



Nicorandil — an Effective Multitarget Drug for Cardioprotection?

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Introduction

Although nicorandil has been in clinical use as a treatment for angina since the 1980s, it remains a fascinating drug with potential actions in cardiac ischaemia. Unusually, it has dual properties as both a nitric oxide (NO) donor and K_{ATP} channel opener, by which it can cause coronary artery vasodilation, as well as cardioprotection against ischaemia and reperfusion (I/R) injury. As such, it may be an attractive “multitarget” drug for cardioprotection [1]. A recently published article in *Cardiovascular Drugs and Therapy* presents evidence that nicorandil may suppress ischaemia-induced ventricular arrhythmias (VA) [2]. In this commentary, we discuss this article in the context of the recent CHANGE clinical trial which saw multiple benefits of nicorandil in the setting of ST-elevation myocardial infarction (STEMI) [3].

Nicorandil and Ventricular Arrhythmia

Kobara et al. have recently demonstrated that nicorandil infusion during STEMI can suppress ischaemia-induced VA in rats with left ventricular hypertrophy [2]. Intermittent VA can lead to sustained ventricular tachycardia, which is a major cause of death and out of hospital cardiac arrest [4]. VA occurs as a consequence of I/R injury, activation of the sympathetic nervous system and damage to His-Purkinje fibres of the myocardial conduction system [2].

In this recent animal study [2], nicorandil infusion, during ischaemia in hypertensive rats (with abdominal aortic

constriction), was associated with reduced incidence of VA, and nor-adrenaline release in left-ventricular perfusate (as determined by micro-dialysis). Nor-adrenaline levels are known to increase during the first 20-min of myocardial infarction and were found to be up to three times greater in the abdominal aortic constriction model of hypertension [2]. The authors speculate that during ischaemia, nicorandil can act on K_{ATP} channels of sympathetic neurones to limit nor-adrenaline release, in addition to attenuating calcium overload in cardiomyocytes [2]. Other pre-clinical studies support the findings that nicorandil can suppress ischaemic VA and associated sympathetic nervous system activation [5].

Despite these findings, nicorandil is yet to become an established STEMI drug. Clinical trials have attempted to ascertain whether the cardioprotective benefits seen in animals can be translated to humans [6–8]. One such clinical study, the CHANGE trial [3], may be further evidence in support of nicorandil as a multi-faceted therapy. It is relevant to consider these findings with respect to both myocardial and microvascular protection.

The CHANGE Trial: an Overview

CHANGE is a multi-centre, prospective, double-blind, randomised control trial (RCT), published in the *Journal of American Heart Association*, September 2022 [3]. A total of $n=238$ STEMI patients (18–80 years) were randomised, to receive either intravenous nicorandil or placebo, prior to reperfusion. Primary outcome measure was infarct size (%IS) as determined by cardiac magnetic resonance (CMR). Primary outcomes were analysed at 5–7 days post STEMI and 6 months. Secondary outcomes included measures of ‘no re-flow’ such as Thrombolysis in Myocardial Infarction (TIMI) flow score, ST-segment resolution and microvascular obstruction (%MVO) on CMR [3]. The study also considered MACCE outcomes including all-cause mortality, re-admission for heart failure and unplanned revascularisation.

Commentary on:

Kobara M, Amano T, Toba H, Nakata T (2022) Nicorandil Suppresses Ischemia-Induced Norepinephrine Release and Ventricular Arrhythmias in Hypertrophic Hearts. *Cardiovasc Drugs Ther* <https://doi.org/10.1007/s10557-022-07369-1>.

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Nicorandil Protects the Myocardium

The traditional aim of cardioprotection is to limit the size of an evolving myocardial infarction (MI). Thus, it is exciting to note that infarct size was reduced at both 5 days and 6 months [3]. This reduction remained when primary outcome measures were adjusted for baseline characteristics such as age, sex and diabetes. Whilst the CHANGE trial demonstrated an improvement in both short- and long-term LV ejection fractions (LVEF) in the nicorandil group, this was not associated with a reduction in re-admission for heart failure [3]. This is likely because this cohort of patients had only modestly reduced LVEFs, without prior MI. During the trial, most patients received beta-blockers, aspirin and ticagrelor as background therapy. It might be suggested that beta-blockers could potentially ‘prime’ the cardioprotective effects of nicorandil, by further suppressing sympathetic drive. Importantly, no significant haemodynamic changes were observed with this combination [3]. The study also highlights that nicorandil provides protection in combination with aspirin. This may be significant, since aspirin can attenuate other cardioprotective pathways such as postconditioning [9], and potentially, it has been suggested, remote ischaemic conditioning [10]. Both aspirin and ticagrelor however remain gold standard in the management of STEMI.

The authors speculate that nicorandil protects the myocardium both directly (by acting on cardiomyocytes) and indirectly via the coronary circulation (acting as an NO donor and mixed venous/arterial vasodilator) (Fig. 1) [11]. Nicorandil protects cardiomyocytes by opening ATP-sensitive K⁺ (K_{ATP}) channels, utilising the so-called Reperfusion Injury Salvage Kinase or “RISK” pathway of cardioprotection and preventing the opening of the mitochondrial permeability transition

pore (MPTP) [12–14]. It can also limit the damage caused by oxidative stress [11] and reduce the activity of inflammatory pathways, e.g. NF-κβ/NLRP3 [15].

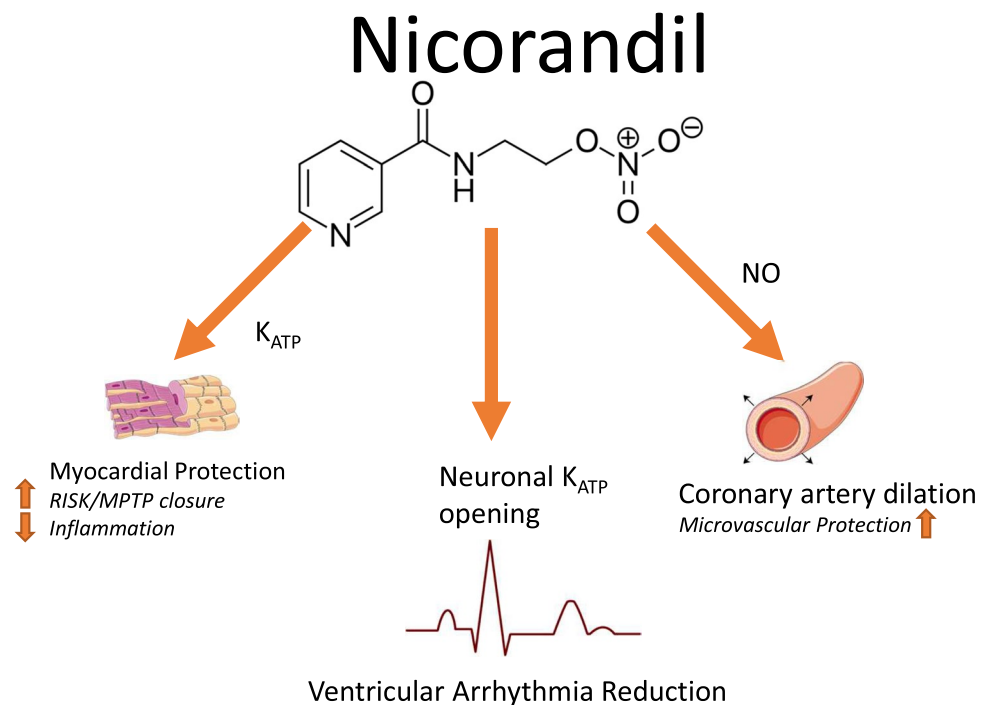
It was demonstrated in the late 1990s, in anaesthetised rabbits undergoing a period of I/R, that nicorandil protects the myocardium via opening K_{ATP} channels [13]. These effects were observed during ischaemia, but not reperfusion [13]. In addition, nicorandil preserved contractility following hypoxia/reoxygenation in isolated human atrial muscle tissue [16]. Interestingly, although ischaemic pre-conditioning reduced nicorandil-mediated protection in human atrial tissue, it did not abolish the protection provided by nicorandil in vivo [13]. Following the results of the IONA trial, (demonstrating that nicorandil improves long-term cardiovascular outcomes in stable angina patients), the drug was established as an anti-anginal and considered less as an acute cardioprotective therapy in STEMI [17, 18].

In terms of therapy for STEMI, there is increasing recognition of the need to address coronary circulation protection and MVO [19], in addition to myocardial protection. Furthermore, the multifactorial nature of I/R likely necessitates a multitargeted approach (Fig. 1) [1].

The Key to Microvascular Obstruction?

Post-STEMI MVO presents a significant prognostic challenge. It is a complex “syndrome” of aetiologies including micro-embolization of debris and clot into the smaller vessels of the coronary circulation, platelet-neutrophil aggregation, vascular smooth muscle cell (VSMC) spasm and capillary rupture [19]. Pericyte constriction may also contribute, alongside external compressive

Fig. 1 Nicorandil is a niacinamide derivative, ATP sensitive K⁺ channel opener and nitric oxide donor. During STEMI, it protects the myocardium, nervous system and coronary circulation. Its vasodilatory actions may confer microvascular protection, by reducing VSMC spasm in resistance vessels. By reducing nor-adrenaline release from sympathetic neurones, nicorandil reduces lethal ventricular arrhythmia. In addition to these novel actions, nicorandil reduces cardiomyocyte death by limiting the opening of the mitochondrial permeability transition pore (MPTP)



forces such as myocardial oedema and haemorrhage [20]. There has been no “one fits all” solution to this dilemma. Moreover, aggressive vasodilatory therapies, e.g. adenosine, mechanical clot retrieval, thrombolysis and anti-inflammatory therapies, have not made a significant improvement [19].

The secondary outcomes of the CHANGE trial demonstrated that patients in the nicorandil arm had significantly improved ST-elevation segment resolution, greater TIMI flow post-procedure and reduced frequency of no-reflow/slow flow [3]. These outcomes are comparable to previously reported effects of nicorandil on the microvasculature and the ‘no-reflow’ phenomenon [21] [7]. Nicorandil significantly reduced the incidence of MVO (32% vs 47%, $p=0.046$) on CMR at 5 days; however, this was not analysed at 6 months.

The ideal MVO drug should target multiple aetiologies [19]. The endothelial-VSMC junction is important at the cellular level [22]. Less attention has been devoted to microvascular spasm, compared to other pathologies, e.g. embolization/endothelial damage, and other factors influencing coronary vasomotion such as the protein kinase, Rho kinase, are of considerable interest [22]. Nicorandil induces VSMC dilation via NO and cGMP [11] and may act predominantly on vessels of diameter < 100 μm [3].

Given the positive results in the CHANGE trial, targeting the VMSC in addition to endothelial and inflammatory factors may be the key to improving outcomes in MVO. This would argue against the opinion that coronary vasodilators may further exacerbate I/R injury [23].

Conclusion

Both recent pre-clinical and clinical studies have demonstrated the cardioprotective effects of nicorandil during ischaemia/reperfusion. The drug has shown promise in attenuating lethal ventricular arrhythmia [2], reducing infarct size and improving post STEMI microvascular obstruction [18]. Its ability to target cardiomyocytes, the coronary circulation and the sympathetic nervous system in tandem is highly beneficial. Larger clinical studies are now required to further support the findings of the CHANGE trial. Nicorandil may be an old drug, but it is arguably capable of new tricks.

Author Contribution The first draft of the manuscript was written by Lucie Pearce, and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

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Declarations

Competing Interests The authors declare no competing interests.

References

- Davidson SM, Ferdinandy P, Andreadou I, et al. Multitarget strategies to reduce myocardial ischemia/reperfusion injury: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73(1):89–99.
- Kobara M, Amano T, Toba H, Nakata T. Nicorandil suppresses ischemia-induced norepinephrine release and ventricular arrhythmias in hypertrophic hearts. *Cardiovasc Drugs Ther*. 2022.
- Qian G, Zhang Y, Dong W, et al. Effects of nicorandil administration on infarct size in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention: the CHANGE trial. *J Am Heart Assoc*. 2022;11(18):e026232.
- Ong MEH, Perkins GD, Cariou A. Out-of-hospital cardiac arrest: prehospital management. *Lancet*. 2018;391(10124):980–8.
- Horinaka S, Kobayashi N, Yabe A, et al. Nicorandil protects against lethal ischemic ventricular arrhythmias and up-regulates endothelial nitric oxide synthase expression and sulfonylurea receptor 2 mRNA in conscious rats with acute myocardial infarction. *Cardiovasc Drugs Ther*. 2004;18(1):13–22.
- Campo G, Pavasini R, Morciano G, et al. Data on administration of cyclosporine, nicorandil, metoprolol on reperfusion related outcomes in ST-segment elevation myocardial infarction treated with percutaneous coronary intervention. *Data Brief*. 2017;14:197–205.
- Ishii H, Ichimiya S, Kanashiro M, et al. Effect of intravenous nicorandil and preexisting angina pectoris on short- and long-term outcomes in patients with a first ST-segment elevation acute myocardial infarction. *Am J Cardiol*. 2007;99(9):1203–7.
- Kitakaze M, Asakura M, Kim J, et al. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. *Lancet*. 2007;370(9597):1483–93.
- Birbaum Y, Ye R, Ye Y. Aspirin blocks the infarct-size limiting effect of ischemic postconditioning in the rat. *Cardiovasc Drugs Ther*. 2021.
- Ye R, Jneid H, Alam M et al. Do we really need aspirin loading for STEMI? *Cardiovasc Drugs Ther*. 2022.
- Tarkin JM, Kaski JC. Vasodilator therapy: nitrates and nicorandil. *Cardiovasc Drugs Ther*. 2016;30(4):367–78.
- Hausenloy DJ, Yellon DM, Mani-Babu S, Duchon MR. Preconditioning protects by inhibiting the mitochondrial permeability transition. *Am J Physiol Heart Circ Physiol*. 2004;287(2):H841–9.
- Imagawa J, Baxter GF, Yellon DM. Myocardial protection afforded by nicorandil and ischaemic preconditioning in a rabbit infarct model in vivo. *J Cardiovasc Pharmacol*. 1998;31(1):74–9.
- Rossello X, Yellon DM. The RISK pathway and beyond. *Basic Res Cardiol*. 2018;113(1):2.
- Chen F, Chen ZQ, Zhong GL, Zhu JJ. Nicorandil inhibits TLR4/MyD88/NF- κ B/NLRP3 signaling pathway to reduce pyroptosis in rats with myocardial infarction. *Exp Biol Med* (Maywood). 2021;246(17):1938–47.
- Carr CS, Yellon DM. Ischaemic preconditioning may abolish the protection afforded by ATP-sensitive potassium channel openers in isolated human atrial muscle. *Basic Res Cardiol*. 1997;92(4):252–60.
- IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet* 359(9314):1269–75.

18. Dana A, Yellon DM. ATP dependent K⁺ channel: a novel therapeutic target in unstable angina. *Eur Heart J*. 1999;20(1):2–5.
19. Heusch G. Coronary microvascular obstruction: the new frontier in cardioprotection. *Basic Res Cardiol*. 2019;114(6):45.
20. Bonfig NL, Soukup CR, Shah AA et al. Increasing myocardial edema is associated with greater microvascular obstruction in ST-segment elevation myocardial infarction. *Am J Physiol Heart Circ Physiol*. 2022;323(4):H818–24.
21. Hongo M, Takenaka H, Uchikawa S, Nakatsuka T, Watanabe N, Sekiguchi M. Coronary microvascular response to intracoronary administration of nicorandil. *Am J Cardiol*. 1995;75(4):246–50.
22. Hubert A, Seitz A, Pereyra VM, Bekeredjian R, Sechtem U, Ong P. Coronary artery spasm: the interplay between endothelial dysfunction and vascular smooth muscle cell hyperreactivity. *Eur Cardiol*. 2020;15:e12.
23. Nazir SA, McCann GP, Greenwood JP, et al. Strategies to attenuate micro-vascular obstruction during P-PCI: the randomized reperfusion facilitated by local adjunctive therapy in ST-elevation myocardial infarction trial. *Eur Heart J*. 2016;37(24):1910–9.

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