Acute Coronary Syndromes


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Abstract: Recently, unstable angina, acute myocardial infarction, and sudden cardiac death have often been put together under the name “acute coronary syndromes”, because almost all of these conditions have been shown to be caused by thrombotic occlusion of a coronary artery following atherosclerotic plaque disruption. Acute coronary syndromes occur more frequently in the coronary arteries with no significant organic stenosis than in those with a high degree of stenosis. A plaque prone to disruption has a thin fibrous cap, a large lipid core, and increased infiltration of macrophages and T lymphocytes. The elimination or control of risk factors for atherosclerosis such as dyslipidemia, hypertension, smoking, diabetes mellitus, obesity, and lack of exercise is essential for the prevention of acute coronary syndromes.

Key words: Acute myocardial infarction; Atherosclerotic plaque; Coronary spasm; Coronary thrombosis; Unstable angina

Introduction

Ischemic heart diseases, including angina pectoris and myocardial infarction, are the leading cause of death in Europe and America. They have also been increasing in Japan and are currently the second highest cause of death in this country as the result of the westernization of Japanese dietary habits, the increased use of automobiles, obesity, lack of exercise, and increased stress induced by our complex society.

Angina pectoris develops by transient ischemia of myocardium, while myocardial infarction is the necrosis of myocardium caused by prolonged ischemia. It has therefore been considered that a precise line should be drawn between the two diseases. Angina pectoris is divided into stable (organic) and unstable angina. The former is stable because advanced organic stenosis is extensively distributed in the coronary artery, but develops only when effort increases oxygen demand. The latter develops even at rest and is characterized by the increased severity and duration of the attack and reduced response to nitroglycerin. The latter has been considered to be at high risk of acute myocardial infarction or sudden death.

Recent studies have revealed that unstable angina, acute myocardial infarction, or ischemic cardiac sudden death develop mostly as a result of plaque disruption in the coronary artery followed by thrombotic formation, thereby com-
pletely or incompletely occluding the coronary lumen. Based on a similar onset mechanism, unstable angina, acute myocardial infarction, and ischemic cardiac sudden death have come to be referred to collectively as acute coronary syndromes.\(^1\) This concept was generated based on rapid advances in clinical medicine, pathology, and molecular biology. At the same time, these advances force us to make a paradigm shift in the existing way of thinking about these ischemic heart diseases and the nature of the corrective actions to be instituted.

**Clinical Advances**

The angina syndrome proposed by Heberden includes various diseases. James Herrick (1912) considered acute myocardial infarction to be an independent disease and inferred that it might result from coronary occlusion by thrombi. Since then, coronary thrombosis has been considered an important potential cause of myocardial infarction. In the 1970s, however, there were investigators, and pathologists in particular, who believed that coronary thrombosis was not a cause of myocardial infarction. The almost simultaneous introduction of coronary angiography during the early stages of acute coronary infarction in major medical institutions throughout the world in the 1980s has allowed clinicians to identify the responsible artery.

The experience of the authors shows that the artery responsible for myocardial infarction was spontaneously recanalized in the early stages of the disease in 18% of the cases examined, and that it was recanalized by the intracoronary injection of nitroglycerin in 16%, and by a thrombolytic agent (urokinase) in 46%.\(^1\) These results indicate that most acute myocardial infarction develop as a result of occlusion by coronary thrombosis, and that coronary spasm also causes myocardial infarction directly. The thrombotic occlusion rate of the coronary artery is higher in the earlier stages of the disease, and the spontaneous re-canalization rate increases over time.

It has been considered that coronary atherosclerosis develops at an early age and progresses slowly over several decades to cause the stenosis of the coronary lumen, and that advanced stenosis is prone to causing myocardial infarction. However, coronary angiograms conducted prior to the attack of myocardial infarction revealed that few cases had significant organic stenoses in the responsible coronary artery. Rather, myocardial infarction frequently occurs in the coronary lesions with no significant stenosis.\(^1,4\) A working group of the Ministry of Health and Welfare reported that the coronary artery responsible for myocardial infarction had no significant stenosis before the onset of the disease in 86% of the patients examined. Improved intravascular echography has disclosed that most coronary arteries that appear normal on angiograms have been affected by atherosclerosis. It has also been shown that plaque progress eccentrically toward the adventitia and do not cause the stenosis of the lumen in the early stages of the disease. This has been confirmed by autopsy and is known as compensatory growth.

Recent studies have indicated that reducing plasma cholesterol with hydroxymethyl glutaryl CoA (HMG-CoA) reductase inhibitors markedly lowers the incidence of cardiovascular accidents, such as cardiac death and acute myocardial infarction, without producing significant changes in stenotic lesions on coronary angiograms. This suggests that the quality of plaque may be more closely involved in the pathogenesis of myocardial infarction than the degree of coronary stenosis.\(^1,3\)

Recent advances in coronary endoscopy and intravascular echography have revealed that coronary thrombi or plaque disruption frequently appear also in unstable angina.\(^3,5\)

**Plaque Prone to Disruption**

Advanced pathological techniques have revealed that the coronary lumen was occluded or narrowed by thrombi in most autopsied cases.
with acute coronary syndrome, and that plaque had been disrupted with fissures in approximately two-thirds of such cases, and had been disrupted with erosion in the remaining third. The disrupted plaque showed inflammation with the infiltration of macrophages and T lymphocytes.

Plaque that is prone to disruption is characterized by (1) large lipid nuclei generated by fused lipids, such as cholesterol, accumulated outside the cells in plaque, (2) thin fibrous cap that separates lipid nuclei and vascular lumen, (3) increased infiltration of macrophages and T lymphocytes, and (4) a decreased number of smooth muscle. The plaque is prone to undergo mechanical stress and disrupt at the border between plaque and normal tissue, known as the shoulder, where a particularly large infiltration of macrophages occurs. The mechanical stress becomes stronger as the diameter of the lumen increases.

Since macrophages produce interstitial metalloprotease that decomposes interstitial collagen and elastin, which are constituents of fibrous caps, they make the caps thin and prone to breaking. Similarly, T lymphocytes secrete interferon-\(\gamma\) to inhibit the production of collagen from smooth muscle cells, thereby making the fibrous caps even more prone to breakage. Furthermore, the tissue factor, which triggers blood coagulation, is expressed in macrophages and lipid nuclei. Therefore, once plaque is disrupted to expose the tissue factor to blood, it activates blood coagulation cascades, which produces fibrin and thrombotic formation.

Factors Precipitating Acute Coronary Syndromes

(1) Plaque disruption

It has been shown that plaque disruption followed by thrombotic formation is the origin of acute coronary syndromes. ST-elevated myocardial infarction develops when thrombi completely occlude the coronary lumen. When the occlusion is incomplete, non-ST-elevated myocardial infarction or unstable angina develops.

(2) Coronary spasm

Various factors other than plaque condition may induce acute coronary syndromes. The onset of acute coronary syndromes tends to develop in the early morning. This is related to the circadian variation of blood coagulation and fibrinolysis systems and blood platelet aggregation. Blood is prone to coagulate, fibrinolytic activity is reduced, and platelet aggregation is accelerated in the early morning. Coronary spasm tends to develop at night and in the early morning. When it develops, it increases the tissue factor and fibrinopeptide in blood and reduces the fibrinolytic activity, thereby making it easier for thrombi to develop and stimulating platelet aggregation. It is therefore considered that coronary spasm triggers acute coronary syndromes through thrombotic formation. Moreover, coronary spasm itself causes unstable angina and acute myocardial infarction.

(3) Stress

Stress triggers acute coronary syndromes by increasing blood pressure to increase the mechanical stress on plaque, by accelerating blood coagulation and platelet aggregation, and by causing coronary spasm. It is well known that the incidence of acute myocardial infarction increased in Israel after the Gulf War and in Hanshin after the Great Hanshin Earthquake.

Pathogenesis and Treatments of Acute Coronary Syndromes

1. Pathogenesis of acute coronary syndromes

Figure 1 summarizes the pathogenesis of acute coronary syndromes. Thrombi are formed after plaque disruption or coronary spasm. Acute coronary syndromes develops when the thrombi become sufficiently large to occlude the coronary artery. In some cases, coronary spasm may induce plaque disruption or directly cause coronary occlusion. It is also
possible that a small artery running through the plaque is ruptured to cause a hemorrhage, which suddenly increases the size of the plaque to mechanically occlude the coronary lumen. It is also known that thrombi cause coronary spasm by serotonin or thromboxane A2 secreted from blood platelets.

2. Treatment of acute coronary syndromes

Since the pathogenesis of acute coronary syndromes is now well understood, it has become possible to apply appropriate treatment for the syndromes. That is, acute coronary syndromes should be treated by combining the treatments for coronary thrombosis, spasm, and plaque disruption. Among such treatments, the treatment for coronary thrombosis is most important.

(1) Treatment for coronary thrombosis

Anti-platelet drugs, such as aspirin and ticlopidine, and anti-coagulants, such as heparin, are now most frequently used to treat coronary thrombosis. The effect of aspirin is relatively weak and inhibits only one platelet coagulation pathway by thromboxane A2. Ticlopidine inhibits the pathway through ADP (adenosine 5’-diphosphate), but may have adverse effects.

The GPIIb/IIIa (platelet glycoprotein IIb/IIIa) receptor antagonists, which block the common final pathways of platelet aggregation, have recently attracted a great deal of attention. Its efficacy and safety have been established via the many clinical trials conducted in Europe and America. It has been demonstrated to be particularly useful when intravenously administered in percutaneous coronary interventions, such as percutaneous transluminal coronary angioplasty (PTCA). However, the effectiveness of these anti-clotting agents when orally administered over long periods have yet to be demonstrated. Its efficacy for acute coronary syndromes by an intravenous route also remains controversial when used without PCI.

Heparin is effective only when it combines with antithrombin III, and is not effective for thrombin combining with fibrin. Heparin is inactivated by platelet factor 4. Therefore, hirudine and hirulog, which acts directly on thrombin, and low-molecule heparin with more stable activity have been studied in clinical settings. Clinical studies on activated protein C, which inhibits thrombotic formation, and the
tissue factor pathway inhibitor (TFPI), which inhibits the tissue factor itself, are also under going trials.

It has been established that thrombolytic therapy using tissue plasminogen activator (t-PA) or urokinase is effective for transmural myocardial infarction with elevated ST on ECG. PTCA or stent insertion without thrombolytic therapy is also performed for quick re-perfusion. However, it should be noted that thrombolytic therapy is ineffective for, or rather aggravates unstable angina.19)

(2) Treatment for coronary spasm
Nitrates, calcium antagonists, and nicorandil are effective for coronary spasm.1) Most cases with unstable angina can be successfully controlled by these medications. However, some cases require percutaneous coronary intervention or coronary bypass. In such cases, PTCA itself can cause plaque disruption, thereby worsening acute coronary syndromes. Therefore, plaque in unstable angina that is prone to thrombi formation, should be stabilized by medical therapy as far as possible before PTCA. The recent introduction of stent insertion techniques has contributed to the prevention of acute coronary occlusion due to PTCA in a considerable number of cases.

3. Prevention of acute coronary syndromes
Although various treatments for acute coronary syndromes have been developed as described above, it is still often difficult to treat these syndromes once they develop. Therefore, preventing the syndromes is quite important. It is necessary to suppress atherosclerosis in order to prevent acute coronary syndromes because atherosclerosis is the base of the syndromes. It is also important to eliminate or control risk factors, such as hypertension, smoking, diabetes mellitus, hyperlipemia, obesity, and lack of exercise.10) The importance of eliminating or controlling such factors was fully established by several multi-center prospective randomized studies which demonstrated that correcting hyperlipemia with HMG-CoA reduc-
tase inhibitors markedly reduced cardiovascular events, such as acute myocardial infarction and cardiac death.

Moreover, recent studies have shown that the following therapies are effective for preventing acute myocardial infarction and sudden death: anti-platelet drugs, such as a small amount of aspirin, anti-coagulants, such as warfarin, angiotensin converting enzyme (ACE) inhibitors, anti-oxidants, such as vitamin E, and estrogen replacement therapy for post-menopausal women.

Conclusion
Recent studies have revealed that most cases with unstable angina, acute myocardial infarction, or ischemic cardiac sudden death result from coronary plaque disruption followed by formation of thrombi, which occlude or narrow the coronary lumen. These diseases have therefore come to be referred to collectively as acute coronary syndromes. The syndromes are characterized by its frequent onset from mildly narrowed coronary arteries and easily disrupted plaque with large lipid nuclei, thin fibrous caps, together with marked infiltration of macrophages and T lymphocytes. Coronary spasm not only triggers acute coronary syndromes, but also occludes the coronary arteries to directly cause acute coronary syndromes.

Eliminating or controlling coronary risk factors including hypertension, diabetes mellitus, smoking, hyperlipemia, and lack of exercise is crucial for preventing acute coronary syndromes. Anti-platelet drugs, such as aspirin, and anti-coagulants, such as warfarin, are also useful. Calcium antagonists are effective for coronary spasm.

REFERENCES


