dogs and, consequently, a valid comparison of experimental and clinical dosages is not possible. However, even oral doses of nicergoline of 30 mg are sufficient to inhibit human platelets in vitro (25,26). On the basis of these results and of our findings, it seems reasonable to suggest a potential antithrombotic action of nicergoline in human subjects. To date, this drug has been used for its vasodilator properties in the treatment of hypertension (23), peripheral vascular disease (23) and congestive heart failure (33,34). The ability of nicergoline to prevent arterial thrombosis would be of benefit in these syndromes and, more generally, in atherosclerotic cardiovascular disease.

An additional consideration is that nicergoline differs from many platelet-active compounds in that it inhibits both platelet aggregation and platelet adhesion to collagen, elastin and endothelial cells (29). Because the interaction between platelets and these elements of the arterial wall might play an important role in the pathogenesis of atherosclerosis (30,41), it is theoretically conceivable that nicergoline might interfere with the progression of this disorder. Therefore, investigation of the effects of nicergoline in patients with atherosclerotic cardiovascular disease seems warranted.

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