Pursuing the goal to improve downstream myocardial tissue perfusion

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This editorial refers to ‘Intravenous administration of nicorandil immediately before percutaneous coronary intervention can prevent slow coronary flow phenomenon’†, by Y. Kawai et al., on page 765

The coronary slow flow phenomenon is an angiographic finding characterized by delayed distal vessel opacification in the absence of significant epicardial coronary disease. Extensively studied both in the experimental and clinical setting, it was clearly associated with unfavourable clinical outcome and prognosis.1,2 Several hypotheses, including embolization of platelet-rich thrombi or atherosclerotic plaque debris that can ‘sludge’ the distal vessel, and release of vasoconstrictive substances causing intense vasospasm of the distal microcirculation, were advocated to justify this event in the context of percutaneous coronary intervention.

If the principal mechanism of the slow flow phenomenon is vasoconstriction, this would explain the favourable response seen with intracoronary administration of calcium antagonists such as verapamil, or vasodilators such as nitroprusside, papaverine, and adenosine.

Nicorandil, a nicotinamide ester, is a vasodilator agent approved as an antianginal agent, with a compound and balanced mechanism of action which relaxes coronary vascular smooth muscle by stimulating guanylyl cyclase and increasing cGMP levels as well as by a second mechanism resulting in activation of K+ channels and hyperpolarization.3 Potassium channel opening effects a titratable and sustained dilating action on both coronary artery conductance and resistance vessels.

Kawai et al. have provided evidence that a prophylactic bolus of 6 mg of nicorandil administered i.v. immediately prior to percutaneous coronary intervention (PCI) reduces the incidence of the slow flow phenomenon without any side effects.4 Conceptually, this strategy improves coronary flow and myocardial perfusion by dilating those vessels with loss of endothelial integrity and reducing capillary and arteriolar blockages resulting from the presence of leukocytes and atheroemboli.

To test this hypothesis, the authors randomly assigned 408 patients to undergo i.v. administration of nicorandil or placebo on top of isosorbide dinitrate just 1 min before PCI. They used the incidence of slow flow established by means of the corrected TIMI frame count as the primary endpoint to assess the efficacy of the drug on distal perfusion. A total of nine (4.4%) patients receiving nicorandil, and 36 (17.8%) receiving placebo, experienced slow flow after angioplasty. Also, the corrected TIMI frame count was lower in the nicorandil group (10.5 ± 5.6 vs. 12.8 ± 7.4, P < 0.0001). Although not powered to show a difference in secondary endpoints, the study achieved consistent findings in patients presenting with either acute coronary syndrome or stable angina. In addition, serum assessment of cardiac enzymes from patients with acute myocardial infarction revealed a beneficial effect of nicorandil in the acute phase of ischaemia.

This study raises some interesting points worthy of discussion.

First, although the occurrence of slow flow is generally associated with reperfusion treatment of myocardial infarction, it could also represent a complication of the elective percutaneous treatment of stable angina in a substantial number of cases. In this case, the fragmentation of atherosclerotic plaque plays an important role, but a full understanding in this setting is probably lacking.

Secondly, once it has been clarified that a number of pieces of evidence on the efficacy of different possible therapeutic approaches may be provided, including those on nicorandil, our attention should be shifted from research of the best drug to the identification of a protocol for a simple, safe, and repeatable administration. As a matter of fact, to date no clear guidelines on the management of slow flow are available, and current protocols which are too complex have often restricted the diffusion and standardization of adjuvant therapy. As a result, this complication is not treated in all cases and on a regular basis.

Thirdly, a preventive approach could represent the best solution to the problem. In this context, nicorandil plays an interesting and somehow a particular role.

When compared with adenosine, in fact, this drug not only improves coronary microvascular circulation, but also dilates
epicardial coronary arteries, and this effect can relieve refractory coronary spasm for which nitrates are not fully effective. In addition, nicorandil has a longer half-life than adenosine, whose half-life in human blood is $<1$ s, which may be too short to maintain its effects during coronary intervention. Finally, adenosine induces coronary steal and negative inotropic effects, which may be detrimental in patients with ischaemic heart disease.

Together with calcium antagonists, nicorandil protects against reperfusion-induced calcium overload. Indeed, ATP-sensitive $K^+$ channel opening by nicorandil shortens the duration of the action potential of ischaemic myocardium, thus inhibiting voltage-dependent $Ca^{2+}$ channels and $Na^+$/Ca$^{2+}$ exchange with consequent cardioprotection. Thus, if sufficient ATP remains available to preserve cell membrane ultrastructure and calcium homeostasis during ischaemia, overloading with calcium will not occur on reperfusion and the mitochondria will not accumulate calcium, ensuring their functional survival. On the other hand, if the cell membrane is disrupted, calcium antagonists and even nicorandil are unlikely to have a beneficial role. Both calcium antagonists and nicorandil have been shown to provide protection against oxygen free radicals, and to possess neutrophil-modulating properties.

Would this be enough to assert that nicorandil should be routinely administered to all patients who undergo PCI? Not at all, at least not before considering the other side of the coin.

First, by opening the ATP-sensitive potassium channels, nicorandil causes hyperpolarization and reduces the duration of the action potential and the effective refractory period, which, in theory, might increase arrhythmias such as accelerated idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation. These undesirable rhythm disorders have not as yet been demonstrated in clinical usage nor in this study, but further evidence would be needed to confirm the extensive and preventive use of this drug as standard practice.

Secondly, despite improvement in the indices of myocardial perfusion used, in the study of Kawai et al. there was no significant difference in the clinical outcome between both groups at 1 year with regards to overall mortality, cardiac mortality, and unplanned re-hospitalization due to worsening congestive heart failure. Even if this trial has not been designed to highlight differences from a clinical point of view, once again the frustrating impasse between the surrogate markers of improving reperfusion and lack of change in clinical outcome has failed to be resolved.

A possible explanation for this could be related to the use of a bolus administration of the active drug before the procedure. One the one hand this is clearly more practical, while on the other hand it does not ensure any lasting protection after the procedure, when coronary slow flow phenomenon can persist for hours. Of note, no episodes of no reflow, which are theoretically related to a poorer outcome compared with slow flow, occurred in this study.

Finally, the failure to find improvement may reflect the complex multiple simultaneous aetiologies associated with the slow flow phenomenon. Any use of an adjuvant therapy to reduce the incidence of slow flow should be complementary and not mutually exclusive as regards the essential regulations of good medical practice taking into account the clinical setting and the prevailing mechanism operating in the individual patient. The ‘structural’ slow flow assumptions, directly determined by the duration and severity of the ischaemic injury, have to be prevented by haemodynamic stabilization, glycometabolic control, and a decrease of door to balloon time. Conversely, ‘functional’ slow flow, whose pathogenesis relates more closely to activation of the neurohumoral system and peripheral dissemination of thrombus or plaque debris, benefits from an accurate stent sizing to avoid overexpansion, by the use of dedicated devices and glycoprotein IIb/IIIa inhibitors.

So, in some targeted cases, a comprehensive simultaneously executed multitargeted approach including a distal ‘protective’ device, in addition to antiplatelet, antithrombotic, and antivasospasm adjunctive pharmacotherapy, could increase the magnitude of the angiographic benefit and put it significantly on the clinical level.

Conflict of interest: none declared.

References