CONSEQUENCES OF MYOCARDIAL ISCHEMIA

Part of "46 - Coronary Blood Flow and Myocardial Ischemia"

Metabolic Consequences

During ischemia, several metabolic changes occur. Adenosine triphosphate (ATP) is degraded to adenosine, which, diffusing out of cardiomyocytes, causes arteriolar dilation and anginal pain. Free fatty acids and acyl-carnitine accumulate and protein synthesis and turnover are impaired in myocardial cells. Furthermore, myocardial ischemia/reperfusion produces free radicals, which contribute to postischemic myocardial cell dysfunction by reacting with proteins, lipids, and nucleic acids. Impaired Ca^{2+} release from sarcolemma and sarcoplasmic reticulum, inhibition of crossbridge cycling,136 and the competition of H^{+} accumulating during ischemia for Ca^{3+} binding sites on contractile proteins, also contribute to systolic dysfunction. Reduced ATP availability, decreasing Ca^{2+} reuptake into sarcoplasmatic reticulum, also prolongs interaction of Ca^{2+} with myofilaments, causing diastolic dysfunction.

Impairment of ion pumps causes loss of intracellular K^{+} and accumulation of intracellular Na^{+}, Ca^{2+}, and H_2O. Alterations of transsarcolemmal ion gradients may cause increased automaticity, triggered activity, and abnormalities of impulse conduction, which favor the development of reentry circuits.137

The consequences of ischemia and ischemia/reperfusion injury may not be limited to the myocytes but extend to endothelial cells, with inflammatory changes138,139 and 140 resulting in vasoconstriction and a local thrombogenic tendency.

Effects on Cardiac Function

The effects of myocardial ischemia have been studied in experimental animals by producing a sudden coronary occlusion, by gradually reducing coronary flow at rest, and by increasing M[V with dot above]o_2 in the presence of a flow-limiting coronary stenosis. Such experimental models mimic, at least in part, the consequences of myocardial ischemia observed in variant angina, unstable angina, and effort angina, respectively (see below).

EFFECTS OF SUDDEN CORONARY OCCLUSION

Occlusion of a major coronary artery is followed within a few seconds by a typical sequence of events that includes a reduction in the velocity of ventricular relaxation and contraction, ST-segment elevation, increased end-diastolic pressure with dyssynchrony

(delayed onset of contraction in ischemic myocardial segments), hypokinesis (reduced contractility), akinesis (cessation of contraction), and dyskinesis (paradoxical expansion of the affected segment during systole). The sequence of hemodynamic and ECG events observed in experimental animals is similar to that observed in patients during episodes of occlusive epicardial coronary artery spasm (Fig. 46-11) or during coronary angioplasty balloon occlusion, typically characterized by the following sequence of events: a decrease

in peak relaxation dp/dt, a decrease of peak contraction dp/dt, an increase in diastolic pressures, and a fall in systolic and in pulse pressure. In patients with transmural ischemia caused by occlusive coronary spasm, anginal pain, when it occurs, usually appears later, several seconds or minutes after the induction of ischemia.

FIGURE 46-11 Sequence of alterations during an ischemic episode caused by left anterior descending coronary artery spasm. The playback at low and high speeds of a spontaneous episode of silent ischemia recorded in the coronary care unit shows a decrease in left ventricular peak relaxation and contraction dp/dt and in systolic pressure; an increase in proto- and end-diastolic pressure clearly precedes the onset of peaking of T waves on the ECG, which is followed by slight ST-segment elevation. The episode resolved spontaneously. This sequence of events is similar to that observed during coronary angioplasty and in the dog following sudden coronary artery ligation. LVP = left ventricular pressure; dp/dt = left ventricular dp/dt; ECG = electrocardiographic tracing. (From Maseri and Sanna.46 With permission.)

EFFECTS OF GRADED REDUCTION OF CORONARY FLOW AT REST

In anesthetized dogs, a 25 percent reduction of basal coronary blood flow through a major coronary branch is associated with increased myocardial extraction of oxygen and decreased oxygen consumption. Further reductions of flow are followed by a decrease in the rate of left ventricular relaxation and contraction, then by ST-segment depression, elevation of end-diastolic pressure, decreased stroke volume, and finally by elevation of the ST segment, which develops when flow reduction is about 70 percent and myocardial ischemia becomes transmural. Local contractile function in subendocardial layers begins to fall slightly when regional subendocardial flow is reduced by 10 to 20 percent and becomes marked as flow decreases by 50 to 80 percent. Segments with a flow reduction greater than 80 percent show paradoxical movement with bulging of the left ventricular wall (Fig. 46-12).

FIGURE 46-12 Effect of decrease of subendocardial blood flow on systolic segment shortening. In conscious dogs, the percentage decrease of subendocardial segment shortening is small until blood flow is reduced by 20 percent. Systolic bulging (segment lengthening) develops only when flow is reduced by more than 80 percent. (Modified from Maseri and Sanna46 and Gallagher et al.170 With permission.)

EFFECT OF INCREASED WORKLOAD IN THE PRESENCE OF A FLOW-LIMITING STENOSIS

When exercise reduces mean transmural blood flow by 30 percent in chronically instrumented dogs with a coronary artery stenosis, a mild reduction of systolic thickening is observed, whereas in the normally perfused wall, thickening increases by 20 percent. During exercise, severe regional dysfunction develops when mean flow is about 80 percent lower than in nonischemic myocardial segments. Thus a severe reduction in coronary blood flow is necessary to produce detectable effects on global ventricular contractile function.

At variance with the late occurrence of pain following sudden coronary occlusion by spasm, anginal pain during effort induced ischemia may precede ECG changes in about one-third of the cases.

PRECONDITIONING

The term *preconditioning* was originally used with reference to the ability of short periods of ischemia to limit infarct size after subsequent prolonged coronary occlusion in animals. However, it is now more broadly used also to indicate the improved tolerance of myocardium to ischemia after exposure to previous ischemic episodes. An early ischemic preconditioning after an ischemic episode was reported during the initial 2 h (early preconditioning), but a later protection was also reported beginning 24 h after the preconditioning stimulus and extending to 48 h (delayed preconditioning).141 Findings compatible with early ischemic preconditioning were reported following balloon occlusion during coronary angioplasty, preinfarction angina, coronary artery bypass surgery, and exercise-induced ischemia (warmup phenomenon).50 In experimental settings, ischemic preconditioning was also shown to reduce ventricular tachyarrhythmias appearing in the ischemic or reperfusion phase of ischemic episodes, and a reduction of ischemia-related ventricular arrhythmias following episodes of transmural myocardial ischemia was reported in patients with vasospastic angina.142 Moreover, preconditioning anginal episodes

preceding acute myocardial infarction have recently been shown to decrease the occurrence of life-threatening tachyarrhythmias during the acute phase of infarction.143 Preconditioning could partly explain the more favorable prognosis of patients in whom acute myocardial infarction is preceded by unstable angina.144,145 The bases of preconditioning are not completely understood. Extrapolation of experimental results to patients should be done with caution. Various mediators released during ischemia, such as adenosine, but also bradykinin, catecholamines, endothelin, opioids and others, can activate G protein–coupled receptors to stimulate phospholipase C and generate diacylglycerol, which is responsible for the translocation and activation of protein kinase C. Other pathways, such as the generation of nitric oxide and intracellular reactive oxygen species, may also activate protein kinase C. Protein kinase C, in turn, activates mithochondrial K^+_{ATP} channels, which appear to play a major role in ischemic preconditioning, probably acting both as mediators and effectors of the protective response.146 Moreover, protein kinase C and other kinases (such as tyrosine kinase) activate a series of transcription factors to enhance the expression of various genes—including heat-shock proteins, manganese superoxide dismutase, and inducible nitric oxide synthase—that contribute to the resistant phenotype of delayed preconditioning147 (see Table 46-1). Preconditioning in the human can be abolished by the administration of the oral hypoglycemic glibenclamide, which is a selective inhibitor of K^+_{ATP} channels.148

TABLE 46-1 Features of Ischemia, Stunning, and Hibernationa

	Coronary Blood Flow	Lactate Production	Contractile Function
Ischemia	Markedly reduced	Yes	Impaired Recovers after relief of ischemia
Stunning	Preserved	No	Impaired Transiently restored by inotropic stimulation Recovers spontaneously over time
Hibernation	Reduced in the presence of typical histologic changes	No	Impaired Recovers only after revascularization

[a]Ischemia is characterized by inadequate perfusion, resulting in lactate production and impaired contractile function. Stunning develops after an ischemia/reperfusion sequence and is characterized by preserved regional blood flow and transient impairment of contractile function, which recovers spontaneously over time. Hibernation may develop after repeated episodes of ischemia/reperfusion and is characterized by myocardial histologic changes, absence of contraction, reduced M[V with dot above]o_2, and reduced regional blood flow but no lactate production. Contractile function recovers following revascularization over a period of weeks and months.

STUNNING

The term *stunning* defines a prolonged but reversible contractile dysfunction observed after an episode of transient myocardial ischemia. It has been observed in animals following sudden coronary occlusion lasting 10 to 15 min or after repeated shorter periods of occlusion as well as in patients after positive exercise test, in ischemic periinfarction regions, and following extracorporeal circulation. The spontaneous recovery of cardiac contractile function may take hours or days, depending on the severity and duration of ischemia, but contraction can be transiently restored by inotropic stimuli such as postextrasystolic potentiation or beta-adrenergic drugs. In stunned myocardium, the

delayed recovery of contractile function is associated with normal average myocardial perfusion in presence of reduced myocardial oxygen consumption. It is not clear to what extent stunning represents a gradual physiologic recovery from the ischemic insult or a consequence of a reperfusion-induced injury, which could delay or reduce the benefits of reperfusion.

Several components may contribute to stunning.149 A decreased Ca^{2+} sensitivity of myofilaments, troponin I degradation by Ca^{2+}-activated proteases, Ca^{2+} overload and free radicals generation,150 slow resynthesis of adenosine nucleotides, microvascular damage with leukocyte activation, myocyte electromechanical uncoupling,151 and extracellular matrix alterations were all observed in experimental models (see also Table 46-1).

HIBERNATION

Myocardial *hibernation* was originally defined as a condition of persistent impairment of contractile function at rest in the presence of both reduced M[V with dot above]o_2 and coronary blood flow and in absence of metabolic evidence of ischemia, which partially or totally recovers when myocardial blood flow is restored. The time to functional recovery of hibernated myocardium after revascularization varies from 10 days to 6 months and is related to the severity of structural changes of cardiomyocytes and interstitium.

Hibernation is characterized152 by progressive loss of sarcomeres, sarcoplasmic reticulum, and T tubules in cardiomyocytes with glycogen replacement. Mitochondria appear small and scattered and nuclei distorted, with uniformly dispersed heterochromatin. Hibernated myocardial cells have normal ATP, total adenine nucleotides, and phosphocreatine content and exhibit normal glucose uptake and no lactate production. Several of these characteristics suggest that hibernation may be the result of a dedifferentiation process related to changes in gene expression, as hibernated cardiomyocytes show many features of neonatal cardiomyocytes.152,152a Hibernation is caused by a severe reduction of coronary flow reserve, as a result of which any increase in M[V with dot above]o_2 and any further reduction in coronary blood flow (e.g., by vasoconstriction or platelet aggregation) results in repeated episodes of myocardial ischemia/reperfusion (see also Table 46-1).

Clinical Manifestations of Myocardial Ischemia

CHEST PAIN

The most obvious clinical manifestation of myocardial ischemia, irrespective of its multiple causal mechanisms, is angina pectoris. However, myocardial ischemia may occur without angina and angina may occur without detectable signs of myocardial ischemia. Typically anginal pain is retrosternal in location, with a crushing, squeezing, or burning character. It may radiate to the throat, neck, ulnar side

of the left and/or right arm, interscapular region, epigastrium, and the jaw and teeth. Headache may also be an unusual manifestation of myocardial ischemia.153 The intensity of the discomfort can vary greatly, from a mild feeling of retrosternal fullness or tingling in only one dermatome to a diffuse, unbearable pain. These features are unrelated to the causes of ischemia and are not completely specific for ischemia, as they may also be due

to nonischemic cardiac and extracardiac causes.

Myocardial ischemia with or without angina may occasionally present with other symptoms, including dyspnea (in the case of extensive ischemia with transient impairment of left ventricular function or ischemia of the papillary muscles with mitral regurgitation), palpitations, syncope, or cardiac arrest.

Anginal pain originates from the stimulation of polimodal receptors (more abundant around small coronary vessels) by chemical mediators produced during ischemia.50 The best-studied of such mediators is adenosine. The algogenic effects of adenosine were studied by its intracoronary infusion and are mediated by A_1 receptors, while its vasodilator effects are mediated by A_2 receptors.154 Comparison of pain location during selective intracoronary infusion of adenosine in the right and left coronary artery has shown that in nearly 70 percent of patients, afferent stimuli from different myocardial regions cannot be discriminated, thus suggesting that they converge on the same neurons of the dorsal roots of spinal cord.155 However, in 30 percent of patients, anginal pain during the infusion of adenosine in the separate coronary beds caused a different location of pain. The possibility that a different location of pain in the same person reflects a different location of myocardial ischemia has been confirmed in patients undergoing PTCA or those with a second myocardial infarction.156,157 Moreover, convergence of afferent painful stimuli from different visceral organs and somatic dermatomes on the same ascending neurons can cause noncardiac pain to have features indistinguishable from angina.

The central transmission of painful stimuli is modulated at the spinal cord level by a gating system regulated by descending and by afferent stimuli. From the dorsal horns of the spinal cord, afferent stimuli reach thalamic centers and are finally projected to the cortex, where their processing and decoding occur. The pain signal may also undergo modulation in supraspinal centers.

PAINLESS ISCHEMIA

Diagnostic techniques capable of detecting myocardial ischemia have shown that ischemic episodes in most cases occur without anginal pain; in some cases, silent ischemia may be the only manifestation of coronary artery disease. Continuous ECG recordings has revealed that about 70 percent of episodes of transient myocardial ischemia do not cause chest pain or any other symptom.50 The percentage of episodes of silent ischemia is similar in chronic stable angina, unstable angina, variant angina and microvascular angina. Thus, the presence or absence of pain is totally unrelated to the actual cause of transient ischemia. Furthermore, also myocardial infarction may be totally silent in about 20 percent of the cases.

The reasons why myocardial ischemia does not elicit pain in the majority of cases are multiple.155 Although angina is less likely to accompany myocardial ischemia when it is short lasting, there is no strict relationship between duration and extension of ischemia and development of chest pain also in the same patient.

The gating system at the spinal cord and possibly at the thalamic level, together with the cortical decoding of afferent stimuli, probably plays a major role in determining the perception of pain. Moreover, personality, emotional status, and previous experience of

pain may modulate such perception (see also Chap. 57).

ARRHYTHMIAS

Arrhythmias are major potential consequences of acute ischemia, as they are responsible for the most part of deaths observed during the early phases of acute myocardial infarction as well as in variant angina, and thus for sudden death in the community.

During ischemia, increased automaticity, triggered activity, conduction delay and re-entry may all cause the development of ventricular tachycardia and fibrillation. Moreover, altered impulse formation and conduction defects may cause asystole and atrioventricular block.

Arrhythmic response to ischemic insult of individual patients is unpredictable, but is influenced by the cardiac anatomical background (left ventricular hypertrophy, previous infarction) and by nervous autonomic imbalance with predominance of sympathetic activity. It may also be related to the regulation of cardiac sodium channels ($Na_V1.5$) by growth factors (FGF12B) whose level of expression in adult heart may vary.158

Fatal ventricular arrhythmias are exceptional during mild subendocardial ischemia, but may develop during or soon after the termination of episodes of transmural ischemia, caused by occlusive spasm or thrombosis, or even of severe subendocardial ischemia. Reperfusion arrhythmias, although particularly common in anaesthetized animals, are less frequently observed both in patients with variant angina and during myocardial reperfusion in acute myocardial infarction.50

Effects of Persistent Myocardial Ischemia: Myocardial Infarction

In dogs, focal cell necrosis begins about 20 minutes following coronary flow interruption. Such foci become confluent in subendocardial layers by 40 minutes, reaching subepicardial layers with a progressive wavefront at about 3–4 hours. By this time, necrosis has developed, on average, to about 90 percent of its final extension, which is reached after 6 hours. Apoptosis has also been shown to accompany necrosis as a mechanism of cell death during myocardial infarction.159

In patients, the extension of myocardial necrosis depends not only on the area perfused by the occluded vessel, the level of myocardial oxygen consumption and the presence of collaterals, but also on the intermittence of coronary occlusion. Actually, myocardial infarction is a dynamic process with intermittence of occlusion occurring in about 2/3 of the cases during the initial 6 hours50. Therefore, it is reasonable to undertake reperfusion strategies in all patients irrespective of actual delay from the onset of symptoms as long as ECG shows persistent massive ischemia without completed necrosis. The impairment of global myocardial function depends on the extension of myocardial necrosis. When infarction involves more than 15 percent of left ventricle, ejection fraction decreases. When it involves more than 25 percent of left ventricle, signs of heart failure develop, and when it involves more than 40 percent, cardiogenic shock occurs.

The development of primary ventricular fibrillation is independent of infarct size, but strongly influenced by high adrenergic tone.