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Coronary artery spasm: a hypothesis on prevention by progesterone

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Abstract — The mechanism of coronary artery spasm has been hypothesized as follows: the dormant gene of the smooth muscle of the human coronary artery is identical or similar to the active gene of the smooth muscle of ductus arteriosus, but can be activated by estrogen. The activation could be preventable by progesterone. The prevention is due to the reduction of the number of estrogen receptors of the smooth muscle of the coronary artery.

Introduction

The clinical spectrum of coronary artery spasm (CAS) is:

- Sudden cardiac death: sudden infant death syndrome (SIDS), sudden unexpected nocturnal death syndrome (SUNDS), sudden cardiac death with coronary atherosclerosis;
- Myocardial infarction: myocardial infarction with endocardial fibroelastosis (infant), juvenile myocardial infarction, myocardial infarction with/without coronary atherosclerosis;
- Angina pectoris: Prinzmetal's angina pectoris with/without coronary atherosclerosis.

SIDS is most likely due to sudden cardiac death during sleep as a result of ventricular arrhythmia (ventricular fibrillation, complete heart block) from right coronary artery spasm (R-CAS). Endocardial fibroelastosis (EFE) with old inferio-lateral myocardial infarction is the supporting evidence for SIDS being due to R-CAS.

Infants with EFE with old inferio-lateral myocardial infarction are probably crying from chest pain due to acute myocardial infarction. This is not recognized by the parents, and the infants are not hospitalized. The age distribution of acute myocardial infarction is typically between 2 and 5 months of age. They later develop EFE and seek the help of a pediatric cardiologist by 7 months of age with congestive heart failure. They usually die by 1 year of age.

Although the old text book of pediatric cardiology described the possibility of myocardial infarction under EFE, the pathological findings by Moore and Lambert are compatible with old inferior lateral myocardial infarction with normal coronary arteries (1). An electrocardiogram revealed a Q wave in leads II, III, aVF with T wave inversion at left lateral chest leads.

The incidence of EFE has sharply decreased. The incidence of SIDS could be declining irrespective of positioning of the infants.

Sudden cardiac death during sleep has been

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reported among young Asian and Oceanian males with an average age of 25. The syndrome is referred to as sudden unexpected nocturnal death syndrome (SUNDS), Pokkuri disease (Japanese) or Bangungut (Phillipino) (2–4). Juvenile myocardial infarction and Prinzmetal's angina pectoris among young Japanese males constitute another spectrum of CAS, matching the age distribution of SUNDS.

With normal coronary arteries, the usual site of CAS is the proximal portion of the right coronary artery (5). With coronary atherosclerosis, the site of CAS usually occurs at the site of coronary athero-

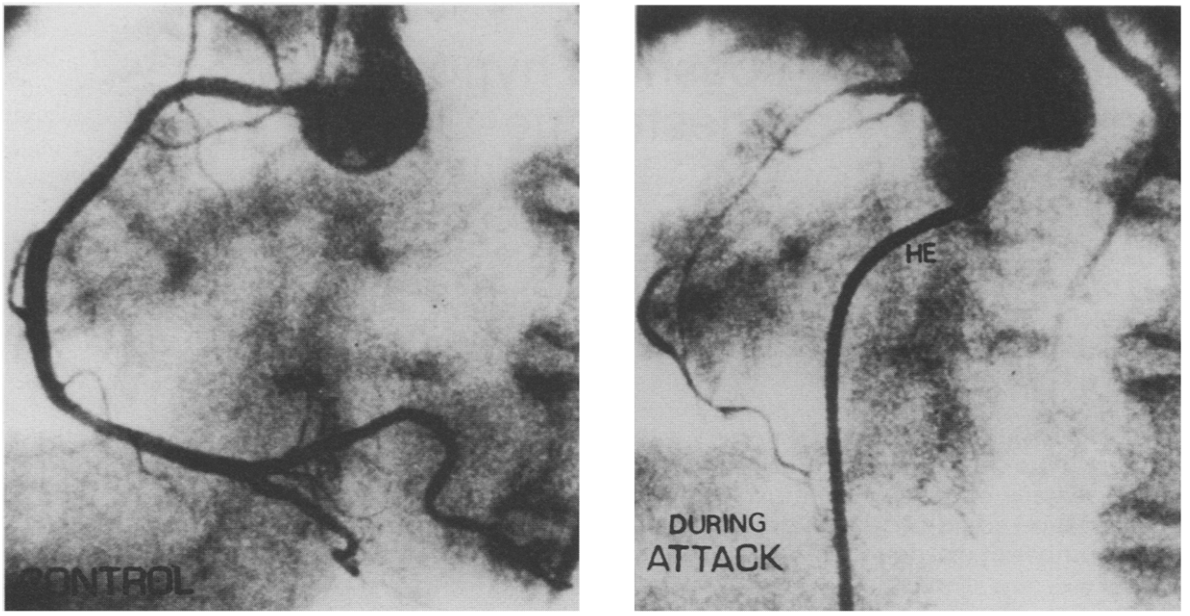

Fig. 1 Provocative test for Prinzmetal's angina pectoris with normal right coronary artery.
Left: control right coronary arteriogram, showing no appreciable stenosis.
Right: arteriogram during an anginal attack; spasms seen from the proximal portion of the right coronary artery. HE = His-bundle electrocardiogram.

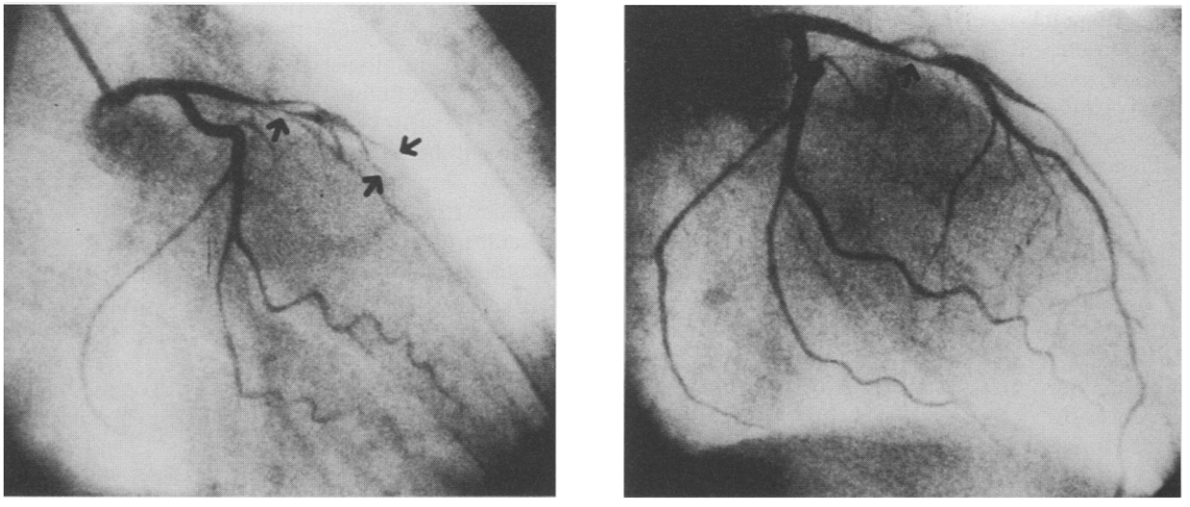

Fig. 2 During an episode of angina (left), the mid portion of left anterior descending branch (LAD) of the left coronary artery went into CAS with disappearance of distal run off. When the pain subsided (right), the distal run off and atherosclerosis of LAD are clearly shown.

sclerosis, necessitating admission to an emergency room for thrombolytic treatment or coronary angiogram followed by invasive procedures.

Hypothesis

The common denominator for CAS is estrogen. Some relevant evidence is as follows.

1. A coronary drug project with estrogen had to be terminated due to increased incidence of coronary events (6).
2. Oral contraceptive users had five times higher coronary events than non-users (7).
3. The estrogen level of the umbilical artery is 100 times higher than in non-pregnant females (8).

All sex steriod hormones are derived from cholesterol (LDL).

The existence of estrogen receptors at the nucleus of the smooth muscle of the human coronary artery has been well accepted. Gene regulation by estrogen has been established, as well as progesterone working as antiestrogen to reduce the number of estrogen receptors (9).

SIDS and acute myocardial infarction are mostly due to the activation of the dormant gene of the smooth muscle of the proximal portion of the right coronary artery to the smooth muscle of ductus arteriosus by estradiol of the umbilical artery. The activation seems to take at least 2 months. A typical CAS lasts only for 3 months. Thus the vulnerable period for an infant to have SIDS or myocardial infarction should be between 2 and 5 months of age.

SUNDS occurs almost exclusively among males, whereas the sex incidence for SIDS is 3 male to 2 female.

Actively menstruating females are protected from CAS because their progesterone works as antiestrogen. After puberty, adolescent males are not protected from CAS; even androgens are antiestrogen. Postmenopausal women are not protected from CAS, due to loss of progesterone.

Instead of progesterone, Tamoxifen (non-steroidal antiestrogen) has been tried for the prevention of CAS with certain effectiveness among adults as antiestrogen (non-controlled study).

A pregnant mother who lost her infants to SIDS could be asked voluntarily to have a single fetal injection of 150 g of Medroxyprogesterone sterile aqueous suspension at 37 weeks gestation to prevent the recurrence of SIDS. The injection should reduce the number of estrogen receptors of fetal smooth muscle of the coronary artery at the time of delivery. Before the clinical trial, animal experiments should be carried out to test the safety of 150 μg of Medroxyprogesterone aqueous suspension to the fetus.

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