Chronic Catheterization of Coronary Artery: Induction of ECG Pattern of Myocardial Ischemia by Intracoronary Epinephrine.*† (26661)

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The relationship between "disturbances of the mind" and angina pectoris was noted by Heberden in his original description of the disease(1); the subsequent disability of his friend, John Hunter, and the latter's death following an argument, served to focus attention on the role of emotional factors in causation of coronary artery disease. In the two centuries which have elapsed since Heberden's account, only scattered reports have been published of experimental data linking "nervous tension" and coronary disease(2). Recently, Magatsian and co-workers(3,4) have described myocardial damage produced in baboons and monkeys by long-continued psychic stress. Friedman *et al.*(5) have reported that "men exhibiting a behavior pattern associated with coronary artery disease" have a high urinary excretion rate of catechol amines. In an attempt to determine whether the alleged effect of "nervous stress" in the pathogenesis of coronary disease may be mediated by neurohumoral transmitters acting directly on the heart, a technic for chronic catheterization of the coronary artery has been developed. Such a preparation affords the opportunity to examine the acute and chronic effects of localized, intracoronary infusions of epinephrine and norepinephrine on the electrocardiogram of the unanesthetized dog.

Methods. Chronic catheterization of the coronary artery has been successfully performed in 5 male dogs (25-50 kg). The animals were anesthetized with pentobarbital and placed on positive pressure respiration. After thoracotomy (left fourth interspace) the pericardium was incised and the edges sutured to the chest wall, forming a cradle for the heart. The left anterior descending coronary artery was dissected from its bed for 4 to 5 cm, umbilical tapes were passed beneath the artery (Fig. 1A), and a double purse-string suture (6-0) was placed superficially in the wall of the artery (Fig. 1B). A polyvinyl catheter (I.D.-0.38 mm and O.D.-0.76 mm) was prepared with a cuff 10 mm from the end (Fig. 1B). To stiffen and facilitate handling the soft catheter a steel wire was inserted to the tip of the tubing. A sharp, short bevel needle was used to make a hole through the arterial wall in the center of the purse-string sutures. The umbilical tapes were pulled in opposite directions to immobilize and occlude the artery momentarily, and the catheter was inserted through the hole up to the cuff. The purse-string sutures were then tied, and looped above the cuff to prevent accidental withdrawal of the catheter. After removal of the wire, the free end of the catheter was passed through the chest wall *via* a large needle. The catheter was filled with heparin (100 mg/ml), and

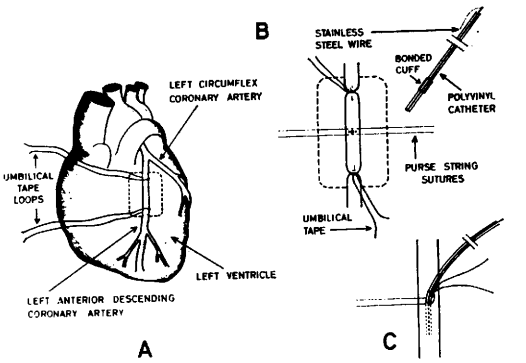

FIG. 1. Operative technic for chronic implantation of catheter into left anterior descending coronary artery.

* Supported in part by grants from Massachusetts Heart Assn. (Greater Boston Chapter), U.S.P.H.S., and from the Eugene Higgins Trust through Harvard University.

† We wish to thank Drs. David G. Freiman, Paul M. Zoll and Ralph E. Thiers for advice and aid in these studies, Dr. Harold Upjohn for a generous supply of heparin, Smith, Kline & French Lab. for Dibenzyline used in these studies, and F. W. Smith for technical assistance.

‡ Fellow of Life Insurance Medical Research Fund.

§ Fellow of National Foundation.

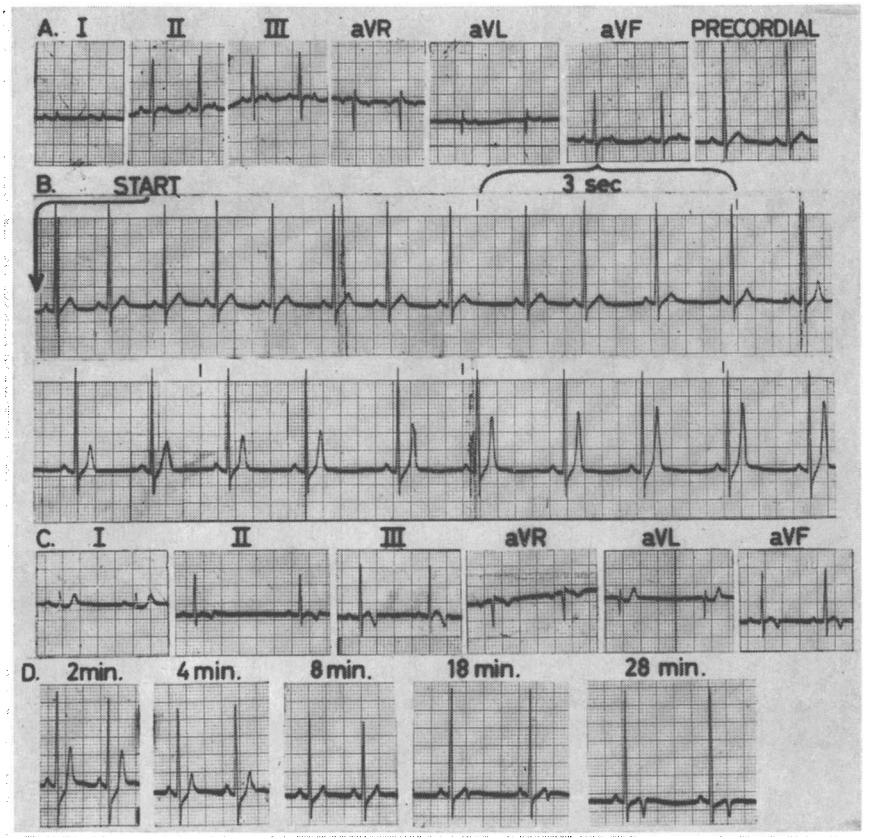

FIG. 2. Electrocardiographic changes induced by intracoronary infusion of l-epinephrine in unanesthetized dog. A. Control. B. Continuous tracing of precordial lead during infusion of 2.0 μg/min. C. Limb leads taken 2 min. later while infusion was continued. D. Precordial lead at 2, 4, 8, 18 and 28 min. after cessation of 1 hr infusion.

sealed with a stainless steel obturator. The pericardium was loosely approximated before closing the chest. In the operations which proceeded uneventfully, the animals were up and eating 8 to 12 hours postoperatively. The catheter was refilled with heparin each day. Although the electrocardiograms were normal by the tenth day, experiments were not performed during the first 3 postoperative weeks. During this period the animals were trained to lie quietly on the right side while electrocardiograms were taken. All infusions were administered through the coronary catheter at the rate of 0.25 ml/min, with the animals in the fasting state. Before infusion of the drugs (dissolved in Krebs-Henseleit solution), control electrocardiograms were recorded while the diluent alone was administered.

Results. Uniform changes in the electrocardiogram were noted in all the dogs during the intracoronary infusion of l-epinephrine hydrochloride (1.0-4.0 μg/min of the base) or l-norepinephrine bitartrate (0.4-4.0 μg/min of base), with l-norepinephrine being 3 to 4 times more potent. Within 10 seconds after onset of the infusion of l-epinephrine the amplitude of the precordial T wave began to increase, reaching a maximum height in 30-60 seconds; simultaneously the ST segment became depressed, and the R and S waves increased slightly in amplitude (Fig. 2B). Changes in the limb leads are depicted in Fig. 2C. If the infusion of the sympathomimetic amines was continued for 1-2 hours, a characteristic electrocardiographic pattern gradually developed following cessation of the infusion (Fig. 2D). There was a depression and upward coving of the ST segment, and inversion of the T wave; these abnor-

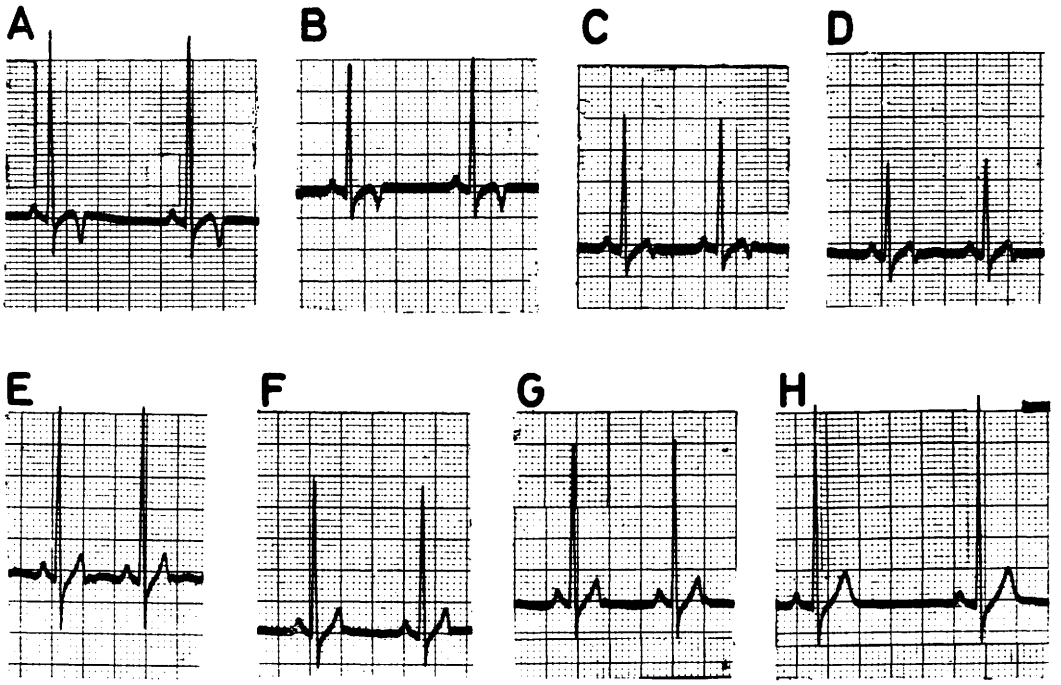

FIG. 3. Restoration of electrocardiogram (precordial) to normal by intracoronary infusion of phenoxybenzamine (100 μg/min.). A. Precordial lead 24 hr after l-epinephrine (control). B.-E. 3, 6, 16 and 30 min. after start of infusion of phenoxybenzamine. Infusion stopped at E. F.-H. 15, 30 and 120 min. post-infusion.

malities persisted for 7-10 days. The behavior of the animals did not suggest any discomfort during this period, and serum lactic dehydrogenase levels were within the normal range. One animal was sacrificed after 3 months of nearly daily infusions of epinephrine or norepinephrine. The heart was normal in appearance, and injection of the coronary artery by the Schlesinger technic(6) revealed patency of all of the coronary arteries. The intracoronary portion of the catheter was enclosed in a sleeve of endothelium open only at the catheter tip. Microscopic examination of the heart showed normal myocardium and coronary arteries.

The abnormal postinfusion electrocardiogram produced by epinephrine or norepinephrine was restored to normal temporarily by intracoronary infusions of 1) l-epinephrine (0.2-.3 μg/min), 2) l-norepinephrine (0.1 μg/min), 3) acetylcholine (25 μg/min), 4) procaine hydrochloride (0.5 mg/min) and 5) phenoxybenzamine hydrochloride (Dibenzyline 100 μg/min). Infusion of low concentrations of the sympathomimetic drugs reverted the T waves to normal, while larger doses produced high, peaked T waves and depressed ST segments as noted above. When infusion of either concentration was stopped, however, the inverted T waves reappeared within several minutes. Acetylcholine produced only a transient restoration of the normal electrocardiogram, with inversion of the T wave reappearing during the infusion. Phenoxybenzamine was slower in onset of action (Fig. 3) but the persistence of the normal ECG was longer than noted with the other drugs mentioned above.

Discussion. The acute electrocardiographic changes noted during intracoronary infusion of the catechol amines in the present study were probably the result of increased rate of depolarization and repolarization in the area supplied by the left anterior descending coronary artery. Hammer and Pisa (7) have, in fact, observed a late systolic bulging of the anterior wall of the left ventricle during intracoronary administration of norepinephrine; the area infused was thus repolarized and relaxing, while the rest of

the left ventricular muscle was still depolarized and contracted. The postinfusion depression of the ST segment and inversion of the T wave may represent abnormal prolongation of the action potential; restoration of the electrocardiogram to normal by small doses of epinephrine or norepinephrine, substances which are known to shorten the action potential, support this view. Acetylcholine, which has little or no effect on the membrane or action potential of ventricular muscle produced transient effects similar to those observed with the catechol amines. The observations of Hoffman(8) and West (9) suggest that the changes induced by acetylcholine may have been the result of the stimulation of intracardiac ganglia and release of norepinephrine from the nerve endings. The mechanism by which procaine and phenoxybenzamine reversed the negative T wave is obscure. The lack of effect of these drugs on the normal electrocardiogram indicates that the reversal was not the result of direct peripheral action, but may represent the blockade of adrenergically induced vasoconstriction, as indicated in the recent reports of Sventivanyi(10).

The postinfusion depression of the ST segment and inversion of the T wave, persisting for 7-10 days, closely resembles the electrocardiographic pattern noted in patients with so-called myocardial ischemia(11,12). Numerous investigators have reported minor, transient ST segment and T wave alterations produced by fear or psychological stresses and have noted the similarities of these changes to those produced by parenteral administration of small doses of epinephrine (13). We are not aware of any previous report of postinfusion changes similar to those noted here. These observations may serve as a clue to the manner in which emotional factors may play a role in pathogenesis of coronary artery disease.

Summary. Infusion of epinephrine or norepinephrine into the coronary artery of dogs produced high, upright, peaked T waves with depressed ST segments. After cessation of the infusion the electrocardiogram approached normal, then gradually developed depressed and coved ST segments and inverted T waves which persisted for 7-10 days. The postinfusion electrocardiogram could be restored to normal by intracoronary infusion of epinephrine, norepinephrine, acetylcholine, procaine, or phenoxybenzamine. The persistent alteration of the electrocardiogram in our animals was remarkably similar to that attributed to subendocardial ischemia in man. No evidence of structural changes was noted in the heart of one dog sacrificed after several months of infusions.

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Received May 1, 1961. P.S.E.B.M., 1961, v107.