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Nicorandil ameliorates cardiac microcirculation in hypertensive myocardial infarction via LKB1/AMPK signaling activation

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Abstract: **Background**: Hypertension is one of the most common chronic diseases in the world, affecting about a quarter of the adult population. Its complication, hypertensive myocardial infarction (HMI), has a complex pathological mechanism, involving myocardial ischemia, oxidative stress and microcirculation dysfunction. **Objective**: This study investigated the cardioprotective mechanisms of nicorandil (Nic), particularly its effects on cardiac microcirculation through modulation of the Liver Kinase B1 (LKB1)/AMP-activated Protein Kinase (AMPK) signaling pathway in HMI rats. **Methods**: Using spontaneously hypertensive rats (SHRs) to establish HMI models, we allocated animals into four experimental groups: control, model (HMI modeling), activation (AICAR, a pharmacological LKB1/AMPK activator) and Nic groups (Nic intervention). The evaluation indexes included cardiac function (LVEDD, LVESD and LVEF measured by echocardiography), serum biochemical markers (cTnI, CK-MB), histopathology (HE and Masson staining), oxidative stress (SOD, GSH-Px, MDA) and inflammatory factors (TNF-α, IL-6, IL-1β). The protein expression of LKB1/AMPK was analyzed by Western blot. **Results**: Compared with the control group, the model group exhibited significant suppression of LKB1/AMPK pathway activity, accompanied by marked myocardial fibrosis, elevated inflammatory cytokines and impaired cardiac function as evidenced by decreased Left Ventricular Ejection Fraction (LVEF) and increased Left Ventricular End-Systolic Diameter (LVESD) ($P<0.05$). Both pharmacological activation with AICAR and Nic treatment effectively restored LKB1/AMPK signaling, attenuated myocardial damage and significantly lowered oxidative stress and inflammatory markers ($P<0.05$ versus model group). Importantly, Nic treatment demonstrated superior efficacy compared to AICAR intervention in ameliorating HMI-induced pathological changes. **Conclusion**: Nic exerts cardioprotective effects in HMI rats through multi-target mechanisms involving LKB1/AMPK pathway activation, which subsequently attenuates oxidative stress and inflammatory responses while facilitating microcirculatory reconstruction, ultimately leading to significant improvement in cardiac function.

Keywords: Hypertension; Inflammation; LKB1/AMPK signaling pathway; Myocardial infarction; Myocardial microcirculation; Nicorandil; Oxidative stress

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INTRODUCTION

Hypertension remains one of the most prevalent chronic diseases worldwide, affecting approximately one-quarter of the global adult population. (Hengel *et al.*, 2022) The pathological mechanisms underlying hypertensive myocardial infarction (HMI) are complex, involving multiple processes such as myocardial ischemia, oxidative stress and microcirculatory dysfunction. (Lee *et al.*, 2023) These abnormalities impair tissue perfusion, exacerbate ischemia-reperfusion injury and promote adverse remodeling. Recent studies highlight that oxidative stress and inflammation form a vicious cycle, further disrupting microvascular homeostasis and contributing to cardiomyocyte loss. (He *et al.*, 2020) Although current therapeutic strategies-including revascularization, antiplatelet therapy and β-blockers-have significantly improved macrovascular blood flow, approximately 30-50 % of patients still experience persistent myocardial ischemia and adverse left ventricular remodeling due to coronary microcirculatory dysfunction. However, pharmacological agents targeting microcirculation in HMI remain scarce. This clinical challenge underscores the urgent need for targeted microcirculatory interventions. (Feng *et al.*, 2023) Nicorandil (Nic), a unique dual-mechanism drug combining nitrate-like vasodilatory effects with ATP-sensitive potassium (KATP) channel-opening properties, has demonstrated potential in improving microvascular perfusion. (Pearce *et al.*, 2023) Studies indicate that Nic not only dilates coronary resistance vessels but also mitigates ischemia-reperfusion injury by modulating mitochondrial KATP channels. However, its precise regulatory mechanisms on cardiac microcirculation in the context of HMI remain incompletely understood, presenting a critical scientific gap for further investigation.

The Liver Kinase B1 (LKB1)/AMP-activated Protein Kinase (AMPK) signaling pathway plays a pivotal role in energy metabolism regulation and microvascular homeostasis. (Chen *et al.*, 2023) As an upstream kinase of AMPK, LKB1 phosphorylates and activates AMPK, thereby modulating endothelial cell function, mitochondrial biogenesis and oxidative stress responses. (Lu *et al.*, 2023) Evidence suggests that under hypertensive conditions, oxidative stress and metabolic disturbances

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suppress LKB1/AMPK pathway activity, exacerbating microvascular endothelial dysfunction and perivascular fibrosis. (Liu *et al.*, 2025) While recent work by Chen *et al*. proposed that Nic may improve myocardial energy metabolism via AMPK activation (Chen *et al.*, 2024), whether it regulates microcirculatory dysfunction through an LKB1-dependent mechanism remains unexplored. This study investigates the effects of Nic on cardiac microcirculation under the dual pathological burden of HMI, addressing a key limitation of prior research focused primarily on non-hypertensive models. (Gong *et al.*, 2024; Y. Liu *et al.*, 2022) Furthermore, we elucidate the role of the LKB1/AMPK pathway in Nic-mediated cardioprotection, aiming to provide comprehensive and reliable evidence for clinical applications of Nic and ultimately improve outcomes in HMI patients.

MATERIALS AND METHODS

Animals and ethics

Specific pathogen-free spontaneously hypertensive rats (SHRs) weighing 240-260g (6-8 weeks old) were obtained from Beijing Vitalstar Biotechnology Co., Ltd. (Animal Use License No.: SCXK [Jing] 2023-0014). All animals were housed at 20°C with 25-50 % humidity and ad libitum access to food and water. SHRs were selected as a well-established genetic model of essential hypertension, characterized by progressive hypertension, endothelial dysfunction and spontaneous myocardial infarction resembling human hypertensive heart disease.

Experimental procedures

HMI Model Establishment: (Cheng *et al.*, 2022) Following a 7-day acclimatization, rats were fasted for 12 hours and anesthetized via intraperitoneal injection of sodium pentobarbital (400 mg/kg). In the supine position, the animals were intubated and mechanically ventilated following standard skin preparation and disinfection. A left thoracotomy was performed through the 3rd-4th intercostal space to expose the heart. After pericardiotomy, the left anterior descending coronary artery (LAD) was permanently ligated. The wound was closed in layers and properly disinfected. Postoperative penicillin sodium was administered to prevent infection. Successful model establishment was confirmed by persistent ST-segment elevation during 6-hour continuous ECG monitoring.

Experimental Grouping and Treatment Protocols: A total of 20 male SHRs (240-260 g, 8 weeks old) were randomized into four groups (n=5/group) using a computer-generated randomization sequence (GraphPad Prism): (1) control (SHR, without MI modeling, only received an equal volume of normal saline by gavage), (2) model (HMI modeling), (3) activation (AICAR, an LKB1/AMPK pathway activator) and (4) Nic (Nic intervention) groups. The HMI model was established in groups 2-4 as described above, while the control group received no intervention. Following modeling, the activation group received a daily gavage of 200 mg/kg AICAR (MedChemExpress); the Nic group was treated with 0.784 mg/kg Nic (Beijing SHKB Pharmaceutical Co., Ltd., Approval No. H20120069) by daily gavage; (Abe *et al.*, 2020) both model and control groups received equivalent volumes of saline by daily gavage. All interventions continued for 21 consecutive days. The sample size was determined based on the effect size of the pilot study (Cohen's f=0.8) and $\alpha=0.05/\beta=0.2$.

Post-intervention Procedures: After 21 days of treatment, cardiac function was assessed by transthoracic echocardiography [Left Ventricular End-Diastolic Diameter (LVEDD), Left Ventricular End-Systolic Diameter (LVESD) and Left Ventricular Ejection Fraction (LVEF) measurements]. Echocardiographic analyses were assessed in a blinded fashion and were performed independently by two investigators who were unaware of the group assignments. The parasternal long and short axis sections were taken for 3 consecutive cardiac cycles and the average value was calculated. Animals were then humanely euthanized via gradual CO2 inhalation (30-70 % volume displacement rate in a sealed chamber until respiratory arrest) followed by cervical dislocation confirmation. Cardiac tissues and blood samples were immediately collected for subsequent analyses.

Western blot analysis

Total protein was extracted from myocardial tissues using a commercial protein extraction kit. Equal amounts of protein (10 μg per lane) were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and electroblotted onto polyvinylidene fluoride (PVDF) membranes. Membranes were blocked in 5 % BSA-TBST for 1 hour at room temperature and incubated overnight at 4°C with primary antibodies (LKB1, 1:800, ab199970; AMPK, 1:1000, ab32047; α-MHC, 1: 1000, ab281902; Col, 1:1000, ab34710; GAPDH, 1:5000, ab8245, all were purchased from Abcam, USA). Following three TBST washes, membranes were incubated with HRP-conjugated goat anti-rabbit secondary antibody (1:1000, ab288151) for 1 hour. The protein bands were visualized using an electrochemiluminescence (ECL) substrate for film development. After exposure, the films were photographed. Quantitative densitometric analysis was conducted using ImageJ software.

Biochemical analysis

Cardiac blood samples were centrifuged to obtain serum, which was analyzed for cardiac troponin I (cTnI) and creatine kinase-MB (CK-MB) levels using an automated biochemistry analyzer.

Histopathological examination

Hematoxylin-eosin (HE) Staining: Myocardial tissues were deparaffinized in xylene, rehydrated through graded ethanol series and washed with distilled water 2-3 times. Sections were then stained with hematoxylin for 10 min

and differentiated in acid water and ammonia water (20 seconds each), followed by washing with distilled water, dehydration in 70 % and 90 % ethanol (10 min each), counterstaining with eosin for 2 min and finally mounting for microscopic examination.

Masson's Trichrome: Following similar processing, sections were stained with Weigert's hematoxylin (5-10 min) for nuclei, differentiated, washed, blued and rinsed. After staining with Ponceau S staining solution (5-10 min), soaking and differentiation, sections were counterstained with aniline blue (5 min) before dehydration and mounting. The area of myocardial fibrosis was quantitatively analyzed by Image analysis software (Image-Pro Plus).

TUNEL assay

TdT enzyme and fluorescein-labeled dUTP were mixed according to the kit instructions. Subsequently, the reaction mixture was applied to cover the tissue sections and incubated in a humidified chamber at 37°C for 1 hour in the dark. At least five non-overlapping fields (200-fold or 400-fold) were randomly selected under a fluorescence microscope. The total number of TUNEL-positive (green fluorescence) nuclei in each field and the total number of nuclei in that field were counted and the apoptotic index of each field was calculated (number of TUNEL-positive nuclei/total nuclei ×100%). Finally, the average value of each field was taken as the apoptotic index of this sample.

ELISA

Serum Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), Interleukin-1β (IL-1β), Superoxide Dismutase (SOD), Glutathione Peroxidase (GSH-Px) and Malondialdehyde (MDA) were measured using ELISA kits (R&D Systems, Minneapolis, MN, USA) following the manufacturer's protocol. Absorbance was read at 450 nm with wavelength correction at 570 nm.

Statistical analysis

Statistical analysis were performed using SPSS 26.0 (IBM). All experiments were performed in triplicate. Data normality was assessed by Shapiro-Wilk test. Data are presented as mean ± SD ($\bar{\chi}\pm s$), generalized linear model (GLM) was used to deal with unequal sample size for comparison among multiple groups and Bonferroni correction was used for pairwise comparison between groups. Differences were considered statistically significant at $P<0.05$.

RESULTS

Modeling results

All rats survived and HMI was successfully established. Protein analysis revealed significantly reduced expression of LKB1 and AMPK in the model group compared to the normal controls ($P<0.05$). In contrast, both the activation and Nic groups exhibited elevated LKB1 and AMPK levels compared to the model group, with the activation group demonstrating the highest expression ($P<0.05$) (Fig. 1).

Histopathological findings

Myocardial tissue staining in the control group displayed intact cardiomyocytes with uniform red staining, distinct nuclei, abundant cytoplasm and well-organized myocardial fibers with minimal collagen deposition. In stark contrast, the model group exhibited extensive cardiomyocyte necrosis, interstitial edema, disrupted and disorganized muscle fibers, widened intermuscular spaces and island-like structures of myocardial tissue survived; the cardiomyocyte structure was damaged and disorganized, with pyknotic nuclei; the infarcted area exhibited significant fibrosis, abundant collagen deposition and significant fibrotic replacement of cardiomyocytes, accompanied by extensive inflammatory cell infiltration and nuclear fragmentation. Both the activation and Nic groups showed marked histopathological improvement, including reduced cardiomyocyte damage, relatively ordered arrangement, narrower intermuscular gaps, diminished necrotic areas and attenuated inflammatory infiltration. Notably, the Nic group exhibited superior restorative effects compared to the activation group. Quantitative analysis revealed a 39.83 % reduction in collagen volume fraction in the Nic group (13.49±1.83) % compared to the model group (22.42±3.45) % ($P<0.05$) (Fig. 2).

Cardiac function

Echocardiographic analysis revealed significant cardiac dysfunction in the intervention groups compared to controls. The model, activation and Nic groups all demonstrated pathological ventricular dilation (increased LVEDD and LVESD) accompanied by impaired systolic function (reduced LVEF; $P<0.05$). Therapeutic intervention with either activation or Nic treatment partially reversed these abnormalities, with both groups showing significantly lower LVEDD and LVESD and higher LVEF than the model group ($P<0.05$). Notably, cTnI levels peaked at 24 hours post-MI in the model group and remained elevated in the activation group, whereas Nic reduced it to 0.28±0.08 ng/mL ($P<0.05$ *vs.* Model group). CK-MB showed a similar pattern, declining by 21.70 % in the Nic group compared to model ($P<0.05$), (Fig. 3).

Oxidative stress and inflammatory response

The model group exhibited significantly reduced SOD and GSH-Px compared to controls, along with elevated MDA, IL-1β, IL-6 and TNF-α ($P<0.05$). Both the activation and Nic groups exhibited ameliorated myocardial stress injury and inflammation, with Nic treatment demonstrating particular efficacy. Specifically, the Nic group demonstrated higher SOD and GSH-Px levels and lower MDA, IL-1β, IL-6 and TNF-α levels than the activation group ($P<0.05$) (Fig. 4).

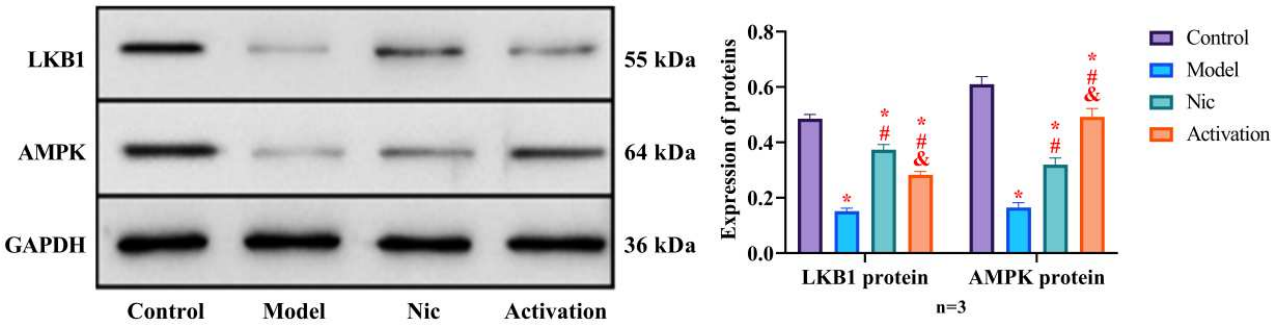

Fig. 1: Detection of LKB1/AMPK pathway expression in 4 groups of rats.
* *vs.* control group P<0.05, # *vs.* model group P<0.05, & *vs.* Nic group P<0.05.

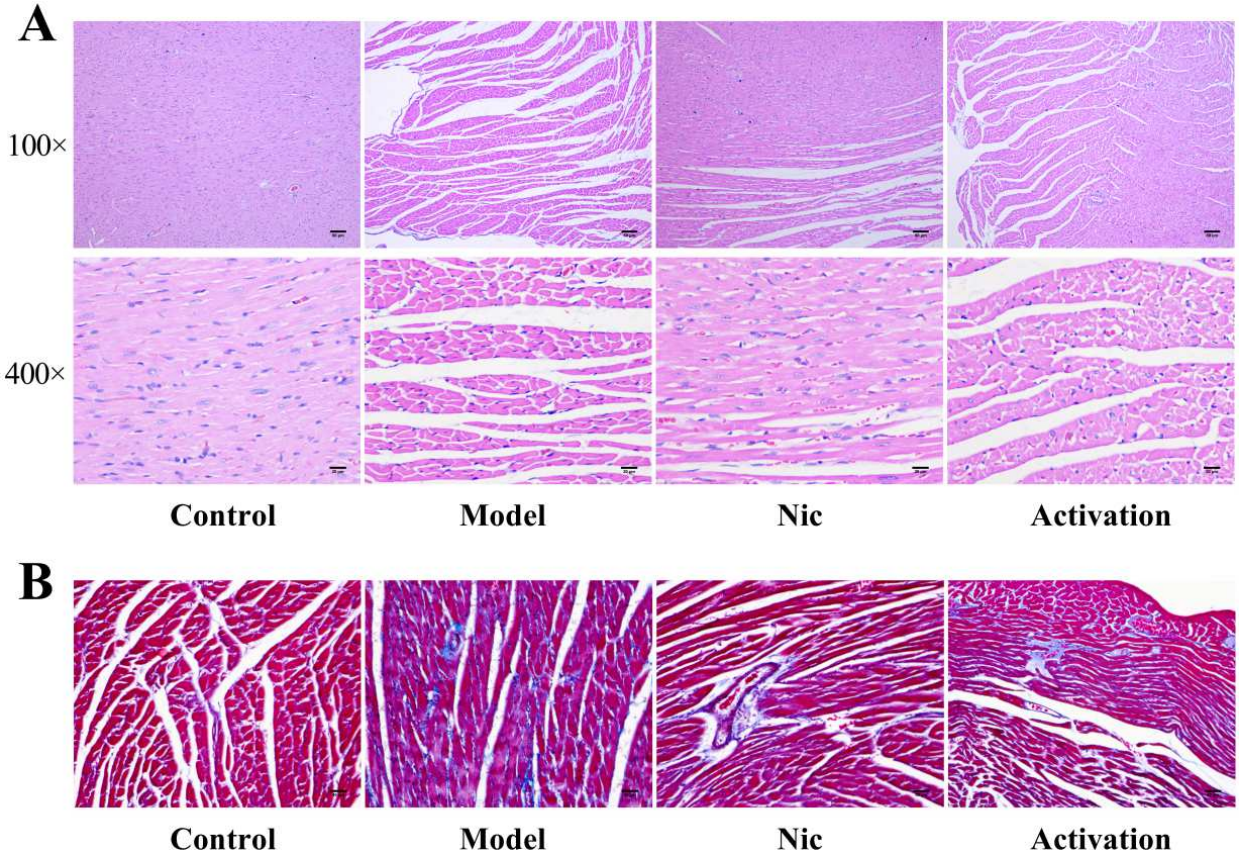

Fig. 2: Effect of Nic on myocardial pathologic damage in HMI rats. A: HE staining of myocardial tissue. B: Masson staining of myocardial tissue.

Myocardial microcirculation

The expression of α-MHC protein in the model group was significantly lower than that in the normal group (P<0.05). However, there was no significant difference in the expression of α-MHC protein between the activation group and the Nic group (P>0.05), which was higher than that in the model group (P<0.05). On the contrary, the expression of Col protein in the model group was higher than that in the control group, while that in the activation group and Nic group was lower than that in the model group (P<0.05). Apoptosis assessment via TUNEL staining showed that although neither activation nor Nic treatment completely normalized cell death rates, both significantly reduced apoptosis compared to the model group (P<0.05), with Nic treatment providing additional anti-apoptotic benefit over activation treatment (P<0.05) (Fig. 5).

DISCUSSION

HMI is associated with significant global morbidity and mortality, underscoring the urgent need for effective and safe therapeutic interventions to ensure patient survival and improve patient outcomes.(Maraey *et al.*, 2021) Our experimental findings establish Nic as a promising therapeutic candidate that effectively ameliorates both functional and structural cardiac impairments in HMI rat

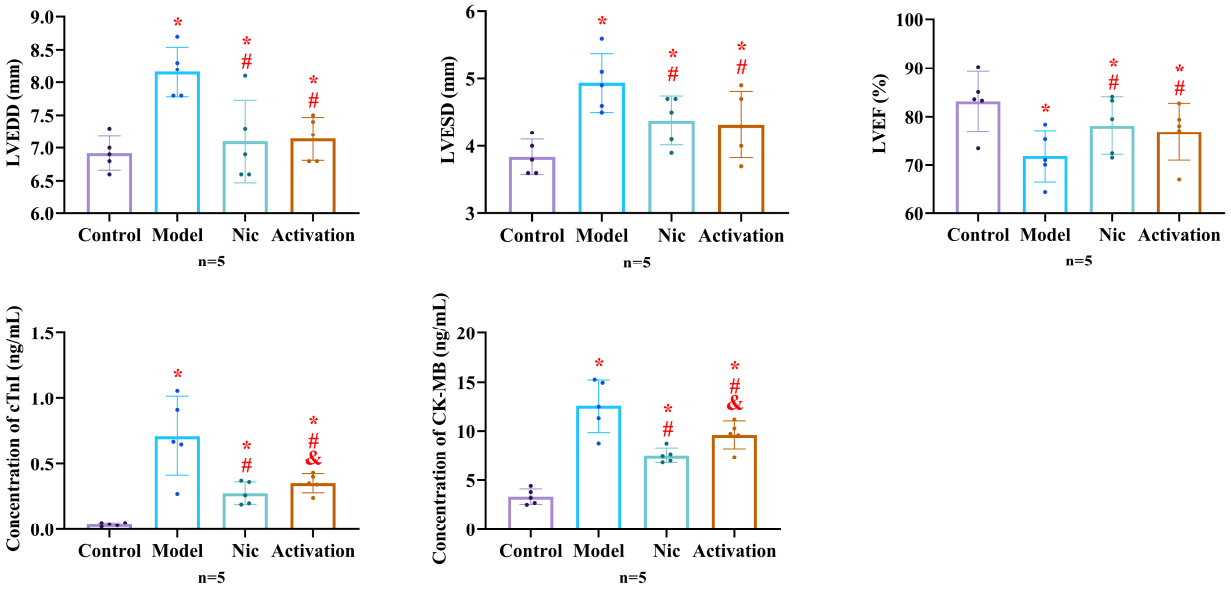

Fig. 3: Detection of LVEDD, LVESD, LVEF, cTnI and CK-MB to analyze the effect of Nic on cardiac function in HMI rats.
* *vs.* control group P<0.05, # *vs.* model group P<0.05, & *vs.* Nic group P<0.05.

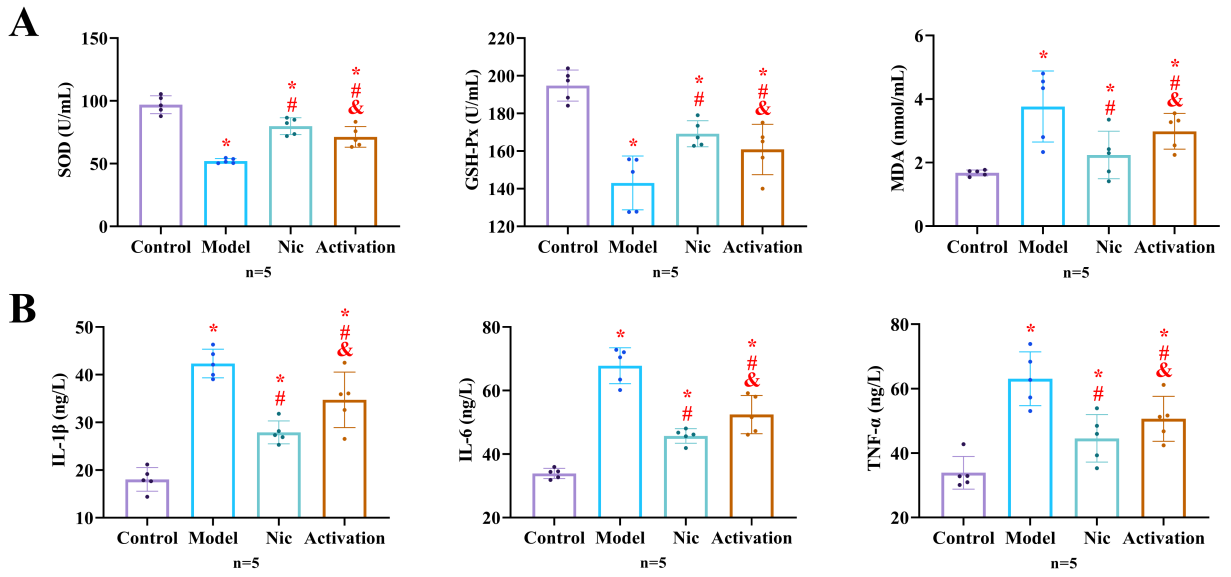

Fig. 4: Effect of Nic on myocardial oxidative stress and inflammatory response in HMI rats.
A: Results of oxidative stress indicators SOD, GSH-Px and MDA.B: Results of inflammatory factors IL-1β, IL-6, TNF-α. * *vs.* control group P<0.05, # *vs.* model group P<0.05, & *vs.* Nic group P<0.05.

models, thereby offering novel clinical insights for managing this life-threatening condition.

Key findings reveal a marked suppression of the LKB1/AMPK signaling pathway in HMI rats, consistent with previous research, (Wu *et al.*, 2023) suggesting the potential involvement of the LKB1/AMPK axis in HMI pathogenesis. AMPK, a cell-based biosensor ubiquitous in mammalian systems, plays a pivotal role in maintaining cellular energy homeostasis. LKB1, as AMPK's primary upstream kinase, predominantly localizes in the nucleus under physiological conditions. During pathological states, phosphorylated LKB1 translocates to the cytosol, thereby mediating AMPK activation. (Li *et al.*, 2020) Supporting our observations, Liu N *et al*. demonstrated that LncRNA LncHrt maintains cardiac metabolic homeostasis and function through LKB1/AMPK pathway activation, (N. Liu *et al.*, 2021) further underscoring this pathway's significance in HMI. While AICAR intervention predictably elevated LKB1/AMPK expression in HMI rats, our novel finding that Nic treatment similarly upregulated LKB1 and AMPK protein expression suggests that Nic may exert its therapeutic effects in HMI through LKB1/AMPK pathway activation. This mechanism

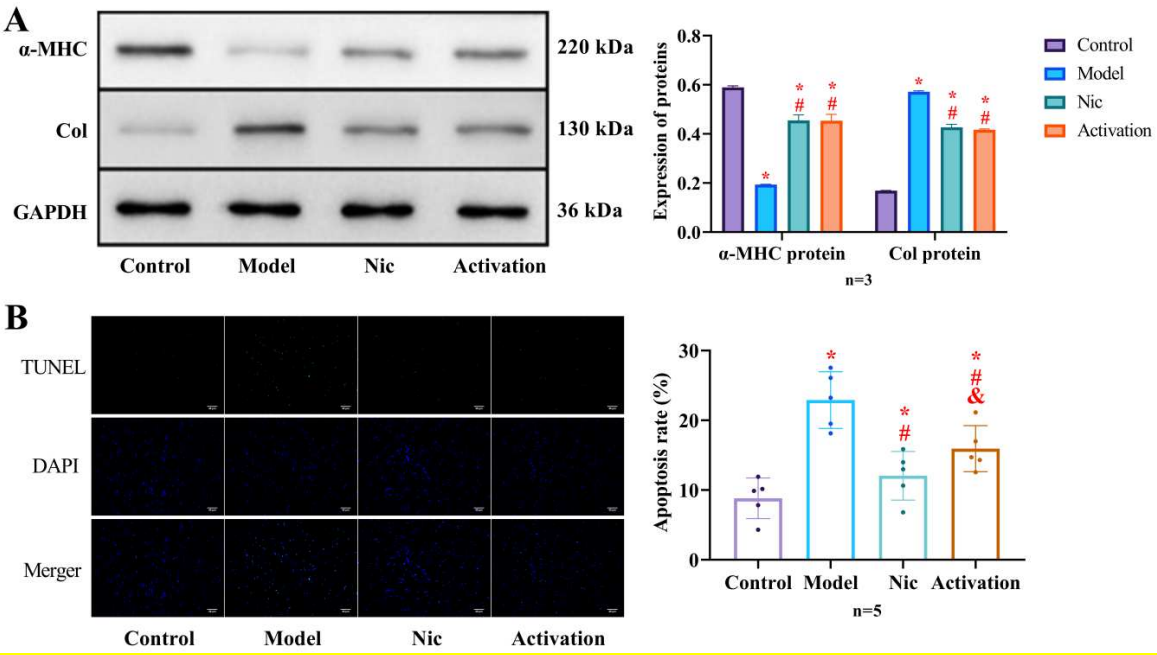

Fig. 5: Effect of Nic on myocardial microcirculation in HMI rats.
A: Detection results of myocardial microcirculation functional proteins α-MHC and Col I. B: Apoptosis rate of cardiomyocytes observed by TUNEL staining. * *vs.* control group P<0.05, # *vs.* model group P<0.05, & *vs.* Nic group P<0.05.

potentially explains Nic's cardioprotective properties observed in our study.

Our investigation of pathological alterations in HMI rats yielded significant findings regarding Nic therapeutic effects. The experimental results demonstrated that Nic treatment effectively ameliorated myocardial pathological damage, enhanced cardiac functional parameters, improved myocardial microcirculation and reduced stress-induced myocardial injury in the HMI rat model. These beneficial effects appear to be mediated through Nic's dual pharmacological mechanisms of action: (1) Functioning as a KATP channel opener, Nic exerts coronary microvascular dilation, thereby increasing blood perfusion in ischemic myocardial regions and attenuating cardiomyocyte apoptosis.(Zhao *et al.*, 2021) This vascular effect contributes substantially to tissue preservation. (2) Through specific activation of mitochondrial KATP channels, Nic stabilizes mitochondrial membrane potential and reduces cytochrome C release, consequently inhibiting the caspase-3-mediated apoptotic cascade.(Zhao *et al.*, 2024) This mitochondrial protection represents a crucial cytoprotective mechanism. Of particular significance, the research by Zhan B *et al*. established that Nic-induced improvement in cardiac function correlates strongly with its capillary angiogenic effects, as evidenced by increased CD31+ microvessel density.(Zhan *et al.*, 2020) This finding strongly suggests that microcirculatory remodeling serves as the structural foundation for functional recovery in the ischemic myocardium. Our finding that Nic activates LKB1/AMPK aligns with Chen *et al*.'s study in diabetic cardiomyopathy, yet differs in the downstream effector pathways.(Chen *et al*., 2024).

Notably, the activation group exhibited pathological improvements comparable to those observed in the Nic group. This finding confirms that activation of the LKB1/AMPK pathway expression exerts beneficial effects on acute myocardial infarction progression, consistent with previous pathological studies investigating LKB1/AMPK signaling.(C. Liu *et al.*, 2022; Xu *et al.*, 2022) Current research indicates that significant upregulation of LKB1 phosphorylation levels and AMPK-Thr172 phosphorylation can effectively suppress NADPH oxidase (NOX2/4) expression while restoring antioxidant activity. (Van der Zande *et al.*, 2023) Building upon these established findings and considering Nic's demonstrated activation of the LKB1/AMPK pathway, we propose that Nic may inhibit NOX-mediated reactive oxygen species (ROS) burst through LKB1/AMPK pathway activation, thereby blocking Nuclear Factor Kappa B (NF-κB) nuclear translocation and reducing pro-inflammatory cytokine release. Secondly, the superior efficacy of Nic over AICAR may stem from its dual pharmacological actions: (1) mitochondrial KATP channel opening-mediated cardioprotection and (2) direct inhibition of mitochondrial fission via Drp1 phosphorylation, as previously reported in *vitro*. It is worth noting that Nic, as a KATP channel opener and nitrate drug, has a potential antihypertensive effect (Shaoqing *et al.*, 2022). In the SHR model, the hypotensive effect of Nic itself may have a positive impact on improving cardiac function, reducing cardiac load and remodeling. Therefore, the observed therapeutic effect of Nic may be partially attributed to its hemodynamic effect (lowering blood pressure) rather than solely to the specific activation of LKB1/AMPK signaling pathway. Despite its clinical benefits, Nic's long-term efficacy remains debated.

A recent meta-analysis raised concerns about increased mortality in chronic heart failure patients,(Mu *et al.*, 2025) possibly due to off-target effects on mitochondrial function. However, our data suggest that short-term activation of LKB1/AMPK may circumvent these risks by enhancing antioxidative defenses. Taking the above results together with previous studies, we suggest that Nic activation of LKB1/AMPK signaling pathway may improve microcirculation through the following pathways: (1) Phosphorylation of eNOS (endothelial nitric oxide synthase) enhanced NO production and promoted vasodilation (Z. Liu *et al.*, 2021); (2) Inhibition of NOX4 expression reduced ROS generation and blocked NF-κB inflammatory pathway; (3) up-regulated PGC-1α mediated mitochondrial biosynthesis and improved energy metabolism. Several critical mechanistic questions remain to be addressed. First, whether Nic directly modulates LKB1 kinase activity or influences its subcellular localization (e.g., by promoting LKB1-STRAD/MO25 complex formation) requires further investigation. Second, comprehensive target validation studies employing molecular docking simulations and surface plasmon resonance (SPR) analysis are needed to determine whether Nic primarily interacts with LKB1, AMPK, or other molecular targets. Third, the potential involvement of alternative AMPK upstream regulators, particularly CaMKKβ, in mediating Nic's pharmacological effects warrants systematic investigation. Fourth, for successful clinical translation, it is imperative to validate whether human cardiac tissues exhibit comparable LKB1/AMPK activation patterns in response to Nic treatment. In addition, a limitation of this study is the absence of CD31 staining to quantify microvessel density, precluding direct assessment of angiogenesis. This study used a sham-operated group of SHR as a control, a design capable of reflecting the influence of the hypertensive background but unable to fully distinguish the independent contribution of hypertension per se from MI to the observed results. The inclusion of a normotensive MI control group would help to more precisely isolate the specific role of hypertension in HMI pathology, but this is beyond the scope of the current study and could be a direction for future research. It is also worth noting that changes in blood pressure during the intervention period were not monitored in the present study. Future studies should measure blood pressure before and after treatment to distinguish the relative contribution of the hypohypertensive effect of Nic from its potential LKB1/AMPK pathway activation or other cytoprotective effects on cardiac function and microcirculation improvement. This should be addressed in future investigations. Future studies should validate these findings in larger cohorts and assess the impact of Nic on post-infarction arrhythmias and heart failure progression.

CONCLUSION

This study identifies Nic as a multifaceted cardioprotective agent in HMI, whose benefits stem from LKB1/AMPK-dependent modulation of oxidative stress, inflammation and microvascular remodeling. These findings position Nic as a promising therapeutic candidate for targeting microcirculatory dysfunction in hypertensive patients with acute myocardial infarction.

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Author's contribution
S.W. designed the study, W.W. wrote and revised the manuscript, S.W. collected and analyzed data, All authors read and approved the final submitted manuscript.

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Data availability statement
The data used to support the findings of this study are available from the corresponding author upon request.

Ethical approval
All the experimental procedures involving animals were conducted in accordance with ARRIVE guidelines and approved by the Animal Ethics Committee of Xishan People's Hospital (NO.kl0056).

Conflict of interest
The authors declare that they have no competing interests.

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