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Research Article

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Study of Markers behavior in Myocardial Infarction

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ABSTRACT

Aim of the study: to determine disturbance in serum Thromboxane B2, CK, SGOT, LDH, NO and urinary catecholamine in acute myocardial infarction, and the effect of exercise on these parameters in patients with old myocardial infarction in order to be taken in account in any prophylactic regimen.
Subjects: Twenty normal subjects (aged 31.5 y) (g1), 15 males of AMI (aged 53.4 y) (g2), 15 male cases of old MI (aged 50.4 y) (g3).
Methods: Blood samples were obtained of each subject before and after exercise test in (g1 and g3), in case of (g2) in 1st 6 – 8 hrs. of onset of attack, and the second sample after 24 hrs. Estimation of thromboxane b2, CK, LDH, NO and urinary catecholamine was done using commercial kits. Statistical analysis was carried out using "t-test". Results indicated that: (g1) Thromboxane B2 showed a significant increase, (g2) increased at the 1st 6-8 hrs., then reduced after 24 hrs., (g3) increased in post exercise than pre-exercise. T. urinary catecholamine. There was a higher conc. in (g2) and (g3) than (g1). In case of serum enzymes (g1), there was an increased post exercise and in (g2), the increase was in 1st of 6-8 hrs. and 24 hrs.from 1st sample, (g3), the increase was in case of post exercise compared to pre-one. Nitrite increased in (g1) post exercise, (g2) non-significant change, also in case of (g3) non-significant change.
Conclusion: The natural inotropic agents increased after AMI, the serum thromboxane B2, CK, S-GOT, LDH, NO with urinary catecholamine beinggood markers in MI.

Key words: *Thromboxane B2, CK, SGOT, LDH, NO, catecholamine's, myocardial infarction.*

INTRODUCTION

Coronary heart disease occupies an eminent position among the different varieties of etiological factors of death. It is the first etiological factor of sudden unexpected natural death in adults (1; 2; 3). Proper understanding of various alterations occurred throughout the course of myocardial infarction, which direct our attention towards the early prophylaxis and treatment. Patients of myocardial infarction are subjected to 2 main hazards: a) occurrence of serious arrhythmias. b) Coronary thrombosis and occlusion. The first event is closely related at least in part to changes in serum catecholamines. While the second event is related at least in part to changes in balance between thrombogenic and antithrombogenic factors and disturbance of vasoactive of blood vessels. These two factors are regulated by various prostaglandins.

Prospective epidemiologic studies have shown that coronary vascular occlusion can account for only 50-60 percent of acute myocardial infarction- AMI- (4; 5). The Remaining has been attributed to myocardial metabolic disturbances not associated with coronary risk factors. Humeral and neurogenic influences are suspected to play a dominant role (6).

Catecholamine and thromboxane B2 are thought to be the main hormones incriminated in the pathogenesis of arteriosclerosis through their local and systemic metabolic effects. There is a good relation between urinary and blood catecholamine concentrations, hence estimation of urinary catecholamine is a reflection of its serum levels.

Numerous investigators have hypothesized that normal vascular integrity and function depend on a balance between thromboxane A2 and prostacyclin. The cardiovascular effect of prostaglandins is complicated by Qualitative species variations (8;9).

Because of these effects of thromboxane B2, serum CK, S-GOT, LDL, (NO) and catecholamines in ischemic heart disease, the present work aims to determine any disturbance in these parameters-serum thromboxane B2, serum CK, SGOT, LDH, NO; and urinary catecholamines in acute myocardial infarction; and the effect of exercise on these parameters in patients with old myocardial infarction in order to be taken in account in any prophylactic regimen-pharmacological or dietary-with the hope for reduction of morbidity and mortality of myocardial infarction.

SUBJECTS AND METHODS

Subjects:

Twenty normal subjects (group 1) were determined as control group, group (2) comprised 15 male cases of acute myocardial infarction, and group (3) comprised 15 male cases of old myocardial infarction affected more than three months with subsequent angina.

Written informed consent was obtained from all patients. The ethic review board for each respective participating center approved the protocol.

The control group's average age is 31.5 years who were volunteers for this study, group (2) has average age of 53.4 years, and group (3) has average age of 50.6 years.

Control group was not receiving any medication for one month before the study, while group (2) received morphine and nitroglycerin medication in the 1st 24 hours of the attack, group (3) received nitroglycerin 2 weeks before the test.

Subjects of group (1), group (3) were at least one week free of any medication or food comprise methyl dopa or banana, cheese or vanilla that may affect the catecholamine tests.

Group (2) have distinct ECG evidence defining location of AMI, defined by pathologic Q waves, normal values of creatine phosphokinase over the ensuing 12 hours, or ECG evidence of previous myocardial infarction, group (3) have distinct ECG evidence of definite old myocardial infarction defined by pathologic Q waves.

Methods:

Blood samples were obtained from the ante-cubital vein of fasting subjects before and after exercise stress test in case of group (1) and group (3), while in case of group (2), blood samples were obtained in the 1st 6-8 hours of the onset of the attack, and the second sample after 24 hours from the previous one.

Blood samples were collected in polypropylene test tubes, the sera were isolated, frozen and stored in freezer (-20ºC), collected sera were subjected for estimation of nitrite (10), prostaglandin B2, using Elisa technique (11). Together with CK, S-G-OT and LDH enzymes by spectrophotometer (12), urinary samples were collected (24 hours), sample to which concentrated HCl were added as preservative for catecholamine analysis (13). Estimation of

serum thromboxane b2 was done using Elisa technique, commercial kit.Estimation of catecholamine in urine was carried out using commercial kit and fluorimeter.Also, estimation of the enzyme CK, S-GOT and LDH was done using commercial kit and spectrophotometer.

Exercise stress test:

Equipment: A bicycle ergometer, an electrocardiograph, blood pressure instrument and pulse meter for pulse rate detection and stop watch as a timing device, also appropriate emergency medication, and appropriate emergency medication, and an oscilloscope.

The subjects were fasting.

A resting ECG was done and a blood sample taken.

Adjustment of the position of the subject on the bicycle ergometer.

The blood pressure cuff and the electrodes were attached.

Bicycle ergometer was initiated using 25 watts' load, then increased every 2 minutes by 25 watts' load. The speed 50-60 rpm, and recording the parameters in second half of second minute.

At the end of the test, the subject continued to pedal slowly at low intensity load.

V5 and a complete ECG was tested together with a second blood sample was drawn from the vein.

The stress test was performed for the control group (1) and group (3) untrained myocardial infarction patients were not stressed more than 125 watts' load on the bicycle. Also, the same for control group. The test was terminated when sign of chest pain, dysnea, ectopic beats or exhaustion occurred. Positive response with horizontal S-T segment depression or in case of 1mm or more from J point, or when R wave amplitude in V5 was increased.

Statistical analysis:

The obtained data was statistically analyzed using (t-test) according to Tamhane and Dunlop (14). The results were expressed as means ± SEM (standard error of means). Significant differences were expressed; $P < 0.05$ values were considered significant.

RESULTS

Table (1): Clinical data of subjects

Groups (No. of cases)	Mean age (Y)	Hypertensive cases	Time of AMI attack	Site of infarction and (cases No.)
Control No. (20)	31.5 26 – 35 (average)	-	-	-
Group (2) No. (15)	53.4 42 – 64 (average)	8	Within 6 – 8 hours	Diaphragmatic (7) Ext. anterior (8)
Group (3) No. (15)	50.6 44 – 57 (average)	4	3 months	Diaphragmatic (6) Ext. anterior (9)

Table (1) indicating clinical data and cases No. in the three groups.

Control group AMI group Old MI group

Table (2): Post exercise test ECG changes in group (3)

Group	ST segment depression (NO)	Change in R wave in V5 (NO)	Total (+) ECG (NO)	Chest Pain (NO)

Group (3) No. (15)	13	Unchanged (2) Increased (11) Decreased (2)	13	7

Table (2) indicating post exercise test ECG changes in group 3.

Table (3): Serum TxB2 values (pg/ml) in control and group (2) AMI

TxA2	Control	Group (2)
mean ± Se	79.2 ± 12.4	204 ± 14.5*

Control group pre-exercise values.

Group (2): 6 – 8 hrs. after the onset of attack. The results indicated significant increase in case of group (2) compared with the control.

Table (4): TxB2 values in pre-myocardial infarction (angine) of group (3) compared to post myocardial infarction group (3) AMI

Prostaglandin	Group 3a	Group 3b
TXb2 mean ± Se	171.2 ± 6.2	196.3 ± 7.8*

The results indicated a significant change of prostaglandin TXb2 value in the comparison.

pre-exercise. Post exercise.

Table (5): Serum thromboxane b2 (pg/ml) in the three groups

Groups	Control		Group (2)		Group (3)	
	a	b	a	b	a	b
mean ± Se	79.2 ± 11.4	102 ± 12.3	204 ± 14.5	186 ± 9.7	171.2 ± 6.2	196.3 ± 7.8

(g1) control group a) pre-exercise. (g2) AMI group b) post exercise.

(g3) Old MI group For AMI group: a) sample of 1st 6-8 hours after attack.

b) sample after 24 hours of the previous one.

Table (6): Pre-exercise thromboxane b2 (pg./ml) in control and group (3)

Group	Control	Group (3)
mean ± Se	79.2 ± 12.4	171.2 ± 6.2*

There are statistical significant changes of control thromboxane b2 compared to values of groups (3) pre-exercise.

Table (7): Post exercise thromboxane b2 (pg/ml) in control and group (3)

Group	Group (1)	Group (3)
mean ± Se	102 ± 12.3	196.3 ± 7.8*

There are statistical significant changes of control thromboxane b2 compare to values of (G3) post exercise.

Table (8): Catecholamine's 24 hours' urine output (μg/24 hrs) concentration in the three groups

Groups	Control	Group (2)	Group (3)
mean ± Se	198.1 ± 42.2	512.7 ± 61.4*	684.6 ± 39.5*

There are statistical significance changes in urinary catecholamine concentration of control group compared to (group 2) and group (3).

Table (9): Studied enzymes values (IU/L) in control and group (2) AMI

Enzymes	Group (1)	Group (2)
CK (IU/L)	16.4 ± 1.8	82.3 ± 7.4*
S-GOT (IU/L)	9.3 ± 1.4	39.5 ± 5.1*
LDH (IU/L)	125.6 ± 10.7	509.3 ± 13.3*

Control group pre-exercise values of enzymes group (2) 6 – 8 hrs. after the onset of attack.

Table (10): Enzymes values in the three groups before and after exercise test

Enzymes	Control		Group (2)		Group (3)	
	a	b	a+	b+	a	b
CK (IU/L)	16.4 ± 1.8	44.3 ± 4.2	82.3 ± 7.4	99.8 ± 6.3	60.1 ± 4.6	7.15 ± 6.3
S-GOT (IU/L)	9.3 ± 1.4	16.6 ± 2.2	39.5 ± 5.1	52.6 ± 4.7	28.7 ± 3.5	36.1 ± 5
LDH (IU/L)	125.6 ± 10.7	234.1 ± 12.3	509.3 ± 13.3	564.1 ± 11.6	321 ± 9.4	351 ± 10.3

Table (10) indicated enzymes values in the three groups.

Group (1) enzymes increased significantly after exercise.

Group (2) (a+) enzymes revealed a high level at 6 – 8 hours of AMI and reach a peak after 24 hours (b+).

Group (3) enzymes increased after exercise.

Table (11): Serum nitrite (Uμ) in the three groups studied

Groups	Control		Group (2)		Group (3)	
	a	b	a+	b+	a	b
mean ± Se	44.2 ± 11.3	56.3 ± 12	30.3 ± 8.2	32.2 ± 9.1	36.4 ± 9.4	38.9 ± 8.7

a = pre-exercise. b = post exercise.

a+ = 6 – 8 hrs. after attack b+ = sample after 24 hrs of the previous one.

$P < 0.05$.

DISCUSSION

Thromboxane A2 promotes platelet aggregation and vasoconstriction, whereas prostacyclin inhibits platelet aggregation and promote vasodilation. The balance between platelet thromboxane A2 and prostacyclin fosters localized platelet aggregation and consequent clot formation, while preventing excessive extension of the clot and maintaining blood flow around it. Since prostaglandins are powerful modulators of vascular smooth muscle tone and platelet aggregation, their potential role in the development of atherosclerosis and mediators of various clinical manifestations of ischemic heart disease is conceptually appealing. Cardiovascular diseases associated with stress mediated by catecholamine induced activation of platelets and thromboxane TA2 production all together promote cardiac infarction.

In Table (5), the results indicated that thromboxane B2 increased in case of normal persons after exercise and a further increase was noted in cases of AMI, which was highly significant. However, the increased thromboxane TXb2 is not harmful as it is an instantaneous increase with exercise compared to the highly significant increase in thromboxane TXB2 when compared to that of the normal. It is well known that thromboxane A2 is converted spontaneously the thromboxane B2, an inactive compound with sufficient stability to allow its quantitation. The results indicating that thromboxane TXb2 is released in excess at the onset of an attack of AMI. These findings are in accordance with the results of Giampaolo et al., (15); Kusama et al., (16); Walles et al., (17), after 24 hours' values of thromboxane TXB2 showed significant decline. Release of thromboxame TXB2 at the onset of AMI can be induced by coronary vasospasm or myocardial ischemia (18). The released thromboxane TXb2 at the onset of AMI may influence the extent of the infarct. Mehta et al., (9) and Paul Walinsky, (19) concluded that generation of the thromboxane A2 occurs during the early stages of AMI and may be an important pathophysiologic phenomenon A in AMI.

TXA2 release also in considered as a mediating factor in the development and maintenance of high blood pressure due to its vasoconstrictor effect

In case of post myocardial infarction in group (3), there was a high significant increase in thromboxane TXA2 at rest and after exercise when compared to normal values (Table 5). This can be explained that platelets of the pathological group (3) are hyper-reactive with increased thromboxane TXA2 production, which may be the cause of increased platelets activation and subsequent platelets plugging.

The above analysis of the results may indicate that the increased thromboxane may increase the extent of the infarct size through local vasospasm and platelet plugging, which may transform the ischemic zone to complete occlusion. Thromboxane TXA2 may be considered as determinants for susceptibility of AMI survivors to angina pectoris.

Many researchers tried to reduce the infarct size through different measure, using FX06 (22) or fibrinogen and its fragments (23), adenosine Kloner et al., (24), a fibri-derived peptide β beta (2007), and intravenous fluosol (25), or through the blockade of the CD11/ CD18 integrin receptor (26).

The results of urinary catecholamines (Table 8) indicated arise of the normal subjects after the stress test, which may be due to the action of stresses of exercise, in case of AMI, urinary catecholamine increased significantly to a very high level. This result is in accordance with that of Bucsneag et al. (13); Lionel, (27); Sharma, (28). The increased urinary catecholamines can be explained by the fact that the infarcted myocardium loses 75% of its catecholamine content within the first 24 hours (29). The increased catecholamines reflect the body reaction to stress associating recurrence of infarction. Hence, the most important is suggested to be the psychological stress resulting in excessive secretion of catecholamine, which may be injurious to the myocardial infarction and may have a relation to both infarct size and the incidence of arrhythmias (30; 31).

As regard group (3), urinary catecholamines showed a higher significant increase compared to the control subjects (Table 8). This result is in accordance with the results of Kohn et al. (32), the increased catecholamine might be due to psychological reactions, tension and anxiety, which may be some causes of the resulted neurohormonal increment (33; 34).

They reported that sympathetic stimulation, which releases nor epinephrine and epinephrine, increases the rate of metabolism of the heart which sets off local blood flow regulatory mechanisms which increases this blood to increase metabolic needs of the heart muscles.

The increased urinary catecholamines responses may be a critical factor in the metabolic process leading to myocardial infarction (35).

Thus, these results suggest that post myocardial infarction subjects who usually sustain high level of stress life or high reactivity to usual stresses, have elevated catecholamine excretions level and may be more susceptible to excessive angina pectoris (36).

Hatfield (37) reported that a number of extensive clinical studies have identified the major risk factors for heart disease such as old age, family history, cigarette smoking, hypertension hypercholesterolemia, diabetes mellitus, Sedentary life style and physical inactivity and obesity and jobs involving sitting for a large part of the day and no recreational pursuit, all these risk factors leading to susceptibility to stress and increasing stress hormones mainly catecholamines and psychological pathology affecting the heart muscle leading to myocardial infarction and heart attack.

In the present study, serum nitrite in case of the control group increased after the stress test due to increased effect of exercise on serum nitrite which is turn induced vasodilation and increased cardiac output (Table 11). This was also recorded by Schnerman (38) indicating that exercise stress test increased blood volume by supplying to the heart and skeletal muscle to compensate the decreased O2 utilization occurring due to hypoxia. In cases with AMI, serum nitrite level in the 1st 6-8 hours of begin of symptoms, showed a significant decreased serum nitrite when compared with control, then increased the serum nitrite after 24 hours'non-significant values. These results indicated that MI led to a lower concentration of serum nitrite 6-8 hrs of the attack and 24 hrs. of the previous attach,and there was a slight increase in serum nitrite.

In case of the post myocardial infarction group (3), both pre-and post-exercise serum nitrite showed a lower level compared to the control group. This can be explained by the pronecity of these patients to multiple stress conditions or they being hyper-reactors to successive stresses. As the post exercise serum nitrite was non-significantly higher than the recorded levels of pre exercise tests.

Barrett et al. (39) stated that serum nitrite is one of the inhibitors of endothelin-1-secretion, which is known by its powerful vasoconstriction activity, they may in part decrease its action in case of myocardial infarction and congestive heart failure and may play a role in the pathophysiology of these diseases.

Ganong (40) reported that nitrates often produce prompt relief of the pain in angina pectoris. These substances dilate normal arterial vessels, and even through atherosclerotic coronary arteries are generally too rigid to dilate to any degree, large doses produce dilation of coronary arteries with eccentric stenosis. However, the main effect of nitrates is to decrease venous return to the heart. This reduces stroke volume and consequently myocardial O2 consumption is reduced. The decreased venous return is secondary to dilation of peripheral veins, with pooling of blood in the periphery.

Renata S. (41) states that regular exercises significantly increase release of nitric oxide (NO), probably the most important and characteristic mediator, and its intrinsic vasodilator function is commonly used as a surrogate index of endothelial function. Training also results in the decreased sensitivity to the vasoconstrictor effects of nor epinephrine. Probably the signal for adaptation may be peak shear stress during exercise and average shear stress over a 24 hours' period of time (42).

Enzymes are important group of biomolecules synthesized by the living cells. They are catalysts of biological systems. They are remarkable molecular devices that determines the pattern of chemical transformations. They also mediate the transformation of different forms of energy. Enzyme assays that are carried out in myocardial infarction commonly done are: creatine phosphokinase (CK), Aspartate transaminase (S-GOT) or (AST) and lactate dehydrogenase (LDH).

Table (10) revealed an elevated enzymes assays after the stress exercise test of the normal subjects. Stress test may influence the enzymes release as a response to the exercise, responsible of the elevated results as severe physical exertion may affect the release (43).

A marked increase in acute myocardial infarction of (CK) together with aspartate transaminase (AS-T) (S-GOT) and lactate dehydrogenase (LDH) was noticed in Table (10), which was also noted by (44; 45; 46). Mougios (47) stated that creatine kinase catalyzes the interconversion of CO and ATP, they are present in the heart, skeletal muscle and smooth muscle and brain, the serum CK concentration rises when an organ that contains the enzyme is damaged as in case of acute myocardial infarction, the same occurs in case of aspartate aminotransferase (AST) and lactate dehydrogenase (LDH).

Table (10) revealed the mean values of the studied enzyme (CK, S-GOT and LDH) in cases of group (3) of old MI, which were higher than the normal subjects after the stress test exercise and lower than cases of AMI, due to the severe constriction and platelets aggregation in the latter group. The high levels of the studied enzymes in case of myocardial infarction and old MI may be a critical factor in the metabolic process leading to myocardial ischemia

due to the injury affecting the heart, which affects its metabolism, major modifications in the metabolism of the studied enzymes and the Thromboxane b2 together with catecholamines have already been found after acute myocardial infarction in man and experimental data suggest that such metabolic changes might play a role in the modification of infarct size and sometimes of arrhythmias (48; 49). Barrett et al. (39) added that in the absence of emergy treatment, ventricular fibrillation that lasts more than a few minutes is fatal. The most frequent cause of sudden death in patients with myocardial infarct is ventricular fibrillation.

Percutaneous coronary intervention (PCI) have been used to evaluate the long-term effectiveness and cost efficacy of drug eluting stent by many researchers. Jonas et al. (22) used FX06 in acute ST elevation myocardial infarction and also Atar et al. (50) measured the effect of FX06 (a fibrin-derived peptide β beta (15 – 42) in patients with myocardial infarction, Zacharwski et al. (23) used fibrinogen and its fragments in patients, Kloner et al. (24) the efficacy of adenosine, Wall et al. (25), Intravenous fluosol in the treatment of MI, Faxon et al. (26),the effect of blockade of the CD11/CD18 integrin receptor on infarct size in patients with MI, Simpson et al. (51) prostaglandins protects ischemic reperfusion myocardium by inhibition of neutrophil activation, Veldt et al. (52), the Gadolinium enhanced cardiovascular, Magnetic Resonance evaluation of infarct size and microvascular obstruction after MI. Many different drugs have been developed that are used in the treatment of arrhythmias because they show conduction in the conduction system and the myocardium.

However, it has now become clear that in some patients, any of these drugs can be proarrhythmic rather than antiarrhythmic. Therefore, they are increasingly being replaced by radiofrequency catheter ablation for the treatment of arrhythmias.

Studying the role of drugs, and food that inhibit release of thromboxane TXA2, catecholamine in the prevention and management of the ischemic heart attack is recommended along with prevention of the disease by regular exercise and better lifestyle.

CONCLUSIONS

The natural inotropic agents are found in increased amounts after acute myocardial infarction. Our experimental data show a role of thromboxane TXb2, catecholamines and enzymes affecting heart muscles (CK, S-GOT, LDH) and NO in myocardial infarction.

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