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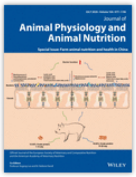

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Adaptation of aerobic training essentially involved autophagy, mitochondrial marker and muscle fibre genetic modulation in rat cardiac muscles

Julia Windi Gunadi, Vita Murniati Tarawan, Iwan Setiawan, Hanna Goenawan, Hana Ratnawati, Yenni Limyati, Oeij Anindita Adhika, Andreas Wardono Santoso, Ronny Lesmana, Unang Supratman

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Adaptation of aerobic training essentially involved autophagy, mitochondrial marker and muscle fibre genetic modulation in rat cardiac muscles

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Abstract

Information about the role of moderate acute treadmill training in modulating autophagy and mitochondrial markers that might be correlated with alteration of muscle fibre gene expression in rat cardiac muscles is very limited. In this present study, the researchers divided twenty male Wistar rats into four groups: sedentary control, 3, 6 and 15 days and subjected them to treadmill training with moderate intensity (20 m/min), 30 min each day. RNA was extracted from cardiac muscles and stored in temperature of −80°C. Specific primers were utilized for semi-quantitative PCR. Treadmill training decreased autophagy-related gene expression (LC3, p62) and upper stream signalling of autophagy (PIK3CA, Akt and mTOR) in 3 and 6 d, but stimulated gene expression of mitochondrial markers (PGC1α, Cox1, Cox2 and Cox4) in 15 days. αMHC gene expression increased while βMHC gene expression decreased in 15 days. In line with this, autophagy-related genes increased in 3 and 6 days and returned to baseline in 15 days. The increment in mitochondrial gene expression might be correlated with shifting gene expression of αMHC and βMHC in 15 days. Taken together, acute adaptation in cardiac muscles is stimulated by genetic modulation of autophagy, mitochondrial marker and muscle fibre that may explain physiological cardiac adaptation after training. This study can be used as a reference for optimizing performance in period of cardiac muscle adaptation stimulated by treadmill training.

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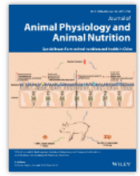

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Adaptation of aerobic training essentially involved autophagy, mitochondrial marker and muscle fibre genetic modulation in rat cardiac muscles

Julia Windi Gunadi[1,2] | **Vita Murniati Tarawan**[3] | **Iwan Setiawan**[3] | **Hanna Goenawan**[3,4] | **Hana Ratnawati**[5] | **Yenni Limyati**[6,7] | **Oeij Anindita Adhika**[8] | **Andreas Wardono Santoso**[9] | **Ronny Lesmana**[3,4,10] | **Unang Supratman**[11]

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This work was supported by World Class Research Grant from Indonesian Ministry of Research Technology and Higher Education (3854/UN6.C/LT/2019) to Iwan Setiawan and World Class University Program managed by Insitut Teknologi Bandung (2019) to Ronny Lesmana and Lembaga Pengelola Dana Pendidikan Research Grant (S-494/LPDP.3/2018) to Julia Windi Gunadi.

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KEYWORDS
adaptation, autophagy, cardiac, mitochondria, myosin heavy chain, training

1 | INTRODUCTION

Regular exercise improves physical health especially the cardiovascular system that protects the heart from injury (Platt, Houstis, & Rosenzweig, 2015; Wei, Liu, & Rosenzweig, 2015). During aerobic exercise, such as treadmill training, there are several phases of cardiac adaptation. It starts with immediate improvement of the cardiac function, increasing the heart rate and stroke volume that augments the cardiac output (Fulghum & Hill, 2018; Weiner & Baggish, 2012), and then followed by an increase in the vascular function together with cardiac output to increase blood flow to skeletal muscles (Fulghum & Hill, 2018). However, the molecular mechanism that explains mitochondria and muscle fibre genetic modulation correlated with autophagy in cardiac muscles during early treadmill training adaptation remains unclear.

In order to cope with cellular stress induced by training, cardiac adaptation might involve cell death that occurs in several ways, such as apoptosis, necrosis and potentially autophagy (Bernardo, Ooi, Weeks, Patterson, & Mcmullen, 2018). Autophagy may play an important role to enhance optimal adaptation to damage due to cellular stress since cardiomyocyte does not have a regenerative capacity (Lee et al., 2017). Autophagy is a generic term for all pathways by which cytoplasmic materials are delivered to the lysosome in animal cells (Mizushima & Komatsu, 2011). Autophagy is divided into macroautophagy, microautophagy and chaperone-mediated autophagy. In macroautophagy, initiation of autophagy is carried out by a phagophore, a non-selective sequestering cytosolic substrate within a double membrane, and then conjugated with ubiquitination-linked proteins, together with light chain 3 (LC3) and p62/sequestosome 1 in a structure called autophagosome. Then, autophagosome will be fused to lysosome, where the

TABLE 1 Primers used for semi-quantitative PCR analysis

Gene symbol	Primer Sequence (5′–3′) Upper strand: sense Lower strand: antisense	Product size (bp)	Annealing (°C)	Cycle	Accession number	References
PIK3CA	ACCTCAGGCTTGAAGAGTGTCG CCGTAAGTCGTCGCCATTTTTA	137	59	35	NM_133399.2	Krusen et al. (2016)
Akt	CTAACTTGAGCCGCAGGAAC GCTTGCTCAGTTTGCTACCC	165	57	35	XM_008764918.2	Primer3
mTOR	CTGATGTCATTTATTGGCACAAA CAGGGACTCAGAACACAAATGC	170	57	35	NM_019906.1	Yin et al. (2013)
LC3	GGTCCAGTTGTGCCTTTATTGA GTGTGTGGGTTGTGTACGTCG	153	59.5	35	NM_022867.2	Yin et al. (2013)
p62	CTAGGCATCGAGGTTGACATT CTTGGCTGAGTACCACTCTTATC	116	56	35	NM_175843.4	Kowalik et al. (2016)
PGC1α	CGCACAACTCAGCAAGTCCTC CCTTGCTGGCCTCCAAAGTCTC	263	62	37	NM_031347.1	Sylviana et al. (2018)
Cox1	GGAGCAGTATTCGCCATCAT CGGCCGTAAGTGAGATGAAT	244	55.3	35	X14848	Javadov, Purdham, Zeidan, and Karmazyn (2006)
Cox2	ACTTGGCTTACAAGACGCTACA TCTTGGGCGTCTATTGTGCTT	162	56.7	35	S67722.1	Primer3
Cox4	CTCCCATCTTATGTTGATCG GTACAATTGGACTTTCTCATCC	144	57	35	NM_017202.1	Lesmana, Sinha, et al. (2016)
αMHC	GCCCTTTGACATCCGCACAGAGT TCTGCTGCATCACCTGGTCCTCC	152	60	35	NM_017239.2	Radik, Doka, Malikova, Krenek, and Klimas (2016)
βMHC	GCGGACATTGCCGAGTCCCAG GCTCCAGGTCTCAGGGCTTCACA	133	59.5	35	NM_017240.2	Radik et al. (2016)
GAPDH	GTTACCAGGGCTGCCTTCTC GATGGTGATGGGTTTCCCGT	177	61	35	NM_017008.4	Wang et al. (2017)

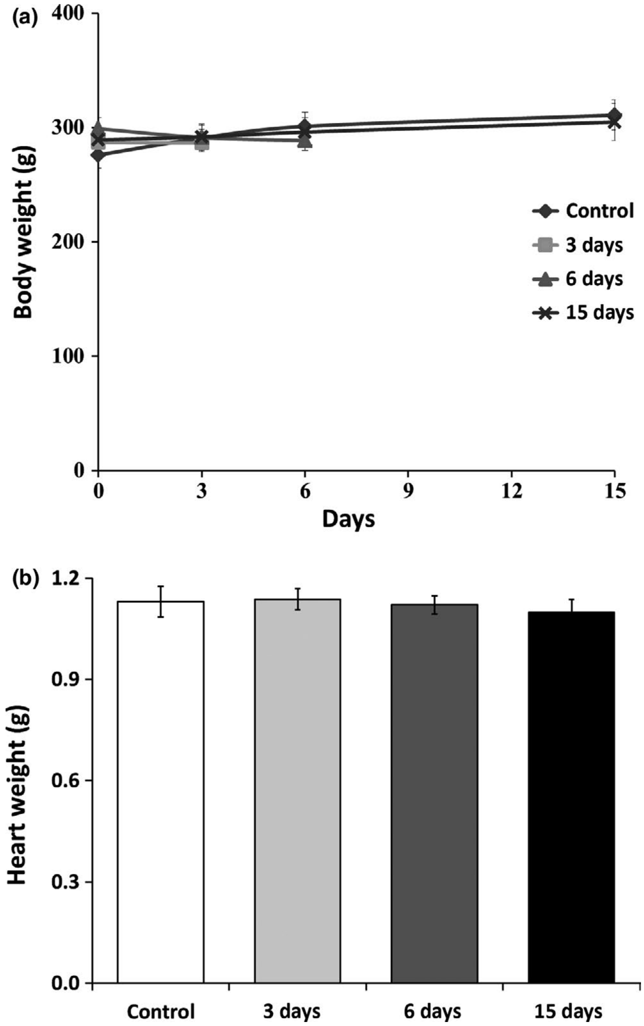

FIGURE 1 Rat body weight and heart weight during treadmill training after several periods of training. Baseline characteristics of the rats in each group. (a) Body weight of each group of the rats. (b) Heart weight of each group of the rats. Data are presented as average mean ± standard error of the mean (*SEM*)

substrate is then degraded by enzymes (Mizushima & Komatsu, 2011; Pankiv et al., 2007).

Stimulation of autophagy is important and essential for mitochondrial biogenesis and activity in skeletal muscles. The role of autophagy in muscle adaptation is connected with autophagy-induced mitochondrial biogenesis in skeletal muscles (Lesmana, Sinha, et al., 2016). Autophagy in mitochondria (mitophagy) determines mitochondrial function and content in skeletal muscles (Chen, Erlich, & Hood, 2018). Mitophagy is a selective autophagy of mitochondria that eliminates damaged mitochondria, as part of quality control mechanism. There is an interplay between mitochondrial dynamics—their movements, fissions and fusions—and the progression of mitophagy; arrest and fragmentation of mitochondria after damage are likely to facilitate the selective clearance of damaged organelles (Ashrafi & Schwarz, 2013; Bloemberg & Quadrilatero, 2019). Mitochondrial biogenesis is regulated by peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α) (Fernandez-Marcos & Auwerx, 2011; Puigserver et al., 1998), while mitochondrial energy metabolism is assessed using Cytochrome c oxidase (Cox) enzyme activity (Kadenbach, Hüttemann, Arnold, Lee, & Bender, 2000). Another important process that plays a role in the adaptation to aerobic training in skeletal muscles is fibre type transformation (Farenia et al., 2019; Yan, Okutsu, Akhtar, & Lira, 2011). This study hypothesizes that adaptation of skeletal muscle by autophagy may also have a role in cardiac muscles adaptation.

Cardiac muscles fibres have myosin heavy chain (MHC) as a chemical and mechanical transducer to drive the sliding of myofilaments (Nadal-Ginard & Mahdavi, 1989). MHC provides structural integrity, and its isoform is a major determinant of contractile and functional properties. Cardiac MHC isoforms exist as homodimer or heterodimer, and a unique gene encodes each subunit. At the protein level, cardiac α or βMHC proteins have a high degree (94%) of sequence identity, and divergence only occurs in clusters, some of which are functionally important sites such as the adenosine triphosphatase (ATPase) catalytic site (Mcnally, Kraft, Bravo-Zehnder, Taylor, & Leinwand, 1989; Rafalski, Abdourahman, & Edwards, 2007). αMHC has twofold to threefold higher actin-activated ATPase activity and actin filament sliding velocity than βMHC (Herron & Mcdonald, 2002; Krenz & Robbins, 2004).

Recent studies have shown that aerobic training induces autophagy gene expression in skeletal muscles (Tarawan et al.., 2019) and in cardiac muscles (He et al., 2012; Lee et al., 2017). Aerobic training stimulated mitochondrial biogenesis markers and increased PGC1α levels in cardiac muscles (Kim, Ahn, & Jung, 2018). Exercise increased αMHC while repressing βMHC genes in rats compared with sedentary control in infracted heart (Hashimoto, Kambara, Nohara, Yazawa, & Taguchi, 2004; Wan, Xu, Zhao, Garza, & Zhang, 2014). Cardiac muscle fibres may shift MHC isoforms (from αMHC to βMHC) as a compensatory response to training, due to increased glycolytic demand and lack of functional capacity in the muscle fibre. This shift occurs in early period and might be responsible in increasing myocardial contractility and preserving cardiac functions (Rafalski et al., 2007). Taken together, modulation of autophagy, mitochondrial marker and muscle fibres may take part in cardiac muscles adaptation stimulated by training.

2 | MATERIALS AND METHODS

2.1 | Animals

Ten-weeks-old male Wistar rats were obtained from the Animal Breeding Centre of PT Biofarma in Bandung, Indonesia. The baseline characteristics for the rats were 10 ± 2 weeks in term of age and 287.8 ± 4.74 g in term of weight. In terms of environment, the rats were subjected to a dark light cycle (12 hr of light cycle and 12 hr of dark cycle) and a stable temperature (±22°C). The rats were fed a pellet rodent diet ad libitum and had free access to water. After one week of acclimatization, 20 male rats were divided into four groups, sedentary control group and three training groups (3, 6 and 15 days). All experimental procedures followed the guidelines for the care and use of laboratory animals (National Research Council, 2011)

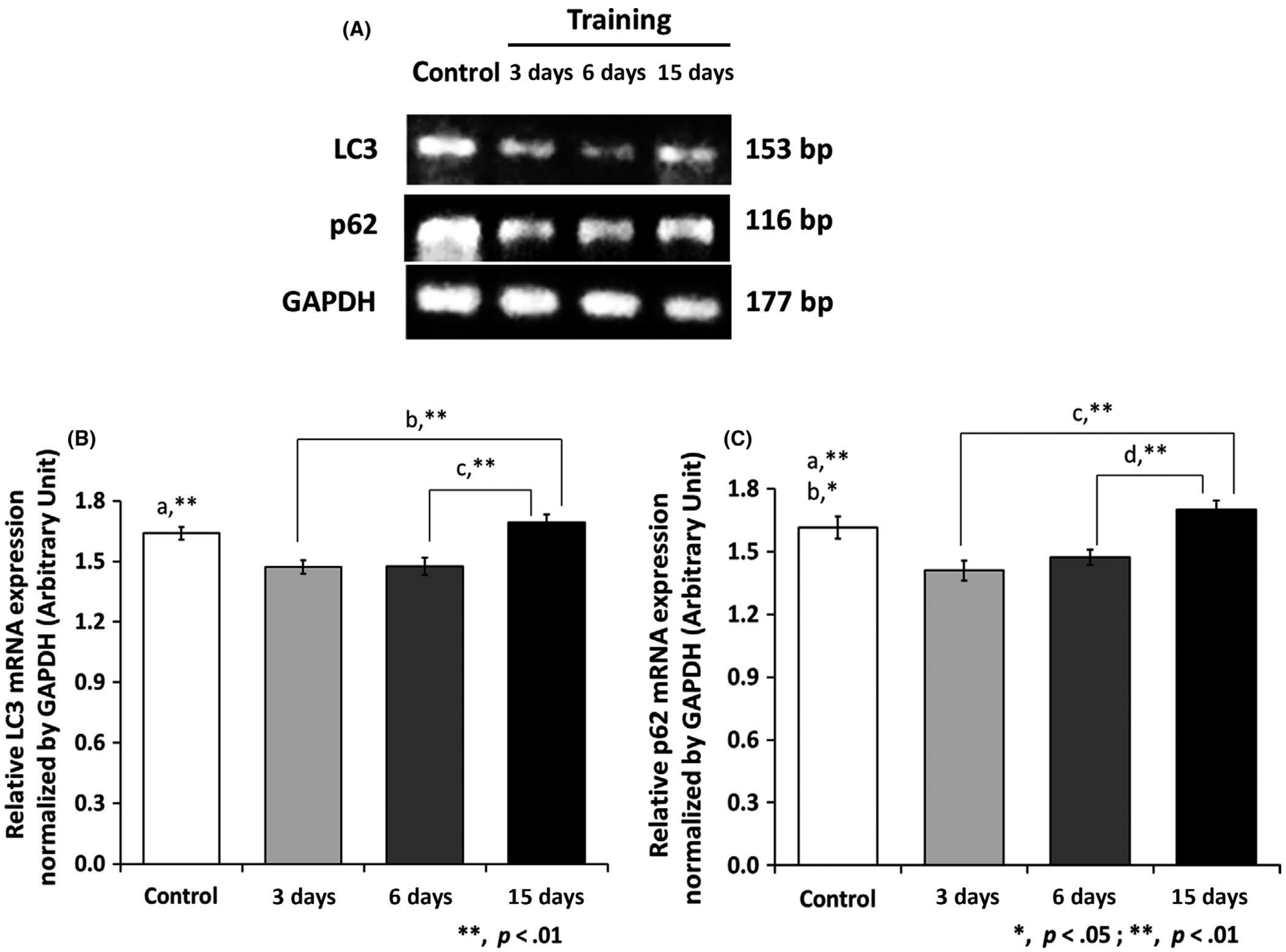

FIGURE 2 Aerobic training modulates autophagy-related gene expression in physiologic adaptation of rat cardiac muscles. (A) Representative electrophoresis result of autophagy-related gene expression in 3, 6 and 15 days after treadmill training. (B) Relative mRNA expression of LC3 was significantly decreased in 3 and 6 days (a) compared with control, and between 3 and 15 days (b), 6 and 15 days (c). (C) Relative mRNA expression of p62 was significantly decreased in 3 days (a) and 6 days (b) compared with control, and between 3 and 15 days (c), and 6 and 15 days (d). Data are presented as average mean ± standard error of the mean (*SEM*); with $p < .05$ considered as significant (*), $p < .01$ considered as very significant (**)

and approved by Research Ethics Committee of Faculty of Medicine Universitas Kristen Maranatha-Rumah Sakit Immanuel Bandung No 013/KEP/V/2019.

2.2 | Treadmill training protocol

A moderate treadmill training protocol (20 m/min), 30 min a day was designed, for three different groups of male Wistar rats, divided into three periods: 3, 6 and 15 days. The study chose moderate treadmill training based on a previous study in rats (Gunadi et al., 2019; Lesmana, Iwasaki, et al., 2016). For the control group, the rats were put on the treadmill without training. After given one week to acclimatize, the rats were put on the treadmill for 3 days with increasing speed and time. The rats were subjected to the treadmill for 30 min a day and a speed of 20 m/min. They were then killed in 3, 6 and 15 days immediately after the last session of the training. All their body weights were monitored and recorded weekly. Control and training groups were euthanized using isoflurane gas, and then, their cardiac muscles were removed, snap-frozen in liquid nitrogen and stored in temperature of −80°C until used. The researchers who analysed the tissues did not know to which group the rats belonged.

2.3 | RNA extraction and semi-quantitative PCR

RNA from cardiac muscles was extracted using TRIsure reagent (Bioline). Total RNA was measured using Multimode Microplate Reader at 268/280 nm absorbance spectrophotometry (M200 Pro; Tecan). Semi-quantitative PCR was performed using the One-Step RT-PCR Kit (Bioline, United Kingdom). Gene expression levels were normalized using GAPDH. BluePad Detection system was used to visualize electrophoresis gels. Visualization and quantification of PCR band were done using ImageJ 1.52 version (Schneider, Rasband, & Eliceiri, 2012). Primer sequences used in this study are presented in Table 1.

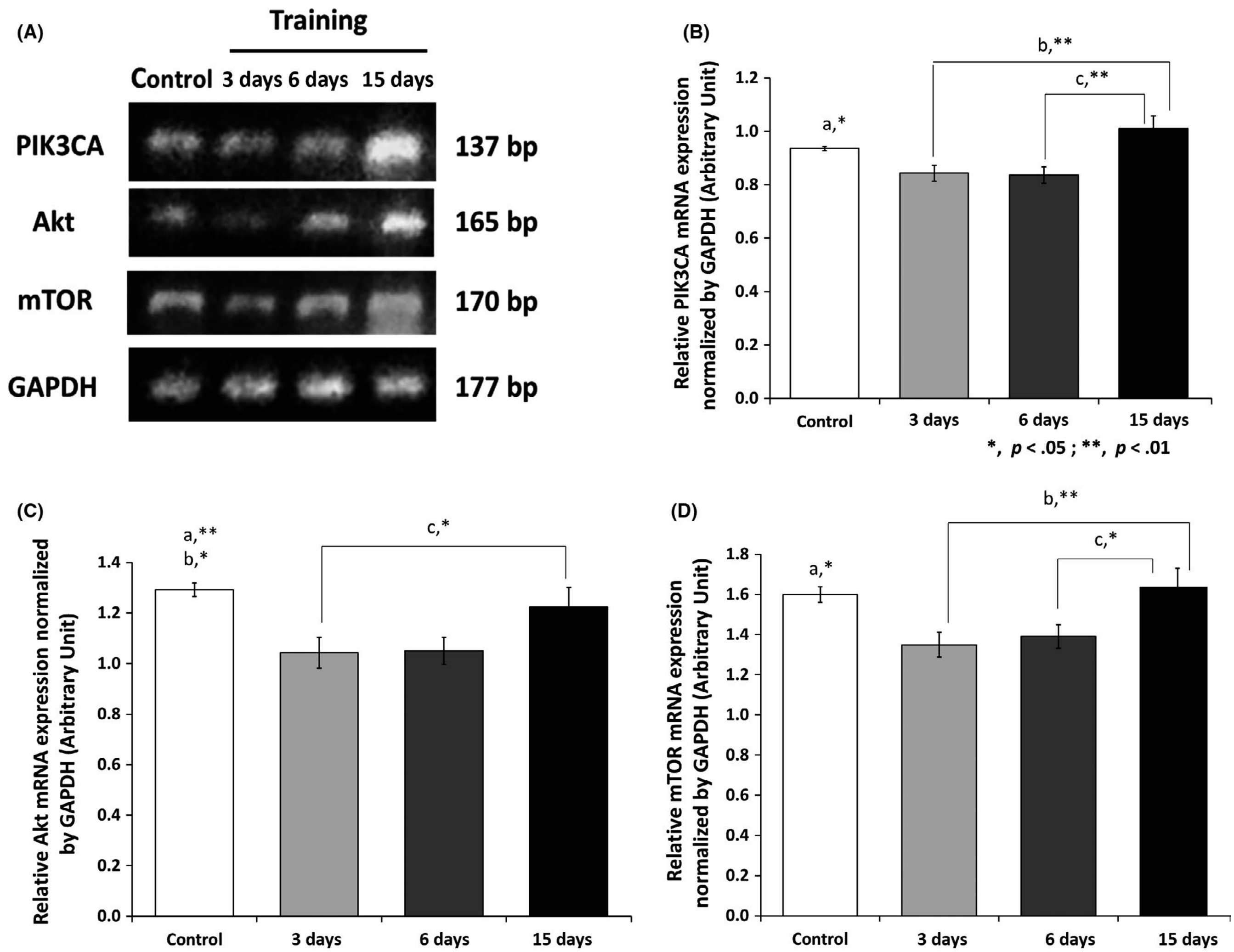

FIGURE 3 Aerobic training modulates PIK3CA, Akt and mTOR signalling gene expression that is involved in modulating autophagy. (A) Representative electrophoresis result of PIK3CA, Akt and mTOR signalling gene expression in 3, 6 and 15 days after treadmill training. (B) Relative mRNA expression of PIK3CA was significantly decreased in 6 days compared with control (a), between 3 and 15 days (b), and between 6 and 15 days (c). (C) Relative mRNA expression of Akt was significantly decreased in 3 days (a), 6 days compared with control (b), and between 3 and 15 days (c). (D) Relative mRNA expression of mTOR was significantly decreased in 3, 6 days compared with control (a), and between 3 and 15 days (b), and 3 and 15 days (c). Data are presented as average mean ± standard error of the mean (*SEM*), with $p < .05$ considered as significant (*), $p < .01$ considered as very significant (**)

2.4 | Statistics

SPSS 19.0 software was used to analyse the data obtained in this study. Results were presented as mean ± standard error of mean (mean ± *SEM*). Mean differences between groups were examined with one-way ANOVA and LSD post hoc test with 95% confidence interval with $p < .05$.

3 | RESULTS

3.1 | There were no significant differences in body weight and heart weight

The rats from the four experimental groups had similar initial body weight (287.8 ± 4.74 g). There were no significant differences found in body weight (Figure 1a) and heart weight (Figure 1b) between 3, 6 and 15 days training groups and control after the rats were subjected to treadmill training for 30 min/day with speed of 20 m/minute.

3.2 | Training stimulated dynamic modulation of autophagy-related gene expressions in cardiac muscles of Wistar rats

There was modulation of autophagy-related gene expression in cardiac muscles of Wistar rats (Figure 2a). LC3 and p62 bands were normalized using GAPDH. Treadmill training decreased autophagy-related gene expression: LC3 by 0.897-fold in 3 days and 0.9 in 6 days (Figure 2b) and p62 by 0.874-fold in 3 days and 0.913 in 6 days (Figure 2c).

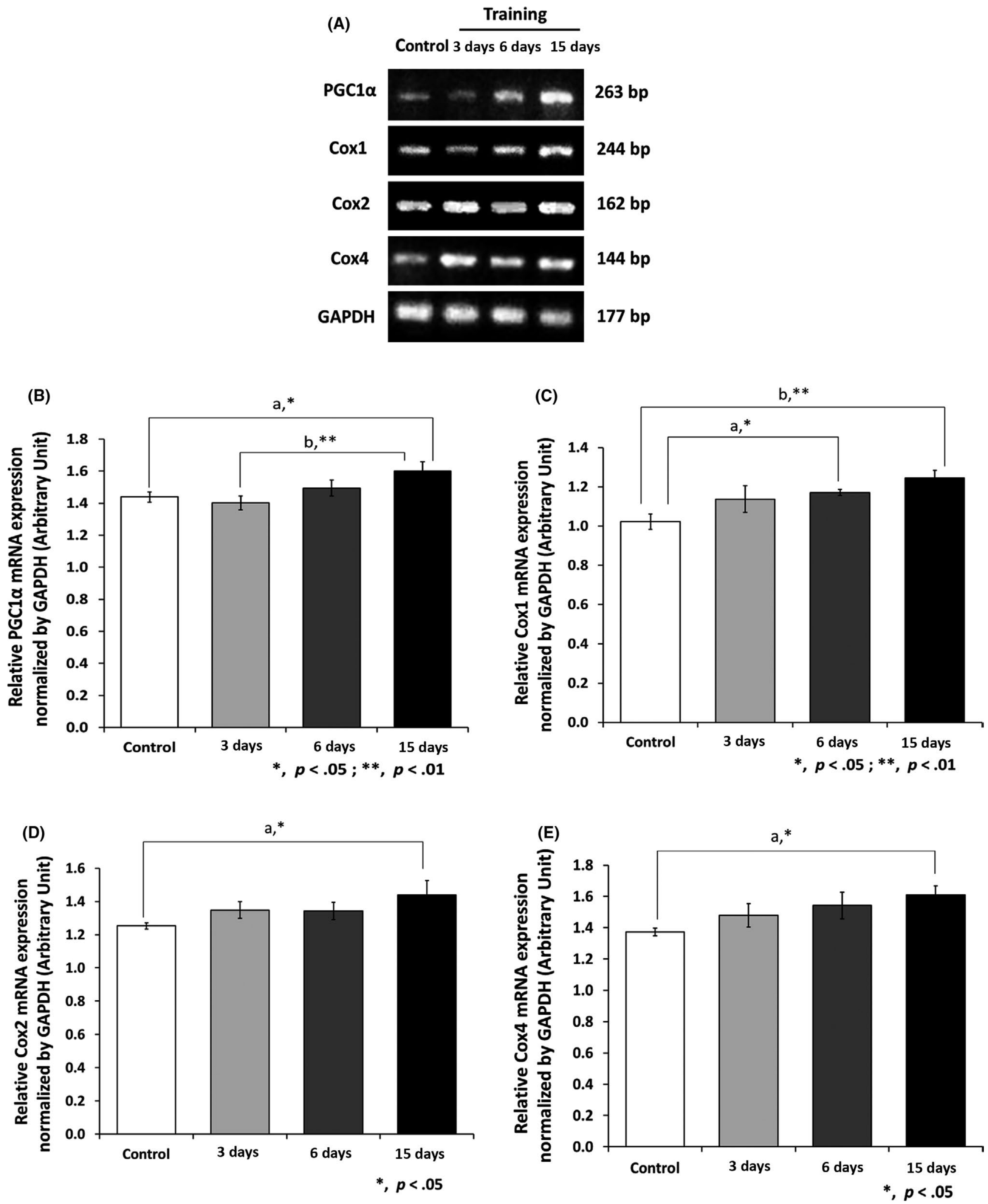

FIGURE 4 Modulation of mitochondrial marker gene expression during aerobic training adaptation in rat cardiac muscles. (A) Representative electrophoresis result of mitochondrial marker gene expression in 3, 6 and 15 days after treadmill training. (B) Relative mRNA expression of PGC1α was significantly increased in 15 days compared with control (a), and between 3 and 15 days (b). (C) Relative mRNA expression of Cox1 was significantly increased in 6 days (a) and 15 days (b) compared with control. (D) Relative mRNA expression of Cox2 was significantly increased in 15 days compared with control (a). (E) Relative mRNA expression of Cox4 was significantly increased in 15 days compared with control (a). Data are presented as average mean ± standard error of the mean (*SEM*); with $p < .05$ considered as significant (*), $p < .01$ considered as very significant (**)

3.3 | Upper stream signalling of autophagy was also modulated after training in cardiac muscles of Wistar rats

This study explored autophagy upper stream signalling and observed the modulation of PIK3CA-Akt-mTOR in cardiac muscles of Wistar rats (Figure 3a). PIK3CA, Akt and mTOR bands were normalized using GAPDH. Treadmill training decreased autophagy upper stream signalling gene expression in 3 and 6 days: PIK3CA by 0.894-fold in 6 days (Figure 3b), Akt by 0.807-fold in 3 days and 0.813-fold in 6 days (Figure 3c), and mTOR by 0.844-fold in 3 days and 0.870-fold in 6 days (Figure 3d).

3.4 | Training induced mitochondrial markers gene expressions in cardiac muscles of Wistar rats

Mitochondrial markers gene expressions were upregulated in rat cardiac muscles through training (Figure 4a). PGC1α, Cox1, Cox2 and Cox4 bands were normalized using GAPDH. This study found increased gene expressions for mitochondrial markers in 15 days: PGC1α increased by 1.111-fold in 15 days (Figure 4b), Cox1 increased by 1.218-fold in 15 days (Figure 4c), Cox2 increased by 1.148-fold in 15 days (Figure 4d) and Cox4 increased by 1.173-fold in 15 days (Figure 4e).

3.5 | Training increased αMHC and decreased βMHC gene expressions in cardiac muscles of Wistar rats

This study also examined muscle fibre gene expression in cardiac muscles of Wistar rats. αMHC and βMHC bands were normalized using GAPDH (Figure 5a). This study found increase in αMHC gene expression by 1.145-fold in 6 days and 1.314-fold in 15 days (Figure 5b) and decrease βMHC gene expression by 0.907-fold in 3 days and 0.887-fold in 15 days (Figure 5c).

3.6 | Summary of gene expression modulation after aerobic training in rat cardiac muscle

Adaptation to aerobic training essentially involved autophagy, mitochondrial marker and fibre shifting in rat cardiac muscles. Autophagy

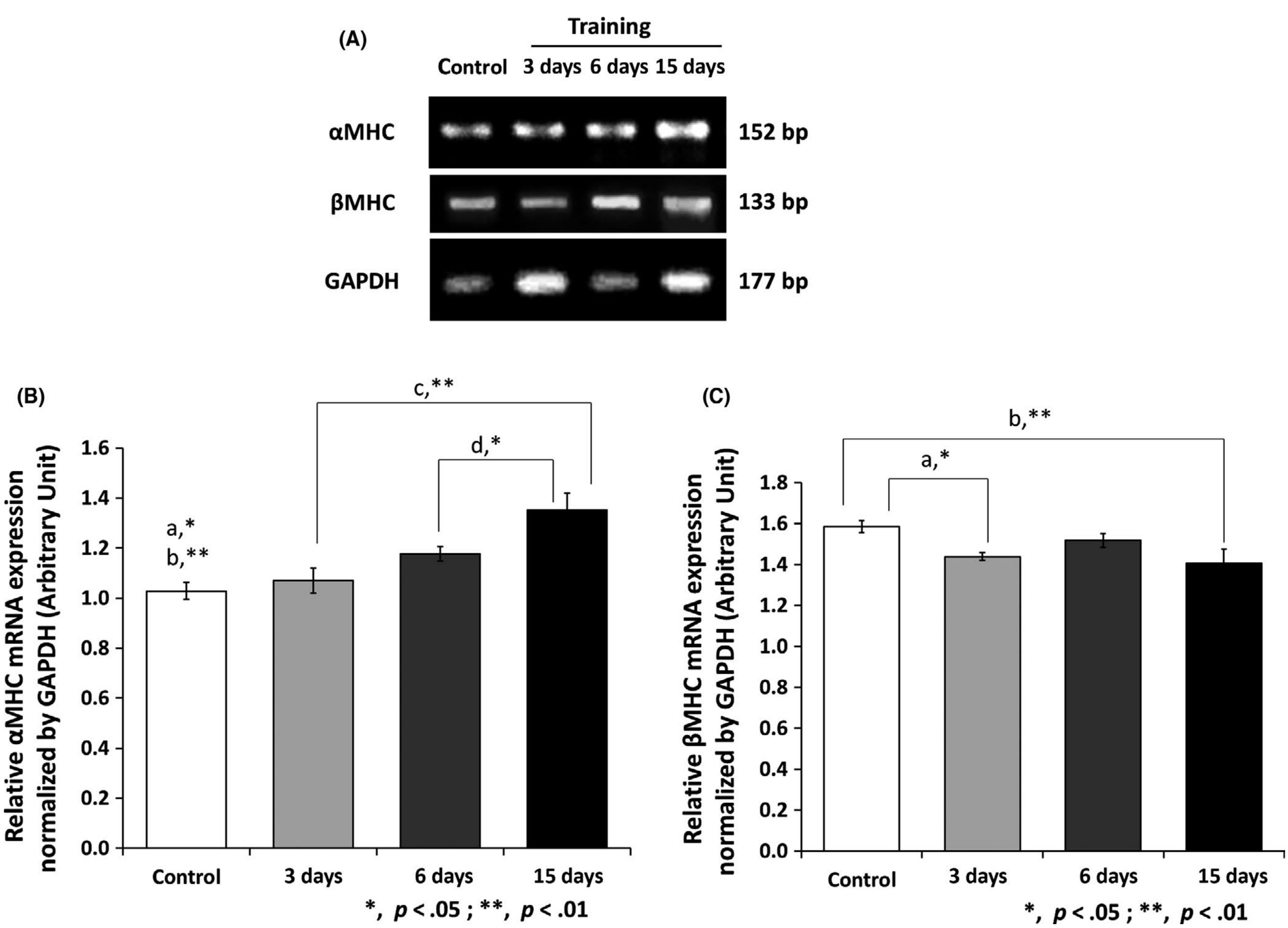

FIGURE 5 Modulation of muscle fibre gene expression after aerobic training in rat cardiac muscles. (A) αMHC gene expression increased while βMHC decreased in 15 days of treadmill training. (B) Relative mRNA expression of αMHC was significantly increased in 6 days (a) and 15 days (b) compared with control, and between 3 and 15 days (c), 6 and 15 days (d). (C) Relative mRNA expression of βMHC was significantly decreased in 3 days compared with control (a), and between 15 days compared with control (b). Data are presented as average mean ± standard error of the mean (*SEM*); with $p < .05$ considered as significant (*), $p < .01$ considered as very significant (**)

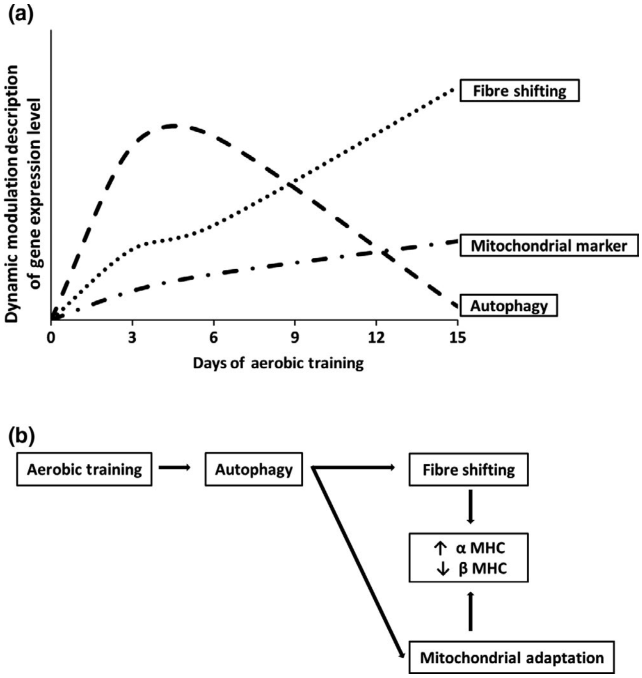

FIGURE 6 Summary of gene expression modulation after aerobic training in rat cardiac muscles. (a) Dynamic modulation description of autophagy, mitochondrial marker and muscle fibre gene expression in cardiac muscles during adaptation to aerobic training. (b) Proposed mechanism of autophagy, mitochondrial marker, and muscle fibre gene expression in cardiac muscles during adaptation to aerobic training

started to increase in 3 and 6 days, then back to baseline in 15 days, while mitochondrial marker and fibre shifting started to occur in 15 days (Figure 6a). The proposed mechanism for this modulation is described in Figure 6b.

4 | DISCUSSION

Cardiac myocytes in adult rat heart represent 70%–85% of the heart's volume, but possess extremely limited regenerative capacity. Thus, it is important to preserve the function of cardiac myocytes to maintain healthy living (Lee et al., 2017; Pinto et al., 2016). There are some key processes in adaptation of training in cardiac myocytes including cellular stress response (proteasome-ubiquitin system, autophagy and apoptosis), mitochondrial adaptation (energy metabolism and redox status) and fibre shifting (Bernardo et al., 2018; Yan et al., 2011). However, the understanding about coregulation of these systems during aerobic training adaptation remains unclear.

This study suggests a time-dependent modulation of autophagy, mitochondrial biogenesis and fibre shifting gene expression during treadmill as an adaptation processes in cardiac muscles of Wistar rats. We try to understand how cardiac muscle autophagy related to and signalling gene expression via PI3KCA-Akt-mTOR are altered by aerobic training at certain periods (3, 6 and 15 days). The results indicate that autophagy increased significantly in 3 and 6 days and then returned to baseline in 15 days supported by decreased gene expression of LC3, p62, PI3KCA, Akt and mTOR in 3 and 6 days (Figures 2 and 3). Other studies have also shown that endurance exercise training induces autophagy in cardiac muscles (He et al., 2012; Lee et al., 2017).

Autophagy plays a role in regulating mitochondrial markers such as PGC1α and Cox enzyme activity (Lesmana, Sinha, et al., 2016). These markers increased due to aerobic training in 15 days (Figure 4). The previous study conducted by Kim et al have also shown that during chronic aerobic training, mitochondrial biogenesis markers were upregulated in the cardiac muscle (Kim et al., 2018).

An interesting physiological transition of cardiac muscle gene expression stimulated by aerobic training was observed, proved by an increase of αMHC and decrease of βMHC in 15 days (Figure 5). Other studies showed that exercise significantly increased αMHC while repressing βMHC gene expression in exercise rats compared with sedentary control, and this shift occurred in early period (Hashimoto et al., 2004; Rafalski et al., 2007; Wan et al., 2014).

This study showed that autophagy, mitochondrial biogenesis and fibre shifting might be correlated and jointly regulated by aerobic training. Autophagy genes increased in 3 and 6 days (Figures 2 and 3), while genes responsible for mitochondrial function (Figure 4) and fibre shifting (Figure 5) were stimulated in 15 days. A summary of this modulation and its proposed mechanism is presented in Figure 6. However, other factors may also regulate these processes and need to be investigated, such as temperature (Puigserver et al., 1998) and nitric oxide (Tengan, Rodrigues, & Godinho, 2011). We had sacrificed all the rats immediately after the last session of the training and reduce all confounding factors by using rats with the same age, standardized food, controlled environment and same intensity of training induction. However, gene expression might be altered by other factors due to post-transcriptional modifications. Thus, it may be beneficial to measure the protein levels in future studies.

5 | CONCLUSION

This study suggests a time-dependent modulation of autophagy, mitochondrial biogenesis and fibre shifting during treadmill adaptation in cardiac muscles of Wistar rats. Autophagy increased in 3 and 6 days and returned to baseline after 15 days of treadmill training. Mitochondrial biogenesis increased after 15 days of treadmill training, along with shift of βMHC to αMHC in cardiac muscles of Wistar rats. The study believes that the adaptation period needs a specific genetic modulation, protein and tissue rearrangements, to improve functional capability improvement. An athlete's performance can be optimized through a time structured training programme by understanding the physiological adaptation period in cardiac muscles.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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