Volume 32, Number 1 January 2008

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INSTRUCTION TO AUTHORS ABOUT UNIFORM MANUSCRIPT WRITING

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Genetic names should generally be used. When proprietary brands are used in research, include the brand name in parentheses in the Methods section.

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References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legend by Roman numerals in parenthesis. Use the styles of the example below, which are based on the formats used by the US National Library of Medicine (NLM) in the Index Medicus.

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Cancer in South Africa (editorial). S Afr Med J 1994; 84-15.

d) Organization as author
The Cardiac Society of Australia and New Zealand. Clinical exercise stress training. Safety and performance guideline. Med J Aust 1996; 164 : 282-4.

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e) Dissertation
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a) Newspaper article
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Vol. 32, No.-1, January 2008

ORIGINAL ARTICLE

Role of 7-Day and 14-Day Courses of Oral Prednisolone Treatment in Acute Exacerbation of COPD

Mohammad Azizul Haque[1], Mostafizur Rahman[2], Rashidul Hasan[2] Mirza Mohammad Hiron[2], Asif Mujtaba Mahmud[3], MA Rouf[4]

Abstract:

Purpose: *The purpose of this study was to compare the efficacy of 7-day and 14-day courses of oral prednisolone treatment in patients with acute exacerbation of COPD with FEV_1<50% predicted.*

Methods: *It was a prospective randomized, single blind study in a tertiary care center, the study patients were included and randomized into two groups: 7-day group received oral prednisolone 30 mg./day for 7 days, and 14-day group was administered the same dosage of oral prednisolone for 14 days. There was no significant difference between the groups for age, smoking pack years, symptoms of COPD in years, no. of previous exacerbations, blood eosinophilia, baseline FEV_1,and FVC levels. One patient from 7-day group developed pneumothorax and one from 14-day group died of acute Myocardial Infarction.*

Results: *Both groups showed significant improvements of FEV_1 and FVC on D-1, D-3, D-5, D-7, D-10 and Day-14 from the baseline (7-day group, p = 0.0001, 0.0001, 0.008, 0.009, 0.008, 0.011and 14-day group, p = 0.000, 0.000, 0.000, 0.000, 0.000, 0.000.) and the improvement of FVC was also significant in both the groups, but there was no significant difference of improvement between the two groups on day-7 and day-14 (p = 0.100, 0.079). There was also significant improvement of symptom score from baseline on day-7 and day-14, but no significant difference of improvement between two groups.*

Conclusions: *In acute exacerbation of COPD there is no difference between 7-day and 14-day courses of treatment with oral prednisolone. The peak of FEV_1 and FVC in 7-day group on day-10 where corticosteroid was already stopped on day-7, (peak in 14-day group was on day-7) might be due to some other factor/ factors responsible which would be cleared by further study.*

Clinical Implications: *There was no difference between 7-day and 14-day courses of prednisolone treatment, so, 7-day might be the shortest effective course of steroid treatment in Acute exacerbation of COPD to avoid the burden of cost and side effects.*

[Chest & Heart Journal 2008; 32(1) : 1-7]

Introduction:

Chronic obstructive pulmonary disease is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years and die prematurely from it or its complications. COPD is currently the fourth leading cause of death in the world and further increase in its prevalence and mortality can be predicated in the coming decades.[1,2,3]

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COPD is also a common health problem in Bangladesh and one of the common conditions seen by physicians. It is the burden for both the developed and developing countries. Although there is no prevalence study done in Bangladesh the problem is increasing in this country like other parts of the world.

COPD is often associated with exacerbations of symptoms, and commonly leads to hospital admission.[4,5,6,7,8] The role of systemic corticosteroid in the management of acute exacerbation of COPD is almost established but their duration of treatment is not well defined and their use is observed to be common place.

One study was carried out with early administration of methyl prednisolone as a single dose in the emergency department and after 5th aerosol treatment, there was no greater improvement in FEV_1 in the group receiving the steroid than the control group.[9] .

Another study was carried out to compare the efficacies of 3 and 10 days courses of methyl prednisolone treatment in severe COPD exacerbation necessitating hospitalization for respiratory failure and they found significant improvement of PO_2 and FEV_1 in patients treated for 10 days than 3 days period.[10]

Another study with early administration of M. prednisolone followed by oral prednisolone for 2 months and they came in conclusion that systemic glucocorticoid results in moderate improvement in patients with exacerbation of COPD and the maximal benefit was obtained during the first two weeks of therapy.[11]

L.Davis et al 1999 assessed by treating the patients of non acidotic exacerbation of COPD by oral prednisolone 30 mg/ day for 14 days with 7 days inpatient Hospitalization and they found that the rate of change in post bronchodilator FEV_1 in patients receiving corticosteroid was 3 times than the patients receiving placebo, maximum improvement in FEV_1 was also seen by Day- 5 in the steroid treated patients significantly earlier than the placebo group but these benefits did not last beyond the immediate hospitalization.[12]

In Bangladesh no study has been carried out to date regarding the use of systemic corticosteroid in patients with acute exacerbation of COPD. But all physicians use this drug in acute exacerbation of COPD randomly without any established study regarding optimum duration. It is an important question- what would be the actual duration of steroid treatment in acute exacerbation of COPD.

In a setting of diminished resources and in the face of infinite challenges, studies are needed to unfold the problem of treating the patients of acute exacerbation of COPD. Keeping all these attributes in mind this study was planned to be conducted at the National Institute of the Diseases of chest and Hospital (NIDCH) in order to gain insight into the efficacy of systemic corticosteroid in the management of acute exacerbation of COPD and to define the optimum duration of treatment for such a common clinical problem of public interest.

Materials and methods :

The study was a two weeks, randomized, single blind, prospective, clinical trial, in National Institute of Diseases of the Chest & Hospital (NIDCH) Dhaka, Bangladesh during the period from September 2002 to December 2003. All the cases were selected in the age group between 40 and 90 years of age, both male and female patients of urban and rural community having history of smoking > 20 pack years with current or ex-smokers, with airflow limitation having initial FEV1 less than 50% predicted and FEV1/FVC <60% predicted. All the patients had history of breathlessness and at least two of the following symptoms for 24 hours or more, increased frequency of cough, increased volume and / or purulence of sputum and increased wheeze. The patients having personal or family history of Asthma, atopy, and allergic diseases, blood eosinophilia, corticosteroid therapy within previous one month, left ventricular failure, pneumonia, uncontrolled hypertension and diabetes mellitus were excluded. 84 newly admitted patients of COPD from Outdoor and Emergency department of NIDCH were decided to include in this study.24 patients did not fulfill the inclusion and exclusion criteria. All sixty patients who fulfilled both inclusion and exclusion criteria were included in this study. The patients were selected by taking history, doing physical examination and investigations and informed written consent of the patients was obtained from every patient. A standard proforma with questionnaire was

designed and filled to select patients with COPD. The patients were identified according to the predetermined criteria of exclusion and inclusion.Following investigations were done on admission full blood count including total circulating eosinophil count, sputum for gram stain, AFB stain, culture and sensitivity, X-ray chest P/A view, fasting blood sugar, spirometry, E.C.G.Urine R/M/E, blood urea, serum creatinine, arterial blood gases of those patients who had FEV_1 <30% predicted.

Study Procedure

All the patients were randomly assigned into two treatment groups.

7-DAY GROUP received the following treatment: Controlled O_2 inhalation 1-2 L/min, nebulised salbutamol 5 mg. and ipratropium bromide 500 microgram. every 6 hourly followed by inhaler form after getting improvement, oral theophyline, patients who were receiving inhaled corticosteroid therapy before randomization continued the therapy, systemic antibiotic oral or parenteral, oral H2 receptor antagonist (Ranitidine) and oral glucocorticosteroid in the form of tab. prednisolone 30 mg. daily at morning after breakfast for 7 days, followed by tab folison for next 7 days.

14-DAY GROUP received the same treatment like 7-Day group with the exception of duration of oral glucocorticosteroid, which they continued for 14 days instead of tab folison.

Routine follow up for all patients was done every morning and specific questionnaire was filled up and bedside spirometry was done after giving nebulised bronchodilator on Day-0, Day-1,Day-3,Day-5, Day-7,Day-10, Day-14. Findings were recorded in the data collection sheet. Study medication was given to the respective groups and swallowing of medication after breakfast was observed.

Symptom scores were obtained by asking the patients to rate their physical and emotional function on a seven point scale, in which higher scores represented better function. Majority of the patients filled in the questionnaires personally; however 24 patients(10 from 7-day group, 14 from 14-day group) could not respond themselves due to difficulty in reading and writing. In that case, they were interviewed by a nurse who was uninformed about the medication given.

Compiling, Presentation and statistical analysis of data

The data collected through the above mentioned procedure were recorded systematically

All the data were collected through data collection sheet and Questionnaire sheet were compiled in a single compilation sheet. These data were then analyzed statistically by standard procedure to arrive at a definitive conclusion in respective to the objective of the study.

Research Instruments

a) A portable spirometer, the FVC meter which shows the following parameters.

1. FEV_1
2. FVC
3. FEV_1/FVC %
4. PEFR

Results:

Table I shows there is no significant difference of demographic findings between two groups like age, sex, height, weight, BMI, duration of COPD in years, history of smoking in pack years, blood eosinophilia, and number of exacerbation in previous years.

One patient in 7-day group developed pneumothorax and referred to surgical unit and I.T. tube was introduced. One patient of 14-day group died of acute severe M.I. He was Diabetic and hypertensive.

Socio-economic condition and occupation : Most of the patients came from poor socio-economic status. Very few from middle class family. Many were Rickshawpullers, poor agriculturists, Gate keepers, small shopkeepers, Hawkers, and some were official clerks.

Educational Background: Most of the patients were illiterate. Ten patients finished the primary and secondary school education. Only two patients were Graduate.

Day wise change of FEV1 : From this observation(Table –III) it has been seen that in 7-day group FEV1 level is increased from base line (day-0) stepwise and is peaked at day-10 and the increment persisted up to day-14. In 14-day group

the FEV1 level(Table-IV) is also increased from baseline day-0 throughout the whole observation period and is peaked on day-7 and followed by persistence of rise of FEV1 up to day-14.

Day wise change of FVC : It has been seen that in 7-day group FVC level(Table-III) is raised from the baseline (day-0) throughout the whole observation period and is peaked on day-10 and the increment persisted up to day-14.

In 14-day group it has been seen that there is stepwise increase of FVC level(Table-IV) form day-0 throughout the whole observation period and is peaked on day-7 and the increment persisted up to day- 14.

Table-II

Demographic findings of the two groups.

Variables	7-day group (n = 30)	14-day group (n = 30)	Significance p value
Age, yr.	63.67 ±10.94	62.73 ± 9.61	0.431
Male/female gender No.	30/0	30/0	
Height in cm.	160.66 ±2.73	160.63±2.55	0.961
Weight in kg.	48.80 ±2.84	49.26 ±2.71	0.518
BMI	18.90 ±1.07	19.10 ± 1.16	0.501
Duration of COPD, yr.	11.10±4.79	10.87± 4.56	0.788
Smoking history, pack yr.	39.63 ± 8.21	43.00 ±7.40	0.826
Blood eosinophilia, %	0.50 ±0 .50	0.46 ±0 .50	0.720
Exacerbation in previous yr, No.	5.93 ± 1.74	5.16 ± 1.59	0.336
FEV_1, ml.	663.33 ±209.13	605.83 ± 191.37	0.557
FEV_1, % predicted	34.16 ±12.97	30.30 ± 11.15	0.212
FVC ml.	1410.83 ±371.02	1273.33 ±447.54	0.240
COPD stage (3/4)	17/13	14/16	0.289

Table-IV

Results of FEV_1 and FVC daywise in 7-day group

Variables	Day-0	Day-1	Day-3	Day-5	Day-7	Day-10	Day-14
FEV_1, ml	661.20 ± 661.20	811.20 ± 377.58	959.48 ± 385.58	1084.48 ± 455.34	± 437.60 1111.20	1117.24 ± 450.25	1093.10 ± 445.15
FVC, ml	1407.75 ± 377.20	1521.55 ± 510.85	1905.17 ± 522.58	2051.72 ± 564.81	2135.34 ± 609.28	2155.17 ± 558.43	2139.65 ± 560.35

Table-V

Results of FEV_1 and FVC daywise in 14-day group

Variables	Day - 0	Day - 1	Day - 3	Day - 5	Day - 7	Day-10	Day-i4
FEV_1 in ml	611.20 ± 192.44	696.55 ± 248.45	877.58 ± 319.76	942.24 ± 302.89	943.96 ± 297.43	931.89 ± 291.92	929.31 ± 295.65
FVC in ml.	1284.48 ± 451.20	1442.24 ± 446.96	1634.48 ± 488.82	1775.86 ± 541.75	1911.20 ± 622.26	1886.20 ± 608.11	1886.20 ± 600.72

Table-VI

Absolute increase of FEV_1 and FVC daywise in 7-day group

Variables	day - 0 to day - 1	day - 0 to day - 3	day - 0 to day - 5	day - 0 to day - 7	day - 0 to day - 10	day - 0 to day - 14
FEV_1 in ml.	150.00 ± 280.30	298.27 ± 313.17	423.27 ± 398.65	450.00 ± 385.04	456.03 ± 394.70	431.89 ± 393.97
FVC in ml.	113.79 ± 411.85	497.41 ± 615.07	643.96 ± 664.79	727.58 ± 707.33	747.41 ± 669.49	731.89 ± 674.69

Table-VII

Absolute increase of $FEV_1$and FVC daywise in 14-day group2

Variables	day - 0 to day - 1	day - 0 to day - 3	day - 0 to day - 5	day - 0 to day - 7	day - 0 to day - 10	day - 0 to day - 14
FEV_1 in ml.	85.34± 162.22	266.37 ± 218.17	331.03 ± 205.35	332.75 ± 203.55	320.68 ± 193.31	318.10 ± 194.44
FVC in ml.	157.75 ± 422.84	350.00 ± 408.83	491.37 ± 421.95	626.72 ± 507.17	601.72 ± 483.01	601.72 ± 473.11

Table-VIII

Daywise increase of symptom score

	7-day group			14-day group		
Variables	day - 0	day - 7	day - 14	day-0	day-7	day-14
Dyspnoea (rest day)	2.62 ± 0.49	5.51 ± 0.57	5.58 ± 0.56	2.24 ± 0.51	5.17 ± 0.80	5.27 ± 0.84
Dyspnoea (night)	2.58 ± 0.50	5.34 ± 0.55	5.37 ± 0.56	2.37 ± 0.49	5.34 ± 0.61	5.51 ± 0.63
Dyspnoea on exertion	2.58 ± 0.56	5.62 ± 0.67	5.65 ± 0.55	2.27 ±0.45	5.20 ± 0.77	5.41 ± 0.73
Sputum volume	2.44 ± 0.50	5.24 ± 0.57	5.34 ± 0.61	2.27 ± 0.45	5.00 ± 0.70	5.17 ± 0.54
Cough	2.41 ± 0.50	5.41 ± 0.62	5.55 ± 0.63	2.20 ± 0.41	5.06 ± 0.65	5.17 ± 0.71

Table-V shows that there is stepwise increase of absolute value of FEV_1 and FVC in group-1 from day-0 up to day-14 and is peaked on day-10.

It have been seen that there is stepwise increase of absolute value of FEV_1 and FVC in group-2(Table –VI) from day-0 up to day-14 and is peaked on day-7.

Symptom score: It has been seen that baseline symptom score is increased stepwise from day-0 to day-7 and day-14(Table-VII).

Adverse effects:

Dyspepsia: According to protocol Ranitidine (150mg) was given twice daily to every patient but no patient developed significant dyspepsia.

Diabetes mellitus and hyperglycemia : Three patients (n = 3) of 7-day group and 5 patients (n = 5) of 14-day group were diabetic and before giving prednisolone their diabetes was controlled by oral hypoglycemic drugs, only one patient of 14-day group was getting Inj. insulin. After 7 days both fasting and postprandial blood sugars were increased and dose of antidiabetic medication was adjusted accordingly.

Blood pressure: Three patients (n = 3) of 7-day group and five patients (n = 5) of 14-day group were hypertensive and they were getting anti hypertensive medications. After 7 days systolic blood pressure of all of those patients was found to be increased but there was no change of diastolic blood pressure.

Myopathy: In this short period patients general condition was improved considerably and quality of life increased by improving FEV1 and FVC, so,

it was difficult to detect any steroid induced myopathy.

Discussion:

The study was designed as a randomized, parallel group, single- blind study comparing the effects of 7 days and 14 days of treatment with systemic corticosteroid in acute exacerbation of COPD. It did not include a control group without any steroid treatment, as five controlled studies have already shown that those drugs were superior to placebo treatment, resulting in fewer treatment failures, shorter hospital stays, and faster improvement in FEV_1 levels.12,13,14 Each of the five studies used treatment regimens differing markedly in duration and dosing of the medication, and were performed on populations with varying disease severity. It is imperative that corticosteroids should be used for the shortest possible duration with optimum doses. Among those five, studies Davis et al concluded that postbronchodilator FEV_1 in patients receiving corticosteroid was 3 times that the patients receiving placebo and maximum improvement in FEV_1 was also seen by Day-5 in steroid treated patients significantly earlier than the placebo group but these benefit did not last beyond immediate hospitalization.

Subsequently, Abdullah saymer et al compared the efficacies of 3 day and 10 day courses of corticosteroid, and demonstrated that 10-day course of corticosteroid was superior to 3 days course. Despite these studiees the exact dose and duration of corticosteroid treatment remains elusive.

Oral or intravenous glucocorticosteroids are recommended as an addition to bronchodilator therapy in the hospital management of exacerbation of COPD. The exact dose that should be recommended is not known, but high doses are associated with a significant risk of side effects. Thirty to 40 mg. of oral prednisolone daily for 10 to 14 days is a reasonable compromise between efficacy and safety. Prolonged treatment does not result in greater efficacy and increases the risk of side effects.[14]

This recommendation of GOLD was taken in light of the result of studies of Davis et al and Niewoehner et al. Devis et al and Niewoehner demonstrated maximal benefit on day-5 and day-7 of treatment. In view of these studies, we should avoid burdening our patients with prednisolone for a long duration. In order to limit the duration of use of prednisolone this study was designed to ascertain whether there is any difference of improvement in between 7 - day and 14- day courses of treatment. In the absence of any difference, short course of corticosteroid may be recommended for patients with acute exacerbation of COPD, as the 7 days duration covers the range of maximum benefit of previous three most valuable studies.[10,12,14,15,16,17,18]

One of the limitations of this study was that the duration of hospitalization was not included as an end point. Instead, the patients remained in the hospital throughout the 14- day period according to protocol. This was both to ensure that all airflow measurements were performed with adequate technique, using the same apparatus, and to avoid the risk of losing patients to follow-up. The latter reason derives from the fact that the majority of the patients have functional and economical limitations for frequent visit to hospital.

The data of this study showed that corticosteroid treatment together with the optimal bronchodilator therapy resulted in marked improvements of FEV_1, FVC, and symptom scores of both 7-day group and 14-day group. There was stepwise increase of both FEV_1 and FVC in both groups, which reached a peak on day –10 in 7-day group and day –7 in 14-day group and sustained in both the groups up to day –14. There is delayed peak in 7-day group who were not getting corticosteroid after day-7, there is no significant difference of improvement of both FEV_1 and FVC on D_1, D_3, D_5, D_7, D_{10} and D_{14} between the groups. In spite of getting corticosteroid for 14 days in 14-day group there is earlier plateau. So, the latter peak in 7-day group is not considered to be due to effect of corticosteroid. In 7-day group the highest value of FEV_1, FVC was reached on day-10 i.e. 3 days after omission of corticosteroid, it may probably be due to some other factors like better general condition, earlier control of respiratory tract infection, which should be further evaluated.

The symptom scores were recorded on day-0, day-7, day-14 in both the groups and there is no significant difference of improvement of symptom score between the two groups on day -7 and day -14.

Saymer et al have demonstrated that a 10-day course of corticosteroid is better than a 3-day course. Similarly, Davis et al have shown highest value of FEV_1 on day-5 of a 14 day course. So it was inferred that the optimum duration lay between 5 to 10 days and hypothesized it to be 7 days. This study shows no significant difference between 7-day and 14-day course, and thereby

establishes the hypothesis that 7 days is the optimum duration of corticosteroid therapy in acute exacerbation of COPD.

In Bangladesh where most of the patients are poor and are unable to purchase expensive injectable corticosteroid, a short course of cheaper oral prednisolone will be a valuable adjunct to bronchodilator therapy along with antibiotics.

Conclusions:

There is no difference between 7-day and 14- day courses of oral prednisolone in the management of acute exacerbation of COPD. Interestingly, the peak in 7-day group on day-10 where corticosteroid was already stopped on day-7, might be due to some other factor/factors responsible which would be cleared by further study.

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Vol. 32, No.-1, January 2008

CASE REPORT

Bird Fancier's Lung in a Twelve Years Boy: A Case Report

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Abstract:
Master Rabbi, a rural boy of 12 had been suffering from exertional breathlessness, low-grade fever, cough & weight loss for one year. He gave history of pigeon breeding for last 5 years.

He was cyanosed and there was crepitation as well as scattered rhonchi in both lungs. HRCT of chest revealed bilateral reticulonodular opacities with apical fibrosis. FOB revealed inflammatory lesion with lymphocytosis in BAL fluid. Spirometry revealed mixed pattern. Patient was diagnosed as a case of Bird Fancier's disease. He was given steroid & responded well. He was advised to avoid exposure to bird & bird products.

[Chest & Heart Journal 2008; 32(1) : 62-64]

Introduction

Hypersensitivity pneumonitis (HP) or extrinsic allergic alveolitis is an immunologically induced inflammatory disorder of the lung parenchyma involving alveolar wall and terminal airways secondary to repeated inhalation of a variety of organic agents by a susceptible host.[1] Bird fancier's lung is one of the common HPs that results from inhalation of pigeon dropping extracts (PDE) or budgerigar dropping extracts (BDE) or antigens from feathers.[2] There are three types of BFL based on clinical features: acute, sub acute and chronic.[3]

Because strict definition of acute, sub acute and chronic stages of HP have not been generally agreed on, interpretation of epidemiologic and clinical studies can be difficult. Therefore it has been proposed that HP may be described as recently diagnosed recurrent or progressive or residual disease. For these categories required diagnostic criteria include the presence of an appropriate exposure, exertional dyspnoea and inspiratory creps and if performed lymphocytic alveolitis on bronchoalveolar lavage. Supportive criteria include recurrent febrile episodes, radiographic infiltrates, diminished pulmonary diffusing capacity, precipitating antibodies to appropriate antigens, histopathologic demonstration of granulomas and improvement in symptoms with avoidance of exposure. As the disease is not so common and the presentation in this early age in our case with definite history of pigeon exposure and many person in our country have had pigeon as pet animal or contact because of breeding purpose, we take the opportunity to report the case as part of social warning as well as academic interest.

Case Report:

Master Rabbi, 12 years old boy hailing from kendua Netrokona had been suffering from cough with occasional sputum, low grade fever of no definite pattern, respiratory distress and weight loss for one year. Respiratory distress was exertion initially but later became progressive .The boy had no history of chest pain, palpitation or coughing out of blood. He did not give any history of close contact

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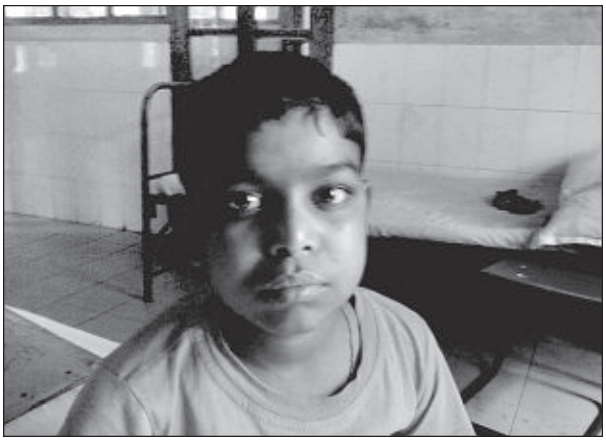

Fig.-1: *Master R after one month treatment with steroid.*

with tuberculosis patient. He had no history of bronchial asthma in the family. With this complaint he had been admitted in MMCH where some investigations were done and the boy was diagnosed as a case of bilateral bronchiectasis. He was given parenteral antibiotic of different kinds with postural drainage but patient did not improve. Then he got admitted in NIDCH for further evaluation & management. In our ward on intense query, he gave history of prolong contact with pigeon. In fact his father was running pigeon breeding business for ten years in his house and the boy was helping his father from a very tender age.Fortunately no other family member was suffering from this kind of disease.

Patient was dyspnoeic, febrile, highest recorded temp 101 °F. He was cyanosed. Pulse was 100-pm & regular, BP 110/70 mmHg and respiratory rate 24/min. Respiratory system examination revealed

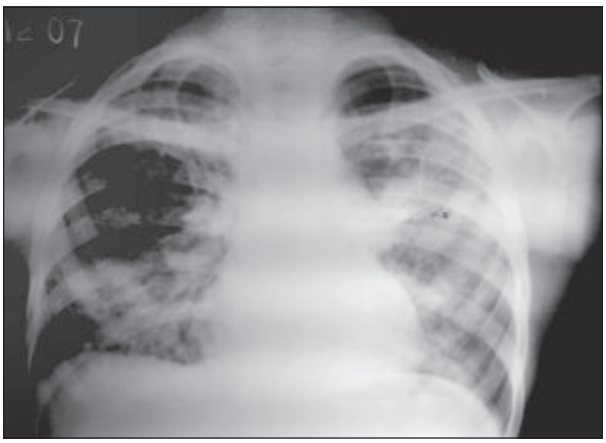

Fig.-2: *CXR PA view showing bilateral reticulonodular shadow.*

bilateral basal end inspiratory coarse creps. There was also bilateral scattered rhonchi.

There was no lymphadenopathy and no organomegaly. Other general and systemic examinations were unremarkable.

Routine blood examination showed neutrophilic leukocytosis, hemoglobin 11.4 gm/dl and ESR~80mm in 1st hour, Sputum negative for AFB, gram staining & C/S revealed no organism. Blood urea, sugar and creatinine were normal. His liver

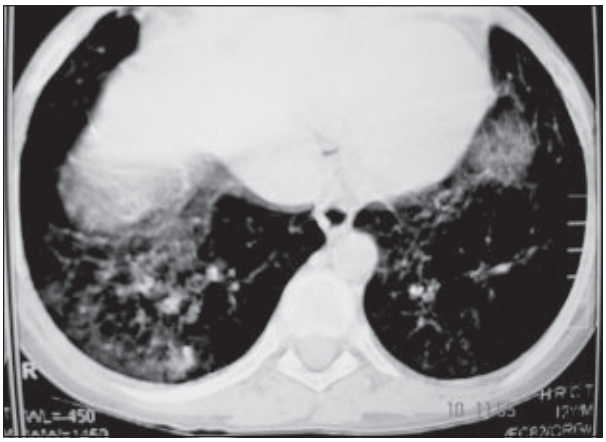

Fig.-3: *HRCT of chest showing reticulonodular and ground glass opacities in posterior basal region (both lungs).*

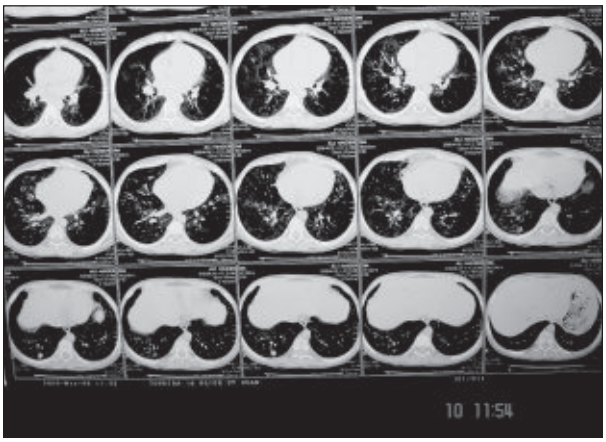

Fig.-4: *HRCT of chest in multiple sections showing bilateral reticulonodular shadow.*

function tests also were normal. Tuberculin test was negative. CXR showed reticulo-nodular shadows, marked on bi-basal area with scattered honey-combing change. RA- negative, ANA-negative. Spirometry revealed mixed pattern. ECG and ECHO were normal. FOB with BAL study was

done. FOB revealed inflammatory change and BAL showed lymphocytosis. Serum precipitin test- not available in all country. HRCT was done & revealed diffuse reticulonldular shadows in both lungs. We considered the case as Bird Fancier's disease (Pigeon breeder's lung).

The patient was prescribed antibiotic along with bronchodilator, Oxygen, fluid and nutritional support but improvement was little. Two weeks later prednisolone was started and patient gradually showed improvement and after 4 weeks of steroid therapy, patient was discharged with advice for follow up monthly. He was also asked to avoid exposure to birds and/or wear dust mask to minimize level of exposure.

Discussion:

Bird fancier's lung is a response to inhalation of bird proteins from feathers and droppings. The pathology of hypersensitivity pneumonitis suggests that both type III and type IV immunological mechanism may be involved[3]. Symptoms of acute BFL occur 4 to 6 hour after exposure to the etiologic antigen and consist of an abrupt onset of a flu-like syndrome characterized clinically by fever, chills, malaise and myalgia.[4] Respiratory symptoms are severe dyspnoea, chest tightness, and a non productive cough. Chest auscultation reveals widespread end inspiratory crackles and squeaks.[5]

Chronic BFL results from continued low-level exposure to the etiologic antigens of HP. Cases of chronic BFL can be classified into two types: One group develops chronic disease with fluctuating and waning acute episodes including a low-grade fever, mild exertional dyspnea and cough (fluctuating chronic BFL). The other group shows no history of acute episodes (insidious chronic BFL). The clinical features of chronic BFL-including imaging and histologic findings are very similar to idiopathic pulmonary fibrosis (IPF). Avian contact is the only clue to the diagnosis of BFL.[6]The chest X-ray shows diffuse micronodular shadowing that is classically more marked in the upper zones. HRCT in patient with acute disease shows bilateral areas of consolidation super imposed on small centrilobar nodular opacities and air-trapping on expiration. In more chronic disease, features of fibrosis with linear opacities and architectural distortion predominate.[7] Pulmonary function tests show a restrictive ventilatory defect.[8] The diagnosis of HP is usually based on the characteristic clinical and radiological features together with the identification of a potential source of antigen at the patient's home or place of work. The diagnosis may be supported by a positive precipitin test or by more sensitive serological tests based on the enzyme-linked immunosorbent assay (ELISA) technique.[9] But this test is not available in our country. Bronchoalveolar lavage fluid usually shows an increase in the number of CD8+ T lymphocytes in chronic case and neutrophils in acute case. Avoidance of exposure to the antigen is the key and steroid is the preferred treatment. In any patient suspected of bronchiectasis or interstitial lung disease occupational or vocational history of potential source of antigen at home or work place should be sought and age is not a bar in developing interstitial lung disease.

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ORIGINAL ARTICLE

Comparative study between Povidone Iodine and Tetracycline Hydrochloride as pleural Wash in Pyothorax

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Abstract:

This prospective comparative clinical study was conducted on empyema thoarcis patients of stage I and stage II disease to make a comparative evaluation of the efficacy of Povidone Iodine and Tetracycline Hydrochloride as adjuvant antimicrobial agents for pleural wash to augment the recovery process. Pleural wash was given following tube thoracostomy with strict adherence to the defined protocol. The findings of the study showed that age and sex were almost identically distributed among the three groups. A male preponderance was observed in all the groups. All the risk factors were found to be almost evenly distributed in all the groups. As outcome variables were compared, apart from culture of pus, all other variables like intercostal drain removed on (day), fever disappeared on (day) and duration of hospital stay were found to be significantly better in povidone group than those in tetracycline and control grup. The amount of pus in povidone group reduced to much lower level than those in tetracycline group. After 8^{th} and 10^{th} cycles of washes the proportion of complete stoppage of pus in povidone group was considerably higher (66.7% and 86.7% respectively) compared to that in tetracycline group (33.3% and 66.7% respectively) ($p < 0.05$). The mean number of wash needed in povidone group were 2 less than that required in tetracycline group. The intercostal drain was also removed 2 days earlier in povidone group than that in tetracycline group and 3 days earlier than that in the control group ($p < 0.05$).. Likewise the fever in povidone group disappeared at least 3 days earlier compared to tetracycline group and 4 days earlier compared to control group ($p < 0.001$). The average duration hospital stay was also found to be 3 days less in povidone group relative to tetracycline group and 5 days earlier relative to control group ($p < 0.001$). Post-wash chest skiagram revealed that 96.7% of the povidone iodine group re-expanded their lungs, while 86.7% of the tetracycline group and 66.7% of the control group did so. In terms of complications encountered by the patients and outcomes achieved the povidone group seems to be superior to tetracycline group.

[Chest & Heart Journal 2008; 32(1) : 14-19]

Introduction:

Presence of pus in pleural cavity is termed as pyothorax. The disease was initially described by Hippocrates[1]. Various therapeutic method can be adapted in the treatment of pyothorax[2] based on the stage of the disease, although great debate still surrounds the question 'what for the best therapy is' for particular stage of the disease[3]. Systemic

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antibiotic and drainage of empyema cavity remains the cornerstone of treatment of acutte pyothorx, though some adjuvant therapies like antiseptic pleural wash are also used to augment early recovery and minimize complications. In NIDCH, Mohakhali, Dhaka tube thoracostomy done in stage I & stage II empyema is invariably followed by pleural wash along with systemic antibiotic gives better outcome as adjuvant therapy.

Empyema thoracis may be non-traumatic or traumatic in origin. Non-traumatic cases are due to direct extension from an adjacent site. Lung infection is the most common cause and accounts for over half of the cases [4]. Cohen described that most pyothorax are the result of bacterial suppuration in the organs that are adjacent to the pleural surfaces. Half of the cases are secondary to the complications to primary pneumonic process. The second most common group includes patients who underwent operation in lung, mediastinum or oesophagus, This group includes instrumentation and rupture of oesophagus, leakage of an oesophageal anastomosis after resection and development of broncho-pleural fistula following tube thoracostomy, pneumonectomy and thoracocentesis[5]. Spontaneous pneumothorax, chest trauma, repeated thoracentesis, tube thoracostomy, sub-phrenic abscess, foreign body retained in the bronchial tree and spontaneous rupture of oesophagus may also produce empyema[4]. Non-surgical penetrating trauma to the chest may occur as a result of Road Traffic Accident, stabbing, gun-shot wounds, blust injuries.

Common aerobic and anaerobic bacteria leading to empyema thoracis are staphylococcus aureas, Streptococcus pneumoniae, Haemophillus influenzae, Pseudomonas aeroginosa, E.Coli, Klebsiella, Bacteroid species, Fusitorm bacterium and peptostreptococcus [1].

The American Thoracic Society divides the formation of an empyema into three stages.

Stage- 1 : Exudative or acute phase characterised by swelling of the pleural mambranes, pleural fluid of low viscosity, low cellular contonts. Glucose, PH and LDH lebel of plural fluid all remain normal. The visecral pleura and underlying lung remain expandable.

Stage II : Fibrino purulent or transitional stage: is characterised by more turbid fluid and an increase in polymorphs. Fibrin deposited on both pleural surfaces and forms the limiting 'peel' that prevent the extension to empyema but also begins to trap the lung. Pleural fluid glucose and PH progressively decrease and LDH increase.

Stage III : Organizing or chronic phase in characterized by organization of the pleural 'peel' or cortex with growth of capillaries and fibroblast. Pleural fluid is viscous and high in sediment. The PH is often less than 7 and glucose is less than 40 mg/dl. Empyema thoracis may also be classified based on duration of illness as: (a) Acute: when the duration of illness is less than 6 weeks and (b) Chronic: An empyema that has been present for 6 weeks or more is chronic phase[6].

Materials and Methods:

The study was conducted at the Department of Thoracic Surgery, NIDCH, Dhaka. from July 2003 to June 2005.

A total of 90 cases of empyema thoracis were selected and were nonrandomly consecutively allocated into Povidone Iodine (Group-A), Tetracycline Hydrochloride (Group-B) and Control Group (Without pleural wash) Containing 30 patients each.

Empyema thoracis patients of stage-I and stage- II with drainage of pus > 100 ml/day for consecutive 3-5 days having bacterial culture of pas exhibiting growth of gram positive and gram negative species sensitivity to Ciprofloxacin and metronidazole were only included in the study.

In Group-A wash was given with 0.5% Povidone Iodene in 1:20 dilution. This was prepared by adding 10 ml of 10% Povidone Iodine to 200 ml of Normal saline. After instillation of povidone Iodine through thoracostomy tube, the tube was clamped for 4 hours and then declamped. In group-B the wash was given with Tetracycline Hydrochloride which was prepared by adding 1 gm. of oily solution of Tetracycline Hydrochloride to 200 ml of Normal saline and was then instilled to the plural space following same procedure as in Group-A.

Data were processed and analyzed using computer software. The test statistics used to analyze the data were descriptive statistics, Chi-square probability test and ANOVA. Categorical data were

expressed as percentage and evaluated using Chi-square probability test. The level of significance was 0.05. P-value <0.05 was considered significant. The summarized information were then presented in the form of tables and charts.

Results:

Out of total 90 subjects selected for study, 30 were in Group-A (Povidone Iodine wash), 30 were in Group-B (Tetracycline hydrochloride wash) and 30 as Group-C (without any wash). The findings derived from data analysis are furnished below:

Age distribution

Table-I

Age distribution of the patients among groups.

Age (yrs)	Croup		
	Group-A (n = 30)	Group-B (n = 30)	Group-C (n = 30)
<20	1 (3.3)	00	2 (6.7)
20-30	3 (10.0)	1 (3.3)	3 (10.0)
30-40	12 (40.0)	9 (30.0)	10 (33.3)
40-50	9 (30.0)	18 (60.0)	9 (30.0)
> 50	5 (16.5)	2 (6.7)	6 (20.0)
Mean + SEM	37.80 + 1.67	39.70 + 1.27	36.90 + 1.11

* Figures in the parentheses indicate percentage;

Table I Compares the distribution of age between groups. The highest frequency of empyema thoracis was observed in between 30-50 years and the least frequency in ages below 20 years. 'the mean ages Group-A, Group-B and Group-C were 37.80 + 1.67, 39.70 + 1.27 and 36.90 + 1.11 years respectively.

Sex distribution

Table-II

Sex distribution of the study patients among groups.

Sex	Croup		
	Group-A (n = 30)	Group-B (n = 30)	Group-C (n = 30)
Male	21 (70.0)	19 (63..3)	20 (66.7)
Female	9 (30.0)	11 (36.7)	10 (33.3)

* Figures in the parentheses indicate percentage;

Table II Demonstrates the distribution of sex among the three groups. Twenty-one (70%) subjects of Group-A 19 (63.3%) of Group-B and 20 (36.7) of Control group were males and the rest 9 (30%) of Group-A, 11(36.7%) or Group-B and 10 (33.3%) of Controls were females. the male-female ration was 7:3 in Group-A 19:11 in Group-B and 2:1 in Group-C.

Type of microorganisms found

Table-III

Distribution of microoganism among groups.

Microorganisma	Croup		
	Group-A (n = 30)	Group-B (n = 30)	Group-C (n = 30)
Staphylococcus aureus	11 (36.7)	13 (43.3)	10 (33.3)
Streptococcus pneumonae	7 (23.3)	6 (20.0)	6 (20.0)
Pneumococcus	4 (13.3)	4 (13.3)	5 (16.7)
Klebsiella	4 (13.3)	2 (6.7)	4 (13.3)
Escherichia coli	2 (6.7)	2 (6.7)	2 (6.7)
Pseudomonas	2 (6.7)	3 (10.0)	3 (10.0)

* Figures in the parentheses denote percentage;

Table III demonstrates the distribution of causative microorganisms among groups. The predominant organism in all the groups were staphylococcus (36.7% in Group-A, 43.3% in Group-B and 33.3% in Group-C), followed by streptococcus (213.3% in Group-A, 43.3% in Group-B and 33.3% Group-C), Pneumococcus (13.3% in Group-A, 6.7% in Group-C), Klebsiella (13.3% in Group-A, 6.7% in Group-B and 13.3% in Group-C), Escherichia coli 6.7% in each group and Pseudomonas (6.7% in Group-a, 10% in Group-B and 10% in Group-C).

Pre-wash X-ray chest findings.

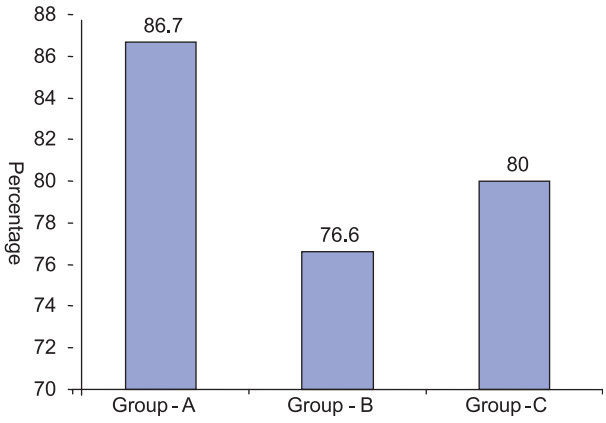

Fig. 1 : *Comparison of Pre-wash X-ray chest findings.*

Fig. 1 Shows comparison of X-ray chest findings among groups. 18 (60%) subjects of group-A, 20 (66.7%) of Group-B and 21 (70%) of Group-C had

hydropneumothorax and the rest of respective groups had hydrothorax only.

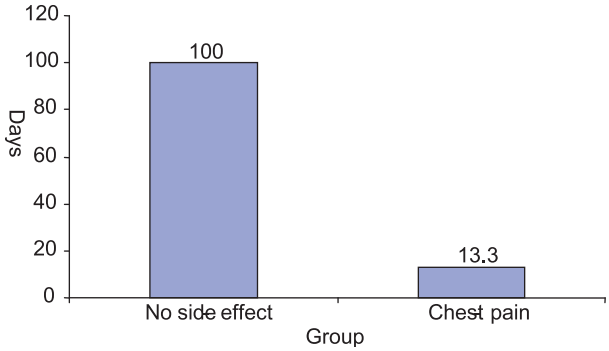

Fig. 2 : *Comparison side effects among groups.*

Side-effects during instillation of drugs.

Fig. 4 Compares the side-effects during instillation of local antimicrobial agents in pleural space. In Group-A (povidone iodine) none of the subjects showed any side effects, while 4 (13.3%) subjects of Group-B (tetracycline hydrochloride) complained of chest-pain. However, the groups were not found to be different in terms of side-effect during instillation of local adjuvant agents ($p > 0.05$).

Cessation of drainage of pus.

Table IV

Comparison of cessation of pus among groups.

Baseline variables	Croup			P-value
	Group-A (n = 30)	Group-B (n = 30)	Group-C (n = 30)	
6th day	6 (20.0)*	4 (13.3)	1 (3.3)	0.127
8th day	20 (66.7)	10 (33.3)	5 (16.7)	0.031
10th day	26 (86.7)	20 (66.7)	15 (50.0)	0.042
12th day	28 (93.3)	25 (83.4)	20 (66.7)	0.045

* Figures in the parentheses indicate percentage;

 # Chi-square (X^2) Test was done to analyze the data.

Table IV compares the rate of cessation of pus following start of treatment among the three groups. Evaluation on 6th day demonstrated that 20% of Group-A, 13.3% of Group-B and 3.3% of Group-C completely ceased the drainage of pus, although the difference was not statistically significant ($p > 0.05$) However, from 8th day onwards the rate of cessation of pus was significantly faster in Group-A and Group-B compared to the of Group-C ($p < 0.05$). One 12th day 93..3% of the Group-A, 83..4% of Group-B and 66.7% of Group-C became completely free of pus ($p < 0.05$). Data also shows that cessation of pus in Group-A was significantly faster that in Group-B at all level of evaluation ($P < 0.05$).

Post wash culture of pus.

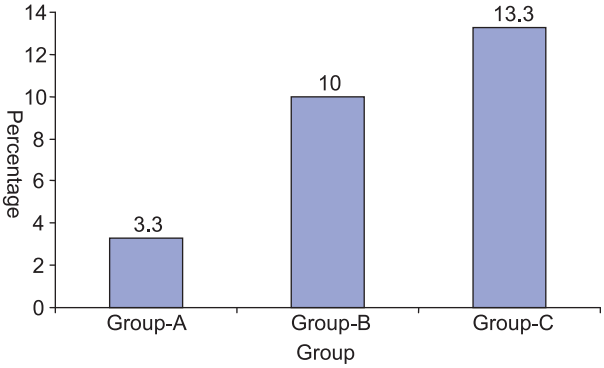

Fig. 3 : *Comparison the postwash culture of pus.*

Fig. 3 Shows the comparison of post-wash culture of pus among groups. In Group-A 1 (3.33) % and in Group-B 3 (10%) patients showed positive culture of pus, while 4 (13.3%) of the Group-C showed culture positive pus.

Post wash X-ray chest findings.

Table-V

Comparison of Post-wash X-ray chest findings among groups.

X-ray finding	Croup			P-value
	Group-A (n = 30)	Group-B (n = 30)	Group-C (n = 30)	
Lung Expanded	28 (93.3)	26 (86.7)	20 (66.7)	0.037
Lung not expanded	2 (3.3)	4 (13.3)	10 (33.3)	

* Figures in the parentheses indicate percentage;

** Chi-square (X^2) Test was done to analyze the data.

Table V compares the post-wash expansion of lungs among groups. In Group-A 28 (93.3) patients exhibited complete expansion of lungs on X-ray chest while in Group-B 26 (86.7%) showed compete expansion of lungs. The Group-C demonstrated significantly less proportion of subjects with compete expansion of lungs 20 (66.7) The three groups were significantly different in terms of complete expansion of lungs with best achievement in Group-A followed by better in Group-B and good in Control group ($p < 0.05$).

Day of removal of intercostals drain tube.

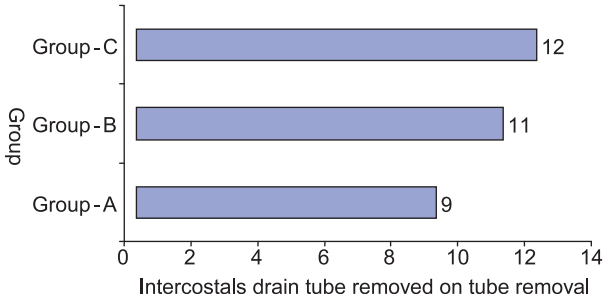

Fig.-4: *Comparison of intercostal drain tube removal.*

Fig. 4 Shows the comparison of removal of intercostal drain tube among three groups. In group A 9.3 + 0.42 days and in group-B 11.07 + 0.37 days were required for removal of intercostal drain tube. The Group-C needed even more days (12.03 + 0.20 days) for removal of the tube.

Fever resolved on the day.

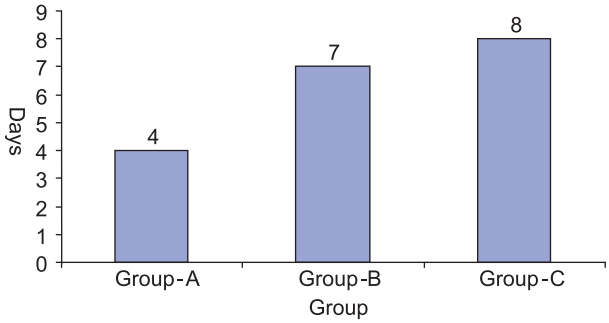

Fig. 5 : *Comparison of resolution of fever.*

Fig.-5 Shows comparison of resolution of fever among three groups. In Group-A 4.2 + 0.33 days, in Group-B 7 + 0.31 days in Group-C 8 + 0.54 days were needed for complete resolution of fever following wash.

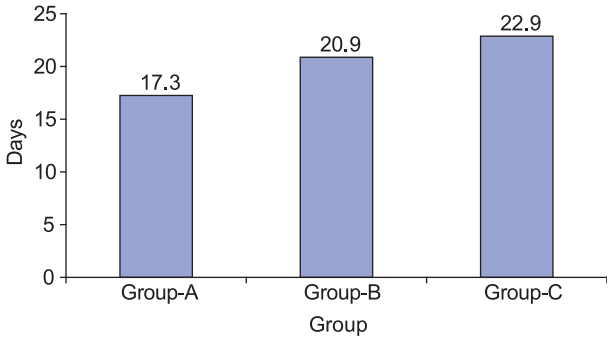

Fig. 6 : *Comparison of hospital stay among groups.*

Total hospital stay (days)

Fig. 6 Shows comparison of total hospital stay among groups. The mean hospital stay in Group-A was observed to be significantly less (17.3 + 4.6 days) compared to Group-B (20.9 + 0.13 days) and Group-C (22.9 + 0.71 days).

Complications encountered by the groups.

Table VI

Comparison of complications between groups.

Complications#	Croup			P-value
	Group-A (n = 30)	Group-B (n = 30)	Group-C (n = 30)	
No complication	28 (93.4)*	25 (83.4)	20 (66.7)	0.049
Infection Persisted	1 (3.3)	3 (10.0)	4 (13.3)	0.039
Collapsed lung	1 (3.4)	1 (3.3)	2 (6.7)	0.021
Thickened Pleura	00	1 (3.3)	2 (6.7)	0.534
Bronchopleural Fistula	00	00	2 (6.7)	

* Figures in the parentheses indicate percentage;
** Chi-square (X^2) Test was done to analyze the data.

Table VI compares the complications developed among groups. Out of 30 patients in Group-A

Post-wash outcome variables.

Table VII

Comparison of post-wash outcome variables among groups.

Outcome variables#	Croup			P-value
	Group-A (n = 30)	Group-B (n = 30)	Group-C (n = 30)	
Complete cessation of pus#	28 (93.4) *	25 (83.4)	20 (66.7)	0.049
Culture of pus (+ ve) #	3.3%	10.0%	13.3%	0.306
Intercostal drain removed on (day) ¶	9.30 + 0.42	11.07 + 0.37	12.13 + 0.54	0.028
Fever resolved on (day) ¶	4.20 + 0.33	7.0 + 0.31	8.0 + 0.54	<0.001
Total hospital stay (days) ¶	17.33 + 0.46	20.97 + 0.13	22.91 + 0.71	< 0.001

Chi-square (X^2) Test was done to analyze the data.
¶ Data were analyzed using ANOVA and presented as mean + SEM.

28 (93.4%) did not have any complications. Only 1 (3.3%) patient showed collapsed lung and 1 (3.3%) continued infection. In Group-B 25 (83.4%) patients showed complete recovery, 3 (10.0%) persisted infection, 1 (3.3%) showed collapsed lung and 1 (3.3%) thickened pleura. In Group-C 20 (66.7%) had no complication and 4 (13.3%) persisted. infection. Collapsed lung, thickened pleura and bronchopleural fistula was each 2 (6.7%) collapsed lung. The Group-C had significantly worse outcome compared to Group-A and Group-B in terms of complications like collapsed lung, persisting infection, ($P<0.05$).

Table VII compares the outcome of intervention among the three groups. Apart from culture of pus, all other outcome variables like complete cessation of pus, intercostal drain removed on (day), fever disappeared on (day) and hospital stay responded significantly better in Group-A and Group-B compared to Group-C with Group-A achieving better result than Group-B ($p = 0.049$, $P = 0.028$, $p < 0.001$ and $p < 0.001$ respectively).

Conclusion

The findings derived form data analysis suggest that povidone iodine is a better adjuvant therapy for pleural wash than tetracycline hydrochloride. However, as the study was conducted on a small sample-size and was unblended, it requires to be validated by a double blinded study with larger sample size. Povidone iodine might be a promising adjuvant therapy for pleural wash, provided its high efficacy and low toxicity stand to large-scale study.

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ORIGINAL ARTICLE

Temporary Cardiac Pacing - Experience In University Cardiac Center, BSMMU, Dhaka

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Abstract:

This prospective study was conducted in the Department of Cardiology. University Cardiac Center, BSMMU, Dhaka from July 2004 to July 2007 to evaluate the indications, complications and in-hospital outcome of Temporary cardiac pacing (TPM) in 96 consecutive patients. There were 76 male and 20 female age ranged between 22-83 years. 80 percent of the patients admitted directly while the rests were referred cases. Degenerative complete heart block was the most common cause. Seventy eight percent of the TPM implantation was done on emergency basis. Majority (96.74%)of the procedures were performed through femoral route. Complications during the procedure and thereafter during hospital stays were noted. Ventricular fibrillation requiring defibrillation occurred in 9 cases and one patient required advanced life support due to cardiac asystole. Displacement of TPM lead occurred in 15 (15.62%) cases, deep vein thrombosis developed in 03 (3.12%) cases and no patient died during hospital stay. Temporary pacing is the most emergency procedure and a potentially life saving intervention used primarily to correct profound bradyarrythmia. The indications and techniques are well established. This life saving cardiac procedure should be one of the essential component of the training programme of junior doctors and to be taught at the bedside by the fellow doctors or consultant cardiology for the proper management of patients requiring temporary cardiac pacing.

Key Word : Cardiac Pacing: Temporary.

[Chest & Heart Journal 2008; 32(1) : 20-23]

Introduction:

Temporary transvenous cardiac pacing is one of the life saving cardiac emergency intervention in the daily practice of interventional cardiology. Initially TPM used to be done by cut down method through cephalic or brachial vein. Later femoral approach came into practice and has become almost a sole route in current years. But information regarding various aspect of this commonly practiced emergency procedure are still lacking remarkably at home and abroad. This prospective observational study aimed to provide information

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on the current practice and complications of TPM which may become useful in guiding management of patients under going such procedure as a part of learning at a junior level of doctors. So information obtained from the study at various aspects of the procedure points to some valuable suggestion that may be useful in the proper management of patients requiring temporary cardiac pacing.

Methods & Material:

This prospective study was carried out in the department of Cardiology, University Cardiac Center (UCC), BSMMU from July 2004 to July 2007 including all consecutive patients who were admitted for TPM implantation. Details history of the patients were taken including indications for TPM and the time when the procedure was done. Who performed and who supervised the procedures were also registered including the route used for venous access. Complications occurring during the procedure and thereafter to till discharge were also recorded. The time lapsed between TPM to permanent pacemaker implantation was also taken into account. The collected datas were analyzed and expressed as percentage.

Result :

Of the 96 patients, 76 were male and 20 female, age ranged from 22-83 years. (Table-1). 80% patients admitted directly and rest of the patients were referred from different hospitals. Syncope, near syncope, dizziness, palpitations, shortness of breath etc. were the characterestic presentation in the study population, (Table-2). The indications (Tabal-3) for TPM were degenerative heart block of various patterns in 46 (47.84%) patients, sick sinus syndrome in 6 (6.24%) patients and acute myocardial Infarction in 14 (14.56%) patients. Majority of the procedure were done between 9 A.M. to 8 P.M. Ten cases were done by the consultant while rest of cases were done by post graduate doctors or house officers or students. Consultant supervised the procedure in 86 cases most of which done by the post graduate students and house officers. In 93 (96.74%) cases femoral route were chosen while in 02 (2.08%) cases subclavian route was used (Table-4). Complications that occurred during the procedure such as femoral artery puncture in 05 (5.2%) cases; in one (1.04%) case there was asystole (VA) which warranted advanced life support after the procedure; lead displacement occurred in 11 (11.44%) cases, deep vein thrombosis (DVT) in 03 (3.02%) cases and in 03 (3.02%) cases there was wound infection (Table-5). No death occurred in the patients of the study. 34 (34.41%) patients out of 96 required permanent pace maker implantation. In case of acute myocardial infarction (AMI) of 14 patients 7 patients required permanent pacing i.e. PPM (Table-6). The time lapsed from temporary to permanent pacing was 08±03 days.

Table-I

Demographic data of the study population (n=96)

Age range (22-83) Year	Male	Female	Total
20-29	01	01	02
30-39	02	02	04
40-49	05	03	08
50-59	19	05	24
60-69	17	04	21
70-79	25	04	29
80-89	07	01	08
Total	76	20	96

Table-II

Clinical characteristics of the study population (n=96)

Symptoms	No. of cases	Percent (%)
Syncope	18	18.75
Near syncope	14	14.58
Dizziness	19	19.76
Palpitations	20	20.83
Shortness of breath	15	15.62
Others- Vertigo, Nausea.	10	10.41

Table-III

Indications for TPM of the study population (n=96)

Parameters	No. of cases	Percent (%)
Degenerative Heart Block :	46	47.84
Complete heart block (CHB)	34	35.36
Intermittent CHB	03	3.12
Type 2^0 HB	05	5.2
Bifascicular block (BFB)	03	3.12
Trifascicular block (TFB)	01	1.004
Sick sinus syndrome (SSS)	06	6.24
In AMI setting :	14	14.56
Anterior MI with CHB	09	9.36
Inferior MI with CHB	02	2.08
Anterior MI with BFB	01	1.04
Anterior MI with TFB	02	2.08
Symptomatic sinus Brady cardia	02	2.08
Bridge to Permanent Pacemaker	09	9.36
During PCI	19	19.76

AMI- Acute myocardial infarction; PCI- Percuteneous coronary intervention.

Table-IV

Routes of approach to TPM (n=96)

Routes	No. of cases	Percent (%)
Femoral Vein	93	96.74
Brachial Vein	01	1.04
Sub. Calvin Vein	02	2.08

Table-V

Complications of TPM in the study population (n=96)

Parameters	No. of cases	Percent (%)
During the procedure		
Arterial puncture	5	5.2
Vasospasm	09	9.36
AV fistula	02	2.08
VES	40	41.6
VT	12	12.48
VF	9	9.36
VA	1	1.04
Vasovegal attack	5	5.2
After the procedure		
Lead displacement	15	15.62
DVT (Deep Vein Thsembosia)	03	3.12
Wound infection	05	5.20
VES	29	30.16
VT	05	5.2
VF	01	1.04
VA	00	00
Adhesion of lead	01	1.04
Bleeding	03	3.12

VES - Ventricular extra systoles, VT-Ventricular Taclycardia, VF-Ventricular Fibril lotion,VA-Ventricular Asystole.

Table-VI

Outcome of TPM in the study population (n=96)

Parameters	No. of cases	Percent (%)
Convert to sinus rhythm	62	64.58
Permanent pacemakers implanted	34	35.41

Discussion:

Temporary transvenous cardiac pacing is the most commonly practiced emergency cardiac procedure. Majority being done on emergency basis and all levels of physiclans are involved. Degenerative complete heart block is the leading indication, followed by management of various complications of acute myocardial infarction (AMI).

Most of the procedures were done between 9 AM. to 8 PM. Majority of the procedures were either done or supervised by qualified cardiologist. For one or other reasons femoral route was the most preferred route of TPM insertion although only in two cases subclavian route was chosen. This is contrast to the study done by others where they found subclavian route as choice in 80% of the cases[1,2]. Arterial puncture was one of the complication that occurred during the procedure. This complication in our study is possibly due to the fact theat many of the procedure are performed by post graduate trainee. Advanced life support was required in 9 cases out of which 8 due to ventricular tachycardia (VT) or fibrillation (VF) and one due to asystole (VA) required. More or less similar results were noted by others at home end abroad[1,5]. This signifies the importance of presence of specialist during the procedure and the necessity of availability of all supportive measures. There was no death during the procedure. Since a significant portion of the cases undergoing TPM

are elderly, and are exposed to syncope prior to admission, special care regarding fluid and electrolyte in them is important.

A significant number of cases required repositioning, some of them on urgent basis. Since the average time lapsed between TPM and PPM in the study was 8±3 days, utmost care should be taken in transferring patients from intensive or intermediate care unit to general ward, as some of them may require repositioning on emergency basis. It will be also worth while to see if TPM done in subclavin route requires less repositioning. Besides displacement of lead 3 patients developed deep vein thrombosis a complication unique to femoral route. Surprisingly septicemia was nil in our series, in contrast to Murphy who found it in 5% of his cases[1]. Although complications like pneumothorax and brachial plexus injury may occur in patients in whom TPM is done through subclavian route, these complications seems to be rare when done in expert hands[3,4]. In this study femoral route was chosen mostly, though these patients required long immobilization and in some of them lower limbs were passively immobilized. As a result lead displacemecet, deep vein thrombosis and wound infection were common in this patients with respect to using subclavian route. The procedure can be made cost effective by reusing cordissheath instead of puncture set. Infection is a particular problem in those patients. Whose electrodes remain in situ for more than 48 hours septicaemia developing in 10 of 53 patients in one series[1]. The patient who has had to wait to be transferred for a permanent pacemaker system is especially valnerable to this complication; the ensuing implant is in turn more likely to become infected which adds further to suffering and expenses[5,6].

In an institution like UCC, BSMMU where majority of working doctors and house officers are trained in Cardiology, the practice of inserting TPM through subclavian route seems to be useful and it will be interesing to compare the convenience and complications among the route used.

This study highlights most of the procedures done under supervision, acute complications were managed very well and thus it has become a safe procedure. But using femoral route and the long time elapsed between TPM and PPM give much discomfort to the patient and also risking them to develop certain complications more[7]. Moreover lead displacement and scarcity of beds in critical and intermediate care unit expose them to high risk of fatal event. Using subclavian route or securing critical care beds for high risk patients or minimizing time between TPM and PPM may mitigate the risk and discomfort that the patients are suffering from present practice.

Conclusion:

Temporary transvenous cardiac pacing is a potentially life saving procedure for patients in whom there is an actual or a high risk of bradyarrhythmias or asystole in the emergency setting. It is important to draw attention to the indications for temporary cardiac pacing. For those doctors who provide or wish to provide an emergency pacing service, guidance on the number of procedures to achieve and maintain competence is required.

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REVIEW ARTICLE

A Vaccine for Hypertension: To Have or not to have

Md. Roushon Ali, ASM Giasuddin

Abstract:

Hypertension or high blood pressure is a chronic condition of dysregulated renin-angiotensin-aldosteron system (RAAS) involved in autoregulation of blood pressure (BP). Hypertension is the level of BP at which the benefits of treatment with drugs outweigh its costs and hazards. Many important and efficient agents have been added to the list of drugs for oral treatment in recent times. However, lack of compliance is a major problem in controlling hypertension with oral treatment. The idea for development of a vaccine for hypertension was therefore conceived for long term control of BP endogenously. However, many important questions such as ethical issues, risks, cost, urgency, justification of complex immunological research, etc have to be answered before saying 'yes' or 'no' to a vaccine development for hypertension. It seems logical to suggest that the debate remains open whether to have or not to have a vaccine for hypertension. In this review article attempts have been made to give an up-to-date account in this regard about a vaccine for hypertension.

[Chest & Heart Journal 2008; 32(1) : 40-45]

Background

History of vaccination goes back to the last decade of the 18th century, i.e. more than 200 years, when Edward Jenner originally designed innoculation against cowpox and subsequently against small pox[1,2]. Vaccines were initially developed to protect mankind from infectious diseases and for eradication of these diseases such as smallpox, poliomyelitis, etc. Their use in billions of people has proved their efficacy for these purposes[2,3,4]. Vaccinology has now advanced to the point that we are able to protect humans against most of the important infectious diseases with vaccines such as polio, DPT, MMR, HBV (HBsAg), etc. However, many more emerging exogenous infectious diseases still remain for which vaccines are urgently needed such as AIDS, SARS, HCV, malaria and other parasitic infections, H5-N1 Avian influenza, Dengue fever, Cancer[4,5,6,7].

High blood pressure (BP) or hypertension is the level of BP at which the benefits of treatment with drugs outweigh its costs and hazards. The Seventh Joint National Committee Report (JNC-VII), USA published in 2003 with key recommendations has changed the understanding and consequently clinical management of hypertension with newer antihypertensive drugs[8,9,10,11]. However, lack of compliance is a major problem in controlling hypertension with oral treatment. The idea for development of a vaccine for long term control of BP endogenously was therefore conceived. However, many important and vital questions such as ethical issues, risks, cost, urgency, etc have to be answered adequately to justify the complex immunoligical research relevant to the development of a vaccine for hypertension.

Historically attempts have been made to blockade the renin-angiotensin-aldosterone-system (RAAS) by immunisation to control BP in animals as well

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as humans. In this review, we have therefore made an attempt to answer the questions posed and to focus on the present status of an effective and viable vaccine for hypertension based on blocking the RAAS immunologically.

The RAAS, Blood Pressure & Hypertension

As past and recent attempts to immunize animals (rats, rabbits, dogs, monkeys) as well as human patients targeted the RAAS, it should be of particular interest to refresh our knowledge about this system. In figure-1 and figure-2, the autoregulation of extracellular fluid volume and blood pressure are presented[12].

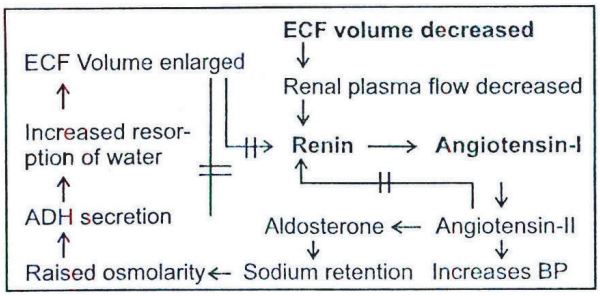

Fig.-1: *Autoregulation of extracellular fluid volume.*

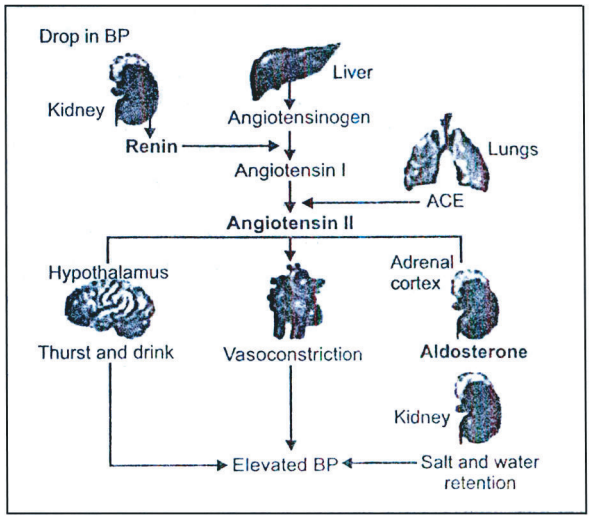

Fig.-2: *Renin-Angiotensin-Aldosterone mechanism.*

Recently, normal systolic blood pressure (SBP), normal diastolic blood pressure (DBP) and hypertension were redefined and classified as stated in Table-1 (According to the JNC-VII, USA)[8,9,10,11].

Table-1

Classification of blood pressure for adults 18 years of age and older in the recommendations of the Sixth and Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI and JNC VII).

JNC-VI (1997)	Blood pressure (mm Hg)	JNC-VII (2003)
Optimal	<120 & <80	Normal
Normal	120-130 & 80-85	Pre-hypertension
High-normal	130-139 & 85-89	
Hypertension		
Stage 1	140-159 or 90-99	Stage 1
Stage 2	160-179 or 100-109	Stage2
Stage 3	>180 or >110	(>160 or >100)

It is obvious that renin and angiotensin-II could be the major target for blocking by immunisation in order to control high blood pressure.

The RAAS & Vaccination

In 1958, Page expressed his vision of the therapeutic possibilities offered by the synthesis of angiotensin I, angiotensin II and the N-terminal sequence of angiotensinogen and the resolution of their structures. He said that the possibility of operating on renin, i.e. to prevent or control the rate at which angiotensin I is formed, or on the converting enzyme to prevent or control angiotensin II formation, is worth considering. A small molecular antagonist (not a peptide) of angiotensin might be found if one had some angiotensin for the pharmacologists to use in a screening test. It took a long time for Page's prediction to become a reality through the discovery of captopril in 1972 and many others more recently[10,13]. (Further discussion in detail about the pharmacological treatment of hypertension is outside the scope of the present review). As science has no boundary and scientists are never contended with their discoveries, they have turned their attention to control hypertension by vaccination.

Historically, vaccination against the RAAS began with the simple administration to hypertensive patients of a slightly modified 'pure' renin to generate antibodies with the aim of decreasing blood pressure[14]. With all that we now know about the required level of quality control for biological products designed to be administered to humans, and the development of ethics concerning the

patients participating in clinical trials, the abridged route used at the time for testing a hypothesis in a small number of patients, with a home-made protein, now seems quite risky. However, at that time little was known about the transmission of diseases by pathogens present in biological extracts (transfused blood, extractable growth hormone, vaccines). In the absence of a widespread pharmacological treatment for severe hypertension, experimental and compassionate objectives were closely linked and this was probably accepted. Initial attempts to immunize patients against the RAAS targeted renin. Several experimental studies involving well described protocols used in monkeys and dogs were published at approximately the same time[15,16]. A burst of experimental activity in the field of anti-RAS immunisation focused on angiotensin-II in rats and rabbits. Antibodies were successfully raised and used towards development of radioimmunoassay for peptides[17,18,19]. Some years ago, clinical & experimental results on anti-angiotensin I vaccination were also published[20,21,22]. Although the results were encouraging they need to be carefully evaluated and considered from ethical point of view.

In a recent article, Ambühl et al described the preclinical development and the phase-I clinical trial of a virus-like particle (VLP) and angiotensin-II derived peptide conjugated to VLPQ-based antihypertensive vaccine (AngQb). AngQb reduced blood pressure to levels obtained with ACE inhibitor in spontaneously hypertensive rats (SHR) and is immunogenic and well tolerated in humans[23]. Therefore, vaccination against angiotensin-II has the potential to become a useful antihypertensive treatment providing long-lasting effects and improving patients compliance[23]. However, the study of Ambühl et al could be seen as a mixture of insufficiently documented animal experiments and preliminary clinical results. Renin immunization decreased blood pressure in marmosets and rats, but also induced an immune disease of the juxtaglomerular apparatus in marmosets due to the use of an unsophisticated immunization procedure[24]. However, it is surprising that so few long-term animal data were generated before trials of angiotensin II immunization in humans were considered, particularly given that one case of renal abnormality was reported in the experimental part of the work[23,24].

Ethical Aspects

Immunological blockade of the RAAS is one way forward and general advances in the field of vaccine development should soon generate new tools. We should not fear these new opportunities and attempts to study immunization against RAAS elements in animal models, and subsequently clinical trials in phases in human to develop an effective and viable vaccine for hypertension. However, a number of ethical issues have to be properly addressed to consider RAAS vaccination as a research priority[25].

The public needs to have confidence in clinical investigations, the experts (doctors) and the external protection systems (institutional ethical, review boards, health authorities, insurance) as the financial incentives persuade people to participate in clinical (experimental) trials. No-one wants to take unnecessary risks and this is a perfectly normal reaction. The risk faced by the volunteers is unacceptable and unpredictable, particularly if the volunteers concerned, regardless of their blood pressure, have no intrinsic risk factors or need for treatment. The acceleration of scheduled clinical investigation protocols does not benefit normal subjects. Therefore, it would be worthwhile to preserve a safety window between individual experiments in old cases. The need for such measures is clearly illustrated by the most recent episode in the clinical inspiration storm: the TGN 1412 trial[25,26,27]. In another context, a vaccine against the â-amyloid substance responsible for Alzheimer's disease has been reported to induce an autoimmune disease[28]. Activists are still fighting against use of hepatitis B vaccines, which they suspect may cause multiple sclerosis[29,30].

Clearly long-term survival studies in various animal models will certainly be required to demonstrate efficacy and safety of RAAS vaccination. Each type of RAAS vaccination will need to be tested in various experimental models, with exploration of the control of sodium (Na^+), potassium (K^+) and water (H_2O) balance in stress situations, the intensity and duration of the

protective immune responses and possible signs of immunological tolerance or dysregulation[25]. The immune responses, protective or harmful, are extremely complex mechanisms involving antigen presenting cells, B-cell subsets, T-helper cell subsets, T-suppressor cell subsets, T-contrasuppressor cells[31,32,33,34,35]. One therefore can not escape the questions: Is RAAS vaccine a research priority? Is the expensive and complex immunological research relevant to the development of a vaccine for hypertension justified? Menard justifiably raised relevant questions: Is an additional vaccination against a dysregulated endogenous system involved in controlling BP an acceptable solution for individuals, when vaccination has the challenging primary aim of protecting both individuals and populations against exogenous infectious risks? Would not the establishment of a more efficient health system be the most reasonable way to transfer the benefits of drug treatment implemented by researchers, physicians and health authorities for 50 years in developed countries rapidly to developing countries[8,9,10,25]?

The development of a vaccine for hypertension cannot be seen as an urgent requirement for developing countries based on a lack of compliance with oral treatment. This poor compliance requires greater investment in behavioural and social research, which costs less and entails fewer risks than the complex immunological research required to develop a vaccine against endogenous dysregulation. If the efforts of WHO, industry and donors succeed in improving the efficacy and feasibility of vaccination against infectious diseases for all, and if vaccines become available at a low price, then developing countries will be faced with the burden of diseases attributable to hypertension at a scale far beyond that observed in Europe, as a direct consequence of improved survival. Therefore, in the long term, vaccine development is essential and will continue to expand because vaccines save millions of lives cost effectively.

In a recent review, Krum and Gilbert suggested that vaccination against the RAAS should still be considered experimental, but have significant appeal as an important additional approach to the management of hypertension[36]. It is therefore too early and premature to say 'yes' or 'no' to a vaccine for hypertension. To us, it seems logical to suggest that the debate remains open whether to have or not have a vaccine for hypertension, until all the delicate ethical issues and complex scientific immunological mechanisms are delineated fully.

Conclusions

Hypertension is a chronic condition of dysregulated endogenous system such as RAAS. Although a number of newer drugs are presently available, lack of compliance is a major problem in controlling hypertension with oral treatment. The idea for development of viable vaccine for long term control of BP endogenously was therefore conceived targeting renin, angiotensin I and angiotensin II of the RAAS. Some of the preclinical and phase I clinical trial results have been very much encouraging. However, a number of scientific, immunological and ethical issues have to be properly addressed to develop an effective and viable vaccine for hypertension: (i) Is the vaccine safe and free of risks, predictable or unpredictable, regardless of the level of BP? (ii) Is the anti-hypertensive vaccine targeting RAAS a research priority? (iii) Is the expensive and complex immunological research relevant to the development of the vaccine justified? (iv) Can it be seen as an urgent requirement for developing countries based on a lack of compliance with oral treatment? (v) Is an additional vaccination against a dysregulated endogenous system an acceptable solution for individuals with hypertension? Logically, the debate remains open whether to have or not to have a vaccine for hypertension until all these delicate ethical issues and complex immunological mechanisms are delineated fully. Certainly immunological approach to modification of the RAAS is worthwhile and has great potential in the long term regulation of hypertension by vaccination.

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ORIGINAL ARTICLE

Primary PCI: Initial experiences at National Heart Foundation Hospital and Research Institute

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Abstract:

Background: Primary percutaneous coronary intervention (PCI) is the treatment of choice following ST-elevation myocardial infarction (STEMI). Due to the limited expertise centers and trained manpower in the developing country like ours, it is not widely accepted strategy. Although few centers are doing primary PCI sporadically there is no available data of short or long term outcome of it. The objective of this observational study was to describe the procedural and short term clinical outcome of patients undergoing primary PCI at a tertiary level specialized high volume cardiac hospital in our country.

Methods: We conducted a prospective observational study at the National Heart Foundation Hospital and Research Institute, Dhaka. A total of 120 consecutive patients undergoing primary PCI between December 2006 and January 2008 were reviewed.

Results: All-cause mortality was 4% at 30 days. Mortality in patients presenting without cardiogenic shock was nill, whereas mortality in patients with shock was higher. The mean symptom-onset-to-emergency department arrival time was 288 minutes; however; mean door-to-laboratory time was 100 minutes.

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Introduction:

Since the late 1980s acute reperfusion with fibrinolytic drugs has been the primary treatment in ST-segment elevation myocardial infarction (STEMI). However, fibrinolytic therapy has several limitations. These are 27% of STEMI cases have contraindication [1], in about 15% cases fibrinolytics are ineffective [2,3], about a quarter of those receiving fibrinolytic therapy have reocclusion of the infarct-related artery within 3 months after the myocardial infarction, with a resultant reinfarction [4]. To minimize these limitations primary percutaneous coronary intervention (PCI) has emerged as the preferred treatment of acute myocardial infarction (MI) and has been proven to be a very effective method to obtain patency of the infarct-related vessel. The advantages of primary PCI are the high rate of reperfusion success, its limited contraindications, and the early risk stratification made possible by angiography. The primary PCI strategy also results in improved clinical outcomes, including reduced rates of recurrent ischemia and infarction, stroke, length of stay, and mortality [5].

Several randomized controlled trials (RCTs) and registries done worldwide have shown clear benefit of it over the fibrinolytic therapies. The benefits of primary PCI are greatest if it is performed in an

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expeditious manner after the onset of symptoms. To facilitate rapid initiation of reperfusion therapy, the medical system goal for patients receiving fibrinolytic is a door-to-needle (or medical contact–to-needle) time of within 30 minutes; for those undergoing PCI, a door-to-balloon (or medical contact–to-balloon) time of <90 minutes is recommended [6]. Another important physiological principle is that the goal of reperfusion is to restore flow in the infarct artery not only as quickly as possible but also as completely as possible, which includes attaining enhanced myocardial perfusion in the infarct zone[7].

Although primary PCI is associated with favorable outcomes when performed rapidly, few hospitals even in the United States consistently perform it rapidly on a full-time, emergency basis.[8,9] As a result, door-to-balloon (DB) times in routine clinical practice are often longer than in randomized, controlled trials, and many patients are transferred for PPCI, which further delays reperfusion. Indeed, transfer patients often experience long delays in the performance of PPCI, and as a consequence, <5% of transfer patients meet American College of Cardiology/American Heart Association (ACC/AHA) guidelines for timely implementation.[10] Mortality rates increase both as DB times increase [11] and as symptom-to-balloon times increase.[12]

Materials and Methods

Patient population. We conducted a prospective observational study on 120 consecutive cases of STEMI undergoing primary PCI at the National Heart Foundation Hospital & Research Institute, Dhaka, Bangladesh between December 2006 and January 2008. The National Heart Foundation Hospital & Research Institute is a non-profit making specialized and dedicated high-volume cardiac hospital. It is a sister concern of National Heart Foundation of Bangladesh and member of World Heart Federation, committed to serve the cardiac patients at low and affordable cost and to develop skilled manpower in this field. We started primary PCI in early 2002 in a limited number with variable in-hospital outcome. Since December 2006 we performed it on a regular basis and a prospective database is maintained and updated regularly. The inclusion criteria for this study required the following: (1) chest pain lasting e" 30 minutes associated with an ST-elevation of > 1 mm in > 2 contiguous leads; plus (2) time from symptom - onset to presentation d" 24 hours; and (3) primary PCI as the reperfusion strategy. Patients receiving fibrinolytic therapy, undergoing primary PCI for stent thrombosis and non ST-elevation myocardial infarction (NSTEMI), and those presenting beyond 24 hours following the onset of symptoms were excluded from this study. At our hospital patients presenting with acute STEMI are offered primary PCI as preferred method of reperfusion. On the basis of various considerations, primarily the financial, patients opt for either PCI or fibrinolytic therapy.

Procedure. Primary PCI of the infarct-related artery (IRA) was performed in standard fashion using varieties of guiding catheters, guidewires, low-profile balloons and other adjunctive devices. All the interventions were performed via the femoral route. Patients received 5000 – 10,000 units of intravenous heparin, aspirin 300 mg, and Clopidogrel (loaded with 300-600 mg at the operators discretion, followed by 75 mg per day). Coronary stenting, glycoprotein (GP) IIb/IIIa inhibitor and intracoronary nitrates and adenosine use were at the discretion of the operators. Stent size selection was primarily based on visual assessment of vessel size and lesion length. All patients received aspirin indefinitely and clopidogrel 150 mg for bare-metal and drug-eluting stents, respectively.

Data collection. The prospective database contains information on variables including age, gender, history of diabetes (defined as fasting glucose > 126 mg/dl or on treatment), hyperlipidemia (fasting cholesterol > 200 mg/dl or on treatment), hypertension (systolic blood pressure e" 140/90 or on treatment), smoking (current, past or ever), left ventricular function (visually estimated ejection fraction [EF] using either echocardiography or left ventriculography), presence of cardiogenic shock (defined as a systolic blood pressure [SBP] of < 90 mmHg for at least 30 minutes, or requirement of inotropes to maintain a SBP > 90 mmHg), angiographic and procedural details (culprit vessels, number of diseased vessels, use of stents, GP IIb/IIIa inhibitors, and Thrombolysis In Myocardial Infarction [TIMI]

flow). Timing variables were computed as follows: chest pain-to-emergency room (ER) was defined as the time difference between the time of onset, as obtained from the history, and the time of presentation to the ER; door-to-laboratory time was defined as the time taken for the patient to reach the latter from the point of entry to the ER. We could not routinely record the first balloon inflation time, thus the door-to-balloon time (time taken from presentation to the ER to first balloon inflation) are not available. TIMI flow rate were visually determined and documented by the individual operator both before and after the PCI. PCI success was defined as achievement vessel patency to a residual d" 30%. Patients were followed up and in some cases contacted over telephone and the records documented. Major bleeding was defined as a hematoma > 10 cm in diameter or bleeding requiring transfusion, vascular surgery or resulting in major morbidity. The primary outcome was all cause mortality studied from the time of intervention out to the maximum time of follow up.

Statistical methods. All variables were entered into the Statistical Package for Social Sciences, version 12 (*SPSS Inc., Chicago, Illinois*). Means and standard deviations were calculated for continuous variables and frequencies for categorical variables.

Results:

A total of 120 subjects were included in this study. The median duration of follow-up was 168 days. Table I shows the baseline demographic and clinical characteristics as well as outcome of the studied cohort. The mean age was under 55 years. More than half of the patient was hypertensive, 46% current smoker, 36% diabetic, and 22% had dyslipidemia. Majority of the patiens (53%) presented with anterior MI and 10% suffered from cardiogenic shock. The mean left ventricular ejection fraction (LVEF) was 45%. The mean time from onset of symptoms to presentation was 288 minutes, and the mean door-to-laboratory time was 98 minutes. Four patients died in hospital, and another two patients died during follow-up. Major bleeding occurred in 3% of patients.

Table-I

Characteristics of patients undergoing primary PCI for AMI at NHFH & RI

Baseline Demographic and Clinical characteristics	N = 120 (%)
Age	53.54 ± 11.01
Male gender	91 (78.45%)
Past medical history	
Hypertension	65(54%)
Diabetes	43(36%)
Current smoker	55(46%)
Dyslipidemia	18(22%)
Admission characteristics	
Anterior MI	53
Inferior MI	41
Lateral MI	6
Cardiogenic shock	10%
LVEF	45%
Timing variables	
Time: Chest pain – to – ED (minutes)	
Mean (SD)	288
Time: door – to - cathlab	
Mean (SD)	100
Events (with 95% confidence limit)	
Death: in-hospital (all patients)	4
Death: in-hospital (cardiogenic shock)	4
Death: in-hospital (no cardiogenic shock)	0
Death: follow-up	2
In-hospital CABG	1
Stent thrombosis	0
Stroke:	
Hemorrhagic	0
Non-hemorrhagic	0
Major bleeding	3

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; ER = emergency room;

Table II. shows the angiographic and procedural details of the patients undergoing primary PCI. Multivessel disease (defined as > 50% Stenosis in > 2 epicardial vessels) was present in 68% of patients. Procedural success was extremely high (98%), and the use of drug-eluting stents was in 18% and bare metal stents in 66% of cases.

Table-II

Angiographic and procedural characteristics of patients undergoing primary PCI for AMI at NHFH & RI

Angiographic and procedural characteristics	N = 120 (%)
Culprit vessel	
LAD / Diagonal	55 (46)
LCX / OM	14 (12)
RCA/PDA	51 (42)
Left Main	0
Single vessel CAD	32
Multivessel CAD	68
Complete revascularization	36
Culprit vessel intervention	64
TIMI flow (preprocedure)	
0	96
I	3
II	1
III	0
TIMI flow (postprocedure)	
0	0
I	0
II	2
III	98
Glycoprotein Iib/Iia inhibitor use	100
Use of DES	18
Use of BMS	68
Use of POBA	14
Use of IABP	7
Urgent / emergent CABG	2
Procedural success	98

LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; OM = obtuse marginal; TIMI = thrombolysis in myocardial infarction; IABP = intra-aortic balloon pump

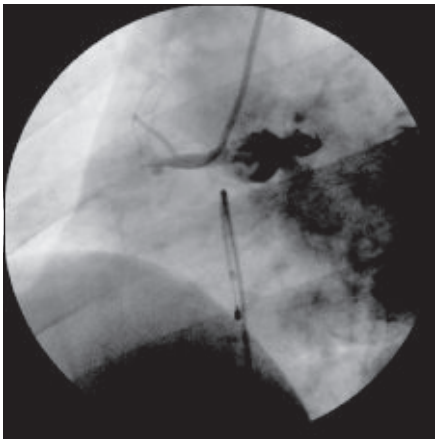

Fig.-1: *Totally occluded right coronary artery after acute STEMI*

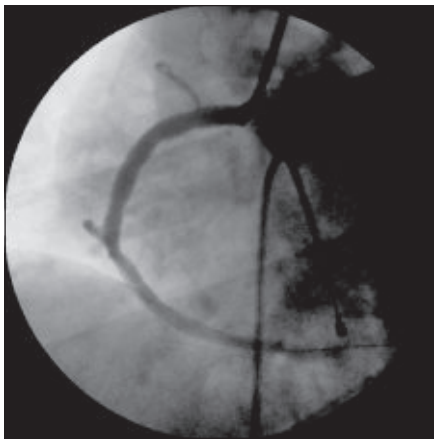

Fig.-2: *Fully opened right coronary artery after primary PCI*

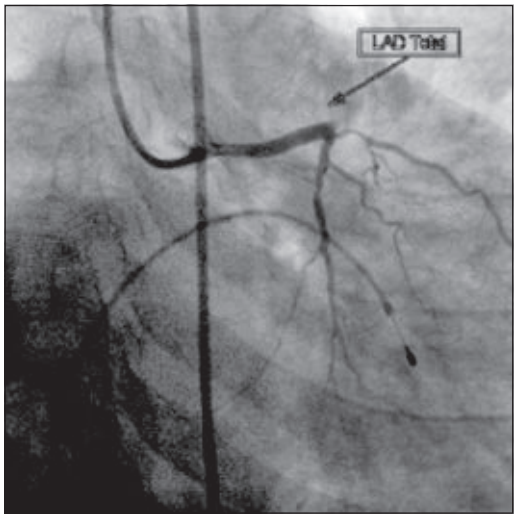

Fig.-3: *Totally occluded left anterior descending arterry after acute anterior STEMI before primary PCI*

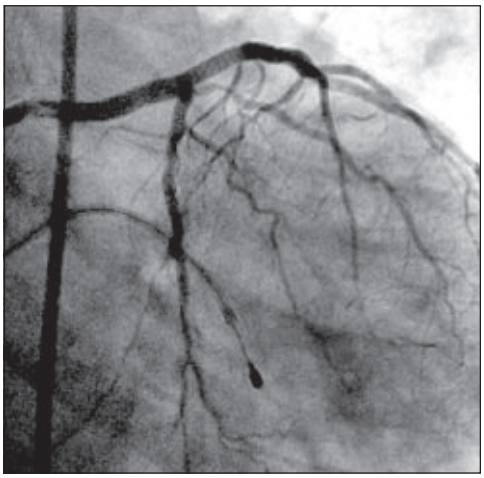

Fig.-4: *Re-opened left anterior descending artery after primary PCI*

Discussion:

This is a comprehensive report for the first time from a tertiary level cardiac hospital of Bangladesh for primary PCI in acute STEMI. We show in an unselected "real world" population, a high success rate (> 95%) of the index procedure and an excellent in-hospital survival rate. The mean age in our study group was < 55 years, lower than seen in developed world. Though this data does not represent the total population, reflects premature occurrence of atherosclerotic process that is commonly seen in this subcontinent. Anterior myocardial infarction and the left anterior descending artery (46%) was the frequent involvement followed by rigth coronary artery (42%). Majority of the patient had multivessel coronary artery disease (68%); complete revascularization was done in 36% cases, in 64% of cases only the culprit lesion intervened. The choice of revascularization pattern was individualized after assessing the nature of lesion, patients condition, affordability and patients wiish. Many of published data reveals increased adversed cardiac events in multivessel PCI in acute STEMI. In 4 caeses intra aortic balloon pump had been used.

We did not found any sinificant association between door-to-laboratory time, unlike other studies, this may reflect the fact that the time of arrival to the emergency department after the onset of chest pain and subsequent transfer to the catheterization laboratory was higher and the smaller number of cases with with short follow-up period. Our mean door-to-laboratory time was 100 minutes, whereas the mean chest pain-to-emergeny department time was 288 minutes. It is well documented that once door-to-balloon times exceed 90 minutes, the benefits begin to decline.[6] Farthermore, as the time-to-PCI increases, so does mortality.[13] The implication of our study needs further dicussion. Wide spread availability of primary PCI, has yet to become a reality, even in the developed world. As Banladesh and Indian sub-continent at the verge cardiovascular epidemic, it is clear that acute STEMI will continue to occur, leading to a loss in productivity. The relative younger mean age group as involved in our study, comprises the workforce of any nation.

Study limitations

Our study has many limitations. First, the sample size is relatively small, larger studies are needed to validate the results. Second, although these are consecutive patients undergoing primary PCI, they do not represent all-comers who presented with acute STEMI. Third, the door-to-balloon time were not directly estimated, the association between this variable and outcomes is poorly defined by our study. A significant proportion of this delay-to-PCI comprises the time taken by patients to decide whether they can proceed with the procedure, based on financial constraints. Fourth, our data represent a single-center experience where the operators are fairly experienced and the hospital was a high volume center. Whether these results can be generalized to other hospitals in developing countries is unclear.

Conclusion:

We report a high initial success rate and and excellent in-hospital and short-term survival after primary PCI for acute STEMI. Our results compare favourably to the western world data in this field despite longer door-to-balloon time. In presence of limitations of resources and financial constraints the procedural success and ever increasing peoples interest to avail this modality of treatment justifies feasibility of primary PCI to be treatment of choice in our country perspective. More outcome data of randomized and non-randomized studies are needed to whether our results are generalizable.

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CASE REPORT

Congenital Right Sided Diaphragmatic Hernia: A Case Report

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Abstract:
A 7month old male child presented with mild respiratory distress and repeated respiratory tract infection, unable to breast feed properly since birth. On examination of respiratory system there was decreased breath sound and presence of bowel sound in right side of the chest. Contrast x-ray revealed presence of loop of bowel in right pleural space. Surgical correction was done with immediate good result.

[Chest & Heart Journal 2008; 32(1) : 58-61]

Introduction:

The diaphragm develops between 8th-10th week from middle part of septum transversum, the pleuro-peritoneal folds and dorsal mesentry of fore gut[1].

Failure of fusion of these component part leads to development of congenital diaphragmatic hernia. Congenital diaphragmatic hernia classified as 1.Postero-lateral or Bochdalek hernia. 2.Retro-sternal or Morgagni hernia. 3.Central or septum transversum hernia.

The diaphragm in adult is a musculotendinous dome shaped structure attached posteriorly to 1st, 2nd and 3rd lumbar vertebra. Anteriorly to the lower sternum and laterally to lateral arches; separates the thoracic and abdominal cavities; it allows the passage of various normal structure through anatomic foramen[1].

Congenital diaphragmatic hernia is not a common problem though actual incidence is not known in our country. Surgeons practicing this field occasionally face the problem. Presentation varies according to the type and degree of herniation but diagnosis and treatment in proper time is important for successful out come.

The postero-lateral type of congenital diaphragmatic hernia though called Bochdalek hernia, after the name of Vincent Bochdalek who describe it in 1848; typically it occurs through the postero-lateral defect of diaphragm, foramen Bochdalek.

Incidence and pathophysiology:

Congenital postero-lateral diaphragmatic hernia (CPLDH) occur in 1:2000 to 1:5000 live birth[2] of these 80% occur in the left side. 10% of lateral hernia has got true hernial sac. True hernia is herniation of abdominal organ through the defect in the diaphragm. The morphology of diaphragmatic muscle are normal. The pathophysiologic effect depends upon the degree of herniation, which in term related to size of the diaphragmatic defect. and ranges from no effect to compression and retardation of development of ipsilateral lung, shifting of the mediastinum to the

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opposite site affecting the contralateral lung as well. The morphologic quality and biochemical property of the lung is retarded in the most case of severe herniation, effects depends upon the intensity of pulmonary hypoplasia and pulmonary hypertension. Hypoplastic lung produces various degree of hypoxia and have got increased sensitivity to hypoxia, acidosis, hypercarbia and hypothermia resulting in pulmonary hypertension which in term reverse the flow through patent ductus arteriosus and opens the foramen ovale with right to left shunt and establish a syndrome of persistent foetal circulation. That eventually lead to vicious cycle of hypoxia, acidosis which ultimately culminates in the death of the baby[3].

Case report:

A 7 month old male child referred from specialized pediatric hospital having difficulty in breathing since birth with gradual increase in severity. Careful history revealed repeated respiratory tract infection, occasional vomiting, difficulty in breast feeding properly. Clinical examination shown diminished breath sound with intestinal borborygmic sound in right chest. No other abnormality detected in any part of body.

Routine investigation finding was normal. Plain X-ray chest and barium contrast x-ray shown presence of bowel loops in right pleural space (Figure-1 and Figure-2).

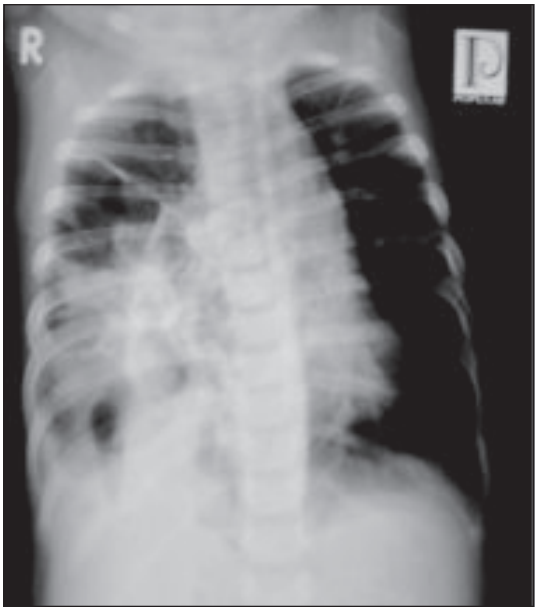

Fig.-1: *Showing bowel loops in right pleural space.*

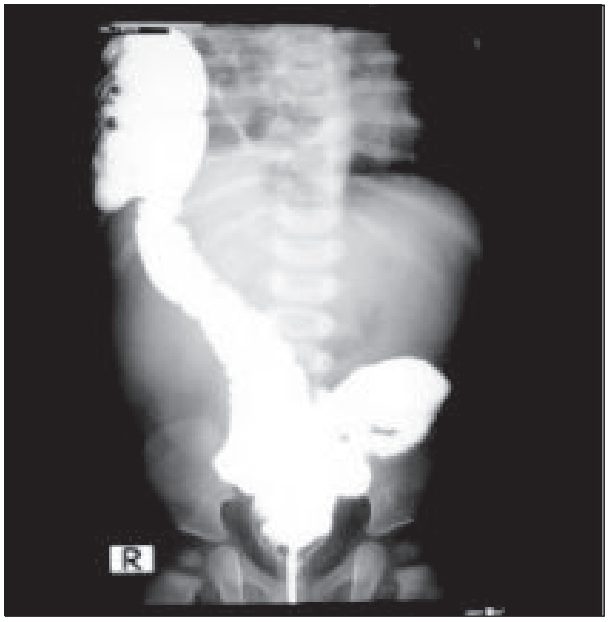

Fig.-2: *Contrast X-ray showing bowel loops in right pleural space.*

After proper detailed counseling with parents, patient was prepared for surgical intervention. Right chest was opened through postero-lateral incision along with upper border of 8th rib. Per operative finding shown part of colon, major part of small gut herniated in to right pleural space(Figure-3).

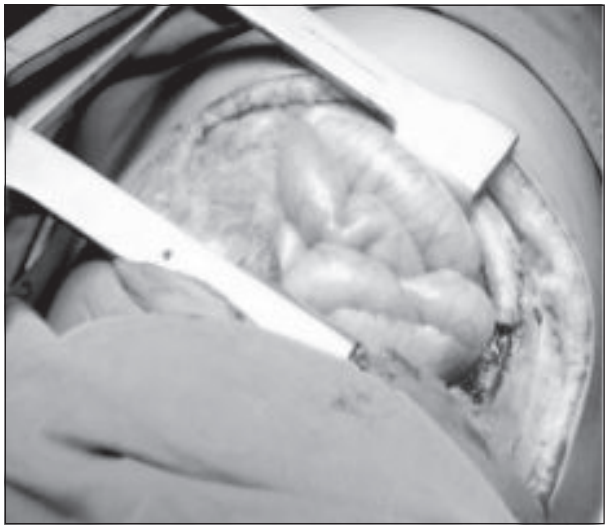

Fig.-3: *Herniated gut in right pleural space.*

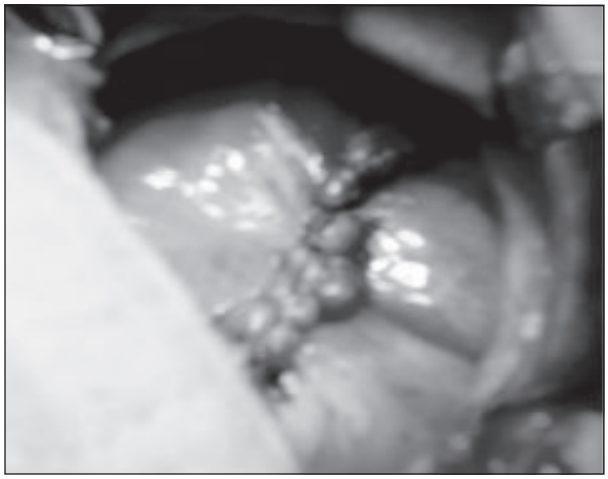

Fig.-4: *Repair done after reposition.*

Lower lobe of right lung had some features of consolidation. After careful reduction of the gut in to the abdominal cavity, it was found that a gap (33 ×1.53) in postero-lateral part of diaphragm. Right lobe of liver displaced more medially and right kidney was attached with the rim of diaphragmatic gap. Assessment was done whether artificial prosthesis needed to repair the gap or not. After proper mobilization of kidney and perinephric fat the margin of the gap became clear and apposed with out any tension. Thus the gap was repaired by standard technique with out any prosthesis (Figure-4). Chest was closed in layers keeping one chest drain in situ with water seal system. No transfusion done.

Post operatively patient was managed properly with special attention to analgesia, sedation and abdominal distension. Nasogastric suction ensured. On 1st postoperative day there was some abdominal distension. But on successive days patient improved significantly. Abdominal distension subsided, bowel sound appeared on 3rd day. Patient allowed breast feeding and was able to suck properly. X-ray chest done and found lung well inflated, center of diaphragm normal (Figure-5). Then chest drain removed. Rest of the post operative days were uneventful. Follow-up shown excellent improvement (Figure-6).

During successive follow up at 6 weeks, 3 months and 6 months it shown absence of previous symptoms and recurrence and x-ray chest shown normal expansion of the lung. Child health and growth was normal.

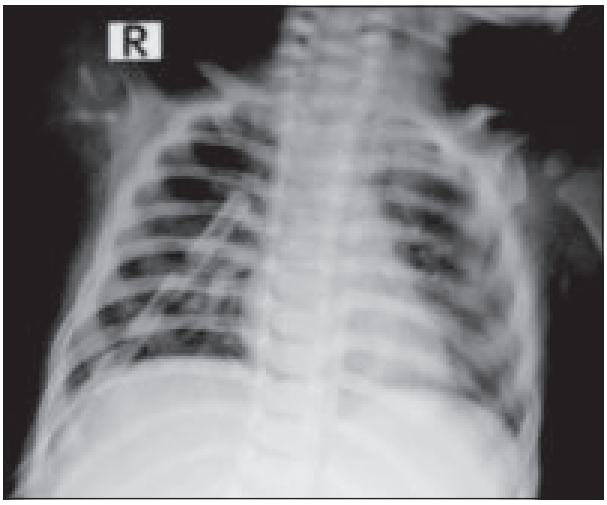

Fig.-6: *Follow up X-ray showing X-ray lung well inflated, diaphragm normal.*

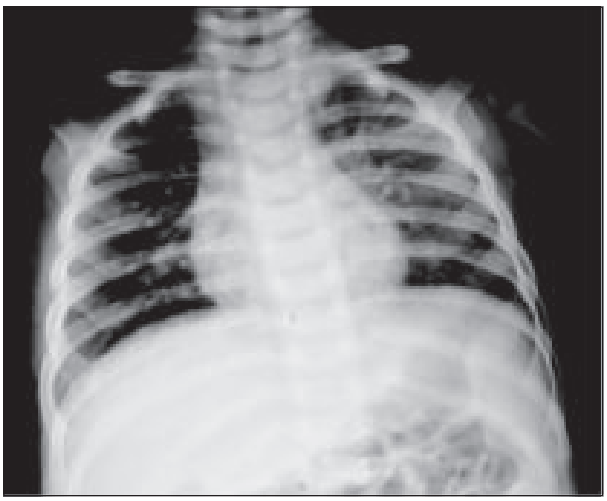

Fig.-5: *Immediate post operative showing chest drain insitu, lung inflated, diaphragm normal in position.*

Discussion:

Congenital diaphragmatic hernia is one of structural birth defect that affects approximately 1 in 2500 live births. Although the aetiology of most cases of congenital diaphragmatic hernia is unknown, it is becoming increasingly clear that genetic factors play an important role in many cases of congenital diaphragmatic hernia[4,5].

Congenital diaphragmatic hernia occurs most frequently in left side (79.4%). Male female ratio nearly 2:1, associated anomaly occur in 8.6% and 65% of children with right sided congenital diaphragmatic hernia present within 1st year of life[6]. In our case male child presented at first year of his life. In our case there was colonic abnormality. Ascending colon not visualizes in contrast x-ray.

Typical clinical presentation is respiratory distress occurring immediate after birth or first few hours or days of a childs life. It is associated with high mortality rate. Congenital diaphragmatic hernia can occur in older children. Symptoms then frequently gastrointestinal obstruction or mild respiratory symptom[7]. Congenital right diaphragmatic hernia usually has clinical manifestations different those of left congenital diaphragmatic hernia; it often masquerades as a pleural effusion, asymptomatic intrathoracic mass, or an intestinal obstruction[8]. In our case it presented with features of respiratory distress and gastrointestinal problem.

Treatment of congenital diaphragmatic hernia has undergone a revolutionary changes in philosophy, from previous urgent repair to the present practice of stabilization and delayed repair[9]. These changes have led to many centers reporting survival rates near 80%, a dramatic improvement from the 50% survival reported 1970s[10]. Surgical repair is the treatment. Laperotomy, thoracotomy or laperoscopic repair can be done. Laperoscopic repair of congenital diaphragmatic hernia is safe and feasible and confers all advantages of minimal access surgery[11]. The defect size was the most important factor that affected out come. Infants with a near absence of the diaphragm had a survival rate of 57% compared with infants having a primary repair with a survival of 95%. Early diagnosis is important, as early surgery is recommended, even those without symptoms[12,13]. Present case treated by primary repair of diaphragm shows excellent out come.

Conclusion:

Incidence of congenital diaphragmatic hernia not exactly known in our country. Occasionally we face the problem. Treatment outcome depends upon the degree of herniation , morphology of diaphragm, associated other anomalies especially cardio pulmonary, time of diagnosis, immediate resuscitation where indicated, reference to proper center where expertise and all facilities available. To achieve satisfactory result, physicians should keep in mind about the possibilities of the problem. So that early diagnosis and management can be taken.

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REVIEW ARTICLE

Cardiovascular Manifestations of Rheumatoid Arthritis

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[Chest & Heart Journal 2008; 32(1) : 55-57]

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints, and extra-articular features may also develop. Joint pain, swelling and limited mobility of the joint are the most prominent features. The disease course varies greatly between patients. Some patients have a mild disease course although in the majority of patients, the disease leads to progressive joint destruction and disability. Besides articular symptoms, RA can be associated with extra-articular features. Extra-articular features, some associated with histological vasculitis, are considered to be one of the prognostic severe signs of RA[1,2]. Among those extra-articular features are cardiovascular diseases, including pericarditis, cardiomyopathy/myocarditis, cardiac amyloidosis, coronary vasculitis, arrythmia, valve diseases and, most importantly, congestive heart failure and ischaemic heart disease. When compared with the general population, RA is associated with an increased mortality the majority of which is originating from cardiovascular diseases [3]

For classification purposes, a patient is said to have RA if he or she has satisfied at least 4 of the following 7 criteria. Criteria I through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable RA is not to be made.

- Morning stiffness: Morning stiffness in and around the joints, lasting at least I hour before maximal improvement.
- Arthritis of 3 or more joint areas: At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician; the 14 possible joint areas are right or left proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, wrist, elbow, knee, ankle, and meta-tarsophalangeal (MPT) joints.
- Arthritis of hand joints: At least I area swollen (as defined above) in a wrist, MCP or PIP joint.
- Symmetric arthritis: Simultaneous involvement of the same joint areas on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
- Rheumatoid nodules: Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
- Serum rheumatoid factor: Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.
- Radiographic changes: Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

In this Review article cardiovascular manifestation of RA will be discussed.

Cardiovascular manifestation

Pericarditis

The most common cardiac involvement in RA is pericarditis. Varying the method of assessment (echographic or postmortem studies), pericarditis occurs in 30-50% of the patients [4]. Classically, pericarditis occurs predominantly in male patients with severely destructive and nodular RA, as is the case with other extra-articular features of RA [5]. The prognosis of RA patients with clinical

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pericarditis appears to be impaired, in particular in the first year after diagnosis, and the age and cardiac status best predict survival Treatment with non-steroidal anti-inflammatory drugs, corticosteroids and/or other immunosuppressive drugs seems appropriate in the majority of patients with a definite diagnosis of RA-associated pericarditis, and in severe cases, pericardiectomy is warranted.

Cardiomyopathy

diseases, often of unknown aetiology Cardiomyopathy consists of a group of, involving the heart muscle itself and are not a result of ischaemic, hypertensive, congenital, valvular or pericardial

diseases. Two classification schemes are frequently used. First, the functional classification includes dilated or congestive cardiomyopathy, hypertrophic cardiomyopathy and restrictive cardiomyopathy. These distinctions are not absolute as overlaps can occur. Second, the primary and the secondary cardiomyopathies, the latter includes RA amongst other aetiologies. The RA-associated cardiomyopathy may be the result of focal non-specific, diffuse necrotizing or granulomatous myocarditis. These entities are histological diagnoses, which may be found in 3-30% of RA patients in postmortem studies [4] Furthermore, some drugs used in the treatment of RA have also been associated with cardiomyopathy, for instance, corticosteroids and anti-malarials, and the aetiology of cardiomyopathies in RA may therefore be difficult to determine [6]

Amyloidosis

Amyloidosis refers to the extracellular accumulation of amyloid fibrils, derived from a circulating precursor, in various tissue and organs. The most common form of amyloidosis worldwide is that which occurs secondary to chronic inflammatory disease, particularly rheumatoid arthritis. The precursor molecule is serum amyloid A (SAA), an acute phase reactant, which can be used as a surrogate marker of inflammation in many diseases. SAA has a number of immunomodulatory roles, can induce chemotaxis and adhesion molecule expression, has cytokine-like properties and can promote the upregulation of metalloproteinases. It enhances the binding of high density lipoprotein to macrophages and thus helps in the

delivery of lipids to sites of injury for use in tissue repair. It is thus thought to be an integral part of the disease process. Moreover, elevated levels of SAA over time predispose to secondary amyloidosis [7.] Intensified immunosuppressive treatment should be considered if a RA patient is diagnosed with amyloidosis

Coronary vasculitis

Vasculitis of the coronary arteries has been observed in RA patients, up to 20% in postmortem studies published in the early 1960s [8,9] although it is diagnosed rarely during life As in the general population, abnormalities of the coronary arteries are mainly due to atherosclerosis. Differentiation between atherosclerosis and diffuse cardiac vasculitis may be obtained by electro beam CT for the detection of coronary artery calcification or endomyocardial biopsy for the diagnosis of vasculitis A rapid and correct diagnosis is relevant, as RA patients with life-threatening vasculitis should be treated promptly with immuno-suppressive drugs .

Rheumatoid nodules or granuloma Rheumatoid nodules (also called rheumatoid granuloma) may occur in all organs and also in the epicardial fat, epicardium, myocardium, interventricular septum, chordae tendinae, aorta and valves. These nodules may cause functional impairment such as arrhythmias and valve disease. There is no evidence that immunosuppressive treatment may resolve these cardiac nodules.

Valve disease

The most prevalent valve disease in RA is mitral valve insufficiency, varying from 30 to 80% in small case series followed by aortic valve insufficiency varying from 9 to 33%[6,10]

Arrhythmia

QT-dispersion and corrected QT-dispersion intervals were significantly longer in RA compared with healthy controls, and it was suggested that QT-dispersion may be a useful marker of cardiovascular morbidity and mortality due to complex ventricular arrhythmias inRA[11].

Precocious atherosclerosis

The risk of cardiovascular (CV) disease increases in patients with rheumatoid arthritis (RA). This is due to a number of different triggers including traditional and disease-related factors. Among established risk factors for CV disease, smoking may exert a more dangerous effect on arterial wall in RA than in the general population by a synergic effect with inflammatory processes of the disease. Although persistent inflammation and immune dysregulation of RA may contribute to favor other well-known CV risk factors, such as dyslipidemia, it is now clear that the disease itself represents an independent risk factor for CV disease by the action of RA chronic inflammatory process as well as humoral and cell-mediated immune mechanisms. There is evidence that CV risk is associated with severity and extension of the disease and it is of interest the fact that the presence of circulating anticyclic citrullinated peptide antibodies appears to be associated with stronger evidence of subclinical atherosclerosis in RA.[13]

Heart failure

Mayo Clinic researchers have found that rheumatoid arthritis patients have twice the risk of heart failure, or a weakening of the heart's ability to pump blood, as those without rheumatoid arthritis.

The risk of developing CHF in RA is twice the risk of developing CHF in persons without RA, and this excess is not explained by traditional cardiovascular risk factors and/or clinical ischaemic heart disease[12].

To conclude: Rheumatoid arthritis is one of the commonest immunoinflammatory disease with multisystem involvement including cardiovascular system and the combined efforts of rheumatologists and cardiologists may help to improve the cardiovascular morbidity and mortality in RA patients.

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REVIEW ARTICLE

Apical Ballooning Syndrome- A Reversible Cardiomyopathy

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Abstract:

The transient left ventricular apical ballooning syndrome (ABS), also known as takotsubo cardiomyopathy, is characterized by transient wall-motion abnormalities involving the left ventricular apex and mid-ventricle in the absence of obstructive epicardial coronary disease. It is a unique reversible cardiomyopathy that is frequently precipitated by a stressful event and has a clinical presentation that is indistinguishable from a myocardial infarction. The incidence of ABS is estimated to be 1% to 2% of patients presenting with an acute myocardial infarction. The pathophysiology remains unknown, but catecholamine mediated myocardial stunning is the most favored explanation. Chest pain and dyspnea are the typical presenting symptoms. Transient ST elevation may be present on the electrocardiogram, and a small rise in cardiac troponin T is invariable. Typically, there is hypokinesis or akinesis of the mid and apical segments of the left ventricle with sparing of the basal systolic function without obstructive coronary lesions. Supportive treatment leads to spontaneous rapid recovery in nearly all patients. The prognosis is excellent, and a recurrence occurs in < 10% of patients. Apical ballooning syndrome should be included in the differential diagnosis of patients with an apparent acute coronary syndrome with left ventricular regional wall motion abnormality and absence of obstructive coronary artery disease, especially in the setting of a stressful trigger.

[Chest & Heart Journal 2008; 32(1) : 31-39]

Introduction

Apical ballooning was first described in the Japanese literature in the early 1990s and was attributed to simultaneous spasm of multiple coronary arteries. The original name given to apical ballooning was takotsubo cardiomyopathy, which was derived from the shape of the narrow-necked bulging "takotsubo" container

used by Japanese fisherman to trap octopus. The shape of the takotsubo pot resembles the distorted ballooning ventricle.[1]

An association between emotional or physical stressful triggers and adverse cardiovascular events such as death and myocardial infarction has been recognized for many years.[2] At a population level, earthquakes, wars, and major sporting events have all been linked to a surge in cardiovascular mortality.[3-5] Among hospitalized patients, noncardiac surgery is one of the most frequent trigger for cardiovascular events, with the highest risk in those undergoing vascular surgery due to coexisting severe coronary artery disease.[6] Myocardial dysfunction may occur in critically ill patients with sepsis due to a pathogen-induced proinflammatory immune response,[7] and a reversible cardiomyopathy in critically ill

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patients has also been reported in the absence of sepsis.[8] Similarly, neurologists have recognized an association between subarachnoid hemorrhage and a reversible cardiomyopathy that has been termed neurogenic stunning, characterized by acute brain injury and the absence of coronary artery disease.[9] Recently, there has been an increasing awareness of a unique cardiac syndrome that has been described as the apical ballooning syndrome (ABS), Tako-Tsubo cardiomyopathy, and stress or ampulla cardiomyopathy.[10-14] It has also been referred to as the Broken Heart Syndrome in the popular press. The syndrome overlaps with the aforementioned conditions in that it is a reversible cardiomyopathy that is frequently precipitated by a stressful event and has a clinical presentation that is indistinguishable from a myocardial infarction. Sporadic case reports followed [15] until the last 5 years or so during which several cases series have been reported from around the world, including Europe,[16] North America, [11,17] and Australia. [18] In 2006, the American Heart Association incorporated ABS into its classification of cardiomyopathies as a primary acquired cardiomyopathy.[19] Apical ballooning syndrome is underrecognized and often misdiagnosed. It is an important differential diagnosis of an acute myocardial infarction.

Incidence

The precise incidence of ABS is unknown due to its novel nature, varied presentation, and evolving diagnostic criteria. Nevertheless, several studies have estimated that approximately 1% to 2% of all patients presenting with an initial primary diagnosis of either an acute coronary syndrome or myocardial infarction have ABS.[20,21] According to American Heart Association statistics, there are 732000 hospital discharges with a primary diagnosis of an acute myocardial infarction in the Unites States each year.[22] Thus, a conservative estimate of the annual rate of ABS in the United States may be 7000 to 14000 cases.

Age and sex

Apical ballooning syndrome is a unique cardiomyopathy in that it usually occurs in postmenopausal women. Recent review of the published case series reveals that approximately 90% of all reported cases have been in women. The mean age has ranged from 58 to 75 years, with <3% of the patients being <50 years.[23] The reason for the female predominance is unknown but raises the intriguing question as to whether withdrawal from estrogens contributes to the pathogenesis. It has been suggested that ABS may be not be diagnosed in males because of the higher prevalence of coronary artery disease, but this seems unlikely given the consistent sex disparity among all published studies.

Clinical presentation

The clinical presentation in most patients is indistinguishable from an acute coronary syndrome; 50% to 60% present with chest pain at rest, which has an angina-like quality. Dyspnea may also be the initial presenting symptom, but syncope or out-of-hospital cardiac arrest is rare.[23] Intensive care unit patients are likely to present with pulmonary edema, ischemic changes on the electrocardiogram, or elevated cardiac biomarkers. In general, hemodynamic compromise is unusual, but mild to moderate congestive heart failure is frequent. Hypotension may occur because of the reduction in stroke volume and, occasionally, because of dynamic left ventricular outflow tract obstruction. Cardiogenic shock has been reported as a rare complication.

A unique feature of ABS is the occurrence of a preceding emotional or physical stressful event in approximately two thirds of patients .[24] Importantly, such a trigger can not be identified in all individuals, despite a careful history, and hence, its absence does not exclude the diagnosis. A rise in the incidence of ABS was reported after the Central Niigata Prefecture earthquake in Japan in 2004,[25] an observation that leads us to believe that some of the cardiovascular morbidity and mortality associated with natural disasters, wars, and sporting events may be related to a stress cardiomyopathy.

Electrocardiogram and cardiac biomarkers

The most common abnormality on the electrocardiogram (ECG) is ST-segment

elevation, mimicking an ST-elevation myocardial infarction (STEMI). However, there is significant variability in the frequency (46%- 100%) of this finding in the published literature. At least 2

reasons may account for the variability in the reported frequency of ST-segment elevation. First, the elevation is transient, and

hence, the time from symptom onset to presentation may determine whether it is detected. Second, there is potential for selection bias for patients presenting with ST-segment elevation who are likely to undergo prompt coronary angiography and assessment of left ventricular function. Typically, the elevation is present in the precordial leads, but it may be seen in the inferior or lateral leads. Nonspecific T-wave abnormality, new bundle-branch block, and in some cases, a normal ECG may be the finding at presentation. When anterior ST-elevation is present, the magnitude of ST shift is usually less in ABS than that seen in a STEMI. The 12-lead ECG by itself is insufficient for differentiating ABS from STEMI.[26] Characteristic and common evolutionary changes that may occur over 2 to 3 days include resolution of the ST-segment elevation, development of diffuse and often deep T-wave inversion that involves most leads, and prolongation of the corrected QT interval. Transient pathological Q waves may rarely develop. The T-wave inversion and QT interval prolongation typically resolve over 3 to 4 months but may occur as early as 4 to 6 weeks and, in some cases, be present beyond 1 year.[27] Most if not all patients have a modest rise in cardiac troponin T that peaks within 24 hour. The magnitude of increase in the biomarkers is less than that observed with a STEMI and disproportionately low for the extensive acute regional wall motion abnormalities that characterize ABS . Circulating brain natriuretic peptide, a marker of ventricular dysfunction, is invariably elevated and correlates with the left ventricular enddiastolic pressure.

Coronary angiogram and cardiac imaging

Most patients with ABS either have angiographically normal coronary arteries or

mild atherosclerosis.Obstructive coronary artery disease may rarely coexist by

virtue of its prevalence in the population at risk. The characteristic regional wall motion abnormalities involve hypokinesis or akinesis of the mid and apical segments of the left ventricle. There is sparing of the basal systolic function. Importantly, the wall motion abnormality typically extends beyond the distribution of any single coronary artery. Transthoracic echocardiography can detect the regional wall motion abnormality; however, visualization of the true anatomic apex can be difficult, particularly in acutely ill patients. The diagnosis is frequently made in the cardiac catheterization laboratory during left ventriculography because the patients are initially suspected of suffering from an acute coronary syndrome and are referred for urgent or emergency coronary angiography. The right ventricle may reveal similar regional wall motion abnormality in approximately 30% of patients who tend to be sicker and more likely to develop congestive heart failure.[28] Recently, variants of ABS have been described, occurring in a significant minority of patients with a clinical presentation similar to that of classic ABS.[29] In these patients, there is preserved function of the apex with wall motion abnormality that involves the mid segments (apical sparing variant) . It is possible that this is simply a manifestation of early recovery of function at the apex in some patients with classical ABS. A rare variant presents with hypokinesis of the base of the heart with preserved apical function (inverted Tako-Tsubo).[3°] Cardiac magnetic resonance appears to be a useful imaging modality for documenting the extent of the regional wall motion abnormality and differentiating ABS (characterized by the absence of delayed gadolinium hyperenhancement) from myocardial infarction and myocarditis in which delayed hyperenhancement is present.[31]

Diagnosis

The diagnosis should be considered in the differential diagnosis of any patient with acute myocardial infarction. However, the classic situation is a postmenopausal woman presenting with chest pain or dyspnea that is temporally related to emotional or physical stress, with positive cardiac biomarkers or an abnormal electrocardiogram. Apical ballooning syndrome should also be considered in the differential diagnosis of inpatients, including those in the intensive care unit, who develop an acute reduction in left ventricular systolic function in association with >_1 of the following: hemodynamic

compromise, pulmonary edema, troponin elevation, or ECG evidence of ischemia or infarction. There may be a higher prevalence of males in the intensive care unit population.

The diagnosis of ABS is most likely to be made at institutions with cardiac catheterization laboratories where primary percutaneous coronary intervention is performed for STEMI and an early invasive strategy is practiced for non STEMI. The absence of obstructive coronary artery disease and characteristic regional wall motion abnormality is likely to lead to the diagnosis. Diagnosing ABS in patients presenting at hospitals without cardiac catheterization laboratories requires a high index of suspicion. Establishing the diagnosis is particularly important if fibrinolytic therapy is being considered for a presumed diagnosis of STEMI.

Inappropriate administration of fibrinolytics to a patient with ABS may lead to harm, and it would be reasonable to transfer a patient suspected of the cardiomyopathy for emergency coronary angiography.

Management

Since the presentation mimics an acute coronary syndrome, initial management should be directed towards the treatment of myocardial ischemia with continuous

ECG monitoring, administration of aspirin, intravenous heparin, and b-blockers. The optimal management of ABS has not been established, but supportive therapy invariably leads to spontaneous recovery. Once the diagnosis has been made, aspirin can be discontinued unless there is coexisting coronary atherosclerosis. The efficacy of (3-blocker therapy has not been formally tested. If tolerated, it is reasonable to initiate (3-blockers empirically because excess catecholamines have been implicated in the pathogenesis. The role of combined alpha-1 and (beta receptor blockade with drugs such as labetalol or carvedilol is unknown.

Congestive heart failure is the most common complication occurring in approximately 20% of patients and is more likely in the presence of right ventricular involvement.[28] Diuretics are effective in most cases. It is important to exclude dynamic left ventricular outflow tract obstruction with echocardiography in patients with severe heart failure or significant hypotension. Aysmptomatic intracardiac pressure gradient may be present in as many one fifth of patients,' but symptomatic obstruction is uncommon. Dynamic outflow- tract obstruction may be associated with systolic anterior motion of the mitral leaflet and mitral regurgitation.[36] In the absence of heart failure, a cautious trial of intravenous fluids and (alpha-blockers may help by reducing the hypercontractility of the base of the left ventricle and increase cardiac filling, thereby reducing the obstruction.[37] Alternatively, an infusion of phenylephrine may be effective by increasing the afterload and left ventricular cavity size in patients in whom beta-blocker or intravenous fluids are contraindicated. Inotropes would be contraindicated in the presence of dynamic outflow tract obstruction. [39] In contrast, cardiogenic shock due to pump failure is treated with standard therapies, which include inotropes and intraaortic balloon counterpulsation.

As with acute myocardial infarction, ABS may rarely lead to mechanical and arrhythmic complications. Mechanical complications reported include free wall rupture[39] and severe mitral regurgitation.36 Atrial and ventricular arrhythmias may occur, but ventricular tachycardia and fibrillation is rare.[1] Anticoagulation should be considered during the initial presentation if severe left ventricular systolic dysfunction is present and continued for a few weeks with warfarin if there is slow functional recovery to prevent thromboembolism. Left ventricular thrombus may rarely be present during the acute phase, and anticoagulation is clearly indicated in this circumstance.[40]

Prognosis

The systolic dysfunction and the regional wall motion abnormalities are transient and resolve completely within a matter of days to a few weeks. In our experience[14] and in other large series, complete recovery is seen in virtually all patients by 4 to 8 weeks. This is such a uniform finding that an alternative diagnosis should be considered in patients in whom the cardiomyopathy does not resolve. Patients with ABS generally have a good prognosis in the absence of significant underlying comorbid conditions. The ejection fraction should be measured in approximately 4 to 6 weeks after

discharge from the hospital to document recovery of cardiac function. Inhospital mortality from ABS is very low and unlikely to be N1% to 2%. Overall, the long-term survival is similar to that of the general age-matched population.

The subgroup of patients in whom there is a physical trigger such as major surgery or illness appear to have a worse prognosis, most likely related to the underlying condition. The recurrence rate of ABS is no >10%.24

Pathophysiology

The pathophysiology of ABS is not well understood. Several mechanisms for the reversible cardiomyopathy have been proposed, including catecholamine-induced myocardial stunning, ischemia-mediated stunning due to multivessel epicardial or microvascular spasm, and myocarditis . Myocarditis is extremely unlikely to be the mechanism since studies reporting endomyocardial biopsy data have consistently shown the absence of myocarditis.[41] Furthermore, cardiac magnetic resonance imaging does not show regional delayed gadolinium hyperenhancement, which is a feature of myocarditis.

Catecholamines may play a role in triggering the syndrome because many patients have emotional or physical triggers. There is an increasing awareness of the close interaction between cortical brain activity and the heart.[42] In clinical studies, mental stress has been demonstrated to reduce left ventricular ejection fraction and, rarely, induce regional wall motion abnormalities in conjunction with a rise in catecholamines.[43] Moreover, wall motion abnormalities and depressed ejection fraction have been observed in diseases associated with high catecholamines such as a pheochromocytoma [44] and subarachnoid hemorrhage.[45] Wittstein et al [17] have reported very high levels of catecholamines in ABS at the time of presentation, which remained elevated for 7 to 9 days. Endomyocardial biopsies in a subset of their patients demonstrated contraction band necrosis, a feature of catecholamine toxicity. However, neither the elevation in circulating catecholamines nor the contraction band necrosis [41] has proven to be consistent finding. Interestingly, in a rat immobilization stress model of ABS, investigators have been able to induce ST-segment elevation and apical ballooning that can be prevented by the administration of combined alpha and P adrenoreceptor antagonist.[46] Early Japanese literature suggested that ABS may result from ischemia due to multivessel epicardial spasm.[47] This has not been confirmed in the recent larger series or in our experience, and we believe that epicardial spasm is unlikely to be the underlying cause of ABS in most cases. It is possible that the routine administration of nitrates for ischemic chest pain may obscure the presence of spasm.

Tsuchihashi et al ' have reported that coronary spasm may be induced with acetylcholine provocation in 21 % of patients in their series. However, the clinical relevance of this finding is questionable because endothelial dysfunction is highly prevalent in postmenopausal women.

Microvascular dysfunction measured using angiographic techniques such as myocardial blush grade can be detected in at least two thirds of the patients at the time of presentation, and its severity correlates with the magnitude of troponin elevation and ECG abnormalities.[48] Similarly, the TIMI frame count is prolonged in all[3] major epicardial coronary vessels in the acute setting, indicating the presence of impaired microvascular flow. Single photon emission computed tomography using thallium and sestamibi tracers and positron emission tomography using 13 N-ammonia have consistently demonstrated impaired perfusion in the regions of the wall motion abnormality.[49] However, the metabolic defect measured as fatty acid or glucose metabolism in these studies has generally been larger than the perfusion defect. This may be either because the primary abnormality in ABS is metabolic dysfunction and not impaired perfusion or because the microcirculation recovers more rapidly than the myocardial metabolism. At this time, it is unknown whether the impairment in microvascular function is the primary mechanism for the injury or an epiphenomenon. It has been suggested that development of a severe intracardiac gradient due to the basal hypercontractility may be a primary mechanism for the disease. A geometric predisposition in elderly females with a sigmoid interventricular septum or hypovolemia in the postoperative patients may lead to outflow tract or

midventricular obstruction in the presence of excessive catecholamines. The resulting elevation in wall stress, oxygen requirement, and ischemia in the apical

segments could cause apical ballooning [51] However, if this was the case, one would expect to document an intracardiac gradient more often than it has been reported in the literature or seen in our experience.

Controversies

There is debate over the most suitable nomenclature for ABS.[51] Tako-Tsubo cardiomyopathy[10] and ABS[1] were the original names proposed by the Japanese. Most non-Japanese-speaking physicians are not familiar with the meaning of Tako-Tsubo. Apical ballooning syndrome has become popular because it is descriptive of the appearance of the left ventricle. However, ABS does not account for the less common variants. Some have favored using stress cardiomyopathy or neurogenic stunning.[51] These descriptions also are not all encompassing because a stressor is absent in one third of patients, and the role of the nervous system in the pathophysiology remains to be established. There is also divergence of opinion as to the reason for the apparent increase in incidence of ABS. We believe that it is not a new disease entity but that its recognition has increased because of the greater use of cardiac imaging, coronary angiography, and sensitive cardiac biomarkers such as troponin. In addition, such cases may have been diagnosed as aborted myocardial infarctions or myocarditis in the past. Others believe that ABS may indeed be a "novel" cardiomyopathy with a true rise in incidence. It is speculated that the decreasing use of hormone replacement therapy among postmenopausal women may have contributed to its emergence. A protective role of estrogens is possible because the cardiomyopathy predominantly occurs in postmenopausal women. Experimental data indicate that estrogen supplementation

may abolish the deleterious effect of mental stress on cardiac function in ovariectomized rats5[1] Similarly, clinical investigations have found that chronic estrogen supplementation attenuates the hemodynamic and catecholamine responses to mental stress, and catecholamine mediated vasoconstriction. An intriguing hypothesis that merits further investigation is that ABS is not a unique cardiomyopathy, but myocardial stunning resulting from a spontaneously aborted myocardial infarction in the territory of a large left anterior descending (LAD) artery. To support their hypothesis, Ibanez et al have published data on five patients demonstrating the presence of plaque rupture by intravascular ultrasound that was not detected by angiography. However, there are several reasons why this mechanism is unlikely to account for the pathophysiology of most cases of ABS. First, the regional wall motion abnormality in typical cases is far greater than what can be accounted for by even a large wrap-around LAD. Second, plaque rupture has not been reported in any large case series. Third, extensive regional wall motion abnormality of the right ventricle in one third of patients cannot be explained on the basis of LAD territory ischemia. Fourth, the female predominance would be unusual for a manifestation of coronary atherosclerosis.

Conclusion

Apical ballooning syndrome is a distinctive reversible cardiomyopathy that mimics an acute coronary syndrome. It should be included in the differential diagnosis of patients with an apparent acute coronary syndrome with regional wall motion abnormality and absence of obstructive coronary artery disease. One of the hallmarks of ABS is that it is almost exclusively seen in postmenopausal women. This is unique to the medical field and warrants further investigation regarding the potential mechanisms. The central hypothesis that a catecholamine surge is

responsible for the cardiomyopathy is challenged by the sex disparity. If this was the predominant mechanism, one would expect similar incidence in men and women. In fact, males have a greater adrenergic response to mental stress. Thus, additional hypotheses should be entertained to explain the phenomenon. It is possible that, in women, estrogen plays a protective role on the vascular bed from the adverse effects of catecholamine surges. Thus, a relative deficiency of estrogen after menopause may predispose them to developing ABS. An alternative potential mechanism for the female predisposition is that

women are more likely to have microvascular disease than men. Thus, the preexisting microvascular dysfunction in women may certainly lead to myocardial ischemia in response to mental or physical stress. This hypothesis is underscored by the observation that women have a higher incidence of acute coronary syndrome with normal epicardial coronary arteries. Future research also needs to explore why (1) a very small proportion of the population appears to be at risk for ABS suggesting a role for genetic predisposition; (2) in the classic variant, there is sparing of the basal segments of the heart with characteristic dysfunction of the apical and mid segments; and (3) the recurrence rate is low despite the repeated exposure to stressful events over a lifetime. Finally, there is a need to establish a registry for ABS to investigate its natural history and conducting randomized trials of pharmacotherapy aimed at strategies to promote myocardial recovery and prevent recurrence.

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REVIEW ARTICLE

Renin and Cardiovascular Diseases: Hope or Hype

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Abstract:

The renin-angiotensin-aldosterone system (RAAS) plays an important role in regulating blood volume and systemic vascular resistance, which together influence cardiac output and arterial pressure. Renin maintains blood pressure through vasoconstriction when there is inadequate salt to maintain volume. In populations where blood pressure is more often high than low, and vascular death more common than haemorrhage or dehydration, therapeutic reductions in renin secretion or response are valuable. Whether long-term benefits are due entirely to blood pressure reduction remains unproved. The pathway can be blocked at its rate-limiting step (b blockade or direct renin inhibition), the synthesis of the active product, angiotensin II, or at the receptor for angiotensin. Because renin and sodium are the two main factors in blood pressure control, and renin levels vary inversely with sodium load, blood pressure control requires a combination of natriuresis and blocking the consequential increase in renin activity. Being a large and stable molecule, renin is among the easiest and cheapest of hormone measurements. Understanding the simple biochemistry and physiology of renin permits optimal use of the drugs acting to raise or suppress this hormone.

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Introduction:

The renin-angiotensin-aldosterone system (RAS) has a central role in acute and chronic regulation of blood pressure (BP). As the name implies, there are three important components to this system: 1) renin, 2) angiotensin, and 3) aldosterone. Renin, which is primarily released by the kidneys, stimulates the formation of angiotensin in blood and tissues, which in turn stimulates the release of aldosterone from the adrenal cortex. Renin is a proteolytic enzyme that is released into the circulation primarily by the kidneys. Its release is stimulated by 1) sympathetic nerve activation (acting via (beta1-adrenoceptors) 2)

renal artery hypotension (caused by systemic hypotension or renal artery stenosis) 3) decreased sodium delivery to the distal tubules of the kidney Without renin, blood pressure cannot be protected in the face of sodium depletion.' Conversely, in the face of salt loss, excess renin production serves only to maintain, not to increase blood pressure. It is in salt-replete humans that renin may be undesirable and contribute both to hypertension and end organ damage.[2-4] Several classes of drugs have therefore been developed which confer benefit by blocking the effects of renin. Their proven roles are reducing mortality in heart failure and lowering blood pressure in hypertension. Although they also protect against many complications of hypertension, diabetes, vascular and renal disease, critical analysis is required to discern benefits additional to those of blood pressure reduction.

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In heart failure, where the physiological compensations can be more harmful than the fall in cardiac output which elicits the compensation, RAS blockade was one of the stunning successes of 20th century medicine. In hypertension, by contrast, RAS blockade has not clearly performed better than other classes of antihypertensive drugs in protecting against the major complications of stroke, coronary heart disease, and (surprisingly) heart failure. This failure can be attributed to the over-riding importance of blood pressure reduction in protecting against complications of hypertension, and to the need for both components of hypertension-salt and renin to be targeted for blood pressure control to be achieved in most patients. [s] The lesson from heart failure is that the maximum potential of RAS blockade is reaped only when all components of the system are fully blocked in patients in whom RAS would otherwise be maximally activated.

RAS: The Main Players

Renin is an enzyme secreted from specialised cells in the afferent arteriole of the glomerulus-the "juxtaglomerular apparatus" (JGA). Its circulating substrate, synthesised in the liver, is the protein angiotensinogen, from which renin generates the decapeptide angiotensin I (Ang I). Ang I is in turn converted to the octapeptide Ang II by angiotensin-converting enzyme (ACE). Ang II is the principal effector molecule of the RAS, whose main actions are to stimulate the ATl receptor on arteries and the adrenal cortex to cause vasoconstriction and stimulation of aldosterone secretion. The AT1 receptor also facilitates noradrenaline release from sympathetic nerves, and has chronic trophic actions promoting growth of muscle cells in the heart and arteries. In addition to the classical pathway leading to Ang II and stimulation of the AT 1 receptor, smaller biologically active angiotensin peptides can be formed from Ang I and II, especially when levels of the former are increased during treatment with ACE inhibitors and angiotensin receptor blockers (ARBs).[6] Whereas Ang(2-8) and Ang(3-8) (Ang III and IV) bind to the AT1 receptors and have similar effects as Ang II, Ang(1-7) binds to the AT2 receptor and stimulates natriuresis and vasodilatation. The role of the AT2 receptor in adult tissue, however, remains uncertain, being mainly linked to apoptosis of developing tissues during embryogenesis.

Factors Controlling Renin Release

Renin secretion from the JGA in the kidney is regulated by four mechanisms: arterial BP, sympathetic nervous system activity, sodium balance and negative feedback regulation by Ang II . Interestingly the four major antihypertensive drug classes all cause changes in plasma renin, through one each of these mechanisms.

Pressure: The unusual site of the JGA endocrine secretory cells around arterioles is testament to the importance of pressure sensing in renin regulation. Renovascular hypertension is the classic example of increased renin secretion due to low pressure at the JGA, which senses the post-stenotic pressure and "thinks" that systemic pressure needs to be increased. Renal hypoperfusion in heart failure and hypovolaemic states is responsible for the hyper-reninaemia and consequent secondary hyperaldosteronism in these conditions. Calcium channel blockers (CCBs) and a blockers increase renin partially through their reduction in afferent arteriolar pressure.

Sympathetic stimulation: This is responsible for the two to threefold increase in renin on standing and exercise, and (through their activation of the baroreceptor) for part of the increase of CCBs and a blockade. The adrenergic receptor on the JGA is the bl adrenoceptor-one of the few extra cardiac sites of the bl-subtype-and is coupled to cyclic AMP production, through a specific isoform of adenylate cyclase (type 6). In hypertension, the b blockers work entirely through blockade of renin secretion.' Side effects due to reduction in cardiac output can be minimised by using the most bl-selective agents and doses[8].

Sodium balance: The macula densa cells in the distal renal tubule sense the Na+ flux through the furosemide-sensitive Na+K+2C12 transporter. The macula densa is a discrete region of specialised columnar epithelial cells at the point of the renal distal tubule, which lies adjacent to the JGA in the afferent arteriole. Prostaglandins and adenosine act as signals from the macula densa to the JGA, respectively stimulating and inhibiting renin release. At steady state-that is, when there has been no recent change in sodium intake or output Na+ flux at the macula densa is largely a measure of salt intake. Hence the concept of renin-sodium profiles , and the major role of dietary salt

in determining plasma renin in healthy people. However, the fascinating and clinically important feature of this mechanism is that when Na+ handling is perturbed either pharmacologically or pathologically, the Na+ flux through the Na+K+2C12 transporter and consequent effect upon renin secretion remain altered until the perturbation is removed or corrected. For this reason, as discussed below, measurement of a low plasma renin has become an invaluable method of detecting patients in whom Na+ retention is present owing to causes such as agerelated nephron loss, primary hyperaldosteronism (Conn syndrome), genetic gain of function in a Na+ channel,24 or the ingestion of excess salt or a drug which reduces Na+ excretion. The non-steroidal anti-inflammatory drugs illustrate this last category. Of most practical import, the increase in renin secretion seen with diuretics is due to reduced Na+ delivery to the macula densa, so that renin measurement allows accurate titration and choice of dose and type of diuretic in patients with resistant hypertension. Negative feedback regulation by Ang 1127: The major tonic regulator of renin secretion is through negative feedback regulation by Ang II. Ang II acts via AT 1 receptors on the juxtaglomerular cells to inhibit the release of renin, thus reducing plasma

renin activity (PRA) and the production of Ang I and Ang II. Although first recognised in the 1960s, it was only the advent of chronic RAS blockade by ACE inhibitors which led to recognition of the physiological importance of Ang feedback. In most people, ACE inhibitors or ARBs lead to several-fold increases in plasma renin. The four regulators of renin secretion can amplify or cancel each other. However, most patients receiving b blockade have a low plasma renin, even if also receiving an ACE inhibitor (ACEi) or ARB. The patients whose PRA remains suppressed despite receiving multiple drugs which stimulate renin secretion must have Na+-dependent hypertension; this recognition has been invaluable in detecting interesting secondary causes, and in tailoring medical treatment of resistant hypertension.

Age and ethnicity

Sodium balance is the main chronic determinant of individual plasma renin values, leading to considerable interest in surrogates for detecting patients with low renin.[9] Of these surrogates, the main are age and ethnic group. Plasma renin falls by 17% each decade. Ethnic variation in renin distribution is also recognised, and in particular younger black subjects have lower levels than Caucasians.[l°] There is little doubt that genetic variation in Na+ handling is the main reason, but none of the genes or alleles has yet been clearly identified; the mechanisms could vary from anatomical variation in nephron number or size to molecular regulation of renal Na+ channels. Although the age and ethnic variation in mean renin levels is striking, it is important to emphasise individual variation; no sudden transition to low-renin hypertension occurs once patients enter their later 50s and 60s. Now that we recognise the importance of determining a patient's place in the spectrum of plasma renin in order to rationalise treatment, there is a case for measuring rather than guessing the renin level from the surrogates of age and race. As will be discussed, renin measurement may be especially helpful in treated patients, where the effects of treatment move patients across the spectrum.

Measuring Renin System Activity

"Renin activity" measures the capacity of renin to generate Ang L"Renin mass" refers to the amount or concentration of renin (not including its precursor, prorenin) in the plasma. "Active renin" was formerly used to describe the amount of renin in the plasma. Renin assays

PRA assays measure by competitive radioimmunoassay the amount of Ang I generated in a 1 hour incubation of plasma. The enzymatic amplification generates a sensitive assay, but at the expense of the labour required to measure each sample with and without the hour's incubation. When PRA is low, there is little amplification, and the log-normal distribution of renin means that a disproportionate number of samples are below detection limits. Because the assay relies on the presence in plasma of saturating levels of renin substrate (ie, angiotensinogen), very high renin levels can be underestimated as a result of substrate exhaustion before the hour's incubation is complete.

Renin mass is measured by a two-site (or "sandwich") assay." An immobilised antibody that binds both renin and prorenin is used to capture

enzyme from the sample. Renin is then measured using a second, labelled antibody specific to renin. Chemiluminescent labelling has enabled cheap, high throughput and highly sensitive ELISA plate assays, which extend the limits for renin detection at both ends of the range. The observation, with the newer assays, that renin concentration varies up to 1000-fold between subjects, compared with the trivial two- to threefold within-subject changes with posture and exercise, supports a more important chronic rather than acute role for renin (the reverse is probably true of the sympathetic system). The observation also has a valuable practical import, telling us that random outpatient samples from seated patients are perfectly adequate for detecting patients with abnormal values at either end of the range.

Clinical Relevance of Plasma Renin Measurements

Because of the textbook teaching that accurate renin assessment required admission to hospital, and the expense of older assays, renin measurements have typically been reserved for research or specialist investigation. The principal clinical value of renin measurement, historically, has been the recognition of patients at the upper and lower

extremes of the distribution who may have secondary causes of hypertension-particularly renal artery stenosis (high renin) and primary hyperaldosteronism (Conn syndrome: low renin). A less well known use of renin measurement is in the assessment of patients with low blood pressure. Here the initial differential usually lies between an autonomic neuropathy, where loss of sympathetic innervation of the JGA b 1 receptor leads to profound renin suppression, and Na+ depletion, where a combination of macula densa and adrenergic stimulation causes a marked increase in renin levels. Renin measurements have also been of interest in epidemiology, where the recently confirmed evidence that high renin is an independent risk factor for myocardial infarction led to placebo-controlled trials like HOPE investigating the benefit of RAS blockade in high-risk patients, and to the hypothesis of benefits from RAS blockade "beyond blood pressure control".[12]

To date, the complexity of the older renin assays has limited the number and size of epidemiological studies measuring renin, with the consequence that its predictive value in individual patients remains controversial and probably small. The high-throughput renin mass assay provides an opportunity for incorporating measurements into adequately powered prospective studies.

However, the main large-scale clinical potential of automated renin assays is in the rationalisation of drug treatment for hypertension, as well as more efficient detection of patients with secondary causes. Samples taken from a patient seated for 10-15 minutes are adequate for interpretation. It is generally unnecessary to change treatment, provided that the effects of drugs are borne in mind, as summarised below. Although blood samples for renin can be taken in the primary care setting-and we ourselves conduct much of our research there, and routinely request renin sampling before patients' first clinic visit-renin should probably remain a specialist measurement until there is good evidence of benefit from more widespread use.

Influence of treatment on plasma renin and other components of RAS

All drugs in use for hypertension have an influence on plasma renin and other components of RAS .[13] In the case of "B, C, D" drugs, the change in plasma renin reflects the change in overall RAS activity-suppressed by b blockers ("B"), activated by CCBs ("C"") and diuretics ("D") in compensation for their reduction of BP and Na+ excess. The "A" drugs, by contrast, act like "B" to suppress RAS, but cause an increase in renin secretion by blocking the negative feedback of Ang II upon renin . Whether this increase in renin and consequently Ang I levels can lead to escape from ACE inhibitors and/or ARBs remains uncertain. Interestingly, the increase in renin mass is probably the best "downstream" measurement of the RAS pathway because the more effective the blockade, the greater the loss of negative feedback. Plasma renin rises more on treatment with a combination of an ACE inhibitor and an ARB than with either alone, indicating that neither alone is maximal. The recently introduced class of direct renin inhibitor (DRI) also blocks the negative feedback, but causes a dissociation between the rise in renin mass and reduction in renin activity. Plasma levels of Ang (both I and II) fall on b blocker and DRI treatment, whereas they are dissociated on ACEi treatment (high Ang I,

low Ang II) and increased on ARB treatment. Aldosterone is a variable downstream marker of RAS activity, because even slight increases of its major secretagogue, K+, can over-ride the expected reduction owing to RAS blockade. Selection of treatment

That hypertension must be due to either or both of excess vasoconstriction and volume is as incontrovertible as the law of physics-Poiseuille's law-from which the assertion is derived. That renin is the major chronic vasoconstrictor was suggested long ago, but remains a conjecture based on the difficulty of maintaining blood pressure during salt depletion after RAS blockade, and the absence of new vasoconstrictor candidates from the genome project. That all successful drugs for hypertension work primarily through either RAS blockade or Na+ elimination is also still a theory, based partly on studies comparing the same patient's response to the major drugs, and partly on the failure of drugs blocking alternative pathways (eg, the sympathetic) to achieve similar efficacy in BP reduction. The concept of two types of hypertension, each with their preferred initial treatment, is now enshrined in the NICE and BHS treatment guidelines.[14] Based on the original AB/CD algorithm,20 these recommend "A" (exceptionally "B") for younger Caucasians, and "C" or "D" for all others. However, the guidelines also recognise that most patients should have a combination of the two pairs, given that most patients do not lie at the extremes of plasma renin, and need both vasoconstriction and volume components to be blocked. Recent outcome trials have, indeed, reported an average of more than two drugs per patient once target BP is achieved. At present all guidelines, except the American (JNC 7)[15] recommend initial treatment with monotherapy. But the failure of the less well controlled BP in one arm of the VALUE [16] and ASCOT [17] studies to "catch up", despite more add-on treatment eventually being used in that arm, has raised the interesting possibility that monotherapy stimulates overcompensation, from the component of hypertension that is not blocked (vasoconstriction or Na+ retention). Studies are planned, therefore, to determine the idea that initial combination therapy should be the norm in most patients.

Treatment guidelines: evidence and details

Evidence for the AB/CD approach came initially from two crossover studies, which examined the effects of multiple antihypertensive treatments in younger patients (<55 years) rotated through the main classes of antihypertensive agents: ACE inhibitor (A), b blocker (B), CCB (C) and diuretic (D). Patients were almost twice as responsive to ACE inhibitors or b blocker treatment as to a CCB or diuretic. The exceptions were either in the oldest patient quartile or those who had the lowest PRA, consistent with previous studies. [18] In both crossover studies, the correlation between responses to the different pairs of treatments was only strong between A and B (ie, patients who responded to A also responded to B), and between C and D. Small crossover studies do not usually influence NICE guidelines. However, AB/CD correctly predicted the poorer BP control, and therefore outcome, in older patients receiving an "AB" drug in each of VALUE, ASCOT and ALLHAT.[19] The main difference between the NICE/BHS 2006 guideline and the original AB/CD rule is the demotion of "B" to special indications. This was a response to the higher stroke rates with atenolol treatment in recent trials, particularly when compared with "A" in the LIFE study. Interestingly, this unexpected result may also be explained by one of the crossover studies, which reported a threefold increase in both augmentation index the now popular measure of arterial wave reflection from a stiffened aorta-and plasma B-type natriuretic peptide during b blocker treatment. This adverse effect was confirmed in the atenolol group of the CAFE sub study of ASCOT.[20] The diabetogenic effect of "B" has also been blamed, but the similar effect of thiazides is less clearly harmful, and the long-term consequence of new-onset diabetes in patients receiving "B" or "D" remains to be resolved. From guidelines to practice.

Although the mass of outcome data and their meta-analysis in hypertension is perhaps unique in medicine, it is ironic that we are left with a smaller choice of first-line drugs than a decade ago when the studies were planned. If, however, there are only two physiological routes to developing hypertension, it was inevitable that we would eventually recognise only two main categories of drugs. Within these categories we still have some

genuine choices to help cope with patients who do not tolerate or respond to the first choices. There are two classes of "A"; and with excellent timing the renin inhibitor class has arrived as a potential replacement for "B", acting at the rate-limiting step of RAS, but expected to lack the downsides of "B" owing to extra renal b blockade.Within "CD", we have several classes of diuretics other than thiazides. But the reason why an understanding of the renin system is important, and the availability of cheap measurement so exciting, is that it is now both necessary and possible to adopt an efficient, rational approach to optimising the choice of drug(s) and doses from the two categories of drugs.

If understanding renin helps us to understand the evidence underpinning the guidelines, the understanding is even more important in progressing beyond where NICE/BHS left off because of lack of evidence. Poiseuille's law holds, whether or not a patient has started medication, but the patient's place in the renin spectrum may shift with treatment. For instance, RAS activation by diuretic may convert a volume-dependent patient to a renin-dependent patient, in whom a combination of RAS blockers becomes worthwhile. Conversely, the relief of renin-driven vasoconstriction may reduce pressure natriuresis, and convert a vasoconstricted- patient to a volume-dependent patient requiring higher doses of thiazide or combination with other diuretics. In theory, at least, even the most difficult hypertension should yield to a combination of sufficient RAS blockade and diuretic.

Diuretic choice and dose in low-renin hypertension

Choice of diuretic and dose may sound obvious but this was ignored for years in the development of fixed-dose combinations of thiazide, usually HCTZ 12.5 mg, with various RAS blockers: b blockers, ACEi and, till recently, ARBs. The view that low-dose thiazide is maximal came from small parallelgroup studies of untreated, often younger patients (ie, those with high renin). The older patient, as we have seen, typically has low renin and requires combination treatment. Figure 5A shows the dramatic effect of doubling even a 25 mg dose of HCTZ in several hundred patients, aged 55-80, randomly assigned to "C" or "D". And in a recent crossover study of patients with low renin despite treatment with a CCB, we found that a dose of bendroflumethiazide 5 mg was necessary to achieve the same BP reduction as spironolactone 50 mg or amiloride 20 mg. "The "de-suppression" of plasma renin by bendroflumethiazide was also dose related, but even at 5 mg bendroflumethiazide was only half as effective as the K+-sparing diuretics in increasing renin. So in patients with resistant hypertension-uncontrolled despite use of A + C + D- the value of adding spironolactone or amiloride is due partly to natriuresis, but partly also to their renin activation and hence potentiation of the RAS blockade. Currently we use spironolactone only in such resistant patients. For first-line treatment we use thiazides, sticking to low doses to avoid diabetes, with a "whiff' of amiloride to avoid hypokalaemia.

Perhaps it would in the future be more logical to use an effective dose of amiloride or spironolactone to avoid diabetes, with a "whiff' of thiazide to avoid hyperkalaemia. Outcome data may be lacking, but we also lack outcome data to support the benefits of thiazides at their currently recommended doses. Treatment combinations for patients with high renin, and their titration.

Once patients are receiving multiple diuretics and a CCB, they resemble another condition associated with very high renin levels-namely, heart failure-in which a combination of multiple RAS blockers has been shown to be beneficial.

However, as mentioned earlier, a downstream demonstration of complete RAS blockade is difficult with most of the drugs. Plasma aldosterone is affected by small rises in K+, and plasma Ang II is either unmeasurable or unmeaningful after ACEi or ARB treatment, respectively. Dose-related changes in renin activity or Ang II can be demonstrated after b blockade or DRI, and show that the latter reduces PRA even when combined with the drugs that normally increase PRA.

Tissue renin

Local production within the heart, arteries and kidneys is likely, but its importance is much harder to ascertain than that of circulating renin. That may change with the discovery of a "renin receptor" in these tissues, which binds both renin and its precursor, prorenin, causing nonproteolytic

activation of renin system activity with production of Ang I and the activation of intracellular mitogen-activated protein kinases, ERK1 and ERK2, independently of angiotensin production. [21] Blockade of the non-proteolytic activation of prorenin by a decoy peptide inhibits the development of left ventricular fibrosis and hypertrophy in stroke-prone spontaneously hypertensive rats. These are early and exciting days in

our unravelling of the renin receptor, and determination of whether it provides another target to be considered in achieving full RAS blockade.

Benefits beyond BP control?

One of the reasons for interest in tissue renin is as an explanation for the still controversial notion that RAS blockade confers outcome benefits not explained by BP reduction alone. [21] This seems most widely accepted, if still not completely proved, in the treatment of diabetes and some other nephropathies, with some evidence also for benefit of combined RAS blockade to reduce proteinuria.[23] For more major complications of hypertension, the most up to date retrospective meta-regression analysis of data from almost 150 000 patients provides some encouragement, reporting that ACE inhibitors achieve BP independent reduction in the relative risk of coronary heart disease of about 9% (95% CI 3 to 14%). In trying to dissect this observation, it is tantalising that in support of the strictest interpretation of the hypothesis, a number of ACE inhibitors have demonstrated outcome benefit for patients with controlled blood pressure, despite blood pressure falls of ,5 mm Hg. [24] In similar normotensive populations, calcium blockers have not achieved benefit [25]; and meta-analysis of "more versus less" BP lowering in uncontrolled hypertension shows benefit of "intensive" BP control only in patients with diabetes. But in prospective analyses the RAS hypothesis remains not so much unproved, as untested, because of the failure closely to match BP between groups.[26] As this article has now explained, the failure was inevitable because of the age-related

fall in renin, and change in pattern of BP response. To test the RAS hypothesis, renin needs first to be de-suppressed by "C" or "D", as now recommended for first-line treatment of older hypertensive patients, and a pilot study conducted to match BP on the selected RAS-blocking and non-blocking regimens.[27]

Conclusion

So, renin: friend or foe? Given the number of drug classes we employ to block renin, it is certainly seen mainly as foe. For middle-aged and older populations eating Western diets rich in salt and fat, renin may indeed be at best unnecessary and at worst harmful. Yet in the contest between renin and Na+ which, as this article has explained, underpins hypertension, it is Na+ which wins in Western society, leading to suppression of renin secretion from ageing kidneys. So when it came to the large outcome trials in older hypertensive patients comparing drugs which targeted renin or Na+ as their primary mode of action, the latter have generally outperformed simply by lowering BP more effectively.

These trials teach us that we should use renin as a friend in order to reap maximum benefit from RAS blockade. This means rendering hypertension renin-dependent by optimal use of diuretics, and by measuring renin to help determine when more diuretic or more RAS blockade is required. Despite considerable progress in the past decade, most patients with hypertension have failed to achieve target BP, and we have failed to ascertain the true benefits of renin blockade. Rational understanding and exploitation of the renin-salt interaction allows these failures in the clinic and research to be reversed.

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ORIGINAL ARTICLE

Evaluation of Effectiveness of Dobutamine Stress Echocardiography (DSE) For Peri-Operative Assessment of Cardiac Risk in Patient Undergoing Elective Non-Cardiac Surgery with Preexisting Cardiac Disease

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Abstract:

Introduction: During pre-operative workup for cardiovascular risk assessment prior to noncardiac elective surgery, conventional stress testing and invasive procedures are not always feasible. DSE can be a valuable tool in such situations. This prospective observational study was carried out in the JRR Medical College Cardiology Departement, Sylhet, Bangladesh from January 2005-June-2007. Objectives: The main objective of the study was to assess the accuracy of DSE in identification of peri-operative cardiac complications in patients undergoing elective non-cardiac surgery.

Materials & methods: 74 Patients with mean age 55.70(SD 11.67) years, male: female (1:1.55) were studied. DSE was performed according to the Mayo Protocol. On the basis of DSE results, patients were categorized into high (new or worsened wall motion abnormality of >2 segments at low dobutamine dose (10-20 mgm/kg/min) or at low (<120 beats/min) heart rate), intermediate (new or worsened wall motion abnormality of <2 segments at higher doses(30-40 mgm/kg/min) of dobutamine) and low risk (normal wall motion) groups.

Results: Accordingly 05(6.8%), 26(35.1%) and 43 (58.1%) patients were categorized as high, intermediate and low risk respectively. The low and intermediate risk patient's underwent the required surgical procedure and in high risk patient's surgery was postponed pending further cardiac assessment. Among patients who had undergone surgery, two (2.8%) suffered major perioperative cardiovascular complications. The estimated negative predictive value of the test is 97.10%.

Conclusions: From this study it can be concluded that DSE is an excellent method for pre-operative risk-stratification in patients undergoing elective non-cardiac surgical procedure with high negative predictive value.

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Introduction

Peri-operative cardiovascular complications such as myocardial infarction, unstable angina, acute left ventricular failure and serious ventricular arrhythmias are major causes of mortality and morbidity in surgical patients with existing cardiac disease[1,2]. Patients known or suspected to have cardiac disease and planned for elective non-

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cardiac surgery should be assessed before surgery and appropriate management should be taken to avoid and minimize these complications. A successful pre-operative evaluation of cardiac patients undergoing non cardiac surgery requires close teamwork between the patient, anesthesiologist, surgeon and cardiologist [1, 2].

The peri-operative cardiovascular risk is not similar in all patients with cardiac disease. The risk is related to preexisting cardiac disease, co-morbidity and type of surgery. It is found that patients with prior myocardial infarction suffer acute myocardial infarction at a rate of 6.6% peri-operatively compared to 0.13% in patients with no history of myocardial infarction [3,4]. The incidence of peri-operative myocardial infarction is as high as 37% when the prior myocardial infarction is within 3 months and 16% when the event has occurred within 4 to 6 months [3, 4]. Patients who presents with clinical symptoms of unstable angina are at increased risk of peri-operative myocardial infarction and acute congestive heart failure [3, 4, 5]. Severe aortic stenosis carries the greatest risk of sudden death - 15% in asymptomatic patients and 20% in patients with prior symptoms. Mitral stenosis and regurgitation carries a significant risk of acute pulmonary edema in the peri-operative period [2,3,4,6].

Patients with arrhythmias are at increased risk of cardiac mortality in presence of cardiac disease during surgery [7]. The presence of congestive heart failure in the preoperative period had been associated consistently with increase morbidity and mortality in non-cardiac surgery. Severe systemic hypertension (systolic BP> 180 and or diastolic BP> 110 mm Hg) are found to have some increase risk and there is no evidence that mild-to-moderate hypertension independently increases peri-operative risk [8]. Pulmonary hypertension irrespective of cause carries significant risk for cardiac complication. It is found that an elevated gradient >5 mmHg between the pulmonary artery diastolic pressure and the pulmonary capillary wedge pressure raises the mortality rate to about 60% [9]. Diabetes mellitus is by itself independent strong predictors of cardiac complication during surgery. It is observed that there is a twofold increase in mortality among diabetic patients compared with non-diabetic patents during surgery [10]. Preoperative creatinine greater then 2 mg/dl is also associated with increased peri-operative cardiac morbidity[11].

Vascular disease is commonly associated with coronary artery disease and should be considered as a risk factor for peri-operative cardiac complications. In a large review, Hertzer found that one half of the peri-operative mortality in vascular surgery was due to cardiac disease [12].

The nature of surgery is also responsible for increased cardiac complication and it is found that high risk surgery had higher cardiac complication. High risk surgery includes major emergency surgery, major vascular surgery, anticipated prolonged procedures associated with large fluid shift or blood loss. Intermediate risk procedure include intraperitoneal and intrathoracic surgery, carotid endarterectormy, head and neck surgery, orthopedic surgery and prostate surgery and low risk include endoscopic and superficial procedures, cataract surgery and breast surgery[1,11, 12,13].

So the pre-operative assessment should focus on identification of potentially serious cardiac disorders, including coronary artery disease, other co-morbid conditions and also the type of surgery for effective surgical outcome. [1,2, 11,12,13,14,15.]

From this perspective the preoperative cardiac risk assessment is very vital in patients with suspected cardiac disease undergoing non-cardiac surgery. Several methods have been advocated for risk stratification including multi-factorial clinical scoring systems, ambulatory ECG monitoring, stress ECG, stress myocardial perfusion imaging, stress echocardiography and coronary angiography [1,2,13,14,16,17].

It is found from numerous studies that cardiac risk assessment based on clinical scoring system by Detsky's modification of Goldman's cardiac risk index provided little information on individual peri-operative cardiac risk [18,19,20,21]. So non-invasive test is essential and play vital role in the assessment of peri-operative cardiac risk.

Dobutamine, dipyridamole and adenosine are used successfully as pharmacological agents in cardiac risk stratification before non-cardiac surgery [1, 2, 3,16, 17, 22,23]. Nuclear myocardial perfusion imaging and coronary angiography is also used but they are costly and not available in all centers. Patients

selected for elective major non-cardiac-surgery cannot adequately exercise in this situation pharmacologic stress echocardiography have advantages over stress ECG [1,2, 13, 14,16]. It is found from different studies that the positive predictive value of DSE has ranged from 7-33% and negative predictive value has ranged from 93-100% for predicting cardiovascular events [24]. This present study is performed to evaluate the usefulness of DSE in the assessment of cardiac risk before elective non-cardiac surgery.

Materials And Method

This study was prospective, observational study carried out in the Department of Cardiology. JRR Medical College Hospital Sylhet, during the period from January-2005 to June-2007. Seventy four patient with age range 30-58 years irrespective of sex presenting with known or suspected cardiac disease who were referred to the department of Cardiology from general surgical, obstetrics-gynecology and orthopedics department for cardiac risk assessment were included in the study, patients undergoing emergency procedures were not enrolled.

All patients under went a routine clinical evaluation, including a detailed clinical history, a physical examination, and a 12-lead ECG. Risk factors for vascular disease i.e. hypertension, diabetes, smoking were also analyzed. Dobutamine stress Echocardiography study was performed in all cases. No patient underwent coronary angiography or prophylactic myocardial revascularization before surgery.

DSE – After appropriate counseling and written consent all patients had undergone DSE according to standard (Mayo Clinic) protocol [15, 16,23]. The echo image acquisition is taken by ACUSON CV 70 echocardiography machine. Every patient underwent a resting two-dimensional echocardiography examination. Standard four chambers, two chamber apical and parasternal long and short axis views were taken (Figure 1 &2.), and a baseline 12-lead ECG was recorded. Dobutamine was then administered intravenously by syringe pump, starting at 10 mgm/kg/min for 3 minutes, increasing by 10 mgm/kg/ min every 3 minutes to a maximum of 40 mgm/kg/ min and continued for 3 minutes. In patients who did not achieve 85% of their age-predicted maximal heart

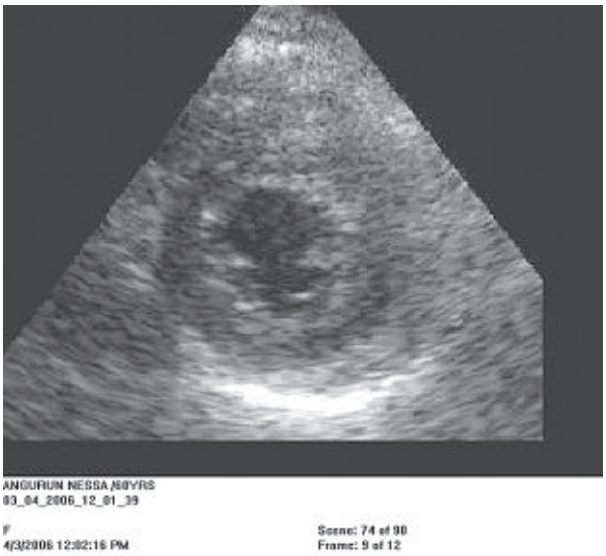

Fig.-1. *DSE in short axis view*

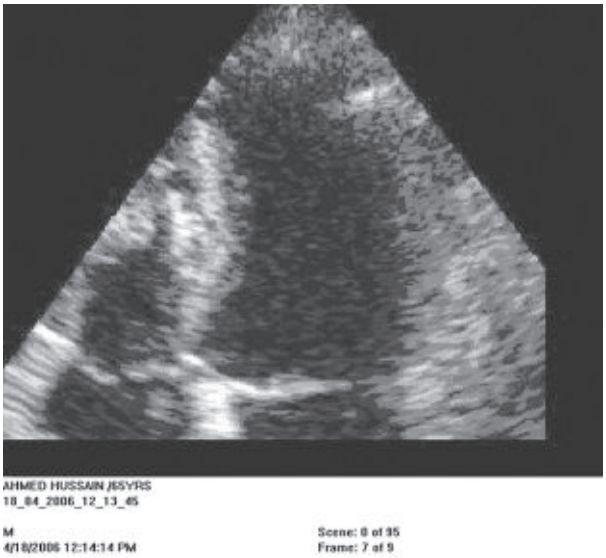

Fig.-2. *DSE in apical 4-chamber view.*

rate and who had no symptoms or signs of ischemia, atropine starting with 0.5 mg and increasing to a maximum of 1 mg was given intravenously every one minute interval at the stage 40 mgm/kg/ min dose, while dobutamine was continued. Throughout dobutamine infusion, the ECG was continuously monitored the 12-lead ECG was recorded every three minute interval, and blood pressure was measured by sphygmomanometer in every 3 minutes. The two dimensional echocardiogram was continuously monitored and recorded during the final minute of each stage and analyzed just after DSE test.

In DSE the left ventricular wall was divided into 16 segments, and each was scored on a four-point scale: 1, normal 2, hypokinetic 3, akinetic and 4, dyskinetic. An increase in score between rest and stress in two or more segments, indicating a new or worsened wall motion abnormality, constituted a positive test. High risk in DSE was defined as echocardiographic wall motion abnormality involving >2 segments at low dobutamine dose i.e 10 mgm/kg/ min or at low heart rate i.e. <120 beats/min and intermediate risk was defined as new or worsening wall motion abnormality of < 2 segments at higher doses of dobutamine and low risk in DSE are those with normal stress echocardiography wall motion [1, 16, 17, 20].

Statistical Analysis

The numerical data obtained from the study was analyzed and significance of deference was estimated by using the statistical methods and formulas. Comparison between groups was done by standard't' test, chi-square test and ANOVA as applicable. All data were analyzed by using computer based SPSS version 11.0. Probability values less than 0.05 was considered as significant.

Results

The mean age of the patients was 55.50 years + 11.67 (range, 30-85 years) Male to female ratio was 1:1.55 with 29 men and 45 women. A history of coronary disease was present in 34 (45.9%) patients; among them old myocardial infarction in 26 (35.1%) patients, chronic stable angina pectoris in 8 (10.8%) patients and remaining 40 (54.1%) patients had ECG changes suggestive of ischemia with Canadian Cardiovascular Society Class I-II chest pain. LBBB was present in 3 (4.05%) patients and AF in one (1.35%) patient. Bi-fascicular block was present in one (1.35%) patient and cor-pulmonale with moderate pulmonary hypertension in one (1.35%) patient.

Hypertension was present in 27 (36.4%) patients, 11 (14.8%) had diabetes mellitus and there were 19 (25.6%) smokers. Peak dose was achieved in 56 (75.6%) of 74 patients. Target heart rate (THR) was achieved in 62(83.7%) patients. Atropine was given in 52 (70.2%) patients to achieve THR. Angina was present in 11 (14.86%) patients and arrhythmia was present in 8 (10.8%) patients. Hypertensive BP response (> 200/ 100 mmHg) was present in 2 (2.7%) patients and hypotensive response (BP <100/ 70 mmHg) in 4 (5.4%) patients. ECG change was present in 19 (25.6%) patients in the form of >1mm ST segment depression. Bradycardic response was present in 2 (2.7%) patients. One (1.35%) patient, who had a preexisting history of ventricular tachycardia and reverted by DC shock two months ago during an acute episode of MI, developed ventricular tachycardia during the test and reverted spontaneously without DC shock and DSE was stopped prematurely. Non-sustained Ventricular tachycardia occurred in 2 (2.7%) patients and it terminated spontaneously and DSE was continued. Transient atrio-ventricular block (AVB) with junctional rhythm was observed in one patient (1.35%) during DSE, which reverted spontaneously and DSE was continued. Marked PVC was observed in 4 (5.4%) patient to whom one was in bigeminy pattern. 01 (1.35%) patient developed AF at peak dose after giving atropine and reverts to sinus rhythm 03 minutes after the test spontaneousely. Technically adequate echocardiography images were obtained in all 74 patients during the test. There were 56 (75.67%) patients who could tolerate the high doses of dobutamine during the test. The test was stopped at the end of 10 mgm/kg/min doses in two patients, at end of 20 mgm/kg/min doses in 8 patients and at 30 mgm/kg/min doses in 8 patients.

Forty three (58.01%) patients showed normal echogradiographic response during DSE test and was categorized as low risk for peri-operative cardiac events. The remaining 31(41.9%) patients showed new wall motion abnormality during DSE test. Among them 16(21.6%) patients had a normal resting echocardiogram and 15(20.2%) patients had worsening of an existing wall motion abnormality (Table -1).

There were 05(6.75%) patients who had wall motion abnormality in more than two segments at dobutamine dose of 10-20 mgm/min and were categorized as high risk patients for peri-operative cardiac complication. Wall motion abnormalities in two segments at doses of 30-40 mgm/kg/min was observed in 26(35.13%) patients and categorized as intermediate risk fro peri-operative cardiac complication. (Table -2).

Table-I

Echocardiography response during DSE in low, intermediate and high group in study population.

Echo-cardiogaphic response in DSE	Low Group	Intermediate group	High group
Normal wall motion response	43	0	0
New wall motion abnormality in 2 segments	0	26	0
New wall motion abnormality in >2 segments	0	0	5
Total	43	26	5

Table-II

Achievement of Dobutamine dose in low, intermediate and high risk group.

Dose	Low risk	Intermediate risk	High risk
10 mgm /kg/min	0	0	02
20 mgm /kg/min	0	05	03
30 mgm /kg/min	0	08	0
40 mgm /kg/min	43	13	0
Total	43	26	05

The patients with low risk group were advised to perform surgery. Patients with intermediate risk group were advised for surgical procedure with addition of some new medication and perioperative precaution as needed. The surgical procedure was postponed in patients with high risk group and they were advised for CAG and adequate treatment before surgical treatment.

Postoperative follow up was performed after surgery by respective department in close coordination with cardiology department. There were two cardiac complications one died due to cardiac arrest just after successful operation in post-operation period and another suffered cardiogenic shock post-operatively due to severe LV dysfunction and the patient later on recovered successfully. In the remaining patients no cardiac complication were found. The estimated negative predictive value of the DSE test is 97.10% but the accurate positive predictive value cannot be estimated as high risk group patients were postponed from the surgical procedure.

Discussion

Preoperative cardiac risk stratification is very important clinically in patients undergoing major non-cardiac surgery. It provides information about the present cardiac status of the patients and guide cardiologist, surgeons and anesthesiologist to take appropriate measure to reduce the cardiac complication during after the surgical procedure.

In this study the cardiovascular risk is predicated by the result of DSE. The patients after DSE are categorized according to extent of wall motion abnormality into low, intermediate and high risk group. It is estimated from different studies that the annual mortality rate is 5-6% in high risk group, 2-3% in intermediate group and 1% in low risk group for the cardiac disease itself. If there is any other extra cardiac factor which imposes load to the heart i.e. surgery, the mortality rate increase [1-12, 24].

From numerous studies it is observed that DSE can be used for preoperative cardiac risk assessment[1,2, 16,17,24,25]. These studies also indicate that the presence of new wall motion abnormalities during dobutamine stress at low ischemic threshold was the most powerful independent predictor for peri-operative cardiac events [19,23]. These studies also showed that DSE is safe, feasible and accurate for eliciting myocardial ischemia by dobutamine infusion[1,2,16,17,24,25.]

In this study new wall motion abnormality found in DSE has been taken as a predictor of future cardiac events. Other risk factors for vascular disease, such as smoking, diabetes mellitus, and hypertension, were not significantly correlated with identifying high risk patients. This finding is similar to the finding of different authors where it is shown that the presence of new wall motion abnormalities during dobutamine was the most

powerful independent predictor of peri-operative events and risk factors for vascular disease such as smoking, diabetes mellitus, and hypertension, were not correlated with cardiac events [24,25]. There was one major side effect during DSE in this study. One patient development sustained ventricular tachycardia during the 30 mgm dose of dobutamine, along with echocardiographic evidence of myocardial ischemia. This finding is consistent with the finding of other authors [1,2,17,20]. In this study 4 patients were found to have hypotensive response to increasing dose of dobutamine with out any adverse effect. This hypotensive response was also observed by others in their study, and the reason for hypotension are not clearly defined [16]. Hypertensive response BP >200/100 mmHg in 2 patients were observed during the test, although the test could be continued without any complication. Transient AV-block and frequent PVC and non-sustained VT were also observed during the test without any complication. These finding is similar with the finding of different authors with their study [1,11,20,26.]

In this study the peak dobutamine dose of 40 mgm /kg min was achieved in 56 of 74 patients, and atropine was then added in patients who fail to achieve target heart rate if signs or symptoms of ischemia were absent. Atropine 0.5 mg was given in 52 patients to provoke adequate myocardial stress and to achieve adequate heart rate response. Additional atropine 0.5 mg was required in 4 patients who did not achieve adequate heart rate response to dobutamine and these 4 patients were under beta-blocker therapy. These findings are similar to Poldermans et. al. who also observed that additional atropine to first dose of 0.5 mg required to achieve THR in patients with prior beta-blocker therapy [2,16,24]

The result of the present study is similar to Lalka et. al., who found positive predictive value of the DSE for peri-opertive cardiac events of 29% and a negative predictive value of 95% [26]. This present study is also similar with the study of Poldermans D et al where they found excellent negative predictive value of 100% and positive predictive value of 39% [2,16,24.]

It is essential to mention here that the significance of DSE is in its high negative predictive value and it is emphasized by different authors in their literature [1,2, 11,16,20,24.]

The negative predictive value of this study is also similar with a large series of studies of different authors where significant negative predictive value ranged from 93-100% with positive predictive value of 39% [24,27.] In this study the estimated negative predictive value of the test is 97.10%.

One potential limitation of the present study is that high risk group defined by DSE cannot be operated as they carry impending risk for high peri-operative cardiac complication evident from different studies so positive predictive value cannot be estimated from this study.

Conclusion

From this study it can be concluded that dobutamine stress echocardiography is an extremely useful non-invasive methods for risk stratification in patients who are candidates for major non-cardiac surgery and it is safe, feasible and effective with high predictive negative value.

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