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Volume 9, Issue 3

Article(s) in June Issue

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Int J Cardiovasc Res

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(<https://www.scitechnol.com/peer-review/risk-evaluation-of-cardiovascular-diseases-among-nurses-aged-more-than-40-years-report-from-a-tertiary-care-center-in-north-india>)

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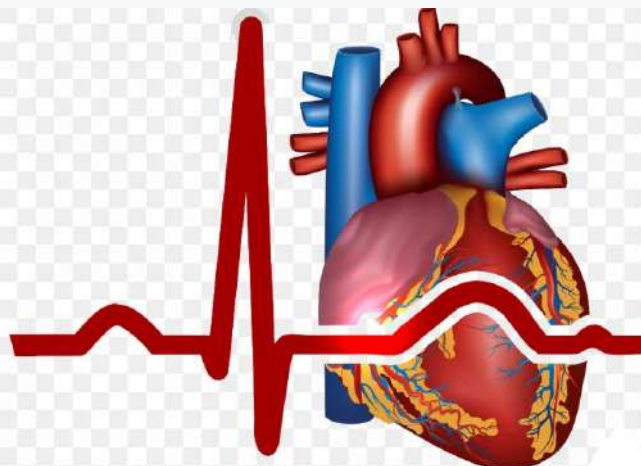
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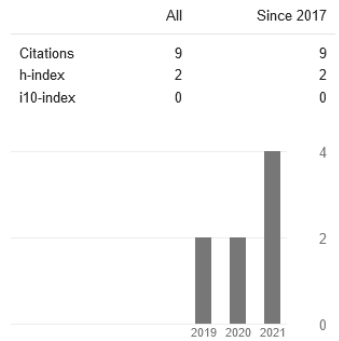
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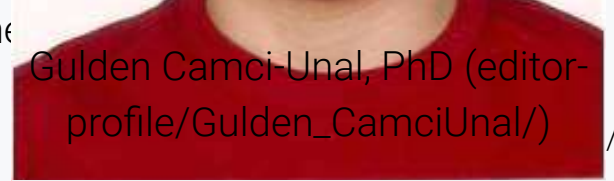
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The Relationship of Hsp-70 with Calcineurin, SOD and Catalase Post-Acute Myocardial Infarction in Wistar Rats Model

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Received: April 01, 2020; Accepted: April 07, 2020; Published: April 15, 2020

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Abstract

Background: Hsp-70 production increased following myocardial ischemia. Hsp-70 helps to reduce infarct area through unclear mechanism. It appears that Hsp-70 activates calcineurin and induce antioxidant enzymes such as superoxide dismutase (SOD) and catalase. No work has been done, however, to show correlation between Hsp-70 and calcineurin, SOD and catalase post-acute myocardial infarction. In the present study, therefore, we sought to investigate the relationship of Hsp-70 with calcineurin, SOD and catalase post-acute myocardial infarction (AMI).

Methods: An experimental study involved 24 Wistar rats as models of chronic coronary occlusion. The rats were randomly divided into 4 group: no-intervention after AMI (N), sedentary intervention after AMI (S), exercise intervention after AMI (E), and sham (C). Intervention consisted of 2 weeks of recovery then 4 weeks of sedentary for group S or exercise for group E. Hsp-70, calcineurin, SOD, and catalase expression in heart were evaluated the difference among groups. Correlation between Hsp-70 to other proteins was analysed also.

Results: Hsp-70 and calcineurin was higher in group S and E compared to group N and C. Hsp-70 (MD=0.97, 95% CI 0.60 to 1.34), calcineurin (MD=1.25, 95% CI 0.68 to 1.82, $p < 0.05$), catalase (MD= 0.57, 95% CI 0.25 to 0.88, $p < 0.05$), and SOD (0.42, 95% CI 0.14 to 0.69, $p < 0.05$) significantly higher in Group E compared to S. Sham group had higher SOD and catalase activity than group E. Hsp-70 was correlated with calcineurin ($r=0.856$, $p < 0.05$). Hsp-70 was correlated with catalase and SOD when the analysis included only groups who had intervention.

Conclusion: Hsp-70 and calcineurin was increased, but catalase and SOD was depleted in post-AMI condition. Exercise improved Hsp-70, calcineurin, catalase, and SOD activities post-AMI. Hsp-70 expression increased directly calcineurin expression.

Keywords: Exercise; Myocard infarct; Hsp-70; Calcineurin; SOD; Catalase

Introduction

70-kDa heat shock proteins (Hsp-70) acts as a molecular chaperone that assist in the correct folding of nascent and stress-accumulated mis-folded proteins and prevents their aggregation [1]. It is well established that ischemia result in an increase in Hsp-70 production in the heart and the amount of Hsp-70 synthesis correlates with the extent of myocardial protection after ischemia/reperfusion injury [2]. Inducing super expression of Hsp-70 reduced significantly infarcted area [3,4].

In ischemic myocardial cells, Hsp-70 helps prevent cell death through binding with proteins that play a role in inhibiting cell necrosis [5]. Hsp-70 activates calcineurin via a calmodulin-dependent and independent pathway [6]. Hsp-70 may induce antioxidant superoxide dismutase (SOD) through reactive oxygen species (ROS). [7] Myocardial catalase activity was induced as well as Hsp-70 after heat shock [8,9]. No work has been done, however, to show correlation

between Hsp-70 and calcineurin, COD and catalase after ischemia *in vivo*. Therefore, we sought to investigate the relationship of Hsp-70 with calcineurin, COD and catalase post-acute myocardial infarction (AMI).

Methods

Male Wistar rats meeting certain criteria, such as the age of 13 ± 2 weeks and body weight of 200-300 grams were used for this study. Procedures of care and animal use were conducted in accordance with the guidelines of laboratory animal care approved by the Ethics Committee of the Faculty of Veterinary Medicine, Airlangga University.

The rats were randomly assigned into one of the following 4 groups. Group N had LAD ligation then had no further intervention and sacrificed on the subsequent day. Group S had LAD ligation then was let to recover for 2 weeks and had sedentary intervention then were sacrificed 4 weeks after. Group E had LAD ligation then had recovery time for 2 weeks and performed mild exercise consisting of swimming exercises 5 times a week for 4 weeks with the duration of exercise was

determined individually by 40% of the maximum time, then was sacrificed. Group C was sham where had thoracotomy without ligation then sacrificed after 6 weeks.

All the animals were distributed in plastic cages (each cage consisted of three rats) under dark condition for 12 hours and light condition for 12 hours. The temperature of the cages was set between 22-27 °C. Drink and pellets were freely distributed to the animals. Exercise was carried out for four weeks.

LAD ligation protocol

The rats were anesthetized with an intramuscular injection of ketamine HCl 50 mg/kg and xylazine 5 mg/kg. The animals were intubated orotracheally using 14 G IV catheter which was inserted wire inside. IV cath was connected to 3-way stop cock. One port was connected to oxygen source ½ L/minute via cannula. Ventilation was performed through open and close the other port of 3-way stop cock with frequency of 70-80 times per minute. The surgery was carried out under sterile conditions. A left parasternal thoracotomy was performed at the fourth and fifth intercostal space, and the heart was exposed by stripping the pericardium. The heart exposed to identify the coronary artery branch. A ligature was then placed around the left coronary artery using prolene 6/0 at 1-2 mm distal to left atrial appendage. After ligation, the surgical wounds were sutured closed. The animals were observed during recovery until fully conscious and then extubated.

Hsp-70, calcineurin, catalase, SOD expression evaluation

According to the prescribed time, rats were sacrificed in anesthetized conditions with Ketamine hydrochloride (50 mg/kgBB). The chest cavity is opened from the middle of the chest and the heart is excised by binding to the aortic ascendens. Then the excised tissue was put into 10% Phosphate-buffered Saline (PBS), then macroscopic morphology was examined and immunohistochemical preparations were made.

Statistical Analysis

The expressions of Hsp-70, calcineurin, SOD, and catalase were examined as much as 10 times with an area width of 125 µm x 125 µm. All data are expressed as means ± SD. Differences among groups were analysed using independent t-test. Correlation was analysed using Pearson correlation. The α-level for statistical significance was set at 0.05.

Results

Hsp-70 expression in the group E was higher than in other groups as shown in Table 1. Group C had the lowest Hsp-70 expression. There was significant difference in Hsp-70 expression between group N and S (Mean difference (MD): -0.30; 95% CI -0.47 to -0.13; p<0.05).

Group	Hsp-70	Mean Difference (95% CI)		
	Mean ± SD	Group S	Group E	Group C
Group N	0.38 ± 0.15	-0.30 (-0.47 to -0.13)*	-1.27 (-1.65 to -0.89)*	0.32 (0.16 to 0.47)*
Group S	0.68 ± 0.12		-0.97 (-1.34 to -0.60)*	0.62 (0.49 to 0.75)*

Group E	1.57 ± 0.43			1.58 (1.22 to 1.94)*
Group C	0.07 ± 0.08			
Note: *Significant result (p<0.05)				

Table 1: Hsp-70 expression in each group.

There was significant difference in calcineurin expression between each group, except between N and C (MD=0.07; 95% CI -0.12 to 0.25; p=0.41) as shown in Table 2. Calcineurin expression in group E was higher than other groups. Sham group had lower calcineurin expression compared to other groups. There was difference in calcineurin expression between group N and S (Mean difference (MD): -0.25; 95% CI -0.42 to -0.08; p<0.05).

Group	Calcineurin	Mean Difference (95%CI)		
	Mean ± SD	Group S	Group E	Group C
Group N	0.40 ± 0.06	-0.25 (-0.42 to -0.08)*	-1.50 (-2.13 to -0.87)*	0.07 (-0.12 to 0.25)
Group S	0.65 ± 0.18		-1.25 (-1.82 to -0.68)*	0.32 (0.09 to 0.54)*
Group E	1.90 ± 0.95			1.57 (1.00 to 2.14)*
Group C	0.33 ± 0.18			
Note: *Significant result (p<0.05)				

Table 2: Calcineurin expression in each group.

There was no significant difference in catalase expression between each group, except between N and S; S and E as shown in Table 3. Group E had higher catalase expression compared to group S (MD= 0.57; 95% CI 0.27 to 0.87; p<0.05). There was significant difference in catalase expression between N and S (Mean difference (MD): 0.27; 95% CI 0.02 to 0.52; p<0.05).

Group	Catalase	Mean Difference 95% CI)		
	Mean ± SD	Group S	Group E	Group C
Group N	0.62 ± 0.24	0.27 (0.01 to 0.52)*	-0.30 (-0.65 to 0.05)	-0.05 (-0.43 to 0.33)
Group S	0.35 ± 0.14		-0.57 (-0.88 to -0.25)*	-0.32 (-0.65 to 0.02)
Group E	0.92 ± 0.30			0.25 (-0.17 to 0.67)
Group C	0.67 ± 0.34			
Note: *Significant result (p<0.05)				

Table 3: Catalase expression in each group.

There was significant difference in SOD expression between each group, except between N and S (MD= -0.07; 95% CI -0.23 to 0.09; p=0.37) as shown in Table 4. SOD expression in group E was higher than group N and S, but not group C. Sham group had higher SOD expression compared to other groups.

Group	SOD	Mean Difference 95% CI)		
		Mean ± SD	Group S	Group E
Group N	0.40 ± 0.13	-0.07 (-0.23 to 0.09)	-0.48 (-0.76 to -0.20)*	-1.10 (-1.37 to -0.83)*
Group S	0.47 ± 0.12		-0.42 (-0.69 to -0.14)*	-1.03 (-1.30 to -0.77)*
Group E	0.88 ± 0.28			-0.62 (-0.97 to -0.26)*
Group C	1.50 ± 0.27			

Note: *Significant result (p<0.05)

Table 4: SOD expression in each group.

Correlation analysis showed that HSP had strong positive correlation with calcineurin (r=0.856, p=0.000). As shown in Table 5, there was no significant correlation between Hsp-70 with catalase and SOD. However, Hsp-70 was correlated with catalase and SOD when the analysis included only group who had intervention.

Variables	Calcineurin	Catalase	SOD
HSP 70a	r=0.856 (p=0.000)	r=0.344 (p=0.099)	r= -0.193 (p=0.366)
HSP 70b	r=0.781 (p=0.003)	r=0.801 (p=0.002)	r=0.646 (p=0.023)

Note: a: Analysis in 4 groups
b: Analysis in group who had intervention (E and S)

Table 5: Correlation Hsp-70 with calcineurin, catalase and SOD.

Discussion

Hsp-70 post-AMI

In our study we found that Hsp-70 in group E was higher than other groups. In reverse, sham group had lower Hsp-70 expression compared to other groups. This indicated that Hsp-70 will be expressed in cardiomyocytes experiencing acute myocardial infarction, and then will increase more after having mild exercises. This result was consistent with previous studies that exercise increased Hsp-70 expression in heart [10-12].

Hsp-70 expression may increase after exercise because of influence of extracellular Hsp-70 caused by exocytosis of skeletal muscle cells and production of intracellular Hsp-70 in the myocardial cells [13,14]. Extracellular Hsp-70 will bind to TLR 4 which is widely found in the cell wall of cardiomyocytes [15]. The Hsp-70-TLR 4 bonding process will help Hsp-70 enter through the help of endolysosomes [16,17]. Increased intracellular Hsp-70 will also be influenced by exercises that directly affect changes in myocardial cells such as increased intracellular calcium, changes in acidity that will activate HSF 1 in the intracellular and release bonds with Hsp-70 [18,19].

Calcineurin post-AMI and its relation to Hsp-70

No calcineurin expression difference between group N and C while it was increased in groups who had intervention indicated that calcineurin was not expressed shortly after infarction. Exercise increased calcineurin expression as shown in higher calcineurin

expression in group E than Group S. It consistent with previous study that calcineurin expression peaked during ischemia [20]. There was a strong positive correlation between Hsp-70 and calcineurin. This result confirmed the conclusion from previous study that Hsp-70 directly interacted with calcineurin and stimulated an increase in calcineurin activity [21,22].

Anti-oxidant enzyme post-AMI and its relation to Hsp-70

Higher catalase and SOD expression in sham group than group who had intervention suggested that endogenous catalase and SOD was depleted post-AMI and exercise cannot return the anti-oxidant enzymes back to normal level. However, there was statistically significant increase of catalase and SOD expression in group E compared to group S. Prolonged exercise training results in improvements in catalase and SOD activities [23-25]. However, they appear to conflict with another study [12]. Age of subjects and duration of exercise appeared to be possible explanation regarding conflicting results. Old subjects may have decline antioxidant enzymes because of an age-related decline in the Hsp-70. There was adaptation response in increasing anti-oxidant enzymes after prolonged exercise [11]. Changes in antioxidant enzymes occurred during the early phase of the exercise but returned to sedentary values over time as the animals adapted to the exercise [10].

There was strong correlation between Hsp-70 and catalase and SOD in group who had intervention. It indicated that Hsp-70 increased anti-oxidant activity in ischemic condition. It was shown that Hsp-70 resulted in reduced ROS accumulation in ischemic hearts [26]. Through its chaperone activity, HPS-70 facilitates the translocation of newly synthesized SOD into the mitochondria and subsequently inhibits the generation of ROS within the mitochondria [26,27].

Conclusion

This study aimed to explain the relationship of Hsp-70 on calcineurin, SOD, and catalase post-AMI. The result showed that Hsp-70 and calcineurin was increased, but catalase and SOD was depleted in post-AMI condition. Exercise improved Hsp-70, calcineurin, catalase, and SOD activities post-AMI. Hsp-70 expression increased directly calcineurin expression.

Author Contributions

Johanes Nugroho conceived, conducted the research work, performed the investigations, and reviewed the manuscript. Christo Darius conducted literature search, data acquisition and performed the investigations. Maria Probohoesodo conducted the research work, designed and supervised the study. Cornelia Ghea analyzed the data, performed statistical analysis, and drafted the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

Authors have no conflict of interest to declare.

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