Delayed myocardial ischemia induced by anger

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ABSTRACT The objectives of this study were to develop a reproducible behavioral model that simulates the anger state and to characterize its influence on myocardial blood flow in both the normal and compromised coronary circulations. Fourteen mongrel dogs of both sexes were studied. The animals were instrumented for the recording of electrocardiogram, arterial blood pressure, and left circumflex coronary arterial blood flow. A critical level of coronary stenosis was achieved with an adjustable occluder placed just distal to the flow probe. Anger was induced in the instrumented animals by having another dog challenge their access to food. In the absence of coronary artery stenosis, provocation of anger increased heart rate from 107 ± 6 to 215 ± 15 beats/min, arterial blood pressure from 95 ± 4 to 142 ± 5 mm Hg, and coronary blood flow from 31 ± 5 to 72 ± 9 ml/min. These variables returned to the preanger levels within 2 to 4 min. Induction of anger was repeated after a critical stenosis was applied to the left circumflex coronary artery. Anger increased heart rate from 112 ± 6 to 210 ± 16 beats/min, arterial blood pressure from 99 ± 3 to 142 ± 6 mm Hg, and coronary arterial flow from 23 ± 5 to 35 ± 7 ml/min. Within 2 to 4 min after the bout of anger, all dogs exhibited significant reductions in coronary arterial flow (35% of baseline; p < .001), increases in coronary vascular resistance (557% of baseline; p < .002), and ischemic ST segment changes in leads II, III, and aVF. On the basis of these results and our preliminary findings that the delayed ischemia can be induced by stellate ganglion stimulation, we conclude that the poststress period is associated with a marked propensity for coronary vasoconstriction and that the sympathetic nervous system is implicated. Circulation 75, No. 1, 249–254, 1987.

MENTAL STRESS has been increasingly implicated in the etiology of coronary vasospastic disease.1-3 Ambulatory monitoring studies reveal that ischemic episodes can be provoked by activities as routine as conversation, reading, or driving a car.3 In many cases the perfusion abnormalities appear to be caused by coronary vasoconstriction and are unrelated to changes in heart rate or increases in cardiac metabolic requirements. Recently, Deanfield et al.1 and Specchia et al.2 have shown that mental arithmetic can produce significant myocardial ischemia in patients with coronary artery disease.

The affective state that has been most commonly associated with cardiovascular disorders is anger.1-8 The relationship was recognized by 18th century physicians and was impressed on medical consciousness by the well-known fate of Heberden’s bilious colleague, John Hunter.5,6 In contemporary studies, Reich et al.7 found that anger was the affective disorder most frequently associated with recurrence of malignant ventricular arrhythmias. Whereas these observations point to an important connection between behavioral stress and arrhythmogenesis, they do not establish causality nor do they provide insights into the underlying mechanisms.

The objectives of this study were therefore to develop a reproducible behavioral model that simulates the anger state and to define the influence of this state on myocardial blood flow in both the normal and compromised coronary circulations.

Methods

Subjects. The following investigations were carried out in a total of 14 healthy adult mongrel dogs, unselected by sex, and weighing between 15 and 23 kg. The animals ranged between 2 and 7 years of age, as ascertained by examining the teeth, genitals, facial hair, and eyes. The dogs were all supplied by Harvard University’s Animal Resources Center and were free of parasitic worms (such as Dirofilaria immitis) and respiratory infections.

The animals were screened for a positive anger response by simulating the experimental conditions described below. Approximately half of the dogs were found to provide an adequate behavioral response and were used in the study. No differences were noted in the size, age, or sex of nonresponders as compared with responders.
Surgical preparations. All procedures for long-term instrumentation were carried out under aseptic conditions. The animals were anesthetized with intravenous sodium pentobarbital (30 mg/kg) and a thoracotomy was performed in the left fourth intercostal space. A Bird Mark 14 positive-phase ventilator (Bird Corp., Palm Springs, CA) was used to deliver humidified, oxygen-enriched air. Lead II of the surface electrocardiogram was monitored throughout the surgical procedure.

The heart was exposed and suspended in a pericardial cradle. A section of the left circumflex coronary artery was dissected for a length of approximately 1 to 2 cm, and a thoracotomy was performed in the first intercostal space. A polyethylene catheter (0.05 inch id × 0.09 inch od) was positioned in the descending aorta by the Herd-Barger technique. All leads were routed subcutaneously and exited from a site on the left thorax approximately 5 cm from the original incision. The chest was closed in five layers and the pleura was then evacuated. The incision was covered with a compress saturated with 0.2% nitrofurazone in a soluble carrier. This dressing was secured with an elasticized bandage, which was in turn protected by a specially designed denim jacket. Antibiotic and analgesic drugs were administered postoperatively as required. The animals were allowed to recover for 4 to 6 weeks.

Data collection and analysis. During the experimental interventions, a lead II surface electrocardiogram (ECG) was obtained by means of adhesive, pregelled electrodes. The ECG, along with aortic blood pressure (obtained with a Gould-Statham P50 pressure transducer) and coronary arterial blood flow (from either a Gould-Statham electromagnetic flow probe or a Valpey-Fisher Doppler transducer), was conducted via a flexible, multistrand ribbon connected to a Gould 2600 six-channel polygraphic recorder (Gould Inc., Cleveland).

Preamplifiers provided time-averaged values for aortic blood pressure and coronary arterial blood flow. In the case of blood pressure, the mean was calculated with an RC constant of 3.2 sec, whereas both the electromagnetic and Doppler flowmeters used a time constant of approximately 4 sec. The Doppler shift velocities were converted to the corresponding volume flows by multiplying the velocities by the vascular cross-sectional area. Mean coronary vascular resistance was continuously plotted as the quotient of mean aortic pressure and mean coronary arterial blood flow and was derived with an analog divider circuit. The actual resistance values used for the data base were determined by individual calculation rather than by reading them from the chart. The pressure transducers and electronic circuits were calibrated against a mercury manometer at the beginning of each experimental session.

The transcribed data were analyzed according to the following conventions: (1) Control values were determined only after the animal had remained in a stable state for at least 30 sec. (2) Heart rates were calculated by counting the R waves occurring in a 10 sec sample of the ECG and multiplying by 6. (3) The first four experiments in this series were performed with a pressure processor that provided only a phasic output. In these experiments, mean pressure was calculated manually, using the approximation that mean pressure is equal to the diastolic pressure plus one-third of the pulse pressure. When this formula was applied to the results from later experiments, the calculated mean pressures were found to be essentially the same as those obtained by the specialized circuity. (4) The angle response was judged to be adequate if it resulted in a mean aortic blood pressure increase of at least 25 mm Hg and/or a rate-pressure product increase of at least 40%. Data were taken during the plateau phase of the response, typically between seconds 20 and 25 of the 30 sec anger bout. (5) Many of the animals were used in more than one experimental session and repeatedly displayed the delayed flow reduction. The data base consists of the first successful run for each dog.

The data were analyzed for statistical significance with an analysis of variance program (two-way ANOVA, SAS Inc., Cary, NC) running on a Digital Equipment Corp. VAX 11/780. Results were considered significant if the null hypothesis could be rejected with at least 95% confidence.

Experimental procedure. Induction of the angerlike state was carried out according to methods previously used in this laboratory. This protocol has been approved by the Harvard University Standing Committee on the Use of Animals. The instrumented dog was attached to the recording apparatus and allowed to adapt to the laboratory environment for at least 5 min. Upon achieving a steady state, a baseline recording was obtained at a chart speed of 2 mm/sec. After ensuring that the hemodynamic status was stable, the chart speed was increased to 25 mm/sec and a complete set of limb lead ECGs (3 sec each of I, II, III, aVR, aVL, and aVF) was recorded. The polygraph was returned to a speed of 2 mm/sec. While restrained by a leash, the animal was presented with a dish of food and allowed to take a few bites. The dish was then moved just out of the animal’s reach. The first dog was next confronted by a “provoker” dog, also restrained, who attempted to eat the remaining food. This led to a characteristic suite of behavioral responses, including growling, piloerection, and baring of the teeth. At no time did the dogs come into physical contact.

Physiologic alterations evoked by the arousal state included increases in heart rate, systemic blood pressure, and coronary arterial blood flow. These variables reached a plateau after approximately 10 to 15 sec. This was designated as the starting point, and the angerlike state was maintained for another 30 sec. The provoker dog was then removed from the room, and both the hemodynamic variables and behavioral status of the study animal rapidly returned to normal. The end of the anger bout was defined as the time when the provoker dog left the experimental site. Recording was continued at 2 mm/sec. Two minutes after the end of the angerlike state, the chart speed was increased to 25 mm/sec and the limb lead ECG sequence was repeated.

After a 10 to 15 min rest period, this sequence was repeated in the presence of coronary artery stenosis. A critical vessel narrowing was produced by inflating the previously implanted balloon occluder by means of a calibrated screw-drive syringe (Hamilton, Inc., Reno, NV). With thestenosis set according to this criterion, the effects of inducing anger were studied as described above. After completion of the experiment, the balloon occluder was deflated and rapid renormalization of myocardial perfusion occurred. The occlusion was terminated earlier in those cases in which an ischemic response developed so rapidly that delaying release would have jeopardized myocardial tissue.

Results

In the absence of coronary stenosis, induction of angerlike state significantly increased heart rate, arterial blood pressure, and coronary blood flow.
Coronary vascular resistance was substantially reduced. Upon removal of the provoker dog, the arousal state subsided rapidly, and heart rate, blood pressure, and coronary flow returned to control values in 12 of the 14 dogs. In the other two animals, coronary blood flow decreased by 62% and 47%, respectively, and coronary vascular resistance increased by 233% and 100% within 2 min after cessation of the behavioral stress.

The experimental sequence was repeated after induction of critical coronary stenosis. The angerlike state again elicited substantial elevations in heart rate, arterial blood pressure, and coronary flow (figures 2 and 3). Because arterial pressure and coronary flow changed in parallel, there was no net alteration in coronary vascular resistance. Cessation of anger led to rapid reductions in heart rate and arterial blood pressure. However, this was associated with a significant decrease in coronary flow (to 35% of baseline; p < .001) and a corresponding increase in coronary vascular resistance (to 557% of baseline; p < .002). This transpired 20 to 210 sec after the provoking dog was removed from the experimental site (figure 3). There were concomitant alterations in the ST segments of the
ECCG, indicative of ischemia in the region of the myocardium perfused by the left circumflex coronary artery (figure 4). It is noteworthy that in the presence of stenosis, the delayed vasoconstrictor response occurred in all 14 animals.

Discussion

The main objective of this study was to define the effect of inducing intense behavioral stress on coronary hemodynamic function in an experimental preparation. We focused on anger because this affective state has been associated with the occurrence of sudden cardiac death in man.7 Our results indicate that provocation of anger in dogs with coronary artery stenosis results in myocardial ischemia after cessation of arousal. The ischemic response ensued within 2 to 3 min after the anger bout and was characterized by reduced coronary arterial blood flow, increased coronary vascular resistance, and electrocardiographic changes indicative of impaired myocardial perfusion. These alterations occurred at a time when heart rate and arterial blood pressure had returned to the preanger levels. The vasoconstriction state generally persisted until the applied stenosis was removed.

These findings represent the first experimental demonstration of significant myocardial ischemia in response to behavioral stress. This is probably due to the fact that previous behavioral studies have used animals with normal coronary vasculature.9, 14, 15 For example, Rayford et al.14 described the effects of excitatory stimuli on hemodynamic function in conscious animals with an intact coronary circulation. They found that loud noises or sudden squirts of water to a dog's face increased mean coronary arterial blood flow. Other investigators subsequently reported increases in coronary arterial blood flow in response to diverse behavioral stresses. Vatner et al.16 also concluded from a study of unrestrained conscious baboons that coronary arterial blood flow adapts appropriately to the enhanced cardiac metabolic requirements associated with various states of arousal.

The work of Billman and Randall9 presents an exception to this pattern. These investigators demonstrated in normal dogs a transient coronary vasoconstriction after presentation of a classically conditioned aversive stimulus. This response lasted less than 1 min and was followed by a longer lasting period of vasodilation. However, there was no evidence of significant myocardial ischemia.

MacAlpin17 has provided important insights into the mechanisms whereby stenosis predisposes to myocardial ischemia. He defined the extent of occlusion that
is produced as a result of varying degrees of vascular smooth muscle contraction. He found that during constriction the lumenal radius decreases at a rate proportionally faster than does the outer radius. Thus wall thickness acts as a lever that amplifies hemodynamic effects of smooth muscle contraction. The fourth-power effect of the radius on coronary resistance described by Poiseuille implies that for a vessel with an 80% stenotic lesion, the lumenal decrements in adjacent normal segments required to occlude the vessel completely may be as slight as 0.5% of the unconstricted radius. This magnitude of change in vessel diameter is well within the range described by Vatner et al. Indeed, these investigators have provided evidence for α-adrenergically mediated constriction of the left circumflex coronary artery of a magnitude sufficient to result in a significant increase in total coronary vascular resistance.

It is noteworthy, however, that the delayed myocardial ischemic response could be elicited in two dogs without the need to produce coronary artery stenosis by inflating the balloon occluder. Thus vessel narrowing appears to be a predisposing but not essential factor. An additional element that may be involved relates to the role of the vasa vasorum. Barger et al. have found that an extensive plexus of vasa vasorum is formed in response to coronary vascular injury. They have proposed that this network facilitates the delivery of blood-borne vasoconstricting substances to the coronary smooth muscle. The vascularization is also thought to be associated with the proliferation of autonomic nerve fibers, resulting in high local concentrations of norepinephrine during conditions of enhanced sympathetic activity. Both of these factors would be expected to augment the coronary vasoconstrictor response observed after stress and would predispose to ischemia even in the absence of coronary artery stenosis.

The identity of the vasoconstrictor substance(s) responsible for delayed myocardial ischemia, however, remains to be defined. There are a number of neurohumoral transmitters released during behavioral stress that could be involved. Certainly the role of catecholamines needs to be considered as they have a rapid time course of action and have been shown in conscious animals to exert a potent influence on coronary vasomotor tone.

The factors responsible for the delayed nature of the coronary vasoconstrictor effects of behavioral stress also require further exploration. There is evidence suggesting the involvement of an interplay between neurohumoral and hemodynamic factors. It remains to be established whether or not alterations in the disposition of myocardial catecholamines or other substances plays a role. This putative mechanism would correspond to that proposed by Masuda and Levy to account for the delayed time course of recovery of heart rate and contractility after cessation of sympathetic stimulation.

**Clinical implications.** There have been several reports of patients who experienced chest pain and electrocardiographic abnormalities indicative of myocardial ischemia 1 to 3 min after emotional stress or exertion. In one case, the patient first experienced angina pectoris 3 to 4 min after coitus. Upon subsequent evaluation with thallium-201 imaging it was found that the myocardial perfusion deficit invariably occurred not during but 3 to 4 min after the exercise stress test. Lahiri et al. reported results in five patients with known ischemic heart disease who exhibited ST segment alterations and chest pain within a few minutes after cessation of exercise. Three of the five patients had a myocardial infarction within 8 weeks of diagnosis and two died. The authors concluded that the phenomenon of poststress ischemia is associated with severe coronary artery disease and has a poor prognosis. Finally, it is noteworthy that it is not unusual to observe serious arrhythmias such as closely coupled extrasystoles, ventricular tachycardia, and fibrillation in the period after an exercise stress test.

It remains to be determined whether these clinical events and the delayed myocardial ischemic phenomenon share a common mechanism. Should this prove to be the case, the availability of a biological model could lead to better understanding and improved treatment and prevention of coronary vasospastic diseases.

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**References**


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