Effect of noise stress on cardiovascular system in adult male albino rat: implication of stress hormones, endothelial dysfunction and oxidative stress

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Abstract. Noise pollution has been realized as an environmental stressor associated with modern life style that affects our health without being consciously aware of it. The present study investigated the effect of acute, chronic intermittent and chronic continuous exposure to noise of intensity 80–100 dB on heart rate and mean systemic arterial blood pressure in rats and the possible underlying mechanisms. Noise stress causes significant increase in heart rate, mean systemic arterial blood pressure as well as significant increase in plasma levels of corticosterone, adrenaline, noradrenaline, endothelin-1, nitric oxide and malondialdehyde with significant decrease in superoxide dismutase and these values are significantly more worse in chronic continuous exposure to noise than acute or chronic intermittent exposure. These findings suggest that noise stress has many adverse effects on cardiovascular system *via* increasing plasma levels of stress hormones, oxidative stress and endothelial dysfunction. These findings have major implication in the management of adverse cardiovascular reactions of people subjected to daily noise stress.

Key words: Noise — Cardiovascular system — Stress hormones — Oxidative stress — Endothelial dysfunction

Abbreviations: ECG, electrocardiogram; ET-1, endothelin-1; MDA, malondialdehyde; SOD, super-oxide dismutase; ROS, reactive oxygen species.

Introduction

Noise has recently gained more attention as it becomes an integral part of our daily lives especially in industrial countries. Noise is defined as disturbing loud sound. Prevalence of noise is implicated in various illness of human and it is responsible for increased rates of morbidity and mortality (Franssen et al. 2004). This has encouraged scientists to study the effects of noise pollution on human's health (Mahmood et al. 2004). Beyond the direct damaging effect of noise, higher than 90 dB on the inner hair cells of the organ of Corti resulting in hearing loss, it also has several non-auditory effects including strokes (Münzel et al. 2014), sleep disturbance, decreased school performance, cognitive impairment, changes in the immune system (Babisch 2011),

disturbed serum lipid, triglycerides, platelet count, plasma viscosity, glucose level and reduced motor efficiency (van Kempen et al. 2002). Noise is also associated with increased rates of work place accident as well as stimulating aggression and other anti-social behaviors (Maschke et al. 2002).

The cardiovascular effects of noise have been source of growing interest in recent years. This comes from the strong evidence that noise affects the cardiovascular system especially in industrialized countries and increases the risk of hypertension and ischemic heart diseases including atherosclerosis and myocardial infarction. Medium and high levels of urban traffic noise near kindergartens causes increased vascular tone and both systolic and diastolic blood pressure in preschool children (Regecová and Kellerová 1995). The general stress theory states that noise affects the autonomic nervous system and the endocrine system. However, to determine the magnitude of exposure-response and the possible modifying factors, more epidemiological and experimental studies are still needed (Babisch 2011).

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So we aimed in this study to investigate the effect of noise of intensity (80–100dB) on heart rate and mean systemic arterial blood pressure in adult male albino rats and the possible role of stress hormones, markers of oxidative stress and endothelial dysfunction.

Materials and Methods

Animals

The present study was carried out on thirty two pathogen-free adult male albino Wistar rats 8–12 weeks old, weighing 200–250 g. The rats were housed in polypropylene cages under standard lightening (12 h light/dark cycle; 08:00 a.m.–08:00 p.m. light on) in a temperature-controlled room (25 ± 2°C) and humidity (50–70%). Rats were fed with a balanced diet and tap water. They were acclimatized to their environment for at least 2 weeks before starting the study. The animal procedures were performed in accordance with NIH guidelines and also were approved by the Local Institutional Animal Ethical Committee. Apart from the investigator, the animal care technician was the only person who entered the rooms. Background noise in experimental rooms did not exceed 35 dB.

Chemicals

Xylazine (2%) and ketamine (10%) used in this study were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA).

Experimental design

After the acclimatization period, the rats were randomly divided into four equal groups (8 rats *per* group) as follow according to Rahma et al. (2011).

Group I (Control group): This group was kept away from any noise stress source for 20 days.

Group II (Acute stress): Exposed to white noise (80–100 dB, 8000–16000 Hz) for 12 hours once (from 8 a.m. to 8 p.m.)

Group III (Chronic intermittent stress): Exposed to white noise at the same intensity and frequency (80–100 dB, 8000–16000 Hz) for 8 hours daily (from 8 a.m. to 4 p.m.) for 20 days (3 days exposure and 2 days without exposure). This intermittent exposure was to prevent the rats from becoming adapted to the noise.

Group IV (Chronic continuous stress): Exposed to white noise at same intensity and frequency (80–100 dB, 8000–16000 Hz) for 8 hours daily (from 8 a.m. to 4 p.m.) for 20 consecutive days.

For this exposure, the groups were transported to a room of $3 \times 4 \times 3$ m with wooden ground that has the same envi-ronmental and experimental conditions as the room where rats of the control group were kept, within which a noise generator (Tanta, Egypt) was placed.

Calculation of heart rate

After the last stress regimen of each group, the rats were anesthetized by xylazine (10 mg/kg) and ketamine (100 mg/kg) and electrocardiograhic electrodes were connected to the four limbs by subcutaneous needles. The electrocardiograph was adjusted (each 20 mm height represent 1 mV and the speed was 50 mm/s). Heart rate was detected from Lead II as it is the most informative of all leads (Chan et al. 1987).

Measurement of arterial blood pressure

For measuring systolic and diastolic arterial blood pressure, a longitudinal incision in the anterior aspect of the neck was done and the trachea was elevated to explore the carotid artery in which a carotid cannula connected to the oscillograph was inserted (The bioscience 400 series Washington oscillograph). Then mean systemic arterial blood pressure was calculated (Hicman 2001).

Blood sample collection and biochemical assays

After the blood pressure measuring, a cranio-caudal incision of about 2 cm was made, parallel and slightly to the left of the sternum through the skin and pectoral muscles to expose the ribs. A blunt curved forceps is then binged between the 5th and 6th ribs, through the intercostal muscles. The gap is widened so that the rapidly beating heart becomes visible. Intracardiac blood sample was drawn from the right ventricle and centrifuged at $5000 \times g$ for 15 minutes at room temperature (25 ± 2°C). The red blood cells (RBCs) will be separated at the bottom of the tube leaving clear plasma above. The clear supernatant (plasma) was kept at −20°C for not more than 2 weeks to be used for biochemical assessment. Plasma corticosterone was measured by enzyme linked immunosorbent assay (ELISA) kits (DSL-10-81100, Diagnostic systems laboratories Inc, USA) and plasma adrenaline and noradrenaline were measured using ELISA kits (EIA4776 and EIA4317, DRG International, Inc., USA) according to the method of Burtis and Ashweed (1994). The plasma level of nitric oxide (NO) was assessed indirectly by determining nitrite/nitrate level in the sample using standard commercial kits (ABIN955866, Antibodies Online, Germany) following Miranda et al. (2011) method. Plasma endothelin 1 (ET-1) was measured by radioimmunoassay using an antibody specific for ET-1 (RAS 6901, Peninsula Laboratories International, Inc., USA) following method of Brunner et al. (1994). Oxidative stress was as-

sessed by measuring the plasma level of malondialdehyde (MDA) and superoxide dismutase (SOD) using commercial kits (ABIN627297 and ABIN2543481, Antibodies Online, Germany) following the method of Placer et al. (1966) and Kakkar et al. (1984).

Statistical analysis

All analyses were performed using the program "Statistical Package for Social Sciences (SPSS) version 16" (SPSS Inc, Chicago, IL, USA). The data are presented as the mean ± standard deviation (SD). Comparisons among groups, in all studied parameters, were analyzed by using one-way analysis of variance (ANOVA) test and Post-Hoc multiple comparisons (Bonferroni's test). Probability of chance ($p < 0.05$) was considered statistically significant.

Results

Evaluation of heart rate (HR) and mean systemic arterial blood pressure (MSABP)

Table 1 shows that there is significant difference in heart rate and mean systemic arterial blood pressure among groups ($p < 0.001$). Mean systemic arterial blood pressure is significantly increased in acute stress, chronic intermittent stress and chronic continuous stress groups as compared with the control group. Heart rate and mean systemic arterial blood pressure are significantly higher in chronic continuous stress

group as compared with both acute and chronic intermittent stress groups. However, there are non-significant changes between acute stress group and chronic intermittent stress group ($p > 0.05$).

Evaluation of stress hormones

Table 2 shows that there is significant difference in plasma levels of corticosterone, adrenaline and noradrenaline among groups ($p < 0.001$). Plasma levels of stress hormones are significantly increased in acute stress, chronic intermittent stress and chronic continuous stress groups as compared with the control group. This increase is significantly higher in chronic continuous stress as compared with both acute and chronic intermittent stress groups. However, there are non-significant changes between acute stress group and chronic intermittent stress group ($p > 0.05$).

Evaluation of endothelial function

Table 3 shows that there is significant difference in plasma levels of NO and ET-1among groups ($p < 0.001$). The plasma levels of NO and ET-1 are significantly increased in the acute stress, chronic intermittent stress and chronic continuous stress groups as compared with the control group. This increase is significantly higher in chronic continuous stress as compared with both acute and chronic intermittent stress groups. However, there are non-significant changes between acute stress group and chronic intermittent stress group ($p > 0.05$).

Table 1. Heart rate and mean systemic arterial blood pressure (MSABP) in the studied groups

Parameter	Group I (Control)	Group II (Acute Stress)	Group III (Chronic Intermittent Stress)	Group IV (Chronic Continuous Stress)	F test
Heart rate (beats/min)	274.17 ± 17.44	322.5 ± 30.94	325.83 ± 25.77	433.33 ± 42.74*[†‡]	28.88
MSABP (mmHg)	86.66 ± 1.50	93.5 ± 2.43*	94.33 ± 3.83*	118.83 ± 5.45*[†‡]	90.6

Data is expressed as mean ± standard deviation ($n = 8$ per group). $p < 0.05$ is significant tested by using One-way analysis of variance (ANOVA) and Post Hoc multiple comparisons (Bonferroni's test). * $p < 0.001$ vs. control group; [†] $p < 0.001$ vs. acute stress group; [‡] $p < 0.001$ vs. chronic intermittent stress group.

Table 2. Plasma level of corticosterone, adrenaline and noradrenaline in the studied groups

	Group I (Control)	Group II Acute Stress)	Group III (Chronic Intermittent Stress)	Group IV (Chronic Continuous Stress)	F test
Corticosterone (ng/ml)	219.83 ± 18.52	400.33 ± 23.64*	398.50 ± 17.07*	586.83 ± 27.21*[†‡]	278.7
Adrenaline (pg/ml)	402.60 ± 69.69	456.50 ± 77.91*	457.83 ± 82.08*	539.67 ± 32.07*[†‡]	63.67
Noradrenaline (pg/ml)	208.33 ± 69.76	245.17 ± 69.69*	247.67 ± 76.07*	298.33 ± 15.33*[†‡]	85.08

Data is expressed as mean ± standard deviation ($n = 8$ per group). $p < 0.05$ is significant tested by using One-way analysis of variance (ANOVA) and Post Hoc multiple comparisons (Bonferroni's test). * $p < 0.001$ vs. control group; [†] $p < 0.001$ vs. acute stress group; [‡] $p < 0.001$ vs. chronic intermittent stress group.

Assessment of oxidative stress

Table 4 shows that there is significant difference in plasma levels of MDA and SOD among groups ($p < 0.001$). The plasma levels of MDA is significantly increased while SOD is significantly decreased in acute stress, chronic intermittent stress and chronic continuous stress groups as compared with the control group. These changes are significantly higher in chronic continuous stress as compared with both acute and chronic intermittent stress groups. However, there are non-significant changes between acute stress group and chronic intermittent stress group ($p > 0.05$).

Discussion

World Health Organization (WHO) declared noise as an international health problem being one of the most wide spread sources of environmental stress in human life. Noise stress has many negative effects on various organs of our body especially the cardiovascular system (Passchier-Vermeer and Passchier 2000; Wallenius 2004). The results of the present study revealed that heart rate is significantly elevated in rats exposed to chronic continuous noise stress as compared to the control, acute stress and chronic intermittent stress groups. Mean systemic arterial blood pressure is significantly elevated in rats exposed to acute or chronic noise stress as compared to the control group and this elevation is significantly higher in chronic continuous noise-stressed rats as compared with acute or chronic intermittent stress groups. These findings are consistent with previously published

studies (van Kempen et al. 2002; Bluhm and Eriksson 2011; Lercher et al. 2011). The adverse effects of acute or chronic noise stress on cardiovascular system may be explained by increased reactive oxygen species, increased release of stress hormones, activation of sympathetic nervous system, increasing blood viscosity, endothelial dysfunction, peripheral vasoconstriction, and increase peripheral vascular resistance (Baldwin 2007; Baldwin et al. 2008; Babisch 2011; Münzel et al. 2014).

Stress hormones; cortisol, adrenaline and noradrenaline are used as indicators of body response to stress upon noise exposure (Spreng 2000; Li et al. 2009). Pituitary-adrenocortical axis is involved in the extra-auditory effects of noise (Ising and Braun 2002; Kanitz et al. 2005). The results of the current work show that rats exposed to acute or chronic noise have significantly elevated plasma levels of corticosterone, adrenaline and noradrenaline as compared to the control rats unexposed to noise and this elevation is significantly higher in chronic continuous stress group as compared with both acute or chronic intermittent stress groups. These findings are congruent to the previous studies which concluded that rats exposed to noise showed elevated plasma levels of corticosterone (Soldani et al. 1999; Samson et al. 2007; Gannouni et al. 2013), adrenaline and noradrenaline (Maschke et al. 2002; Lenzi et al. 2003; Maschke 2003; Di et al. 2011; Schmidt et al. 2013). These endocrinal changes in response to exposure to noise stress can be explained by activation of autonomic nervous system (Turner et al. 2005) or structural and functional modifications occurring in the adrenal cortex and medulla which are supposed to be mediated by increased free oxygen radicals (Soldani et al. 1999; Kanitz et

Table 3. Plasma level of nitric oxide (NO) and endothelin 1 (ET-1) in the studied groups

	Group I (Control)	Group II (Acute Stress)	Group III (Chronic Intermittent Stress)	Group IV (Chronic Continuous Stress)	F test
NO (µmol/ml)	50.91 ± 3.81	71.21 ± 3.12*	72.08 ± 4.17*	91.72 ± 4.13*[†‡]	113.37
ET-1 (pg/ml)	41.08 ± 2.41	51.75 ± 2.44*	52.50 ± 2.54*	70.08 ± 3.41*[†‡]	115.56

Data is expressed as mean ± standard deviation ($n = 8$ *per* group). $p < 0.05$ is significant tested by using One-way analysis of variance (ANOVA) and Post Hoc multiple comparisons (Bonferroni's test). *$p < 0.001$ *vs.* control group; [†] $p < 0.001$ *vs.* acute stress group; [‡] $p < 0.001$ *vs.* chronic intermittent stress group.

Table 4. Plasma level of malondialdehyde (MDA) and superoxide dismutase (SOD) in the studied groups

	Group I (Control)	Group II (Acute Stress)	Group III (Chronic Intermittent Stress)	Group IV (Chronic Continuous Stress)	F test
MDA (nmol/ml)	3.05 ± 0.42	4.10 ± 0.32*	4.16 ± 0.39*	5.65 ± 0.33*[†‡]	49.68
SOD (U/ml)	30.66 ± 1.08	28.25 ± 0.93*	27.96 ± 1.05*	24.5 ± 0.89*[†‡]	39.17

Data is expressed as mean ± standard deviation ($n = 8$ *per* group). $p < 0.05$ is significant tested by using One-way analysis of variance (ANOVA) and Post Hoc multiple comparisons (Bonferroni's test). * $p < 0.001$ *vs.* control group; [†] $p < 0.001$ *vs.* acute stress group; [‡] $p < 0.001$ *vs.* chronic intermittent stress group.

al. 2005; Gannouni et al. 2013). Also it was postulated that elevated corticosterone accelerates the generation of free oxygen radicals (McIntosh and Sapolsky 1996). Increased level of stress hormones, activation of sympathetic nervous system, increasing the density of noradrenergic fibers in the heart and catecholamine-induced increase in Ca^{2+} entry to the myocardium can explain the increase in heart rate and systolic blood pressure upon exposure to loud noise (Lenzi et al. 2003).

Reactive oxygen species (ROS) or free oxygen radicals are normally produced as sequence of aerobic metabolism. They cause breakdown of lipid molecules of cell membrane which is known as lipid peroxidation as well as impairment of proteins and deoxyribonucleic acid (DNA) (Van Campen et al. 2002). Under normal conditions, the endogenous antioxidants protect the cell from the damaging effect of free oxygen radicals (Henderson et al. 2006). Oxidative stress is a state of imbalance between oxidants and antioxidants leading to cellular damage, dysfunction or death (Demirel et al. 2009). Oxidative stress is found to be a common denominator in many aspects of heart-related diseases (Blum 2009). One of the consequences of noise exposure is increased production of ROS, as superoxide, hydrogen peroxide and hydroxyl radicals (Gannouni et al. 2013). In this study, the lipid peroxidation level, indicated by increased the plasma level of MDA (Nielsen et al. 1997), is significantly increased in rats exposed to acute, chronic intermittent or continuous noise stress compared to the normal control rats and this increase is significantly higher in chronic continuous stress than acute or chronic intermittent stress. Also in the current study, it is found out that exposure to acute or chronic noise decreases the antioxidant enzyme, SOD. These findings agreed the previous studies done in rats (Demirel et al. 2009), rabbits (Derekoy et al. 2001) and human (Yildirim et al. 2007). Free oxygen radicals generated as a result of exposure to acute or chronic loud noise are involved in nervous, endocrine and cardiovascular disorders (Manikandan et al. 2005).In cardiovascular system, they cause hypertrophy of smooth muscle cells and arterial wall, cardiomyocyte necrosis and apoptosis and myocardial damage that can be attributed to increased heart rate and systolic blood pressure in noise-stressed rats (Gesi et al. 2002; Abu-Amara et al. 2013).The findings of the present study regarding SOD are in contrast to other findings which postulated that the plasma levels of antioxidant enzymes as SOD and catalase are elevated in rats exposed to long-term noise of moderate intensity (70 and 85 dB) and this might be a protective mechanism (Gannouni et al. 2013). This difference may be due to the difference in the duration and/or the amplitude of the noise applied in the study.

Noise impairs endothelial function which may be partly mediated by ROS (Schmidt et al. 2013, 2015). In the current work, acute, chronic intermittent and chronic continuous stress, cause significant increase in the plasma levels of NO and ET-1 as compared with the control group. This increase is significantly higher in chronic continuous noise stressed rats when compared with acute or chronic intermittent stress groups. Elevated plasma level of ET-1 in response to noise stress causes peripheral vasoconstriction and increases arterial blood pressure (Wang et al. 2002). The increase in NO level may be due to elevated NO synthase activity and elevated nitrate/nitrite levels in the heart and aorta (Bernatova et al. 2007). Increased generation of reactive oxygen species induced by elevated corticosterone level in response to noise stress (McIntosh and Sapolsky 1996) can also explain increased NO level *via* enhancing inactivation of nitric oxide (Vaziri et al. 1999) or inducing the signal transduction pathways for nitric oxide synthase (iNOS) (Yoshikawa et al. 2000). NO is accepted as oxygen free radical that has harmful effects on cardiovascular system (Demirel et al. 2009). This finding is in agreement with the study of Puzserova et al. who postulated that long-term exposure to chronic social stress reduced the NO-independent relaxation in normotensive rats that might be the initial step in chronic stress-induced cardiovascular disorders (Puzserova et al. 2013). In contrast to our finding, other researchers postulated that the level of NO in erythrocytes of workers in noisy workplaces is lower than the workers in non-noisy places and this could be an adaptive mechanism to chronic exposure to loud noise (Pinar et al. 2011).

From the results of the current work, we conclude that exposure to noise has deleterious effects on the cardiovascular system as indicated by increased heart rate and mean systemic arterial blood pressure and therefore we suggest the precise monitoring of noise exposure. Because oxidative stress, endothelial dysfunction and elevated stress hormones are implicated in the negative effects of noise on cardiovascular system, they should be considered in the strategy for controlling the adverse effect of noise on the human health.

Conflict of interest. The authors declare that they have no conflict of interest.

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