# **Relationship between ECG pattern, Heat Shock Protein 70 and oxidative biomarkers among workers occupationally exposed to noise**

Nagat Amer, Safia Beshir, Weam Shaheen\*, Eman M. Shahy and Eman EL-Tahlawy

Environmental and Occupational Medicine Department, Division of Environmental Research, National Research Centre, El-Buhouth St., Dokki, Giza, 12622, Egypt.

# ABSTRACT

Noise health hazards include hearing affection, ischemic heart disease, hypertension and headache. This study aimed to explore a possible link between heat shock protein 70 level, oxidative status and electrocardiogram changes among workers occupationally exposed to noise. A crosssectional comparative study was carried out on 91 male textile workers. Environmental sound level assessment, electrocardiogram, and measurement of blood pressure were done. Serum levels of heat shock protein 70, total antioxidant concentration, malondialdehyde, total cholesterol and triglycerides were measured. Forty-three workers showed normal electrocardiogram while 48 workers showed electrocardiogram abnormalities. Serum levels of heat shock protein 70 and total antioxidants were significantly higher, while malondialdehyde level was significantly lower among workers with normal electrocardiogram compared to those who showed abnormalities. Heat shock protein 70 and total antioxidant levels were significantly lower among workers with systolic blood pressure  $\geq 140$ mmHg compared to workers with systolic blood pressure < 140 mmHg and total antioxidants were significantly lower among workers with diastolic blood pressure  $\geq$  90 mmHg compared to those with diastolic BP < 90 mmHg. Serum heat shock protein 70 and oxidative markers may serve as biomarkers for early detection of cardiovascular impacts and as markers of environmental stress among noise-exposed workers.

**KEYWORDS:** noise, electrocardiogram, heat shock protein 70, total antioxidants capacity, malondialdehyde.

## **INTRODUCTION**

Industry and traffic are considered the main sources of noise. Globally, noise pollution is an environmental problem that affects the community health greatly after air and water pollution [1].

Noise health hazards include hearing affection, ischemic heart disease (IHD), hypertension and headache [2]. A previous study showed that workers occupationally exposed to high noise are at a higher risk for hypertension and myocardial infarction [3].

Stress mainly targets the cardiovascular system. Cardiomyocyte death is the main cellular basis for stress-induced cardiovascular injury [4].

Heat shock proteins (HSPs) are divided according to their molecular weights into several families namely HSP 60, HSP 70, HSP 90 and small HSP families. HSP 70 is the most studied group because it is expressed in stressed cells. During stress, HSP 70 moves to the nucleus and links with nucleoli. It shares many of the HSP functions and, in addition it protects against ischemic injury, and

<sup>\*</sup>Corresponding author: weamshaheen@gmail.com

its expression represents the capability of cells to deal with adverse situations [5].

HSPs exist in the serum of clinically normal persons, but are induced at high levels when exposed to a high temperature or other stress as noise. High level noise exposure damages proteins and hence HSPs are expressed at high levels to stabilize proteins and protect them from denaturation. These proteins not only protect cells against stresses but also play a very important role in normal functioning of numerous cellular processes [6]. HSPs were found to be highly induced in heart cells, in numerous conditions such as congestive heart failure, vascular disease or after acute myocardial infarction. Hsp70 has been shown to exert cardioprotection [7].

Oxidative stress is a state of augmented production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which go beyond the ability of the antioxidant systems in the body to scavenge them. The shift in the balance between oxidants and antioxidants in favor of oxidants is named oxidative stress. Exposure to noise stress stimulates ROS and RNS production, leading to breaking of lipid and protein molecules and damaging DNA, resulting in loss of function and cell death. This in turn causes irreversible damage to hearing structures and other health impacts, such as cardiovascular diseases [8].

Oxidative stress plays an important role in launching noise-related health diseases. The role of oxidative stress in the pathogenesis of atherosclerosis had been documented [9].

Harmful effects of free radicals on cells have been documented. However, the biological systems protect themselves by inducing HSP in response to these reactive species (ROS); otherwise it may lead to oxidative stress [10].

HSPs and the antioxidant system work together to inhibit the deteriorating effects of ROS. A recent study suggests that HSP would counterpart the existing endogenous antioxidants during and following cellular oxidative stress [11].

The present study aimed to explore a possible link between Hsp70 level, oxidative status and ECG pattern among workers occupationally exposed to noise.

## MATERIALS AND METHODS

#### Study design and population

This study was carried out on 91 male workers in a textile factory located in Greater Cairo Governorate, Egypt, with mean duration of exposure ( $16.73 \pm 5.10$ ) years). Their work was 12 hours per day with one day off. None of the workers used any protective equipment during working hours. Workers known to be diabetic or hypertensive or smoke were excluded. Written informed consent was taken from all participants prior to the study. The study was approved by Medical Research Ethics Committee (National Research Centre, Cairo, Egypt) No. (16401).

#### Methods

#### **Environmental sound level assessment**

Done using a portable Sound Level Meter Standard (Model CR 306) at different sites in the open and spinning sector.

## Questionnaire

Was filled by one of the authors. The questionnaire included personal data, smoking habits, detailed current and past occupational exposure to noise, cardiovascular symptoms of ischemic heart disease (chest pain, dyspnea, palpitation) and past history of hypertension and diabetes.

# Electrocardiogram (ECG)

Was done using CARDIMAX portable apparatus, FX-7102 electrocardiograph Ver. 02. FUKUDA DENSHI CO., LTD, Japan. The ECG was interpreted by a clinician (one of the authors) according to Goldberger *et al.*, 2017 [12].

Resting ECG recording with depression of ST segment and T-wave inversion or flattening was considered as sign of ischemic heart diseases. Also other abnormalities in the ECG were considered.

## Measurement of blood pressure

Was done to all participants. A standard mercury sphygmomanometer with a 14-cm cuff was used to measure systolic BP (SBP) and diastolic BP (DBP) in the sitting position. According to Blood Pressure UK Association, if the SBP is 140 or more regardless the DBP or the DBP is 90 or more regardless the SBP it refers to high blood pressure. Blood pressure (140/90 or higher) refers to hypertension [13].

# **Blood sample**

Was collected by venipuncture with 5 ml syringes from each subject. Clotted blood was centrifuged to separate serum to estimate serum total cholesterol (TC), triglycerides (TG), Total antioxidant capacity (TAC), malondialdehyde (MDA) and human HSP 70.

## Laboratory investigations

Serum human HSP 70 was measured by Elisa Kit purchased from Bioassy Technology Laboratory, China (www.bt-laboratory.com). Antioxidant biomarker: Total antioxidant capacity (TAC) was estimated colorimetrically [14].

- Biomarker of oxidative stress: The determination of malondialdehyde (MDA) as a marker for lipid peroxidation using colorimetric method [15].
- Serum total cholesterol (TC) was measured by enzymatic colorimetric test-GPO-PAP method [16].
- Serum triglycerides (TG) was measured by enzymatic colorimetric test-GPO-PAP method [17].

All the previous kits were purchased from Centronic GmbH AM Kleinfeld 11, 85456 Wartenberg/Germany.

#### Statistical analysis

The data was statistically analyzed using the "Statistical Package for Social Science (SPSS) version 18 Inc., Chicago, IL, USA". Independent t-test and chi-square (X2) were used to compare quantitative and qualitative data of the studied groups. Pearson's bivariate correlation coefficient was also calculated. The alpha level of significance was set at p < 0.05.

#### RESULTS

Environmental measurements in the factory where the present study was done revealed elevation of sound level at four tested sites in the opening and spinning section. The noise level ranged between 100 and 110 dB.

The present study was a cross-sectional comparative study that included two male groups: noise-

exposed workers with normal ECG (n = 43) and noise-exposed workers with ECG abnormalities (n = 48), with comparable ages ( $38.02 \pm 6.70$ ,  $38.17 \pm 5.62$  years respectively). Mean duration of exposure is  $16.73 \pm 5.10$  years.

Forty-three noise exposed workers (47.3%) showed normal ECG, while 48 workers (52.7%) showed ECG abnormalities. ECG abnormalities were in the form of ischemic changes, left ventricular hypertrophy (LVH), conductive abnormalities and ventricular extra systole. Some workers showed more than one abnormality in the ECG.

There was no effect of age on serum HSP 70 level in the current study (r = 0.104, p = 0.327).

Mean systolic and diastolic blood pressure among noise-exposed workers with abnormal ECG was higher (130.31  $\pm$  18.58, 83.33  $\pm$  11.78 respectively) compared to those with normal ECG (126.51  $\pm$  18.27, 81.28  $\pm$  10.41 respectively).

Eleven workers (12.1%) complained of cardiac symptoms: chest pain 5 (5.5%), dyspnea 5 (5.5%), palpitation 1 (1.1%).

Table 1 shows the number and percentages of the recorded ECG changes among workers who showed ECG abnormalities.

Table 2 shows that mean serum levels of TAC and HSP 70 were significantly higher among workers with normal ECG compared to those who showed ECG abnormalities. However, MDA level was significantly lower among workers with normal ECG compared to those with abnormal ECG.

Table 3 shows that the comparison between mean HSP 70 levels among the exposed workers with normal ECG and each group of ECG abnormality revealed highly significant decrease of mean serum level of HSP 70 among those with ischemic changes, LVH and ventricular extra systole compared to those with normal ECG.

Table 4 shows highly significant decrease of TAC among those workers with ischemic changes and LVH, while MDA was significantly higher among all recorded abnormalities compared to those with normal ECG.

Table 5 shows that mean serum TAC and HSP levels were significantly lower among workers with systolic blood pressure  $\geq 140$  mmHg compared to those with < 140 mmHg.

ECG abnormalities (48)	NO.	%
Ischemic changes	29	60.4%
LVH	10	20.8%
Conductive abnormalities	5	10.4%
Ventricular extra systole	9	18.8%
Tall T wave	1	2.1%

**Table 1.** Frequency distribution of ECG abnormalities among noise-exposed workers.

Table 2. Mean serum levels of investigated parameters among studied groups.

	Normal ECG (43)	Abnormal ECG (48)	T. Tost	P-value
	Mean ± SD	Mean ± SD	1- Test	
HSP 70 (ng/ml)	$2.39\pm0.95$	$1.44\pm0.31$	2.8	$0.005^{**}$
TAC (Mm/L)	$1.35\pm0.36$	$1.06\pm0.26$	4.2	0.001**
MDA (nmol/ml)	$5.81 \pm 2.983$	$8.45 \pm 1.892$	5.08	0.001**
TC (mg/dl)	$134.51\pm48.38$	$141.88\pm52.79$	0.69	0.48
TG (mg/dl)	$124.60 \pm 63.80$	$110.26 \pm 67.73$	1.04	0.301

TAC, Total antioxidants capacity; MDA, Malondialdehyde; HSP 70, Heat shock protein 70; TG, Triglycerides. \*\*p < 0.001.

Table 3. Mean levels of HSP 70 in each ECG abnormality compared to normal ECG.

HSP 70 (ng/ml)					
	Mean ± SD	t-test	P-value		
Normal ECG	$2.39\pm0.95$				
Ischemic changes	$1.47\pm0.39$	3.09	0.0001**		
LVH	$1.39\pm0.18$	2.04	0.002**		
Conductive abnormalities	$1.34\pm0.13$	1.15	0.06		
Ventricular extra systole	$1.44\pm0.21$	1.97	0.005**		

LVH, Left ventricular hypertrophy; \*\*p < 0.001.

Table 6 shows that mean serum TAC level was significantly lower among workers with diastolic  $BP \ge 90$  mmHg than those with diastolic BP < 90 mmHg.

Figure 1 shows that there is a statistically significant positive correlation between HSP 70 and TAC (p < 0.05).

Figure 2 shows statistically negative correlation between HSP 70 and MDA (p < 0.05).

#### DISCUSSION

The noise level in the current study ranged between 100 and 110 dB which exceeded the level recommended (90 dB) by the Egyptian

Mean ± SD				P-value
Normal ECG	TAC (Mm/L)	$1.35\pm0.36$		
	MDA (nmol/ml L)	5.81 ± 2.983		
Ischemic changes	TAC (Mm/L)	$1.06\pm0.27$	2.384	0.0008**
	MDA (nmol/ml)	$8.21 \pm 1.36$	2.162	0.0003**
1.5711	TAC (Mm/L)	$1.01\pm0.24$	1.838	0.007**
	MDA (nmol/ml)	8.41 ± 1.24	1.465	0.009**
Conductive abnormalities	TAC (Mm/L)	$0.96\pm0.34$	1.2	0.08
	MDA (nmol/ml)	$10.49 \pm 2.41$	2.3	0.01*
Ventricular extra systole	TAC (Mm/L)	$0.98\pm31.0$	0.08	0.935
	MDA (nmol/ml L )	8.69 ± 3.16	2.62	0.012*

Table 4. Mean l	levels of TAC a	nd MDA in eacl	h ECG abnorm	ality com	pared to norma	al ECG.

LVH, Left ventricular hypertrophy; TAC, Total antioxidants capacity; MDA, Malondialdehyde. \*\*p < 0.001; \*p < 0.01.

Table 5. Comparison	of mean serum	levels of investig	ated parameters	among workers	with systolic	$BP \ge 140$
mmHg and those with	< 140 mmHg.					

	Systolic blood I		P value	
	≥ 140 mmHg (31)	≥ 140 mmHg (31) < 140 mmHg (60)		
	Mean ± SD	Mean ± SD		
HSP 70 (ng/ml)	$1.70\pm0.45$	$1.99 \pm 0.97$	1.950	0.054*
TAC (Mm/L)	$1.04\pm0.29$	$1.28\pm0.34$	3.439	0.001**
MDA (nmol/ml)	$7.46 \pm 2.67$	$7.06 \pm 2.86$	0.660	0.511

TAC, Total antioxidants capacity; MDA, Malondialdehyde; HSP 70, Heat shock protein 70. \*p < 0.01; \*\*p < 0.001.

**Table 6.** Comparison of mean serum levels of investigated parameters among workers with diastolic  $BP \ge 90 \text{ mmHg}$  and those with < 90 mmHg.

	Diastolic blood pressure			
	≥ <b>90</b> (35)	< 90 (56)	t-test	P value
	Mean ± SD	Mean ± SD		
HSP 70 (ng/ml)	$1.78\pm0.78$	$1.96\pm0.87$	1.040	0.302
TAC (Mm/L)	$1.05\pm0.28$	$1.29\pm0.34$	3.646	0.001**
MDA (nmol/ml)	$7.55 \pm 2.55$	$6.98 \pm 2.93$	0.968	0.336

TAC, Total antioxidants capacity; MDA, Malondialdehyde; HSP 70, Heat shock protein 70; \*\*p < 0.001.



Figure 1. Person correlation between HSP 70 and TAC among the studied group.



Figure 2. Person correlation between HSP 70 and MDA among the studied group.

Environmental Law No. 4 (1994). Noise exposure is a powerful stressor as it raises the levels of the stress hormone corticosterone. Long-standing exposure to noise affects the cardiovascular system causing hypertension, IHD, and stroke [18].

ECG is used to diagnose cardiovascular diseases. Certain changes in the ECG patterns may be used as markers for progression of these diseases [19]. About fifty three percent (52.7%) of the noiseexposed workers in the present study showed ECG abnormalities. A recent study that was conducted on workers exposed to noise showed that workers with ECG abnormalities represented 34.3% of the total number of the exposed group which was 35 workers [20]. A previous study which was done among automobile workers exposed to different noise levels showed that the group with abnormal ECG had been exposed to a significantly higher level of noise than the normal ECG group [21]. Prolonged occupational exposure to high noise level causes biochemical changes which make the workers liable to cardiovascular impacts [22]. Moreover, a recent study [23] stated that occupational noise exposure makes workers at higher risk of developing IHD.

In our study, the recorded ECG abnormalities included 60.4% ischemic changes, 20.8% LVH, 10.4% conductive abnormalities, while 18.8% had ventricular extra systole and only 1 case (2.1%) showed tall T wave in the ventricular leads (suggestive of impending infarction). A recent study [20] recorded ECG abnormalities among the noise-exposed workers including 14.3% ischemic changes, 5.7% LVH and 14.3% showed conductive abnormalities. Another previous study [24] done among 29 workers exposed to stress (heat) showed 20.6% IHD and 20.6% tall T-wave.

Despite these recorded ECG abnormalities in the present study, the complaints of cardiac symptoms were found only in 12.1% of the studied group. Previous studies [25, 26] stated that the occurrence of ischemic changes (ST-segment depression and T-wave inversion) in the resting ECG without clinical evidence of definite IHD is somewhat a marker and a strong predictor of underlying heart disease, including IHD.

HSP are intracellular molecules with cytoprotective functions. However, they can be released

extracellularly as a response to several stressors such as noise [27].

In our study noise exposed workers with normal ECG have mean serum HSP 70 level  $(2.39 \pm 0.95)$  ng/ml while those who showed ECG abnormalities have mean serum HSP 70 level  $(1.44 \pm 0.31)$  ng/ml, especially among those who showed ischemic changes, LVH and ventricular extra systole  $(1.47 \pm 0.39, 1.39 \pm 0.18, 1.44 \pm 0.21$  respectively). There was no significant correlation between mean serum level of HSP and duration of exposure. Similarly, a previous study done among workers exposed to noise in a textile factory also showed no significant correlation between level of HSP 70 and the duration of exposure [28].

Experimentally, Hsp70 was elevated in rat aorta and adrenal glands after restraint stress [29] and in hearts of Japanese quails exposed to loud noise [30].

Previous follow-up study [31] done to report that serum Hsp70 levels predict the progression of atherosclerosis in hypertensive subjects showed that increases in carotid intima thicknesses was significantly less prevalent in subjects having high serum Hsp70 levels. This points out that Hsp70 is not only a specific and early marker for the cardiovascular disease but also that it might protect against the progression of atherosclerosis. Another study [32] done to assess whether HSP 70 is associated with CAD showed that serum HSP 70 was significantly higher in non-CAD patients than in CAD patients.

An experimental study found that mice having high levels of HSP 70 are more resistant to ischemic abnormalities [33]. Also, another study [5] done on Westar rats under stress observed that elevated HSP 70 was correlated significantly with decreased ECG abnormalities.

The relation between the low risk of IHD and HSP 70 might be due to its protective effect on cells exposed to stress. HSP 70 is internalized by human endothelial cell and this mechanism might be tangled in the seeming atheroprotective properties of this protein [34].

Exposure to noise proved to cause firstly improvement in cochlear blood flow, and then after a short period of time sudden decline in cochlear circulation occurs. This prompts formation of ROS [35]. Cardiac diseases like ischemia and atherosclerosis were observed to be associated with oxidative stress [36]. The present study showed significant depression in mean serum level of TAC and significant elevation in mean serum level of MDA among workers who showed ECG abnormalities ( $1.06 \pm 0.26$ ,  $8.45 \pm 1.89$ nmol/ml, respectively) compared to workers with normal ECG ( $1.35 \pm 0.36$ ,  $5.81 \pm 2.98$  nmol/ml, respectively), especially among those with ischemic changes ( $1.06 \pm 0.27$ ,  $8.21 \pm 1.36$ , respectively) and LVH ( $1.01 \pm 0.24$ ,  $8.41 \pm 1.24$ , respectively).

Both oxidative stress and antioxidants seem to regulate Hsp70 expression. On the other hand, reduction in Hsp70 expression can increase ROS generation [37]. Elevated HSP expression reduces the ROS generation and facilitate antioxidant defenses reducing cellular damage caused by oxidative stress [38]. This is evident in our study as there was a significant positive correlation between HSP 70 serum level and TAC, and significant negative correlation between HSP 70 serum level and MDA. A previous study [39] demonstrated that HSP 72 (a major protein in HSP 70 family) enhances manganese superoxide activity. This enzyme preserves mitochondrial function and limits mitochondrial-related apoptosis during myocardial ischemia.

Physiological changes may occur on exposure to noise over 97dB. Noise activates the hypothalamicpituitary-adrenal axis, resulting in release of stress hormones. High sympathetic tone is associated with increased vascular tone and hypertension [40].

Mean levels of HSP 70 and TAC were significantly higher among workers with mean systolic and diastolic blood pressure < 140 and < 90, respectively. This may suggest the protective effect of HSP 70 and TAC against hypertension among our workers exposed to noise stress.

Stress may lead to hypertension [4]. Workers occupationally exposed to noise are at a higher risk for high blood pressure [3].

Stress contributes to high cholesterol level and other cardiac risk factors [4]. The present study showed no significant difference with regard to cholesterol and triglyceride mean levels between both studied groups with normal and abnormal ECG. This may support that ECG abnormalities which were recorded among our studied group were due to other factors rather than the lipid levels.

Similarly, results of a previous study [41] showed no relation between occupational noise exposure and serum lipid levels. The authors added that change of lipid levels is not included in the causal pathway between occupational noise exposure and cardiac diseases.

Finally, results of the present study showed that levels of HSP 70 and antioxidants were lower among noise-exposed workers with ECG abnormalities compared to those workers with normal ECG and among workers with systolic and diastolic pressure ( $\geq$  140 mmHg,  $\geq$  90 mmHg, respectively). This suggests the synergistic cardioprotective role of HSP 70 and antioxidants among workers occupationally exposed to stress such as noise.

## CONCLUSION

Serum Hsp70 and oxidative markers may serve as biomarkers for early detection of cardiovascular impacts and as markers of environmental stress among noise-exposed workers

## RECOMMENDATION

Measurement of HSP 70, TAC and MDA levels as a routine periodic investigation for workers occupationally exposed to stress such as noise as well as performing ECG for early detection of affected workers.

Exercise increases HSP expression [42]; so, performing exercise regularly is recommended.

Administration of exogenous antioxidants as they augment the induction of endogenous antioxidant enzymes and improve their ROS scavenging ability.

# ETHICAL CONSIDERATIONS

The study was approved by Medical Research Ethics Committee (National Research Centre, Cairo, Egypt) No. (16401). Written informed consent was taken from all participants prior to the study.

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# CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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