UNIT NO. 5

CLINICAL SEQUELAE OF ATHEROTHROMBOSIS: ACUTE CORONARY SYNDROMES

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ABSTRACT

Acute coronary syndromes is an important sequelae of coronary atherosclerotic disease. Clinical diagnosis is important in defining if it is unstable angina, non ST segment elevation (NSTEMI) myocardial infarction or ST-elevation myocardial infarction (STEMI). The definitions carry important therapeutic and prognostic implications. Treatment of unstable angina/NSTEMI requires rigorous risk stratification with maximal antithrombotic therapy and early invasive treatment reserved for the highest risk cohort; whereas reperfusion therapy is the mainstay for STEMI.

INTRODUCTION

Atherosclerosis is a systemic disease that affects not only the coronary circulation, but also extracerebral, intracerebral and peripheral vessels. Recent intensified clinicopathology investigations have increased the insights from cell and molecular biology that led to advances in the understanding of atherosclerosis development and its clinical sequelae. Acute coronary syndrome (ACS), defined as an expressed clinical state of intracoronary occlusive or subocclusive thrombus formation with intense regional ischaemia or infarction, manifests in a wide clinical spectrum ranging from unstable angina to acute myocardial infarction (AMI) and sudden death.

PATHOGENESIS

The central pathophysiological mechanism of ACS is the fissuring or erosion of an atheromatous plaque with superimposed platelet aggregation and thrombosis. The clinical manifestations are dependent upon the severity of obstruction in the affected coronary artery, the presence or absence of collateral perfusion, and the volume and myocardial oxygen demand within the affected territory. The resultant thrombi may fragment and embolise distally with alteration in the vascular tone causing myocardial injury; or they may fail to occlude the vessel and remain clinically silent. Local prevailing haemostatic and fibrinolytic balance is decisive in determining the fate of a given disruption.

In clinical practice, ACS is classified by the American College of Cardiology/American Heart Association (ACC/AHA) as the presence of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA). UA and NSTEMI are considered to be closely related conditions whose pathogenesis and clinical presentations are similar, but with differing severities. The distinction comes from the detection of elevated quantities of markers of myocardial injury, namely troponin T, troponin I or CK-MB (creatine kinase MB isoform) in the latter group. Patients who have no biochemical marker of myocardial necrosis are considered to have only experienced UA.

DIAGNOSIS AND CLINICAL ASSESSMENT

Early diagnosis is crucial in the successful management of ACS. As ACS is a continuum of disease processes, it is imperative that treatment is targeted according to the risk status of the patient. The diagnosis of AMI is dependent on the fulfillment of two out of the three following criteria:

- Typical symptom;
- Elevated biochemical cardiac markers; and
- Electrocardiographic changes (ST-segment elevation or depression).

Biochemical cardiac markers are macromolecules released into the peripheral circulation following myocardial necrosis, with the resultant loss of cellular membrane integrity. Troponins T and I are both cardiac contractile proteins that are highly specific for myocardial damage compared with the traditional gold standard of CK-MB, as they possess an amino acid sequence that is distinct from skeletal muscle forms. Troponin elevation, like creatine kinase, is detectable 4 to 6 hours after the onset of myocardial necrosis and can persist for 2 weeks after the event. Troponin testing bestows both diagnostic and prognostic benefits at the same time. There are, however, two weaknesses of troponin – a low sensitivity prior to 6 hours (a weakness shared with CK-MB), and a low sensitivity for late re-infarction – because of the long time it takes troponin levels to become undetectable after the index event.

The electrocardiogram (ECG) is critical to the diagnosis and the management of patients with AMI. Patients who present with ST-segment elevation of $^{3}0.1$ mV in $^{3}2$ contiguous leads should be considered potential candidates for acute reperfusion therapy, either fibrinolytic therapy or primary percutaneous coronary intervention (PCI). Patients with reversible ST-segment depression ($^{3}0.05$mV) should undergo rigorous risk stratification with the high-risk cohort receiving current state-of-the-art intensive antithrombotic therapy followed by invasive management.

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MEDICAL MANAGEMENT

There are essentially three categories of treatment for patients presenting with AMI: anti-ischaemic, anti-thrombotic and coronary revascularisation. These therapies are to be considered and administered concurrently.

Anti-ischaemic therapy

The objective of anti-ischaemic therapy is to reduce myocardial oxygen demand and to reduce vasoconstriction and hence ischaemia. It should include general measures, such as bed rest with continuous ECG monitoring, supplemental oxygen to maintain adequate arterial oxygen saturation, and intravenous morphine to relieve ischaemic symptoms.

An intravenous nitrate infusion is generally given to patients who require hospitalisation. Beta-adrenergic blockers should be administered to all ACS patients without contraindications. They act by reducing heart rate, blood pressure and myocardial contractility. There is no evidence to suggest that any one beta-blocker is more effective than another. *Examples of commonly used beta-blockers include propranolol, atenolol and metoprolol.* If beta-blockers are contraindicated, a heart-rate-slowing calcium antagonist (verapamil or diltiazem) should be employed.

Antithrombotic therapy

The benefits of aspirin therapy in ACS are substantial and well defined. It acts by inhibiting cyclo-oxygenase and blocks the formation of thromboxane A2, thus preventing platelet aggregation. When given acutely in patients with STEMI, it reduced the risk of mortality by 25% in ISIS-2 (International Study of Infarct Survival 2). The ACC/AHA guidelines recommend that aspirin should be the first choice of antiplatelet therapy and should be initiated promptly. The starting dose is 300 mg stat (chewed aspirin) followed by a maintenance dose of 75 to 160 mg per day (enteric or non-enteric formulation).

Ticlopidine and its derivative, clopidogrel, are ADP-receptor antagonists, which in turn inhibit platelet aggregation. Potential additive benefits may be derived by combining them with aspirin, as a result of their different antiplatelet mechanisms. The recently published CURE (Clopidogrel in Unstable Angina to Prevent Ischemic Events) trial showed that the combination of aspirin and clopidogrel reduced the composite risk of death, myocardial infarction and stroke in patients presenting with unstable angina/NSTEMI compared with aspirin alone (9.3% vs. 11.4%), albeit with an increased risk of major bleeding.[1,2] The ACC/AHA guidelines recommend that ticlopidine or clopidogrel be administered to patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance. A loading dose of ticlopidine 500 mg is recommended for rapid onset of action followed by 250 mg twice daily. Alternatively, clopidogrel 300 mg is to be given as a loading dose followed by 75 mg daily. The adverse effects of ticlopidine, particularly neutropenia, which occur in 2.4% of patients, limit its usefulness. Monitoring of ticlopidine therapy requires a full blood count to be done every 2 weeks for the first 3 months. Clopidogrel has considerably fewer side effects and has a faster mode of action. With a loading dose, clopidogrel achieve 68% of platelet inhibition within 2 hours and 80% after 5 hours. The duration of effect is prolonged and normal platelet aggregation occurs when the drug is discontinued for at least 5 days.

In high-risk cohorts of patients with NSTEMI, in whom PCI is planned, intravenous platelet glycoprotein (GP) IIb/IIIa receptor antagonists may be administered. The activation of platelet GP IIb/IIIa receptors represents the final and obligatory pathway for platelet aggregation, and selective inhibition of these receptors is a potent strategy in preventing thrombosis mediated by platelet-fibrinogen interaction. Numerous trials have shown that administration of these agents reduces the risk of death and MI in patients with NSTEMI undergoing invasive therapy.

Unfractionated heparin (UFH) is widely used in the management of patients with UA/NSTEMI, although the evidence supporting its use in the absence of aspirin is less robust than in the presence of aspirin. In clinical practice, UFH is hampered by unpredictable levels of heparin binding to plasma proteins and relative ineffectiveness against platelet-rich and clot-bound thrombin. It is also associated with rebound ischaemia upon discontinuation of heparin infusion. Low-molecular weight heparins (LMWHs), generated by enzymatic depolymerisation of standard heparin, have enhanced anti-Xa activity in relation to anti-IIa (anti-thrombin) activity. They have better bioavailability, a more predictable anti-thrombotic effect, are less protein-bound and are less likely to cause bleeding. The use of LMWHs is now preferred in routine clinical practice.

INTERVENTIONAL PROCEDURES

NSTEMI: early invasive revascularisation strategy

Patients with UA/NSTEMI may be managed medically with the above-mentioned anti-thrombotic therapy to stabilise the unstable plaque and may undergo expeditious angiography with a view to revascularisation (PCI or coronary artery bypass grafting [CABG]).

TACTICS-TIMI 18 compared an early (within 4 to 48 hours) invasive strategy with a conservative, symptom-driven strategy in NSTEMI patients treated with intravenous tirofiban (platelet glycoprotein IIb/IIIa receptor antagonist), aspirin and UFH, and showed a greater benefit in the invasive group: lower rates of death, MI or re-hospitalisation (15.9% vs. 19.4%, P=.025). This supports a policy involving broader use of the early and 'upstream' inhibition of GP IIb/IIIa receptors in combination with an early invasive strategy.

Revascularisation procedures are associated with an increased incidence of peri-procedural MI. In patients at high risk, this increased incidence is potentially balanced by a subsequent decrease in ischaemic events. However, if patients at low risk are exposed to the peri-procedural events, little benefit may be derived from revascularisation. Both the European Society of Cardiology (ESC) and ACC/AHA guidelines have correctly refrained from recommending routine intervention for all patients but proposed that coronary angiography and revascularisation be performed in high-risk patients. These include patients with recurrent ischaemia, haemodynamic instability, major arrhythmias, signs of congestive cardiac failure, elevated troponin levels, recent PCI and prior CABG.

STEMI: fibrinolytic therapy

Fibrinolytic therapy is the mainstay of therapy in patients with STEMI, but not those with NSTEMI. Studies have consistently shown that early, prompt and complete restoration of coronary blood flow is the principal mechanism by which reperfusion therapy improves outcome of patients with STEMI. Regardless of the types of fibrinolytic agents used, the earliest possible administration of any fibrinolytic salvages more muscles and saves more lives. The Fibrinolytic Therapy Trialists' (FTT) group estimated that every hour of delay from symptom onset to the initiation of fibrinolytic therapy resulted in a loss of 1.6 lives per 1,000 in the first 24 hours of infarction.

The common fibrinolytics used locally are intravenous streptokinase and recombinant tissue plasminogen activator (rt-PA). In the GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial, front-loaded rt-PA administered over 90 minutes with intravenous heparin and aspirin was shown to achieve higher 90-minute infarct-related artery patency (in TIMI grade 3 flow) and improved survival. However, the use of rt-PA was associated with a higher incidence of intracranial haemorrhage. Because of its high cost, the use of rT-PA is generally reserved for patients with large infarction who present late (>4 hrs) or had previous streptokinase therapy.

STEMI: primary angioplasty

A mechanical reperfusion strategy, in the form of acute percutaneous coronary angioplasty (PTCA), has become an important therapeutic modality in the treatment of patients with AMI. This technique is superior to fibrinolytic therapy in achieving a higher rate of TIMI 3 flow, a lower rate of recurrent ischaemia, improved 30-day mortality and a lower incidence of haemorrhagic strokes. In a meta-analysis of 23 different randomised trials of thrombolytics and primary angioplasty, the latter therapy was shown to be associated with a greater reduction in mortality, re-infarction and intracranial haemorrhage. However the procedure must be carried out by experienced operators in an institution dedicated to the provision of such services round the clock.

It is clear that if a patient presents himself in the right place and the right time with an evolving AMI, then primary PTCA would be preferred. The important issue must be which of the reperfusion therapies could be delivered more efficiently in the respective hospitals and should not be accompanied by any delay. Primary PTCA must be considered the treatment of choice should there be any contraindication to fibrinolytic therapy or if the patient is in cardiogenic shock.

REHABILITATION AND SECONDARY PREVENTION

Following initial stabilisation and subsequent definitive treatment of ACS, patients need to continue with medical therapy for potential prognostic benefits. These include aspirin, beta-blockers, cholesterol-lowering agents and angiotensin converting enzyme (ACE) inhibitors, especially in those with impaired left ventricular systolic function (ejection fraction <40%).

Statins, which are hydroxymethylglutaryl (HMG)-CoA reductase inhibitors, have been shown to substantially decrease mortality in patients with coronary artery disease and high or average low-density lipoprotein (LDL)-cholesterol levels. In fact, early administration of atorvastatin (80 mg/day) within 24 to 96 hours of ACS reduced recurrent ischaemic events, as shown in the MIRACL (Myocardial Ischemia Reduction with Acute Cholesterol Lowering) trial. The recommended target LDL-cholesterol level is <100 mg/dL (2.6 mmol/L). In patients with high triglyceride and low high-density lipoprotein (HDL)-cholesterol level, fibric acid derivatives may be given to reduce cardiovascular risk. Blood pressure control is an important goal and hypertensive patients should be educated on maintaining target goal reading of <140/90 mmHg. Particular attention should also be paid to smoking cessation, tight glucose control in diabetics (glycosylated haemoglobin <7%), weight loss in overweight patients, and regular exercise.

CONCLUSIONS

The optimal approach for the treatment of patients with AMI should include careful history taking, physical examination, ECG and biochemical marker assays. Distinguishing between STEMI and NSTEMI carries important prognostic and therapeutic implications. Current treatment for STEMI mandates reperfusion therapy (either pharmacological or mechanical), while NSTEMI requires intensive antithrombotic therapy followed by early cardiac catheterisation for the high-risk cohort. Acute management must obviously also be followed by secondary preventive medications, and good long-term modification of risk factors – blood pressure control, cessation of smoking, good metabolic control of diabetes and cholesterol, and a regular exercise programme.

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LEARNING POINTS

1. **Acute coronary syndrome is an inflammatory mediated process, occurring as a result of intracoronary thrombus formation following atheromatous plaque erosion or rupture.**
2. **The determination of the types of acute coronary syndromes, viz, ST elevation or non ST-elevation/ unstable angina, carries important therapeutic and prognostic implications**
3. **The mainstay of therapy for patients with STEMI is reperfusion therapy, be it pharmacologic or mechanical**
4. **The treatment of NSTEMI/UAP requires a risk stratification process with early invasive therapy recommended for high risk cohort.**
5. **Treatment of acute coronary syndromes requires intensive risk factor control for secondary prevention following initial stabilization, and these include cholesterol-lowering with statins, use of beta-blockers and ACE-inhibitors.**