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REVIEW ARTICLE

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Hypothesis: The potential therapeutic role of nicorandil in COVID-19

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Abstract

At present, there is yet no specific antiviral treatment or immunization against the newly identified human severe acute respiratory syndrome virus (SARS-CoV2) that results in a rapidly progressive pandemic coronavirus disease 2019 (COVID-19). We believe in a crucial need for a clinical strategy to counteract this viral pandemic based on the known pathogenesis throughout the disease course. Evidence suggests that exaggerated patient's inflammatory response and oxidative stress are likely to aggravate the disease pathology. The resulting endothelial dysfunction further induces fibrosis and coagulopathy. These disturbances can generate severe acute respiratory distress syndrome (ARDS) that can progress into respiratory and circulatory failure. Nicorandil is an anti-anginal vasodilator drug acts by increasing nitric oxide bioavailability and opening of the K_{ATP} channel. Recently, nicorandil has been recognized to possess multiple protective effects against tissue injury. Here, we address a possible modulatory role of nicorandil against COVID-19 pathogenesis. We hypothesise nicorandil would be an effective form of adjuvant therapy against COVID-19.

KEYWORDS

anti-coagulation, anti-fibrosis, anti-inflammatory, anti-oxidative, COVID-19, nicorandil

1 | INTRODUCTION

Soon after the start of the coronavirus disease 2019 (COVID-19) pandemic, it was recognized that its causative severe acute respiratory syndrome virus (SARS-CoV2) virus was somehow less deadly than its pervious fellow, SARS-COV. Yet some features of the new virus qualified it to be a tremendously greater threat to humanity than its older version and those included very high infectivity, transmission from asymptomatic people and great variability of its clinical features.

COVID-19 manifestations range from mild to rapidly progressive severe acute respiratory distress syndrome (ARDS), respiratory and circulatory failure, sepsis, and death.[1] Older age and various forms of comorbidities were found to be associated with poorer outcomes, including fatalities. Reported risk factors included: cardiovascular, chronic kidney disease, and diabetes mellitus. As until 14 of July, 13 266 181 cases have been reported worldwide in about 4.34% mortality rate.[2]

The angiotensin-converting enzyme 2 (ACE2), is a cell surface enzyme present in almost all organs. ACE2 is widely expressed in the lower respiratory tract cells besides its cardiac, renal, and intestinal expression.[3] ACE2 is believed to be the SARS-CoV2 receptor. It facilitates cellular invasion, replication, and viral pathogenicity.[4] This could explain its ability to affect various organs, especially the gastrointestinal tract, the heart and the kidneys.

A precise antiviral or a specific immunization has not been identified yet, raising a need for adjuvant pharmacologic therapy. We believe that targeted therapies based on the known COVID-19 pathogenesis should be considered.

Nicorandil (N-[2-hydroxyethyl]-nicotinamide nitrate) is a therapeutic agent used clinically for the treatment of angina. Nicorandil is believed to act by increasing nitric oxide availability and by opening ATP-sensitive K channels (K^+_{ATP}).[5] Several studies have also shown the involvement of nicorandil in inflammatory process and oxidative stress regulation.

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In this context, we hypothesise a potential benefit of nicorandil administration as an adjuvant drug therapy in COVID-19 management, based on the currently addressed pathogenesis.

2 | INFLAMMATION, OXIDATIVE STRESS-INDUCED PULMONARY CELL DEATH AND DYSFUNCTION IN COVID-19 AND ITS POSSIBLE MODULATION BY NICORANDIL

Following SARS-CoV2 lung invasion, the primed dendritic cells and epithelial cells initiate vast amounts of pro-inflammatory cytokines, including interleukins (IL-1β, IL-2, IL-6, IL-8), tumour necrosis factor (TNF), and C motif chemokines (CCL) 2, 3, and 5. This augmented inflammatory response would promote cellular injury and apoptosis.[6] Such inflammatory response is promoted by the expression of adhesion molecules.[7]

The intense inflammatory response may activate a 'cytokine storm' and hence, marked cell death.[8,9] The inflammatory mediators released from dying cells would further promote inflammation and pulmonary cellular injury,[10] initiating a vicious circle of intensified inflammatory and immune responses that may end in critical outcomes.

The extent of pulmonary inflammation in COVID-19 ranges from patchy inflammatory cellular infiltration to bilateral diffuse infiltrates and pneumocytes desquamation with hyaline membrane degeneration.[11]

In a study by Solaimanzade, COVID-19 radiologic findings of pulmonary ground-glass opacification and patchy infiltrates characterized up to 86% of patients. The impaired oxygenation initiates hypoxia and tachypnea.[12] In ARDS patients, hypoxemia and mechanical ventilation with high oxygen pressure generate extensive reactive oxygen and nitrogen species.[13] The liberated oxidants target and destruct cellular proteins, lipids, carbohydrates, and DNA and exacerbate tissue inflammation and injury.[14]

Combating acute lung injury by nicorandil may be possible via multiple mechanisms. In fact, the anti-inflammatory and anti-oxidative properties of nicorandil have been previously shown in several studies. Nicorandil has an ability to attenuate lipopolysaccharide-induced human pulmonary artery endothelial cells (HPAEs) injury. It can also abort the inflammatory process by suppressing monocyte-endothelial adhesion, the key step in the inflammation pathogenesis. In a study by He et al, nicorandil abolished HPAECs nuclear factor (NF-κB) and mitogen-activated protein kinase (MAPK) and hence, aborted inflammatory cytokine formation and suppressed apoptosis.[15] Nicorandil protected the HPAECs against hypoxia-induced injury. It restored the diminished HPAEs endothelial nitric oxide synthase (eNOS) production and the activation of mitoK$_{ATP}$ channels.[16]

Nicorandil exhibits anti-free-radical characteristics since it could scavenge hydroxyl radicals through its nicotinamide moiety. Nicorandil efficiently inhibits superoxide anion production by the activated neutrophils.[17] In addition, nicorandil can correct the lipoperoxidation and free radical injury induced by diabetes mellitus in rat kidneys, cardiac muscle and liver tissues.[18]

In a rat model of silica-induced lung injury, nicorandil effectively downregulated the elevated inflammatory markers NF-κB, TNF-α, and MPO in the lung tissues. Moreover, nicorandil restored the oxidant/antioxidant balance through inhibiting iNOS and up regulated GSH, SOD, Nrf-2 and HO-1.[19]

Pre-treatment with nicorandil (100 μg/kg/h) protected non-ventilated lung collapse and re-expansion in one-lung ventilation rabbit model.[20] Nicorandil's effect was mediated through the notable oxidation/inflammation suppression. The expression levels of MDA, TNF-α, and the NF-κB were significantly reduced. Meanwhile, phosphatidylinositol-3-kinase (PI3K), hypoxia-inducible factor (HIF-1α), and SOD were upregulated in the injured lungs treated with nicorandil. The immunomodulatory effect of nicorandil and lung tissue protection against apoptosis was reflected on improved arterial oxygen saturation and oxygen partial pressure.

Recently, Abe and co-workers documented an effective rat lung protection from ischaemic injury when preconditioned with nicorandil. The drug decreased the extent of pulmonary microvascular permeability at 60 mins following reperfusion. Nicorandil's effect on the permeability was evidenced by a prominent reduction in the filtration coefficient and the wet-to-dry lung weight ratio.[21]

A bronchodilator effect of nicorandil has also been shown when a dose of 6 mg/h infused intravenously prevented thiamylal-fentanyl-induced bronchoconstriction in humans.[22] The airway smooth muscle relaxing action of nicorandil presumably was established through NO donation[23,24] and the K^+_{ATP} opening activity.[25]

3 | FIBROSIS INDUCED BY SARS-CoV2 AND THE ANTI-FIBROTIC POTENTIAL OF NICORANDIL

About one-third of the Middle East Respiratory Syndrome-related coronavirus (MERS-CoV) and the old SARS-COV cases have been associated with radiological findings of lung fibrosis.[26,27] Likewise, SARS-CoV2 infection has a high tendency for pulmonary parenchymal and interstitial fibrosis[28,29] especially encountered in the advanced-phases.[30] The risk of such changes is higher in the older age group owing to an observed more intense lung pathology in the acute phase of the disease in this group of patients.[10]

The prevention of pulmonary fibrosis in patients infected with SARS-CoV2 is an issue that urgently needs to be addressed.

Experimentally, nicorandil has been shown to produce improvement in a number of lung fibrosis models. Nicorandil improved the lung tissue histological picture of a rat model of cyclophosphamide-induced lung fibrosis,[31] silica-induced lung inflammation and fibrosis,[19] and bleomycin-induced lung fibrosis[32] and in more recently published study of Kseibati and co-workers.[33] The fibrosis-ameliorating effect of nicorandil was attributed to its ability to relieve pulmonary oxidative stress. Its beneficial actions were signalled by a reduction in the inflammatory markers present in the

bronchoalveolar lavage fluid and a decrease in the profibrotic marker, transforming growth factor-β (TGF-β) and the indicator of pulmonary collagen deposition (hydroxyproline content). These studies support the nicorandilanti-fibrotic potential.

The antifibrotic potential of nicorandil was further documented in acute myocardial infarction patients subjected to coronary angioplasty. Acute intravenous nicorandil followed by 6 months of treatment decreased the patient's plasma level of procollagen type III amino-terminal peptide (PIIINP) and ameliorated left ventricular remodelling and improved function.[34]

4 | COAGULATION DISORDERS ACCOMPANYING COVID-19 AND POSSIBLE MODULATION BY NICORANDIL

Coagulopathy is becoming an increasingly recognized feature of cases severe COVID-19. Disseminated intravascular coagulation (DIC) was identified in the majority of post-mortem specimens of COVID-19 patients.[35] The alveolar capillaries of COVID-19 acute lung injury cases developed fibrin-rich thrombi holding extensive platelets and neutrophils infiltration.[36]

Hypoxia in severe COVID-19 was found to initiate thrombus formation through systemic vasoconstriction, endothelial injury, and the consequent poor tissue perfusion. Hypoxia-inducible transcription factor is the proposed mediator for this coagulation-dependent pathway.[37]

Sepsis-induced coagulopathy is a newly described category for the earlier phases of sepsis-associated DIC.[38] Early application of anticoagulant therapy in severe COVID-19 was suggested for Chinese patents aiming at improving the patient's outcome. In fact, 21.6% of severe COVID-19 patients in the study by Tang et al, presented by sepsis-induced coagulopathy; those patients got benefit from low molecular weight heparin administration.[39]

SARS-CoV2 infection induces not only pulmonary vascular endothelial injury[40] but it also targets vascular endothelial cells all over the body and markedly affects patients with cardio metabolic comorbidities as well as hypertensive patients as SARS-CoV2 has been shown to inhibits eNOS activity and decreases NO bioavailability.[41]

The intact vascular endothelium resists spontaneous platelets activation and consequently aborts the coagulation cascade, and so can prevent pathologic thrombus formation. Physiologically produced NO protects the endothelium and prevents tissue factor secretion upon activation by several pro-inflammatory cytokines.[40] In addition, NO inhibits platelets activation and limits endothelial-leukocyte adhesion.[42]

Thus, treatment with nitric oxide or nitric oxide liberators represents an attractive anti-COVID-19 measure.[42] NO was shown to suppress SARS-CoV replication through dual mechanisms. NO can attenuate the viral receptor (ACE2) interaction through inducing morphological changes in the viral spike (S) protein and may inhibit viral replication through diminishing viral RNA production.[43]

In the absence of specific and effective therapy for COVID-19, and based on the proposed important modulatory role of NO on the interstitial lung thrombo-inflammation, NO inhalation has been suggested by some authors to be an alternative or adjuvant therapy.[44] In fact the American Food and Drug Administration (FDA) has recently granted the safety of NO-releasing drugs as a supportive therapy in COVID-19 treatment.[45]

Nicorandil is a known NO-donner and its beneficial role in the context of thrombosis has been documented. In a study in 2015, nicorandil was shown to protect the human coronary artery endothelial cell injury and it could prevent sirolimus-induced thrombus formation by virtue of its antioxidant property.[46] In another study, nicorandil protected pulmonary vasculature from the monocrotaline-induced endothelial injury and further thromboembolic formation.[47]

Some clinical studies have investigated the effect of nicorandil on platelet function in patients with unstable angina. Peng et al documented diminished serum inflammatory factors and matrix metalloproteinase-9 in the nicorandil-treated patients accompanied by elevated anti-oxidation factors. Platelet function was assessed by measuring the expression level of platelet membrane glycoproteins GP-VI, CD42b, PAC-1, and CD63. These glycoproteins were found to be significantly reduced in the nicorandil-treated group compared to controls.[48]

Another study carried out by Lu and co-workers indicated that adjuvant nicorandil therapy in patients with unstable angina alleviated the inflammation-mediated thrombus formation. Nicorandil prevented the peripheral blood platelet activation as indicated by reduced CD63, CD42b, PAC-1 and GP-VI fluorescence intensity.[49]

5 | CARDIOVASCULAR MANIFESTATION IN COVID-19 AND THE SUSPECTED ROLE OF NICORANDIL

It is of great importance to highlight the acute myocardial injury manifestations in COVID-19. The involvement of myocardial injury may be linked to the cardiac ACE2 expression.[50] In addition to the inflammatory storm caused by SARS-CoV2 infection, respiratory dysfunction and the consequent hypoxaemia may be other precipitating factors for the COVID-19 induced cardiac injury. Interestingly, myopericarditis was documented in a case report of COVID-19 infected female patients. The myocardial dysfunction was described without evidence of obstructive coronary disease, and even without interstitial pneumonia manifestations.[51] Moreover, acute cardiac injury was reported in the severe cases admitted to the ICU. Myocardial injury was confirmed by the elevation of high-sensitivity troponin I (hs-cTnI) biomarker, particularly in patients having higher plasma inflammatory cytokines and higher blood pressure measurements as compared to the non-ICU patients.[52]

The anti-inflammatory antioxidant property of nicorandil protected the coronary endothelial cell injury in patients undergoing percutaneous coronary intervention[53] and reduced the incidence

of death following acute myocardial infarction.[54] In a direct cardiac tissue effect, nicorandil protected the heart against doxorubicin-induced cardiotoxicity. Nicorandil fixed the doxorubicin-impaired NO bioavailability and NF-kB activation and the resulted apoptosis and consequently improved cardiac functions and the myocardial histological picture.[55] In another study, nicorandil counteracted cardiac fibrous tissue formation through inhibiting cultured rat cardiac fibroblasts proliferation.[56]

In patients undergoing percutaneous coronary intervention, intravenous nicorandil administration just before reperfusion significantly improved the epicardial flow and tissue perfusion that was reflected on the ST-segment resolution.[57]

The vasodilatory effect of nicorandil refers to its nitrate-like characteristics as well as the K^{+}_{ATP} channel opening activity, resulting in vascular smooth muscle cells relaxation and consequently both venous and arterial blood vessels vasodilation.[58]

Intravenous bolus administration of nicorandil in congestive heart failure patients significantly reduced the pulmonary capillary wedge pressure accompanied by an increased cardiac index. This was accompanied by a decrease in arterial blood pressure only with doses of nicorandil exceeding 398 μg/kg.[59] Similar cardioprotective effects were shown by using nicorandil 200 μg/kg loading dose.[60]

Minami et al supported the acute haemodynamic safety of the intravenous administration of nicorandil 200 μg/kg in acute heart failure patients following excluding patients with SBP <90 mm Hg.[61]

In acute heart failure (AHF) admitted to the ICU, 100 μg/kg nicorandil bolus injection followed by 5 days 60–100 μg/kg/h, significantly diminished the myocardial stress markers and gave better echocardiographic findings and that was reflected on the patients' clinical picture. Furthermore, nicorandil improved the haemodynamics in the patients that expressed high baseline systolic arterial blood pressure (SBP)(>140 mm Hg), and in cases with low SBP (<140 mm Hg) the drug was shown to be safe without producing marked hypotension.[62] Nicorandil also improved patients' haemodynamics regardless of their baseline systolic arterial blood pressure.[62]

These clinical studies demonstrate that nicorandil is a safe and effective medication for the treatment of acute heart failure emergencies.

A more recent study by Mehra et al looks into the relationship between cardiovascular disease, drug therapy, and mortality in COVID-19 hospitalised patients. Mehra and co-workers found that the increased risk of mortality was associated with older age groups (>65 years), coronary artery disease, heart failure, cardiac arrhythmias, chronic obstructive pulmonary disease, and current smokers. No increased risk of in-hospital death was found to be associated with the use of vasodilator drugs like angiotensin-converting enzyme inhibitors or the use of angiotensin receptor blockers.[63] Denoting vasodilator safety in COVID-19 treatment.

Furthermore, the European Society of Cardiology guidelines indicate the efficacy of intravenous vasodilators at an early stage for AHF patients without excessively low blood pressure (SBP > 90 mm Hg).[64]

6 | KIDNEYS AS SARS-CoV2 TARGET AND THE NICORANDIL POSSIBLE CONTROL

Since ACE2 is recognized as a functioning SARS-CoV2 receptor, and since it has marked adrenal tissue expression, direct renal affection can be expected. The electron microscopic examination of the human post-mortem renal tissues revealed clusters of coronavirus particles, with detectable spike proteins in the tubular epithelium and in podocytes. Light microscopic picture denoted diffuse proximal tubular injury in the form of indistinct luminal brush border, and even frank necrosis.[65]

Also, other factors may mediate acute kidney injury during the course of COVID-19 infection; those include systemic hypoxia, coagulopathy, and possible drug nephrotoxicity. The renal protective effect of nicorandil was previously reported. Nicorandil administration significantly restored mitochondrial enzymes and oxidative phosphorylation efficacy mediated through enhanced mitoK_{ATP} channel function.[66]

Nicorandil treatment of cultured podocytes could increase the antioxidant mitochondrial manganese superoxide dismutase content and suppress macrophages xanthine oxidase expression.[67] Nicorandil supported renal functions in salt-sensitive hypertensive rats. Significant glomerular upregulation of endothelial nitric oxide synthase (eNOS) expression was verified.[68]

The nephro protective effects of nicorandil have been assessed in several clinical studies. The acute renal haemodynamic effects of nicorandil were compared to those of nitroglycerin in patients with stable coronary artery disease and normal renal functions. The coloured Doppler ultrasound revealed increased renal artery peak-systolic, end-diastolic, and mean blood flow velocities in the nicorandil-treated group compared to the pre-treatment values and compared to those of the nitroglycerin-treated group.[69]

A retrospective chart review on patients with coronary vascular disorders receiving haemodialysis for end-stage renal disease suggested a valuable role of the nicorandil treatment in improving patient clinical outcomes and increased the patient's survival.[70]

In this review, we have tried to shed light on the possible benefits of nicorandil therapy in the COVID-19 management. Nicorandil possesses multiple potential modulatory properties on the currently known pathogenesis of the disease.

7 | CONCLUSION

Based on the reported pathophysiological modulatory effects in similar models of organ injury discussed in this review, we recommend clinical trial conduction to evaluate the safety and efficacy of nicorandil in patients with COVID-19.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

PEER REVIEW

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REFERENCES

1. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intens Care Med* [Internet]. 2020;46(5):854-887. Available from http://link.springer.com/10.1007/s00134-020-06022-5
2. Huang C, Wang Y, Li X, Ren L, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020;395(10223):497–506. http://dx.doi.org/10.1016/s0140-6736(20)30183-5
3. Organization WH.COVID-19 CORONAVIRUS PANDEMIC [Internet]. Vol. 3, The Journal of Health Technology Assessment. 2020. Available from: https://www.worldometers.info/coronavirus/
4. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol [Internet]*. 2004;203(2):631-637. Available from: http://doi.wiley.com/10.1002/path.1570
5. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intens Care Med* [Internet]. 2020;46(4):586-590. Available from http://link.springer.com/10.1007/s00134-020-05985-9
6. Taira N. Nicorandil as a hybrid between nitrates and potassium channel activators. *Am J Cardiol* [Internet]. 1989;63(21):J18-24. Available from https://linkinghub.elsevier.com/retrieve/pii/0002914989902002
7. Cheung CY, Poon LLM, Ng IHY, et al. Cytokine responses in severe acute respiratory syndrome Coronavirus-infected macrophages in vitro: possible relevance to pathogenesis. *J Virol*. 2005;79(12):7819-7826.
8. Liu Y, Ma S, Wang X, et al. The role of β2 integrin associated heparin-binding protein release in ARDS. *Life Sci* [Internet]. 2018;203:92-98. Available from https://linkinghub.elsevier.com/retrieve/pii/S0024320518302108
9. Veerdonk FL, Netea MG, Deuren M, Meer JWM, Mast Q, Brüggemann RJ, et al. Kinins and cytokines in COVID-19: a comprehensive pathophysiological approach. 2020. https://doi.org/10.20944/preprints202004.0023.v1
10. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* [Internet]. 2020;109:102433. Available from https://linkinghub.elsevier.com/retrieve/pii/S0896841120300469
11. Luo W, Yu H, Jizhou Gou XL, Sun Y, Li J, Liu L.Clinical Pathology of Critical Patient with Novel Coronavirus Pneumonia (COVID-19) : First Case of the Whole Lung Biopsy. 2020. p. Preprint.
12. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* [Internet]. 2020;8(4):420-422. Available from https://linkinghub.elsevier.com/retrieve/pii/S221326002030076X
13. Solaimanzadeh I. Acetazolamide, Nifedipine and Phosphodiesterase Inhibitors: Rationale for Their Utilization as Adjunctive Countermeasures in the Treatment of Coronavirus Disease 2019 (COVID-19). *Cureus* [Internet]. 2020;12(3):e7343. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7096066/
14. Zhang H, Downey GP, Suter PM, Slutsky AS, Ranieri VM. Conventional mechanical ventilation is associated with bronchoalveolar lavage-induced activation of polymorphonuclear leukocytes. *Anesthesiology* [Internet]. 2002;97(6):1426-1433. Available from http://journals.lww.com/00000542-200212000-00014
15. Sarma JV, Ward PA. Oxidants and Redox Signaling in Acute Lung Injury. In: Terjung R, eds. *Comprehensive Physiology*, Vol. 3. Hoboken, NJ: John Wiley & Sons, Inc.; 2011:1365-1381. Available from: https://doi.org/10.1002/cphy.c100068
16. He M, Shi W, Yu M, et al. Nicorandil Attenuates LPS-induced acute lung injury by pulmonary endothelial cell protection via NF- κ B and MAPK pathways. *Oxid Med Cell Longev* [Internet]. 2019;10(2019):1-13. Available from https://www.hindawi.com/journals/omcl/2019/4957646/
17. Wang H, Zuo X, Wang Q, et al. Nicorandil inhibits hypoxia-induced apoptosis in human pulmonary artery endothelial cells through activation of mitoKATP and regulation of eNOS and the NF-κB pathway. *Int J Mol Med [Internet]*. 2013;32(1):187-194. Available from https://www.spandidos-publications.com/10.3892/ijmm.2013.1379
18. Pieper GM, Gross GJ. Anti-free-radical and neutrophil-modulating properties of the nitrovasodilator, nicorandil. *Cardiovasc Drugs Ther [Internet]*. 1992;6(3):225-232. Available from http://link.springer.com/10.1007/BF00051143
19. Mano T, Shinohara R, Nagasaka A, et al. Scavenging effect of nicorandil on free radicals and lipid peroxide in streptozotocin-induced diabetic rats. *Metabolism* [Internet]. 2000;49(4):427-431. Available from https://linkinghub.elsevier.com/retrieve/pii/S0026049500800037
20. El-Kashef DH. Nicorandil ameliorates pulmonary inflammation and fibrosis in a rat model of silicosis. *Int Immunopharmacol* [Internet]. 2018;64:289-297. Available from https://linkinghub.elsevier.com/retrieve/pii/S1567576918306489
21. Wang C, Ke H, Xu X, Chen J, Sun D, Ji F. Protective effect of nicorandil on collapse-induced lung injury in rabbits by inhibiting apoptosis. *Int J Mol Med* [Internet]. 2019;6(44):725-736. Available from http://www.spandidos-publications.com/10.3892/ijmm.2019.4236
22. Abe K, Horiguchi T, Enzan K, Masaki Y, Nishikawa T, Kimura T. Nicorandil, a KATP Channel Opener, Attenuates Ischemia-Reperfusion Injury in Isolated Rat Lungs. *Lung* [Internet]. 2020;198(2):315-321. Available from http://link.springer.com/10.1007/s00408-020-00339-0
23. Wajima Z, Yoshikawa T, Ogura A, et al. Intravenous nicorandil prevents thiamylal-fentanyl–induced bronchoconstriction in humans*. *Crit Care Med* [Internet]. 2003;31(2):485-490. Available from http://journals.lww.com/00003246-200302000-00022
24. Scatena R, Bottoni P, Martorana GE, Giardina B. Nitric oxide donor drugs: an update on pathophysiology and therapeutic potential. *Expert Opin Investig Drugs* [Internet]. 2005;14(7):835-846. Available from http://www.tandfonline.com/doi/full/10.1517/13543784.14.7.835
25. Knox AJ, Tattersfield AE. Airway smooth muscle relaxation. *Thorax* [Internet]. 1995;50(8):894-901. Available from http://thorax.bmj.com/cgi/doi/10.1136/thx.50.8.894
26. Pelaia G, Gallelli L, Vatrella A, et al. Potential role of potassium channel openers in the treatment of asthma and chronic obstructive pulmonary disease. *Life Sci* [Internet]. 2002;70(9):977-990. Available from https://linkinghub.elsevier.com/retrieve/pii/S0024320501014874
27. Das K, Lee E, Singh R, et al. Follow-up chest radiographic findings in patients with MERS-CoV after recovery. *Indian J Radiol Imaging* [Internet]. 2017;27(3):342. Available from: http://www.ijri.org/text.asp?2017/27/3/342/215587
28. Ketai L, Paul NS, Wong KT. Radiology of Severe Acute Respiratory Syndrome (SARS). *J Thorac Imaging* [Internet]. 2006;21(4):276-283. Available from http://journals.lww.com/00005382-200611000-00005
29. Hosseiny M, Kooraki S, Gholamrezanezhad A, Reddy S, Myers L. Radiology perspective of Coronavirus disease 2019 (COVID-19):

lessons from severe acute respiratory syndrome and middle east respiratory syndrome. *Am J Roentgenol* [Internet]. 2020;28:1-5. Available from https://www.ajronline.org/doi/10.2214/AJR.20.22969
30. Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. *Eur Radiol* [Internet]. 2020; Available from: http://link.springer.com/10.1007/s00330-020-06801-0
31. Zhou S, Wang Y, Zhu T, Xia L. CT Features of Coronavirus disease 2019 (COVID-19) pneumonia in 62 patients in Wuhan, China. *Am J Roentgenol* [Internet]. 2020;5:1-8. Available from https://www.ajronline.org/doi/10.2214/AJR.20.22975
32. Ahmed LA, EL-Maraghy SA, Rizk SM. Role of the KATP channel in the protective effect of nicorandil on cyclophosphamide-induced lung and testicular toxicity in rats. *Sci Rep* [Internet]. 2015;5(1):14043. Available from: http://www.nature.com/articles/srep14043
33. Patel S, Patel N, Patel V. Anti-fibrotic potential of nicorandil in the treatment of bleomycin induced pulmonary fibrosis. *J Young Pharm [Internet]*. 2017;9(3):376-380. Available from http://www.jyoungpharm.org/article/1022
34. Kseibati MO, Shehatou GSG, Sharawy MH, Eladl AE, Salem HA. Nicorandil ameliorates bleomycin-induced pulmonary fibrosis in rats through modulating eNOS, iNOS, TXNIP and HIF-1α levels. *Life Sci [Internet]*. 2020;246:117423. Available from https://linkinghub.elsevier.com/retrieve/pii/S0024320520301703
35. Kasama S, Toyama T, Sumino H, et al. Long-term nicorandil therapy improves cardiac sympathetic nerve activity after reperfusion therapy in patients with first acute myocardial infarction. *J Nucl Med* [Internet]. 2007;48(10):1676-1682. Available from http://jnm.snmjournals.org/cgi/doi/10.2967/jnumed.107.043075
36. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* [Internet]. 2020;18(4):844-847. Available from https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.14768
37. Mitchell WB. Thromboinflammation in COVID-19 acute lung injury. *Paediatric Respiratory Reviews*. 2020. http://dx.doi.org/10.1016/j.prrv.2020.06.004
38. Gupta N, Zhao Y-Y, Evans CE. The stimulation of thrombosis by hypoxia. *Thromb Res* [Internet]. 2019;181:77-83. Available from https://linkinghub.elsevier.com/retrieve/pii/S0049384819302956
39. Iba T, Levy JH, Warkentin TE, Thachil J, Poll T, Levi M. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. *J Thromb Haemost* [Internet]. 2019;17(11):1989-1994. Available from https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.14578
40. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* [Internet]. 2020. https://doi.org/10.1111/jth.14817
41. DiNicolantonio JJ, McCarty M. Thrombotic complications of COVID-19 may reflect an upregulation of endothelial tissue factor expression that is contingent on activation of endosomal NADPH oxidase. *Open Hear* [Internet]. 2020;7(1):e001337. Available from: http://openheart.bmj.com/lookup/doi/10.1136/openhrt-2020-001337.
42. Green SJ. Covid-19 accelerates endothelial dysfunction and nitric oxide deficiency. *Microbes Infect* [Internet]. 2020;22(4–5):149-150. Available from https://linkinghub.elsevier.com/retrieve/pii/S1286457920300848.
43. Isidori AM, Giannetta E, Pofi R, et al. Targeting the NO-cGMP-PDE5 pathway in COVID-19 infection. The DEDALO project. *Andrology* [Internet]. 2020;andr.12837. Available from: https://doi.org/10.1111/andr.12837
44. Åkerström S, Gunalan V, Keng CT, Tan Y-J, Mirazimi A. Dual effect of nitric oxide on SARS-CoV replication: Viral RNA production and palmitoylation of the S protein are affected. *Virology* [Internet]. 2009;395(1):1-9. Available from https://linkinghub.elsevier.com/retrieve/pii/S0042682209005558.
45. Martel J, Ko Y-F, Young JD, Ojcius DM. Could nasal nitric oxide help to mitigate the severity of COVID-19? *Microbes Infect* [Internet]. 2020;22(4–5):168-171. Available from https://linkinghub.elsevier.com/retrieve/pii/S1286457920300800.
46. Dharavath RN, Dutt M, Kumar S, Badyal P, Rawat N, Kaur T, et al.Repurposing of FDA approved drugs as COVID-19 therapeutics: Safety concerns and contraindications of drugs in clinical trials [Internet]. 2020. p. preprint. Available from: https://www.preprints.org/manuscript/202006.0232/v1. https://doi.org/10.20944/preprints202006.0232.v1
47. Aizawa K, Takahari Y, Higashijima N, et al. Nicorandil prevents sirolimus-induced production of reactive oxygen species, endothelial dysfunction, and thrombus formation. *J Pharmacol Sci* [Internet]. 2015;127(3):284-291. Available from https://linkinghub.elsevier.com/retrieve/pii/S1347861315000341
48. Sahara M, Sata M, Morita T, Hirata Y, Nagai R. Nicorandil Attenuates Monocrotaline-Induced Vascular Endothelial Damage and Pulmonary Arterial Hypertension. Gaetano C, editor. *PLoS One* [Internet]. 2012;7(3):e33367. Available from: https://doi.org/10.1371/journal.pone.0033367
49. Peng R, Yang X, Liang X. Nicorandil effects on platelet function, Hs-CRP, MMP-9 and myocardial antioxidation in patients with unstable angina. *Exp Ther Med* [Internet]. 2019;8(4):3095–3099. http://www.spandidos-publications.com/10.3892/etm.2019.7918
50. Lu L, Gao F, Liu Z-C, Jing X-W. Effect of adjuvant nicorandil therapy on inflammation, plaque stability and platelet function in patients with unstable angina. *J Hainan Med Univ*. 2017;23(2):92-96.
51. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* [Internet]. 2020;17(5):259-260. Available from: http://www.nature.com/articles/s41569-020-0360-5
52. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with Coronavirus disease 2019 (COVID-19). *JAMA Cardiol* [Internet]. 2020;5(7):819. Available from: https://jamanetwork.com/journals/jamacardiology/fullarticle/2763843
53. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* [Internet]. 2020;395(10223):497-506. Available from https://linkinghub.elsevier.com/retrieve/pii/S0140673620301835
54. Xu X, Liu X, Yu L, Ma J, Yu S, Ni M. Impact of intracoronary nicorandil before stent deployment in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Exp Ther Med* [Internet]. 2019;19(1):137–146. http://www.spandidos-publications.com/10.3892/etm.2019.8219
55. Sakata Y, Nakatani D, Shimizu M, et al. Oral treatment with nicorandil at discharge is associated with reduced mortality after acute myocardial infarction. *J Cardiol* [Internet]. 2012;59(1):14-21. Available from: https://doi.org/10.1016/j.jjcc.2011.08.001
56. Abdel-Raheem IT, Taye A, Abouzied MM. Cardioprotective effects of nicorandil, a mitochondrial potassium channel opener against doxorubicin-induced cardiotoxicity in rats. *Basic Clin Pharmacol Toxicol* [Internet]. 2013;113(3):158-166. Available from https://doi.org/10.1111/bcpt.12078
57. Liou J-Y, Hong H-J, Sung L-C, et al. Nicorandil inhibits angiotensin-II-induced proliferation of cultured rat cardiac fibroblasts. *Pharmacology* [Internet]. 2011;87(3–4):144-151. Available from http://www.ncbi.nlm.nih.gov/pubmed/21346392
58. Ishii H, Ichimiya S, Kanashiro M, Amano T, Matsubara T, Murohara T. Effects of intravenous nicorandil before reperfusion for acute myocardial infarction in patients with stress hyperglycemia. *Diabetes*

Care [Internet]. 2006;29(2):202-206. Available from http://care.diabetesjournals.org/cgi/doi/10.2337/diacare.29.02.06.dc05-1588
59. Coltart DJ, Signy M. Acute hemodynamic effects of single-dose nicorandil in coronary artery disease. *Am J Cardiol* [Internet]. 1989;63(21):J34-J39. Available from https://linkinghub.elsevier.com/retrieve/pii/0002914989902026
60. Giles TD, Pina IL, Quiroz AC, et al. Hemodynamic and neurohumoral responses to intravenous nicorandil in congestive heart failure in humans. *J Cardiovasc Pharmacol* [Internet]. 1992;20(4):572-578. Available from http://journals.lww.com/00005344-199210000-00010
61. Tanaka K, Kato K, Takano T, et al. Acute effects of intravenous nicorandil on hemodynamics in patients hospitalized with acute decompensated heart failure. *J Cardiol* [Internet]. 2010;56(3):291-299. Available from https://linkinghub.elsevier.com/retrieve/pii/S091450871000136X
62. Minami Y, Nagashima M, Kajimoto K, Shiga T, Hagiwara N. Acute efficacy and safety of intravenous administration of nicorandil in patients with acute heart failure syndromes: usefulness of noninvasive echocardiographic hemodynamic evaluation. *J Cardiovasc Pharmacol* [Internet]. 2009;54(4):335-340. Available from http://journals.lww.com/00005344-200910000-00009
63. Shirakabe A, Hata N, Yokoyama S, et al. Efficacy and safety of nicorandil therapy in patients with acute heart failure. *J Cardiol* [Internet]. 2010;56(3):339-347. Available from https://linkinghub.elsevier.com/retrieve/pii/S0914508710001425
64. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. *N Engl J Med* [Internet]. 2020;382(25):e102. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2007621
65. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* [Internet]. 2016;37(27):2129-2200. Available from https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehw128
66. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* [Internet]. 2020;98(1):219-227. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253820303690
67. Shiraishi T, Tamura Y, Taniguchi K, et al. Combination of ACE inhibitor with nicorandil provides further protection in chronic kidney disease. *Am J Physiol Physiol* [Internet]. 2014;307(12):F1313-F1322. Available from https://www.physiology.org/doi/10.1152/ajprenal.00521.2014
68. Tamura Y, Tanabe K, Kitagawa W, et al. Nicorandil, a K atp channel opener, alleviates chronic renal injury by targeting podocytes and macrophages. *Am J Physiol Physiol* [Internet]. 2012;303(3):F339-F349. Available from https://www.physiology.org/doi/10.1152/ajprenal.00158.2012
69. Tashiro Y, Yogo K, Serizawa K, Endo K. Nicorandil suppresses urinary protein excretion and activates eNOS in Dahl salt-sensitive hypertensive rats. *Clin Exp Nephrol* [Internet]. 2015;19(3):343-349. Available from http://link.springer.com/10.1007/s10157-014-0998-6
70. Shimamoto Y, Kubo T, Tanabe K, et al. Effects of intravenous bolus injection of nicorandil on renal artery flow velocity assessed by color Doppler ultrasound. *J Cardiol* [Internet]. 2017;69(1):364-368. Available from https://linkinghub.elsevier.com/retrieve/pii/S0914508716301903
71. Ishii H, Toriyama T, Aoyama T, et al. Efficacy of oral nicorandil in patients with end-stage renal disease: A retrospective chart review after coronary angioplasty in japanese patients receiving hemodialysis. *Clin Ther* [Internet]. 2007;29(1):110-122. Available from https://linkinghub.elsevier.com/retrieve/pii/S0149291806003237

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