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Mechanisms of Coronary Spasm of Isolated Human Epicardial Coronary Segments Excised 3 to 5 Hours After Sudden Death

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Isolated segments of epicardial coronary artery with and without severe atherosclerotic lesions excised from human hearts 3 to 5 hours after sudden coronary death demonstrated spontaneous contractile activity that was dependent on the external calcium level and was inhibited by calcium antagonists and activation of beta-adrenoceptors (isoproterenol and high concentrations of norepinephrine). Isoproterenol, with a median effective dose (ED_{50}) of 6.3×10^{-7} *M*, relaxed coronary segments that had been precontracted with 30 m*M* potassium. Stimulation of the alpha-adrenoceptors activated spontaneous contractions and increased tension. Norepinephrine ED_{50} (in the presence of 10^{-6} *M* propranolol) was 2.3×10^{-7} *M*, and tension at a maximal concentration of 10^{-4} *M* was 385.4 ± 51.4 mg. The ED_{50} for acetylcholine and histamine, the potent activators of coronary segment tone and phasic contractility, was 3.98×10^{-7} and 8.9×10^{-7} *M*, respectively; the maximal increase in tension was 1,079.5 ± 175 (at 10^{-4} *M*) and 1,131.3 ± 302 mg (at 10^{-5} *M*), respectively. Acetylcholine and histamine increased whereas high concentrations of norepinephrine failed to inhibit rhythmic activity and tension of coronary artery segments with severe atherosclerotic lesions. Membrane electrogenic mechanisms and ways of activating the contractile elements of human coronary artery smooth muscle are discussed.

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It is generally believed that coronary artery spasm is one of the main causes of disturbances in cardiac function. In particular, conduit coronary artery spasm may be the potential cause of unstable, variant and effort angina pectoris and of myocardial infarction (1,2). Angiographic investigations (3–6) during anginal attacks have demonstrated epicardial coronary spasm and proven its important role in the genesis of cardiac pain and myocardial infarction.

The reason for coronary artery spasm is not yet understood. However, adrenergic and cholinergic agonists have been able to provoke coronary spasm in patients with cardiac disease, and corresponding antagonists have been able to abolish coronary spasm in these same patients (7–9). Other possible endogenous mediators of surface coronary artery spasm may be histamine, which is released from myocardial mast cells (10–12), thromboxane A_2, certain prostaglandins and 5-hydroxytryptamine, which is released from platelets. Ergonovine used clinically to provoke coronary spasm mimics the action of 5-hydroxytryptamine. Besides disturbances in autonomic control, local metabolic changes, increased reactivity of the coronary artery smooth muscle to circulating vasoactive agents or a combination of these factors (13) may be pathogenic mechanisms of coronary spasm.

Isolated human coronary arteries exhibit rhythmic activity (12,14–18). The increase in responsiveness of atherosclerotic human coronary artery to histamine, but not to norepinephrine, was reported by Ginsburg et al. (11) in 1981. In 1984, Kalsner and Richards (19) showed that the level of histamine was increased in the coronary arteries of patients with cardiac disease as compared with the coronary arteries of patients without cardiac disease, whereas the content of serotonin and norepinephrine did not differ. The reactivity of atherosclerotic segments of the coronary artery to all of the amines was increased.

The aim of this report is to demonstrate certain influences on the spontaneous contraction of isolated segments of human coronary artery examined early after death. Their possible significance in the pathogenesis of coronary spasm is discussed.

Methods

Study preparation. Pieces of the left and right coronary arteries were excised from the hearts of 43 persons (6 women and 37 men, aged 42 to 55 years, except for 3 men who

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were 26, 30 and 36 years old) at 8 to 10 cm from the ostia, 3 to 5 hours after sudden cardiac death. The arteries were placed in a physiologic preservative medium and transported to the laboratory, where segments 3 mm in width were cut and positioned between two parallel nickel wires, one fixed in the chamber and the other connected to a force displacement transducer. The artery segments were suspended in a 15 ml organ bath in a physiologic salt solution containing (in m*M*) sodium chloride, 118.5; potassium chloride, 4.7; magnesium sulfate, 1.16; sodium phosphate monobasic, 1.18; calcium chloride, 2.52; sodium bicarbonate, 25.55; dextrose, 11.0 and ethylenediaminetetraacetic acid, 0.025. The bath solution was maintained at 37°C with a pH of 7.35 to 7.4 by bubbling with a gas mixture of 95% oxygen and 5% carbon dioxide under a tension of 2*g*. During the equilibration period of 2 to 2.5 hours, the solution was changed within 15 to 20 minutes by overflow. The isometric force change was recorded with Grass FT-03 or Harvard transducers on a Grass Polygraph 7D or Harvard Biograph 2120. The coronary artery segments were subdivided visually (at transverse sections) into segments with and without severe atherosclerotic lesions. The diagnosis at autopsy in most of the cases was coronary heart disease and atherosclerosis of the coronary arteries.

Drugs. The drugs used included: norepinephrine bitartrate, histamine (Serva), adrenalin bitartrate, acetylcholine, isoproterenol, propranolol (Sigma), sodium nitroprusside (Fluka), verapamil (LEK), D-600 (gift of Dr. K. Mandrek, University of Marburg/Lahn, West Germany) and phenoxybenzamine (Ciba-Geigy). Stock solutions (10^{-2} *M*) of the drugs were made in double distilled water (containing 0.1% ascorbic acid in the case of monoamines) and stored at −20°C before they were used. The desired concentrations were prepared by dissolving the stock solution in the physiologic salt solution (containing 0.01% ascorbic acid in the case of monoamines). All substances were added directly to the muscle bath in a volume of 10 to 100 μl. The concentrations reported are the calculated concentrations for the final bath. The results are expressed as the mean ± SE.

Results

Spontaneous contractile activity. Isolated segments of human epicardial coronary arteries showed phasic spontaneous contractions after 1.5 to 2 hours of incubation in physiologic salt solution. These contractions were characterized by an increase in basal tone in 3 to 20 minute intervals, with superimposed oscillation, lasting from 2 to 10 minutes. Spontaneous phasic activity remained unchanged during 6 to 10 hours of incubation. The patterns of spontaneous contractions of the left and right coronary arteries varied and could differ in adjoining segments of the same artery. No qualitative difference could be postulated between the left and right coronary arteries with respect to spontaneous contraction patterns. Spontaneous contractions disappeared after some agonist applications but were evoked again after other agonist treatments. The spontaneous contractions of the coronary arteries with severe atherosclerotic lesions were irregular and had less amplitude than the contractions of the segments without visible atherosclerotic lesions. Autonomic nervous system antagonists did not abolish spontaneous contractile activity (15).

Norepinephrine, adrenalin and isoproterenol. In coronary artery segments without severe atherosclerotic lesions, norepinephrine in concentrations of 10^{-9} to 10^{-6} *M* increased the rhythm of spontaneous contractions and tension and, in concentrations above 10^{-6} *M*, decreased spontaneous contraction amplitudes and tone (Fig. 1A). After blockade of the alpha-adrenoceptors with phenoxybenzamine, the coronary segments only relaxed after norepinephrine application (Fig. 1A). Blockade of the beta-adrenoceptors with propranolol abolished the relaxation produced by norepinephrine (Fig. 1B). Stimulation of the beta-adrenoceptors with isoproterenol abolished spontaneous contractions and decreased the tension of the coronary artery segments (Fig. 1C). The median effective dose (ED_{50}) for isoproterenol on coronary artery segments that were precontracted with 30 m*M* of potassium chloride was 6.3 ± 0.8 × 10^{-7} *M* (n = 10) (in the presence of phenoxybenzamine, 10^{-6} *M*). After pretreatment with propranolol (10^{-6} *M*), adrenalin, norepinephrine and isoproterenol produced an increase in coronary segment tension with a relative activity of 1.0, 0.95 and 0.37, respectively. In the presence of propranolol (10^{-6} *M*), the ED_{50} for norepinephrine was 2.3 ± 0.6 × 10^{-7} *M* and the maximal increase in tension at 10^{-4} *M* was 385.4 ± 51.4 mg (n = 21). Thus, human coronary artery smooth muscle possesses both alpha- and beta-adrenoceptors which produce contrary effects on spontaneous contractions and tone when activated.

Acetylcholine and histamine. Acetylcholine and histamine proved to be potent activators of isolated human coronary artery segments with an ED_{50} of 3.98 ± 0.8 × 10^{-7} *M* and 8.9 ± 0.7 × 10^{-7} *M*, respectively, although the maximal tension produced, 1,079.5 ± 175 mg at 10^{-4} *M* (n = 17) and 1,131.3 ± 302 mg at 10^{-5} *M* (n = 8), respectively, did not differ significantly.

Certain difficulties arise in the quantitative analysis of agonist action on isolated human coronary artery segments, because of rhythmic spontaneous activity. In spontaneously active segments and in silent segments or in those in which rhythmic activity has disappeared after a preceding activation (for example, after activation with a high concentration of potassium), application of the agonists led to activation of the pacemaker and stimulation or reappearance of spontaneous rhythmicity with its own periodicity. It is therefore difficult to analyze the effect of agonists and to follow the dose-response relation specifically, because of the appearance of these rhythmo-inotropic dependencies.

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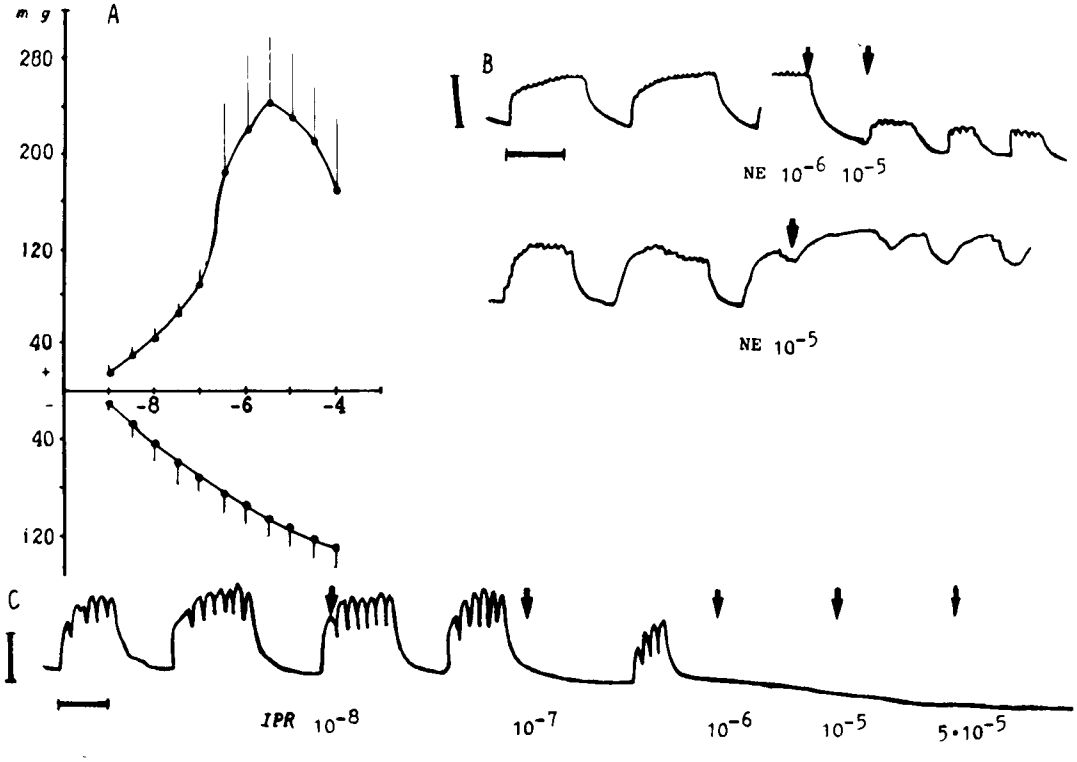
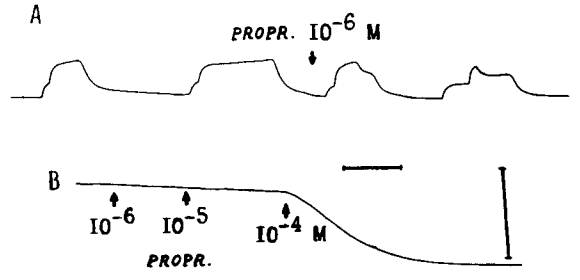


Figure 1. Effects of adrenoceptor stimulation on spontaneous contractions and tone of human coronary artery segments. **A**, Norepinephrine action on tension before (**top**) and 30 minutes after (**bottom**) incubation with phenoxybenzamine (10^{-6} *M*). **Abscissa** = molar concentration (− log); **ordinate** = change in milligrams of tension (n = 4). **B**, Effects of high concentrations of norepinephrine (NE) before (**top**) and 30 minutes after (**bottom**) incubation with propranolol (10^{-6} *M*). **C**, Effect of isoproterenol (IPR) (concentrations in moles). **Vertical bars** = 500 mg; **horizontal bars** = 5 minutes.

Phenoxybenzamine and propranolol. Although blockade of the alpha- and beta-adrenoceptors did not abolish spontaneous contractions of the isolated human coronary artery segments, a small increase in the frequency of contractions was seen after the addition of phenoxybenzamine (10^{-6} *M*) and a small decrease in contraction amplitude was seen after the addition of propranolol (10^{-6} *M*). These effects do not appear to be related to the specific action of the agents on the autonomic receptors. Figure 2 illustrates the decrease in amplitude of spontaneous contractions of human coronary artery segment after the addition of propranolol (10^{-6} *M*), a small relaxation of contracture at 10^{-6} *M* propranolol with a high concentration of potassium (118 m*M*) and complete relaxation after 10^{-4} *M* propranolol. This finding agrees with published data on the calcium antagonist property of propranolol (20). Apparently, the effect of propranolol on coronary artery smooth muscle not only depends on the beta-adrenoceptors but also results from its calcium-blocking property or prostacyclin-releasing action, as shown in perfused rabbit heart (21).

Calcium. Spontaneous contractile activity of human epicardial coronary artery smooth muscle depends on the presence of calcium in the bath solution. The increase in calcium content in the present study led to an increase in amplitude and an increase in the interval between contractions. The same effect was seen after decreasing the sodium level in the medium by 50%. Lowering the calcium level in the bath solution by 50% produced almost no change in the frequency and amplitude of phasic contractions. In a calcium-free solution (without the addition of EDTA or EGTA), phasic spontaneous contractions disappeared and reappeared only after the normal calcium level had been restored. Evidently, activation of the pacemakers in coronary artery smooth muscle, which leads to the propagation of excitation and activation of smooth muscle cells, depends on extracellular calcium.

Figure 2. Effects of propranolol (PROPR.) on spontaneous contractions (**A**) and high potassium (118 m*M*) contracture (**B**) of human coronary artery segment. **Vertical bar** = 1 g; **horizontal bar** = 5 minutes.



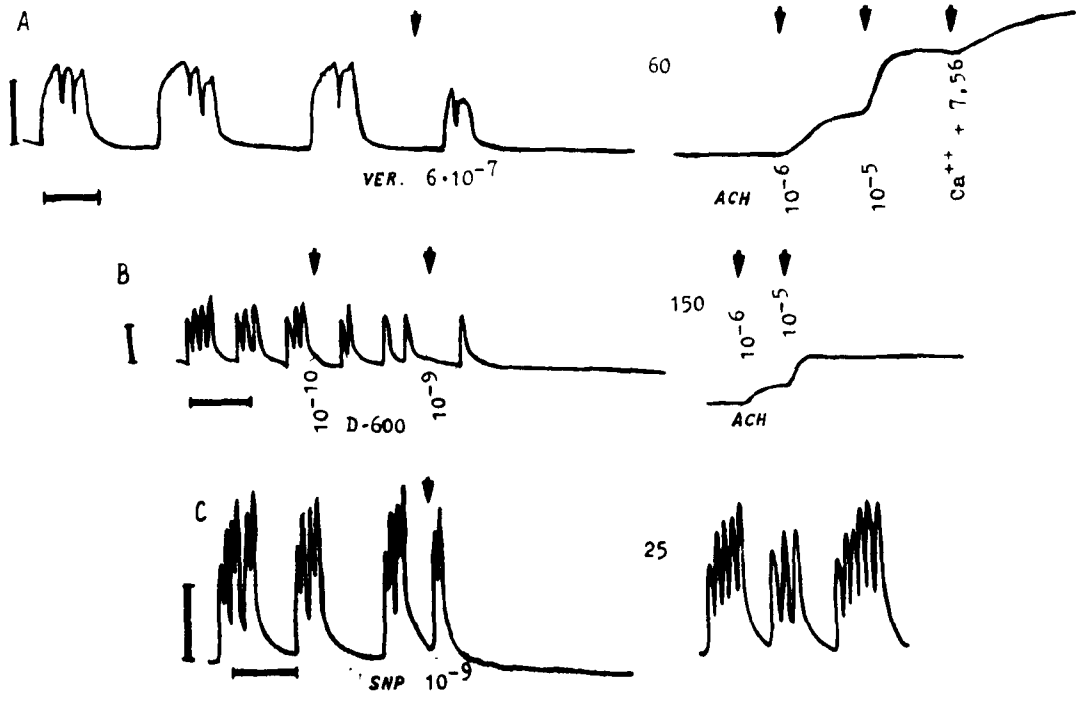


Figure 3. Action of verapamil (VER.) (**A**), D-600 (**B**) and sodium nitroprusside (SNP) (**C**) on spontaneous contractions of human coronary artery segments. Agent concentrations in moles (except calcium which is in millimoles). Numbers in intervals = time of washing in minutes. **Vertical bars** = 500 mg in **A** and **B**, and 200 mg in **C**; **horizontal bars** = 5 minutes. See text for explanation. ACH = acetylcholine.

Calcium channel blocking drugs (verapamil and D-600). The role of extracellular calcium in the activation of the pacemakers and in the initiation of phasic spontaneous contractions is illustrated by the calcium channel blocking drugs. In a concentration of 10^{-8} *M*, verapamil decreased spontaneous contractions; in concentrations of 10^{-7} to 10^{-6} *M*, it abolished such contractions. A similar effect was seen with D-600. In concentrations of 10^{-10} to 10^{-9} *M*, D-600 decreased spontaneous contractions, and in higher concentrations it abolished the spontaneous contractions of isolated human coronary arteries (Fig. 3). Apparently, calcium antagonists possess a very high affinity for smooth muscle cells of human coronary arteries and, after washing out, spontaneous activity was not restored. An increase in the calcium level in the medium did not increase the tension or restore the spontaneous contractions in these experiments. Acetylcholine, which activated rhythmic contractile activity or evoked rhythmic activity in silent coronary artery segments, led to an increase in basal tone without oscillations in experiments with preliminary application of calcium antagonists. The increase in calcium concentration in this case led to a further increase in tension (Fig. 3A and B). In contrast to the calcium antagonists, the suppressive action of sodium nitroprusside, in concentrations of 10^{-9} *M* and higher, on spontaneous contractile activity and tension of coronary segments was abolished after washing out with a physiologic salt solution (Fig. 3C).

Atherosclerotic versus normal coronary artery segments. As mentioned, coronary artery segments with severe atherosclerotic lesions demonstrated a less regular rhythm and a smaller amplitude of spontaneous contractions than did segments without visible atherosclerotic lesions. The patterns of change in tone and in spontaneous contractions after the addition of acetylcholine and histamine, namely, increases in tension and activation of spontaneous contractions, were preserved. The addition of norepinephrine, however, had a different effect on the coronary artery segments with severe atherosclerotic lesions than on the coronary segments without visible atherosclerotic lesions. This difference was related to the action of high concentrations of the amine. Norepinephrine produced an increase in spontaneous contractions and tension in concentrations of 10^{-9} to 10^{-6} *M* and, in the higher concentrations, decreased the spontaneous contractions and tension of coronary artery segments without severe atherosclerotic lesions (Fig. 1). In coronary artery segments that were severely affected by atherosclerosis, high concentrations of norepinephrine failed to relax the segments and only activated spontaneous contractions and increased the tension (Fig. 4). After pretreatment with phenoxybenzamine, the relaxing action of norepinephrine in segments with severe atherosclerotic lesions did not appear or was extremely weakened (Fig. 4B). Apparently, the atherosclerotic process leads to a decrease in density or sensitivity of the beta-adrenoceptors in coronary artery smooth muscle.

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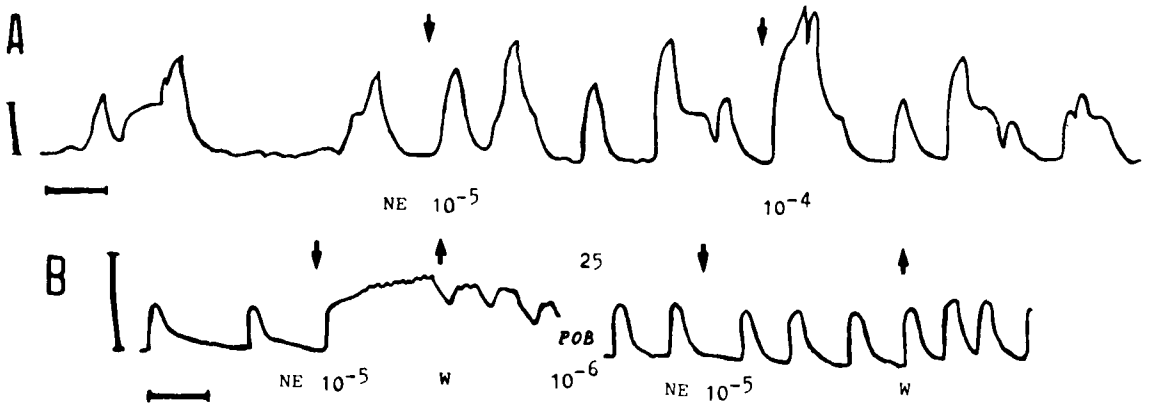


Figure 4. **A**, Action of high concentrations of norepinephrine (NE) on spontaneous contractile activity of human coronary artery segment with severe atherosclerotic lesions. **B**, Effects of norepinephrine before and 25 minutes after incubation with phenoxybenzamine (POB). Concentrations in moles. **Vertical bars** = 200 mg; **horizontal bars** = 5 minutes. See text for explanation. w = washing.

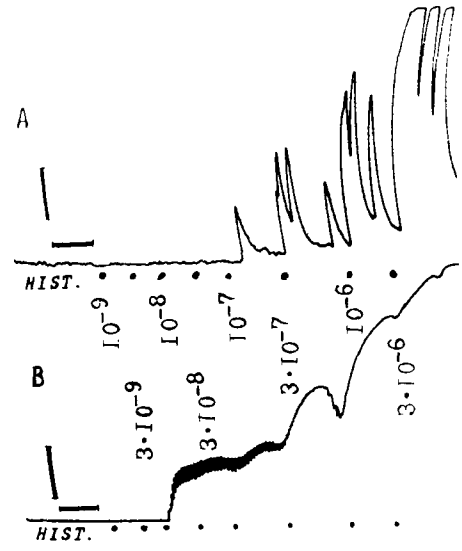
Other factors affecting spontaneous contractile activity. The dependence of spontaneous contractile activity of isolated segments of human coronary artery on extracellular calcium, which is similar to that of spike-generating vessels of smooth muscle (for example, the portal vein), suggests that the mechanism of activation of the contractile machinery is the same. For human coronary smooth muscle, the presence of pacemakers, a spontaneous change in membrane permeability to some ions and gradual depolarization with the development of action potentials may trigger phasic spontaneous contractions. There is some indirect evidence for the role of a membrane electrogenic mechanism in the activation of spontaneous contractions. Hypoxia and lowering of the temperature of the bath solution (15) led to a disappearance of the phasic spontaneous contractions. At room temperature, spontaneous contractions of human coronary artery segments rarely occurred, the pattern of segment activation by the agonist changed and the tension gradually increased in a dose-dependent manner (Fig. 5).

The existence of an electrogenic membrane mechanism of human coronary smooth muscle activation is confirmed by the following. A high concentration of potassium abolished phasic spontaneous contractions and produced contracture (Fig. 6A). The inhibition of the membrane sodium-potassium pump by ouabain led to a disappearance of phasic contractions and produced sustained contracture (Fig. 6B). The blocker of the outward current for potassium, tetraethylammonium, in a concentration of 1 m*M*, produced a transitory increase in the amplitude of spontaneous contractions; in a concentration of 5 m*M*, it produced an increase in amplitude of the phasic contractions and tension and, in a concentration of 10 m*M*, it led to the development of sustained contracture (Fig. 6C).

Discussion

Spontaneous coronary contractions and relation to age and atherosclerosis. Spontaneous phasic contractions of isolated human coronary artery segments excised 3 to 5 hours after sudden coronary death appear to be an intrinsic property of coronary smooth muscle which is inhibited in vivo by the higher levels of regulation. We cannot, however, correlate the appearance of spontaneous contractions with age or the atherosclerotic process, although some authors believe that phasic spontaneous contractions appear in persons who are more than 40 years of age (22). Nevertheless, in the reference cited, rhythmic activity was evoked by serotonin in a human coronary artery segment from a 9 year old child.

Figure 5. Change in pattern of activation of human coronary artery segment by histamine (HIST.) as dependent on the temperature of the bath solution. **A**, 37°C. **B**, 20°C. Concentrations in moles. **Vertical bars** = 500 mg; **horizontal bars** = 5 minutes.



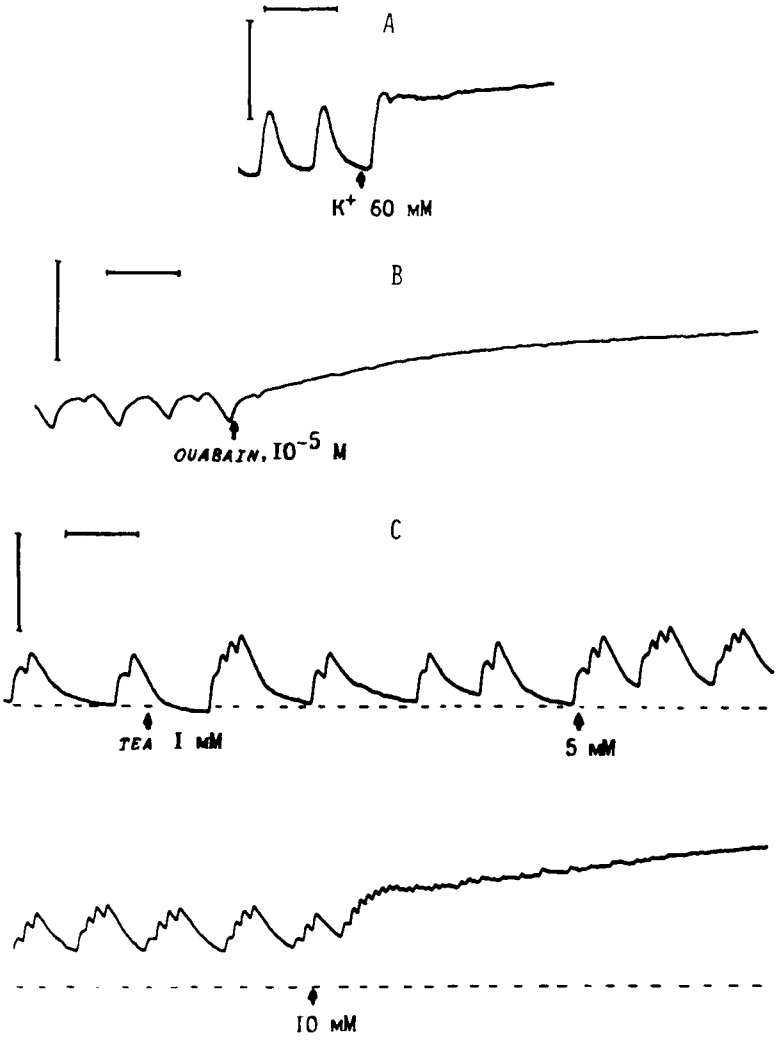


Figure 6. Action of a high concentration of potassium (**A**), ouabain (**B**) and tetraethylammonium (TEA) (**C**) on spontaneous contractile activity of human coronary artery segments. **Vertical bars** = 1 g; **horizontal bars** = 5 minutes.

We examined isolated coronary artery segments from a 26 year old man with severe atherosclerotic lesions that showed spontaneous contractility. Coronary segments of a 30 year old man who died accidentally and who did not have visible atherosclerotic lesions demonstrated phasic spontaneous activity. Coronary artery segments from a 36 year old man who died of cardiac insufficiency combined with valvular disease also demonstrated spontaneous contractile activity. We believe that the ability to contract spontaneously is a property of human coronary artery smooth muscle and that the occurrence of spontaneous contractions depends on the conditions of pacemaker activation and the propagation of excitation along the smooth muscle cells. This effect has been demonstrated by experiments that showed that the appearance of phasic spontaneous contractions in collateral vessels developed after ligation of the conduit coronary artery in dogs and even in the conduit artery after blockade of the potassium current with tetraethylammonium (23,24). Thus, the impairment of normal regulatory influences at the level of smooth muscle cells can lead to the appearance of spontaneous contractions of the coronary artery.

Spontaneous coronary contractions, coronary spasm and angina pectoris. Disturbance in the control mechanisms of the coronary arteries in atherosclerotic disease, leading to a diminished inhibition of the intrinsic property of human coronary smooth muscle to contract spontaneously, may be one of the mechanisms of coronary artery spasm underlying angina pectoris. It has been shown that cholesterol increases the sensitivity of canine coronary artery smooth muscle to calcium ions and produces, by itself, an increase in tension (25). Calcium content in human coronary arteries increases with age (26), as does atherosclerosis of the coronary arteries. The change in sensitivity of atherosclerotic segments of human coronary artery to certain agents has been demonstrated (11,19). Thus, the increase with age in the occurrence of angina pectoris and sudden coronary death can result from a changed reactivity of coronary artery smooth muscle to certain endogenous neurohumoral and local metabolic factors. This reactivity is ag-

gravated by atherosclerotic lesions, especially plaque, which decrease the size of the vessel lumen. In such situations, a small change in the diameter of the artery can lead to a greater narrowing of the lumen and impairment of blood supply in the myocardium. Another factor in increasing the reactivity of the coronary artery to endogenous neurohumoral and local metabolic substances may be a change in the endothelial coating of the artery, which is seen in human atherosclerotic coronary arteries (27). We believe that the ability of human coronary smooth muscle to contract spontaneously is the main cause of spontaneous coronary artery spasm and angina pectoris. In experiments on isolated, epicardial coronary arteries of dogs and cats, for example, we did not see phasic spontaneous contractions. We believe that there is no single, definitive mediator of coronary artery spasm, but that its genesis in humans is probably multifactorial.

Mechanisms of spontaneous coronary contractions. The mechanism activating the contractile machinery of human coronary smooth muscle seems to operate through both the entrance of extracellular calcium and the release of calcium from membrane-bound and intracellular stores. The disappearance of spontaneous contractions in a calcium-free medium, or after the addition of calcium antagonists, supports the first suggestion. The interference with intracellular calcium translocation by sodium nitroprusside appears to confirm the role of membrane-bound or other intracellular calcium stores in activating the contractile apparatus of human coronary artery smooth muscle. The increase in tension of the coronary artery segments produced by acetylcholine in the experiments with calcium antagonists is also evidence for the release of calcium from membrane or intracellular calcium stores. Coexistence of the double calcium mechanism of activation supports the concept of a multifactorial genesis of coronary artery spasm and suggests that the calcium antagonists, which are effective agents in treating vessel spasm, are not able to relieve the spasm produced by calcium release from intracellular or membrane-bound stores. The most comprehensive agents, in this respect, must be drugs that prevent the formation of the intracellular calcium-calmodulin-myosin light-chain kinase complex required for actin-myosin interaction. These agents must possess a much higher affinity for this complex in coronary artery smooth muscle than agents in other vessels or smooth muscle organs.

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