CERTIFICATE

I, **DR. K. P. BALAKRISHNAN** here by declare that I have actually performed all the procedures listed / carried out the project under report

Signature.....

Name in Capital letters.....**DR. K. P. BALAKRISHNAN**

Place : **TRIVANDRUM**

Date : 4/4/'99

Forwarded. He has carried out the minimum requirement of procedures / etc.

Signature
Head of the department

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY THIRUVANANTHAPURAM - 695 011	Name	
	Page	of
	Date	

PROJECT REPORT

TITLE OF THE PROJECT: **1. THE CLINICAL PROFILE OF CARDIAC MYXOMA AND THE LONG TERM POST OPERATIVE FOLLOW UP**

2. STUDY OF TRACE ELEMENTS IN AETIOLOGY OF CORONARY ARTERY DISEASE

NAME ..... **DR. K. P. BALAKRISHNAN**

PROGRAMME ..... **DM CARDIOLOGY**

MONTH & YEAR OF SUBMISSION ..... **NOVEMBER, 1999**

SREE CHITRA TIRUNAL INSTITUTE FOR
MEDICAL SCIENCES & TECHNOLOGY
THIRUVANANTHAPURAM - 695 011

Name	
Page	of
Date	

CONTENTS

The Clinical Profile of Cardiac Myxoma and The Long Term Post Operative Follow up

Introduction

INTRODUCTION

In the last 40 yrs, cardiac neoplasms have progressed from clinical curiosities with diagnosis mainly at autopsy to fairly rapid antemortem diagnosis and curative surgical therapy, thanks to the advent of cardiac imaging. Cardiac neoplasms may be divided into primary and secondary or metastatic tumours, of which the latter are far more frequent than the former by at least 30:1 ratio (1,2,3,4) in various autopsy studies.

Among the primary neoplasms, myxomas are the most common, comprising 30 to 50% of the total in most of the pathological series (1,3,4). Approximately 75% of myxomas occur in the left atrium and over 90% are solitary (4,5). Around 23% of myxomas occur in the right atrial cavity and about 2% in the venticular cavity (6,7,8,9,10,11,12,13). On rare occasion myxomas can occur in more than one cavity (14) or as multiple tumours. The cell of origin of myxoma is still unclear (15). How fast atrial myxoma grows is also to be clarified. In atrial myxomas the usual site of attachment is in the area of fossa ovalis. Although myxomas can occasionally occur on the posterior left atrial wall this site is reported to be particularly uncommon, so that a search for malignant

lesion is adviced. Myxomas of the mitral and tricuspid valves are also reported, but are rarities (16,17).

Familial cardiac myxomas constitute approximately 10% of patients with myxoma and transmission is autosomal dominant (18,19,20,21). The familial myxomas occur in younger patients and they have less female gender predominance when compared to the nonfamilial ones in which the females dominate at a ratio of 7:3. The familial myxomas tend to be multiple and tend to have a ventricular location (13% when compared to 2% in nonfamilial). These familial myxoma patients tend to have a syndromic phenotype and hence are grouped under syndrome myxoma or Carney Syndrome, which consists of myxomas in other locations, lentigines / pigmented naevi and endocrine tumours (22,23,24). Two syndrome complexes NAME (25) [Naevi, atrial myxoma, myxoid neurofibroma, ephelides) and LAMB (26) [Lentigines, atrial myxomas, blue naevi] are associated with the familial variety of cardiac myxoma.

Myxomas present the most variant clinical picture of all primary cardiac neoplasms (7,9,10). Several major symptoms have been observed including presentation with systemic / pulmonary embolism, obstruction to blood flow and various constitutional syndromes. Clinically myxomas

can mimic valvular stenotic and / or regurgitant lesions and can masquerade signs and symptoms of infective endocarditis, collagen vascular disease or occult malignancy. The constitutional symptoms associated with myxomas are protean and include fever, weight loss, Reynaud's phenomenon, digital clubbing, anaemia and features like elevated ESR, elevated leukocyte count, decreased platelet count, positive C creative protein and hypergammaglobulinaemia.

The proper treatment of myxoma in any cavity of the heart is operative resection (6,11,27,28). Most surgeons advice a biatrial approach for full visualization of both sides of the heart for complete removal of an atrial myxoma excising the full thickness of septal attachment of myxoma producing an iatrogenic ASD which is then closed by pericardial patch. Recurrence of atrial myxomas are rare (1-5%) and if they do occur it is usually within 4 years after initial resection (29,30). Numerous reports document complete cure of atrial myxomas with follow up periods of 10-15 years (31,32,33,34,35,36). Possible causes of recurrence include incomplete excision, growth from a second pretumorous focus or intracardiac implantation from the original tumour. Hence careful echocardiographic follow up for detection of recurrence is

recommended in all patients following surgical resection of myxoma (30).

We reviewed the clinical profiles of cardiac myxoma patients who attended our centre on a retrospective basis and evaluated their long term surgical outcome.

Aim of the study

AIM OF THE STUDY

To evaluate all patients with histopathological diagnosis of cardiac myxoma, retrospectively to find out the clinical profile and long term surgical outcome.

Materials and Methods

MATERIALS AND METHODS

Subjects :- We analyzed the case records of all patients who had undergone surgical excision for cardiac mass during the period of 1988-1999 and identified patients with diagnosis of cardiac myxomas. These patients were taken up for retrospective analysis of clinical profile of cardiac myxoma and their post surgical long term outcome. Those patients with clinical / echocardiographic / surgical / histopathological suspicion of lesion other than cardiac myxoma were excluded from the study. Four patients were excluded because of pre operative mortality. One patient had a large RA mass which on histopathology was suspicious of a thrombus. Hence, this patient was not taken up for analysis. Five patients who were lost from follow up were also excluded from the study.

60 patients met the above inclusion criteria and were taken up for analysis.

Clinical data

Clinical profile of the patients, including symptoms, signs, non invasive and invasive diagnostic modalities was assessed from the medical records. Data regarding surgical methods, perioperative findings and complications were

analysed. The post operative follow up data for primary outcome (defined as recurrence of tumour / cardiovascular death) and secondary outcome (arrhythmia, LV/RV dysfunction, functional class) were analysed. For follow-up assessment, the following protocol was used - clinical evaluation, ECG, Chest X-ray, echocardiography.

Statistical analysis

Results were expressed as mean $\pm$ SD. Statistical significance was analyzed by Student t test. p value of 0.01 is taken as statistically significant.

Results

RESULTS

60 patients with biopsy proven cardiac myxoma were included in the study. There were 21 males (35%) and 39 females (65%) with age ranging from 9-72 years. The mean (±SD) age was 40.1(±16.3) years. The study population was dominated by the age group of 3rd to 5th decade (65% of total). Only one patient was below 10 years. There were 15 patients in the age group of above 50 years. There was no significant difference in the age at presentation in the male and female patients.

Clinical profile

Symptomatic status

The commonest symptom the patients experienced was dyspnoea (64%) in the whole population. When LA myxomas alone were considered dyspnoea was seen in 75% of the patients at presentation. As expected there was no significant breathlessness in patients who had right sided myxomas. 8% of the patients had palpitation. Syncope / presyncope / transient loss of consciousness was seen in 11%. The typical postural symptoms were seen in only one patient. 15% of patients were asymptomatic. Evidence of right

heart failure was obtained in 8.3%. 22% febrile, but only 4% had arthralgia / arthritis.

In patients with left sided myxomas (LA or LV myxoma) evidence of systemic embolization was obtained in 24%. 5 patients had embolic stroke, 2 patients had history of multiple transient ischaemic attacks (TIA), 4 patients had embolic peripheral arterial occlusion and one patient had ECG and historical evidence of myocardial infarction and normal coronaries on coronary angiogram.

In clinical examination, 7% had evidence of clubbing and 2 patients (3.7%) had hepatomegaly / splenomegaly or both. Of the 60 patients 49 had LA myxoma (81.7%) and 5 had RA myxoma (8.3%). 2 patients had biatrial myxoma, both patients having large LA myxoma and small dumbbell RA myxoma, protruding through the fossa ovalis into RA. 3 patients had RV myxoma (5%) and only one patient had LV myxoma.

29 patients (59%) of LA myxoma mimicked mitral stenosis (MS). 9 patients (18.4%) had clinical finding suggestive of mitral regurgitation (MR). 10 patients (21%) had features suggestive of combined mitral stenotic and regurgitant lesion. 9 patients had evidence of pulmonary

arterial hypertension (PAH). Majority of the patients (95.4%) were in sinus rhythm and only 2 patients were in atrial fibrillation. 52% of patients had raised ESR. ECG criteria of left atrial overload, defined as positive p terminal force of 0.04mm/second in VI and / or interpeak distance of 40 m seconds or more in lead II with second peak taller was seen in only 30% of patients with LA myxoma. In other words left atrial overload was absent in 70% of patients with LA myxoma.

SITE OF ATTACHMENT OF MYXOMAS

1. LA myxoma

25 out of 49 LA myxomas were directly attached to the fossa ovalis region of interatrial septum (IAS). Another 16 patients had primary attachment to the IAS, but also were attached to some part of posterior LA wall or mitral leaflets. The majority (n=13) had attachment to posterior LA wall and required excison of tumour from posterior wall of LA and subsequent repair of the region. 2 patients had direct attachment to the mitral leaflets with no attachment to the interatrial septrum. One each of the above was attached to AML and PML. 6 patients had attachments in and around the orifrices of right pulmonary veins 3 were closer to the right lower pulmonary vein and 3 were closer to right upper pulmonary vein and roof of LA.

2. RA myxoma

There were five RA myxomas, 2 of which were attached to IAS at the SVC-RA junction and 3 were attached to the fossa ovalis region.

3. Ventricular myxomas

There were 3 patients with RV myxomas. All were large and prolapsing into the RVOT producing mild RVOT obstruction. All were attached to interventricular septum. The single LV myxoma was attached to the apical interventricular septum and was an accidental detection in a 25 year old male who had clinical findings of mitral valve prolapse and mild MR.

Surgical outcomes

All patients underwent transatrial approach of tumour resection. Adequate removal of tumour was obtained in all the patients. There was one immediate post operative mortality in a patient with LA myxoma with severe PAH in whom the PAH persisted with low output cardiac failure. One patient developed empyema in the immediate post operative period. There were no other immediate post surgical events in any of the other patients.

Long term outcome

The patients were followed up for a period ranging from 6 months to 11 years. The mean follow up period was 4.5 years. There were two tumour recurrences (3.3%) of whom one had earlier LA myxoma resected in 1988, who after a period of 5 years developed recurrence of LA myxoma with dense embolic stroke. The other patient had biatrial myxoma which was resected completely, but after a period of 6 months developed multiple embolic episodes with no evidence of mass in heart. The former was not reoperated because of his poor general health. All the other patients were doing well. On long term follow up, 90% of them were asymptomatic and 10% had NYHA functional class II symptoms. No patients had NYHA class III or class IV symptoms. None had arrhythmias or LV/RV dysfunction. 2 patients required mitral valve replacement for MR at the time of surgery. Both are in NYHA Functional class II with good LV function and prosthetic valve function.

Tables and Figures

BASELINE CLINICAL CHARECTERISTICS

TABLE I

Number of patients (n)	60
Sex distribution	
Male	21 (35%)
Female	39 (65%)
Age (mean ± S.D.)	40.1 ± 16.3 yrs
Range (yrs)	9-72
<10 years	1(1.7%)
10-20 years	5(8.3%)
21-30 years	15(25%)
31-40 years	12(20%)
41-50 years	12(20%)
51-60 years	7(11.7%)
>60 years	8(13.3%)

SITE DISTRIBUTION

TABLE II

	n	%
LA myxoma	49	81.7
RA myxoma	5	8.3
Biatrial myxoma	2	3.3
RV	3	5
LV	1	1.7

CLINICAL FINDINGS IN LA MYXOMA

TABLE III

Masquerading mitral stenosis	29 (59%)
Mitral regurgitation	9 (18.4%)
Mitral stenosis + mitrial regurgitation	10 (21%)
Pulminary arterial hypertension	9 (18%)

ECG FINDINGS IN LA MYXOMA

TABLE IV

Sinus rhythm	95.4%
Atrial fibrillation	4.6%
Evidence of left atrial overload	30%
No evidence of left atrial overload	70%

LA MYXOMA SITE OF ATTACHMENT

TABLE V

Attached to Interatrial septum	25
Attached to PML	1
Attached to AML	1
Attached to pulmonary vein	3
Attached to Roof of LA	3
Combind attachments to above sites	16

SYMPTOMS AND SIGNS

TABLE VI

Fever	22%
Arthralgia	4%
Asymptomatic	15%
Dyspnoea	64%
Palpitation	8%
Syncope / presyncope / TIA	11%
Right heart failure	8.3%
Postural Symptoms	1.6%
Clubbing	7%
Hepatosplenomegaly	3.7%
Increased ESR	52%

SYSTEMIC EMBOLISM IN LEFT SIDED MYXOMA

TABLE VII

Systemic embolism	**22%**
Stroke	5
Transient ischaemic attack	2
Arterial occlusion	4
Myocardial infarction	1

SURGICAL DATA

TABLE VIII

Surgical mortality	1 1.7%
Recurrence	2 3.3%

Figure - 1

RV Myxoma

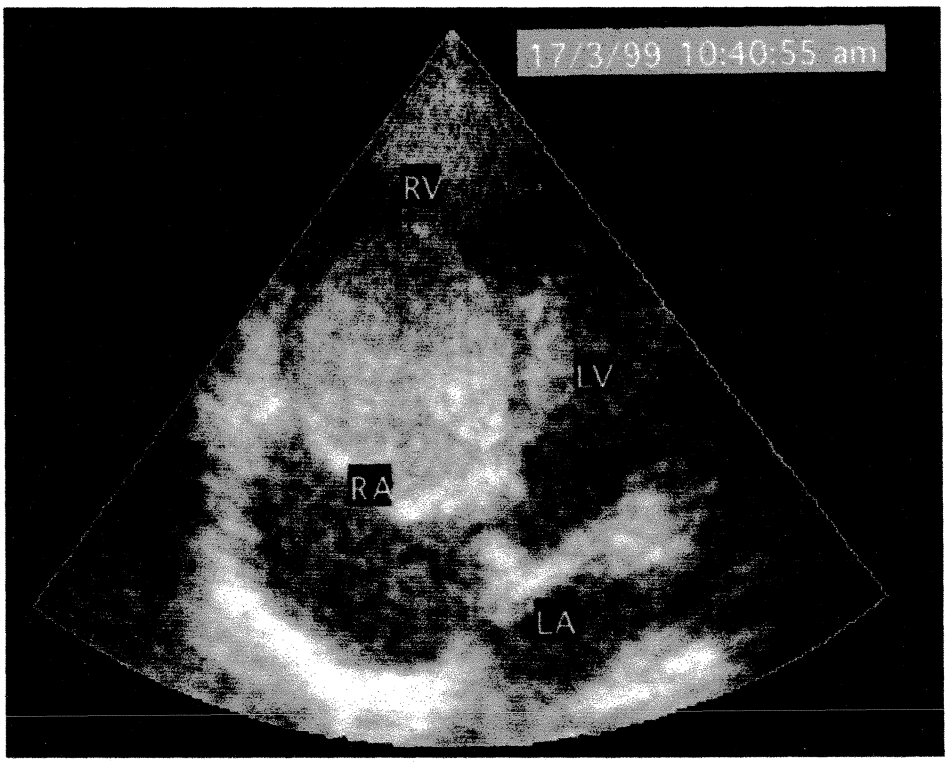


Figure - 2

RV Myxoma with mild RVOT obstruction

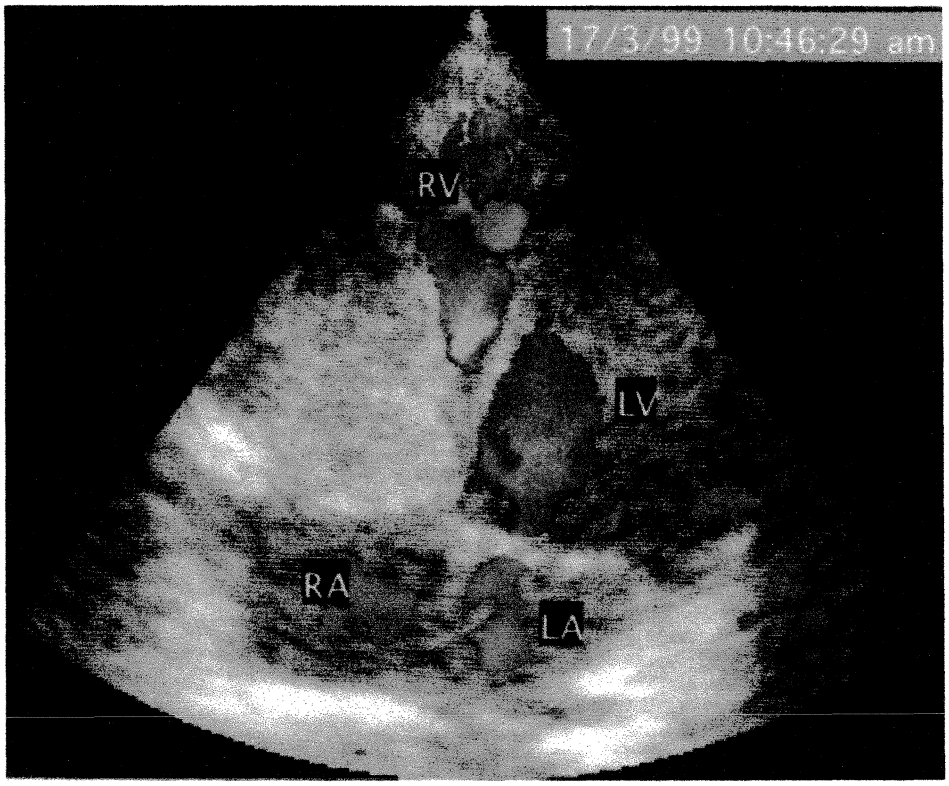


Figure - 3

RA Myxoma

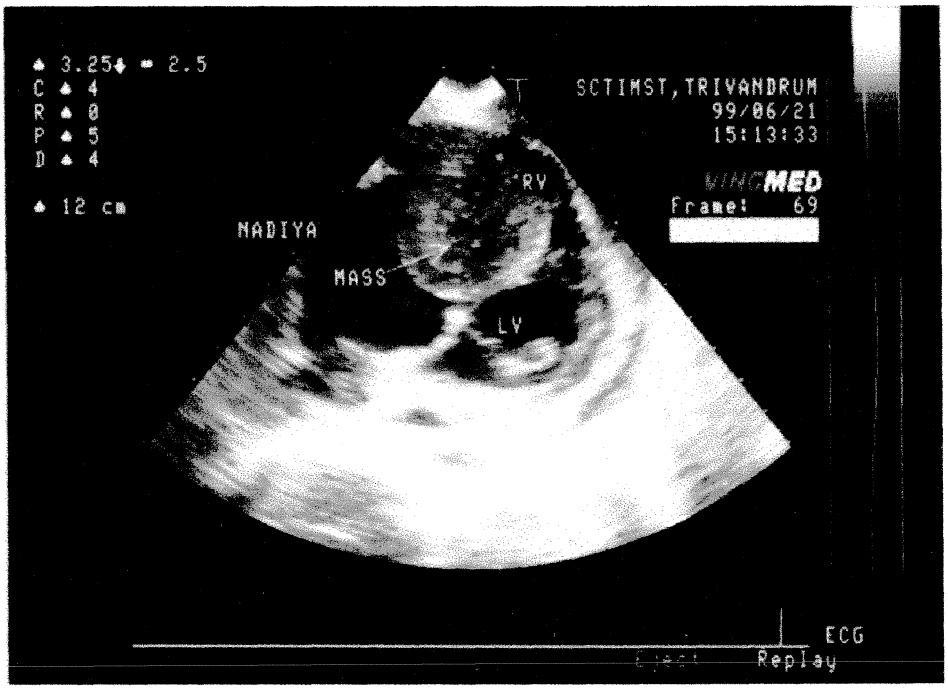
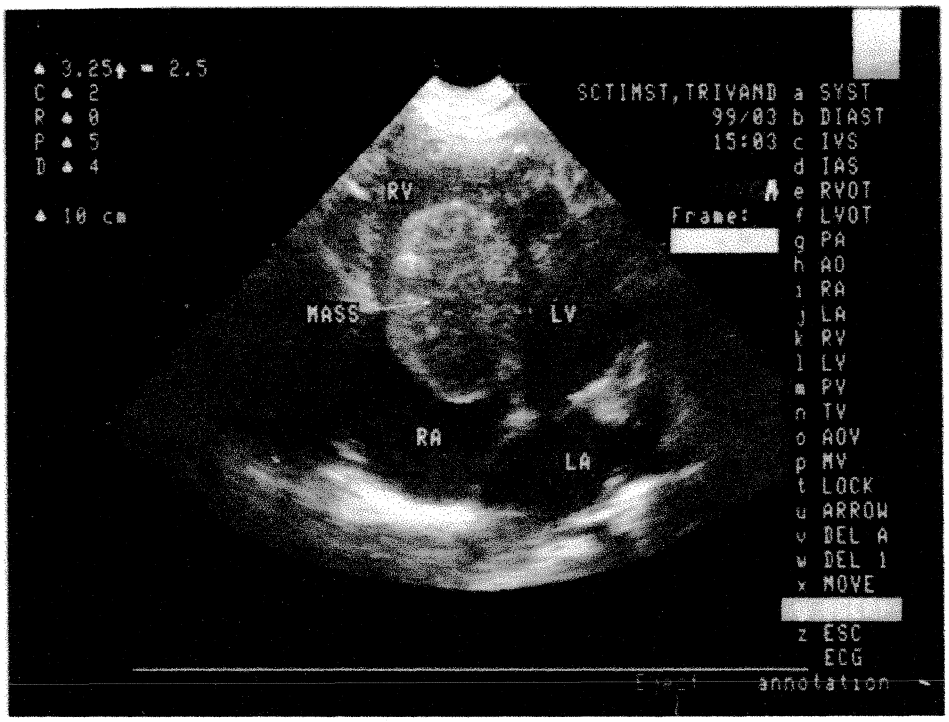


Figure - 4

RA Myxoma prolapsing into RV during diastole



DISCUSSION

In the study there was female preponderance constituting 65% of the cases. This goes along with the previously reported female sex predomiance of nonfamilial myxomas (1,2,3) in which a ratio of 7:3 was found. We didn't come across any syndrome myxomas or familial myxomas. Even though the age group was varying between 9-72 years in the study population, majority (65%) were in the age group of 20-50 years and 45% were in the age group of 20-40 years. This data is also similar to the incidence in earlier reported series. We had three patients below the age of 15 years, indicating the fact that myxomas do occur in adolescent age groups. When the male patient group was compared with the female group, there was no significant difference in the age at presentation.

The commonest symptom, the patients experienced was dyspnoea and in fact 3/4 of patients with LA myxoma had dyspnoea as the presenting symptom. The pathognomonic and classically described postural symptoms were seen in only one patient. Hence eventhough the postural symptom may be diagnostic in a patient with cardiac myxoma, they are so rarely found to be clinically useful. In fact 15% of

patients were totally asymptomatic. Other symptoms were less commonly seen. 20% of patients were febrile, but only a minority had clubbing or arthralgia. Only half of the patients had raised ESR.

One fourth of the patients with left sided myxoma had evidence of systemic embolization, manifested as either embolic stroke, TIA or peripheral arterial occlusion. Majority of right sided myxomas were asymptomatic. None of right sided myxomas had evidence of tumour embolism.

The percentage of LA myxoma in the present series (81%) is more than the previously reported series (75%) (4,5,6,7,8) whereas RA myxoma is less commonly seen in the present series (8% Vs 23%). 6% of total were ventricular myxomas which is clearly high to the 2% described in the above series.

The majority of LA myxomas clinically mimic MS, whereas 1/5 of patients had clinical features of combined MS & MR and 18% had clinical features suggestive of pure MR. The patients who had pure MR tended to have post surgical MR on follow up, unless mitral valve was also tackled at the time of surgery, whereas those patients who had clinical mimics of MS, tended to do well with no valvular lesion in the

post surgical follow up period. This would indicate that clinical / echo features of MS is primarily due to tumour obstructing the LV inflow which on removal relieve the obstruction and normalises the haemodynamics. In contradiction to this pure MR is probably due to the structural damage of the valve by the tumour infiltration or by the prolapsing tumour.

Atrial arrhythmia was a rarity and majority (95%) were in sinus rhythm. Even though most of the LA myxomas (80%) were large (>3.5cm in diameter) the ECG criteria for left atrial overload was fulfilled in only 30% of the patients. In other words 70% of LA myxoma patient did not have left atrial overload pattern on ECG. This finding was not reported in any of the previously reported LA myxoma series. This finding requires further study as for the cause. This would indicate that in a patient with clinical features of mitral valve disease with no evidence of left atrial overload on ECG one should consider LA myxoma as a possibility.

Even though the majority of LA myxomas were attached to the fossa ovalis region of IAS, we had clear aberration from the above theme in that 16% patient had no attachment to the IAS. We had two cases of mitral valve myxoma, one each getting attached primarily to AML and

PML. The other patients had attachment in and around the opening of right pulmonary veins. Hence we hypothesise that LA myxoma can arise from anywhere around the area of fossa ovalis and posterior LA wall near the openings of right upper and lower pulmonary veins. In this context, it is interesting to note that 1/3 of patients had attachments also to some part of posterior LA wall in addition to the interatrial septum, necessitating excision of part of posterior LA wall as well at the time of tumour excision, strengthening our above concept. Even though the reported cases of mitral valve myxomas are very few, we had two cases in the present series.

The ventricular myxoma in our series tended to be asymptomatic at presentation, and all were attached to the interventricular septum. All RA myxomas had attachment primarily to the interatrial septum.

Surgical outcome

59 patients underwent surgical resection successfully, but one patient succumbed post operatively due to low cardiac output and non regression of PAH. The recurrence rate in the follow up period was 3.3% which is similar to that of previously reported series. Most of the patients (95%) were doing well on follow up.

Conclusion

CONCLUSION

1. Even though the majority of myxoma patients belong to the 20-50 year group, cardiac myxoma can occur in adolescence, as well as in middle aged and elderly.
2. Systemic embolization was quite common in left sided myxomas (22%).
3. Even though majority of cardiac myxoma occur at left atrial site, biatarial, RA and ventricular locations are not uncommon.
4. Majority of the patients remain in sinus rhythm.
5. Left atrial overload pattern in ECG is rather uncommon in patients with LA myxoma.
6. Though the commonest attachment of LA myxoma is to interatrial septum, tumour may be primary originating from the posterior LA wall medial to the opening of right pulmonary veins.
7. Two cases of mitral valve myxoma are highlighted.
8. Right sided myxomas tend to be asymptomatic
9. Most of the myxomas can be successfully removed transatrially with acceptable mortality and less than 4% chance of tumour recurrence on long term follow up.

References

REFERENCES

1. Lam K.Y., Dickens P, Chan ACL. Tumours of the heart. A 20 year experience with review of 12485 consecutive autopsies Arch Pathol Lab Med. 1993; 117: 1027-1031.

2. Reynan K. Frequency of primary tumours of the heart Am. J. Cardiol 1996; 77:107.

3. Tazelaar, H.D, Locke TJ and McGreger, C.G.A. Pathology of surgically excised primary cardiac tumours. Mayo clin. Proc 67:957, 1992.

4. Salcedo, E.E, Cohen G.I, white R.D and Davison, M.B: Cardiac tumours : Diagnosis and treatment. Curr. Probl. Cardiol 17:73, 1992.

5. Hanson, E.C : Cardiac tumours. A current perspective N-Y state J.Med. 92:41, 1992.

6. Bahnson HT, Spencer FC, Andrus EC: Diagnosis and treatment of intra cavitory myxomas of the heart. Ann surg 1957; 145:915-926.

7. Peters MN, Hall RJ, Cooley DA, Leachman RD, Garcia E. The clinical syndrome of atrial myxoma, JAMA 1974; 230:695-701.

8. Morgan DL, Palazola J, Reed W, Bell HH, Kindred LH, Beauchamp GD. Left heart myxomas Am.J.Cardiol. 1977; 40:611-614.

9. St.John Sutton MG, Mercier LA, Guliani ER, Lie JT. Atrial myxomas. A review of clinical experince in 40 patients Mayo Glia Proc. 1980; 55:371-376.

10. Markel ML, Waller BF, Armstrong WF, Cardiac myxoma, A review Medi-cine 1987; 66:114-125.

11. Murphy MC, Sweeney MS, Putnam J BJr, Walken WE, Frazier OH, Ott DA, Cooley DA Surgical treatment of cardiac tumours : a 25 year experience, Ann Thoracic surgery 1990; 49:612-618.

12. Burke AP, Virmani R. Cardiac myxomas: a clinicopathologic study Ann J Clin Path. 1994; 100: 671-680.

13. Morrow AG, Kahler RL, Reis RL. Primary myxoma of the right ventricle. Clinical, hemodynamic and angiographic findings before and following operative treatment Am J Med 1966; 40: 954-960.

14. Leonhardt ET, Kullenberg KP. Bilateral atrial myxomas with multiple arterial aneurysms - a syndrome mimicking polyarteritis nodusa. Am J Med 1977; 62:792-794.

15. Ferrans VJ, Roberts WC. Structural features of cardiac myxomas. Histology, histochemistry and electron microscopy. Human Pathol. 1973; 4:111-146.

16. Pessotto R, Santini F, Piccin C, et al Cardiac myxoma of the tricuspid valve, Description of a case and review of the literature J.heart valve dis. 3:344, 1994.

17. Gosse P, Herpin D, Roundant R, et al Myxoma of the mitrial valve diagnosed by echocardiography. Am Heart J, 111:803, 1986.

18. Allard M.F, Taylor G P, Wilson JE and McManus B.M Primary cardiac tumours. In Gold haber, SZ and Braunwald, E(eds) Cardiopulmonary diseases and cardiac tumours. Atlas of heart diseases. vol.3. Philadelphia, Current Medicine 1995, pp, 15,1 - 15.22.

19. Carney J A : Hruska L S, Beau Champ, G.D and Gordon H Dominant inheritance of the complex of myxomas, spotty pigmentation and endocrine overactivity. Mayo clin. pro 61:165, 1986.

20. Van Gelder H.M, O' Brien D.J, staples, E.D and Alexander J A : Familial cardiac myxoma. Ann Thorac Surg. 53:419, 1992.

21. Koopman R.J and Happle R, Autosomal dominant transmission of the NAME syndrome (nevi, atrial myxoma, mucinosis of the skin and endocrine over activity) Hum Genet 86:300, 1991.

22. Carney J A, Gordon J, Carpenter, P.C. et al: The complex of myxomas, spotty pigmentation and endocrine overactivity. Medicine 64:270, 1985.

23. Vidaillet H.J, Jr, Seward J.B, Fyke F.E, et al. "Syndrome myxoma". A subset of patients with cardiac myxoma associated with pigmented skin lesions and peripheral and endocrine neoplasms Br.Heart J 57:247, 1987.

24. Bernet W.S, Skelton T.N, and Lehan P.H : The complex of myxomas, pigmentation and endocrine overactivity. Am J Cardiol 65:399, 1990.

25. Vidaillet, H.J. Jr, Seward J.B, FyKe, E, and Tajik A.J. NAME syndrome [naevi, atrial myxoma, myxoid neurofibroma, ephelides): A new and unrecognized subset of patients with cardiac myxoma Minn Med 67 : 695, 1984.

26. Rhodes A.R, Silverman R.A, Harrist T. J., and Perez - Atayde AR, Mucocutaneous lentigenes, cardiomucocutaneous myxoma and multiple blue nevi. The LAMB syndrome Am.Acad.Dermatol 10.72, 1984.

27. Widtrowska, B.A, Walley, V.M, Masters R.G., et al : Surgery for cardiac tumours : The University of Ottawa Heart institute experience (1980-1991) Can J. Cardiol 9:65, 1993.

28. Aru G.M. Falchi S, Cardu G, et al. The role of transoesophageal echocardiography in the monitoring of cardiac mass removal. A review of 17 cases J Card Surg 8:554, 1993.

29. Waller D.A, Ettles D.F, Saunders NR, and Williams G : Recurrent cardiac myxoma. The surgical implications of two district groups of patients. Thorac Cardiovasc Surg. 37:226, 1989.

30. Mc Carthy P.M. Prehler J.M. Schaff, H.V, et al. The significance of multiple recurrent and complex cardiac myxomas. Thorac Cardio-vasc surg. 91:389, 1986.

31. Larsson, S., Lepore, V., and Kennergren, C; Atiral myxomas; Results of 25 years experience and review of the literature. Surgery 105; 695, 1989.

32. Bortolotti U., Maraglino G, Rubino M, et al: Surgical excision of intracardiac myxoma : A 20 year follow up Ann. Thorac Surg 49:449, 1990.

33. Lukais L, Lengyel M, Szedot F, Haan A, Nagy L, Thomka I, Kassai I, Meszaros R Long term results of surgical treatment of cardiac myxomas. OrV Hetil 1996 Jun 2; 137 22:1187-90.

34. Tsukamoto S, Shiono M, Orime Y, Hata H, Yagi S, Kimura S, Hata M, Sezai A, Negishi N, Sezai Y. Surgical treatment of 22 cardiac myxomas. A review Ann Thorac Cardiovasc surg 1999 June : 5 - 3 : 146-9.

35. Lukais L, Lengyel M, Szedot F, Haan A, Nogy L, Thomka I, Kassai I H Surgical treatment of cardiac myxomas : a 20 year follow up. Cardiovasc surg 1997. Apr 5(2): 226-8.

36. Gawdzinski MP, Sypula S the long term results of treatment of heart myxomas with special attention to very rare myxoma of the right ventricle. J Cardiovasc. Surg. 1996 Dec 37 (6 Suppl I) 121-9.

Study of Trace Elements in Aetiology of Coronary Artery Disease

Introduction

INTRODUCTION

The classical risk factors (RF) for coronary artery disease (CAD) including unmodifiable ones (age, male sex, family history) and modifiable ones (smoking , lipoprotein abnormalities, diabetes, hypertension, obesity and sedentary habits) account for only 50-70% of variation in the incidence of coronary artery disease on epidemiological studies. A group of patients with CAD have none/ few classical risk factors. Hence there are other factors causal or modifying that have not yet been identified and some factors which are identified and categorised as minor risk factors.

Trace elements are a group of minerals which are required by the body in quantities less than few milligrams/day. The role of trace elements in human health and disease is not clearly known. Earlier workers have correlated vascular disease with the hardness (Mineral content) of potable water (1,2). A higher serum magnesium is said to have a protective effect on dysrrhythmia and sudden death (3). On the contrary Abraham et al (4) reported that concentration of magnesium was not associated with aetiopathogenesis of CAD. Patterns of trace element concentration in tissues of subjects who died of atherosclerosis differ from those of healthy controls (5). Other trace elements that appear to be

consistently related to malfunctioning of cardiovascular system and atherosclerosis include copper (6,7) Zinc (7,8) nickel (9) cobalt (8) and iron (10) These data, though not overwhelming suggest that trace elements can have an aetiological role in cardiovascular risk, especially in CAD .

Trace elements function as cofactors for many vital enzymes in the human body. Selenium is an integral part of glutathion peroxidase system and iron is coupled to heme. In other words it can be seen that most of the trace elements are coupled to protein moieties, preventing their free access to biochemical reaction. It has been shown that iron can function as a pro oxidant by functioning as a co factor in Fenton reaction producing free radicals . It may be hypothesised that trace elements and minerals can similarly act as prooxidants in the free state. This may be one of the mechanisms culminating in the development of atherosclerosis.

This provoked us to probe into the hypothetical aetiological role of trace elements in human coronary artery disease.

Aim of the study

AIM OF THE STUDY

To look into the possible aetiological association of serum levels of trace elements and coronary artery disease in the population.

Materials and Methods

MATERIAL AND METHODS

We prospectively analyzed the serum samples of patients admitted for coronary angiogram for serum levels of Magnesium (Mg), Calcium (Ca), Zinc (Zn), Copper (Cu), Nickel (Ni), Cobalt (Co) and Manganese (Mn). The serum biochemical analysis was done by an investigator blinded to the results of coronary angiogram (CAG). The clinical profile including the anginal status, history of myocardial infarction and classical risk factors for CAD were analyzed. All the patients underwent a detailed clinical evaluation, Electrocardiogram (ECG) & echocardiography for left ventricular (LV) function and regional wall motion abnormality (RWMA) and a stress test for inducible ischaemia prior to CAG.

Depending on the CAG findings patients were divided into those with evidence of CAD (group I) and people with normal coronaries (group II). Patients in the group II included those with typical /atypical anginal pain with either positive or borderline positive stress test and those who underwent coronary angiogram for risk stratification prior to valve surgeries.

Group I was further subdivided into Group I a including patients with extensively diseased coronary arteries and group Ib, those patients with single discrete lesions or ≤ 2 discrete lesions

in the entire coronary tree. Any identifiable intraluminal narrowing with more than 30% of luminal diameter loss was considered as an atherosclerotic lesion. The patients who had more than two discrete lesions in the entire coronary tree were grouped in group Ia. The serum samples of various trace elements in group I and group II were compared. The serum levels were also compared between the subgroups of group I.

Blood was sampled into plastic syringes from patients and control subjects on empty stomach and collected in glass tubes provided with plastic caps. Serum was separated from each sample within one hour and stored at -10^{o}c until analyzed . The serum levels of trace elements were analyzed by atomic absorption spectrophotometry.

STATISTICAL ANALYSIS -

The results were expressed as mean $\pm$ standard deviation (SD). The statistical significance is expressed as p value which was derived by the application of student t test.

Results

RESULTS

There were 31 patients with coronary artery disease and 11 patients with normal coronaries. As mentioned earlier, the former was classified as group I and the latter group II. There were 29 males and 2 females in group I. Group II consistsed of 9 males and two females. The baseline clinical charaterestics are given in table I.

Serum levels of magnesium in group I was 1.9 $\pm$ 0.2 (mean $\pm$ SD) mg% and in groupII was 1.89 $\pm$ 0.33 mg%. This was not statistically significant. The calcium level in the two groups were 11.1 $\pm$ 0.98 Vs 11.12 $\pm$ 0.87 mg%. The results of analysis of cobalt, nickel and manganese also were similar in the two groups. The serum levels of zinc varied between the two groups significantly (907 $\pm$ 121.2 Vs 1051.82 $\pm$ 115.65 µgm / litre) ($p<0.01$). See Table II. Serum copper levels were 999 $\pm$ 69 Vs 945 $\pm$ 72.6 µgm/ litre in the two groups. The difference was not statistically significant. The ratio of zinc / copper was shown in certain studies to be useful (11) Hence we compared this ratio of zinc / copper in the two groups. The zinc / copper ratio was 0.99 $\pm$ 0.14 Vs 1.13 $\pm$ 0.21 ($p<0.05$). See table II.

Subgroup analysis of group I between extensively diseased coronary arteries Vs patient with ≤ 2 lesions in the entire coronary tree showed significant difference between the serum level of zinc between the two groups 904.9 ± 91.26 Vs 1017 ± 62 μgm/litre ($p<0.01$) . The copper levels did not vary significantly in group I a and group Ib.

The ratio of serum levels of zinc/copper varied significantly ie 0.9 ± 0.15 Vs 1.03 ± 0.08 ($p<0.04$). see Table III.

Figure I shows the schematic representation of the difference in zinc levels between group I a, group I b and group II Figure II shows the Zn / Cu ratio in the three groups.

Tables and Figures

Table I

BASE LINE CHARACTERESTICS

Total no. 42

	Group I n=31	**Group II n=11**
Age (yrs)	52.5 ± 7.6	51.6 ± 11.7
Range	35-72	35-81
Sex (M : F)	29 : 2	9 : 2
Angina		
FC II	26	2
FC III	2	0
Breathlessness		
FCII	3	6
FC III	0	3
CHF	0	0
Risk factors		
Smoking	58%	18%
Hypertension	20%	9%
Diabetes	32%	Nil

Table II

Elements	Group I n=31	Group II n=11
Mg(mg/dl)	1.9 ± 0.2	1.89 ± 0.33
Ca (mg/dl)	11.1 ± 0.98	11.12 ± 0.87
Co(µg/L)	0.24 ± 0.06	0.23 ± 0.05
Ni (µg/L)	1.63 ± 0.78	1.56 ± 0.6
Mn(µg/L)	0.71 ± 0.09	0.78 ± 0.04
Zn(µg/L)	907 ± 121.2	1051.82 ± 115.65 ($p<0.01$)
Cu(µg/L)	999 ± 69	945 ± 72.6 (NS))
Zn/Cu ratio	0.99 ± 0.14	1.13 ± 0.21 ($p<0.05$)

SUBGROUP ANALYSIS OF GROUP I

Table III

Element	**Normal CAG** (Group II) n = 11	**SVD/discrete 2D** (Group Ia) n = 13	**TVD** (Group Ib) n = 18
Zn	1051.82±115.65	1017±62	904.9±91.26 $p<0.01$
Ratio of Zn/Cu	1.13±0.21	1.03±0.08	0.9±0.15 $p<0.05$

Figure - 1

SERUM Zn LEVEL IN THE VARIOUS GROUPS

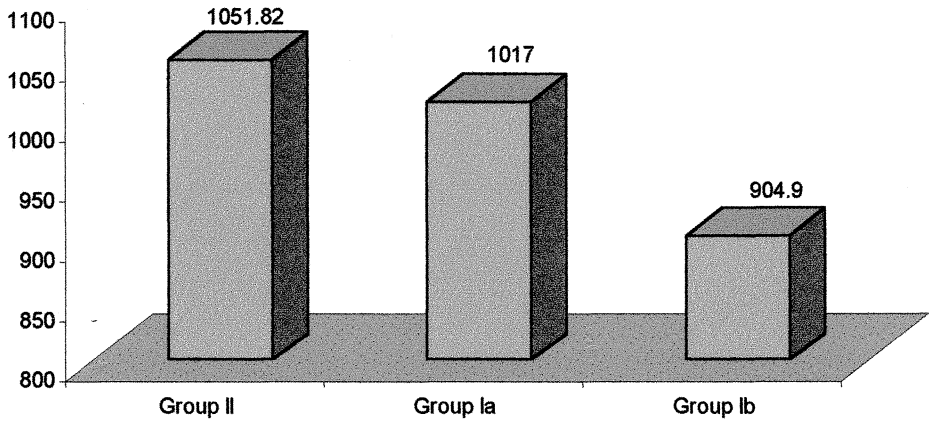
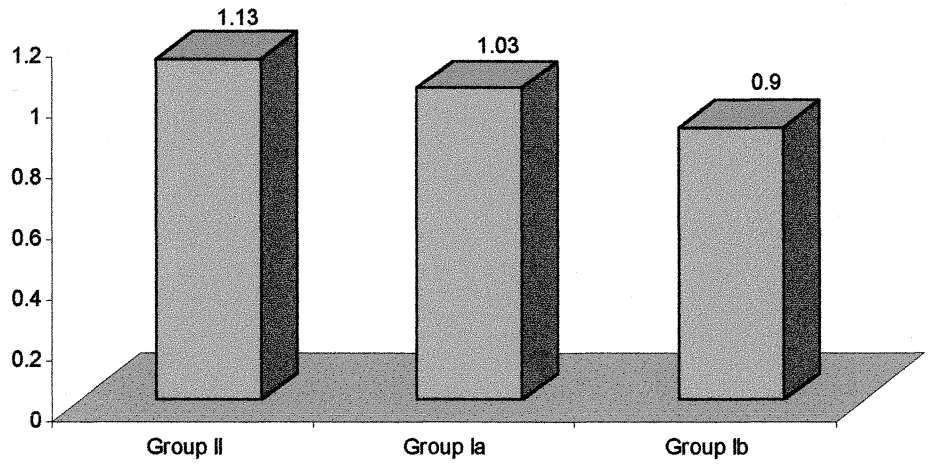


Figure - 2

Zn / Cu RATIO IN THE VARIOUS GROUPS



Discussion

DISCUSSION

The serum levels of magnesium, calcium,cobalt, nickel and manganese were comparable in patients with CAD to those without. But the serum levels of zinc varied significantly between the two groups. Serum zinc level was lower in patients with CAD when compared to normal controls. When the subgroup analysis of group I was done, it was found that patients with extensively diseased CAD had significantly lower serum zinc level when compared to those with ≤ 2 lesions in the entire coronary tree. These two findings are corroborative and mutually supportive. It is hence shown that low serum zinc level may be an aetiological factor in the development of CAD.

Serum copper levels showed a similar but inverse trend which did not attain statistical significance ($p=0.1$). The higher levels of serum copper in patients with CAD goes along with the still higher levels of serum Cu in extensively diseased coronary arteries although it failed to acheive statistical significance.

As was shown in previous studies (11) a high ratio of serum levels of Zn / Cu may be a negative risk factor for the aetiology of CAD. When we analyzed the ratio, it was noted that a low ratio

goes along with patients with CAD with still lower value for those with extensively diseased coronary arteries (See Figure II).

From the above estimations we infer that a higher serum Zn level and a Lower serum Cu level may be a negative risk factor for CAD. Whether these changes in serum trace element levels are primary to the aetiology of CAD or occur secondary to the effects of CAD is a debatable issue. It is also possible that some of the patients with valvular disease (total number of 3) were on diuretics which could have altered the homeostasis of above elements but since most of our patients belong to chest pain with normal coronary arteries group, the possibility for the above, affecting the overall picture in patients with normal coronaries is minimal. It could also be debated that the changes occured secondary to the effects of other classical risk factors which were present in 70% of our patients with CAD. We didn't analyze the serum trace element levels by subgrouping patients depending on the classical risk factors due to the small number of patients included in the study.

There are conflicting data on Cu and zn levels and CAD. Experimental studies showed that dietary Cu deficiency either alone or associated with elevated intake of Zn can produce hypercholesterolaemia in rats (12,13,14) Based on the studies it was postulated that extrahepatic cell utilization of cholesterol and bile acid synthesis and excretion are defective in copper deficient animals (13). In humans there is only fragmentary evidence of

significant interrelationship between Cu and Zn intake and lipoprotein levels and of the role of these elements in the devolopment of CAD. Similar to our results Harman (19) in 1963 found similar elevations of serum concentrations of Cu in patients with CAD.

Morgan et al (15) in 1972 found that hepatic Cu content is raised in patients with CAD. Two studies reported the reduction in cholesterol with pharmacologic doses of Zn (16,17) Tyber et al (18) found no association between dietary Zn and Cu level and aetiology of CAD.

This is the first study which had an angiographically defined study population with CAD and control with normal coronaries in the evaluation of role of trace elements in CAD. Previous studies had either patients with CAD suspected clinically/ post MI patients or patients with positive TMT. Hence the definition of CAD was not dependant on the gold standard coronary angiogram. This can explain some of the disparity between the previous studies and the present study..

Based on our results it is worth pondering over the role of supplemental zinc in primary and secondary prophylaxis of CAD Being a small study the results need corroboration with a larger randomized study and an interventional trial with dietary supplementation of zinc.

Conclusion

CONCLUSION

1. Patient with CAD have higher Cu and lower Zn levels when compared to persons with normal coronary arteries. The Zn / Cu ratio tend to be low in patients with CAD when compared to people with normal coronaries.

2. Patients with extensive coronary artery disease have still lower Zn, higher Cu and lower Zn/Cu ratio when compared to patients with less extensive coronary involvement.

3. Dietary Zn supplementation may have some role in prophylaxis of CAD but requires further research.

References

REFERENCES

1. Masironi R.Cardiovascular mortalilty in relation to radioactivity and hardness of local water supplies in the USA Bull WHO 43, 687 - 697 (1970).

2. Craw ford MD, Gardner MJ, MorrisJN charges in water hardness and local death rates. Lancet, ii, 327 - 329 (1971).

3. Seelig MS, Heggtveit HA Magnesium interrelation in ischemic heart disease : A review Am J clin Nutr 27, 59-79 (1974)

4. Abraham AS, Weinstein M, Eylath V, Czaczkes E. Magnesium level in patients with chronic ischaemic heart disease AM Clin Nutr 31, 1400 - 1402 (1978)

5. Masironi R. Trace elements in relation to cardiovascular diseases. In Nuclear activation techniques in the life sciences, Int Atomic Energy Agency, Vienna, 1972, pp 503 - 516.

6. Kanabrocki EL, Fields E, Grahm L, et al Non dialyzable manganese and copper levels in serum of patients with various diseases J Nucl Med. 8, 166 - 172 (1967)

7. Tan IK, Chua KS, Toh Ak . Serum magnesium, copper and Zincconcentration in acute myocardial infarction J clin Lab Anal 1992; 6 (5) : 324 - 8.

8. D'Alonzo CA, Pell S.A study of trace metals in myocardial infarction Arch Environ Health 6, 381, 385 (1963)

9. Wester P.O Trace elements in human myocardial infarction determined by neutron activation analysis Acta Med Scand 178, 765 - 788 (1965).

10. Masironi R. Trace elements and cardiovascular diseases. Bull WHO 40, 305 - 312 (1969).

11. Thuillier - Juteau Y, Jaudon Mc, Clavel JP, Delattre J, Galli A, Serum zinc and copper in hypercholesterolemia Pathol Biol (Paris) 1987 Apr : 35(4) : 387 - 90.

12. Allen, K.G.D and klevay, L.M. (1978): Cholesterolemia and cardiovascular abnormalities in rats caused by copper deficiency atherosclerosis, 29, 81 - 93.

13. Allen, K.G.D and Klevay, L.M. (1978) : Copper deficiency and cholesterol metabolism in rat, Atherosclerosis 31: 259 - 271.

14. Allen, K.G.Dand Klevay, L.M. (1980) : Hyperlipo proteinaemia in rats due to copper deficiency. Nutr. Rep Intern, 22 : 295 - 299.

15. Morgan, J.M (1972) : Tissue copper and lead content in ischemic heart disease Arch Environ Health, 25:26 - 28.

16. Freeland - Graves J.H.Freedman, B.J. Han, W.H., Shorey, R. L., and Young R (1982) Effect of zinc supplementation on plasma high density lipoprotein - cholesterol and zinc Am J clin Nutr, 35 : 988 - 992.

17. Hooper, P.L, Visconti L, Garrry P J and Johnson G E (1980) Zinc lowers high density lipoprotein cholesterol levels JAMA, 244 : 1960 - 1961.

18. Tiber AM, Sakhaii M, Joffe CD, Ratnaparkhi MV, Relative value of plasma copper, zinc, lipids and lipoproteins as markers for coronary artery diseases Atherosclerosis 1986 Nov; 62(2) : 105 - 10.

19. Harman, D. (1963) : Role of serum copper in coronary atherosclerosis. Circulation, 28 : 658.