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## Editorial

# Nicorandil: a drug for many purposes: too good to be true?

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Nicorandil, a drug approved for the treatment of ischaemic heart disease, is believed to have a dual properties. The intrinsic mechanism of the drug (selective activation of  $K^+_{ATP}$  channels at the sarcolemmal and mitochondrial level) allows coronary and peripheral vasodilatation with subsequent reduction of preload and afterload. Secondly, because of the role  $K^+_{ATP}$  channels in ischaemic preconditioning, nicorandil has been attributed cardioprotective effects.<sup>1</sup>

The drug has been available in Europe for years, classified as a new class of therapy for coronary artery disease, but failed till now to truly penetrate on the 'European market'. The large scaled, randomized IONA trial evaluated the efficacy of nicorandil on top of 'conventional' antianginal drugs for the treatment of stable angina pectoris.<sup>2</sup> The primary end-point (a composite of cardiac death, myocardial infarction, unplanned hospital admission for chest pain) occurred significantly less in the nicorandil (13.1%) than in the placebo group (15.5%,  $P=0.014$ ). Nevertheless, only about half of patients were on  $\beta$ -blockers and 'unplanned hospital admission for chest pain' is a very weak end-point despite the randomized character of the trial. Inherent of these limitations, nicorandil may be considered as a safe additional drug to  $\beta$ -blockers for angina relief in patients with stable angina pectoris. Weather, it may be an alternative to

$\beta$ -blockers in post myocardial infarction patients remains to be established.

Nicorandil has a long tradition in Japan, where it has been studied extensively. The present issue of the journal publishes two papers from Japan. The first study by Matsuo et al. evaluates again the efficacy of nicorandil in ischaemic preconditioning in the human angioplasty model while the second paper by Izawa et al. investigates the impact of the drug on left ventricular filling pressures in exercising patients with hypertrophic cardiomyopathy.<sup>3,4</sup> A potential benefit of the drug is demonstrated in both trials, characterized by a heavy, 'high-tech' methodology applied to small study cohort. Nevertheless, they merit our consideration as both authors have improved and extended prior research in the field, providing thereby relatively solid data.

Matsuo et al. previously demonstrated by simple ST-segment analysis that nicorandil enhances preconditioning in the human PTCA model.<sup>5</sup> However, the potential contribution of collateral blood flow was not adequately assessed. In the present study, a homogeneous group of 44 patients with isolated proximal LAD stenosis and normal left ventricular function, was randomized to intravenous nicorandil or saline prior to angioplasty.<sup>3</sup> In addition to ST-segment analysis, <sup>99m</sup>Tc tetrofosmin SPECT acquisition was performed at the end of the PCTA as a surrogate for myocardial perfusion to the related myocardium. A trend but no significant flow increase to the ischemic bed was demonstrated together with a significant attenuation of ST-segment elevation in the nicorandil group. This implies that nicorandil seems to possess a cardioprotective effect independent of myocardial

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(collateral) blood flow to the ischaemic bed. The message is clear and easily understood.

The second paper by Izawa et al. studied the effect of nicorandil on left ventricular end-diastolic pressure during exercise in patients with non-obstructive hypertrophic cardiomyopathy.<sup>4</sup> These authors too, added an additional step to previous research. They could previously distinguish a distinct behaviour of left ventricular filling pressures during exercise in these patients depending of the severity of myocardial hypertrophy.<sup>6</sup> A continuous increase in pressure was observed in patients with severe hypertrophy, while those with mild hypertrophy experienced a biphasic pattern with an initial increase following by a decrease prior to peak exercise. Both groups could further be distinguished by more severe Thallium-201 scintigraphy perfusion defects in case of severe hypertrophy. The biphasic pattern in the mild hypertrophy group was abolished by pre-treatment with propranolol, suggesting a  $\beta$ -adrenergic mediated coronary vasodilatation induced by exercise. Vasodilatation may prevent myocardial ischaemia in a vascular bed that has not grown in proportion to the hypertrophy, therefore preventing further rise in filling pressures. Without providing clear anatomic cut-off values to predict these haemodynamic alterations, the authors have now conducted a second trial published in this issue of the journal. A total of 23 patients with non-obstructive hypertrophic cardiomyopathy were randomised to pre-treatment to nicorandil or propranolol prior to any knowledge of the haemodynamic conditions induced by exercise. Again, patients could be categorized according to the evolution of the pressure pattern during exercise: gradual increase (13 patients, group 1) or a biphasic pattern (10 patients, group 2). The current study further confirmed their initial observation that the pressure pattern was related to the extent of myocardial hypertrophy and perfusion defects on myocardial scintigraphy. After completion of the first exercise, the study medication was administered and exercise was repeated to analyse its impact on left ventricular filling pressures. Therefore, four subgroups were available for analysis: group 1 (nicorandil: eight patients, propranolol: five patients) and group 2 (nicorandil: four patients, propranolol: six patients). Obviously, propranolol produced the same effect as during their first study with a disappearance of the biphasic pattern in group 2. This biphasic pattern was maintained in group 2 after administration of nicorandil but more importantly four out of eight patients in group 1 converted from a gradual increase to a biphasic pattern. The authors postulated that this

beneficial effect was related to an augmented left ventricular contractility as a result of improved ischaemia and its impact on the coronary microcirculation.

The results of this complex investigation are intriguing and many questions remain unanswered. How may we predict the haemodynamic pattern in these patients during exercise by non invasive means? One may assume that even if all patients in both studies are pooled, statistics may fail to produce clear anatomic or scintigraphic cut-off values to predict the 'bad' patients. At a second level, not all patients, who experience a gradual increase in left ventricular filling pressures during exercise, benefit from nicorandil administration. Even if a potential mechanism (improvement in contractility and decrease in ischaemia) is postulated, no single clue to this beneficial effect in particular patients is suggested. Significant epicardial coronary disease was not present but the authors do not provide any insight into a potential abnormal resistance at this level to potentially explain the failure of nicorandil in four patients in group 1.<sup>7</sup> Intracoronary pressure measurements may therefore have elucidated one of the confounding factors interacting in these patients.

What will be the clinical relevance of the studies with nicorandil in the present issue of the journal? Both papers indicate that nicorandil may act beneficial at the myocardial cellular level. The first investigation demonstrates a cardioprotective effect during angioplasty independent of collateral flow to the ischaemic bed. Tremendous progress has been achieved in interventional cardiology in recent years and interventions appear 'easier and quicker done with excellent angiographic results and few clinical complications'. There are however no 'hard' clinical data to state this common belief. As operators expand their indications to more complex clinical and angiographic conditions, one may suggest a potential role for this drug in patients with an anticipated high interventional risk. Furthermore, the drug should probably more extensively be investigated during reperfusion strategies for acute myocardial infarction. Finally, in the particular setting of minimal invasive cardiac surgery further research seems indicated. The second paper again is only a 'second' small step. Complex investigation with invasive haemodynamic assessment during exercise in patients with non obstructive cardiomyopathy might allow selection of patients who benefit 'acutely and in the experimental setting' from the drug. At present, we ignore the clinical impact of this therapy and lack non invasive tools to guide us. However, as in many

success stories, we are confident that a 'third' episode will further reveal current uncertainties.

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