Assessmenmt of Some Cardiovascular and Biochemical Parameters Induced in Rats by Chronic Noise Stress

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Abstract: The present study aimed to assess some cardiovascular and biochemical parameters induced in rats by chronic noise stress. Moreover, changes produced in the histological architecture of the heart and aorta were also investigated. For this purpose, forty healthy adult male albino rats weighting 200±30 grams were used in the study. They were divided equally into two main groups; noise group (n=20) which was exposed to chronic white noise stress (100 dBA) 6 hours daily for 30 days and control group (n=20) which was kept away from any stress source and was hold in the same conditions. After 30 days, animals exposed to chronic noise stress exhibited significant increase in the heart rate, systolic, diastolic, and mean arterial blood pressure associated with a significant decrease in serum Mg^{++} levels. There was a strong significant negative correlation between reduction in serum Mg^{++} and elevation in mean arterial blood pressure. A significant elevation in serum levels of ACTH, corticosterone, and leptin was detected after exposure to noise stress. Moreover, the data obtained indicated that, under these conditions of chronic and high noise exposure levels, there was significant increases in the serum levels of TC, TGs,VLDL and LDL-C and a significant decrease in the level of serum HDL-C. The histopathological examination of the heart tissue demonstrated that, exposure of rats to chronic noise stress has resulted in areas of hemorrhage inbetween the cardiac myocytes, necrosis and small areas of myocardial infarction. Microscopic examination of the aorta showed the presence of thickening of elastic fibers in the media with perivascular infiltration by acute inflammatory cells (neutrophils & eosinophils) and non-specific inflammatory cells.
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1. Introduction:

Noise is a type of unwanted sound pollution that penetrates the environment. Noise pollution can be caused by many sources including vehicles, factories, concerts, air conditioners, engines, machines, aircraft, ,helicopters, alarms, public address systems, industrial development and construction work, walkman –type headphones and power garden tools. In general, noise pollution refers to any noise irritating to one's ear which comes from an external source (**Mahmoud *et al.*, 2008**).

Selye (1979) defined loud noise as an environmental stress factor. Nowadays, a large number of people are exposed to potentially hazardous noise levels not only in work background (**Kawecka-Jaszcz, 1991; Lang *et al.*, 1992 and Zhao *et al.*, 1993**) but also during everyday life, i.e., in urban traffic, with electric household appliances, discos, etc. (**Parrot *et al.*, 1992 and Maschke, 2011**). Apart from the well-known hearing impairment, the noise bath causes slow but widespread injuries at several levels in human organs and apparati. (**Gloag, 1980**)

Noise is ubiquitous in every day interaction, and no one on the earth can escape the sound of noise wanted or unwanted (**Binhi, 1999**). Millions of persons are exposed daily to equivalent noise levels of at least 55 dB, 65 dB and 75 dB or more (**Elise *et al.*, 2002** and **Mahmoud *et al.*, 2008**).

Health risks attributed to noise have increasingly attracted political attention in recent years, this is due to continuous growth of noise encumbrance in the surroundings of daily life and progressive number of protests by noise plagued citizens or those representing their interests (**Maschke and Hecht, 2000**).

Noise can act as a non-specific stressor inducing stress reactions, anxiety disorders, insomnia, syndromes of immune disregulation, fatigue as well as hearing impairment (**Ising *et al.*, 1999**). A sound above 80 dB has been considered to produce ill effects on the health of animals and human beings, affecting functional ability, biochemical parameters, immunological system and histology. Some of stressor induced alterations have been attributed to an imbalance in autonomic system and involving hypothalamo-pituitary-adrenal axis activation; this is followed by changes in physiological function of the organism, including total peripheral resistance, cardiac output, and blood lipid metabolism (**Gehlot *et al.*, 2002**).

Acute exposure to maximum sound pressure level above 90 dB has the potential to stimulate the sympathetic nervous system to increase catecholamines

and cortisol secretions. However, if the noise disturbed activities such as conversation, concentration, recreation and sleep; acute increase of catecholamines and cortisol secretions were observed even at an environmental noise level > 50 dB (**Ising *et al.*, 1999 and Goyal *et al.*,2010).**

Chronic exposure to environmental and industrial noise may be a risk factor for cardiovascular disease (CVD) and the possible pathway that links noise exposure to CVD may be elevated serum lipid levels (**Saha *et al.*, 1996 and Maschke and Hecht, 2000**).

Exposure to noise causes many health problems such as hearing loss, sleep disturbance, and impairs performance as well as effecting cognitive performance. It also increases aggression and reduce the processing of social cues seen as irrelevant to task performance as well as leading to coronary heart disease, hypertension, higher blood pressure, increased mortality risk, serious psychological effects, headache, anxiety, and nausea (**Lenzi *et al.*, 2003; Stansfeld and Matheson, 2003; Abbate *et al.*, 2005 and Ravindran *et al.*, 2005**). Children chronically exposed to noise tend to have poorer reading ability and less cognitive capacity to understand (**Stansfeld and Matheson, 2003**). Some studies are being conducted on causation of exposure to noise near airports to the higher risk of developing hypertension, cardiovascular diseases and incidence of cancer (**Jarup *et al.*, 2005 and Visser *et al.*, 2005**).

Noise exposure of any kind that exceeds 90 dB has been reported to be a source of stressor (**Ravindran *et al.*, 2005**). A study showed that, working and reference memory error increased significantly following the noise-stress exposure, 100 dBA/4h per day for 30 days, when compared to control animals (**Manikandan *et al.*, 2006**). Acute as well as long term exposure to noise can produce excessive free radicals such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) (**Manikandan *et al.*, 2005**). Oxygen free radicals can attack protein, nucleic acids and lipid membranes thereby disrupting normal cellular functions and integrity (**Endo *et al.*, 2005 and Manikandan and Devi, 2005**).

Nervous system is relatively more susceptible to free radical damage (**Scarfiotti *et al.*, 1997**). According to **Ravindran *et al.* (2005),** neurotransmitters in discrete brain regions were found to be increased during noise stress even after 15 days of exposure. In addition to generating free radical species, it also leads to increase in radical induced lipid peroxidation end products such as malondialdehyde (MDA) which is an indicator of lipid peroxidation processes (**Derekoy *et al.*, 2001**).

Similar to other types of stress, noise stress has also been shown to increase levels of stress hormones like corticosterone and norepinephrine (**Agnes *et al.*, 1990 and Archana and Namasivayam, 1999**). Many studies indicated that corticosterone can stimulate the secretion of adiposite-derived hormone, leptin (**Slieker *et al.*, 1996 and Wabitsch *et al.*, 1996**). As noise increases corticosterone secretion, it may be proposed that, the exposure to stressors like noise could induce alterations in serum leptin levels. Such a possibility has not been fully investigated.

The present study was designed to investigate the influence of exposure of adult male albino rats to chronic noise stress on:

1. Some cardiovascular parameters such as the heart rate and the arterial blood pressure.
2. Serum leptin, ACTH, and corticosterone levels.
3. Serum lipid profile and magnesium ion concentration.
4. Histological architecture of the heart and aorta.

2. Materials and Methods

Animals

In the present study, forty healthy adult male albino rats weighing between 200 – 250 gm were enrolled. They were obtained from the laboratory animals' farm unit, faculty of Veterinary Medicine, Zagazig University, Egypt. All the animals were housed in the animal facility, 3 per open mesh-steel wire cage (29 cm x 22 cm x 14 cm), fed ad-libitum (allowed free access to food and water), kept under closely controlled hygienic and environmental conditions [12 hour reverse light/dark cycle, constant humidity and room temperature (20°-24°)]. The diet consisted of mixed commercial rat laboratory chow and was supplied in separate clean containers. Animals were allowed to adapt to the environment for at least 1 week prior to noise experiment to minimize all undesired stressors.

The animals were divided into 4 equal groups:

Group I: Consisted of 10 rats in which the arterial blood pressure (ABP) and electrocardiogram [ECG, to measure the heart rate] was recorded in vivo by using the MD4 osccillograph. This group served as a control group.

Group II : Consisted of 10 rats from which

A- Blood samples were collected and sera were separated for the determination of the levels of Mg^{++}, ACTH, corticosterone, leptin, total cholesterol, triglycerides, low density lipoprotein, very low density lipoprotein and high density lipoprotein.

B- The heart and the aorta were isolated and prepared for hsitopathological examination using the light microscope. This group served also as a control group.

Group III : Consisted of 10 rats which were exposed to chronic noise stress and immediately after the last exposure, they were used for the in vivo recording of the arterial blood pressure (ABP, mmHg) and ECG [to measure heart rate (HR, beats/min)] using MD4 Oscilograph. This group served as a noise exposure group.

Group IV : Consisted of 10 rats which were exposed to chronic noise stress and immediately after the last exposure,

A- The blood samples were collected and the sera were separated and used for the determination of the levels of Mg^{++}, ACTH, corticosterone, leptin, total cholesterol, triglycerides, low density lipoprotein, very low density lipoprotein, and high density lipoprotein.

B- The heart and the aorta were isolated and prepared for histopathological examination using the light microscope. This group served as a noise exposure group.

Noise-stress induction procedure:

When noise stress of any kind exceeds 90dB, noise becomes a stressor (**Ramsey and Flangan, 1982**). Noise was produced by two loud speakers mounted 40 cm a part on opposite sides of the cage (15 w) and driven by a white noise generator (range 0 – 26 KHz) installed (suspended) 30 cm above the cage. The noise level was set at an intensity of 100 dBA uniformly throughout the cage and monitored by a sound level meter (RAT-M Model RE-120, Germany). This noise level was delivered continuously to 20 males rats 6 hours daily for 30 days.

To avoid the influence of handling-stress on evaluation of the effects due to noise exposure, control rats (20 males) were kept in the above, described cages during the corresponding period of time without being exposed to noise **(Pellegrini *et al.*, 1997 and Lenzi *et al.*, 2003).**

Measurement of blood pressure and ECG recording

For calibration of the pressure, a mercury sphygmomanometer and 500 ml – capacity glass bottle with very light rubber stopper were used. Through one of the two holes in the stopper, an L- shaped rigid glass tube was forced to enter until it reached 0.5 cm from the bottom of the bottle and it was connected to the blood pressure transducer. Through the other hole, one limb of T- shaped rigid glass tube was forced just to pass through the rubber cover of the bottle and it was connected to the air pump of the sphygmomanometer.

Preparation of the recording system:

1) The ECG limb cable was attached to the FC 123 ECG facility coupler, which was fitted to one of the 4- channels of the oscillograph MD4 ***(Bioscience, Washington).***
2) The blood pressure transducer (PT 400) was connected to the FC 137 strain gauge coupler that was fixed to another channel of the oscillograph.
3) About 10cm length polyethylene tube with a clamp was connected to one side limb of the PT 400 transducer and the other limb of the transducer was connected through polythene tube with a clamp to the arterial cannula.
4) The 500 ml capacity glass bottle was filled with normal saline solution containing 16 l.u. herparin /ml to inhibit blood clotting **(Tuttle and Milts, 1975)**. The external limb of the L- shaped tube, previously fitted in the bottle stopper, was connected to the side limb of the transducer, all valves were opened; the pressure inside the bottle was raised by pressing on the pump, so that, the solution would be pushed to fill the connections to the transducer and the valve of the other limb of the transducer was reclosed. Calibration of the pressure was done by gradual elevation in the bottle by 10 mmHg increment, theraby, in the mercury manometer, starting from zero to 200 mmHg (10, 20, 30,……..etc) and record on the chart paper of the oscillograph. After that, all valves were closed and transducer was disconnected from the bottle.

Intra – arterial cannulation and recording of the systemic arterial pressure:

The arterial blood pressure of the animals was determined by employing the method of **Burden *et al.* (1979)**. after stabilization of anesthesia which was induced by intraperitoneal injection of ethylcarbamate (urethane) [1.2 gm / weight) **(Niu *et al.*, 2000)].**

Recording of the electrocardiogram [ECG] :

The ECG limb of the cable was attached to hypodermic needles inserted and fixed subcutaneously, in axilla (for each fore limb); just above the ankle (for each hind-limb). According to the manufacturer recommendation; the red lead was attached to the right arm, the yellow lead to the right leg; the white lead to the left arm; the green lead to the left leg.

The FC123 was switched on lead II that gives good signals for analysis of ECG. The selected paper chart speed for recording the ECG by the oscillograph was 25 mm/sec. [i.e 150 cm/minute]. Calculation of the heart rate/minute was carried out by counting the number of cardiac cycles (n) per fixed distance of the chart paper e.g. 5 cm and the heart rate/minute was then calculated by division of 150/5 multiplied by (n) **(Gay, 1995).**

Sampling of blood

Upon completion of all noise exposure regimens (immediately after the end of the last exposure), the animals were anesthetized with an intraperitoneal injection of intraval sodium (60 mg/kg body weight) and exanguinated. Approximately 5 ml of blood was

collected from each rat for hormonal assay, using ELISA method. The ELISA kits used were stored at 4ºC. In order to avoid variations in the results due to circadian rhythm of hormones, all blood samples were collected at the same time of the day.

Separation of serum:

The blood was collected from all the studied groups in clean centrifuge tubes and was allowed to clot over a period of 2 hours. Serum was separated by centrifugation of blood at 3000 rpm for 20 minutes. The supernatant serum was pipetted off using fine tipped automatic pipettes and was stored frozen at – 20ºC until assayed. The reagents and specimens were brought to the room temperature before use **(Chandralekha *et al.*, 2005 and Mahmoud *et al.*, 2008**).

Determination of serum Magnesium level:

Serum Magnesium was estimated according to the method described by ***Tietz (1995)*** using ELITECH MAGNESIUM CALMAGITE kits [SEPPM S.A.S. ZONE INDUSTRIELLE – 61500 SEES FRANCE].

Determination of the serum ACTH levels:

Serum ACTH levels were determined according to the immunoassay method of **Odell *et al.* (1989).** The ACTH Immunoassay is a two-site ELISA [Enzyme-Linked Immuno Sorbent Assay] for the measurement of the biologically active 39; amino acid chain of ACTH.

Kits for determination of ACTH: (SIEMENS-5210 Pacific concourse drive Los Angeles, CA 90045-6900-USA)

Determination of the serum cortieosterone levels:

Serum corticosterone level were determined by the application of the immunoassay method of **Vazquez-Palacios (2001)**. Cortieosterone ELISA Kit is a solid phase enzyme-linked immunosorbent assay (ELISA), based on the principle of competitive binding.

Kits for determination of corticosterone : (DRG instruments GmbH, Germany).

Determination of serum leptin levels:

The method used for hormonal assay of serum leptin level was Enzyme linked lmmuno sorbant Assay [ELIZA] with the aid of Micro ELIZA plate reader. Leptin concentrations were calculated according to **Considine *et al.* (1996).**

Active leptin ELISA kits: For the quantitative measurement of leptin in serum by leptin Enzyme – Linked immuno sorbent (ELISA) [DSL – 10 – 23100 Diagnostic Headquarters 445 medical center BLvd Webster, Texas 77598 – 4217 USA].

Determination of serum cholesterol:

Cholesterol serum level was estimated according to the method described by (**Tietz ,1995).**

The cholesterol CHOD – POD, Enzymatic colorimetric kits [SPINREACT, S.A. ctra. Santa Coloma 7E – 17176 SANT ESTEVE DE BAS (GI) SPAIN] and spectrophotometer or colorimeter measuring at wavelength 505 nm were used.

Determination of serum Triglycerides:

Triglycerides were estimated according to the method described by **Tietz (1995).**

The Triglycerides GPO – POD Enzymatic colorimetric kits

[SPINREACT , S.A Ctra Coloma, 7E – 17176 SANT ESTEVE DE BAS (GI) SPAIN] and spectrophotometer or colorimeter measuring at wavelength 505 nm were used.

Determination of serum high density lipoprotein cholesterol (HDL-C):

HDL-C was estimated according to the method described by **Tietz (1995)**. The HDL –C precipitating reagent kits [SPINREACT , S.A Ctra Coloma, 7E – 17176 SANT ESTEVE DE BAS (GI) SPAIN] and spectrophotometer or colorimeter measuring were done at wavelength 505 nm.

Determination of serum low density lipoprotein cholesterol (LDL-C):

LDL–Cholesterol was calculated according to the **Friedewald *et al.* (1972)** formula:

$$\text{LDL-C} = \text{Total cholesterol (TC)} - \frac{\text{Triglyceri des (TGs)}}{5} - \text{HDL- C}$$

Determination of serum very low density lipoprotein (VLDL)

VLDL was calculated according to the **Friedewald *et al.* (1972)** formula:

$$\text{VLDL} = \frac{(\text{TGs})}{5}$$

Statistical Analysis

All data were expressed as mean ± SE and statistically analyzed according to the methods described by **Kirkwood (1989)**. Differences were considered significant if $P < 0.05$. The statistical methods used in this study for analysis of the data include: Arithmetic mean ($\bar{X}$), Standard deviation (SD), Standard error of mean (SEM), Student's t-test. Correlation coefficient (r)

Histological and Histopathological studies:

After decapitation,small pieces of the heart and aorta were taken immediately from both control rats and those exposed to chronic noise stress, then fixed in

alcoholic Bouins fluid for 24 hours. Paraffin sections of 6 microns thickness were used. Dehydration of materials was carried out in an ascending series of ethyl alcohol, followed by clearing in terpineol for 2 days and then immersing quickly in 3 changes of benzol before embedding in molten wax. Paraffin sections were mounted on chemically clean glass slides without using any adhesive mixture and the standard procedure of routine histological staining using Haematoxylin (H) and Eosin (E) was used as described by **Humason (1979).**

3. Results

Changes in arterial blood pressure and heart rate after exposure to noise:

Animals subjected to chronic noise stress 6 hours daily for 30 days demonstrated a statistically significant increase ($P < 0.001$) in systolic (175 ± 4.97 mmHg), diastolic (130.5 ± 5.29 mmHg) and mean arterial blood pressure (145.497 ± 5.02 mmHg) when compared to the respective control values (systolic 123 ± 5.54 mmHg , diastolic 72.5 ± 3.18 mmHg and mean arterial blood pressure 89.3 ±3.95 mmHg) as shown in tables (1,2 & 3) and figs. (1,2 & 3) respectively .

Regarding the changes in the heart rate after chronic exposure to noise stress, it was found that, the mean value of heart rate was significantly increased in noise exposed group (351±11.00 beats/min, $P<0.001$) when compared to that of the control group (279±7.81 beats/min) as shown in table (4), figs. (4&5)

Changes in serum Mg^{+2} levels after exposure to noise:

Exposure of rats to chronic noise stress for 30 days resulted in a significant decrease ($P < 0.001$) in serum Mg^{2+} levels (0.871 ± 0.021 mM / L) when compared to the control group (0.988 ± 0.012 mM / L), as shown in table (5) and fig. (6). There was a significant strong negative correlation between reduction in serum Mg^{2+} and elevation of the arterial blood pressure (r= -0.921) as shown in table (6) and fig. (7).

Changes in serum ACTH and corticosterone levels after exposure to noise:

Exposure of rats to chronic noise stress for 30 days resulted in a significant increase ($P<0.001$) in serum ACTH and corticosterone levels (66.604±1.716 ng/ml; 57.186±2.1246 nmol/L respectively) compared to the respective control values (44.47±1.597 ng/ml; 33.325±1.2279 nmol/L respectively) as shown in tables (7&8) and figs. (8&9).

Changes in serum Leptin levels after exposure to noise:

Serum leptin concentrations were significantly ($P< 0.001$) higher in animals which were exposed to chronic noise stress for 30 days (8.52±0.3158 pg/ml) when compared to the control (6.05± 0.126 Pg/ml) (Table 9, Fig. 10).

Changes in serum lipid and lipoprotein levels after exposure to noise :

A. **Non exposure or control group :**

The mean serum TC level was (60.21±1.19 mg/dl) and the range was (51.00-64.00 mg/dl).

The mean serum TGs level was (53.21±1.088 mg/dl) and the range was (47.00-59.00 mg/dl) as shown in tables (10&11) and figs. (11&12).

The mean serum levels of lipoproteins VLDL, LDL-C and HDL-C were (10.642±0.217 mg/dl, 10.568±1.22 mg/dl and 40.00±1.29 mg/dl) respectively, as shown in tables (12,13&14) and figs. (13,14&15).

B. Noise exposure group :

The mean serum TC level was (70.61 ± 1.001 mg/dl) and the range was (63.5 – 74.2 mg/dl).

The mean serum TG_S level was 63.49 ± 0.98 mg / dl and the range was (58.2 – 68.00 mg/dl) as shown in tables (10&11) and figs. (11&12).

The mean serum levels of lipoproteins VLDL , LDL.C and HDL.C were (12.498 ± 0.237 mg/dl, 26.912 ± 1.28 mg/dl and 31.2 ± 0.986 mg/dl respectively), whereas their ranges were (11.2 – 13.6 mg/dl , 18.86 – 34.4 mg/dl and 26.00 – 36.00 mg/dl respectively), as shown in tables (12,13&14) and figs. (13,14&15).

It was found that, exposure of the animals to chronic noise stress resulted in a significant increase in serum TC, TG_S, VLDL and LDL.C levels ($P<0.001$) and a significant decrease in serum HDL.C levels ($P < 0.001$).

Histopathological changes in the heart and aorta after exposure to noise:

Comparing to the histological picture of **hearts** isolated from control rats (Fig. 16), the histopathological changes observed in **the hearts** isolated from rats exposed to chronic noise stress were the presence of: Areas of hemorrhage in between the cardiac myocytes (Fig. 17), homogenous pale pink areas of necrosis (Fig. 18), multiple areas of myocardial infarction (Fig. 19), multiple areas of hemorrhage inbetween cardiac myocytes (Figs. 20 & 21) and slitting of cardiac muscles (Fig. 22)

When comparing to the histological picture of the **aortae** isolated from control rats (Fig. 23), the histopathologhical changes observed in the **aort**e isolated from rats exposed to chronic noise stress were thickening or hypertrophy of elastic fibers in the media (Fig. 24), perivascular infiltration by nonspecific

inflammatory cells (Fig. 25) and acute inflammatory cells mainly neutriphils and eosinophils (Fig. 26).

Table (1): Changes in systolic blood pressure (mmHg) of studied groups

	Control group	Noise-exposed group
1	120	175
2	120	170
3	100	160
4	100	150
5	150	200
6	140	190
7	105	160
8	140	190
9	130	180
10	125	180
$\overline{X}$	123	175.5
SD	17.5	15.7
SE	5.54	4.97
t	7.056	
p	< 0.001	

Table (2): Changes in diastolic blood pressure (mmHg) of studied groups

	Control group	Noise-exposed group
1	70	130
2	70	110
3	60	120
4	60	110
5	90	150
6	80	140
7	65	120
8	85	140
9	75	150
10	70	125
$\overline{X}$	72.5	130.5
SD	10.069	16.74
SE	3.18	5.29
t	9.4	
p	< 0.001	

Table (3): Changes in mean arterial pressure (MAP, mmHg) of studied groups

	Control group	Noise-exposed group
1	86.66	145.00
2	86.66	130.00
3	73.33	133.33
4	73.33	123.33
5	110.00	173.33
6	100.00	156.66
7	78.33	133.33
8	103.33	156.66
9	93.33	160.00
10	88.33	143.33
$\overline{X}$	89.33	145.497
SD	12.478	15.87
SE	3.95	5.02
t	8.7939	
p	< 0.001	

Table (4): Heart rate (beats/min) changes in studied groups

	Control group	Noise-exposed group
1	270	360
2	270	390
3	240	360
4	2408	390
5	300	300
6	300	330
7	270	390
8	300	330
9	300	300
10	300	360
$\overline{X}$	279	351
SD	24.698	34.785
SE	7.81	11.00
t	5.337	
p	< 0.001	

Table (5) : Serum levels of Mg^{2+} (mM/l) in studied groups

	Control group	Noise- Exposed group
1	1.01	0.86
2	1.03	0.88
3	0.99	0.93
4	0.92	0.98
5	0.98	0.78
6	0.95	0.79
7	0.02	0.94
8	0.96	0.83
9	1.04	0.82
10	0.98	0.90
X-	0.988	0.871
SD	0.0379	0.066
SE	0.012	0.021
t	4.875	
p	< 0.001	

Table (6): Correlation coefficient between mean arterial blood pressure (mmHg) and Mg^{2+} serum levels (mM/l) in chronic noise stress exposed group

	MAP	Mg
1	145.00	0.86
2	130.00	0.88
3	133.33	0.93
4	123.33	0.98
5	173.33	0.78
6	156.66	0.79
7	133.33	0.94
8	156.66	0.83
9	160.00	0.82
10	143.33	0.90
r	-0.921^{**}	
P	P < 0.001	

Table (7): Serum ACTH (ng/ml) levels of studied groups

	Control group	Noise-exposed group
1	45.50	68.50
2	42.02	57.80
3	39.00	65.20
4	35.90	59.06
5	51.21	72.00
6	45.07	70.08
7	40.60	62.40
8	50.80	70.00
9	46.20	74.02
10	48.40	67.00
$\overline{X}$	44.47	66.604
SD	5.05	5.428
SE	1.597	1.716
t	9.4508	
p	<0.001	

Table (8): Serum corticosterone (nmol/l) levels of studied groups

	Control group	Noise-exposed group
1	34.20	58.20
2	33.50	56.50
3	29.00	50.30
4	25.80	44.06
5	38.00	65.60
6	35.60	61.10
7	30.05	52.05
8	36.02	62.22
9	34.00	57.80
10	37.08	64.03
$\overline{X}$	33.325	57.186
SD	3.88	6.7186
SE	1.2279	2.1246
t	9.73918	
p	< 0.001	

Table (9) : Serum levels of leptin (Pg/ml) in studied groups.

	Control group	Noise- Exposed group
1	5.7	7.1
2	5.9	7.2
3	6.1	7.4
4	6.0	8.2
5	6.1	9.4
6	6.3	9.1
7	5.6	9.5
8	5.5	9.3
9	6.6	8.4
10	6.7	9.6
X-	6.05	8.52
SD	0.4	0.998
SE	0.126	0.3158
t	7.1594	
p	< 0.001	

Table (10): Serum level of cholesterol (mg/dl) in studied groups

	Control group	Noise-exposed group
1	59.00	69.00
2	63.00	73.5
3	58.00	68.8
4	64.00	74.2
5	60.00	70.5
6	62.00	72.4
7	59.9	69.2
8	62.2	72.8
9	51.00	63.5
10	63.00	72.2
$\overline{X}$	60.21	70.61
SD	3.77	3.165
SE	1.19	1.001
t	6.688	
p	< 0.001	

Table (11): Serum level of triglycerides (mg/dl) in studied groups

	Control group	Noise-exposed group
1	51.00	62.2
2	55.00	66.00
3	49.80	59.6
4	56.30	67.00
5	59.00	68.00
6	55.00	64.00
7	53.00	63.40
8	52.00	62.00
9	47.00	58.20
10	54.00	64.50
$\overline{X}$	53.21	63.49
SD	3.44	3.11
SE	1.088	0.98
t	7.017	
p	< 0.001	

Table (12): Serum level of VLDL (mg/dl) in studied groups ($\frac{TG}{5}$) (**Friedewald *et al.*, 1972**)

	Control group	Noise-exposed group
1	10.2	12.44
2	11.00	11.2
3	9.96	11.92
4	11.26	13.4
5	11.8	13.6
6	11.00	12.8
7	10.6	12.68
8	10.4	12.4
9	9.4	11.64
10	10.8	12.9
$\overline{X}$	10.642	12.498
SD	0.688	0.75
SE	0.217	0.237
t	5.8	
p	< 0.001	

Table (13): Serum level of LDL (mg/dl) in studied groups [Tc-(HDL + $\frac{TG}{5}$)] (**Friedewald *et al.*, 1972**)

	Control group	Noise-exposed group
1	9.8	25.56
2	11.00	29.3
3	11.04	27.88
4	7.74	24.8
5	8.2	25.9
6	4.00	24.6
7	13.3	28.52
8	17.8	34.4
9	8.6	18.86
10	14.2	29.3
$\overline{X}$	10.568	26.912
SD	3.866	4.06
SE	1.22	1.28
t	9.244	
p	< 0.001	

Table (14): Serum level of HDL (mg/dl) in studied groups

	Control group	Noise-exposed group
1	39.00	31.00
2	41.00	33.00
3	37.00	29.00
4	45.00	36.00
5	40.00	31.00
6	47.00	35.00
7	36.00	28.00
8	34.00	26.00
9	43.00	33.00
10	38.00	30.00
$\overline{X}$	40.00	31.2
SD	4.08	3.119
SE	1.29	0.986
t	5.432	
p	< 0.001	

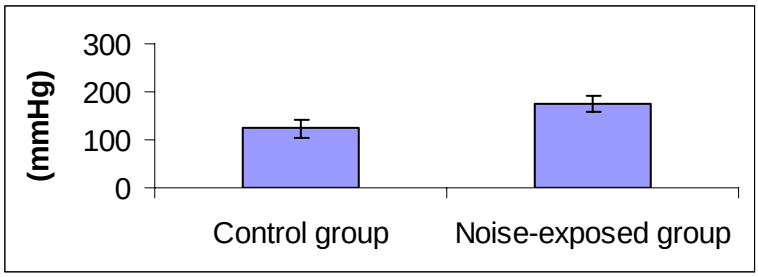

Fig. (1): The mean value ±SE of systolic blood pressure (mmHg) in chronic noise stress exposed group compared to the control group.

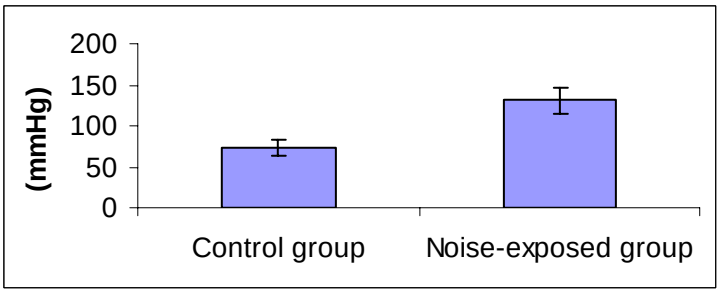

Fig. (2): The mean value ±SE of diastolic blood pressure (mmHg) in chronic noise stress exposed group compared to the control group.

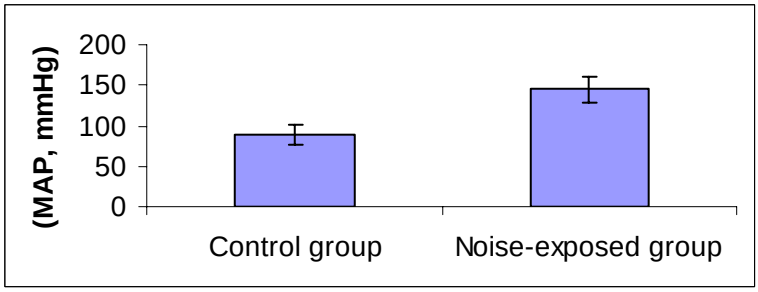

Fig. (3): The mean value ±SE of mean arterial pressure (MAP, mmHg) in chronic noise stress exposed group compared to the control group.

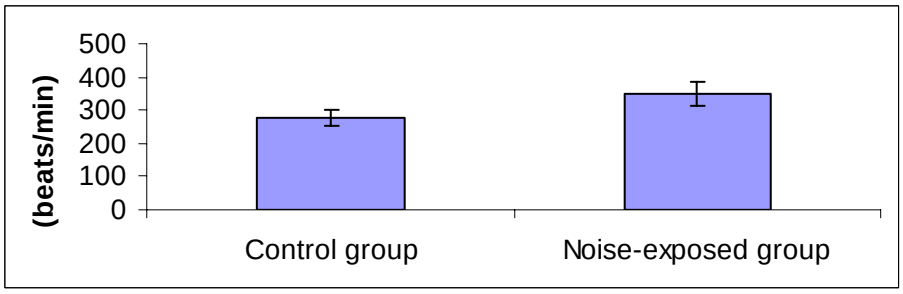

Fig. (4): The mean value ±SE of heart rate (beats/min) in chronic noise stress exposed group compared to the control group.

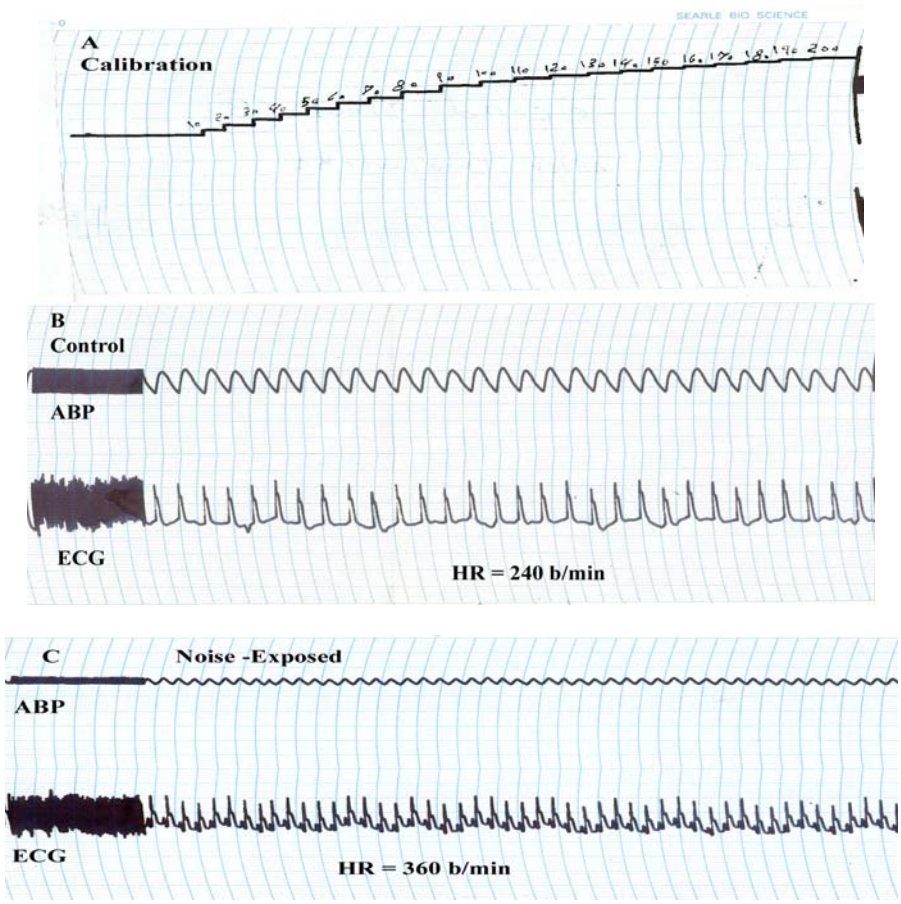

Fig. (5): Tracings illustrating the calibration used to measure the arterial blood pressure (A), a record of the arterial blood pressure and ECG in control group (B) and chronic noise stress-exposed group (C)

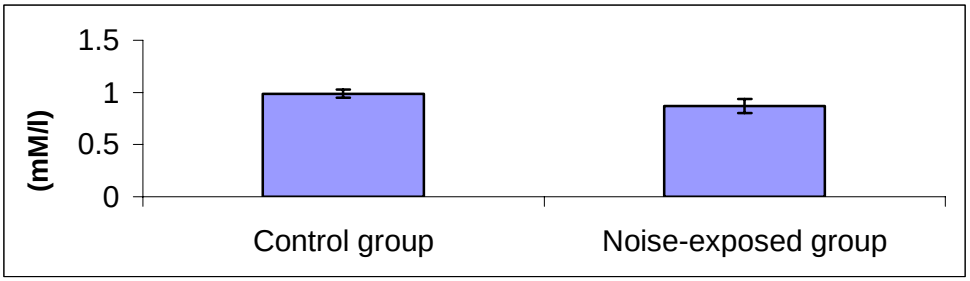

Fig. (6): The mean value ±SE of Serum Mg^{2+} (mM/l) levels in chronic noise stress exposed group compared to the control group.

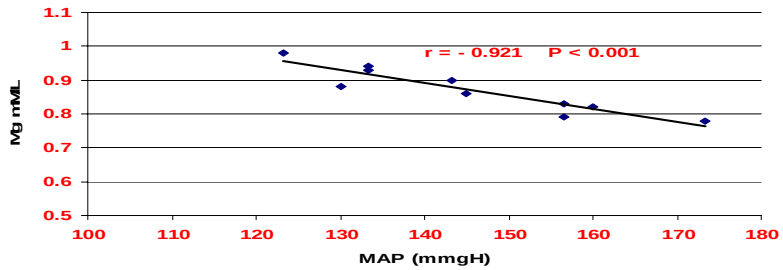

Fig. (7): Correlation coefficient between mean arterial blood pressure (mmHg) and Mg2+ serum levels (mM/l) in chronic noise stress exposed group.

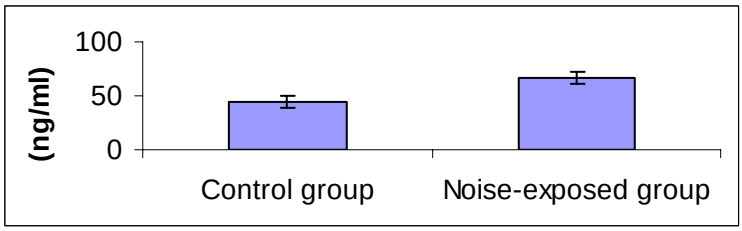

Fig. (8) The mean value ±SE of Serum ACTH (ng/ml) levels in chronic noise stress exposed group compared to the control group.

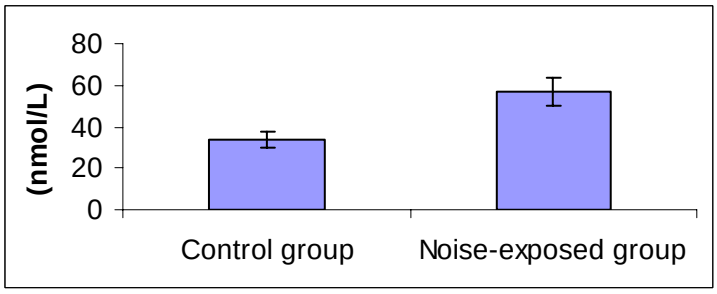

Fig. (9): The mean value ±SE of Serum corticosterone (nmol/l) levels in chronic noise stress exposed group compared to the control group.

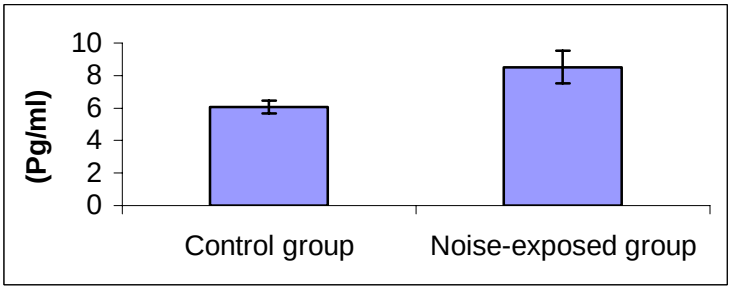

Fig. (10): The mean value ±SE of Serum levels of leptin (Pg/ml) levels in chronic noise stress exposed group compared to the control group.

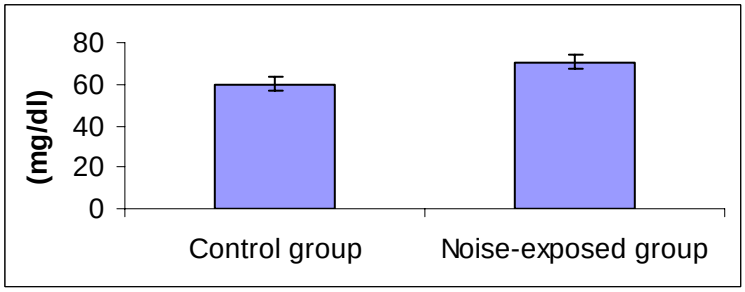

Fig. (11): The mean value ±SE of Serum level of cholesterol (mg/dl) in chronic noise stress exposed group compared to the control group.

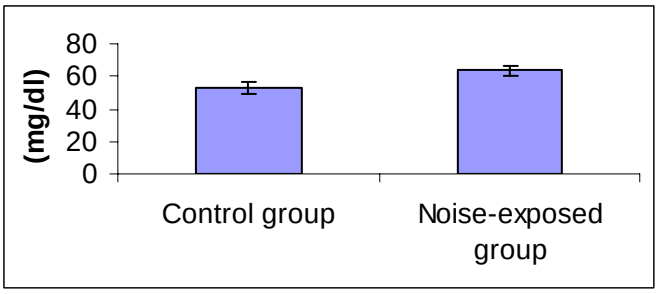

Fig. (12): The mean value ±SE of Serum level of triglycerides (mg/dl) in chronic noise stress exposed group compared to the control group.

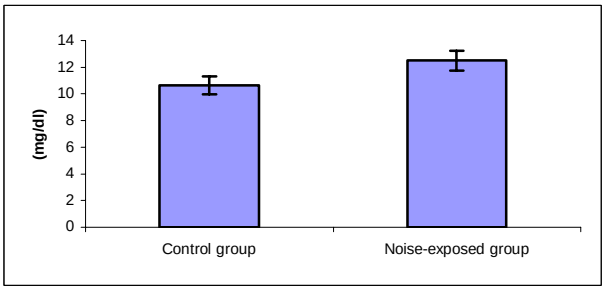

Fig. (13): The mean value ±SE of Serum level of VLDL (mg/dl) in chronic noise stress exposed group compared to the control group.

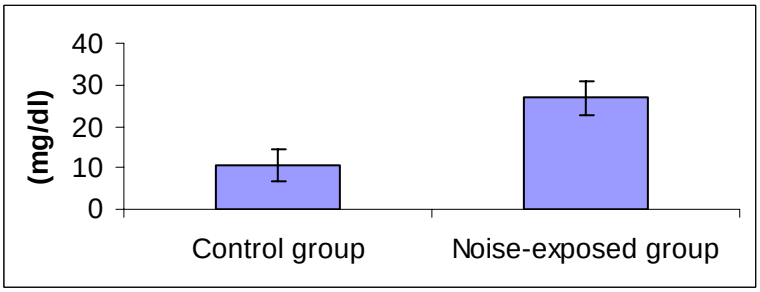

Fig. (14): The mean value ±SE of Serum level of LDL (mg/dl) in chronic noise stress exposed group compared to the control group.

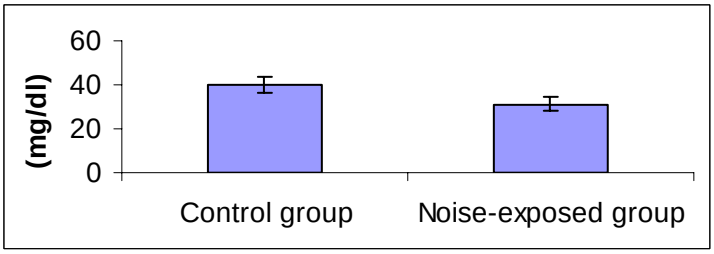

Fig. (15): The mean value ±SE of Serum level of HDL (mg/dl) in chronic noise stress exposed group compared to the control group.

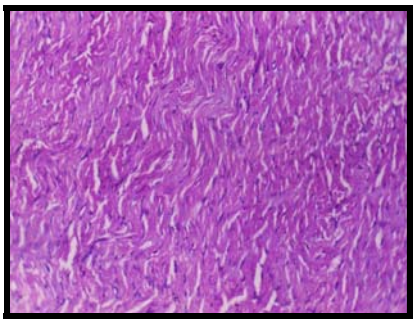

Fig. (16): A section in the heart taken from a control male albino rat showing normal arrangement and cross striation of myocardial cells; H&E X 100.

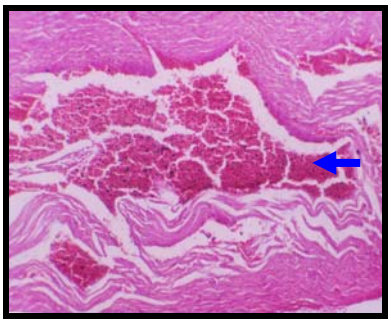

Fig. (17):A section in the heart taken from a male albino rat exposed to chronic noise stress showing areas of haemorrhage in between cardiac myocytes; H&E X 100

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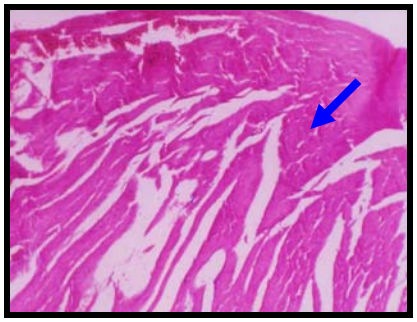

Fig. (18): A section in the heart taken from a male albino rat exposed to chronic noise stress showing homogenous pink areas of nucleated necrotic cardiac myocytes; H&E X 100.

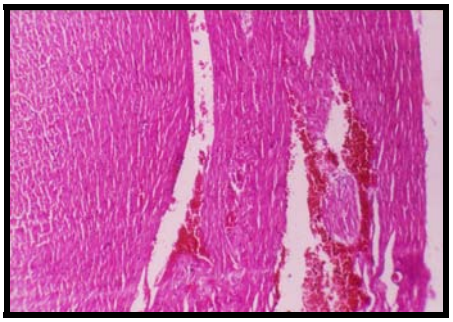

Fig. (19):A section in heart taken from a male albino rat exposed to chronic noise stress showing myocardial infarction; H& E X 100.

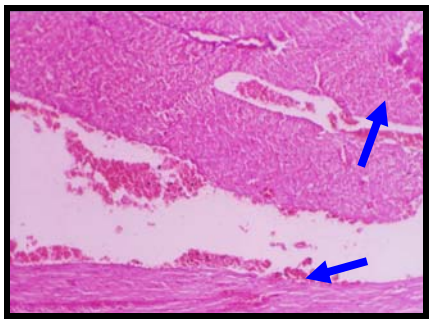

Fig. (20): A section in heart taken from a male albino rat exposed to chronic noise stress showing multiple areas of haemorrhage in between cardiac myocytes and multiple areas of myocardial infarction ; H & E X 100.

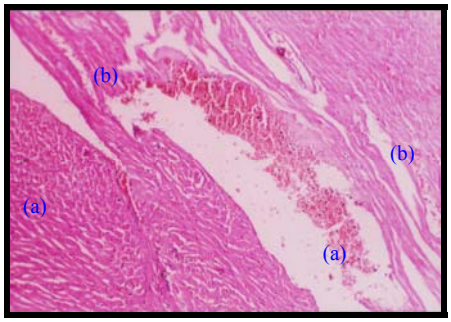

Fig. (21): A section in heart taken from a male albino rat exposed to chronic noise stress showing multiple areas of haemorrhage in between cardiac myocytes (a) and multiple areas of myocardial infarction (b);H & E X 100.

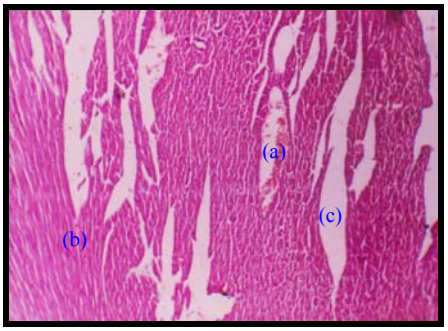

Fig. (22):A section in heart taken from a male albino rat exposed to chronic noise stress showing small areas of haemorrhage in between cardiac myocytes (a), small areas for myocardial infarction(b) and splitting of cardiac muscle(c); H&E X 100.

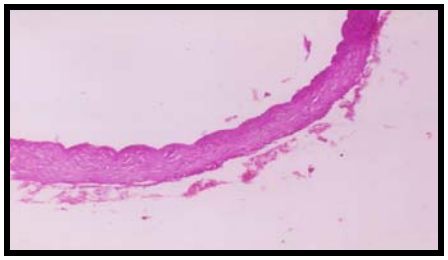

Fig. (23): A section in aorta taken from a control male albino rat showing normal wall thickness with normal intima, media and adventitia; H&E X 40.

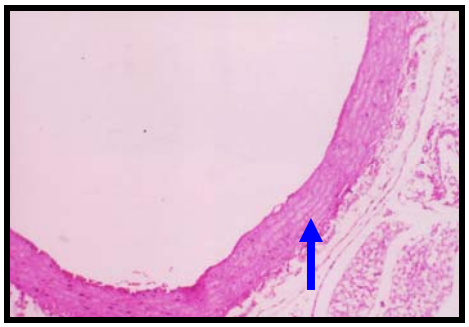

Fig. (24): A section in aorta taken from a male albino rat exposed to chronic noise stress showing thickening of elastic fibres in the media; H & E X 100.

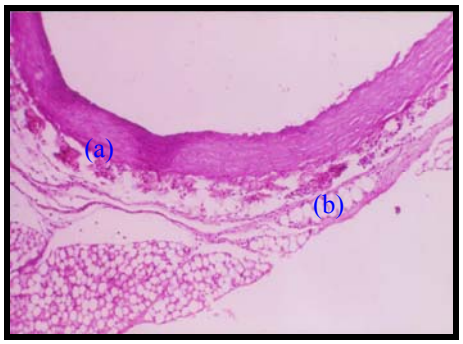

Fig. (25): A section in aorta taken from a male albino rat exposed to chronic noise stress showing thickening of elastic fibres in the media (a) with perivascular infiltration by non-specific inflammatory cells (b); H&E X 100.

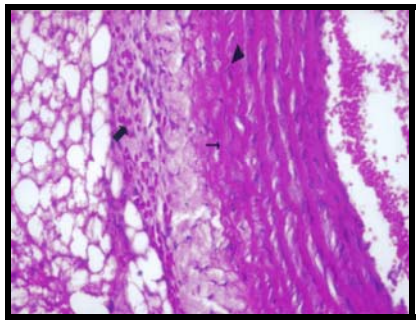

Fig. (26):A section in aorta taken from a male albino rat exposed to chronic noise stress showing hypertrophied eleastic fibres as well as perivascular infiltration by acute inflammatory cells mainly neutrophils and esinophils; H&E X400.

4. Discussion

Noise is considered a kind of stress, which produces significant physiological and biochemical changes in animals as well as in humans **(Borg, 1981).** The damaging effect of noise on hearing has been extensively studied **(Ogale, 1999).** However, very little information are available regarding the effect of noise on other body functions. The present study revealed that, exposure of adult male albino rats to chronic noise stress has resulted in a significant increase in systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and heart rate which were recorded immediately at the end of the last exposure. These changes were accompanied with a significant increase in blood levels of ACTH, corticosterone, and leptin together with a significant decrease in serum levels of magnesium. These results are in accordance with those of many other investigators **(Archana and Namasivayam, 2000 and Chandralekha *et al*., 2005),** but at variance with those of others **(Fernandez *et al* .,2010)**

Research on the effect of noise exposure has focused not only on behavioral disturbances and mental diseases but also on chemical and physiological modifications of endocrine, cardiovascular, and nervous systems **(Alario *et al*., 1987).** In particular, noise has been recognized as one of the risk factors for cardiovascular diseases because it increases heart rate **(Linden *et al*., 1985)**, peripheral vascular resistances **(Bach *et al*., 1991)**, arterial blood pressure **(Altura *et al*., 1992 and Sawada, 1993)** and causes electrocardiogram disorders **(Tomei *et al*., 1992)**. In this respect, there is evidence for an enhanced activation of the sympathetic nervous system, as assessed by increased levels of circulating catecholamines **(Lagercrantz *et al*., 1990 and Goyal *et al* .,2010)**. Animal experiments and hormone plasma assays in humans have demonstrated that noise stimulus can increase catecholamine secretion **(Vogel and Jensh, 1988).** A previous study **(Breschi *et al*., 1994)** has shown that, a more prolonged exposure time induces a parallel enhancement of the sympathetic network.

Evidence is accumulating to suggest that, prolonged exposure to noise may induce long-term and permanent changes in cardiovascular function in animals and human subjects **(Babisch, 1998).** It was reported that, noise – induced hearing loss in animals and human subjects is associated with alterations in serum and perilymph magnesium (Mg) **(Joachims *et al*., 1987).** Some of these experiments indicated that, noise-induced hearing loss was associated with elevation of myocardial calcium content **(Ising *et al*., 1999),** vasoconstriction of the arterioles in the cochlea and the organ of corti (**Nakai and Matsutani, 1988)** as well as energy deficit of the cochlea hair cells **(Gunther *et al*., 1989).**

Several recent studies point to a causal relationship between decreased (Mg^{2+}) in blood or tissues and hypertension **(Gunther *et al*., 1989 and Altura and Altura, 1990)**. In the present study, we observed that, elevation of the arterial blood pressure was associated with a significant decrease in serum levels of Mg^{++} in animals exposed to chronic noise stress. Further more, a strong significant negative correlation was found between the reduction in serum Mg^{++} level and the elevation in mean arterial blood pressure (MAP). The incidence of hypertension is

often high in geographic areas with soft drinking water or Mg-poor soil **(Altura and Altura; 1990;).** Hypomagnesemia has been reported in a number of hypertensive patients **(Altura and Altura, 1990).** Considerable evidence indicates that, oral and parenteral administration of Mg^{+2} can lower blood pressure in hypertensive patients and animals **(Altura and Altura, 1990)** and can decrease blood pressure induced by stress **(Ising *et al.*, 1999)**. It has been demonstrated that, low dietary intake of Mg can result in hypertension in rats **(Altura *et al.*,1992)** and can aggravate hypertension in both spontaneously and deoxycorticosterone acetate-salt hypertensive rats **(Chrysant *et al.*, 1988).** A microcirculatory basis for these Mg-linked alterations has been suggested. **(Altura and Altura, 1990).**

It has been also suggested that environmental and/or occupational noise stress may be an important environmental factor in the etiology of hypertension **(Andren *et al.*, 1983).** A high positive correlation has been found between exposure of individuals to noise and high blood pressure in a number of retrospective epidemiological studies **(Cohen *et al.*, 1981).** According to **Eggertsem *et al.* (1987),** noise-induced elevation of arterial blood pressure in rats and human subjects has been associated with increased peripheral vascular resistance and cardiac hypertrophy**.** This peripheral vasoconstriction takes place in all types of microvessels, i.e., arterioles, venules and precapillary sphincters **(Alutra *et al.*, 1992).** There is evidence of increased activation of the sympathetic nervous system during noise stimulation **(Andren *et al.*, 1983*).*** Some investigators reported that the elevation of the blood pressure during noise exposure is independent of elevated levels of catecholamines, cortisol and prolactin or growth hormone **(Andren *et al.*, 1983).** In addition, central $\alpha 2$ – adrenoceptors are not involved **(Eggertsen *et al.*, 1987).**

Altura *et al.* (1992) demonstrated that, dietary deficiency of Mg can aggravate hypertension caused by noise-induced stress and that this relationship is associated with 1) intense vasoconstriction of terminal arterioles, precapillary sphincters, and venules in the microcirculation; 2) reduced capillary blood flow; 3) rarefaction of capillaries; 4) increased reactivity of intact muscular microvessels to neurohumoral agonists and 5) decreased responsiveness to the vasodilator histamine.

Several experimental and clinical studies have reported that, disturbances of the metabolism of Mg^{+2} may have profound effects on the contractile state of vascular smooth muscle, peripheral blood flow, and thus arterial blood pressure **(Altura and Altrua, 1990).** A number of recent studies in humans and experimental animals suggest that, Mg^{2+} may exert beneficial therapeutic actions via their circulatory actions **(Altura and Altrua, 1990). Peterson *et al.* (1977)** found an inverse correlation between serum (Mg^{+2}) and blood pressure. **Resnick *et al.* (1984)** noted an inverse relationship between diastolic blood pressure and intracellular free Mg^{2+} in erthrocytes. Elevation of extracellular Mg^{2+} has been demonstrated to produce vasodilation of arterioles, precapillary sphincters, and venules in the intact microcirculation of mesentery, skeletal muscle, and brain in a dose dependent manner **(Nishio *et al.*, 1989).** In addition, elevation of Mg^{2+} has been shown to attenuate, in a dose-dependent manner, constriction of these muscular, microvessels induced by a variety of neurohumoral agents **(Nakai and Matsutani, 1988).** According to **Altura *et al.* (1992),** the effects of ionized Mg^{2+} on vascular tone are reflections of this metal's influence on membrane permeability to Ca^{2+} as well as on binding, translocation, intracellular release, and on membrane stability**.** Studies have shown that Mg^{2+} sites in the blood vessels membrane act physiologically to regulate entery and exit of Ca^{2+} **(Altura and Altrua, 1990).** Lowering Mg^{2+} increases total exchangeable and intracellular Ca^{2+} fractions in blood vessels **(Altura *et al.*, 1987).** Mg^{2+} has been demonstrated to be a week Ca^{2+} channel antagonist **(Altura *et al.*, 1992),** which can act on voltage, receptor, and leak-operated membrane channels in vascular smooth muscules **(Altura *et al.*, 1992).**

In vitro and in vivo experiments clearly indicate that, when Mg^{2+} inlowered, Ca^{2+} influx and intracellular release are enhanced, causing contraction and an increase in basal tone **(Altura *et al.*, 1992).** It has also been shown that, reduction in serum Mg^{2+} attenuate endothelium-derived relaxant factors **(Altura *et al.*, 1987).** Several reports in experimental animals and in humans indicate that, noise –induced stress results in the release into blood stream of various stress hormones, i.e., catecholamines, prolactin, cortisol, growth hormone, and oxytocin. Most of these changes are, however, transient and do not seem to be associated with the Noise-induced sustained elevation of arterial blood pressure **(Eggertsen *et al.*, 1987).** It is distinctly possible that, alteration of the Mg^{2+} to Ca^{2+} ration induced by the noise stress in endocrine end organs is responsible for the transient release of the various hormonal secretions. The Mg^{2+} to Ca^{2+} ratio in such end organs and nerves is well known to excitation-secretion coupling mechanisms **(Mordes and Wacker, 1978).**

It was speculated that, Noise-induced stress releases cellular Mg^{2+} via intense vibrations bombarding various bodily tissues resulting in microtrauma to internal cellular and surface celleular membranes, may be similar to what has been noted in

patients and animals subjected to circulatory shock and body trauma **(Chaudry *et al.*, 1988).** An alternative possibility may be that Noise-induced stress releases catecholamines and adenosine $3^{/},5^{/}$ cyclic monophosphate, which may increase membrane permeability and thus allow Mg^{2+} to leak out of cells **(Altura *et al.*, 1992).**

The present study demonstrated that, exposure to chronic noise stress resulted in histopathological changes in the heart and aorta. The heart showed areas of hemorrhage inbetween cardiac myocytes, homogenous pale pink areas of necrosis and myocardial infarction. The aorta showed thickening of elastic fibers in the media with perivascular infiltration by non-specific inflammatory and acute inflammatory cells mainly neutrophils and eosinophils. These results are in agreement with those of **Kempen (2011)** and **Bluhm and Eriksson (2011).** Furthermore, our results are supported by the findings of **Soldani *et al.* (1997)** who examined the ultrastructure of the heart of albino rat by transmission and scanning electron microscopy after exposure to white noise (100 dBA) and found mitochondrial alterations, areas of enlargement in intercalated disc membranes and decreased density of sarcoplasm. In addition, **Paparelli *et al.* (1995)** showed structural modifications of rat myocardium after acute noise stress.

Our observations are also consistent with those caused by other stressors **(Lopes *et al.* 1992)** or with those observed in certain pathological conditions **(Ghadially, 1988). Ferrans and Roberts *(1972)*** described similar focal lesions following exogenous catecholamine administration. In a previous research **(Paparelli *et al.*, 1995),** it was pointed out that, noise exposure provokes a modification in the sympathetic innervation pattern depending on the increase in catecholamine synthesis. Catecholamines are released under various conditions, from alarm reactions to acute stress **(Selye, 1979),** and their action primarily concerns the cardiovascular system because they cause a rise in blood pressure and can cause a significant ischemic alteration **(Yamamura and Aoshima, 1980).** In humans exposed to short-term noise stress, the ischemic damage does not seem to be caused by direct coronary vasoconstriction but rather indirectly as a result of peripheral circulatory alterations such as arterial hypertension**.** Cardiac ischemia causes subcellular changes including mitochondrial alterations and an increase in the space at the level of the intercalated disc **(Ashraf and Halverson, 1978).**

Jennings *et al.* (1969) recorded a correlation between structural abnormalities of isolated mitochondria from the ischemic dog myocardium and a deficient Krebs citric acid cycle. Both oxidative phosphorylation and anerobic glycolysis contribute to the formation of ATP in the presence of low concentrations of oxygen. Hypoxia enhances glycolytic flux in myocardial tissue **(Burlington *et al.*, 1970),** and the ability to maintain cardiac performance during hypoxia has been related to this increased glycolysis**.** Therefore, ischemia seems to alter the cardiac fiber metabolism by increasing oxygen consumption or impairing its utilization. Thus, our structural observations may be related to a certain degree to hypoxia at the mitochondrial level, which induces loss of membrane stabilization with a consequent failure of the enzymatic pattern and a mild local deficiency of ATP that affects the Na^{+}-Ca^{+2} exchanger. Moreover, the alterations of mitochondria and sarcoplasmic reticulum, involved in maintaining a low concentration of Ca^{+2} in the cytoplasm close to the intercalated discs **(Forbes and Sperelakis, 1985),** could be resposible for structural changes observed in the junctions. Under stress conditions, some labile intracellular organelles such as mitochondria bear an intense biochemical activity **(Tomanek and Banister, 1972)** that can subsequently predispose to morphological changes. According to **Ising *et al.* (1999)**, chronic Noise-induced stress accelerates the ageing of the myocardium and thus increase the risk of myocardial infarction. The involved pathomechanisms included : **1)** Increased circulating levels of stress hormones such as catecholamines, cortisol, corticosterone, growth hormone, and prolactin which are associated with peripheral vasoconstriction, coronary spasm, increased peripheral resistance, hypertension and ischaemic heart disease**).**

In the present study, we found a significant increase in the circulating levels of ACTH, corticosterone and leptin in chronic stress-exposed group compared to the control group. These results are in agreement with those of other investigators **(Chandralekha *et al.*, 2005).**

Raised serum corticosterone levels following noise stress in rats have been reported before **(Archana and Namasivayam, 2000)**. In addition, elevation of glucocorticoid levels following many types of stressors is also well known. The precise mechanism for this remains unclear, but it may be related to altered activity of the hypothalamic-pituitary-adrenal axis secondary to noise stress and may involve alterations in the secretion of corticotropin releasing hormone (CRH), ACTH and proopiomelanocortin (POMC) gene expression. The increase in glucocorticoid secretion during stress appears to be important for the appropriate defense mechanism to be put into place.

In the present investigation, significantly higher levels of corticosterone were evident in rats exposed

to chronic noise stress for 30 days indicating poor or absent adaptation of the rats to noise stress. This is in contrast to what has been observed before by others investigators where a somewhat decreased corticosterone response to noise was observed on chronically stressed rats **(Archana and Namasivayam 2000).**

Several reports indicated that, glucocorticoids are capable of stimulating the synthesis and secretion of adipocyte-derived leptin **(Slieker *et al.*, 1996),** which regulates food intake and energy expenditure. According to **Slieker *et al.* (1996)**, leptin secretion is under the influence of hormonal and neural control**.**

The results of the present study indicated a significant elevation in leptin levels after chronic exposure to noise stress. **Heiman *et al.* (1997),** in earlier study examined the influence of exogenous administration of leptin on plasma corticosterone and ACTH in animals subjected to restrainst stress. They reported that, leptin was able to inhibit the release of corticotropin releasing hormone (CRH) from the hypothalamus in vitro and also blunted the plasma ACTH and corticosterone elevation due to restraint stress. They also speculated the possibility for reduction of leptin level during acute and chronic stress and thus facilitating the responsiveness of hypothalamic-pituitary-adrenal axis. However, they failed to demonstrate any reduction in leptin levels in their study on restraint stress and thus the speculation remains unsubstantiated. In fact, the data indicated an elevation of serum leptin levels after restraint stress though the levels were not statistically significant. In another study chronic subcutaneous leptin infusions have been shown to diminish responsiveness of the hypothalamo-pituitary adrenal axis in female Rhesus monkeys **(Wilson *et al.*, 2005).** Therefore it seems that, there is a significant interplay between leptin and the hypothalamo-pituitary adrenal axis.

The results of the present study in rats subjected to chronic noise stress clearly indicated simultaneous elevation of corticosterone and leptin levels. It appears that, the inhibitory effect of leptin on corticosterone secretion was somewhat absent during noise stress in this study. The reason for the variation between our observation and those mentioned in other studies is unclear but may be due to species variation or the different nature of stress. Nevertheless, our study suggests that, one arm of the hypothalamic-pituitary-adrenal axis appears disabled during noise stress, which permits for increase corticosterone secretion during stress.

Hence, continuous exposure to noise stress may have adverse effects on some of the vital physiological functions. **(Saha *et al.*, 1996)** in which the alterations in the levels of these two hormones (corticostrone & leptin) may play a significant contributory role, these two hormones have wide ranging effects on metabolism, growth and reproduction **(Chehab, 2000 and Goumenou *et al.*, 2003).**

Altura *et al.* (1992) recorded Ca^{2+}/Mg^{2+} shifts in the vascular walls of chronically noise-stressed rats**.** Besides an increased vasoconstriction under the action of noradrenaline. This effect was confirmed in humans by measuring the increase of the total peripheral resistance (TPR) during infusion of noradrenaline. The noradrenaline induced TPR increase was reduced by Mg –injections **(Ising *et al.*, 1992).** Further analysis of the experimental results led to an interaction model between chronic stress and intracellular electrolyte shifts **(Ising *et al.*, 1992).** Chronic stress caused a loss of extracellular and intracellular Mg^{2+} and an increase of intracellular Ca^{+2} **(Gunther *et al.*, 1978).** A decrease of Mg^{2+} was correlated to an increased physiological noise sensitivity **(Ising *et al.*, 1992).**

Ising *et al.* (1999), found a positive feedback mechanism between stress-caused by noise and/or other stressors and intracellular Ca^{2+}/Mg^{2+} shifts which may increase the cardiovascular risk. Since chronic noise stress significantly increased the ratio of Ca^{2+}/Mg^{2+} and the collagen content of the interstitial space of myocardium i.e. significant increase of cardiac fibrosis [which can be interpreted as accelerated aging **(Hermann *et al.*, 1994)** and increased Ca^{2+}/Mg^{2+}ratios were found in the myocardium of ischemic heart disease deaths. **Ising *et al.* (1999)** concluded that, chronic noise stress also accelerates the aging of the heart in humans. It was observed that, infarction size and complications during two weeks after the myocardial infarction depend upon the increase of circulating levels of catecholamines and the associated decrease in serum levels of Mg^{2+} **(Jeremias *et al.*, 1996).**

Another explanation for the histopathological changes of the cardiovascular system encountered in the present study may be the changes in mitochondrial ATP and free radicals. **Ceremuzynski *et al.*, (1991)** studied the injury of pigs' myocardium after 24h of immobilization stress. Electromicroscopic examination revealed microtraumate of the myocardium. Among other biochemical alterations they observed decrease of mitochondrial ATP and increased generation of free radicals which may be components of the stress-induced myocardial injury. In earlier experiments, infusions of adrenaline into healthy dogs resulted in marked decrease in myocardial ATP**.** Catecholamines i.e. adrenaline and noradrenaline stimulate the activity of c-AMP. Furthermore, catecholamines increased via c-AMP and thromboxane A2 the influx of Ca^{2+} into the smooth muscle cells thus increasing

the risk of a coronary artery spasm. **(Ceremuzynski *et al.*, 1991).**

Reactive oxygen species (ROS), also known as free oxygen radicals, are normal by products of cellular aerobic metabolism. These unstable molecules can impair cellular lipids, proteins and nucleic acids in DNA if the balance of corresponding antioxidants is disrupted **(Van Campen *et al.*, 2002).** Oxidative stress is a state where significant imbalance between oxidants and antioxidants occurs that leads to damage, dysfunction or cellular death **(El-Sayed and Gorbunov, 2003; Mercan, 2004).** Under normal conditions, sufficient concentrations of endogenous antioxidants as well as redundant protective systems exist to protect from environmental oxidant attacks. However, repeated exposure to environmental oxidants such as air pollution, smoking, disease states or blast overpressure (blast) exposure, can result in accelerated rate of antioxidant depletion tipping the balance from sufficiency to deficiency producing oxidative stress **(El-Sayed and Gorbunove , 2003).**

Manikandan *et al.* (2005) reported that, acute as well as long term exposure to noise can produce excessive free radicals (Reactive oxygen species) such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) and causes disorders involving extra-auditory organs such as nervous, endocrine, and cardiovascular system (CVS)**.** Oxygen free radicals can attack protein, nucleic acids and lipid membranes thereby disrupting normal cellular functions and integrity **(Endo *et al.*, 2005 and Manikandan and Devi, 2005).** According to **Scarfiotti *et al.* (1997),** nervous system is relatively more susceptible to free radical damage**. Ravindran *et al.* (2005)** reported that, neurotransmitters in discrete brain regions were found to be increased during noise stress even after 15 days of exposure**.** In addition, to generating free radicals species, it also leads to increase in radical induced lipid peroxidation end products such as malondialdehyde which is an indicator of lipid peroxidation **(Derekoy *et al.*, 2001). Demirel *et al.* (2009)** investigated the effect of exposure to chronic noise stress (20 days/ 4 hours, 100 dB-A)on oxidative stress parameters in rats. They observed an elevation in malondialdheyde, an indicator of lipid peroxidation as well as nitric oxide (NO) level and glutathione peroxidase (GSH-Px) activity by noise exposure. They suggested the presence of oxidative stress which may lead to various degrees of damages in the cells, mainly via lipid peroxidation pathways, leading to coronary heart disease, hypertension, increased mortality risk, serious psychological effects, headache, anxiety and nausea. **(Abbate *et al.*, 2005 and Lenzi *et al.*, 2003)** in addition to hearing loss, sleep disturbance, impairement of performance, impairement of cognition , increased error in working and reference memory and higher incidence of cancer **(Jarup *et al.*, 2005 and Manikandan *et al.*, 2006).**

As regards the changes in serum levels of total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) in adult male albino rats exposed to chronic noise stress, the present study showed a significant increase in serum levels of TC, TG, LDL and VLDL while there was a significant decrease in serum levels of HDL. These findings are supported by the work of **Mahmoud *et al.* (2008)** who found that, textile factory workers exposed to high ambient noise level generated by big machines used in the factory for more than 6 hours daily at a strength of 90 deci-Bel (db) without using ear protectors (i.e. chronic and high noise exposure levels), showed a significant increase in the level of fasting serum TC, a non significant increase in the levels of fasting serum TGS, VLDL and LDL and significant decrease in the level of fasting serum HDL.

The noxious effects of sound stress have been the subject of numerous investigations. **Zhasminova *et al.* (1991)** studied serum lipids in workers of a mining enterprise who were affected by unfavorable occupational noise and found that, the miners have greater mean levels of triglycerides and potentially atherogenic lipoprotein cholesterol. The effect of stress caused by aircraft noise was studied on 14 female and 11 male volunteers, who were of age ranging from 21-42 years and of mean age of 25 years by **Marth *et al.* (1988)** and they found an increase in the serum levels of ACTH, TC and free fatty acids. **Maschke and Hecht (2000) and Gehlot *et al.* (2002)** reported in their studies a significant increase in the levels of serum TC, TGs and lipoprotein profile in workers exposed to high noise levels. **Tappila *et al.* (2001)** conducted a study on 406 paper mill workers exposed to noise levels of 91-94 dB, 124 forest workers exposed to noise levels of 96-99 dB and 176 shipyrad workers exposed to noise levels of 95-97dB and reported also an increase in the level of serum cholesterol. In another study done by **Jovanovic and Jovanovic (2004)** on 150 workers working in relatively silent environment found that, industrial noise caused an increase in the serum levels of TC, TGs and LDL.C and decrease in the level of HDL-C.

It is now well established that, there is a relationship between high cholesterol and low HDL-C levels and increased risks of cardiovascular and circulatory diseases. Whereas enhanced total cholesterol encourages atheroscelerosis, HDL-C is more likely to prevent the development of

atheroscelerosis. Total cholesterol should therefore always be considered together with HDL-C. In terms of the current state of knowledge, an increased level of TGs also has to be seen as an independent risk factor for heart disease, especially in connection with low level HDL-C. **(Maschke and Hecht, 2000).**

Ising *et al.* (1999) in a case control study with 395 myocardial infraction (MI) patients 31-65 years and 2148 controls found a significant increase in the rate of (MI) with the loudness of work noise, and they reported that, work noise appeared to be the second greatest external risk factor in (MI) after smoking. **Elise *et al.* (2002)** in a met-analysis study to investigate the relation between occupational noise exposure and blood pressure and/or ischemic heart disease found a statistically significant increase in systolic blood pressure. In another study carried out by **Melamed and Bruhis (1996)** to explore the effect of noise attenuation on urinary cortisol excretion, fatigue and irritability among 35 healthy industrial workers chronically exposed to high ambient noise levels (> 85 dB) without using ear protectors found an increase in urinary cortisol excretion at the end of work shift.

The alteration in the levels of lipids and lipoproteins found in the present study could be due to sound stress-induced hypothalamo-pitutitary adrenal axis and sympathetic system stimulation. The stimulation of the hypothalamo–pituitary axis and sympathetic system causes an increase secretion of their corresponding hormones (Glucocoricoids and Catecholamines). These hormones increased lipolysis, gluconeogenesis in liver and inhibition of insulin secretion **(Maschke and Hecht, 2000).** The excess glucocorticoids and catrcholamines increase also stored lipid mobilization leading to the activation of the enzyme lipase in fat cells. Consequently, there will be an increase in the release of fatty acids from these cells **(Murray *et al.*, 1993 and Spreng, 1998).** The excess released fatty acids undergo, metabolism and causing an increase of hepatic cholesterol contents which down regulates the activity of hepatic LDL-C receptor resulting in an increase in the levels of serum TC, LDL-C and TGs rich lipoproteins **(Mabuchi, 1996 and Mahmoud and Ahmed, 2003).**

Leptin directly inhibits intracellular lipid concentrations by reducing fatty acid and triglycerides synthesis and concomitantly increasing lipid oxidation **(Shimabukuro *et al.*, 1997).** This effect on lipid metabolism may be mediated by an inhibitory effect of leptin on acetyl-co-A carboxylase activity, the rate limiting enzyme in fatty acid synthesis. Inhibition of this enzyme leads to a reduction in malonyl coA, an inhibitor of carnitylacyl transferase-I and mitochondrial B- oxidation so that, inhibition of acetyl co A carboxylase will thus block fatty acid synthesis and favor mitochondrial fatty acid uptake and oxidation, resulting in lower intracellular fatty acid and triglyceride concentration **(Bai *et al.*, 1996)**. **Muoio *et al.* (1997)** showed that, leptin attenuates insulin's antioxidative lipogenic actions on muscle fatty acid metabolism without inhibiting insulin-stimulated glucose disposal. Hence, they concluded that, leptin and insulin had opposite effects on lipid metabolism, with leptin favoring lipid oxidation and insulin favoring lipid storage. On the other hand, **Emilsson *et al.* (1997)** have provided evidence that leptin can directly reduce insulin secretion**.**

Leptin causes an increase in noradrenaline turnover to the brown adipose tissue **(Collins *et al.* 1996)** suggesting that leptin increases the sympathetic outflow. **Sebiha *et al.* (2005)** reported that, leptin and neuropeptide-y (NPY) may be involved in the pathogenesis of arterial hypertension. They found that, both leptin and NPY showed a significant positive correlation with both systolic and diastolic blood pressure in preeclamptic women. Both hormones are involved in the regulation of sympathetic nervous system activity **(Michael and Rascher, 1995 and Haynes *et al.*, 1998)** and vascular remodeling and water electrolyte metabolism **(Zukowska *et al.*, 1997 and Oda *et al.*, 1997).** Moreover, intracerebroventricular or chronic (over 1 week) intravenous infusion of leptin was found to increase arterial blood pressure in rats **(Dunbar *et al.*, 1997 and Shek *et al.*, 1998)**. Thus, the participation of leptin in the pathogenesis of hypertension observed in the present study seems very likely.

In view of relevant results, the present study recommends the use of ear protectors which can reduce the noise level to minimize the stress and other effects of noise. People in general and workers of plants of heavy industries (eg. iron and steel & textile…. etc.) should be educated through radio, TV, newspapers about the grave effects of noise pollution. Further studies are necessary to examine the effects of noise on other biochemical, haematological and histopathological parameters.

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