

Original Paper

Exercise Training Protects Against Acute Myocardial Infarction via Improving Myocardial Energy Metabolism and Mitochondrial Biogenesis

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Key Words

Acute myocardial infarction • Exercise training • Metabolism • Mitochondria • PGC-1 α

Abstract

Background/Aims: Acute myocardial infarction (AMI) represents a major cause of morbidity and mortality worldwide. Exercise has been proved to reduce myocardial ischemia-reperfusion (I/R) injury. However it remains unclear whether, and (if so) how, exercise could protect against AMI. **Methods:** Mice were trained using a 3-week swimming protocol, and then subjected to left coronary artery (LCA) ligation, and finally sacrificed 24 h after AMI. Myocardial infarct size was examined with triphenyltetrazolium chloride staining. Cardiac apoptosis was determined by TUNEL staining. Mitochondria density was checked by Mito-Tracker immunofluorescent staining. Quantitative reverse transcription polymerase chain reactions and Western blotting were used to determine genes related to apoptosis, autophagy and myocardial energy metabolism. **Results:** Exercise training reduces myocardial infarct size and abolishes AMI-induced autophagy and apoptosis. AMI leads to a shift from fatty acid to glucose metabolism in the myocardium with a downregulation of PPAR- α and PPAR- γ . Also, AMI induces an adaptive increase of mitochondrial DNA replication and transcription in the acute phase of MI, accompanied by an activation of PGC-1 α signaling. Exercise abolishes the derangement of myocardial glucose and lipid metabolism and further enhances the adaptive increase of mitochondrial biogenesis. **Conclusion:** Exercise training protects against AMI-induced acute cardiac injury through improving myocardial energy metabolism and enhancing the early adaptive change of mitochondrial biogenesis.

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Introduction

Acute myocardial infarction (AMI) is in many cases the first manifestation of coronary artery disease (CAD) and represents a major cause of morbidity and mortality worldwide [1–3]. The cardiac cell death comprising necrosis, apoptosis, and autophagy is one of the most important pathological features of AMI [4–8]. Cardiac cell death can be triggered by a complexity of interrelated events such as dysregulated myocardial energy metabolism and mitochondrial injury during prolonged myocardial ischemia [4–8].

Accumulating evidence indicates the protective effect of exercise against diverse cardiovascular diseases, which is supposed to be related with reduced cardiovascular risk factors, as well as improved physiological cardiac growth, cytosolic antioxidant capacity and mitochondrial viability in response to endurance exercise activity [9, 10]. Notably, exercise-based cardiac rehabilitation has been shown to improve exercise tolerance and reduce mortality in CAD patients [11–13]. Meanwhile, it has been documented in animal models that short-term exercise training (e.g. several bouts of endurance exercise) is sufficient to produce preconditioning stimuli [14–19], thus making the heart more resistant to cardiac injury following myocardial ischemia-reperfusion (I/R) [20–23]. Also, it has previously been demonstrated that long-term exercise training (e.g. 4-week voluntary exercise training) protects the heart from myocardial I/R injury via stimulation of β_3 -adrenergic receptor (β_3 -AR) and activation of nitric oxide (NO) signaling in mice [24]. However, little is known about whether, and (if so) how, long-term regular exercise training could attenuate AMI.

Here we show that mice subjected to a 3-week swimming protocol are more resistant to AMI, as indicated by reduced infarct size and attenuated cardiac cell death 24 h after the ligation of left coronary artery (LCA), where long-term exercise training improves myocardial glucose and lipid metabolism and further enhances adaptive increase of mitochondrial biogenesis following MI accompanied by an activation of PGC-1 α signaling.

Materials and Methods

This study was approved by the ethical committees of the Nanjing Medical University and all animal experiments were conducted under the guidelines on humane use and care of laboratory animals for biomedical research published by National Institutes of Health (No. 85-23, revised 1996).

Animals

Male C57BL/6 mice aged 10–12 weeks were purchased from Nanjing University (Nanjing, China). Mice were maintained in a temperature-controlled room on a 12/12 h light/dark cycle. Mice received a swimming training program to induce cardiac physiological hypertrophy. Briefly, mice received a ramp protocol, which lasted for 10 minutes 2 times daily and increased with 10 minutes each day until training time reached 90 minutes 2 times per day. The protocol was ended after 21 days. To induce AMI, mice received coronary artery ligation surgery after anesthetized with ketamine and sevoflurane. The left coronary artery (LCA) about 2 mm under the left auricle was ligated with 7-0 silk sutures. Twenty-four hours after the establishment of AMI, the hearts were harvested. The heart weight/body weight ratio and the heart weight/tibia length ratio were determined to evaluate exercise-induced cardiac growth. Myocardial infarct size was examined with triphenyltetrazolium chloride (TTC) staining and quantified with the ratio of area-at-risk relative to total area (AAR/Total) and the ratio of infarct size relative to AAR (INF/AAR).

Tunel staining

Heart tissues were harvested and embedded with paraffin. The 4 μ m-thick tissues were subjected to TdT-mediated dUTP nick end labeling (TUNEL) staining using in situ cell death detection Kit (cat. 11684817910, Roche) according to the manufacturer's instructions.

Mito-Tracker immunofluorescent staining

Primary rat neonatal cardiomyocytes were isolated and subjected to serum deprivation with or without treatment of Insulin-like Growth Factor-1 (IGF-1, 0.1 μM) for 24 h. Cells were then stained with Mitotracker (Beyotime Biotechnology, Nantong, Jiangsu, China) at a concentration of 200 nM for 45 minutes, and after that cells were fixed in 4% formaldehyde in pre-warmed media and stained with DAPI (Invitrogen, Carlsbad, CA, USA) to marker cell nuclei. 15-20 fields/well (400x magnification) were imaged by using confocal microscope (Carl Zeiss, Thuringia, Germany). Cell fluorescence intensity were measured with Zeiss software.

Western blot

The heart tissues were lysed in RIPA buffer (Beyotime, China) containing 0.5 mM PMSF (Beyotime, China). Western blot was done using standard 12% SDS-PAGE gel and loading 20 μg of protein per lane, with detection by ECL system (Bio-Rad, USA) after incubated with proper antibodies. The expressions of autophagy-associated protein LC3-I/II and p62 were detected with specific primary antibodies against LC3I/II (1:1000, Cell Signaling Technology, Boston, Massachusetts, USA, #4108) and p62 (1:1000, Cell Signaling Technology, Boston, Massachusetts, USA, #5114). Apoptotic protein expressions were detected with primary antibodies against Bax (1:1000, Cell Signaling Technology, Boston, Massachusetts, USA, #2772), Bcl-2 (1:1000, Cell Signaling Technology, Boston, Massachusetts, USA, #3498), caspase-3 (1:1000, Cell Signaling Technology, Boston, Massachusetts, USA, #9662), and cleaved-caspase-3 (1:1000, Cell Signaling Technology, Boston, Massachusetts, USA, #9661). PPAR-α, PPAR-γ, and PGC-1α expressions were measured with primary antibodies against PPAR-α (1:1000, Abcam, Cambridge, UK, ab8934), PPAR-γ (1:500, Abcam, Cambridge, UK, ab19481), and PGC-1α (1:1000, NOVUS, Colorado, Littleton, USA, NBP1-04676). GAPDH (1:10000, Kangchen) was used for loading control. All the primary antibodies were incubated overnight at 4°C.

Quantitative reverse transcription polymerase chain reactions (qRT-PCRs)

Total RNA of heart tissues was extracted using TRIZOL reagent (Invitrogen). A total of 300 ng RNA was used for cDNA synthesis with the PrimeScript RT Reagent Kit Perfect Real Time (TaKaRa, China). PCR amplification was performed with SYBR Premix ExTaq TM II (TaKaRa, China). For each sample, 18s rRNA expression was analyzed to normalize target gene expression. The utilized primers are listed in Table 1.

Table 1. List of utilized primers for qRT-PCR

Gene	Species	Forward Primer	Reverse Primer
Atg3	mouse	ACACGGTGAAGGAAAGGC	TGGTGGACTAAGTGATCTCCAG
Atg5	mouse	TGTGCTTCGAGATGTGTGTT	GTCAAATAGCTGACTTTGGCAA
Atg7	mouse	GTTCGCCCCCTTAATAGTGC	TGAACTCCAACGTC AAGCGG
Beclin1	mouse	ATGGAGGGGTCTAAGGCGTC	TCCTCTCTGAGTTAGCCTCT
LC3	mouse	GGTACGGCTACTATCGCAC	AGGAGGGCATGACAAAGGAGA
CathepsinB	mouse	TCCTTGATCCTTCTTTTGCC	ACAGTGCCACACAGCTTCTTC
CathepsinD	mouse	GCTTCCGGTCTTTGACAACT	CACCAAGCATTAGTTCTCTCTC
GSY1	mouse	GAGAACGCAGTGCTTTTGA	TCATCCCTGTCACCTTCG
GLUT-1	mouse	TCTCGGCTTAGGGCATGGAT	TCTATGACGCCGTGATAGCAG
GLUT-4	mouse	ACTTGTGCCACACAGGCTCT	CCTTGCCCTGTGAGGATGAT
CPT-1	mouse	CTCCGCTGAGCCATGAAG	CACCAAGTATGATGCCATTCT
MCAD	mouse	TTTCTAGATAGGTTTGGCTTTGG	ACAGAAATGCTGCTATGTCACAGT
LPL	mouse	GGTTGCGCGTAGAGAGGATG	CTCAGCTCTGACATGCCCTTC
PPAR-α	mouse	AGAGCCCATCTGCTCTCTC	ACTGGTAGTCTGCAAACCAAAA
PPAR-γ	mouse	TCCTGTAAAAGCCCGAGTAT	GCTCTGGTAGGGCAGTGA
16sRNA	mouse	TGCCTGCCAGTGACTAAAGT	AACAAGTGATTATGCTACCTTTGCA
ND1	mouse	GCGCTTTGAGACCTGGA AAAA	GGCCAGTCCGATAAAAAGTTTCA
ND6	mouse	GCTCAAGAACTAATCACAGCCA	GGTGGCTTATTCTACCATG
CYTB	mouse	AAGTCATGGTGGCAACTAAT	TGTAGTGTGAACATCCTCTCCAT
SSBP1	mouse	CAACAATGAGATGTGGCGATCA	ACGAGCTTCTTACCAGCTATGA
TWINKLE	mouse	TTCTCCGACGTGCATATCCC	GCGCTTTTCTGTACCTTCT
TOP1MT	mouse	GTTTCCAGCATGTCCCCTG	TTGCCATCGTAGAGGAAGTGC
PLOG	mouse	GAGCCTGCCTTACTTGGAGG	GGCTGCACCAGGAATACCA
PGC-1α	mouse	TATGGAGTGACATAGAGTGTGCT	CCACTTCAATCCACCCAGAAAG
NRF1	mouse	AGCACGGAGTGACCCAAAC	TGTACGTGGCTACATGGACCT
NRF2B2	mouse	GCTGGGAATTTGCACTCCAT	CTGTGGTATTCTGGGCCTC
TFAM	mouse	ATTCCGAAGTGTTTTCCAGCA	TCTGAAAGTTTGCATCTGGGT
TFB2M	mouse	GGCCCATCTTGCACTTAGGG	CAGGCAACGGCTCTATATTGAAG
18s rRNA	mouse	TCAAGAACGAAAGTCGGAGG	GGACATCTAAGGGCATCAC

Statistical analysis

Relative mRNA expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method. All data were presented as mean \pm SEM. A Chi-squared test or one-way ANOVA was conducted to evaluate the one-way layout data. If a significant difference was observed, Bonferroni's post-hoc test was conducted to identify groups with significant differences. All analyses were performed using SPSS 19.0. A two-sided P value less than 0.05 was considered to be statistically significant.

Results

Exercise training reduces the infarct size following AMI

To determine whether long-term exercise training attenuates acute myocardial ischemia, mice were subjected to a swimming protocol for 3 weeks. At the end of training period, acute

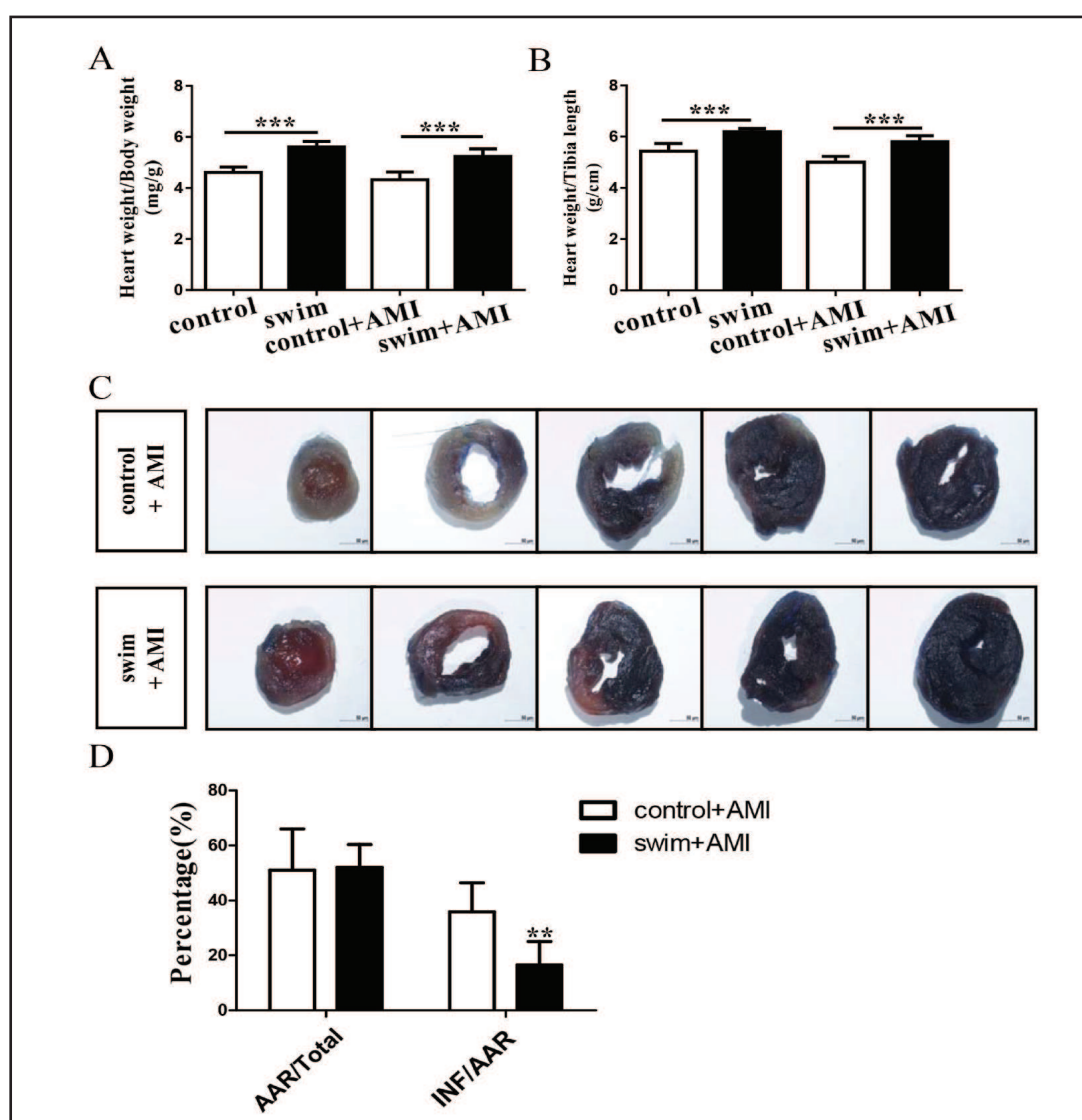


Fig. 1. Exercise training reduces myocardial infarct size after acute myocardial infarction. Exercise training induces an increase in the heart weight/body weight ratio (A) and the heart weight/tibia length ratio (B) compared with sedentary mice regardless of the LCA ligation. Myocardial infarct size was measured with TTC staining (C) and quantified with the ratio of area-at-risk (AAR) to total area (AAR/Total) and the ratio of infarct size to AAR (INF/AAR) (D). N=6 per group. **, p<0.01; ***, p<0.001.

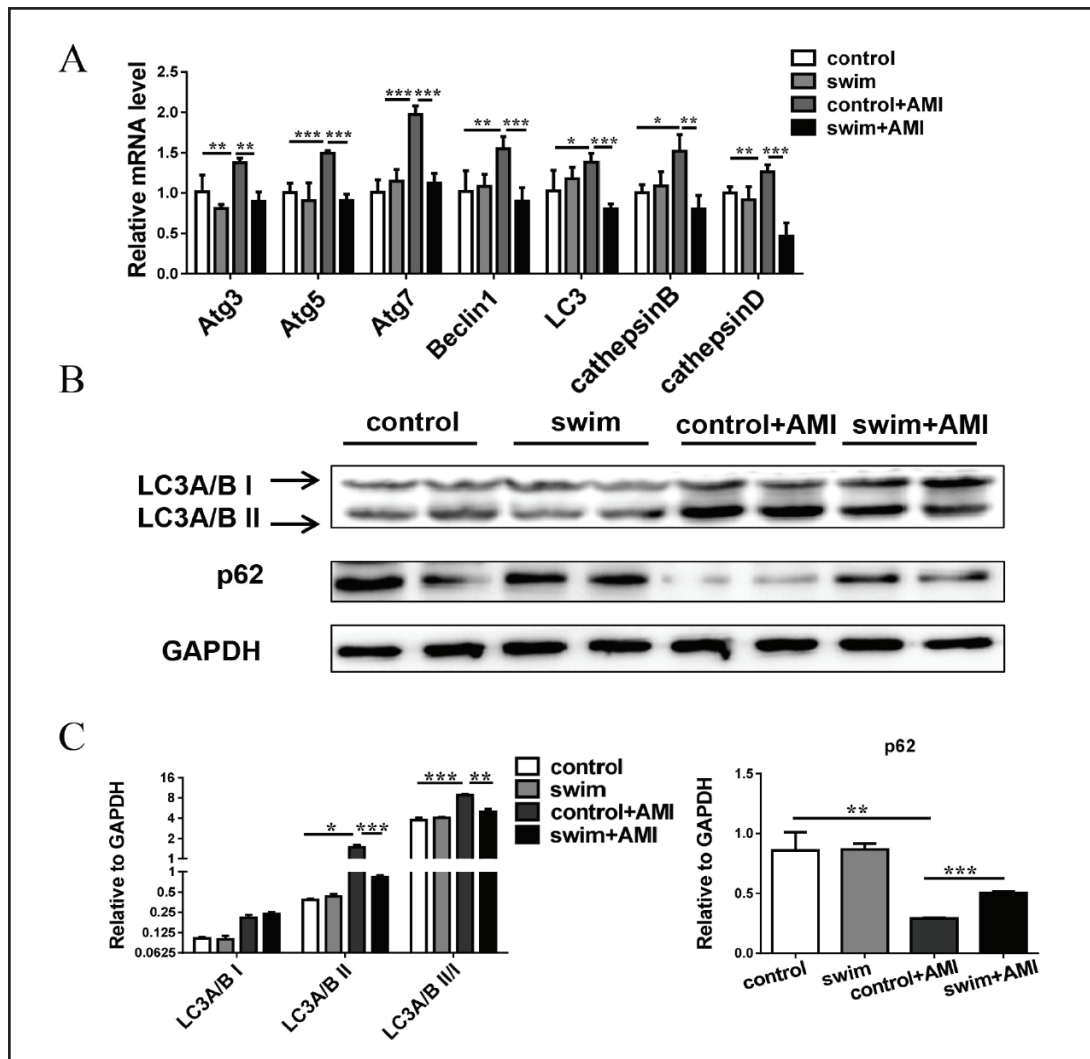


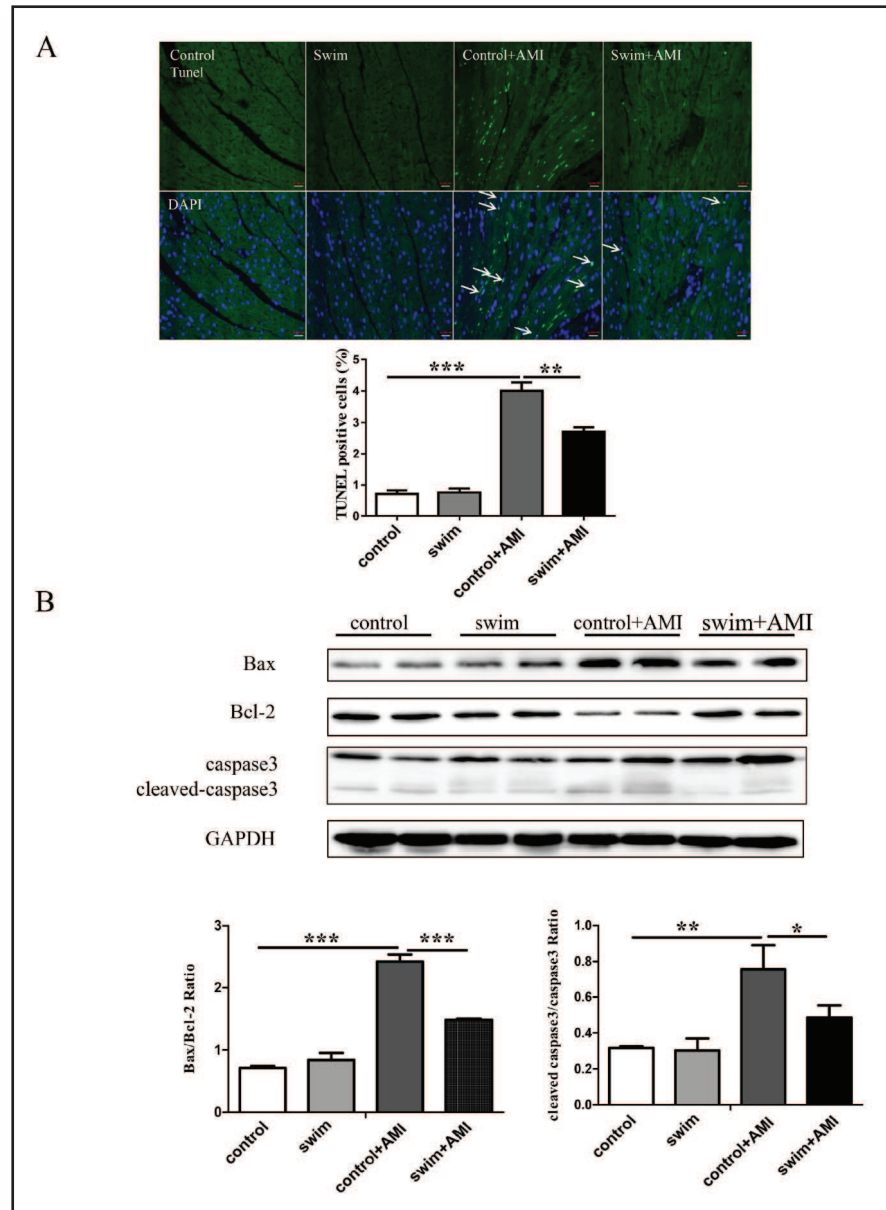
Fig. 2. Exercise training attenuates acute myocardial infarction induced autophagy. (A) mRNA levels of autophagy-associated genes. N=6 per group. Western blot (B) and quantitative analysis (C) for protein levels of LC3A/BI, LC3A/BII and p62 relative to GAPDH. N=3 per group. *, p<0.05; **, p<0.01; ***, p<0.001.

myocardial ischemia was induced by LCA ligation and 24 h later the subsequent infarction was evaluated. Exercised mice displayed an increase in the heart weight/body weight ratio and the heart weight/tibia length ratio compared with sedentary mice regardless of the LCA ligation, indicative of a physiological cardiac growth due to endurance exercise (Fig. 1A and B). Exercise was associated with a reduction in the infarct size as demonstrated by TTC staining (Fig. 1C and D).

Exercise training attenuates AMI-induced autophagy and apoptosis

Permanent myocardial ischemia induces autophagy and apoptosis of cardiomyocytes [6]. In this work, the autophagy-associated genes, including Atg3, Atg5, Atg7, Beclin1, LC3, cathepsin B and cathepsin D, were significantly induced 24 h after LCA ligation (Fig. 2A). Meanwhile, immunoblotting analysis showed that the conversion of LC3 from LC3I to LC3II was increased, while the expression of p62, a selective autophagy substrate, was downregulated in hearts subjected to LCA ligation (Fig. 2B and C). Markedly, exercise training reversed upregulation of autophagy-associated genes (Fig. 2A), and was associated with reduced conversion of LC3I/II and increased protein level of p62 (Fig. 2B and C) in

Fig. 3. Exercise training reverses acute myocardial infarction induced apoptosis. (A) TUNEL staining for evaluation of the apoptosis in the heart. N=6 per group. Scale bar, 20µm. (B) Western blot analysis for the ratio of Bax/Bcl-2 and the ratio of cleaved-caspase3/caspase3 at protein levels. N=3 per group. *, p<0.05; **, p<0.01; ***, p<0.001.



the hearts with myocardial ischemia, indicating that AMI-induced autophagy was attenuated by exercise training. Meanwhile, TUNEL staining was performed to evaluate the apoptosis in the heart and the protein levels of pro-apoptotic Bax and anti-apoptotic Bcl-2, as well as the caspase-3 activation (cleaved-caspase 3 relative to caspase 3) were measured with immunoblotting. AMI caused an increase in the TUNEL positive cells (%) as well as an increase in the Bax/Bcl-2 ratio and the cleaved-caspase 3/caspase 3 ratio at protein level in heart tissues, which was abolished by exercise training (Fig. 3A and B).

Exercise training abrogates glucose and fatty acid metabolic changes in ischemic hearts

Myocardial enzymes related to glucose and fatty acid metabolism change rapidly after myocardial ischemia with and without reperfusion, which can be importantly regulated by peroxisome proliferator-activated receptors (PPAR) [25–29]. Here we demonstrated that the mRNA levels of glucose transporter (GLUT)-1 and glycogen synthase 1 (GSY1) were significantly induced in ischemic hearts, despite unchanged expression of GLUT-4 (Fig. 4A). Meanwhile, the enzymes involved in fatty acid metabolism, including carnitine

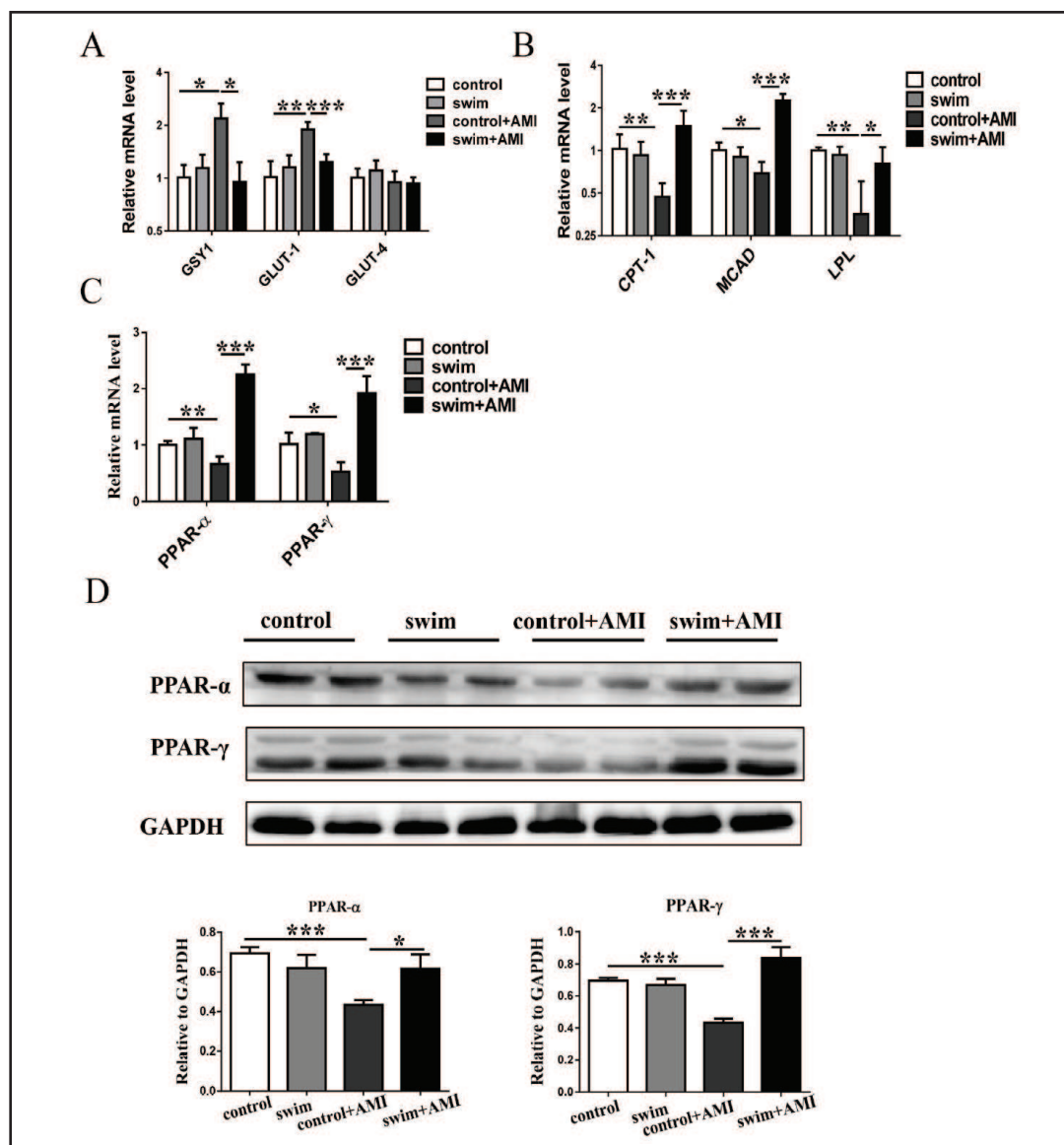


Fig. 4. Exercise improves myocardial glucose and fatty acid metabolism following acute myocardial infarction. (A) mRNA levels of transporters and enzymes involved in glucose metabolism. (B) mRNA levels of enzymes involved in fatty acid metabolism. mRNA (C) and protein (D) levels of PPAR- α and PPAR- γ . N=6 for qPCRs and N=3 for Western blot per group. *, p<0.05; **, p<0.01; ***, p<0.001.

palmitoyltransferase 1 (CPT1), medium-chain acyl-CoA dehydrogenase (MCAD), and lipoprotein lipase (LPL) were downregulated in the hearts subjected to LCA ligation (Fig. 4B). In addition, myocardial ischemia was associated with a downregulation of PPAR- α and PPAR- γ at mRNA and protein levels (Fig. 4C and D). All of these changes were reversed by exercise training (Fig. 4A-D).

Adaptive increase of mitochondrial biogenesis and activation of PGC-1 α pathway following AMI is further induced by exercise training

Although impaired mitochondrial biogenesis following AMI is responsible for altered energy production in hearts, the adaptive regulation of mitochondrial biology in the acute phase after myocardial ischemia is largely unknown. Our results demonstrated that mtDNA encoded genes (16sRNA, ND1, and ND6), as well as genes involved in mtDNA replication

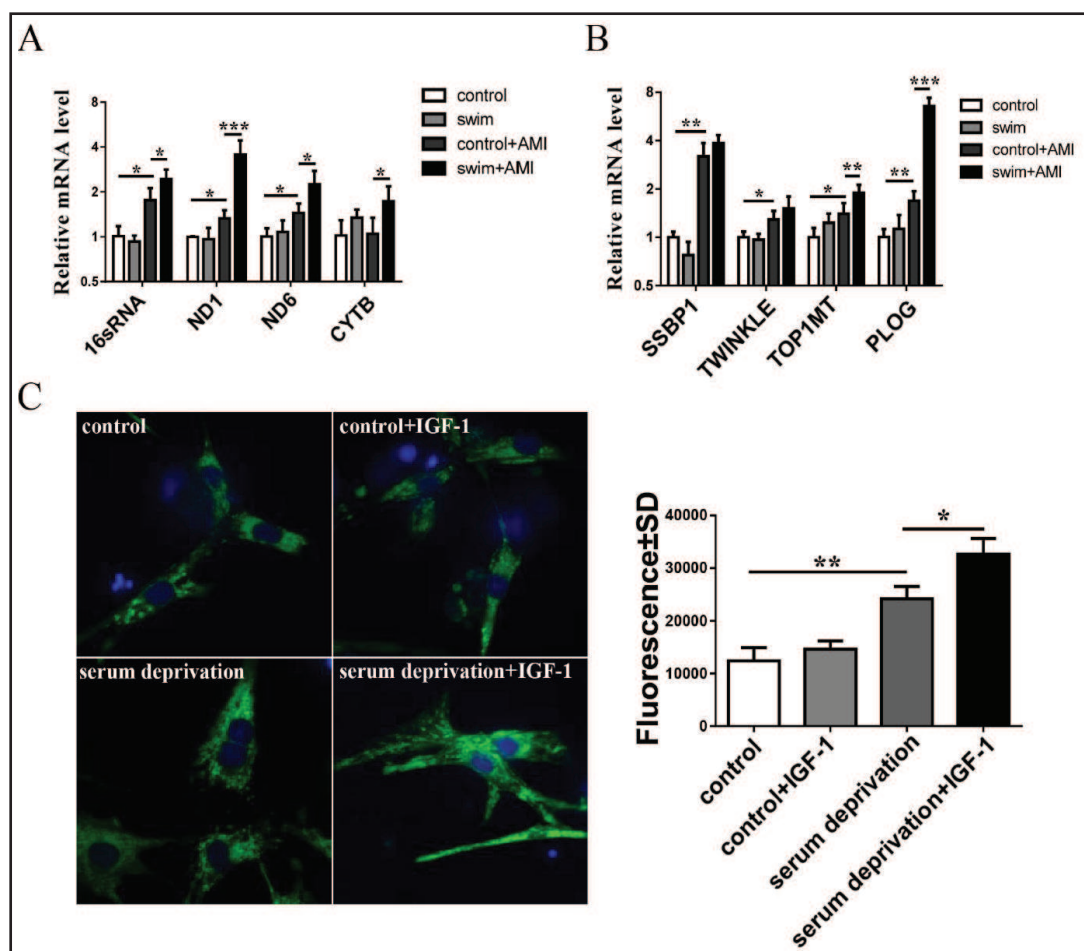
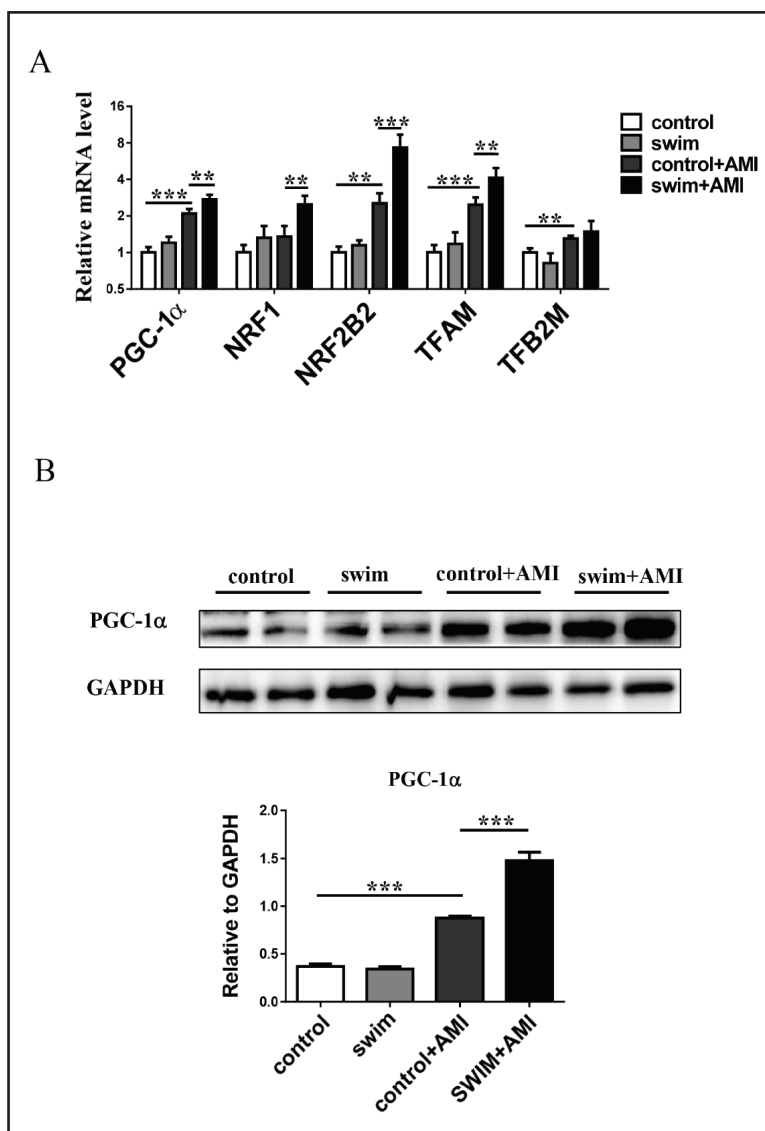


Fig. 5. Exercise enhances the adaptive increase of mitochondrial biogenesis in the acute phase of AMI. (A) mRNA levels of mtDNA encoded genes. (B) mRNA levels of genes involved in mtDNA replication. (C) Representative images and quantitative analysis of immunofluorescent staining for mitochondria. AMI, mimicked by serum deprivation; Exercise, mimicked by Insulin-like Growth Factor-1 treatment. N=6 for qPCRs and N=3 for immunofluorescence per group. *, p<0.05; **, p<0.01; ***, p<0.001.

(SSBP1, TWINKLE, TOP1MT, and PLOG), were upregulated in hearts 24 h after AMI (Fig. 5A and B). Noteworthy, the genes encoding 16sRNA, ND1, ND6, CYTB, TOP1MT and PLOG were induced to a greater extent in exercised mice with AMI (Fig. 5A and B). Meanwhile, immunofluorescent staining for mitochondria showed that the mitochondria fluorescence intensity was markedly increased by serum deprivation mimicking AMI *in vitro*, which was further enhanced with IGF-1 treatment mimicking exercise (Fig. 5C). These data indicate that the adaptive increase of mitochondria biogenesis could be further enhanced by exercise training.

As PGC-1 α is a key regulator of mitochondrial biology which can be induced by exercise, and plays critical roles in the metabolic control of myocardium in cardiac diseases [30, 31], we further investigated the PGC-1 α cascade in ischemic hearts with and without exercise. In the present study, AMI was associated with an upregulation of PGC-1 α at both mRNA and protein levels (Fig. 6A and B). In addition, its downstream transcription factors such as NRF2B2, TFAM and TFB2M were also upregulated at mRNA level in ischemic hearts (Fig. 6A). The gene expressions of PGC-1 α , NRF2B2 and TFAM were further induced in exercised mice with AMI (Fig. 6A). Although cardiac NRF1 gene expression was not significantly changed in ischemic hearts, its mRNA level was markedly upregulated by exercise in mice subjected to LCA ligation (Fig. 6A).

Fig. 6. PGC-1 α pathway is activated to a greater extent in the acute phase of AMI. (A) mRNA levels of PGC-1 α and its downstream effectors. (B) Western blot and quantitative analysis for protein level of PGC-1 α . N=6 for qPCRs and N=3 for Western blot per group. *, p<0.05; **, p<0.01; ***, p<0.001.



Discussion

Although exercise has been shown to be effective to reduce I/R-induced myocardial injury, it remains unclear whether long-term regular exercise training could attenuate acute cardiac injury following myocardial ischemia. Here we demonstrate that a 3-week swimming training reduces infarct size and attenuates the apoptosis and autophagy of cardiomyocytes. The cardioprotective effect of exercise is attributable to improved myocardial glucose and lipid metabolism, as well as enhanced adaptive increase of mitochondrial biogenesis, which is accompanied by PGC-1 α activation.

It is known that the autophagy is induced in the acute phase of MI as an adaptive response of the heart to protect itself from cardiac injury [32, 33]. In the current study, we show that AMI upregulates a set of autophagy-associated genes and increases the conversion of LC3I/II and p62 degradation, indicative of augmented autophagy 24 h after LCA ligation. However, long-term exercise training significantly reduces myocardial infarct size and abolishes the induction of autophagy in mice with AMI, which might be an important phenomenon of reduced myocardial injury due to exercise activity. The increased apoptosis is a hallmark of the loss of cardiomyocytes during AMI [34, 35]. It has previously been demonstrated that Bax deficiency or Bcl-2 overexpressing mice displayed reduced infarct size after MI [36, 37].

Noteworthy, our data show that the AMI-induced increase in Bax/Bcl2 ratio and caspase3 cleavage can also be attenuated by exercise training, suggesting that the exercise-induced cardioprotection against AMI is at least in part attributable to reduced apoptosis.

Cardiac ischemia has a strong influence on myocardial glucose and fatty acid metabolism [38]. The upregulation of GLUT-1 has been widely demonstrated in acute myocardial ischemia with and without reperfusion [25–27, 39], although the expression of GLUT-4 could be either upregulated [25] or downregulated [26] due to different animal models of myocardial ischemia. In the present study, we show that GLUT-1 was markedly induced in hearts with AMI, while no significant change was found with GLUT-4. Meanwhile, we found that GSY1, an enzyme involved in glucose metabolism, was also induced in mice subjected to LCA ligation. In addition to increased glucose uptake and metabolism, the downregulation of genes encoding enzymes involved in fatty acid metabolism has previously been reported in hearts with AMI [27, 28]. Consistently, we detected a reduction in the expression of CPT-1, MCAD and LPL in ischemic hearts, indicative of impaired fatty acid transport and oxidation during AMI. Genes encoding enzymes of glucose and fatty acid metabolism are transcriptionally regulated by PPAR [40–42]. Although some studies fail to show a cardioprotective effect of PPAR activation in myocardial ischemia [43–45], some lines of evidence indicates that agonists of PPAR- α or PPAR- γ are beneficial to protect the heart from ischemia injury [46–48]. Here we detected a downregulation of PPAR- α and PPAR- γ at both mRNA and protein levels in hearts with AMI. Intriguingly, we found that AMI-induced derangement of cardiac metabolism as well as impaired expression of PPAR- α and PPAR- γ could be remarkably reversed by exercise training. These data indicate that long-term exercise training could be an effective way to improve cardiac glucose and fatty acid metabolism in AMI, although the potential roles of PPAR- α and PPAR- γ need to be further elucidated.

A decline in mitochondrial biogenesis and function plays a key role in the development of heart failure after MI [23]. Of note, previous studies particularly focused on the mitochondrial impairment during the late stage of MI (e.g. several weeks after establishment of MI) [49, 50], whereas the early change of mitochondria in the acute phase of MI remains largely unclear. In the current study, we detected an increase in mtDNA encoded gene expressions and an upregulation of genes involved in mtDNA replication 24 h after LCA ligation. These data reveal that mitochondria might have a rapid adaptation to AMI through increasing mtDNA replication and transcription. Furthermore, we demonstrated that long-term exercise training could further enhance mtDNA biogenesis in mice with AMI. Knowing that the impaired mitochondrial biogenesis is a central mechanism responsible for myocardial injury following MI, we propose that the early change of mitochondrial replication and transcription might probably be a beneficial response in the acute phase of MI which could be further enhanced by exercise. PGC-1 α is a master transcriptional regulator of mitochondrial biology, which can be induced by exercise [51]. Decreased cardiac PGC-1 α level has been demonstrated in the late stage of MI in rats [52]. However, it has also been reported that PGC-1 α could be induced and detected in the blood samples of patients 72 h after the onset of an ST-segment elevation AMI, which is supposed to be a cellular response to AMI and probably serves as a potential marker for cardiac recovery capacity after AMI [53]. In the present study, we found that the enhanced mitochondrial biogenesis in the acute phase of AMI was accompanied with an induction of PGC-1 α . Importantly, the AMI-induced upregulation of PGC-1 α could be further enhanced by exercise, suggesting that long-term exercise might be beneficial to enhance the early adaptive response of mitochondrial biogenesis in the acute phase of AMI which might be related to an upregulation of PGC-1 α .

It has to be mentioned that the protective effect of exercise against the acute myocardial injury following AMI should be more complex than involving myocardial energy metabolism and mitochondrial biogenesis. It has recently been reported that telocytes, a novel interstitial cell type, with extremely long and thin processes, play important roles in tissue repair and regeneration [54–58]. Telocytes have been found to be decreased in myocardium during AMI and increased number of telocytes was beneficial to induce angiogenesis and reduce myocardial infarction [59–61]. Besides that, although the current study shows that

exercise exerts protection against acute myocardial injury after AMI, the effect of exercise in ameliorating the adverse remodeling after permanent occlusion of coronary arteries still remains to be explored. Finally, though we have showed data based on TUNEL stainings, it would be interesting to use PI uptake to show directly cell death differences in the future.

In summary, the present study shows that long-term exercise training exerts cardioprotective effects to reduce infarct size and attenuates cardiomyocyte apoptosis and autophagy in the acute phase of AMI. Furthermore, exercise training improves myocardial glucose and lipid metabolism and further enhances the adaptive increase of mitochondrial biogenesis in response to AMI which is accompanied by an induction of PGC-1 α . Further knowledge on the molecular mechanisms that mediate protective effects of exercise against AMI might enable us to develop novel pharmacological strategies to salvage cardiac function in the acute phase of AMI.

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Disclosure Statement

The authors declare there are no conflicts of interest.

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