Editorial corner
From syndromes to specific disease mechanisms.
The search for the causes of myocardial infarction

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Optimal treatment and prevention of myocardial infarction (MI) are currently based on evidence-based medicine , the principle that indicates the treatments proven to be significantly better than placebo or other treatments for the average patient. This approach represents considerable progress but it implicitly assumes that the predisposing and precipitating factors of MI are basically the same in all patients. As it is the case for many other clinical syndromes, the symptoms and consequences of MI are similar regardless of its causes, but growing evidence suggests that the validity of the traditionally established paradigm that MI is a single disease entity needs to be reconsidered in order to begin to personalize treatment and prevention.

Acute MI is a very rare, occasional event even in patients with extensive coronary atherosclerosis and with prothrombotic states. Any single, common, putative trigger cannot explain such rarity. Thus MI is either the result of a very exceptional local event or of a very unusual coincidence of multiple, adverse local and possibly systemic events that may not have the same prevalence in different ethnic, geographical, age and sex groups. Distinct clinical presentations of acute MI might provide clues of specific coronary and systemic pathogenetic components.

This editorial corner provides the interested readers with a concise review of the most relevant pieces of evidence. The readers should judge for themselves whether or not the time has come to challenge the paradigm that MI is a single disease. Only essential, recent references will be included, the older ones can be found in reference 1.

The multiple, acute triggers of myocardial infarction

An acute MI develops whenever blood flow through a major coronary artery is suddenly and persistently interrupted, regardless of the actual cause of the interruption which, besides thrombosis, may include occlusive spasm, massive small vessel constriction and their variable combinations (Fig. 1).

Each of the less common potential primary mechanisms may have multiple caus-

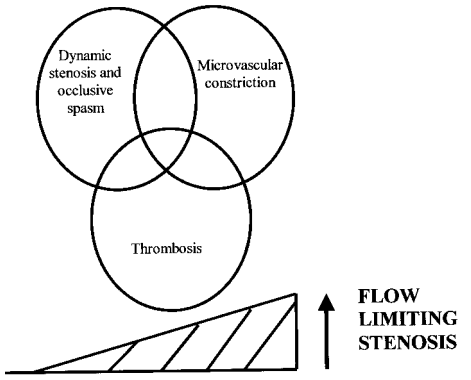

Figure 1. *Diagram of the potential triggers of sudden, persistent interruption of coronary blood flow in myocardial infarction. These acute triggers may develop in the presence of variable severity of atherosclerosis. The most obvious and prevalent trigger is thrombosis; its persistence also makes it detectable at angiography, angioscopy and* postmortem. *The role of other potential triggers is much more elusive. The presence of spasm and dynamic stenoses can only be revealed by repeating angiography after nitrates or by provocative tests; it appears to be much more prevalent among Japanese[2]. The role of microvascular dysfunction can only be inferred, in some cases, by a very early coronary "no-reflow phenomenon" or by special studies. Thrombosis is also a much more effective target for therapy and prevention than vasoconstriction because of its prevalence as a final common trigger and because vasodilators administered systemically are unlikely to overcome the constrictor activity of locally released thrombotic products, or of very strong, local vasoconstrictor, stimuli. From Maseri[1].*

es. Occlusive, epicardial, coronary artery spasm may be caused by local smooth muscle hyperactivity, as observed in variant angina, or by isolated, occasional, intense, local constrictor stimuli. Massive small vessel constriction may be caused by neuropeptide Y or endothelin, by serotonin and tromboxane A_2 released by platelets, and by diffuse endothelial activation by inflammatory cytokines.

In turn, also coronary thrombosis, the most common final event, may develop as a result of strong or weak thrombogenic stimuli.

1. Strong thrombogenic stimuli cause rapid thrombus growth with massive inclusion of red blood cells in the fibrin mesh (red thrombi) leading to persistent, uninterrupted vessel occlusion within few minutes (like the copper coil animal model). A strong thrombogenic stimulus may be caused by a purely mechanical rupture of a large lipid rich atherosclerotic plaque, occurring at random as a result of local vascular stress and strain (in this case the growth of the thrombus is mainly determined by the thrombogenicity of the plaque). This mechanism should be more prevalent in patients with multiple plaques with large central lipid core and a thin fibrous cap, not necessarily determining flow-limiting stenosis.
2. Weak thrombogenic stimuli cause slow, progressive deposition of platelets and formation of platelet-fibrin thrombi (white thrombi), according to their intensity, duration and recurrence (like the electrical wire animal model). Weak thrombogenic stimuli may result from fissure of non strongly thrombogenic plaques or from local activation of the vascular wall by inflammatory cytokines, with or without plaque fissure (in this case the growth of the thrombus is mainly determined by the intensity, duration and recurrence of the local inflammatory process). Inflammatory cytokines cause endothelial expression of tissue factor, of other procoagulant and vasoconstrictor factors, of adhesive receptors for platelets and leukocytes, together with inhibition of its physiological antithrombotic and vasodilator properties, sufficient to initiate thrombosis and to sustain it when persistent. In addition, cytokines may also activate metalloproteases with consequent endothelial erosions and lysis of the plaque s caps[3]. In turn, the causes of such an inflammatory process may be multiple, acute or chronic, infectious or non-infectious[4] and be variably modulated by the individual inflammatory and immune responses[5,6].

Thrombus growth

As thrombosis is the first physiological self-limiting step of vascular injury repair, it would be useful to examine the potential co-factors, which, under some very occasional circumstances, cause it to become such a major acute disease mechanism. These mechanisms are multiple and may often act in combination (Fig. 2).

1. Both strong and weak, but persistent, thrombogenic stimuli may exceed the physiological repair function of thrombosis, either because of their strength or because of their persistence, resulting in occlusive thrombi. Such occlusive thrombi may develop in spite of the continuous dilution of local prothrombotic factors and of the continuous supply of anticoagulant and fibrinolytic factors by blood flow, as well as and in spite of antiplatelet and of anticoagulant therapy.

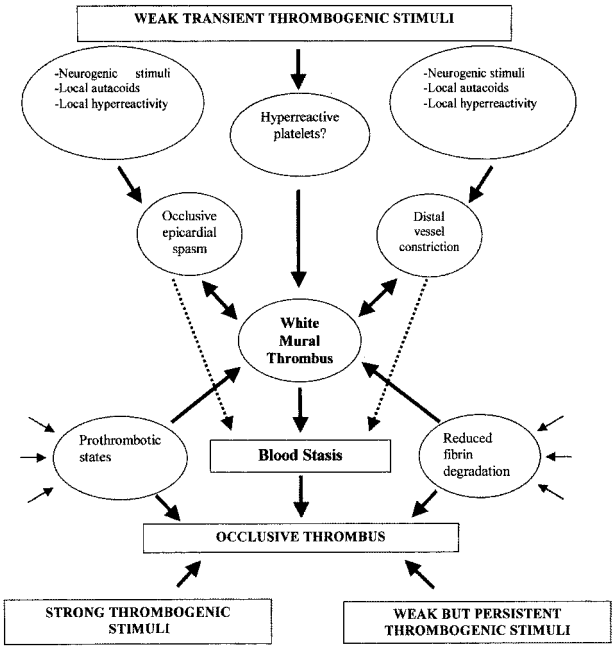

Figure 2. *Vicious circles leading to the formation of an occlusive thrombus. An occlusive red thrombus can form rapidly within minutes at the site of a highly thrombogenic injury (for example the rupture of a strongly thrombogenic plaque). An occlusive platelet thrombus can form gradually at the site of weak, but very persistent thrombogenic stimuli (for example a persisting inflammatory process). A mural thrombus resulting from a plaque fissure or from a local inflammatory process may evolve in an occlusive thrombosis in the presence of prothrombotic states or of blood flow stasis induced by local or distal coronary constriction. The components of these vicious circles and their gain may be of variable importance and prevalence in different groups of patients. Prothrombotic states may result from any acquired or genetic alteration that leads to enhanced platelet reactivity and/or thrombin formation or to reduced fibrinolysis. From Maseri[1], modified.*

2. Also weak, non-persistent, thrombogenic stimuli may cause occlusive thrombosis, but only when associated with prothrombotic or deficient fibrinolytic states, whatever their multiple environmental or genetic origin, and when combined with blood flow stasis resulting from local spasm or massive distal small vessel constriction.

These different mechanisms of coronary blood flow interruption, the type of thrombogenic stimuli and the variable association of prothrombotic, deficient, fibrinolytic and vasoconstrictor components may not have the same prevalence in different geographical, ethnic, age and sex groups; yet, they may influence the individual response to antiplatelet, antithrombotic and acute reperfusion strategies.

Clues from the culprit coronary artery

In patients who died within 6 hours of symptom onset, in those with a history of unstable angina as well

as in most fissured plaques, the prevalent features of thrombi provide intriguing clues about their origin:

they are usually composed of platelets, consistent with weak local thrombogenic stimuli;

they often do not occlude the coronary lumen completely suggesting a frequent association of a vasoconstrictor component of the occlusion;

they may be multilayered, consistent with repetitive local thrombogenic stimuli;

they may be occasionally found also in non-infarct-related arteries and in association with multiple plaque fissures, consistent with simultaneous multifocal thrombogenic stimuli.

Collectively these observations suggest that purely mechanical fissures of weakly thrombogenic plaques, or local effects of inflammatory cytokines, represent the most common, transient or persistent or even recurrent, local thrombogenic stimuli which sometimes may be multifocal involving more than one plaque.

A possible local source of inflammatory cytokines is represented by inflammatory cell infiltrates commonly found underneath fresh coronary thrombi, both in the presence and in the absence of plaque fissures. However, the possibility that inflammatory cell infiltrates could be, by themselves, the triggers of thrombosis in acute MI and in unstable angina, appears rather simplistic. Indeed similar infiltrates are also frequently found in coronary plaques of stable patients[7], and in carotid endoarterectomies[8], together with ulcerated plaques[9]. Therefore, they appear to be a common component of the atherosclerotic process rather than specific, occasional triggers of MI or unstable angina.

The hypothesis of vulnerable coronary plaques is attractive and is currently stimulating new research tools for their clinical detection. However plaques may be vulnerable for different reasons: they may be prone to mechanical rupture because they have a large central lipid pool and a thin cap, or because they are the site of inflammatory processes or for a combination of these two mechanisms. Their vulnerability may last days, weeks or months.

So far no distinctive inflammatory features have been identified at the site of coronary thrombi that caused MI and death which were absent in inflamed plaques of stable patients. Thus the thrombogenic effect of coronary plaque infiltrates might require the contribution of systemic inflammatory components.

Initial clues on the prevalence of inflammatory thrombogenic stimuli and of other, non-inflammatory causes could be provided by the different forms of presentation of acute MI and by its prodromal symptoms.

Clues from the mode of presentation of acute myocardial infarction

In some patients MI develops totally unheralded with the first single episode of uninterrupted anginal pain that brings them to hospital. In others, the final persistent episode of pain is preceded by a typical history of unstable angina. In an intermediate group the final episode of persistent pain is preceded by one or two isolated anginal attacks, compatible with a hyperacute presentation of preinfarction unstable angina. During the initial 6 hours from symptom onset, in unselected patients with acute MI, the infarct-related artery recanalizes spontaneously in 40% of the cases and exhibits occasional, transient reperfusion in about 70% of the cases, and spontaneous and early reperfusion seems to be more frequent in patients in whom MI is preceded by unstable angina[10].

Thus in some patients coronary occlusion appears to develop like lightning out of a blue sky and to be persistent and uninterrupted, compatible with the fissure of a strongly thrombogenic plaque, with a persistent coronary inflammatory stimulus or with persistent spasm or distal coronary vessel constriction. In some with a history of preinfarction unstable angina, coronary occlusion is transient and very occasional before the final episode, in others, final coronary occlusion exhibits spontaneous, transient or persistent recanalization, consistent with waxing, waning and recurrence of weak inflammatory thrombogenic stimuli.

The presence of systemically detectable inflammatory markers in about 70% of patients with Braunwald class IIIB unstable angina and the much higher recurrence of instability among the 50% of patients in whom the elevation persists at discharge and at 3 months[11], may represent an objective marker of inflammatory thrombogenic triggers. This possibility is supported by the elevation of such markers at the time of hospital admission in nearly all patients in whom MI was preceded by unstable angina but only in less than 50% of those in whom MI was totally unheralded[12]. The absence of inflammatory markers also allows an objective distinction of variant angina[13] which sometimes has a clinical presentation indistinguishable from the more common form of unstable angina.

Different pathogenetic components of coronary occlusion are also suggested by the earlier recanalization in response to tissue-type plasminogen activator observed in patients with preinfarction angina, compared to those with a totally unheralded MI[14].

Clues from the prodromal symptoms

In some patients MI occurs without any apparent cause, in others a history of severe psychological distress[15,16] or of flu-like syndromes can be elicited on careful questioning. These prodromal symptoms may be associated with a different mode of presentation of acute MI and might provide clues of distinct pathogenetic mechanisms, which may not have the same prevalence in different age, sex, geographical and ethnic groups. These clinical clues are subjective, hence not always reliable, but they are available and their incidence and significance should be systematically assessed.

Risk factors for myocardial infarction

As the potential mechanisms of coronary flow interruption, of plaque vulnerability and of the co-factors that contribute to make thrombosis a major acute disease mechanism are multiple, also the role and prevalence of any established and novel environmental or genetic risk factor for MI may vary greatly in different age, sex, social, geographical and ethnic groups.

The estimated average risk attributable to any putative risk factor in a population or in unselected patients is the result of two components: the risk conferred by the factor to susceptible individuals and the prevalence of such susceptible individuals in the group studied[17] (Fig. 3). The low risk ratios commonly found for many putative risk factors[18,19] may not necessarily be the result of a small pathogenetic role of such factors, but of a low prevalence of individuals that are susceptible to them in the group studied or of a high prevalence of other major risk factors[18,20]. The risk conferred by a MI before the age of 60 in a fist degree relative[21] indicates that genetic factors play a detectable role only in premature MIs but does not imply that the genetic component is the same in different families. Therefore, the role of risk factors and the prevalence of individuals susceptible to each of them should be assessed separately in different age, sex, social, geographical and ethnic groups.

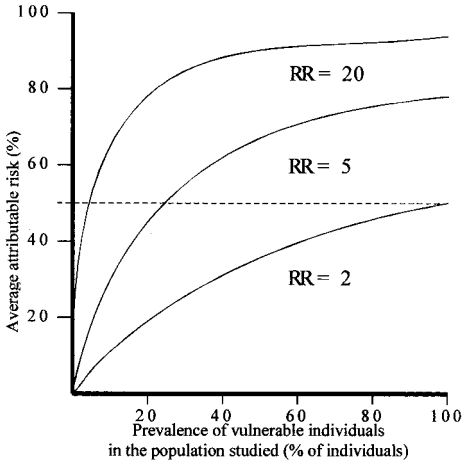

Figure 3. *Effect of the prevalence of individuals with increased vulnerability to a given risk factor on the estimated risk attributable to the population studied. For any given risk factor the average risk attributable to the total, unselected study group increases progressively with the prevalence of individuals susceptible to it in the group. The practical implications of this concept are considerable: for example, for a given risk factor, a 50% attributable risk to the total population can result from: (a) a 100% prevalence of individuals susceptible to that risk factor with a risk ratio (RR) of 2 relative to individuals without the risk factor, (b) a 25% prevalence of individuals with an RR of 5 or (c) a 5% prevalence of individuals with an RR of 20. Therefore, for any given risk factor, only those individuals who are susceptible to it require treatment. From Hopkins and Williams[17], modified.*

Clinical implications

The very ambitious goal of beginning to search for the multiple causes of MI and for their role and prevalence in specific patient groups appears justified by two considerations:

more efficacious coronary reperfusion strategies in acute MI should be reserved for those patients who are unlikely to respond to simpler ones. Clinically useful markers of high probability of prompt response to streptokinase plus aspirin and to tissue-type plasminogen activator (and derivatives) plus heparin should be identified in order to reserve newer and more complex strategies, including primary angioplasty, for non-responders. The alternative is to treat indiscriminately all patients with the newest, most efficacious but possibly also more complex and expensive coronary reperfusion strategies;

the subgroups of patients that benefit from antiplatelet drugs, anticoagulants, beta blockers, statins and ACE inhibitors should be identified. The alternative is to prescribe indiscriminately all these preventive treatments to each patient, with the consequent burden of polytherapy, risk of low compliance and costs.

These considerations have major implications for the design of future clinical trials[22,23].

The new avenues of research

Research is presently focused on finer and finer details of single putative mechanisms of MI. These discoveries should be seen as pieces of a gigantic jig-saw puzzle which needs to be assembled in order to provide us with a global view of the causes of this multifaceted syndrome. Like in the fight against international criminal organizations, the identification of individual killers may be of limited value without discovering the network and the brains behind them.

In order to foster the coordination of research approaches on the mechanisms of MI, in the coming issues of the Journal, research leaders will be invited to act as Guest Editors in a series of Mini Symposia under the heading *The Search for the Causes of Myocardial Infarction*. The task of the Guest Editors will be the selection of a series of short, punchy invited articles on the directions research should be taking in order to accelerate the identification of the role and prevalence of specific disease mechanisms of MI and to write their chelating comments.

The following Mini Symposia have been planned so far:

1. How to search for the substrates of coronary thrombosis and their prevalence
   Guest Editors: A. Becker*, E. Arbustini*
2. How to search for the precipitating role of platelet hyperactivity and its prevalence
   Guest Editors: Z. Ruggeri*, R. Landolfi*
3. How to search for the precipitating role of the multiple prothrombotic states and their prevalence
   Guest Editors: T. Edgington*, P.M. Mannucci*
4. How to search for the precipitating role of the multiple defective fibrinolytic states and their prevalence
   Guest Editors: C. Kluft*, F. Andreotti*

5. How to search for the precipitating role of inflammation and its prevalence
   Guest Editors: P. Ridker*, L.M. Biasucci*
6. How to search for the predisposing role of psychological distress and its prevalence
   Guest Editor: R. Verrier*
7. How to search for the precipitating role of vasoconstriction and its prevalence
   Guest Editors: J. Willerson*, F. Crea*
8. How to search for the predisposing role of traditional risk factors and their prevalence
   Guest Editor: G. Tognoni*
9. How to search for the predisposing role of infections and their prevalence
   Guest Editors: J.C. Kaski*, G. Liuzzo*
10. How to search for the predisposing role of oxidative stress and its prevalence
    Guest Editors: G. Fitzgerald*, C. Patrono*
11. How to search for the role of gene-environment interactions
    Guest Editors: S. Humphries*, B. Donati*
12. How to search for the role and prevalence of genetic factors
    Guest Editors: to be selected
13. Implications for the design of future clinical trials
    Guest Editors: S. Yusuf*, A.P. Maggioni*

Each Mini Symposium should include two or three invited points of view and one editorial comment (approximate length: 1000-2000 words, time 3-6 months).

As soon as the publication of all Mini Symposia in the *Italian Heart Journal* will be completed, the contributors will be invited to a workshop in Rome for a joint discussion of the conclusions. Then the Mini Symposia will also be collected in a volume together with a Precis of this discussion.

We hope that these Mini Symposia will contribute to stimulate novel pathogenetic research avenues on this major common cause of death, disability, and health costs.

* indicates acceptance. The choice of topics is largely based on a brainstorming seminar held in Rome on April 11-13, 1999, The Search for the Causes of Myocardial Infarction supported by the Fondazione Internazionale per il Cuore, ONLUS.

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