Understanding the Pathophysiology of Acute Coronary Syndromes

A CRUSADE Educational Tool
Coronary Artery Disease\textsuperscript{1,2}

Coronary artery disease (CAD) is the nation’s leading cause of death. CAD is caused by the life-long progression of atherosclerosis, a process that ultimately leads to plaque rupture, clot formation, and obstruction of blood flow to the heart. If blood flow to the heart is reduced for a prolonged period of time, ischemia and significant heart muscle damage may occur. This can lead to sudden death or heart muscle dysfunction, precipitating congestive heart failure.

The artery shown above is free of obstruction from atherosclerotic disease, allowing blood to efficiently carry oxygen to the heart.

The Beginning of Atherosclerosis

Atherosclerosis begins when cholesterol and other fatty substances attach to and infiltrate the endothelial lining of coronary arteries (shown above). These fatty deposits eventually form a large atherosclerotic plaque, increasing in size and bulging into the artery.

Atherosclerotic Plaque

The plaque in this image is similar to a stalactite in a cave, jutting out into the lumen of the artery, and partially obstructing blood flow. While this plaque may not appear to be significant, most thrombotic events are caused by small plaques such as this one, which rupture and result in occlusive thrombus (blood clot).

Any plaque may rupture due to natural causes (shear forces in the artery or gradual decay) or mechanical injury (stent implantation or balloon angioplasty). When plaque rupture occurs, platelet activation, adhesion, and aggregation follow.

Plaque Rupture

Plaque rupture exposes the inner lining (endothelium) of the artery to foreign substances. Platelets that come in contact with the sub-endothelium will stick to it, binding to von Willebrand factor (vWf), and begin to form the platelet monolayer that covers the injured site, which protects against continued exposure of the sub-endothelium and allows the healing process to begin. The sub-endothelium also contains a potent platelet agonist called collagen, which causes the bound platelets to activate and undergo a conformational shape change. At this time, platelets will express 70,000 – 100,000 glycoprotein (GP) IIb-IIIa receptors and release internal pools of signaling agents, including ADP (adenosine diphosphate), thromboxane A₂, serotonin, and epinephrine into the bloodstream.

Platelet Activation

Platelet Activation\textsuperscript{1,2}

ADP, serotonin, and thromboxane A\textsubscript{2} are also platelet agonists that will activate additional platelets in the vicinity of the injured endothelium; serotonin induces vasoconstriction, further reducing the flow of blood to heart muscle. These are just a few examples of the cascade of events that occur in response to vessel injury. Importantly, there are more than 70 known agonists that can cause platelet activation, conformational change, GP IIb-IIIa receptor expression, and degranulation. Disrupting this cycle is the target of all anti-thrombotic therapies.

The platelet above has been activated and has undergone the conformational shape change. Normally platelets are small and disc-shaped, but upon activation they extend pseudopods and express GP IIb-IIIa receptors on their surface.

Platelet Aggregation

Once platelets have expressed these GP IIb-IIIa receptors, they are able to bind with fibrinogen, which occurs naturally in plasma. Fibrinogen can bind simultaneously to two GP IIb-IIIa receptors, allowing platelets to “clump” together. With so many GP IIb-IIIa receptors, and plenty of fibrinogen, platelets are able to bind together repeatedly, resulting in the beginning of thrombus. The image above shows fibrinogen strands cross linking with platelets, even at this early stage disrupting the flow of red blood cells (RBCs), which become trapped in the growing net.

Microembolization

Microembolization\textsuperscript{1,2}

As platelet aggregation ensues and thrombus begins to form, microembolization will occur. This happens when platelet aggregates are washed downstream from the thrombus, and occlude tiny arterioles and capillaries (shown above) that deliver oxygen to the heart. The resultant ischemia may lead to myocardial necrosis, or death of small sections of heart muscle at multiple sites throughout the coronary vasculature. While microembolization and the resultant myocardial necrosis are not visible to physicians except by blood tests, they cause an increased risk of cardiovascular co-morbidities (e.g., CHF) and death.

Clot Stabilization

As platelets continue to aggregate, the body begins to produce thrombin. Thrombin causes unbound fibrinogen circulating in and around the thrombus to convert to fibrin, forming a mesh-like network around the thrombus. This occurs by the cross-linking of fibrin strands, and this process helps to stabilize the thrombus. As the network thickens, the mesh begins to trap red blood cells, macrophages, and other plasma contents as it becomes stable. The thrombus will now become a more solid “red” clot (due to the large quantities of red blood cells trapped within).

Myocardial Ischemia\textsuperscript{1,2}

If unchecked, the clot may completely occlude the coronary artery, or severely limit the flow of blood to the heart. The clot shown above is a mass of platelets, red blood cells, and fibrin mesh, and is capable of preventing blood flow into the microvasculature. If this occurs, the lack of oxygen will result in myocardial ischemia, myocardial necrosis, or even sudden death.

Myocardial Infarction

Myocardial Infarction\textsuperscript{1,2}

Once myocardial necrosis begins, approximately 500 heart cells die every second until the ischemia is alleviated or all of the tissue downstream of the occlusion is dead. As myocardial cells die, they release structural molecules, such as Creatine-Kinase Myocardial Band (CK-MB) and troponin (Tn), into the bloodstream. These molecular fragments can be measured, and help physicians to diagnose myocardial infarction.

In the sample of heart tissue shown above, significant myocardial necrosis has occurred, and very little viable tissue remains, visible as the smooth, striated muscle. The extent of irreparable damage is evident, visible as the gray, dead heart tissue.

\textsuperscript{2} Photos courtesy of Boehringer Ingleheim International GmbH, by Lennart Nilsson.
Cardiovascular Death

Photos courtesy of Boehringer Ingleheim International GmbH, by Lennart Nilsson.

Cardiovascular Death$^{1,2}$

Myocardial infarction can kill a patient, as occurred in this case. A bisection of the coronary artery shows that this patient died from a large thrombus that occluded greater than 90% of the artery. If aggressive anti-thrombotic treatments are not administered in a timely manner, this fatal result can occur in any patient experiencing an acute coronary syndrome.

ACC/AHA NSTE ACS Guidelines Recommendations

The earliest opportunity to intervene in this process is when patients with unstable angina or Non-ST-segment Elevation Myocardial Infarction present to the hospital emergency department for treatment. Aggressive identification and treatment can help prevent progression to extensive myocardial necrosis, ST-segment Elevation Myocardial Infarction, or sudden death.

The ACC/AHA Guidelines recommend that patients with high-risk NSTE ACS be treated immediately with aspirin, unfractionated or low-molecular-weight heparin, and a GP IIb-IIIa inhibitor, and scheduled for diagnostic catheterization within 24 – 48 hours. PCI or CABG surgery, if indicated, should also be performed during this period. The objective of this treatment is to ensure that the culprit artery is identified and treated pharmacologically and mechanically to remove the obstructive thrombus and plaque. Early and aggressive treatment will increase the flow of oxygen to the heart, thereby averting additional myocardial necrosis and/or death.

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