Mechanisms of Pain in Angina Pectoris—A Critical Review of the Adenosine Hypothesis

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Summary. Clinical characteristics: Angina pectoris represents a visceral pain caused by reversible myocardial ischemia. The majority of ischemic attacks are symptomless. When pain is manifested, it appears late during the ischemic event. The pain is complex in its quality and bears little relation to the region of myocardial ischemia. Pain shows a sensitive dependence on initial conditions suggesting a mechanism with deterministic chaotic dynamics for the association between myocardial ischemia and pain. Neurophysiological substrate: Ganglia are present within the heart, particularly in epicardial fat. The blood supply of intrinsic cardiac ganglia arises primarily from branches of the proximal coronary arteries. Both afferent and efferent neurons within the intrinsic cardiac nervous system exist, while the majority of neurons in that location may be local circuit neurons. Integration takes place not only in the intrinsic cardiac nervous system, but also in mediastinal, middle cervical, and stellate ganglia. Cardiac afferent receptors are also connected to cell bodies in dorsal root and nodose ganglia, as well as intrathoracic ganglia. Myocardial regions have no spatial representation in these ganglia. Adenosine, among a number of substances, can modulate the activity generated by cardiac afferent nerve endings and intrinsic cardiac neurons. Such effects appear to be exerted at A1 receptors. Adenosine as a pain messenger: During myocardial ischemia adenosine is released in large quantities into the interstitial space. The endothelium takes up the major amount of adenosine. Thus only small increments of adenosine are detected in the bloodstream. Given as an intravenous bolus to healthy volunteers or to patients with ischemic heart disease and angina pectoris, adenosine provokes angina pectoris-like pain, which is similar to habitual angina pectoris with regard to quality and location. Pain is provoked in the absence of ECG signs of ischemia. Patients with asymptomatic myocardial ischemia are less sensitive to adenosine, whereas patients with Syndrome X are more sensitive with respect to adenosine-provoked pain. When adenosine is given intraarterially, including into the coronary arteries, pain is provoked in the corresponding vascular bed. Adenosine-provoked pain and ischemic pain are counteracted by previous administration of the adenosine receptor antagonist theophylline. Adenosine-provoked pain is enhanced by nicotine or substance P. Conclusion: Angina pectoris displays complex characteristics at both the clinical and neural substrate levels. Adenosine is the only candidate substance identified that fulfills criteria for a messenger between myocardial ischemia and the genesis of pain. It is concluded that ischemically released adenosine causes specific spatiotemporal neural summation of afferent neuronal activity, which elicits an alarm reaction with manifestation of pain.

Key Words. angina pectoris, autonomic nerves, adenosine, mechanism of anginal pain, silent ischemia

History of Angina Pectoris

Heberden was the first to propose the concept of angina pectoris (Heberden, 1772). With the introduction of electrocardiography, distinctions were made between acute myocardial infarction and reversible myocardial ischemia. In 1928 Keefer and Resnik depicted angina pectoris as chest pain related to transient myocardial ischemia alone (Keefer and Resnik, 1928). Four years later, Lewis (1932) further elaborated on the subject and suggested that angina pectoris was due to an unfavorable myocardial oxygen supply/demand ratio. In addition, Lewis hypothesized that ischemia gives rise to pain-producing substances that can provoke angina pectoris.

Clinical Characteristics of Angina Pectoris

As with other visceral pains, angina pectoris is not always manifested during damage to myocardial tissue. For instance, pain is normally not induced during myocarditis or mechanical manipulation of the myocardium as such occurs when myocardial biopsies are obtained. When present, the character of cardiac pain does not differ during acute myocardial infarction, reversible ischemia, or other causes treated in a coronary care unit (Eriksson et al., 1993). Compared to somatic pain or abdominal colic pain its intensity is rated as of moderate degree. Patients describe its character as complex, consisting at the same time of an average of three to four sensory qualities (Figure 1). Patients with Syndrome X report pain characteristics that are similar to those of ischemic cardiac pain.

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Fig. 1. Quality and intensity distributions of chest pain in patients suffering from acute myocardial infarction. Pain was quantitated by the Borg CR-10 scale.

Angina pectoris may be viewed as an undifferentiated and therefore primitive type of pain.

Asymptomatic myocardial ischemia occurs not only in patients without any pain at all, but also in patients with stable or unstable angina pectoris (Collins and Fox, 1990, Maseri et al., 1991a). In these patients, 60–80% of ischemic attacks are asymptomatic, irrespective of whether they are due to stable or unstable angina pectoris. Also about 25% of myocardial infarction attacks are symptomless or display uncharacteristic symptoms. About half of patients treated for acute myocardial infarction with chest pain as the presenting symptom do not have anginal pain before or after the acute myocardial infarction (Kannel and Abbott, 1989).

One reason for the high frequency of asymptomatic reversible ischemic attacks is that angina pectoris occurs late during the ischemic cascade (Nesto and Kowalchuk, 1987). After PTCA is initiated ECG abnormalities begin after about 20 seconds, while angina pectoris develops after 30 seconds or later if it occurs. During spontaneous attacks of vascular disease, the onset of angina pectoris can be delayed several minutes. This chain of events differs from somatic pain inasmuch as that occurs after a very short delay relative to the onset of the noxious event. These data infer that certain duration and severity of an attack are necessary, but not sufficient prerequisites for manifestation of angina pectoris (Maseri et al., 1991a). Thus, empirically, manifestation of pain is characterized by nonlinearity and a sensitive dependence on initial conditions suggesting a mechanism with deterministic chaotic dynamics for the association between the severity of myocardial ischemia and pain generation.

A significant group of patients, presenting with severe anginal pain that limits daily life, have normal coronary arteries and no signs of coronary spasm. This constellation is referred to as Syndrome X. Although multifactorial, it has also been called microvascular angina pectoris, in spite of the fact that objective signs of myocardial ischemia seldom are demonstrated (Maseri et al., 1991). Compared to patients with ischemic heart disease, during catheterization they more often experience the movement of catheters in the right heart accompanied by sensations of discomfort or pain. Thus, these patients frequently are abnormally sensitive to mechanical cardiac manipulations (Shapiro et al., 1988; Cannon et al., 1990).

These data indicate that angina pectoris may involve a continuum of conditions. Patients range from those with a hyper-reactive cardiac nervous system and no signs of coronary artery disease to patients with severe coronary artery disease with a hyporeactive cardiac nervous system and no manifestations of angina pectoris.

Cardiac Nervous System

Myocardial nerve endings of primary sympathetic afferents are thought to be excited by mechanical and chemical stimuli. Neuroexcitation may take place via at least two different processes (Alberts et al., 1989). One is via a channel-linked receptor with a rapid, immediate, and spatially exact response. The other is via a non-channel-linked receptor causing synaptic modulation. The latter function is a slow process, several hundreds of milliseconds longer than the channel-linked process. Modulatory processes are spatially diffuse and involve changed metabolism of the neuron mediated by G proteins and enzymatic reactions. Another important process is spatial and temporal summation. With increasing intensity of stimulus, the afferent neuronal response becomes enhanced with time to a level that a simple stimulus could not effect.

According to the classical neurophysiological view of angina pectoris, nerve transmission is thought to exist in primary afferent fibers, as with somatic pain, travelling from the end organ to spinal cord nerves, with the cell bodies of these neurons being located in dorsal root ganglia (Hillarp, 1960). Of the total number of afferent neurons, only about 2% have been estimated to be associated with visceral organs (Droste, 1988). This low representation has been suggested to be one factor that explains the high degree of asymptomatic myocardial attacks. Visceral afferents convey impulses to the same spinothalamic neurons as somatic afferents. This explains why pain, when it occurs, could be referred to a dermatome associated with the threatened organ.

Cardiac neural control exists at different levels of the nervous system, acting via axonal and synaptic reflex arcs (Armour, 1991). It has been proposed that the intrinsic cardiac nervous system acts as a little brain on the heart (Armour, 1991), utilizing a variety of neurochemicals such as calcitonin gene related pep-