# How to search for the precipitating role of vasoconstriction and its prevalence in myocardial infarction

James T. Willerson, Filippo Crea*

*Department of Internal Medicine, University of Texas Health Science Center and Texas Heart Institute, Houston, TX, USA, *Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy*

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*Address:*

Prof. Filippo Crea

*Istituto di Cardiologia*
*Università Cattolica*
*del Sacro Cuore*
*Policlinico A. Gemelli*
*Largo A. Gemelli, 8*
*00168 Roma*
*E-mail:*
*f.crea@tiscalinet.it*

The demonstration in the late 1970's that spasm was the cause of myocardial infarction and sudden death in patients with the syndrome of variant angina generated a surge of interest in the possibility that coronary spasm might be the prevailing cause of acute coronary syndromes at large[1]. The subsequent demonstration by DeWood et al.[2] that occlusive coronary thrombosis is almost universally present early after acute myocardial infarction and the evidence in several clinical trials that antithrombotic agents consistently improve the outcome of acute coronary syndromes while the beneficial effects of nitrates and calcium antagonists are, to say the least, very inconsistent made the pendulum to swing to the opposite direction[3]. Nowadays, it is well recognized that thrombosis is the main cause of coronary instability in the vast majority of patients. Nevertheless some observations indicate that proximal and distal vasoconstriction might play an important contributory role potentially amenable to specific forms of treatment. Already in the early days of thrombolysis, Hackett et al.[4] found that in patients with acute myocardial infarction, treated with intracoronary administration of streptokinase and intravenous infusion of nitrates, intracoronary administration of isosorbide dinitrate reestablished the patency of the coronary artery in about 50% of episodes of reocclusion that were observed in about 70% of the patients, thus highlighting coronary constriction, unresponsive to intravenous nitrates, in the early phases of myocardial infarction.

This timely minisymposium provides insight into the role of vasoconstriction in acute coronary syndromes which can be summarized in four main points:

• coronary thrombus, a key feature of the unstable plaque, has the potential to release powerful vasoconstrictors which are likely to reach remarkably high local concentrations;

• the unstable plaque is more reactive to constrictor stimuli than the stable plaque. The hyperreactivity is considerably more pronounced in patients in whom coronary instability is associated with systemic evidence of inflammation. Endothelin secreted by activated cells is a possible mediator of smooth muscle cell hyperreactivity;

• in patients with unstable angina massive distal coronary constriction may occur in addition to stenosis constriction during transient ischemic episodes. Early observations suggest that distal coronary constriction might be caused by platelet adhesion to activated endothelial cells followed by aggregation and release of potent constrictors;

• in patients with recent myocardial infarction coronary artery branches are much more reactive to constrictor stimuli in Japanese than in Caucasian patients. These findings suggest that the genotype can profoundly affect the relevance of coronary vasoconstriction in acute coronary syndromes.

Taken together these observations explain why systemic administration of traditional vasodilators works so well in patients with variant angina but not in patients with unstable angina or during the early phases of acute myocardial infarction. Indeed, in patients with variant angina the key alteration is segmental coronary smooth muscle

cell hyperreactivity[5]. In patients with unstable angina the mechanisms of enhanced vasoconstriction are more complex as hyperreactive smooth muscle cells are exposed to high local concentrations of potent constrictors released by the thrombus and by activated inflammatory cells[6,7]. Furthermore, endothelial cell activation in distal coronary vessels may favor microvascular dysfunction resulting in paradoxical vasoconstriction during ischemia[8]. It is obvious from these brief considerations that abnormal coronary vasomotion in patients with acute coronary syndromes is a potentially important pharmacological target, in particular in unstable angina refractory to maximal medical therapy and during the early dynamic phases of myocardial infarction.

What is the way forward? In order to dissect out the complex mechanisms responsible for the alteration of coronary vasomotion in acute coronary syndromes it is important: i) to study phenotypically and genotypically homogeneous groups of patients; ii) to utilize an appropriate methodology for the induction and measurement of coronary vasoconstriction; and iii) to choose specific pharmacological tools.

## Patient selection

Patients with acute coronary syndromes are not homogeneous and the pathogenetic relevance of an abnormal vasomotor response in precipitating coronary instability might be different in different subsets of patients. Serum levels of C-reactive protein are a first useful branching point. Studies on coronary vasoconstriction should, therefore, be performed in patients in whom the inflammatory status is well characterized. Patient characterization should also include the genotype. Indeed, the different coronary reactivity observed in Japanese and Caucasian patients with recent myocardial infarction underscores the importance of genetically determined susceptibility to coronary vasoconstriction. The recent demonstration that a polymorphism (-231A/G) of endothelin type A receptor is associated with migraine (known to be more frequent in patients with vasospastic angina) suggests a possible point of attack[9].

## Methodology

A key methodological problem is the utilization of an appropriate trigger of coronary vasoconstriction. Indeed, vasoconstriction which contributes to myocardial ischemia in patients with acute coronary syndromes is transient. Although the utilization of vasoconstrictors in this setting can raise some important ethical issues, several clinical studies have shown that physiological stimuli (for instance cold pressor test and hyperventilation) and pharmacological stimuli with a short half-life (for instance intracoronary administration of ergonovine, acetylcholine and serotonin) are safe if utilized by expert operators. Quantitative coronary angiography remains the main tool in the measurement of the abnormal vasomotor response of large epicardial vessels. However, new invasive and noninvasive imaging techniques such as intravascular thermography and nuclear magnetic resonance can provide information on the cellular content of the atherosclerotic plaque and, therefore, new insights into the mechanisms that determine the local vasomotor response. The study of the abnormal vasomotor response of distal coronary vessels is more difficult because not only vasomotor abnormalities are transient but they cannot be imaged in man using current technology. Nevertheless, in the presence of a critical stenosis the simultaneous measurement of distal coronary pressure and of coronary blood flow using Doppler technology allows us to dissect out the contribution given by proximal and distal resistance to myocardial perfusion impairment.

## Pharmacological tools

An appropriate patient selection and an appropriate methodology for the measurement of coronary vasoconstriction are not sufficient to establish the causes of coronary vasoconstriction in acute coronary syndromes. To this end the careful utilization of specific antagonists, initially in pathophysiological studies in a small number of patients and subsequently, if appropriate, in clinical trials in a larger number of patients, can shed some light on the mediators responsible for proximal and distal vasoconstriction. As noted before on the one hand plaque inflammation may increase the reactivity of smooth muscle cells to constrictor stimuli, probably through the release of endothelin, on the other hand powerful constrictors are released in proximity of hyperreactive smooth muscle cells by coronary thrombus and activated cells. This same deleterious combination of events may occur downstream in distal coronary vessels. Thus, specific antagonists of i) vasoconstrictors released by thrombus and activated cells, ii) key cytokines responsible for the activation of inflammatory cells, and iii) adhesion molecules (which play a key role in distal platelet adhesion and aggregation) are needed to identify the mediators of proximal and distal vasoconstriction. Some of these specific antagonists such as bosentan (an endothelin antagonist) or monoclonal antibodies anti-tumor necrosis factor are already available, others will hopefully be available in the near future.

In conclusion, coronary thrombosis is an important cause of coronary instability. Yet, about 10% of patients with unstable angina are refractory to maximal antithrombotic treatment and about 50% of patients with acute myocardial infarction do not achieve TIMI 3 flow despite early thrombolysis. It is possible that, at least in

a subset of these unresponsive patients, proximal and/or distal vasoconstriction plays an important pathogenetic role. The limited effect of the systemic administration of nonspecific coronary vasodilators in this setting does not rule out the potential pathogenetic role of coronary vasoconstriction and might be due to the impossibility to reach sufficiently high concentrations in the coronary circulation without unacceptable side effects. The recent demonstration by Olausson et al.[10] that epidural sympathetic denervation can treat severe refractory angina suggests that vasoconstriction might indeed be an important pharmacological target. This goal will be fully achieved only if we will understand the mechanisms of coronary vasoconstriction operating in different subsets of unstable patients and if we will be able to prevent constriction selectively in coronary circulation. The stage appears to be set for this important leap forward.

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