Coronary Artery Spasm in Intact Dogs Induced by Potassium and Serotonin

Julio E. Pérez, Jeffrey E. Saffitz, Fernando A. Gutiérrez, and Philip D. Henry
From the Department of Medicine, Cardiovascular Division, and Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri

SUMMARY. Although coronary artery spasm has been implicated as an important cause of myocardial ischemia in humans, mechanisms underlying its pathogenesis remain largely unclear (Gensini et al., 1962; Maseri et al., 1978). Evaluation of coronary spasm in man is difficult, since permissible exploratory maneuvers are limited. An experimental approach to the study of coronary spasm appears desirable, but an appropriate animal model has not become generally available.

In this study, we have evaluated effects of selected vasoconstrictors on intact coronary arteries in open-chest dogs. Viscous gels containing adsorbed vasoactive agents were applied topically to epicardial coronary arteries, and local vasomotor responses were monitored. The new technique permitted a comparison of the vasoconstrictor potency of endogenous agents and of the spasmolytic efficacy of vasodilators administered systemically.

Methods

Animal Preparation

Mongrel dogs (n = 34) weighing 25–35 kg were anesthetized with α-chloralose (100 mg/kg, iv) and ventilated under positive pressure with room air supplemented with oxygen. Arterial blood gases were monitored with an Instrumentation Laboratories gas analyzer model 213, and pH, oxygen tension, and carbon dioxide tension were maintained between 7.35 and 7.45, 95 and 105 mm Hg, and 35 and 45 mm Hg, respectively. A thoracotomy was performed through the 5th left intercostal space. The pericardium was opened, and the heart was suspended in a pericardial cradle. Catheters connected to Statham P23Db pressure transducers were inserted in the left ventricular cavity and ascending aorta. An electromagnetic flow probe (Narcomatic C2.0-141) was placed around the left anterior descending coronary artery proximal to the first diagonal branch and connected to a flowmeter (Narcomatic model RT-500) for the measurement of mean and phasic flow. This allowed calculation of diastolic-to-systolic coronary flow ratios which indicated the severity of coronary artery obstruction, as described by Folts et al. (1974, 1975). A snare was placed downstream of the flow probe to occlude the artery temporarily (15 seconds) and elicit reactive hyperemia. In four dogs, piezoelectric crystals measuring 2 mm in diameter were positioned on opposite surfaces of the artery with small droplets of cyanoacrylate glue, 5–10 mm distal to the arterial probe. The crystals were connected to an ultrasonic amplifier (Théroux et al., 1976) with improved signal-to-noise ratio to provide a linear resolution of 10 μm (Pérez et al., 1980). The ultrasonic caliper was precalibrated in vitro in isotonic saline at 37°C. Intraexperimental drift was tested with the use of exogenous-timed pulses displayed on a Tektronix model 560 oscilloscope. The system permitted a continuous monitoring of external mean coronary artery diameter. Transducer signals were amplified and differentiated with Honeywell model 143 amplifiers and model 132 differentiators, and recorded with a Honeywell Visicorder model 1858.

Three dogs were instrumented with intracoronary catheters with an outer diameter of 0.9 mm proximal to the flow probe and infused with subpressor doses of methoxamine (30 μg/kg in 1 minute). Effects of methoxamine were evaluated before and after postjunctional α-blockade with prazosin (0.2 mg/kg, iv). In six dogs, similar catheters were inserted into the distal left anterior-descending coronary...
artery through a side branch near the ventricular apex and connected to Statham P23Db to monitor peripheral coronary pressure.

In five dogs, coronary vasomotion was further evaluated by selective coronary angiography. A Cordis French 5 left coronary catheter was introduced into a femoral artery and positioned in the left coronary ostium under fluoroscopic control. Multiple views were obtained and filmed after intracoronary hand injection of 5-7 ml of diatrizoate meglumine.

Preparation of Gels with Adsorbed Vasoactive Agents

To provide a continuous and controlled release of drug to epicardial coronary arteries, cationic vasoactive agents were adsorbed to SP-Sephadex C-50, a strongly acidic ion exchanger (Pharmacia Fine Chemicals). SP-Sephadex gels carrying different cations were produced as follows:

Na⁺-SP-Sephadex

One gram of SP-Sephadex C-50 in the Na⁺-cycle was swollen at room temperature in 30 ml 1 m NaCl with gentle stirring, and the supernatant fraction was decanted and replaced with fresh NaCl. This procedure was repeated three times, the last suspension being allowed to equilibrate for 24 hours. The gel then was exhaustively washed with 5% dextrose in water on a Buchner funnel to remove unbound sodium ions. The final eluates contained <3 mEq of Na⁺/liter, as measured by flame photometry.

K⁺-SP-Sephadex

One gram of SP-Sephadex C-50 in the Na⁺-cycle was treated exactly as described for the preparation of Na⁺-SP-Sephadex, except that 1 m NaCl was replaced by 1 m KCl. K⁺ concentration in the final eluates was monitored by flame photometry and contained <3 mEq/liter.

SP-Sephadex Equilibrated with Vasoactive Amines

Since norepinephrine, tyramine, and serotonin (5-HT) exist predominantly (>90%) as cations below pH 8 (Miller, 1978), they are adsorbable to cation exchangers at neutral pH. One gram of dry SP-Sephadex in the Na⁺-cycle was swollen in 100 ml of 10 mm Tris-HCl, pH 7.0, containing 25 μM EDTA and 1 mm ascorbic acid as anti-oxidants, and equilibrated overnight at 0°C with 25 mg of norepinephrine, 5-hydroxytryptamine, or tyramine. Tracer amounts of some monoamines (~ 2000 counts/min of 7-3H-norepinephrine, 1,2-3H-5-hydroxytryptamine, or 3H(G)-tyramine (NET-377, NET-498, NET 132; New England Nuclear) were coequilibrated to monitor adsorption. After 24 hours of equilibration and rapid wash of the gel on a Buchner funnel with 300 ml of ice-cold 5% dextrose in water, the combined washes contained less than 30% of the added radioactivity, indicating at least 70% adsorption for the three amines.

SP-Sephadex Equilibrated with Angiotensin II

Angiotensin II at neutral pH is quantitatively adsorbed to cation exchangers (Boucher et al., 1961). Angiotensin gel was prepared by equilibrating 11.7 mg of valine-S-angiotensin with 1 g dry SP-Sephadex in the Na⁺-cycle swollen in 10 mm Tris-HCl, pH 7.0. After overnight equilibration, the gel was washed with 100 ml of 5% dextrose. The combined washes were centrifuged at 40,000 g, and UV absorption at 280 nm of the supernatant fraction was measured in a Gilford model 250 spectrophotometer. The polypeptide in solution was estimated on the basis of appropriate standards curves. Calculated adsorption to the gel was in excess of 72%.

The water content of the final gels was approximately 2 ml of water per gram dry gel.

Topical Application of Gel

The various gels were deposited on the adventitial surface of the left anterior descending coronary artery. A 3-cm long arterial segment encompassing the region of the ultrasensitive crystals was covered with a 0.5- to 1.0-cm thick layer of gel. Gel on the surface of the artery was removed with a cotton-tip applicator as needed, and residual material was flushed away with warm (37°C) saline. Effects of different gels or of the same gel applied repeatedly could thus be tested in the same animal.

Intravenous Administration of Vasodilator

In selected dogs in which sustained coronary constrictor responses had been elicited, vasodilators were given intravenously. Nifedipine (1.5 ± 0.5 μg/min; sr, n = 4), nisoldipine (0.8 ± 0.3 μg/min; n = 3), and nitroglycerin (58 ± 12 μg/min; n = 3) were infused at a rate which reduced mean arterial pressure by 5-10 mm Hg.

Scanning Electron Microscopy of Arterial Segments

In five dogs undergoing coronary constriction, the venous cavae and ascending aorta were cross-clamped and a cannula was inserted into the aorta proximal to the clamp. The heart was perfused retrograde through the cannula under a pressure of 80 mm Hg with 1 liter of 100 mM sodium phosphate buffer (pH 7.4) containing 1% glutaraldehyde and glucose to adjust osmolality to 300 mOsm/kg. Segments of the gel-treated artery, and of the circumflex coronary artery (control), were quickly excised from the perfusion-fixed heart, minced into small tissue blocks (1 mm³), and further fixed in glutaraldehyde for 3 hours. The tissue was rinsed in 100 mM sodium phosphate (pH 7.4), postfixed in 1% osmium tetroxide in sodium phosphate buffer for 30 minutes, dehydrated in a graded series of ethanol, and dried in a Sorvall critical point drier. The specimens were mounted on viewing stubs, sputter-coated with gold-palladium (60-40), and examined at 20 keV in either a Cambridge Mark IIA or JEOL 100C scanning electron microscope.

Summary of Protocols

Na⁺-gel was tested in all dogs. Six animals instrumented with distal coronary artery catheters underwent K⁺-gel application and analysis of reactive hyperemia. The remaining 28 dogs underwent a variety of procedures. In 18 animals, gels with other adsorbed vasoactive agents were tested [norepinephrine (5), serotonin (5), angiotensin (4), tyramine (4)] followed by K⁺-gel application and assessment of reactive hyperemia. In three of these with sustained K⁺-induced constrictions, arterial samples were examined by scanning electron microscopy. Among the other 10 dogs, three were instrumented with proximal intracoronary catheters for methoxamine infusions, before and after intravenous prazosin and K⁺-gel application for evaluation of reactive hyperemia. Arteries from two of these were studied by scanning electron microscopy. Among the other seven dogs, five underwent coronary angiography, four of which had vessel diameter crystals implanted. K⁺-gel was applied for evaluation of reactive hyperemia and subsequent intravenous infusion of vasodilators [nitroglycerin (3), nifedipine (4), nisoldipine (2)] administered sequentially in each dog to evaluate relative spasmolytic efficacy.

Drugs

Nifedipine (Bayer), nisoldipine (Miles), prazosin (Pfizer), and nitroglycerin (Eli Lilly) were gifts from the respective
companies. Care was taken to avoid exposure of nifedipine and nisoldipine to light at any time. Norepinephrine, tyramine, and serotonin were purchased from Sigma Chemicals. Valine-5-angiotensin II was obtained from Calbiochem.

Statistical Evaluation

The significance of differences between sequential values in the same group was evaluated by Student's t-test for paired samples.

Results

Effects of K⁺-SP-Sephadex on Coronary Blood Flow

Application of gel in the K⁺-cycle (n = 34) to the left anterior descending coronary artery evoked slow coronary constrictor responses. Maximal reductions in mean external coronary diameter of −25 ± 2% and phasic flow by −40% without altering systemic hemodynamics. Ten minutes after removal of gel, coronary diameter and flow return to control values.

<table>
<thead>
<tr>
<th>Before application of K⁺-SP-Sephadex</th>
<th>After application of K⁺-SP-Sephadex</th>
<th>After removal of K⁺-SP-Sephadex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean coronary blood flow (%)</td>
<td>100</td>
<td>57 ± 6*</td>
</tr>
<tr>
<td>External mean coronary diameter (%)</td>
<td>100</td>
<td>74 ± 5*</td>
</tr>
<tr>
<td>Systolic aortic pressure (mm Hg)</td>
<td>130 ± 5</td>
<td>132 ± 7</td>
</tr>
<tr>
<td>Diastolic aortic pressure (mm Hg)</td>
<td>112 ± 6</td>
<td>112 ± 11</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>119 ± 6</td>
<td>121 ± 5</td>
</tr>
<tr>
<td>Left ventricular pressure (mm Hg)</td>
<td>130 ± 3</td>
<td>133 ± 6</td>
</tr>
<tr>
<td>dp/dt (mm Hg/sec)</td>
<td>1805 ± 305</td>
<td>1759 ± 520</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>128 ± 10</td>
<td>126 ± 12</td>
</tr>
</tbody>
</table>

Mean coronary blood flow (n = 34) and mean external coronary diameter (n = 4) are expressed as percentages (mean ± se) of values before application of K⁺-SP-Sephadex gel. Measurements were obtained 30 minutes after application of gel and 10 minutes after its removal. dp/dt = first time derivative of left ventricular pressure.

* P < 0.001 compared to control value (t-test for paired samples).
minutes (Fig. 1; Table 1). Re-application of gel reduced flow by $-45 \pm 5\%$, a value that did not differ from that obtained with the first application. At peak reduction in coronary flow, animals with implanted distal coronary artery catheters exhibited aortoperipheral coronary artery mean pressure gradients of 7.5 ± 1.2 mm Hg (± SE; n = 6). Although modest, this gradient was consistent in all dogs examined and was significant, inasmuch as gradients were not detected before application of gel ($P < 0.05$).

**Effects of Na+-SP-Sephadex**

Application of Na+-SP-Sephadex to the surface of the left anterior descending coronary artery before (n = 34) or after constriction evoked by K+-gel (n = 34) produced no coronary or systemic hemodynamic effects for periods lasting up to 2 hours.

**Effect of K+-SP-Sephadex on Reactive Hyperemia**

Before application of gel, 15-second occlusion of the left anterior descending coronary artery produced during the peak of the reactive hyperemia a 2.5- to 4.0-fold increase in flow compared to the preocclusion value. After application of K+-SP-Sephadex, preocclusion flow was reduced by $-38 \pm 8\%$, and peak hyperemia after occlusion was only $1.1 \pm 0.2$ times the preocclusion value (n = 34; $P < 0.001$). Therefore, in addition to reducing coronary flow, K+-SP-Sephadex limited coronary vasodilation in response to ischemia (Fig. 2).

**Effect of K+-SP-Sephadex before and after α-Adrenergic Blockade**

To ascertain whether K+ acted in part indirectly by promoting the exocytotic release of norepinephrine from vascular nerves, we evaluated effects of K+-SP-Sephadex gel in the absence and presence of α-adrenergic blockade. In addition, effects of SP-Sephadex gel with adsorbed norepinephrine were studied. In three dogs, an initial application of K+-SP-Sephadex to the left anterior descending coronary artery reduced coronary blood flow by $-35 \pm 4\%$. After removal of gel and return to baseline flow, intracoronary infusion of methoxamine (30 μg/kg in 1 minute) increased mean aortic pressure from 95 ± 5 to 125 ± 5 mm Hg. The hypertensive response was accompanied by an elevation in coronary blood flow of 11 ± 0.5%, corresponding to an augmentation in total coronary artery resistance of 18 ± 3%. Subsequent administration of prazosin (0.2 mg/kg, iv) suppressed

![Figure 2](http://circres.ahajournals.org/DownloadedFrom)
the constrictor effects of methoxamine, indicating effective postsynaptic \( \alpha \)-adrenergic blockade. During \( \alpha \)-blockade, application of K\(^+\)-SP-Sephadex gel evoked unattenuated coronary constrictor responses, reduction in coronary flow averaging \(-33 \pm 6\%\). Additional prazosin (0.1 mg/kg, iv) failed to influence the spasms.

In another five dogs, SP-Sephadex gel with adsorbed norepinephrine was applied. Three to 5 minutes after application of norepinephrine gel, mean external coronary diameter was shortened by \(-6 \pm 1\%\) and mean coronary blood flow was reduced by \(-12 \pm 2\%\). These minor effects were not sustained, however, and measured parameters were back to baseline values within 5–15 minutes. Subsequently, norepinephrine gels produced systemic hemodynamic effects consistent with overflow into the circulation. Mean arterial pressure rose by \(20 \pm 2\%\) (±SE), and heart rate decreased by \(15 \pm 5\%\), changes which were accompanied by minor increases in coronary flow (5 ± 3%; \(n = 5\), \(P > 0.05\)). Challenge with K\(^+\)-SP-Sephadex gel immediately after stimulation with norepinephrine elicited the usual coronary constrictor responses.

**Effects of Serotonin, Tyramine, and Angiotensin**

Additional vasoconstrictors including serotonin, tyramine, and angiotensin II were adsorbed to SP-Sephadex. Results obtained with these gels are summarized in Figure 3. Serotonin gel produced moderate, but sustained, decreases in mean coronary flow of \(-22 \pm 6\%\) (\(n = 5\)). Angiotensin gel likewise evoked small reductions in coronary flow (\(-9 \pm 3\%\); \(n = 4\)), but the effects were transient. Subsequently, these gels elicited invariably systemic hypertension accompanied by increases in coronary flow (15 ± 2%), probably reflecting overflow of angiotensin into the systemic circulation. Tyramine gel produced mild reductions in coronary blood flow (\(-6 \pm 2\%\); \(n = 4\)) which, as in the case of norepinephrine gel, were not sustained and returned to control values spontaneously within 5 minutes. As in the case of norepinephrine-gel application of serotonin, tyramine and angiotensin gels did not modify the response to K\(^+\)-gel applied subsequently.

**Relief of Coronary Spasm by Vasodilators**

The present preparation enabled us to test the effects of various dilators on blood-perfused intact coronary arteries undergoing sustained constriction. Results obtained with nitroglycerin, nifedipine, and nisoldipine are summarized in Table 2. Sequential infusions of nitroglycerin followed by nifedipine, or nitroglycerin followed by nisoldipine, were administered in doses that produced similar hypotensive effects (5–10 mm Hg reduction in mean arterial pressure). Nitroglycerin significantly relieved coronary vasospasm, although residual vasoconstrictor effects of K\(^+\)-gel remained. Upon discontinuation of nitroglycerin, permitting flow values to return to baseline spasm levels, nifedipine or nisoldipine restored or further augmented, respectively, the measured coronary flow as compared to values present before application of K\(^+\)-gel.

In five experiments, coronary constrictor responses and their relief by vasodilators were monitored by coronary arteriography. Reductions in coronary flow of \(-43 \pm 3\%\) evoked by K\(^+\)-gel were associated with narrowing of the instrumented artery. With reductions in flow of this order of magnitude, the arteries downstream of the spasm were not visualized, simulating "complete occlusion" during reduced flow. Intravenous administration of nisoldipine (1.1 \(\mu\)g/min, iv) abolished coronary constriction completely (Fig. 4).

**Scanning Electron Microscopy of Arterial Intima**

Scanning electron micrographs of control arteries not exposed to K\(^+\)-SP-Sephadex revealed a normal
FIGURE 4. Coronary arteriography in a dog with K+-SP-Sephadex-induced spasm. The panel on the left shows the left anterior descending coronary artery instrumented with a pair of ultrasonic crystals and a flow meter. The panel in the middle visualizes a coronary constriction at the level of the applied gel. The iv infusion of nifedipine promptly relieve the spasm.

endothelial surface without evidence of cellular disruption (fig. 5A). Arteries stimulated with K+-gel and undergoing spasm for 1 hour exhibited occasional small areas of exposed subendothelial tissue with platelet attachment (Fig. 5, B and C). However, significant endothelial desquamation, platelet aggregates, or microthrombi were not observed.

Discussion

Although coronary artery spasm has been the focus of considerable attention, its pathogenesis remains unclear. α-Adrenergic (Yasue et al., 1974), cholinergic (Endo et al., 1976), and histaminergic (Ginsburg et al., 1981) constrictor mechanisms have been incriminated, but the importance of these effects have been questioned and remain in doubt (Robertson et al., 1981b). Patients with angiospastic angina appear to be susceptible to the coronary constrictor effects of ergotamine and ergonovine. However, ergot compounds act on multiple monoaminergic receptors, and their action yields little specific receptor-pharmacological information (Henry and Yokoyama, 1981). An important role by platelets and vasoactive lipids in the pathophysiology of coronary spasm has been suggested, although it has been difficult to determine whether vasoactive lipids in coronary venous blood are a cause or an effect of myocardial ischemia (Robertson et al., 1981a; Hirsh et al., 1981; Chierchia et al., 1980b).

Study of coronary spasm in patients undergoing arteriography is difficult, since exploratory procedures are not without hazard and may not be permissible. In addition, vasoactive effects of angiographic dye may influence coronary vasomotion and possibly obscure spasm (Bentley and Henry, 1980). Coronary reactivity may be studied in vitro with isolated human coronary arteries. Unfortunately, isolated human coronaries exhibit striking oscillations in resting tone (Ross et al., 1979), making reproducible dose-response experiments difficult, if not impossible. Moreover, hematogenic and endothelial effects are either not preserved or inadequately preserved in isolated vessels (Morrison et al., 1976). Yet, current evidence suggests that the functional integrity of the endothelium may be essential for the maintenance of normal vascular reactivity (Furchgott and Zawadski, 1980).

Another disadvantage of in vitro studies is that neurogenic mechanisms that may contribute to abnormal constrictor responses (Bertrand et al., 1980; Grondin and Limet, 1977) are not preserved.

In view of the difficulties encountered in evaluating coronary spasm in the clinical setting and of the shortcomings of in vitro experiments, it would be desirable to study the phenomenon of coronary spasm in intact animals. Unfortunately, appropriate animal models have not been developed thus far. In some studies, coronary constriction evoked by drugs were characterized as spasms, although the responses appeared to represent diffuse, transient coronary constrictions. However, diffuse constrictor responses as evidenced by coronary hemodynamic measurements or arteriographic visualizations (West and Guzman, 1959) must be distinguished from localized spasms. In other reports, the term spasm was used to characterize slowly developing thrombotic occlusions produced by intra-arterial foreign bodies and/or sustained local electrical stimulation (Kordenat et al., 1972). Such thrombotic occlusions do not resemble acutely reversible, vasodilator-sensitive spasms as observed in patients with variant angina.

In this study, we have provoked sustained, non-thrombotic segmental coronary constrictions by direct application of drug to the adventitial surface of large epicardial coronary arteries. To obviate actions related to local overflow and systemic distribution of drug, we have adsorbed the vasoactive agents to viscous gels, thereby confining drug delivery to the desired site of action. One important finding of this study is that intact, blood-perfused arteries in situ are not readily constricted by stimuli which induce sustained spasms in isolated arteries in vitro. This suggests that coronary spasm as observed in patients may reflect predominantly an abnormal reactivity of the vascular
Among the various agents tested, the only one that produced appreciable localized constrictions was potassium. Although membrane depolarization with potassium is used routinely to contract isolated arteries, effects of high potassium concentrations on arteries in situ have been incompletely characterized. However, there is little doubt that the adventitial surface of intramyocardial arteries within zones of myocardial ischemia are exposed to high extracellular potassium concentrations. Recent studies with potassium ion-selective electrodes have shown that the potassium activity of extracellular fluid in ischemic zones of canine myocardium may exceed 15 mm (Hill and Gettes, 1980). Thus, although high potassium may not act as a trigger mechanism of spasm at the level of large epicardial arteries, it might constrict large intramural arteries in myocardium transiently accumulating extracellular potassium, a mechanism that could perpetuate or aggravate myocardial underperfusion. The observation that spasms induced by potassium suppressed reactive hyperemia demonstrates that such constrictor responses may limit the vasodilator reserve of the coronary circulation. In addition, the possibility must be considered that diseased arterial smooth muscle may release excess potassium in response to constricting stimuli. In a previous study, we have demonstrated that canine coronary smooth muscle may release substantial amounts of potassium during hypoxia in vitro (Borda et al., 1980).

Our experimental preparation cannot exclude the possibility that effects of K+-gel on measured coronary flow are mediated in part by arteriolar vasoconstriction. Although it is conceivable that, in the vicinity of the large epicardial artery, some K+-gel acted on arteriolar tone in the surrounding myocardium, several observations suggest that the major effect occurred at the level of the epicardial coronary artery. The significant reduction in diastolic-to-systolic coronary flow ratio in response to K+-gel is consistent with results previously obtained by mechanical constriction of epicardial coronary arteries with plastic ocluders (Folts et al., 1975; Gallagher et al., 1978). Similar observations have been made during openheart surgery in aorta-coronary grafts of dogs and humans with proximal obstructions (Folts et al., 1975). Blunted reactive hyperemic responses measured in the presence of K+-gel are consistent with results previously obtained with proximal large-vessel obstruction (Feldman et al., 1978; Gallagher et al., 1978) or obstructed grafts (Reneman and Spencer, 1972). Blunted reactive hyperemia is not pathognomonic of proximal segmental reduction in flow, and may occur in association with various conditions, including left ventricular hypertrophy (Wright et al., 1980) and reduction in myocardial oxygen requirement during hypothermia (Badeer, 1965). Although it is possible to evaluate the contribution of large epicardial coronary arteries to total coronary resistance (Kelley and Feigl, 1978), there is no technique available to distinguish between coronary arterial (epicardial plus intramyocardial arteries), coronary microvascular (arteriolar plus capillary plus venular vessels), and coronary venous resistances. In the present experiments, the drop in arterial pressure across the macrovascular (epicardial) segments was similar in magnitude to that measured by mechanical obstructions evoking comparable reduction in coronary flow (Feldman et al., 1978). Therefore, results of the present experiments can be explained on the basis of changes in epicardial coronary arterial resistance without the need to invoke an appreciable contribution by the nonepicardial coronary circulation. In dogs given vasoconstrictors, cor-
Coronary constrictor responses, to our knowledge, have not been reported to produce a hold-back of angiographic dye at the level of large epicardial arteries (West and Guzman, 1959). Similar angiographic patterns are observed in patients suffering from Prinzmetal's variant angina, a form of angina thought to be precipitated by epicardial coronary artery spasm. Nevertheless, neither in the present study nor in patients with Prinzmetal's is it possible to exclude the possibility that distal coronary constriction contributes to the reduction in coronary flow.

We have considered the possibility that potassium might act in part by promoting the exocytosis of norepinephrine from vascular nerves (Borda et al., 1977; Borda et al., 1980). However, spasms induced by potassium were not altered by effective α-blockade with prazosin. Moreover, norepinephrine adsorbed to gel failed to induce spasms. Therefore, it appears unlikely that noradrenergic mechanisms contributed to the vasoactive effects of potassium. Besides potassium, the only agent tested that evoked sustained coronary constrictions was serotonin. However, compared to potassium, effects of serotonin were modest.

We wondered whether spasmogenetic effects of potassium were associated with localized intimal changes or whether potassium promoted adhesion and aggregation of platelets in constricting segments (Folts et al., 1976). Results obtained with the scanning electron microscopic technique suggest that appreciable intimal changes or platelet thrombi were not produced.

The provocation of reproducible coronary spasms permitted us to compare the spasmolytic effects of selected vasodilators administered systemically in equi-hypotensive doses. Both nitroglycerin and dihydropyridine Ca ++-blockers were effective. Nisolpine, a drug that relaxes isolated, potassium-contracted arteries in subnanomolar concentrations (Kazda et al., 1980), was particularly potent. These observations confirm that calcium antagonists are particularly effective in relieving smooth muscle contractions elicited by membrane depolarization with potassium (Kazda et al., 1980; Henry, 1980).

One important angiographic observation of this study is that nonvisualization of an artery downstream of a localized constriction does not necessarily imply the presence of a "complete occlusion." Epicardial arteries that were well delineated under control conditions failed to visualize, on repeat arteriography, when flow rates were as high as 55% of control flow. Canine epicardial coronary arteries, compared to human epicardial coronary arteries, have in general a smaller diameter, a difference that might facilitate their nonvisualization with only moderate decreases in flow.

In conclusion, the present experiments demonstrate that local coronary spasms are difficult to elicit with potent vasoconstricting agents such as norepinephrine, angiotensin II, and serotonin. On the other hand, potassium is capable of evoking segmental constriction, a phenomenon that might be important for the regulation of flow at the level of intramyocardial arteries.

References

INDEX TERMS: Coronary artery spasm • Nifedipine • Nisoldipine • Myocardial ischemia • Potassium • Serotonin
Coronary artery spasm in intact dogs induced by potassium and serotonin.
J E Pérez, J E Saffitz, F A Gutiérrez and P D Henry

Circ Res. 1983;52:423-431
doi: 10.1161/01.RES.52.4.423

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/52/4/423