

Acute Coronary Syndromes: From Pathophysiological Pathways to Pharmacological Challenge

Gianluca Di Micco*

Complex Unit of ICCU and Cardiology – Fatebenefratelli Hospital – Naples, Italy

Complex Unit of ICCU and Invasive Cardiology – Fatebenefratelli Hospital – Benevento, Italy

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The clinical presentation of ischaemic heart disease includes stable and unstable angina pectoris, silent ischaemia, myocardial infarction, heart failure and sudden death [1]. For many years, unstable angina has been considered an intermediate syndrome between chronic stable angina and acute myocardial infarction. In recent years, its pathophysiology has been clarified and acute coronary syndrome (ACS) is now a common term for unstable angina pectoris and evolving myocardial infarction (MI) [2]. Two different syndromes outline, distinguished in ST elevation and non ST elevation coronary diseases [3].

ACS is the most common cause of cardiovascular disability and death in the western world and in the United States, affecting approximately 1.8 million Americans annually. Of these, 450.000 are admitted to hospitals through the emergency department. Approximately, 1.4 million hospital admissions annually in the USA are for patients with ACS. Of these patients, the risk of cardiovascular death or acute myocardial infarction (AMI) is 6% to 8% during both the initial hospitalization and the following two years [4]. Evidence has demonstrated that risk stratification prior to treatment is essential to appropriate management as well as to reduction of mortality. Recent studies, in fact, indicate that mortality from ACS can be more effectively reduced with new treatments [5].

All forms of ACS are characterized by an imbalance between myocardial oxygen supply and demand, and many other factors also contribute to this imbalance. The common pathophysiological mechanism of ACS is atherosclerotic plaque rupture or erosion, with differing degrees of superimposed thrombosis and distal embolisation. The degree of ischaemia or infarct size, in fact, is related to the degree and location of thrombosis [6].

Plaque rupture, platelet activation and thrombus formation are recognised as key events in the pathogenesis of ACS. Despite the widespread use of many pharmacological compounds, the rate of plaque rupture remains high and additional strategies for vulnerable plaque detection and

passivation by means of local delivered therapy are being developed in conjunction with systemic pharmacological treatment [7]. The challenge for the future, in fact, is to identify vulnerable plaques before the thrombus formation. Most plaques may cause no symptoms for decades, however, a few plaques disrupt and cause thrombosis. Thus, a vulnerable plaque is a plaque assumed to be a high short term risk of thrombosis, causing ACS. There are mainly three forms of vulnerable plaque, all documented by pathology studies: 1) thin-cap fibro atheroma, an atheromatous core with a thin fibrous cap with macrophage and lymphocyte infiltration and decreased smooth cells, 2) erosion, that is plaque rich in proteoglycans, 3) calcified nodule, that is a thrombosis covering a calcified nodule, projecting into the lumen [8].

It is now clear, that the ACS still poses challenge for every day's clinical practice. Non ST elevation has been more effectively managed, since the advent of effective tools of risk stratification. In this regard, medical and invasive approaches are no longer mutually exclusive, but complementary strategies for most patients [9]. In the last few years, especially last five years, the invasive approach for all ACS has begun to be favourite. For acute coronary syndromes with ST elevation treatment, epidemiological data available from the literature gave equivalent results for the percutaneous approach (PCI) and pharmacological approach (thrombolysis), especially in the first three hours from the clinical onset, yet, in the following time the pharmacological reperfusion loose most of its power if compared to benefit of invasive strategy. In those hospitals equipped with 24 hours invasive cardiology, the mechanical reperfusion, in fact, is preferred for both STEMI-ACS (primary angioplasty or facilitated angioplasty) and NSTEMI-ACS (PCI within 24-48 hours). As we underlined before, two procedures are mutual and not excluding each other, obtaining a facilitated angioplasty. In fact, a part of usual therapy composed of nitrates, beta-blockers, ace-inhibitors and statins. The PCI is performed, treating patient with antiaggregant (aspirin, thienopiridines and IIb IIIa antagonists) and anticoagulant (heparin UHF or low weight or finally direct thrombin inhibitors) [10].

Antithrombotic management of ACS should focus on the prevention of two key underlying processes, namely formation of a platelet-rich thrombus with old and new antiplatelet

*Address correspondence to this author at the Complex Unit of ICCU and Cardiology - Fatebenefratelli Hospital - Naples, Italy;
E-mail: pdimicco@libero.it

agents and formation of a fibrin-rich mesh with antithrombin agents from heparin, unfractionated or low molecular weight to new direct inhibitor from argatroban and lepirudin to bivalirudin. Although there is variety of approaches to enhance anticoagulant effects, none is completely satisfactory as single agent therapy. Combined use of antiplatelet and antithrombin agents ultimately translates into reduced rates of adverse outcome, such as death or MI [11].

In this way, if a patient presents with suspected ACS, but further evaluation is necessary to confirm diagnosis, the recommended course of treatment is to give a minimum dose of aspirin (initial dose of 160 to 325 mg followed by 75 to 160 mg) until the diagnosis is confirmed. It is also well recommended that a patient who presents with likely or definitive ACS will receive aspirin, thrombin inhibitor (heparin UF or LMWH) and clopidogrel (75 mg/day; loading dose of 300 mg to 600 mg for rapid onset). Patients who have a definitive presentation of ACS with continued ischaemia and who exhibit other high risk features and are definitely proceeding directly to cardiac catheterisation should receive a combination of aspirin, thrombin inhibitor and a GP IIb IIIa inhibitor as well as clopidogrel [12].

In conclusion, two important keys must be kept clear in the clinical practice for a correct management of ACS. First of all, the reperfusion strategy, pharmacological, mechanical or better both, must be started as soon as possible, because "Time is muscle" and this can improve left ventricular function and long term outcome. The second point automatically follows because of aggressive patients risk stratification. Only the identification of high risk features, including dynamic ST-segment changes, refractory angina, haemodynamic or rhythmic instability, diabetes and renal failure, can help to choose the right, faster and more appropriate therapy. There are various usable drugs ranging from antiaggregant to direct and selective inhibitors of thrombin. Unfortunately not all these drugs are always present in all the hospitals because of their cost and their availability.

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