Ultra structuralEvaluation of Rat Myocardium underEffect of High Altitude Hypoxia

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Abstract: Background: Hypoxia is condition in which the percentage saturation of hemoglobin with oxygen is determined in blood. The body functions are suppressed at high altitude (1,500 to 3,500 meters), resulting in diminished inspiratory oxygen pressure and decline arterial oxygen saturation leading to increase in the ventilation, heartbeat, blood pressure, and decreased exercise performance. This can lead to medical problems; from the mild symptoms of acute mountain sickness to the potentially fatal high altitude pulmonary edema and high altitude cerebral edema. The higher is the altitude is the greater is the risk. However, above 8,000 meters (zone of death) the human body cannot adapt and will eventually die. This work is designed to report the structural alteration of the rat myocardium under effect of the high altitude hypoxia**.** Material and Methods: Fifty healthy young male albino rats, having average weight of 200 grams for each, were used in this study. The rats were divided into five groups (10 rats for each). The control group was kept in normal environment for one month, the second, third and fours groups admitted in high altitude environment for three days, one week, two weeks and one month respectively. At the end of the above periods the blood gases were investigated and the myocardium specimens were token and prepared for light and electron microscopic examination. *Results:* The myocardial structure of the rates were affected by the high altitude hypoxia, where the cardiomyocytes hypertrophy, disorganization of the micro filaments with areas of degeneration, the mitochondrial and nuclear alteration were clarified also In our work the direct measurement of Oxygen Pressure (PO2)values in the blood were reveled significant decline.
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Key Words: high altitude hypoxia and Ultra structure of rat myocardium

1. Introduction

Oxygen is an essential substrate for cell survival. It acts as a final electron acceptor in the electron transport chain (ETC). In humans, oxygen tension varies from 100 mm Hg in alveolar arterioles to between 40 and 20 mm Hg in systemic tissues (Webster and Abela, 2007).When oxygen is scarce, the ETC is compromised. Since the ETC is coupled to oxidative phosphorlyation, Adensosine Triphosphate (ATP) levels also drop significantly creating energy disparities within the cell. Hypoxia occurs when the oxygen tension is lower than physiological levels and the demand for oxygen exceeds the supply available (Patterson and Zhang, 2010). The most frequent diseases of modern times undoubtedly include hypoxic states of the cardiopulmonary system. They originate as a result of disproportion between the amount of oxygen supplied to the tissue and the amount actually required. The degree of hypoxic injury depends, however, not only on the intensity and duration of the hypoxic stimulus but also on the level of cardiac tolerance to oxygen deprivation. It has been repeatedly observed that cardiac tolerance to acute oxygen deprivation can be significantly increased by previous adaptation to permanent or intermittent hypoxia, both in populations living at high altitude and in animals under experimental conditions (Asemu*et al.,* 1999, Baker *et al,.* 1999 and Neckar *et al.,*2002).

There are three altitude regions that reflect the lowered amount of oxygen in the atmosphere (high altitude 1,500-3,500 meters, very high altitude 3,500-5,500 meters and extreme altitude above 5,500 meters), Finally, the death zone in mounts refers to altitude above a certain point where the amount of oxygen is not high enough to sustain human life. This point is generally tagged as 8,000 meters (West. 2002, Zubieta et al., 2008andBrenner et al., 2011).

The high altitude can lead to mild symptoms of acute mountain sickness or potentially fatal high altitude pulmonary edema and high altitude cerebral edema. The people have different susceptibilities to altitude sickness; for some otherwise healthy people, acute mountain sickness can begin to appear at around 2000 meters above sea level. Symptoms include headache, fatigue, stomach illness, dizziness, drowsiness and general weakness, insomnia, nasal bleed and peripheral edema. The manifestation of these symptoms appeared six to ten hours after ascent and generally subsides in one to two days, but they occasionally develop into the more serious conditions

such as pulmonary edema and cerebral edema(Bates et al., 2007and Baillie et al., 2010).

In addition to the protective effect, adaptation to chronic hypoxia may induce adverse influences on the cardiopulmonary system. It exerts opposite effects to compancete the hypoxic condition. Resulting hypoxic pulmonary hypertension leads to right ventricular hypertrophy and eventually even to congestive heart failure. Both ventricles are therefore under the influence of chronic hypoxia, but the load of right ventricle is increased (Bauer *et al.,* 1997 and Neckar *et al,.* 2004). The most frequently used experimental model in research on chronic hypoxia is that of high altitude, either in a mountain environment or simulated under laboratory conditions in a normobaric or hypobaric chamber. This model permits to study the time-course of development of beneficial and adverse adaptive changes (Tadal*et al,.* 1994). In order to contribute in the understanding of molecular mechanisms involved in the process of cardiac adaptation to chronic hypoxia, we studied theultra structure of rat myocardium under effects of high altitude hypoxia

2. Materials and Methods

Fifty healthy young male albino rats, having average weight of 200 grams for each, were used in this study. The animals obtained from the animal house of Gazain University at sea level where they were fed with standard feed and allowed free water excess. The rats were divided into five groups (10 rats for each). The control group was kept in normal environment in Darb city at sea level for one month, where the animals housed in open mesh-wire cages in temperature-controlled room at 22-24°C and 50-60 % relative humidity with 12-hr light d a r k cycle (Soldani et al., 1997). The second, third and fours groups were kept at high altitude environment (in the animal house of Collage of Medicine King Khaled University Abha city 2200 meters above sea level) for three days, one week, two weeks and one month where they were fed with standard feed and allowed free water excess.

At the end of the previous mentioned above the rats were anesthetized by an intraperitoneal injec-tion of chloral hydrate (400 pl/100 g), thora-cotomy was done and the fixative solution is dropped on the still beating heart in situ. The myocardial specimens from the right ventricle were prepared for light and electron microscopy (Griffith et al., 1973, Paparelli et al., 1995). The specimens were be fixed in 2.5% gluteraldehyde for 2 hours, again washed 3 times (5 minutes each) in phosphate buffer and were post fixed in 1% osmium tetroxide for 2 hours, then washed 3 times (5 minutes each) in phosphate buffer. The specimens dehydrated in ascending grades of ethyl alcohol: 50%, 60%, 70%, 80 %, 90 % and in absolute alcohol (two changes, 30 minutes each), then in propylene oxide (two changes, 30 minutes each). They were ultimately immersed in a propylene-epon mixture (1:1) for 24 hours. The specimens will embedded in plastic capsules containing epon and left to polymerize in an incubator at 60 cº for 3 days. An ultramicrotome was used for semithin (1u section cut, stained with toluidine blue and examined by light microscopy). Ultrathin sections (200 Å thick) were cut and collected on copper grids and left to dry. The ultrathin sections stained with 1% uranyl acetate and 1% lead citrate was examined by transmission electron microscope. Also, the arterial blood samples were taken and investigated for blood gases in Asser university hospital to determine the degree of hypoxia.

3. Results

The First group (control):

The animals werekept in normal environment in Darb city atsea levelfor one monththeirmeanarterial blood Oxygen Pressure (PO2) was 94.955 / mmHg, Carbon dioxide Pressure (PCO2) was 35.739/ mmHg and the PH 7.387. Table (1).

The myocardial structure of the control group:-

Light microscopic examination revealed that the cardiomyocytes have cross-striations with central nuclei and arranged as parallel and branched cords, with narrow intercellular spaces intervened by the capillaries (Figs. 1,2 and 5). Also it appeared polyhydral in shape with rounded or oval nucleus in the transverse section (Figs. 3 and 4).

Ultrastructural examination showed change in the organization of microfilaments in cardiomyocytes, the mitochondria had a dense matrix, visible fine cristae and arranged in lines between the microfilaments (Figs. 6, 7 and 8). The nucleus appeared rounded or oval in shape with regular nuclear membrane and prominent nucleolus (Figs.6 and 7). The microfilaments of the cardiomyocytes (Fig.8) were organized as "**A**" bands the part of the sarcomere where thick and thin filaments overlap, "**H**" band Area of **A**-band includes thick filaments only, "**M**" line is the region of thick filaments connections at the centre of the "**H**" band, "**I**" band Area includes thin filaments only, the **Z** line at the center of **I** band and it form the site of acting filaments.

The second group

The animals were kept at high altitude environment (*Abha city 2200 meter above sea level*) for three days, their mean arterial blood Oxygen was significantly decline to about 18.646/mmHg than the control group and the mean arterial carbon dioxide pressure (PCO2) value was significantly increased to

about 4.313 / mmHg than the control and decline of the PH. Table (2).

The myocardial structure of the second group:-

The light microscope, of the myocardium of this group revealed that thickness of muscle fibers and congestion of the blood capillaries (Figs. 9) of longitudinal sections and variable shaped cardiomyocytes with central and peripherally located nuclei of transverse sections, also the intracellular spaces were increased (Fig 10).

The third group

The animals were kept at high altitude environment for one week. The mean arterial blood Oxygen was significantly declined to 15.964 /mmHg than the control group and the mean arterial carbon dioxide pressure (PCO2) value was significantly increased in this group to3.891 / mmHg than the control and declined of the PH was seen(Table 3).

The myocardial structure of the third group:-

Light microscope of the myocardium of this group revealed the increased thickness of muscle fibers and the intercellular space (Figs. 11and 12) was congestion in the capillaries(Fig. 12).

The fourth group:

The animals were kept at high altitude environment for two weeks their mean arterial blood oxygen was significantly declined to14.926 /mmHg than the control group and the mean arterial carbon dioxide pressure (PCO2) value was significantly increased in this group about 2.128 / mmHg than the control, and decline of the PH. Table (4).

The myocardial structure of the fourth group:-

With the light microscope, the myocardium of this group revealed hypertrophy of muscle fibers with large vacuolated nuclei(Figs. 13, and 14) and congested blood capillaries (Fig 15).

With the electron microscope, the changes in cardiomyocytes include disorganization of the microfilaments with interrupted or lost of **Z** lines (Figs 17, and 18), areas of degeneration (Figs. 18 and 19). Some mitochondrials were appeared normal while others were degenerated and vacuolated (Figs 16 and 17). The indentation in the nuclear envelop were demonstrated with heterogeneous distribution of the nucleoplasm (Fig.16), also increase of the collagen fibers in the intracellular spaces (Figs16 and 19).

The fifth group

The animals were kept at high altitude environment for one month their mean arterial blood oxygen reveled significantly declinedto12.21 /mmHg than the control group and the mean arterial carbon dioxide pressure (PCO2) value was insignificantly increased in this group about 0.405/ mmHg than the control and decline of the PH. Table (5).

The myocardial structure of the fifth group:-

With the light microscope, the myocardium of this group revealed hypertrophy of cardiomyocytes with vacuolated cytoplasm and large vacuolated nuclei(Figs.2 0, 21, and 22) and areas of degeneration (Figs 20 and 21).

With the electron microscope, the cardiomyocytes showed disorganization of the microfilaments (Fig.25) and vacuoles between its bands(Fig.24).Hyper chromatic nucleus with indentation in the nuclear envelop (Fig.23), areas of degeneration (Figs. 23 and 26).Vacuolated mitochondria were seen(Figs.26 and 27). Also the collagen fibers increase in the intracellular spaces (Fig.25).

Table (1) (control group) The blood gasses of the animals lived at the sea level.

Animals	The blood samples		
	Oxygen Pressure (PO2) / mmHg	Carbon dioxide Pressure (PCO2) / mmHg	PH
1	98.53	32.61	7.455
2	95.25	36.91	7.390
3	91.41	38.23	7.340
4	96.75	37.21	7.398
5	96.64	35.71	7.388
6	93.52	33.85	7.335
7	90.28	38.29	7.422
8	95.81	36.42	7.332
9	93.65	34.65	7.399
10	97.71	33.51	7.411
Mean	94.955	35.739	7.387
S-D	2.696394	1.887986	0.040

Table (2): The blood gasses of the second group showing that the mean arterial blood Oxygen Pressure (PO2) 76.309/ mmHg, Carbon dioxide Pressure (PCO2) 40.052/ mmHg and the PH 7.174.

Animals	The blood samples		
	Oxygen Pressure (PO2) / mmHg	Carbon dioxide Pressure (PCO2) / mmHg	PH
1	78.55	39.68	7.100
2	75.55	44.99	7.180
3	81.48	38.81	7.110
4	76.75	41.28	7.210
5	68.74	43.75	7.110
6	80.42	37.85	7.150
7	80.25	38.85	7.200
8	75.80	36.99	7.280
9	67.85	40.44	7.150
10	77.70	37.88	7.250
Mean	76.309	40.052	7.174
S-D	4.6666	2.6201	0.061

Table (3): The blood gasses of the third group showing that the mean arterial blood Oxygen Pressure (PO2) 78.991/ mmHg, Carbon dioxide Pressure (PCO2) 39.63/ mmHg and the PH 7.279.

Animals	The blood samples		
	Oxygen Pressure (PO2) / mmHg	Carbon dioxide Pressure (PCO2) / mmHg	PH
1	78.90	39.21	7.250
2	79.58	41.80	7.270
3	80.66	38.22	7.260
4	77.25	40.35	7.280
5	77.94	41.75	7.310
6	80.50	39.80	7.250
7	78.59	37.95	7.270
8	79.85	39.93	7.300
9	76.85	40.11	7.350
10	79.79	37.18	7.250
Mean	78.991	39.63	7.279
S-D	1.319701	1.52972	0.032

Table (4): The blood gasses of the fourth group showing that the mean arterial blood Oxygen Pressure (PO2) 80.029 / mmHg, Carbon dioxide Pressure (PCO2) 37.867/ mmHg and the PH 7.315.

Animals	**The blood samples**		
	Oxygen Pressure (PO2) / mmHg	**Carbon dioxide Pressure (PCO2) / mmHg**	**PH**
1	**79.95**	**36.29**	**7.300**
2	**80.50**	**37.80**	**7.290**
3	**81.61**	**38.22**	**7.310**
4	**78.80**	**37.35**	**7.290**
5	**80.34**	**38.15**	**7.310**
6	**80.90**	**38.20**	**7.290**
7	**78.59**	**37.95**	**7.370**
8	**79.85**	**39.00**	**7.320**
9	**79.85**	**38.19**	**7.320**
10	**79.90**	**37.52**	**7.350**
Mean	**80.029**	**37.867**	**7.315**
S-D	**0.897**	**0.7141**	**0.026**

Table (5): Group five the animals were exposed to environmental hypoxia for one month showing (PO2) 82.745/ mmHg, (PCO2) 36.144/ mmHg and PH 7.349

Animals	The blood samples		
	Oxygen Pressure (PO2) / mmHg	Carbon dioxide Pressure (PCO2) / mmHg	PH
1	82.35	34.95	7.360
2	83.50	35.82	7.340
3	84.90	36.95	7.350
4	81.80	35.35	7.330
5	83.60	36.90	7.340
6	83.40	36.20	7.330
7	82.20	35.95	7.390
8	81.90	37.30	7.320
9	81.80	36.50	7.350
10	82.00	35.52	7.380
Mean	82.745	36.144	7.349
S-D	1.0478	0.765	0.022

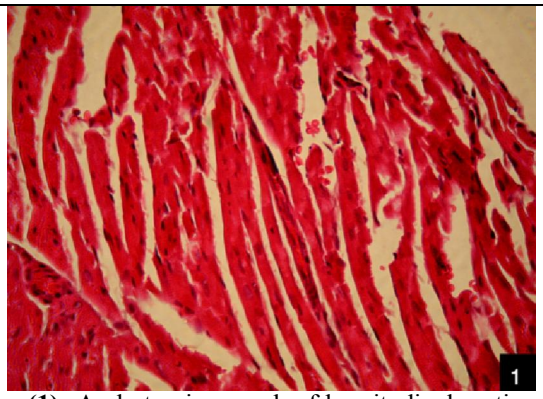

Fig. (1): A photomicrograph of longitudinal section in right ventricle of adult male albino rat control group showing a group of cardiomyocytes which appeared as parallel and branched cords with central nuclei(Hx& E. x 400).

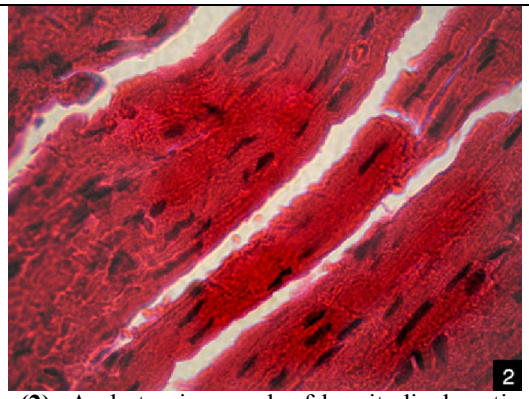

Fig. (2): A photomicrograph of longitudinal section in right ventricle of adult male albino rat control group showing a group of cardiomyocyteswith central and peripherally located nuclei(Hx& E. x 1000).

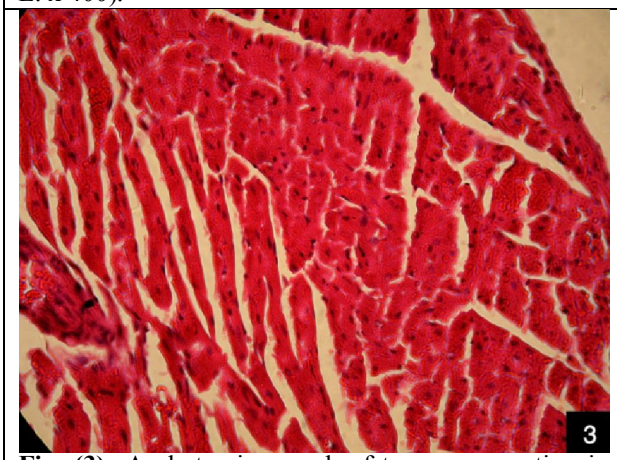

Fig. (3): A photomicrograph of transverse section in right ventricle of adult male albino rat control group showing a group of cardiomyocytes(Hx& E. x 400).

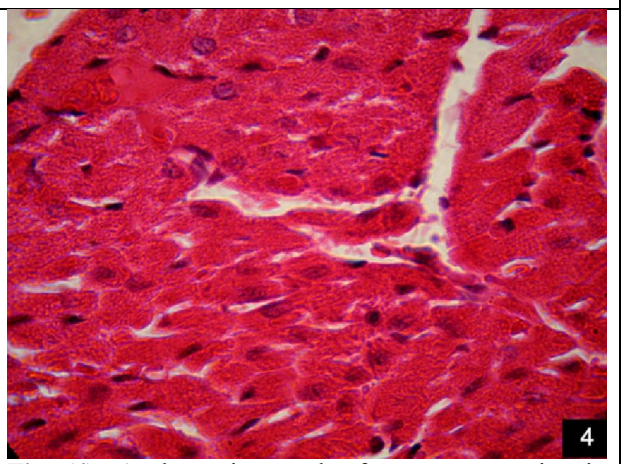

Fig. (4): A photomicrograph of transverse section in right ventricle of adult male albino rat control group showing a group of cardiomyocytes polygonal in shape withcentral and peripherally located nuclei(Hx& E. x 1000).

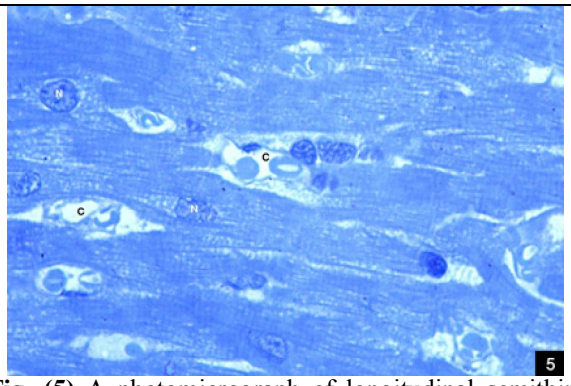

Fig. (5) A photomicrograph of longitudinal semithin section in right ventricle of adult male albino rat control group showing a group of cardiomyocytes which appeared as parallel and branched cords with cross-striations and central nuclei (N), blood capillaries (C). (Toludine Blue X l000).

Fig. (6): Electron micrograph of an adult rat's myocardium (control group) showing that organization of microfilaments in cardiomyocytes, blood capillaries contains R B Cs, and nucleus (N).

Fig (7): Electron micrograph of an adult rat's myocardium (control group) showing the organization of microfilaments in cardiomyocytes, oval shape nucleus (N) with center nuclease (n) andmitochondrials(M).

Fig. (8): Electron micrograph of an adult rat's myocardium (control group) showing the organization of the microfilaments in cardiomyocytes"A" band, "H" band, "M" line, "I" band and "Z" lines and fine cristae mitochondria (M).

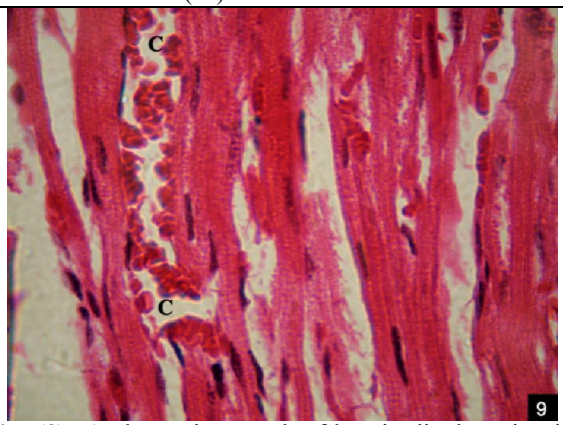

Fig. (9): A photomicrograph of longitudinal section in right ventricle of adult male albino rat second group showing a group of cardiomyocytes with thickness of muscle fibers and congested capillaries (C) withthe blood elements (Hx& E. x 1000).

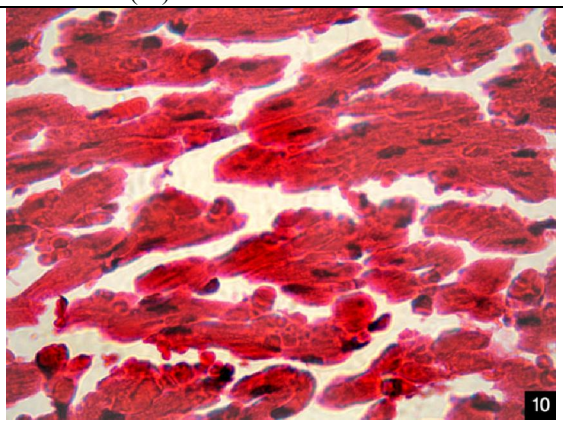

Fig. (10): A photomicrograph of transverse section in right ventricle of adult male albino rat second group showing a group of cardiomyocytes variable in shape withcentral and peripherally located nuclei and widens of the intercellular spaces(Hx& E. x 1000).

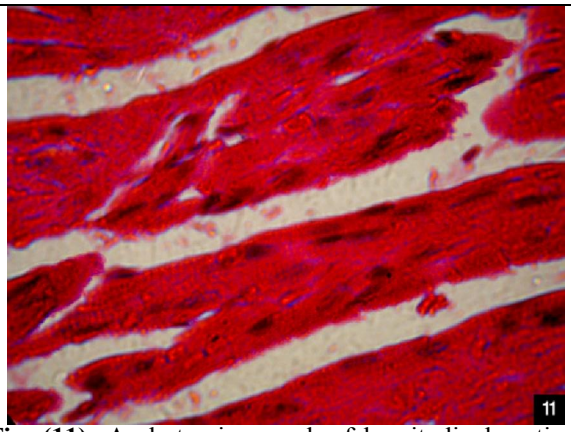

Fig. (11): A photomicrograph of longitudinal section in right ventricle of adult male albino rat third group showing a group of cardiomyocytes with clarified thickness of muscle fibers and increase the intercellular spaces (Hx& E. x 1000).

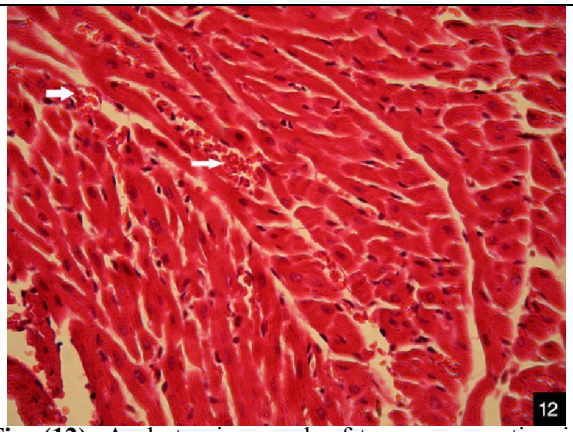

Fig. (12): A photomicrograph of transverse section in right ventricle of adult male albino rat third group showing a group of cardiomyocytes with thickness of muscle fibers and widens of the intercellular space and congested capillaries (arrow) (Hx& E. x 400).

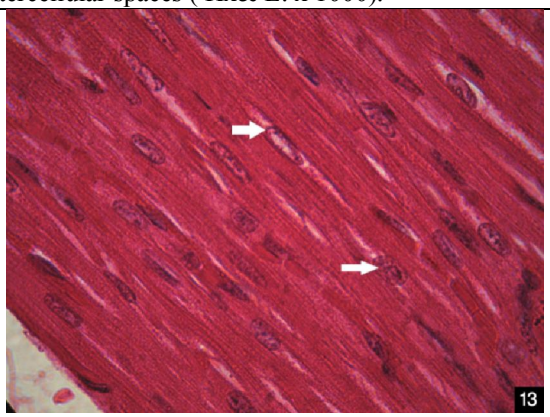

Fig. (13): A photomicrograph of longitudinal section in right ventricle of adult male albino rat fourth group showing a group of cardiomyocytes with hypertrophy of muscle fibers and large vacuolated nuclei (arrows) (Hx& E. x 1000).

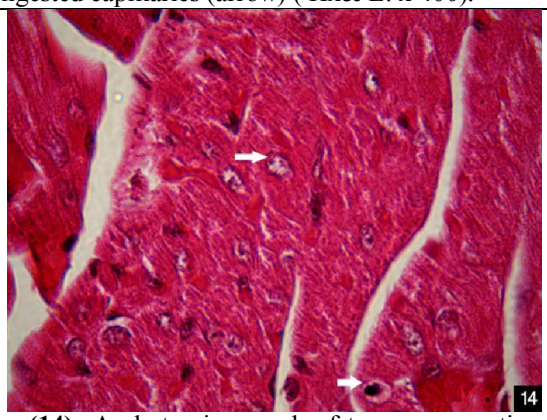

Fig. (14): A photomicrograph of transverse section in right ventricle of adult male albino rat fourth group showing a group of cardiomyocytes with muscle fibers hypertrophy and vacuolated nuclei (arrows) (Hx& E. x 1000).

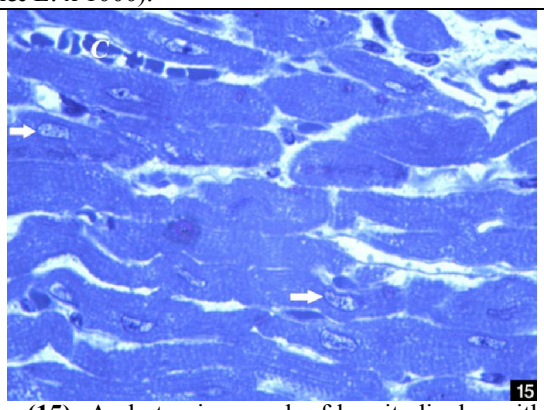

Fig. (15): A photomicrograph of longitudinal semithin section in right ventricle of adult male albino rat fourth group showing a group of cardiomyocytes with hypertrophy of muscle fibers and large vacuolated nuclei (arrow) and blood capillaries (C). (Toludine Blue X l000).

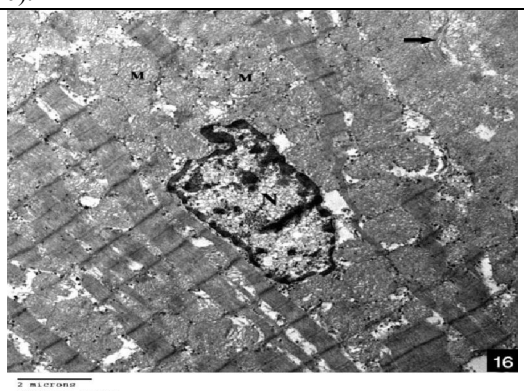

Fig. (16): Electron micrograph of an adult rat's myocardium under effect of high altitude hypoxia (fourth group) showing, vacuolated nucleus (N)disorganization of microfilaments,vacuolated mitochondria(M) and collagen in between the microfilaments (arrow).

Fig (17): Electron micrograph of an adult rat's myocardium under effect of high altitude hypoxia (fourth group) showing, disorganization of the microfilaments, the Z lines werelost in some areas (arrows),and vacuolated mitochondria were (M).

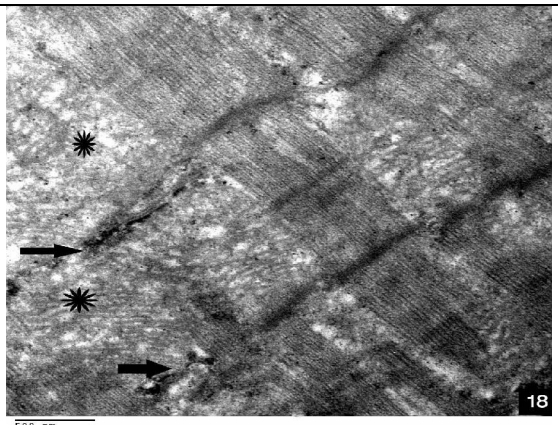

Fig. (18): Electron micrograph of an adult rat's myocardium under effect of high altitude hypoxia (fourth group) showing, interrupted Z lines(arrows) of the microfilaments, and areasof degeneration (*).

Fig (19): Electron micrograph of an adult rat's myocardium under effect of high altitude hypoxia (fourth group) showing, group of cardiac cells, increase the collagen fibers in the intracellular spaces (arrows) and areas of degeneration(*).

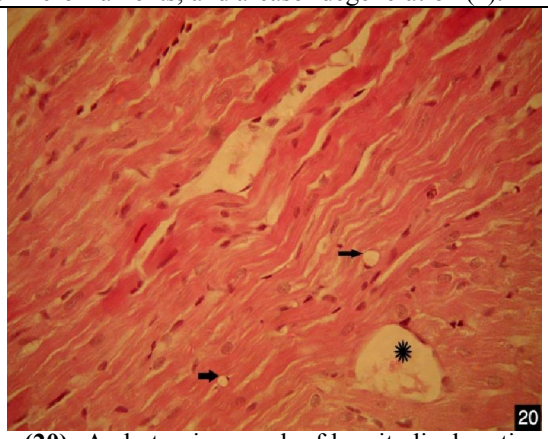

Fig. (20): A photomicrograph of longitudinal section in right ventricle of adult male albino rat fifth group showing hypertrophy of cardiomyocytes with vacuolated cytoplasm(arrow) and area of degeneration (*) (Hx& E. x 400).

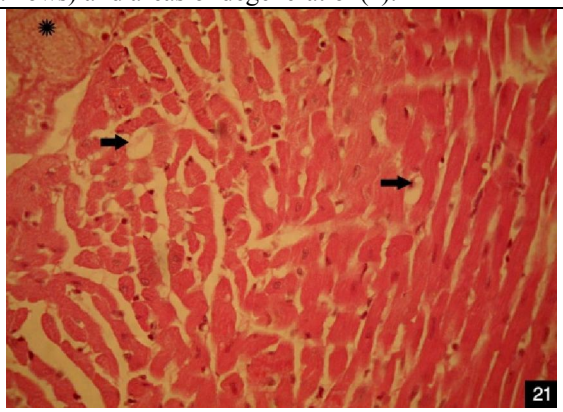

Fig. (21): A photomicrograph of transverse section in right ventricle of adult male albino rat fifth group showing hypertrophy of cardiomyocytes with vacuolated cytoplasm(arrow) and area of degeneration (*) (Hx& E. x 400).

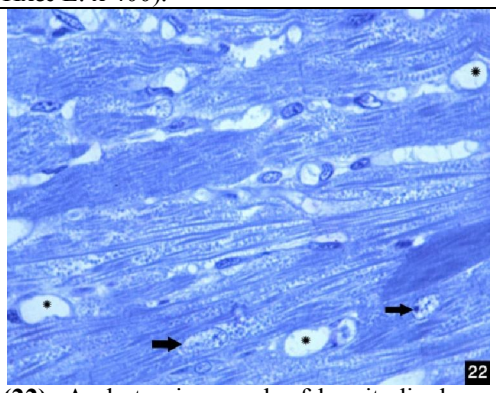

Fig. (22): A photomicrograph of longitudinal semithin section in right ventricle of adult male albino rat fifth group showing hypertrophy of cardiomyocytes with variable vacuoles (*)scattered in the cardiomyocytes and large vacuolated nuclei(arrow). (Toludine Blue X l000).

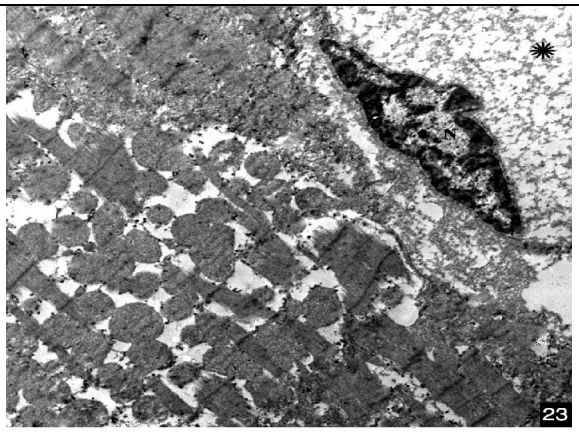

Fig (23): Electron micrograph of an adult rat's myocardium under effect of high altitude hypoxia (fifth group) showing, disorganization of microfilaments, hyper chromatic nucleus (N),and areasof degeneration (*).

Fig. (24): Electron micrograph of an adult rat's myocardium under effect of high altitude hypoxia (fifth group) showing, vacuolated in between the microfilaments (*).

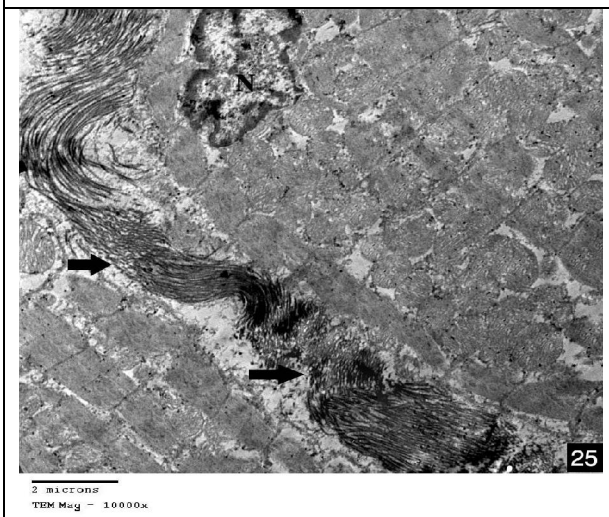

Fig (25): Electron micrograph of an adult rat's myocardium under effect of high altitude hypoxia (fifth group) showing, increase the collagen fibers in the intracellular spaces (arrows), and hyper chromatic nucleus (N).

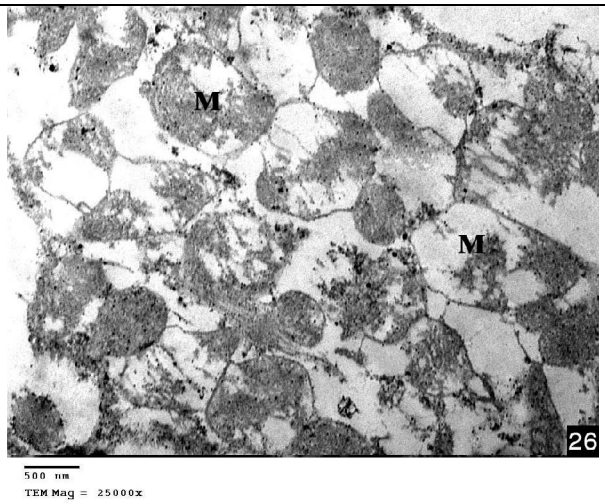

Fig. (26): Electron micrograph of an adult rat's myocardium under effect of high altitude hypoxia (fifth group) showing,vacuolated mitochondria (M).

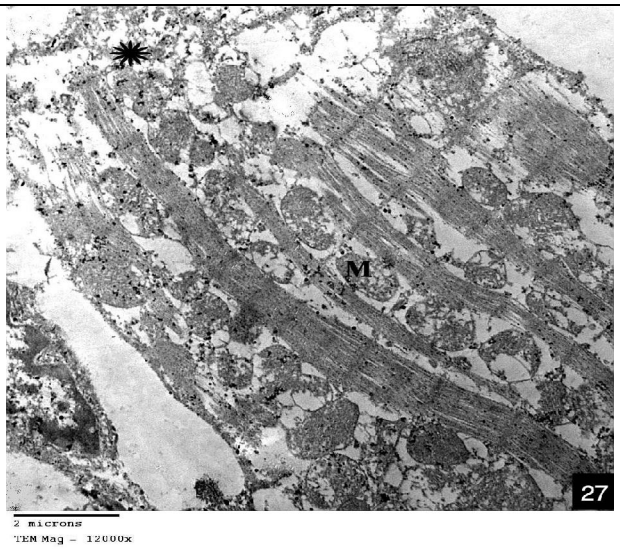

Fig (27): Electron micrograph of an adult rat's myocardium under effect of high altitude hypoxia (fifth group) showing, disorganization of microfilaments, vacuolated mitochondria (M), and areasof degeneration (*).

4. Discussion

Hypoxia is known to have critical effects on the vitality of living bodies particularly the cardiovascular system hence we designed our work to evaluate alterations of myocardial structure under effect of high altitude hypoxia 2200 meters above sea level at Abha city in which about 200,000 persons live. About 140 million people live at high altitude environment worldwide and high altitude is considered to be elevations above 2500 meters (Moore et al; 1998). In our work the direct measurement of pO_2 values in the blood were done and revealed significant decline of pO_2 values in the arterial blood to18.646 mmHg, 15.964 mmHg,14.926 mmHg and 12.21 mmHg second, third, fourth and fifith groups respectevlly. These resultes are in agrement with (Gross, et al. 1995, Raleigh et al. 1998, Flueck. 2009 and Ivanovic. 2009) who reported that the hypoxia identified by direct measurement of pO_2 values and/or significant induction of hypoxia-inducible genes, suggest oxygen tension between 1% (-7 mm Hg) and 3% (-21 mm Hg) as physiological hypoxia. The animals are typically subjected to between 8% and 12% oxygen in order to significantly reduce arterial pO_2 to comparable values Fisher, et al. (2007).In our work the gradually diminition of the arterial pO_2 values between the treated groups and control one could be expand by stimulation of erythropoiesis. The mean arterial carbon dioxide pressure (PCO2) values were significantly increased to4.313 /mmHg, 3.891 / mmHg, 2.128/ mmHg and 0.405/ mmHg second, therd, fourth and fifith groups respectevlly.

In the present study, the light microscopic examination of the myocardium in the animals subjected to high altitude hypoxia revealed right ventricular hypertrophy, increased intracellular spaces, congested blood capillaries and areas of degeneration. This result was in agrement with that obtained by Barbera *et al.* (2000) which demonstrated that right ventricular wall thickness increases in response to pulmonary artery occlusion, which increase the systolic pressure load. The findings from this study suggested that the increase in heart size was primarily due to hyperplasia of cardiomyocytes, although some growth could be attributed to hypertrophy. Indeed, arterial hypertension in fetal sheep increases the weight of hearts, stimulates proliferation, size and binucleation of cardiomyocytes resulting in increased growth and accelerated maturation of the myocardium as a compensatory response to increased after load (Jonker *et al;* 2007). Therefore, ventricular wall mass is influenced by the hemodynamic stress under which it develops. Laplace's law explains the relationship between wall thickness and increases in the load. It states that increases in intraluminal pressure will produce increased wall stress for a given radius. It is compensated by increased wall thickness or decrease internal radius. This phenomenon is seen in individuals with pulmonary hypertension that increases the intraventricular end diastolic pressure resulting in thickening of the right heart wall.

In our work, the electromicroscopic finding includes disorganization of the micro filaments with areas of degeneration and z lines interruption or loss. This result is in agrement with that obtained by Singh

et al., (1980) who mention the changes of the cardiac muscle under effect of pressure overload and exercise stress included disorganization of myofibrils, disintegration and broadening of Z-bands, swelling and aggregation of mitochondria, electron-dense deposits in mitochondria, decreased cristal density and vacuolization of mitochondria, intracellular edema, margination and clumping of nuclear chromatin, and S-T segment elevation for the first 2-10 days after inducing pressure overload. Thus, the combined effect of pressure overload and exercise stress can produce focal subendocardial ischemia in the compensated, hypertrophied heart.

In the present study the mitochondria appeared in three grades: normal mitochondria, vacuolated mitochondria and degenerated mitochondria.These could be explained by the extent of damaging factors to the organelles where the organelles gets affected centrally by the damage lead to loss of its matrix with subsequent vacuolation and cavity formation. Furthermore, the organelles exposed to the damaging factors lead to loss of the outer membrane and subsequent degeneration. This result was in agrement with that obtained by Paparelli et al., (1992), Breschi et al., (1994), Soldani et al., (1997) and Marco et al., (2002). James (1997) reported that, an abnormal accumulation of collagen is a major distinguishing factor between physiologic and pathologic hypertrophy while an abrupt decrease in collagen concentration results in a ventricular remodeling similar to that of a heart in failure. In our work the collagen fibers were increased in the intracellular spaces particularly in the fifth group.

The hyper-chromate nuclei and indentation in the nuclear membrane was demonstrated with heterogeneous distribution of the nucleoplasm. These could also be explained by observation of Andrews &Porter (1973) who noticed the irregularity of the nuclear membrane after chronic exposure to hepatotoxic drugs and they attributed these results to the possibility of increased cellular activity.

Recommendations:

The myocardial structure of the rats affected by the high altitude hypoxia, in which the intracellular spaces are increased and the cardiomyocytes hypertrophy and includes disorganization of the micro filaments with areas of degeneration also the mitochondrial and nuclear alteration were clarified. So we invite more researches on the high altitude areas in the world.

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