BMC Cardiovascular Disorders

RESEARCH

Open Access

The role of COX2 deficiency attenuates cardiac damage in acute myocardial infarction

Jing Zhu[1] and Jianqiu Liang[1*]

Abstract

Cardiac cell damage frequently occurs as a consequence of acute myocardial infarction (AMI), a critical complication of coronary atherosclerotic heart disease. There is an escalating recognition of the association between COX2 and myocardial damage induced by ischemia. The objective of this study is to investigate the inhibitory effect of the COX2 on cardiomyocyte damage in the context of AMI. To create an AMI model, mice with the genetic background of wild-type C57BL6/J (WT) and COX2-/- mice were utilized. The left anterior descending (LAD) coronary artery in their hearts was obstructed, and subsequent assessment of hemodynamic parameters and heart function was conducted. Notably, increased levels of COX2 were observed in AMI mice. Through correlational analysis between COX2 expression and cardiac function following AMI, it was revealed that COX2 knockout mice had smaller infarct sizes, better cardiac performance, and suppressed levels of reactive oxygen species (ROS) compared to WT mice. Additionally, we discovered that COX2 knockout mice exhibited significantly higher mRNA levels of smooth muscle actin, collagen I, and collagen III than normal mice with AMI. Conversely, the levels of superoxide dismutase (SOD), malondialdehyde (MDA) were higher but iron content was decreased in COX2 knockout mice compared to normal mice with AMI.In summary, our research demonstrates that the downregulation of COX2 enhances cardiac tissue recovery in the context of AMI.

Keywords Acute myocardial infarction, COX2, Myocardial tissue

Introduction

Myocardial infarction, also known as acute myocardial infarction (AMI), is a critical medical condition characterized by the necrosis of heart muscle due to a disrupted blood supply caused by atherosclerosis and acute thrombosis [1]. AMI is a leading cause of mortality and morbidity in middle-aged and older individuals across society [2]. The development of AMI involves various genetic and environmental factors, including obesity, hypertension, diabetes, and hypercholesterolemia [3]. Cardiomyocyte death plays a significant role in AMI by hindering the regeneration of cells. These dead cardiomyocytes cannot be replaced by surviving ones [4]. Hence, it is crucial to employ interventions that limit myocardial cell death for the successful treatment of AMI. This involves prompt reperfusion therapy and restoration of coronary blood flow. While percutaneous coronary intervention and thrombolytic therapy have their limitations, there is potential in exploring new biological markers and therapeutic approaches for AMI. Additionally, further research into the molecular mechanisms of myocardial cell death can provide valuable insights for early diagnosis and treatment of AMI [5, 6]. Although there are limitations in identifying early myocardial infarction, mild myocardial injury, or stable coronary artery disease, the pursuit of novel biological markers, therapeutic

*Correspondence:
Jianqiu Liang
chenchu202222@163.com
[1]Department of Cardiology, The Second People's Hospital of Foshan, Foshan, Guangdong, China

tools, and in-depth research on molecular mechanisms remains highly significant in the clinical context. Detecting and treating acute myocardial infarction (AMI) at an early stage is of paramount importance [7–9], Therefore, investigating new biological markers, therapeutic tools, and the molecular mechanisms underlying myocardial cell death holds crucial clinical implications for AMI diagnosis and treatment.

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin (PG) formation by targeting cyclooxygenase (COX) 1 and 2 [10, 11]. Long-term use of NSAIDs that selectively inhibit COX2 increases the risk for thrombotic events, cardiac failure, and hypertension [3, 12]. Moreover, cardiomyocyte-specific deletion of COX2 results in reduced heart functions and diminished exercise tolerance in mice, strongly suggesting that COX2 inhibitors have direct effects on cardiac function independent of renal insults [13, 14]. And rats are valuable models for understanding the pathophysiology and genetics of cardiovascular diseases, since they can spontaneously develop such diseases with relatively larger organ size compared to routinely-used mice [15, 16]. COX2 is closely associated with oxidative stress and ferroptosis [17–19].Additionally, ferroptosis has been associated with the development and progression of several human disorders. Recent studies have indicated that under conditions of increased oxidative stress, the expressions and activities of COX isoforms are altered, resulting in changes in production of various prostanoids and thus affecting vascular tone [20]. Furthermore, it has been implicated in azithromycin-induced cardiotoxicity and ischemia-reperfusion damage-related heart failure [21]. These findings suggest a strong association between COX2 and oxidative stress and ferroptosis underlying cardiovascular disease [22, 23].

Albeit the exact processes driving ferroptosis in acute myocardial infarction (AMI) remain unknown, this study initially examined the ferroptosis-related genes available in public databases. The investigation revealed that COX2 may hold significant importance in this particular process. To validate the diagnostic potential of COX2 in AMI, we utilized both the AMI mouse model and the COX2 KO mouse model. The outcomes of this research open up new avenues for studying the molecular foundations of ferroptosis in AMI, and provide a fresh perspective on personalized approaches to diagnosing and treating AMI.

Materials and methods

It is important to note that this research was carried out at a single center. The institutional review board and the ethical committee of our hospital both granted their approval (IRB). The studies conducted adhere to the principles outlined in the Declaration of Helsinki. Any animal research involved in this study strictly adheres to the ARRIVE standards, and is conducted in line with either the UK's Animals (Scientific Procedures) Act, 1986, along with its related recommendations, or the National Research Council's Handbook for the Care and Use of Laboratory Animals, or the EU Regulation 2010/63/EU for animal research.

Bioinformatics

To identify gene expression chips related to myocardial infarction (MI), we conducted a search in the Gene Expression Omnibus (GEO) Database (https://www.ncbi.nlm.nih.gov/geo/). Specifically, the GSE97320 dataset was employed for the tests performed in our study. The Affy package in the R language (Gautier, Cope, Bolstad, & Irizarry, 2004) was employed to perform standardized preprocessing on the expression data. This was done utilizing the robust multiarray average (RMA) technique after acquiring the gene chip expression data and annotating the file (Irizarry et al., 2003). In order to identify differentially expressed genes related to myocardial infarction (MI), the Limma package was utilized with the following criteria: p-value less than 0.05 and absolute value of LogFoldChange greater than 2. Subsequently, a heatmap displaying the differentially expressed genes was generated. To compare the differentially expressed genes across three different chips, we employed the Venn online Analyse tool (http://bioinformatics.psb.ugent.be/webtools/Venn/). This tool enables the calculation and creation of custom Venn diagrams.

Animal model establishment

As for the mice used in our study, C57BL/6 wild-type mice were acquired. COX2 heterozygous mice with a C57BL/6 genetic background were kindly provided by The Jackson Laboratory. To establish colonies, COX2+/+ and COX2-/- mice were generated by intercrossing heterozygous mutant mice [24, 25]. All maintenance and laboratory animal experimentation was carried out under the authorization of the Institutional Ethics Committee of The Second People's Hospital of Foshan.

Experimental protocol

For our investigation, only male mice at the age of 10 weeks were employed. To induce an acute myocardial infarction (AMI) condition, WT and COX2-/- mice were anesthetized with 1.5% isoflurane inhalation. The left anterior descending branch (LAD) was ligated using a 7−0 silk suture. In the sham group, the LAD was not ligated and was simply threaded. After a duration of 7 days, the mice were euthanized, and their hearts were extracted for further analysis.

Echocardiography

Echocardiography was used to measure the left ventricular function of the mice in each group seven days following surgery. In mice that had been given isoflurane (1%) inhalation anesthesia, we performed M-mode and B-mode echocardiography utilizing a 12 MHz probe (VisualSonics Vevo 2100, Canada). Measurements were done in the left ventricular end-diastolic diameter (LVIDs), left ventricular end-systolic diameter (LVIDs), and left ventricular fractional shortening (FS%). Echocardiographic acquisition and analysis were performed by a technician who was blinded to the.

groups.

ELISA

The COX2 and cTnT levels in peripheral tissues were assessed using a mouse COX2 and cTnT ELISA kit (BOSTER, China) blood that was drawn seven days after surgery.

Histological analysis

Mice were sacrificed with injections of 1% sodium pentobarbital into the cavum abdominous. The chest was opened quickly, perfused, and fixed with 4% paraformaldehyde. 4% paraformaldehyde was used to fix the hearts overnight; then. The hearts were sectioned for H&E staining, immunohistochemical analysis, and Masson trichrome histopathology analyses.

Detection of cardiac hemodynamic parameters

The mice were supinely positioned on the operation table after being given 1% sodium pentobarbital sodium anesthesia. By inserting a left cardiac catheter through the carotid artery and into the left ventricle of the rats, the multichannel physiologic recorder was connected, and measurements and recordings of the left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), and maximum rate of left ventricular pressure development and decay (dp/dtmax) were made.

Measurement of infarct size

The infarction area was estimated by the 2,3,5-triphenyltetrazolium chloride (TTC, Sigma-Aldrich, St. Louis, USA) staining. The mice were sacrificed three days after ligation, and hearts were taken out, washed, and dissected into 2 mm thick slices. The sections were immersed in 1% TTC at 37 ∘C for 10–20 min. The infarct area was stainless, and the other area was red. The infarcted size was expressed as the percentage of the left ventricle (LV). The infarct size was calculated using Image ProPlus 5.0 software (Media Cybernetics, Wokingham, UK).

Quantitative real-time PCR

After various treatments, total RNA was isolated from the ischemic region of the left ventricles using Trizol reagent (Invitrogen, Waltham, USA) in accordance with the manufacturer's instructions. Using a reverse transcription reagent kit, cDNA was created (Sangon Biotech, Shanghai, China). The SYBR Green PCR Master Mix was used to measure the target genes, and the Light Cycler 480 was used to detect them (Roche, USA). The miR-15a-5p, COX2, GPX4, and Egr-1 target primers were the three. Internal control was provided by U6 or -actin. The 2-Ct relative quantification approach was used to identify the gene levels.

Tissue iron assay

Mice's left ventricles were removed, and phosphate buffered saline was utilized to homogenize them. Using an iron assay kit from Nanjing Jian Cheng, Nanjing, China, the supernatants were gathered and analyzed following the manufacturer's instructions.

Reactive oxygen species (ROS) production assay

The media were taken out, the cells were washed, and DCFH-DA was suitably diluted before being incubated at 37 °C for 20 min. The cells were cleaned once again. Leica, Heidelberg, Germany's fluorescence microscope was used to measure the intracellular ROS' fluorescence intensity at 488 nm and 525 nm.

MDA content and SOD activity

Superoxide dismutase (SOD) and malondialdehyde (MDA) were utilized as markers of oxidative stress damage. As a result, MDA and SOD detection kits (Beyotime, Shanghai, China) were used to test the level of MDA and the activity of SOD in accordance with the manufacturer's instructions.

Statistical analysis

The program GraphPad Prism 5.0 is utilized to analyze and show the data as means and SEM. Two-tailed Student's t-test was used to compare the two groups. One-way ANOVA was utilized to compare compare several groups. All statistical analyses were calculated by SPSS19.0 software. $P<0.05$ was considered to be a significant difference statistically.

Results

COX2 was selected in our study after bioinformatics analysis

The GSE97320 expression microarray was used to select differential gene expression in AMI. Figure 1A, B show the analysis of PCA and volcano maps, while Fig. 1C shows in the differential expression of 204 genes. Figure 1D shows an examination of the KEGG and KO

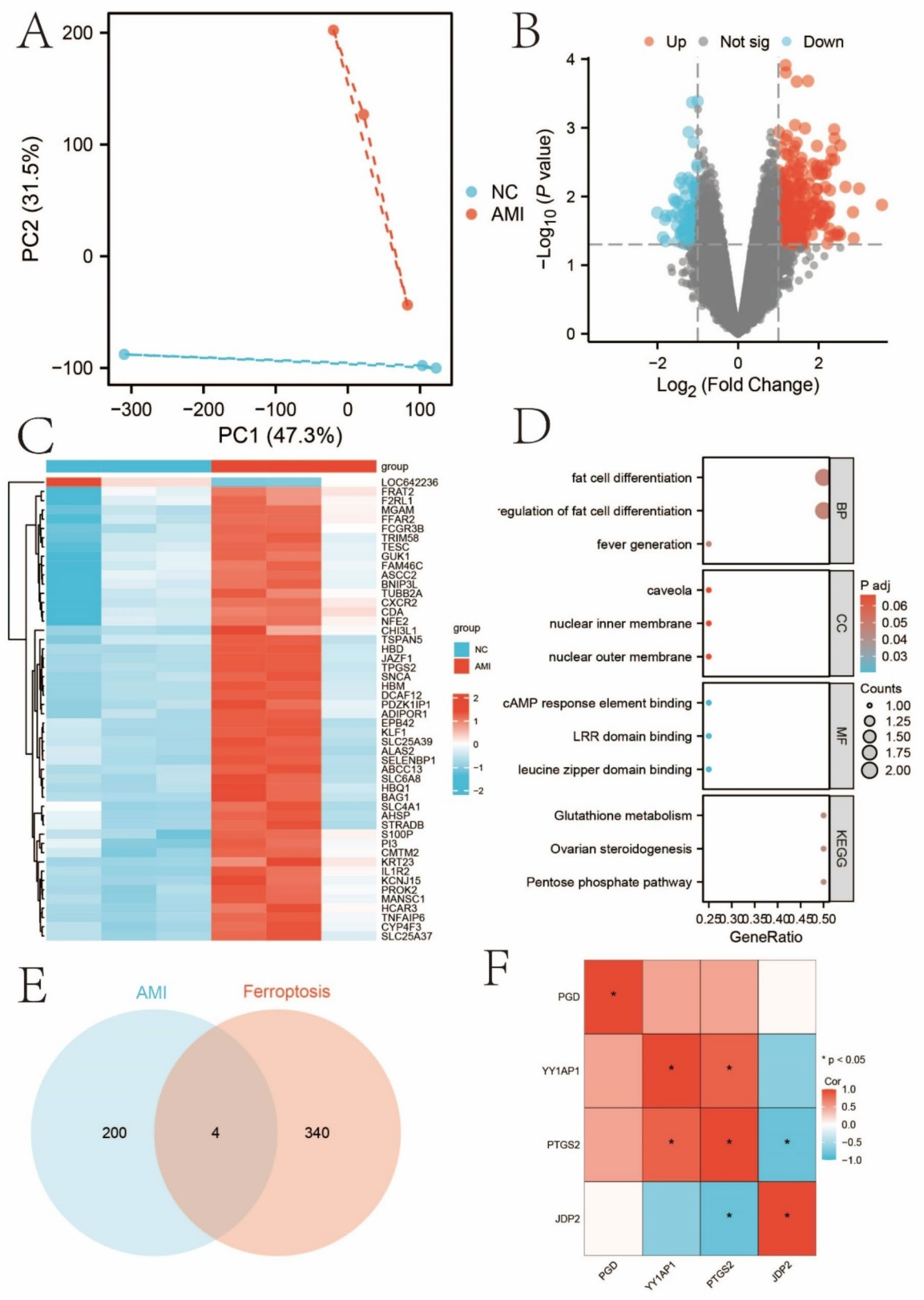

Fig. 1 COX2 was selected in our study after bioinformatics analysis. (**A**) PCA analysis. (**B**) Volcano Plot. (**C**) heatmap analysis. (**D**) KEGG and GO analysis. (**E**) Venn map between AMI dateset and ferroptosis gene. (**F**) correlationship between PGD, YY1AP1, COX2 and JDP2

pathways. and discovered that a total of 4 common genes were chosen using a Venn map after cross-tabulating with ferroptosis genes. The findings of the correlation analysis are shown in Fig. 1F, and they show that the GSE60993 microarray has a high level of COX2 expression. Moreover, there was a strong correlation between COX2 and the other three differential gene markers. The hippo signaling pathway was also found to be highly enriched in our study, and although it is shown in Fig. 1 to be the most enriched signaling pathway. The activation of the Hippo signaling pathway was shown to result in altered cardiac function following AMI after literature screening [26, 27], which helped to further anticipate the molecular mechanism of COX2. Moreover, it has been shown that COX2 may adversely impact the Hippo signaling pathway [28]. As COX2 is a crucial enzyme in prostaglandin manufacture and functions as both a peroxidase and a dioxygenase, we hypothesize that abnormally elevated COX2 expression in AMI has an impact on the Hippo signaling pathway(Figs. 1E).

Overexpression of COX2 in myocardial tissue and peripheral mouse blood after AMI

We established an AMI model and analyzed COX2 expression levels in myocardial tissue and peripheral blood in the infarcted area. The findings of ELISA analysis revealed that COX2 levels were considerably higher in the peripheral blood of AMI mice compared to healthy controls and sham-operated groups ($P<0.05$), which may help explain the alterations in COX2 expression after myocardial infarction(Fig. 2B, C). The findings also showed that the WT ischemia group's COX2 mRNA expression was higher than that of the control group and WT sham group ($P<0.05$). In our study, the results showed that cTnT levels were significantly increased in the AMI group, and the results of correlation analysis showed a clear positive correlation between cTnT and COX2(Fig. 2F, G). EF% and LVIDd were assessed by echocardiography 7 days after an AMI, and the correlation between these variables was determined to better understand the connection between COX2 expression and cardiac function after an AMI (Fig. 2D, E). The findings revealed a negative correlation between COX2 expression and LVEF (R2 = -0.9483, $P<0.001$) and a positive correlation between COX2 expression with LVIDs (R2=0:9358, $P=0.0115$). Together, the information demonstrated that following AMI in mice, COX2 expression considerably increased(Fig. 2H, I). A substantial association between COX2 expression and heart function after myocardial infarction was found using correlation analysis.(Fig. 2).

Mice knockout COX2 had increased LVSP, LVEF, and LVFS while decreased LVEDP

Initially, several parameters were used to determine cardiac hemodynamics and cardiac ultrasound results in mice with COX2 deletion. As compared to WT ischemia, the LVEDP,+dp/dt and −dp/dt were dramatically reduced but LVSP rose considerably ($p<0.05$) in the KO ischemia groups(Fig. 3; Table 1).

Inhibition of highly expressed COX2 reduced infarct size and improved heart function after AMI in mice

We created COX2-knockout mice to investigate the function of COX2 in myocardial damage. We examined the infarct size, inflammation, echocardiograms, and myocardial fibrosis of the mice in the WT and COX2-/- ischemic groups seven days following LAD artery ligation surgery. The findings of the echocardiography revealed that the COX2 -/- ischemia group had substantially lower LVEF (28.25±3.25% vs. 40.18±6.58%, $P=0.05$) and LVFS (9.25±4:09% vs. 19.25±1:2.08%, $P<0:05$) than the WT ischemia group. Compared to the WT ischemia group, the LVIDd (5.89±0:47 vs. 4.85±0:36, $P<0:05$) and LVIDs (4.89±0:18 vs. 4.08±0.28, $P<0:05$) were higher. The infarct size was lower in the COX2-/- ischemia group, as seen by the findings of TTC staining (42.61±3.58% vs. 30.58±2.91%, $P<0:05$). Our data showed that inhibiting the highly expressed COX2 gene after AMI decreased the infarct size and facilitated the recovery of heart function. (Fig. 3)

Reduced ROS level benefits of COX2 knockout in cardiac repair after myocardial infarction

Figure 4 illustrates the involvement of ROS level in the modulation of cardiac function after AMI. Nevertheless, it is unclear how ROS level and COX2's effects on the modulation of cardiac function after AMI related to one another. We initially looked at the levels of VEGF, collagen I, and collagen II in cardiac tissue to investigate this association. We discovered that KO ischemia considerably decreased the levels in the WT ischemia group but significantly raised the level in ischemia group. In terms of oxidative stress levels, iron content was considerably lower but MDA and SOD were increased significantly in the KO ischemia group than in the WT ischemic group. The findings above indicating that COX2 silencing greatly lower levels of oxidative stress.

Discussion

AMI may cause illnesses when the heart's blood flow is inadequate for the rest of the body's organs [29–31]. The side effects of left ventricular remodeling that happen after AMI continue to play a role in heart failure brought on by AMI, despite major improvements in reperfusion and pharmaceutical treatment of AMI [32–34]. COX2 is

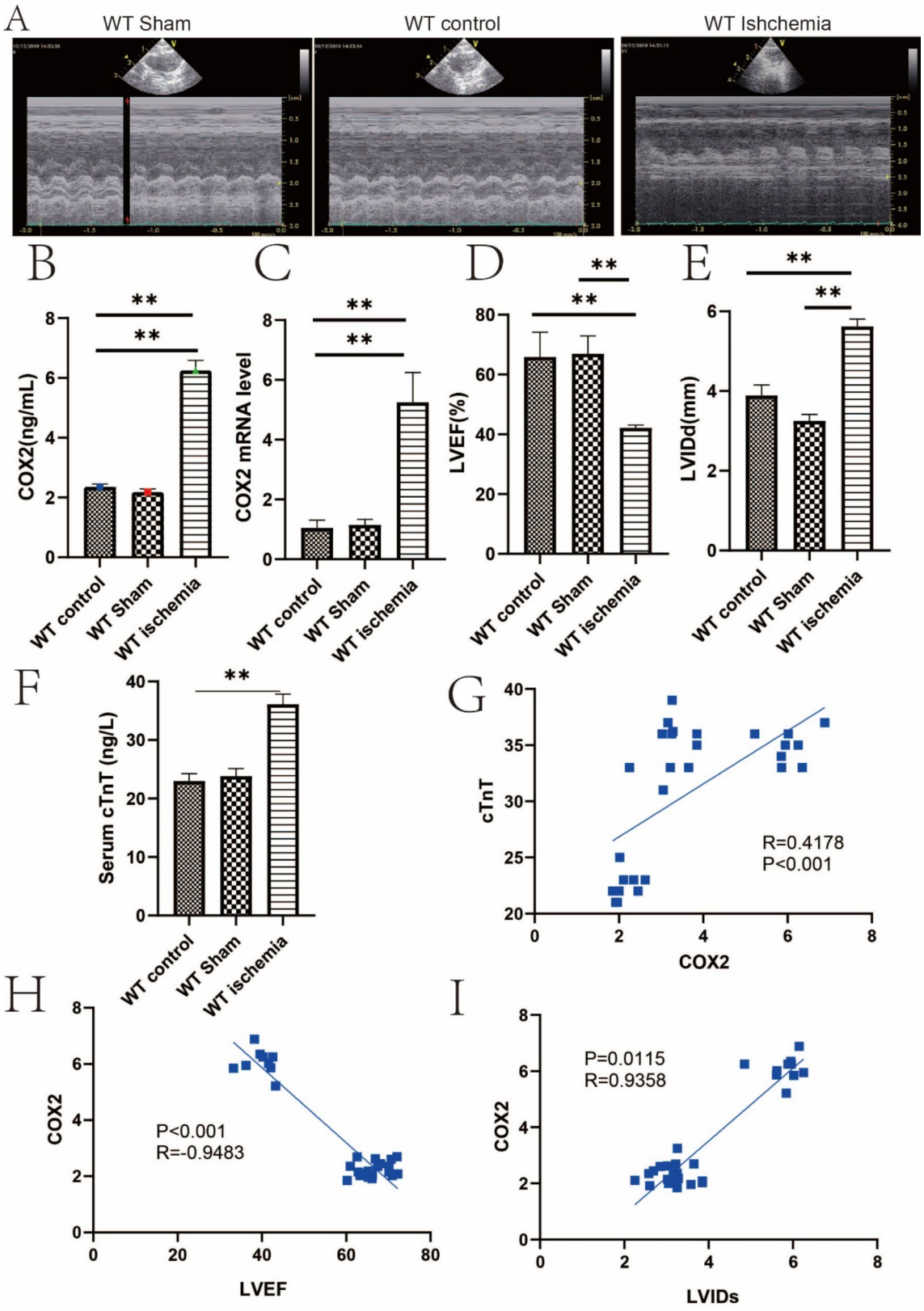

Fig. 2 Plasma/serum COX2 level and cardiac COX2 expression in mice following AMI. (**A**) Echo test. (**B**) COX2 level (**C**) COX2 mRNA. (**D**) LEVF. (**E**) LVIDd. (**F**) serum cTnT. (**G**) The correlationship between COX2 and cTnT. (**H**) The correlationship between COX2 and LVEF which show COX2 related with heart fuction. (**I**) The correlationship between COX2 and LVIDd which show COX2 related with heart fuction

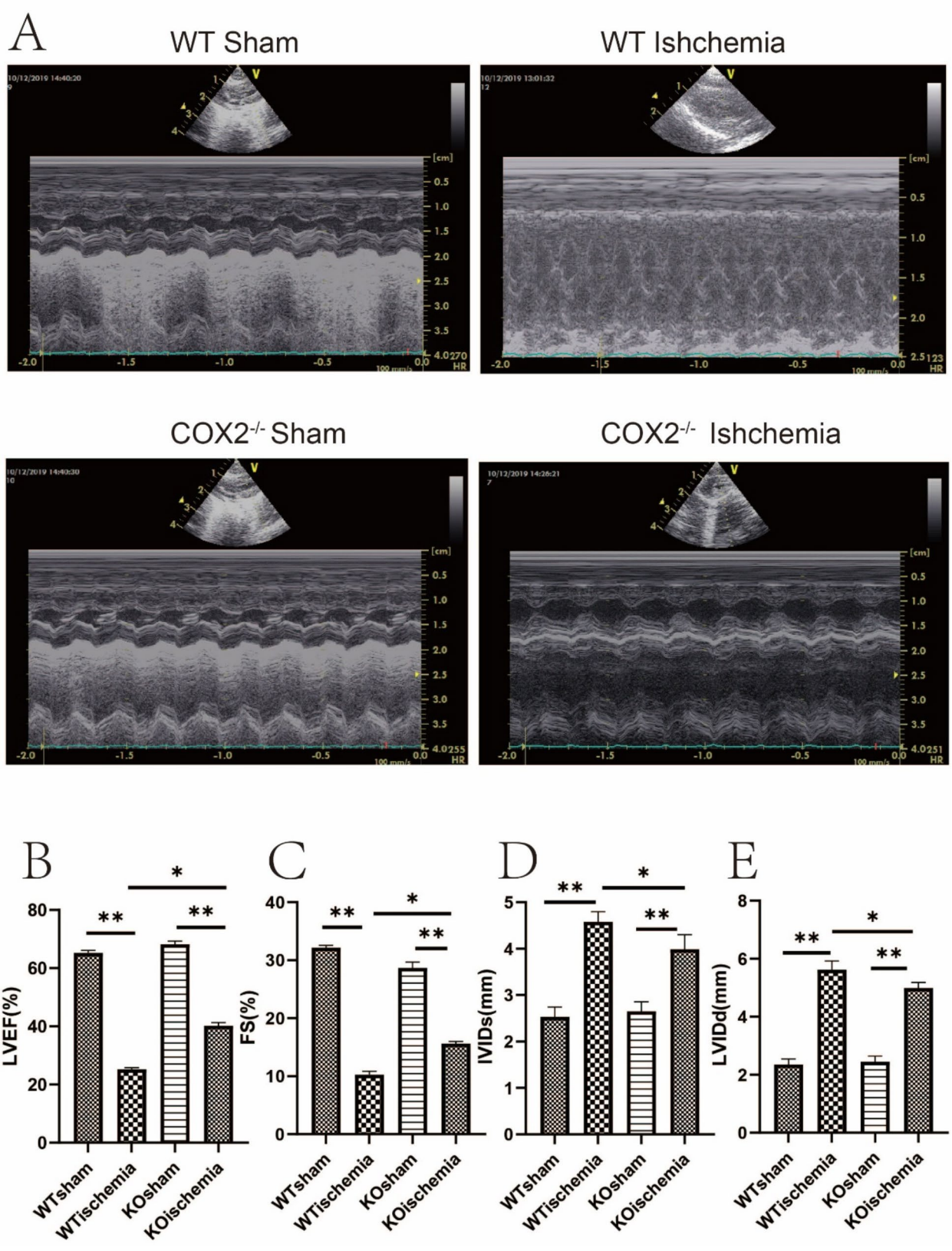

Fig. 3 Mice knockout COX2 had increased LVEF, FS while decreased LVIDs and LVIDd. (**A**) Echo test. (**B**) LVEF. (**C**) FS. (**D**) IVIDs. (**E**) IVIDd

Table 1 Physiological recorder results of LVSP, LVEDP, +dp/dt, −dp/dt 72 h after surgery in rats

Index	LVSP(mmHg)	LVEDP(mmHg)	+dp/dt (mmHg/ms)	−dp/dt (mmHg/ms)
WTSham	122.65 ± 11.92	2.61 ± 0.84	3.78 ± 0.58	3.65 ± 0.88
WTischemia	85.11 ± 15.69	11.08 ± 0.98	1.54 ± 0.45	1.67 ± 0.81
KOSham	135.26 ± 14.85	2.12 ± 0.84	3.08 ± 0.72	2.94 ± 0.44
KOischemia	105.64 ± 9.24	8.45 ± 1.15	2.59 ± 0.57	2.99 ± 0.51

implicated in oxidative stress mechanisms, according to earlier studies [35, 36]. In this work, we want to know the molecular mechanism by which COX2 influences myocardial cells in AMI. Hence, our work reveals that the Hippo signaling pathway was blocked by the down regulation of COX2, which promoted the healing and repair of cardiac tissues in AMI.

Firstly, our findings demonstrated that COX2 was markedly elevated in both the myocardium of AMI patients and peripheral blood. In obese mice, COX2 in adipose tissue macrophages controls adipose tissue dysfunction [37]. In addition, COX2 expression significantly increased in a number of tumor tissues, including breast cancer, oesophageal adenocarcinoma, and colorectal cancer [38–40]. According to David et al., macrophage COX2 increases the capacity for efferocytosis and efferocytosis-dependent reprogramming, which enhances the ability of macrophages to repair intestinal epithelium [41]. A possible biomarker and therapeutic target in melanoma are COX2 [42].

In our research, suppressing COX2 led to considerable improvements in heart function and myocardial oxidative stress levels. The present work, according to Zhao et al., provides proof that obese ATM-exosomal miR-140-5p promotes ferroptosis via controlling COX2 and offers a potential therapeutic approach for focusing on obese ATM-Exos in obesity-induced cardiac injury [43]. We further demonstrate that PGE2 levels are elevated in cardiac tissue that overexpresses COX2, supporting higher enzyme activity [44]. From the aforementioned information, it follows that gene silencing contributes to improved cardiac function, cell healing, and cell repair. Based on WGCNA, Liu et al. discovered that COX2 was a key gene associated with ferroptosis and hypoxia in acute myocardial infarction [45]. Selective COX-2 inhibitors include parecoxib (predrug of vadixib) and celecoxib (celecoxib). This class of drugs has a "class effect" of increasing cardiovascular risk [46]. COX2 is induced possibly participates in the regulation of vessel wall remodelling and ongoing inflammation [47]. By COX2-VEGF/NF-B signaling, thrombosis and inflammation were prevented in zebrafish [48]. Nevertheless, chronic COX2 overexpression is not linked to any obvious negative consequences, and induced cardiac-specific overexpression of COX2 has a significant cardioprotective benefit against myocardial infarction in rats. It has been found in the literature that COX2 has no clear conclusion on cardiac function, and previous studies have found that inhibition of COX-2 improves cardiac function after myocardial infarction (MI) in the mouse [49]. In contrast, another study has reported that COX-2 inhibition increases mortality, enhances left ventricular remodeling, and impairs systolic function after myocardial infarction in the pig [50]. However, in our study, we found a benefit of COX2 inhibition on improved cardiac function. We hypothesize that the possible cause is related to the level of oxidative stress intervened by COX2. However, there are differences in different literatures, which may need to be further explored.

Limitations

There are some points of limitations in our study, firstly, this study mainly investigated the role of COX2 in animal experimental models, and cellular models need to be added for further validation. In addition this study found that iron death has an important role in the data set analysis, but this study mainly analyzed the role of COX2 and did not analyze analyze the relationship between COX2 and iron death, which needs to be added to this part of the study in the future. Finally COX2 inhibitors have some research in clinical studies and it is recommended to supplement the clinical studies.

Conclusion

Protection effect provided by COX2 down regulation against myocardial defects in AMI is achieved, as we have shown. In addition. This study provides a possible reference for analyzing the role of cox2 in myocardial infarction and cardiovascular complications caused by cox2 inhibitors.

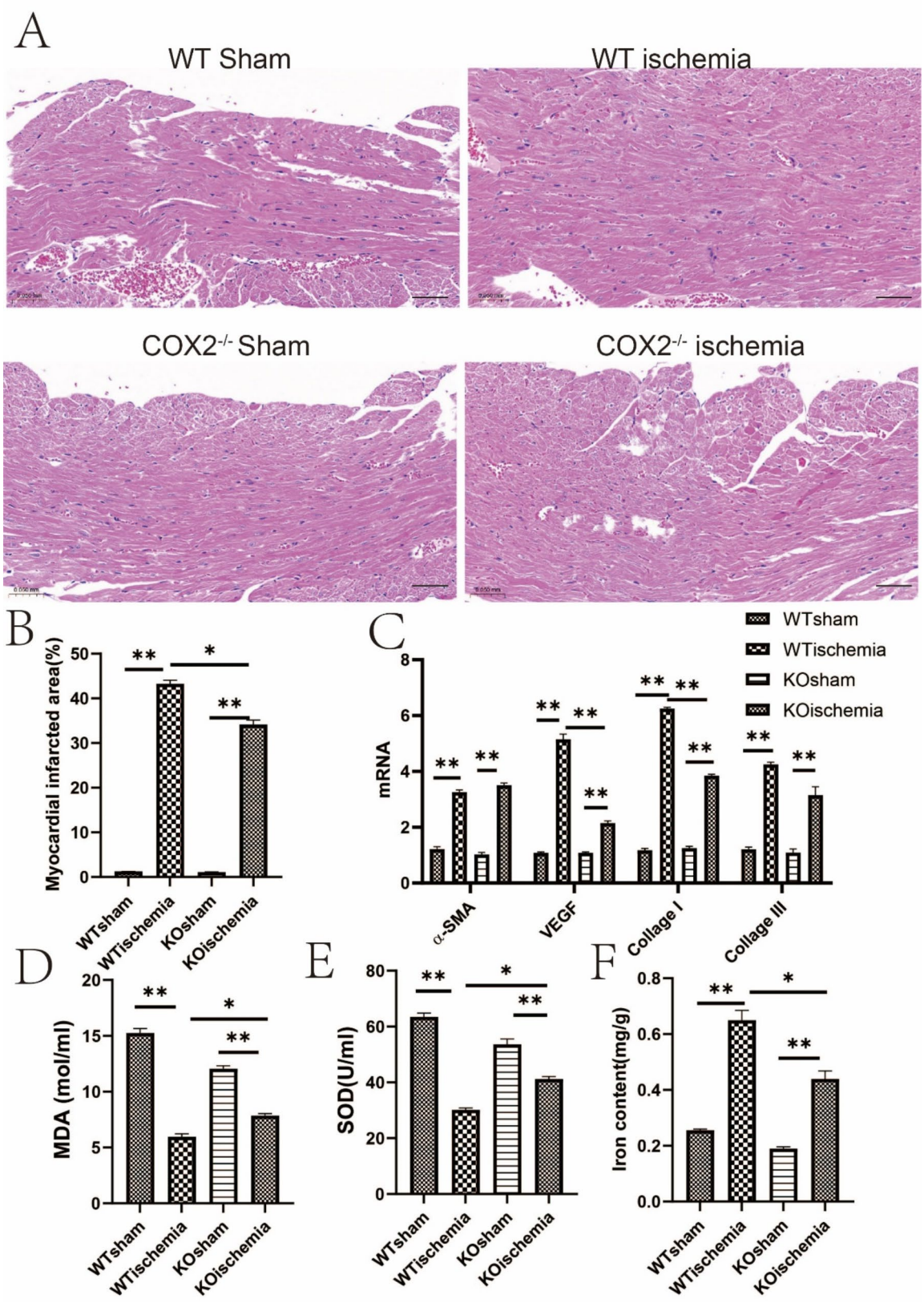

Fig. 4 Inhibition of Highly Expressed COX2 Reduced Infarct Size of area tissue and Improved Heart Function after AMI in Mice. (**A**) Masson trichrome histopathology analyses. (**B**) Myocardial infraction. (**C**) mRNA level after AMI in Mice. (**D**) MDA. (**E**) SOD. (**F**) Iron content

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04233-y.

Supplementary Material 1

Acknowledgements
We would like to thank all participants and our hospital.

Author contributions
Conceptualization: JZ, JQL; Data collation: JZ, JQL; Formal analysis: JZ, JQL; Funding acquisition: JZ, JQL; Investigation: JZ, JQL; Methodology: JZ, JQL; Project administration: JZ, JQL; Resources: JZ, JQL; Software: JZ, JQL; pervision: JZ, JQL; Validation: JZ; sualization: JZ, JQL; Writing – original draft: JZ; Writing – review & editing: JZ.

Funding
This research was not financed.

Data availability
The datasets generated and/or analysed during the current study are available in the GSE97320 repository（https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE97320）. The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
It is important to note that this research was carried out at a single center. The institutional review board and the ethical committee of The Second People's Hospital of Foshan both granted their approval (IRB) (IACUC-AEWC-F240112021).

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Received: 19 March 2024 / Accepted: 3 October 2024
Published online: 07 November 2024

References

1. Cai S, Zhao M, Zhou B, et al. Mitochondrial dysfunction in macrophages promotes inflammation and suppresses repair after myocardial infarction. J Clin Invest Feb. 2023;15(4). https://doi.org/10.1172/jci159498.
2. Danchin N. Improved long-term survival after acute myocardial infarction: the success of comprehensive care from the acute stage to the long term. Eur Heart J Feb. 2023;7(6):499–501. https://doi.org/10.1093/eurheartj/ehac714.
3. Wan Q, Kong D, Liu Q, et al. Congestive heart failure in COX2 deficient rats. Sci China Life Sci Jul. 2021;64(7):1068–76. https://doi.org/10.1007/s11427-020-1792-5.
4. Xin M, Olson EN, Bassel-Duby R. Mending broken hearts: cardiac development as a basis for adult heart regeneration and repair. Nat Reviews Mol cell Biology Aug. 2013;14(8):529–41. https://doi.org/10.1038/nrm3619.
5. Wang J, Liu Y, Liu Y, et al. Recent advances in nanomedicines for imaging and therapy of myocardial ischemia-reperfusion injury. J Controlled Release: Official J Controlled Release Soc Jan. 2023;353:563–90. https://doi.org/10.1016/j.jconrel.2022.11.057.
6. Yang T, Zhang D. Research progress on the effects of novel hypoglycemic drugs in diabetes combined with myocardial ischemia/reperfusion injury. Ageing Res Reviews Apr. 2023;86:101884. https://doi.org/10.1016/j.arr.2023.101884.
7. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. Jama Aug. 2000;16(7):835–42. https://doi.org/10.1001/jama.284.7.835.
8. Bhatt DL, Lopes RD, Harrington RA. Diagnosis and treatment of Acute Coronary syndromes: a review. Jama Feb. 2022;15(7):662–75. https://doi.org/10.1001/jama.2022.0358.
9. Braunwald E. Unstable angina and non-ST elevation myocardial infarction. American journal of respiratory and critical care medicine. May. 2012;1(9):924–32. https://doi.org/10.1164/rccm.201109-1745CI
10. Hashemi Goradel N, Najafi M, Salehi E, Farhood B, Mortezaee K. Cyclooxygenase-2 in cancer: a review. J Cell Physiol May. 2019;234(5):5683–99. https://doi.org/10.1002/jcp.27411.
11. Hu KQ. Cyclooxygenase 2 (COX2)-prostanoid pathway and liver diseases. Prostaglandins, leukotrienes, and essential fatty acids. Nov. 2003;69(5):329–37. https://doi.org/10.1016/j.plefa.2003.07.001
12. Streicher JM, Wang Y. The role of COX-2 in heart pathology. Cardiovascular & hematological agents in medicinal chemistry. Jan. 2008;6(1):69–79. https://doi.org/10.2174/187152508783329948
13. Xing Z, Yang C, He J, et al. Cardioprotective effects of Aconite in Isoproterenol-Induced myocardial infarction in rats. Oxidative Med Cell Longev. 2022;2022:1090893. https://doi.org/10.1155/2022/1090893.
14. Sun X, Wang Z, Cong X, et al. Mitochondrial gene COX2 methylation and downregulation is a biomarker of aging in heart mesenchymal stem cells. Int J Mol Med Jan. 2021;47(1):161–70. https://doi.org/10.3892/ijmm.2020.4799.
15. Wirrig EE, Gomez MV, Hinton RB, Yutzey KE. COX2 inhibition reduces aortic valve calcification in vivo. Arteriosclerosis, thrombosis, and vascular biology. Apr. 2015;35(4):938–47. https://doi.org/10.1161/atvbaha.114.305159
16. Zarraga IG, Schwarz ER. Coxibs and heart disease: what we have learned and what else we need to know. J Am Coll Cardiol Jan. 2007;2(1):1–14. https://doi.org/10.1016/j.jacc.2006.10.003.
17. Pellati F, Borgonetti V, Brighenti V, Biagi M, Benvenuti S, Corsi L. Cannabis sativa L. and Nonpsychoactive cannabinoids: their Chemistry and Role against oxidative stress, inflammation, and Cancer. Biomed Res Int. 2018;2018:1691428. https://doi.org/10.1155/2018/1691428.
18. Vallée A, Lecarpentier Y. Crosstalk between peroxisome proliferator-activated receptor Gamma and the canonical WNT/β-Catenin pathway in chronic inflammation and oxidative stress during carcinogenesis. Front Immunol. 2018;9:745. https://doi.org/10.3389/fimmu.2018.00745.
19. Wang Y, Liao S, Pan Z et al. Jun. Hydrogen sulfide alleviates particulate matter-induced emphysema and airway inflammation by suppressing ferroptosis. Free radical biology & medicine. 2022;186:1–16. https://doi.org/10.1016/j.freeradbiomed.2022.04.014
20. Zhao S, Cheng CK, Zhang CL, Huang Y. Interplay between oxidative stress, cyclooxygenases, and Prostanoids in Cardiovascular diseases. *Antioxidants & redox signaling*. Apr. 2021;1(10):784–99. https://doi.org/10.1089/ars.2020.8105.
21. Ajoolabady A, Aslkhodapasandhokmabad H, Libby P, et al. Ferritinophagy and ferroptosis in the management of metabolic diseases. Trends Endocrinol Metabolism: TEM Jul. 2021;32(7):444–62. https://doi.org/10.1016/j.tem.2021.04.010.
22. Bal E, Hanalıoğlu Ş, Apaydın AS et al. Can chlorogenic acid reduce oxidative stress and in an experimental spinal cord injury? Ulusal Travma ve acil cerrahi dergisi = Turkish journal of trauma & emergency surgery: TJTES. Jan 2022;28(2):125–33. Klorojenik asit tedavisi deneysel spinal kord yarlanmasında oksidatif stresi azaltabilir mi? https://doi.org/10.14744/tjtes.2020.89499
23. Hou L, Gu T, Weng K, et al. Effects of oxidative stress on the Autophagy and apoptosis of Granulosa cells in Broody Geese. Int J Mol Sci Jan. 2023;21(3). https://doi.org/10.3390/ijms24032154.
24. Gong Z, Li Q, Shi J, et al. Lung fibroblasts facilitate pre-metastatic niche formation by remodeling the local immune microenvironment. Immun Aug. 2022;9(8):1483–e15009. https://doi.org/10.1016/j.immuni.2022.07.001.
25. Yang X, Xu Y, Gao D, Yang L, Qian SY. Dihomo-γ-linolenic acid inhibits growth of xenograft tumors in mice bearing human pancreatic cancer cells (BxPC-3) transfected with delta-5-desaturase shRNA. Redox Biology Jan. 2019;20:236–46. https://doi.org/10.1016/j.redox.2018.10.001.
26. Bugger H, Pfeil K. Mitochondrial ROS in myocardial ischemia reperfusion and remodeling. Biochimica et biophysica acta molecular basis of disease. Jul. 2020;1(7):165768. https://doi.org/10.1016/j.bbadis.2020.165768
27. Song R, Dasgupta C, Mulder C, Zhang L. MicroRNA-210 Controls Mitochondrial Metabolism and Protects Heart Function in Myocardial Infarction. Circulation. Apr 12. 2022;145(15):1140–1153. https://doi.org/10.1161/circulationaha.121.056929
28. Cao Z, Qin H, Huang Y, et al. Crosstalk of pyroptosis, ferroptosis, and mitochondrial aldehyde dehydrogenase 2-related mechanisms in sepsis-induced

lung injury in a mouse model. Bioengineered Mar. 2022;13(3):4810–20. https://doi.org/10.1080/21655979.2022.2033381.
29. Held C. Editorial commentary: emotional distress in women after acute myocardial infarction - still a long way to walk. Trends Cardiovasc Med Aug. 2022;32(6):348–9. https://doi.org/10.1016/j.tcm.2021.08.007.
30. Nevins MA, Lyon LJ. The treatment of acute myocardial infarction. Med Clin North Am Mar. 1974;58(2):435–57. https://doi.org/10.1016/s0025-7125(16)32170-8.
31. Trost JC, Lange RA. Treatment of acute coronary syndrome: part 2: ST-segment elevation myocardial infarction. Crit care Med Jun. 2012;40(6):1939–45. https://doi.org/10.1097/CCM.0b013e31824e18c2.
32. Damluji AA, van Diepen S, Katz JN, et al. Mechanical complications of Acute Myocardial Infarction: A Scientific Statement from the American Heart Association. Circulation Jul. 2021;13(2):e16–35. https://doi.org/10.1161/cir.0000000000000985.
33. DeFilippis AP, Chapman AR, Mills NL, et al. Assessment and treatment of patients with type 2 myocardial infarction and Acute Nonischemic Myocardial Injury. Circulation Nov. 2019;12(20):1661–78. https://doi.org/10.1161/circulationaha.119.040631.
34. Gulati R, Behfar A, Narula J et al. Jan. Acute Myocardial Infarction in Young Individuals. Mayo Clinic proceedings. 2020;95(1):136–156. https://doi.org/10.1016/j.mayocp.2019.05.001
35. Anamthathmakula P, Winuthayanon W. Prostaglandin-endoperoxide synthase 2 (PTGS2) in the oviduct: roles in fertilization and early embryo development. Endocrinol Apr. 2021;1(4). https://doi.org/10.1210/endocr/bqab025.
36. Zhou Y, Zhou H, Hua L et al. Verification of ferroptosis and pyroptosis and identification of PTGS2 as the hub gene in human coronary artery atherosclerosis. Free radical biology & medicine. Aug 1. 2021;171:55–68. https://doi.org/10.1016/j.freeradbiomed.2021.05.009
37. Pan Y, Cao S, Tang J, et al. Cyclooxygenase-2 in adipose tissue macrophages limits adipose tissue dysfunction in obese mice. J Clin Invest May. 2022;2(9). https://doi.org/10.1172/jci152391.
38. Cui HY, Wang SJ, Song F, et al. CD147 receptor is essential for TFF3-mediated signaling regulating colorectal cancer progression. Signal transduction and targeted therapy. Jul. 2021;14(1):268. https://doi.org/10.1038/s41392-021-00677-2
39. Peng Y, Wang Y, Tang N, et al. Andrographolide inhibits breast cancer through suppressing COX-2 expression and angiogenesis via inactivation of p300 signaling and VEGF pathway. J Experimental Clin cancer Research: CR Oct. 2018;12(1):248. https://doi.org/10.1186/s13046-018-0926-9.
40. Spence AD, Trainor J, McMenamin Ú, et al. High PTGS2 expression in post-neoadjuvant chemotherapy-treated oesophageal adenocarcinoma is associated with improved survival: a population-based cohort study. Histopathology Mar. 2019;74(4):587–96. https://doi.org/10.1111/his.13786.
41. Meriwether D, Jones AE, Ashby JW, et al. Macrophage COX2 mediates efferocytosis, Resolution Reprogramming, and intestinal epithelial repair. Cell Mol Gastroenterol Hepatol. 2022;13(4):1095–120. https://doi.org/10.1016/j.jcmgh.2022.01.002.
42. Tudor DV, Bâldea I, Lupu M, et al. COX-2 as a potential biomarker and therapeutic target in melanoma. Cancer Biology Med Feb. 2020;15(1):20–31. https://doi.org/10.20892/j.issn.2095-3941.2019.0339.
43. Zhao X, Si L, Bian J et al. Mar. Adipose tissue macrophage-derived exosomes induce ferroptosis via glutathione synthesis inhibition by targeting SLC7A11 in obesity-induced cardiac injury. Free radical biology & medicine. 2022;182:232–245. https://doi.org/10.1016/j.freeradbiomed.2022.02.033
44. Guo Y, Nong Y, Tukaye DN, et al. Inducible cardiac-specific overexpression of cyclooxygenase-2 (COX-2) confers resistance to ischemia/reperfusion injury. Basic Res Cardiol Jul. 2019;5(5):32. https://doi.org/10.1007/s00395-019-0741-2.
45. Liu K, Chen S, Lu R. Identification of important genes related to ferroptosis and hypoxia in acute myocardial infarction based on WGCNA. Bioengineered Dec. 2021;12(1):7950–63. https://doi.org/10.1080/21655979.2021.1984004.
46. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. Jama Aug 22–29. 2001;286(8):954–9. https://doi.org/10.1001/jama.286.8.954.
47. Keränen S, Suutarinen S, Mallick R, et al. Cyclo-oxygenase 2, a putative mediator of vessel remodeling, is expressed in the brain AVM vessels and associates with inflammation. Acta Neurochir Sep. 2021;163(9):2503–14. https://doi.org/10.1007/s00701-021-04895-z.
48. Wang Z, Liu P, Hu M, et al. Naoxintong restores ischemia injury and inhibits thrombosis via COX2-VEGF/ NFκB signaling. J Ethnopharmacol Apr. 2021;24:270:113809. https://doi.org/10.1016/j.jep.2021.113809.
49. LaPointe MC, Mendez M, Leung A, Tao Z, Yang XP. Inhibition of cyclooxygenase-2 improves cardiac function after myocardial infarction in the mouse. Am J Physiol Heart Circ Physiol Apr. 2004;286(4):H1416–24. https://doi.org/10.1152/ajpheart.00136.2003.
50. Timmers L, Sluijter JP, Verlaan CW, et al. Cyclooxygenase-2 inhibition increases mortality, enhances left ventricular remodeling, and impairs systolic function after myocardial infarction in the pig. Circulation Jan. 2007;23(3):326–32. https://doi.org/10.1161/circulationaha.106.647230.

Publisher's note