ISSN 0975 - 6299 Vol 2 / Issue 4 / Oct - Dec 2011

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE

BIO CHEMISTRY

ROLE OF XANTHINE OXIDASE, LIPID PEROXIDATION AND URIC ACID IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

PRAMOD KAMBLE[*1], DHIRAJ J. TRIVEDI[2], ANIL BARGALE[3], VIJAY PANDHARE[4], PRAKASH ZENDE[5] AND PRADNYA PADALKAR[6]

[1,2,3] Department of Biochemistry, SDMCMSH, Dharwad, Karnataka, India.
[4] Department of Biochemistry, GCSMC, Ahmadabad, Gujarat, India.
[5] Department of Biochemistry, MC, Ahmednagar, Maharashtra, India
[6] Department of Biochemistry, BVUMC, Pune, Maharashtra, India

PRAMOD KAMBLE
Department of Biochemistry, SDMCMSH, Dharwad, Karnataka, India

*Corresponding author

ABSTRACT

The aim of our study is to determine the effects of alcohol intake and cigarette smoking on the activity of Xanthine oxidase (XO), Lipid peroxidation (LPO) and Uric acid in patients with Acute Myocardial Infarction (AMI). This study includes 60 patients of AMI [smokers (n=15), non-smokers (n=15), alcoholics (n=15) and non-alcoholics (n=15)] and 30 normal controls. Xanthine oxidase, Lipid peroxidation and Uric acid levels in smokers, nonsmokers, alcoholics, non-alcoholics and controls are (34.6±2.9, 33.8±2.4, 34.6±2.8, 33.9±2.5, 30.3±1.2), (5.45±0.75, 5.34±0.86, 5.07±0.82, 5.71±0.61, 2.39±0.82) and (6.24±0.36, 5.78±0.86, 5.78±0.85, 6.24±0.37, 5.2 ±1.82) respectively. Our result shows that the levels of XO, LPO and uric acid in smokers are elevated than controls. Regarding alcoholics there is no significant difference in the study parameters. Therefore, these results mainly focus towards smoking habit which can be an additional factor to enhance the severity of AMI.

ISSN 0975 - 6299 Vol 2 / Issue 4 / Oct - Dec 2011

KEYWORDS

Smokers, Alcoholics, Xanthine oxidase, Lipid Peroxidation

INTRODUCTION

Heart disease is the leading cause of death in the world, accounting for more than 30% of total deaths, most of which are due to Acute Myocardial Infarction (AMI). Total number of myocardial infarction related death rates in the world has not declined. The heart disease remains responsible for loss of younger life regardless of gender or race than any other illnesses. The incidence rate among Indians is the sum of fatal and nonfatal attack rates[1,2].

AMI is the term used to describe irreversible injury and necrosis of myocardium of heart muscle, as a consequence of cessation of blood flow producing a complex series of metabolic events with abrupt decrease in coronary blood flow. This follows thrombotic occlusion of coronary artery by atherosclerosis and leads to AMI[3, 4].

Many events occur during reperfusion in the calcium dependent activation which has a damaging effect on cell membrane causing release of free fatty acid. The activity of phospholipases enzyme will release membrane fatty acids including arachidonic acid, which is metabolized by enzymatic oxidation which can result in production of radical species and other cytotoxic products on reperfusion. Cyclooxygenases and lipooxygenases which act on free fatty acid have been shown to produce hydroxyl radical and peroxyl compound. These intermediates exacerbate tissue damage on reperfusion[5]. This metabolism by specific lipooxygenases can result in the formation of mono and dihydro peroxy fatty acids, both of which are capable of initiating further tissue damage under reoxygenated condition[6]. When heart reperfused, there is lysis of endothelial cells and increase in conversion of xanthine dehydrogenase to xanthine oxidase. Therefore, xanthine oxidase has special importance in different diseases including AMI.

Uric acid is the end product of purine metabolism in human. Xanthine oxidase is responsible for the final oxidation of xanthine to uric acid[7]. Khosla et al 1965 postulated that hyperuricemia in cases of AMI is strong diathesis which predisposes to ischemic hearth disease in a similar fashion to cholesterol [8]. However, exact role of serum uric acid in pathogenesis remains to be established. Lal & Lal 1963 have found the occurrence of raised serum uric acid coinciding with the death of myocardium in case of AMI[9]. Sriwastava et al 1975 reported that breakdown of other hypoxic muscle tissue will give rise to high uric acid levels[10]. Therefore, we have planned to study the role of Lipid Peroxidation, Xanthine Oxidase and uric acid in AMI.

MATERIAL AND METHODS

The present study includes 60 cases of confirmed diagnosis of AMI and normal healthy controls. All patients and controls were in the age group 35 to 65 years and they were divided into following groups

Group-A (n=30): smoker (n=15) and nonsmoker (n=15).

Group-B (n=30): alcoholic (n=15) and nonalcoholic (n=15).

Group-C (n=30): normal controls.

Patients with history of hyperuricemia, diabetes, renal diseases, hypertension, cardiovascular illness, and symptomatic infectious diseases were excluded from the control group. All the healthy normal

individuals were symptomless with no history of any complications.

The study parameters such as serum Lipid peroxidation, Xanthine Oxidase and Uric Acid were estimated by following methods;

1. Estimation of serum lipid peroxides: By Colorimetric METHOD[11].
2. Estimation of Serum Xanthine Oxidase: By Spectrophotometric method[12]
3. Estimation of Serum Uric Acid: Uricase-PAP method[13].

The results were expressed as mean ± SD and analyzed by student t-test.

Table No – 1
Biochemical indices and free radical activity in AMI patients and Controls

Groups	Habits	Xanthine Oxidase (Units/L)	Lipid Peroxide (nmol/mL)	Uric Acid (mg/dL)
Group A	Smoker	34.6 ± 2.9	5.45 ± 0.75	6.24 ± 0.36
	Non-smoker	33.8 ± 2.4	5.34 ± 0.86	5.78 ± 0.86
Group B	Alcoholic	34.6 ± 2.8	5.07 ± 0.82	5.78 ± 0.85
	Non-alcoholic	33.9 ± 2.5	5.71 ± 0.61	6.24 ± 0.37
Group C	Controls	30.3 ±1.2	2.39 ±0.82	5.22 ± 1.82

RESULTS & DISCUSSION

AMI is a major cause of mortality in developed as well as developing countries. It is a disease of multifactorial origin, in which a gross necrosis of myocardium occurs due to interruption of blood supply to the tissues. Ross in 1993 propounded the oxidation hypothesis of atherosclerosis, wherein under scored the significance of oxidative modification of LDL and its possible obligatory role in the pathogenesis of the atherosclerotic lesions[14].

Table No. 1 shows the demographic criteria and Biochemical parameters of AMI patients and controls. The levels of LPO between alcoholic (5.07 ± 0.82), nonalcoholic (5.71 ± 0.61), smoker (5.45 ± 0.75) and nonsmoker (5.34 ± 0.86) patients were significantly increased as compared to controls (2.39 ± 0.82). Interesting finding was that the level of LPO showed two fold increase in patients than controls. The free radicals generated in oxidative stress and exogenously entered free radicals by heavy cigarette smoking can cause vascular endothelial dysfunction. The lipid peroxidation occurs as a damaging reaction consequent to free radical production in cells. Chain reactions can directly damage the structure of membrane and indirectly damage the cell components by superoxide radicals[15].

The difference in the levels of xanthine oxidase between alcoholic (34.6 ± 2.8) and nonalcoholic (33.9 ± 2.5) patients are not much compared to controls (30.3 ±1.2) which reveals that alcohol intake may not have any effect on serum xanthine oxidase activity. The xanthine oxidase level in smokers (34.6 ± 2.9) and nonsmokers (33.81 ± 2.4) are marginally elevated as compared to controls (30.3 ± 1.2).

Xanthine oxidase, an iron-sulfur molybdenum flavoprotein, is a multifunctional enzyme present in high concentrations in endothelial cells of capillaries and sinusoids[16]. It exists in two interconvertible isoforms, xanthine dehydrogenase and xanthine oxidase. The dehydrogenase form of XO produces uric acid and reduced NAD^+, and the oxidase form

produces oxygen free radicals, uric acid, and superoxide[17].

The calcium dependant activation of phospholipases occurs by unknown mechanisms. Endothelial cell membrane damage results in the production of free fatty acids including arachidonic acid [5]. The production of reactive oxidant species may be from Cyclooxygenases or xanthine oxidase. The role of cyclooxygenase activity in the evolution of myocardial injury requires further study. Neutrophils accumulate in the vascular space of reperfused ischemic myocardium, where they may adhere to the endothelium and release oxygen free radicals[7]. Although there are multiple stimuli for neutrophils migration, one chemo attractant may arise from the interaction of plasma lipids with oxygen free radicals derived from the activity of Cyclooxygenases or xanthine oxidase on their respective substrates[15].

Xanthine oxidase activity is increased in ischemia, reperfusion injuries, anoxia, and inflammation[18]. This may occur by lysis of endothelial cells and increased conversion of the dehydrogenase form to the oxidase form of xanthine oxidase[19]. Superoxide radicals undergo dismutation reaction to hydrogen peroxide, which has been proposed to be the major oxygen radical which responsible for endothelial damage by the xanthine oxidase. Vascular endothelial cells get damaged by ischemia due to which there is a release of xanthine oxidase into the plasma during reoxygenation or reperfusion[20]. During reperfusion, there is release of histamine which increases the catalytic activity of xanthine oxidase in the plasma as well as intact endothelial cells[21]. The combined result of all these events can be endothelial cell damage resulting in leakage of xanthine oxidase into the plasma.

Serum uric acid level in smokers (6.24 ± 0.36) and non smokers (5.78 ± 0.86) are marginally elevated as compared to controls (5.22 ± 1.82). But, there are no much differences in between smokers and non smokers. In our study, the lack of difference in the levels of uric acid in AMI patients is compared with controls. It can argued that the sample of our study is too small to investigate association of hyperuricemia with AMI.

Potential mechanisms involved with the association of hyperuricemia and AMI includes decreased renal blood flow stimulating urate reabsorption, micro vascular disease resulting in local tissue ischemia[22]**.** It is associated with increased lactate production that blocks urate secretion in the proximal tubule and increases uric acid synthesis due to increased RNA-DNA breakdown as a result of endothelial cell damage and increased purine metabolism, ultimately increases uric acid and ROS through the effect of xanthine oxidase (XO)[23].

We studied the impact of cigarette smoking and alcohol intake in patients with AMI and we found that smokers are more prone to develop AMI than alcoholics. The precise mechanism which is responsible to develop AMI by cigarette smoking remains undetermined. Future studies may be taken to investigate the potential cigarette smoke-inducible endogenous cellular mechanisms for better understanding of the complex pathobiology of cigarette smoke and cardiovascular dysfunction.

REFERENCES

1. Kaplan, Pesce AJ, Clinical Chemistry Williams & Wilkins, 200 ChesterField Parkway Malvern P A 19355 US, (1984).
2. Oliver MF, Diet and coronary heart disease, Br. Med. Bull, 37(1): 49-58, (1981).
3. Wygnaarden JB, Smith LH and Bennett JC: Cecil Textbook of Medicine WB Saunder 19th edn, Vol-1, Company Harcourt Brace Jovanovich, INC Philadelphia London, (1992).
4. Cheesman KH, Slater TF, Free radicals in medicine: British Medical Bulletin, 49/3: 481-493, (1993).
5. Bersohn MM, Philipson KD, Y FJ. Sodium calcium exchange and sarcolemmal enzymes in eschemic rabit hearts, Am. J. Physiol, 242: 288-295, (1982).
6. Hammond B, Kontos HA, Hess ML, Oxygen radicals in the adult respiratory distress syndrome in myocardial ischemia and reperfusion injury and in cerebral vascular damage, Can J Physiol Pharmacol, 63: 173-187, (1985).
7. Ángel Chamorro, MD; Victor Obach, MD; Álvaro Cervera, Prognostic Significance of Uric Acid Serum Concentration in Patients With Acute Ischemic Stroke, Stroke 33; 1048-1052, (2002).
8. Khosla HL, Caroli RK, Gupta SA. J, Asso. Physicians India, 13: 909, (1965).
9. Lal HB and Lal H: Serum uric acid in MI, J. Ind. Med. Asso, 40: 447, (1963).
10. Dosman JA, Crawhall J C, Klassen GA, uric acid kinetic studies in the immediate post MI, Metabolism, 24: 473-480, (1975).
11. Esterbauer H, Cheeseman K. determination of Aldehydic lipid peroxidation products: malonaldehyde and 4-hydoxynoneal methods enzymol, 186: 407-421, (1990).
12. Jensen M H, Jorgensen S: metabolites-2: di and tri carboxylic acid, purines, pyrimidines, derivatives, coenzymes and inorganic compounds, methods of enzymatic analysis 3rd edn, Vol -VII. Editor Bergmeyer publisher.
13. Biolab diagnostics: estimation of uric acid (Uricase-PAP method), J-245 MIDC tarapur, Bolsar. 401501 India.
14. Ross R. the pathogenesis of atherosclerosis: A perspective for the 1990s, Nature, 362: 801-809, (1993).
15. Sashi Guthikonda, Christine Sinkey, Therese Barenz and William G. Haynes, Xanthine Oxidase Inhibition Reverses Endothelial Dysfunction in Heavy Smokers, Circulation 107;416-421, (2003).
16. Ohman EM, Casey C, Bengston JR, et al. Early detection of AMI: Additional diagnostic information from serum concentration of myoglobin. B.H.J. 63, 1542, (1993).
17. Zabel M, Hohnloser S H, Koster W et al, Analysis of creatine kinase (CK-MB), myoglobin and troponin T time activity curves for early assessment of coronary artery reperfusion after intravenous thrombolysis, Circulation, 87: 1542, (1993).
18. Mair J, Morandes D, Genser N et al, Equivalent early sensitivities of myoglobin, Creatine kinase MB mass creatine kinase isoforms ratios, and cardiac troponins I and T for acute myocardial infarction, Clin Chem, 41: 1266, (1995).
19. Gore JM, Goldberg RJ, Matsumoto AS, et al, Valding of serum total cholesterol level obtained within 24 hrs of AMI, Am J Cardiol, 54: 1651, (1984).
20. Achtaberg PW, Nieukoop AS, Schoutsen B, de Jang JW, Different ATP-catabolism in reperfused adult and newborn ret hearts, Am J Physiol. 254: 41091-41098, (1988).
21. Friedl HP, Till GO, Trentzn O, Ward PA, Roles of histamine, compliment and xanthine oxidase in thermal injury of skin, Am. J Pathol, 135: 203-217, (1989).
22. Guzy P M, creatine phosphokinase-MB (CPK-MB) and the diagnosis of myocardial infarction. West. J. Med. 127: 445-460, (1977).
23. Cheesman KH, Slater TF: Free radicals in medicine, British Medical Bulletin, 49/3, 481-493, (1993).