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Journal of Invasive and Clinical Cardiology

INSTRUCTION TO AUTHORS

A. Introduction

The Journal of Invasive and Clinical Cardiology is a biannual, peer-reviewed journal and aims to publish work of the highest quality from all sub-specialties of Cardiology. The aim of the publication is to promote research and serve as platform for dissemination of scientific information in Cardiology.

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The journal accepts original research, review articles, case reports, cardiovascular images and letters to the editor, for publication.

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Original, in-depth research article that represents new and significant contributions to medical science. Each manuscript should be accompanied by a structured abstract of up to 250 words using the following headings: Objective, Methods, Results, and Conclusions. 3 to 5 keywords to facilitate indexing should be provided in alphabetical order below the abstract. The text should be arranged in sections on INTRODUCTION, METHODS, RESULTS, and DISCUSSION. The typical text length for such contributions is up to 3000 words (including title page, abstract, tables, figures, acknowledgments and key messages). Number of references should be limited to 50.

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guiding human research (such as the Declaration of Helsinki) and also that their study has been approved by a local ethics committee. The Results section should be concise and include pertinent findings and necessary tables and figures. The Discussion should contain conclusions based on the major findings of the study, a review of the relevant literature, clinical application of the conclusions and future research implications. Following the Discussion, Acknowledgements of important contributors and funding agencies may be given.

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e. *Acknowledgements*

Collate acknowledgements in a separate section at the end of the article before the references. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

f. *Units*

Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI. Generic rather than trade names of drugs should be used.

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- Abstracts as references may be used; "unpublished observations" and "personal communications" may not be used as references, although references to written, not oral, communications may be inserted (in parentheses) in the text.
- Papers accepted but not yet published may be included as references by adding "In press" after the journal name. Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses).
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Articles in Journals (see also *Journal article on the Internet*)

1. *Standard journal article*

   List the first six authors followed by et al.

   Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002 Jul 25;347(4):284-7.

   More than six authors:

   Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

2. *Organization as author*

   Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension. 2002;40(5):679-86.

3. *Both personal authors and organization as author* (List all as they appear in the byline.)

   Vallancien G, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1,274 European men suffering

from lower urinary tract symptoms. J Urol. 2003;169(6):2257-61.

4. *Volume with supplement*

   Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. Headache. 2002;42 Suppl 2:S93-9.

5. *Issue with supplement*

   Glauser TA. Integrating clinical trial data into clinical practice. Neurology. 2002;58(12 Suppl 7):S6-12.

6. *Type of article indicated as needed*

   Tor M, Turker H. International approaches to the prescription of long-term oxygen therapy [letter]. Eur Respir J. 2002;20(1):242.

   Lofwall MR, Strain EC, Brooner RK, Kindbom KA, Bigelow GE. Characteristics of older methadone maintenance (MM) patients [abstract]. Drug Alcohol Depend. 2002;66 Suppl 1:S105.

7. *Article published electronically ahead of the print version*

   Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002 Nov 15;100(10):3828-31. Epub 2002 Jul 5.

Books and Other Monographs

1. *Personal author(s)*

   Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

2. *Editor(s), compiler(s) as author*

   Gilstrap LC 3rd, Cunningham FG, VanDorsten JP, editors. Operative obstetrics. 2nd ed. New York: McGraw-Hill; 2002.

3. *Organization(s) as author*

   Advanced Life Support Group. Acute medical emergencies: the practical approach. London: BMJ Books; 2001. 454 p.

4. *Chapter in a book*

   Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

5. *Conference proceedings*

   Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.

6. *Dissertation or thesis*

   Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Other Published Material

Newspaper article

Tynan T. Medical improvements lower homicide rate: study sees drop in assault rate. The Washington Post. 2002 Aug 12;Sect. A:2 (col. 4).

Unpublished Material

In press or Forthcoming

Tian D, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. Proc Natl Acad Sci U S A. Forthcoming 2002.

Electronic Material

1. *Journal article on the Internet*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

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Zhang M, Holman CD, Price SD, Sanfilippo FM, Preen DB, Bulsara MK. Comorbidity and repeat

admission to hospital for adverse drug reactions in older adults: retrospective cohort study. BMJ. 2009 Jan 7;338:a2752. doi: 10.1136/bmj.a2752. PubMed PMID: 19129307; PubMed Central PMCID: PMC 2615549.

2. *Monograph on the Internet*

   Foley KM, Gelband H, editors. Improving palliative care for cancer [Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/ 0309074029/html/.

3. *Homepage/Web site*

   Cancer-Pain.org [Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer- pain.org/.

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4. The text is single-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
5. The text adheres to the stylistic and bibliographic requirements outlined in the Instruction to Authors. Make sure that the references have been written according to the ICMJE Recommendations Style.
6. Spell and grammar checks have been performed.
7. All authors have read the manuscript and agree to publish it.

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Prevalence and Severity of Coronary Artery Diseases among Hypertensive and Normotensive Acute Coronary Syndrome Patients

Md. Wareshuzzaman[1], Muhammad Badrul Alam[2], Mahbubur Rahman Babu[3], AKM Monwarul Islam[4], Farhana Ahmed[5], Humaira Hoque[6], Mohammad Saidur Rahman[7], Mahbubur Rahman Khan[8]

Abstract:

Background & objective: Numerous epidemiological studies have shown that the presence of hypertension increases the risk of coronary artery disease (CAD) and its severity. But there are studies as well which did not find any relationship between these two variables. However, no such study has yet been conducted in our population. The present study was done to find the association of hypertension and CAD development and its severity in patients of acute coronary syndrome (ACS).

Methods & Materials: This cross-sectional study was carried out in the Department of Cardiology Sir Salimullah Medical College & Mitford Hospital, Dhaka over a period of one year between January 2016 to December 2016. The study included a total of 226 patients of ACS based on predefined criteria (typical chest pain, Troponin-I > 0.12 ng/ml and/or ECG findings demonstrating ST-segment elevation or depression or T-inversion or Q-wave). Of them 150 had a prior history of hypertension or exhibited blood pressure > 140/90 mmHg on the day of admission before being sent for angiogram and were included as hypertensive (case) and the rest 76 had blood pressure

< 140/90 mmHg and were termed as control. The outcome measures were presence of CAD and its severity. Severity was evaluated in terms of site of lesion, percentage of stenosis and number of vessels affected.

Result: In the present study the demographic characteristics like age, sex and occupation were almost identically distributed between case and control groups. Presence of obese individuals and individuals with sedentary life-style were somewhat higher in cases than those in controls (17.3% vs. 5.3% and 78.7% vs. 63.2% and respectively). Other coronary risk factors like diabetes, dyslipidaemia and smoking habit were no different between case and control groups. Around one-third of the patients had diabetes mellitus and family history of IHD. The family history of IHD was significantly higher in the case group (p = 0.043). Ninety percent of the patients had angiographic evidence of CAD, but no significant association was observed between hypertension and CAD. The proximal and mid parts of RCA and distal parts of LAD were more often involved in the hypertensives than those in the normotensives. Moreover, TVDs were common in the former group than that in the latter group.

Conclusion: The study concluded that hypertension alone is not associated with development of atherosclerosis and CAD, but it is frequently associated with severity of lesion in terms of site of lesion, significant lesion and number of vessels affected.

J Inv Clin Cardiol 2022; 4(2): 44-51

Introduction:

Hypertension is one of the major risk factors of coronary artery and cerebrovascular diseases, and its prevalence is rapidly increasing worldwide. It is the number one attributable risk for death throughout the world[1] and is reported to be responsible for 57% of all stroke deaths and 24% of all cardiovascular deaths in East Asia.[2] In Bangladesh, approximately

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4. Associate Professor of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh.
5. Assistant Professor of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh.
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20% of adult and 40-65% of elderly people suffer from hypertension. High incidence of metabolic syndrome, obesity, and sedentary life-style may play important role in the pathophysiology of hypertension.[3] Bangladesh Non-communicable Disease (NCD) Risk Factor Survey 2010[4] reported that about 18% of the adults (18.5% in men and 17.3% in women) aged ≥25 years are hypertensive in general. Observational studies have shown a strong association between high blood pressure and incidence of ischaemic heart disease (IHD), stroke and peripheral vascular disease,[5] and is supported by intervention trials in which a consistent reduction in cardiovascular events was achieved by lowering blood pressure.[6] The role of hypertension in atherogenesis is unequivocally supported by the evidence that atherosclerotic plaques never develop in low-pressure circulatory zones. However, some experimental models have shown that atherosclerosis could be induced by hypertension, only when high serum lipids were concomitantly present.[7] In Pepine's study the risk of all complications of CAD was shown to be doubled in the presence of hypertension.[8] Other risk factors of coronary heart disease (CHD), such as dyslipidemia, insulin resistance, diabetes, obesity, lack of physical activity, and certain genetic mutants are observed in hypertensive patients more often than those in normotensive ones.[9]

Hypertension leads to adverse events in the brain, heart and kidneys through two mechanisms. First it exerts pressure on the structures causing changes in the function of the heart and arteries and the second it accelerates the development of atherosclerosis. Strokes are closely related to atherosclerosis and the relationship between blood pressure and cardiovascular events is steeper for stroke than for IHD events.[10] The prevalence of CAD varies considerably by populations.[11] South Asians are unduly prone to develop CAD. Most notable features of CAD in this population are the extreme prematurity and severity: 2-4-fold higher incidence of hospitalization and mortality; 5-10 years earlier onset of myocardial infarction (MI) and 5-10-fold higher rates of MI and death before the age of 40 years.[12] The exact prevalence of CAD in Bangladesh is not known. Only a limited number of small-scale epidemiological studies are available. Probably the prevalence of IHD was first reported in 1976, which was 0.33%.[13] A recent study from rural Bangladesh however, demonstrated a dramatic increase in CVD from 1986 to 2006. The age standardized CVD mortality rates increased by 30-fold (from 16 deaths per 100,000 to 483 deaths per 100,000) among males and 47-fold (from 7 deaths per100,000 to 330 deaths per 100,000) in females.[14]

The prevalence and severity of CAD in hypertensive patients have not been studied in our country, and as such, it is not known if the influence of hypertension in the development of CAD is similar to those of Western countries or resembles countries like Japan.[10] The relationship between hypertension and CAD is of complex nature. Whether cardiovascular structural changes may occur independent of CAD or cumulative effect of coronary risk factors is on the play is not delineated clearly when hypertension is present.[15] False positive exercise test is common among hypertensive patients, especially in women.[16] That purpose the present study was conducted to investigate the prevalence of risk factors and severity of CAD in hypertensive and normotensive ACS patients who were the candidate for elective coronary angiography.

Materials & Methods:

This cross-sectional study was carried out in the Department of Cardiology, Sir Salimullah Medical College & Mitford Hospital (SSMC & MH), Dhaka over a period of one year between January 2016 to December 2016. Patients of acute coronary syndrome (screened out by clinical characteristics, ECG examination and biochemical markers, Troponin –I) attending at SSMC & MH, were the study population. Of them who presented with hypertension or had a history hypertension (blood pressure ≥140/90 mmHg, recorded at least twice) before coronary angiography were considered as case, while acute coronary syndrome (ACS) patients who did not have hypertension (blood pressure < 140/90 mmHg) or had not a history of hypertension were considered as control. Adult (age > 18 years) ACS patients of either sex with a diagnosis STEMI, non-STEMI or unstable angina willing to participate in the study were enrolled. However, ACS patients associated with or had a history valvular heart disease, congenital heart disease, cardiomyopathy, concomitant diseases like severe dementia, advanced malignancy, end stage renal disease, severe anemia etc. drug addiction or pregnancy were excluded. The study included a total of 226 ACS patients based on predefined criteria (typical chest pain, Troponin-I > 0.12 ng/ml and/or

ECG findings demonstrating ST-segment elevation or depression or T-inversion or Q-wave). Of them 150(66.4%) were qualified as hypertensive (case) and the rest 76(33.6%) were normotensive (control). Having obtained ethical clearance from Institutional Review Board (IRB) of SSMC & MH, Dhaka and informed verbal consent from the subjects, the study was commenced. While the exposure (independent) variable was hypertension, the outcome variables were coronary artery disease (CAD) and its severity. Besides, there are some other variables known as confounding variables.

Acute coronary syndrome (ACS) was defined as any constellation of clinical symptoms that are compatible with acute myocardial ischemia. It was comprised of STEMI, non-STEMI and unstable angina. Acute myocardial infarction was defined as rise and fall of cardiac biomarkers (preferably Troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with any of the evidences of myocardial ischemia like symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new LBBB), development of pathological Q-wave, and imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. The diagnosis STEMI was based on 12-lead ECG showing ST segment elevation > 1 mm in at least 2 contagious limb leads or > 2 mm in at least 2 contagious chest lead plus either the evidence of 1) prolonged chest discomfort typical of myocardial ischemia or 2) elevated cardiac biomarkers (CK-MB and/or Troponin) more than twice the upper limit of normal lab reference, while the diagnosis of NSTEMI was established if there was evidence of myocardial necrosis based on elevated cardiac serum markers, such as CK-MB and/or troponin T or I in the absence of ST segment elevation. Unstable angina was defined as angina pectoris (or equivalent type of ischemic discomfort) with at least one of the 3 features: 1) Occurring at rest (or minimal exertion) and usually lasting for at least 20 mins (if not interrupted by nitroglycerine administration), 2) being severe and described as frank pain, and of new onset within 1 month and 3) occurring with a crescendo pattern. A person who gave report of smoking cigarettes at entry or quitted smoking within one month of index admission was considered as current smoker. Any direct blood relations (parents, siblings, children) of the participating subjects if developed angina, MI or SCD at ≤55 years of age without any obvious cause were termed as having family history of CAD. Patients were considered diabetic if they suffer from classical symptoms of diabetes along with RBS ≥200 mg/dl (≥11.1 mmol/L) or FBS ≥126 mg/dl (≥7 mmol/L) or 2 HPPBS ≥200 mg/dl (≥11.1 mmol/L) or patients reported taking anti-diabetic drugs. An individual with LDL > 100 mg/dl, or total cholesterol > 200 mg/dl, or HDL < 40 mg/dl or TG > 150 mg/dl was considered dyslipidemic (ATP III criteria). Participants with BMI ≥30 kg/m^2 was defined as obese. Significant stenosis was defined as > 70% stenosis in any of the three major coronary arteries (RCA, LCx or Lad) or > 50% stenosis in the left main artery. Severity of lesion or stenosis was assessed in terms of site of lesion (the proximal lesions were considered more severe and distal lesions less severe), percentage of occlusion (the more the percentage of occlusion, the greater is the severity) and number of vessels affected (while SVDs were less sever and TVDs were more severe).

Data were collected using a semi-structured questionnaire containing the variables of interest and were processed and analyzed using SPSS (Statistical Package for Social Science) for Windows, Version 16. The test statistics used analyze the data were descriptive statistics, Chi-square (χ^2) and Unpaired t-Tests. While the categorical data were compared between groups using Chi-square (χ^2) Test, the data presented on continuous scale were compared between groups using Unpaired t-Test. The level of significance was set at 5% and $p < 0.05$ was considered significant.

Result:

More than half (57.3%) of the cases was e" 50 years old compared to 47.4% of the control. However middle aged (40 – 50 years) and early middle aged (< 40 years) subjects were more in control (31.6% and 21.1% respectively) than that in case groups (29.3% and 13.3% respectively) ($p = 0.235$) with mean ages of the case and control groups being 51.2 and 48 years respectively. In both case and control groups, males were predominant (72% and 76.3% respectively) than their female counterparts (28% and 23.7% respectively) with no significant inter-group difference ($p = 0.488$). Majority (78.7%) of the cases was accustomed to sedentary life-style as opposed to controls (63.2%) ($p = 0.013$). Obese individuals demonstrated their frequent presence in case group (17.3%) than those in control group (5.3%) ($p = 0.027$).

Smoking habit, diabetes, duration of diabetes and dyslipidemia were almost identically distributed between the groups (p = 0.157, p = 0.790, p = 0.475 and p = 0.160 respectively). However, family history IHD was significantly higher in control (36.8%) than that in case groups (p = 0.043) (Table I). Comparison of types of ACS between the study groups revealed that unstable angina (UA) was significantly higher in cases (34.7%) than that in controls (18.4%) (p = 0.40) (Table II).

RCA was found to be more frequently involved in case group (68.0%) than that in control group (47.4%) (p = 0.003). However, there was no significant difference between the groups in terms of involvement of LM, LAD and LCx (p = 0.903, p = 0.439 and p = 0.210 respectively) (Table III). As angiographically significant lesions (> 70% lesions in major coronary arteries) were compared between the groups, both groups were alike with respect to these variables in RCA and LAD (p = 0.088 and p = 0.445 respectively). But the presence of significant lesion in LCx was significantly higher in case than that in control groups (p = 0.047) (Fig. 1). Presence of lesion in proximal and mid part of the RCA was significantly higher in cases (each 41.2%) than that in the controls (33.3% and 11.1% respectively) (p < 0.001). Twenty percent of cases had lesion in distal part of LAD as opposed to none in controls (p = 0.002). There was no significant difference between the groups in terms of parts of LCx involved (p = 0.340) (Table IV). Majorities of the case (90.7%) and controls (89.5%) had angiographic evidence of lesion. Number of vessels involved was almost identically distributed between the groups except TVD which was almost double (29.3%) in case than that in control (15.8%) (p = 0.168) (Table V).

Table-I

Demographic, behavioral and clinical characteristics between the study groups

Demographic, behavioral & clinical characteristics*	Group		p-value
	Case (n = 150)	Control (n = 76)	
Age* (years)			
< 40	20(13.3)	16(21.1)	
40 – 50	44(29.3)	24(31.6)	0.235
≥50	86(57.3)	36(47.4)	
Mean ± SD	51.2 ± 11.0	48.0 ± 13.5	
Sex*			
Male	108(72.0)	58(76.3)	0.488
Female	42(28.0)	18(23.7)	
Life-style			
Active	32(21.3)	28(36.8)	0.013
Sedentary	118(78.7)	48(63.2)	
BMI* (kg/m^2)			
< 25 (underweight & normal)	64(42.7)	42(55.3)	
25 – 29.9 (Overweight)	60(40.0)	30(39.5)	0.027
≥30 (Obese)	26(17.3)	4(5.3)	
Smoking*	84(56.0)	50(65.8)	0.157
DM*	46(30.7)	22(28.9)	0.790
Duration of DM#	7.6 ± 2.2	7.1 ± 2.4	0.475
Dyslipidemia*	72(48.0)	44(57.9)	0.160
Family history of IHD*	36(24.0)	28(36.8)	0.043

Figures in the parentheses indicate corresponding %; *Chi-squared Test (χ^2) was done to analyze the data.
#Data were analyze using Unpaired t-Test and were presented as mean ± SD.

Table-II
Comparison of ACS types between the study groups

ACS type	Group		p-value
	Case (n = 150)	Control (n = 76)	
STEMI	64(42.7)	40(52.6)	
NSTEMI	34(22.7)	22(28.9)	0.040
UA	52(34.7)	14(18.4)	

Figures in the parentheses indicate corresponding %; *Chi-squared Test (χ^2) was done to analyze the data.

Table-III
Angiographic involvement of vessels between the study groups

Vessels involved	Group		p-value
	Case (n = 150)	Control (n = 76)	
LM*	10(6.7)	4(5.3)	0.903
RCA*	102(68.0)	36(47.4)	0.003
LAD*	110(73.3)	52(68.4)	0.439
LCx*	92(61.3)	40(52.6)	0.210

Figures in the parentheses indicate corresponding %; *Chi-squared Test (χ^2) was done to analyze the data.

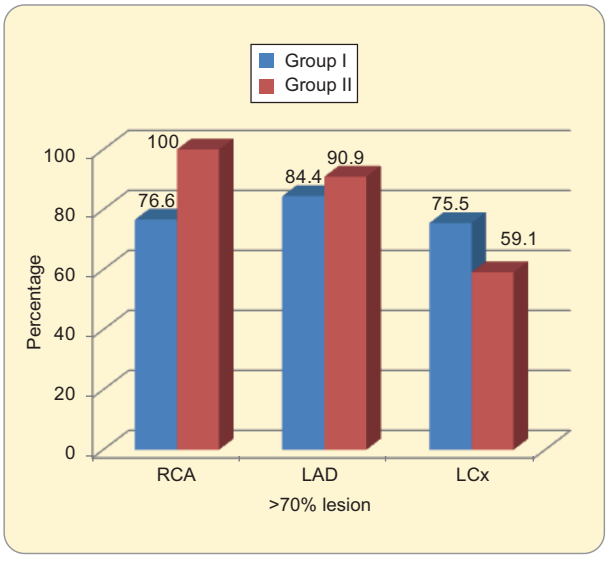


Fig.-1: *Distribution of significant lesion in major coronary arteries*

Table-IV
Angiographic profile between case and control groups

Parts of vessels involved*	Group		p-value
	Case (n = 102)	Control (n = 36)	
Parts of RCA involved*			
Proximal	42(41.2)	12(33.3)	
Mid	42(41.2)	4(11.1)	< 0.001
Distal	18(17.6)	20(55.6)	
Parts of LAD involved*			
Proximal	44(40.0)	25(48.1)	
Mid	44(40.0)	27(51.9)	0.002
Distal	22(20.0)	0(0.0)	
Parts of LCx involved*			
Proximal	31(33.7)	18(45.0)	
Mid	34(37.0)	10(25.0)	0.340
Distal	27(29.3)	12(30.0)	

Figures in the parentheses indicate corresponding %; *Chi-squared Test (χ^2) was done to analyzed the data.

Table-V
Angiographic severity of lesion between case and control groups

Severity of lesion*	Group		p-value
	Case (n = 150)	Control (n = 76)	
Normal coronary artery	14(9.3)	8(10.5)	
SVD	44(29.3)	28(36.8)	0.168
DVD	48(32.0)	28(36.8)	
TVD	44(29.3)	12(15.8)	

Figures in the parentheses indicate corresponding %; *Chi-squared Test (χ^2) was done to analyze the data

Discussion:

Epidemiological studies have shown that the presence of hypertension increases the risk of CAD, not only in "at risk" populations but in the general population as well.[17] In the present study the demographic characteristics like age, sex and occupation were almost identically distributed between groups. Presence of obese individuals and individuals with sedentary life-style were significantly higher in the hypertensives than their normotensive counterparts. Other coronary risk factors like diabetes, dyslipidaemia and smoking habit were no different between the hypertensive and normotensive patients. Around one-third of the patients had diabetes mellitus

and family history of IHD. Contrasting with these findings several studies showed diabetes and hyperlipidaemia to be more frequent in hypertensive patients than in normotensive ones.[18,19]

Ninety percent of the patients in this study had CAD (90.7% in hypertensive group and 89.5% in normotensive group) which compares well with the findings of Akbarzadeh et al[20] who found 84% of the hypertensive patients with CAD, but it sharply contrasts with the findings of a Japanese study which revealed only 26% of hypertensive patients with CAD.[20] In Rotterdam and the United States, the prevalence of CAD was no different between hypertensive and normotensive individuals (74% vs. 71%).[20] Though the frequency of CAD does not vary with respect to blood pressure status of the patients, the proximal and mid parts of RCA and distal part of LAD were often found to be involved in the hypertensives than those in the normotensives. Moreover, TVDs and significant lesions were common in the former group than that in the latter group indicating that hypertension induces the development of severe lesion (in terms of site of lesion, presence of significant lesion and number of vessels affected). In Akbarzadeh's study,

3-vessel disease was predominant in hypertensive patients. Nevertheless, in Rotterdam study the prevalence of single-, double- and triple-vessel disease was reported to be 34, 16, 14% respectively with no significant difference between hypertensive and normotensive subjects.

In studies of clinical BP and also in studies using ambulatory BP measurements (ABPM), the prevalence of CAD has been shown to be closely related to the BP level, especially systolic BP.[17] The relationship between BP level and CAD seems linear, continuous and independent.[21] Indeed, the J-shaped curve of relationship between BP level and the risk of CAD comes from retrospective studies in patients with cardiovascular antecedents before anti-hypertensive treatment was instituted. Prospective therapeutic trials did not show an increase in risk of CAD in the lower levels of BP.[22] An isolated fall in BP with treatment does not completely reduce the risk of CAD in essential hypertension. This confirms the complexity of the relationship between CAD and hypertension since numerous factors other than hypertension are implicated. Treatment of hypertension in patients with CAD must be more aggressive than that in the absence of CAD. Indeed, the risk of a recurrent coronary event in this population is very high and all efforts should be devoted to lower BP, especially since we expect a better compliance with treatment after a coronary event.

In primary prevention, successive studies have shown the benefit of thiazide diuretics and beta-blockers on cardiovascular events. Subsequently, calcium blockers and angiotensin converting enzyme (ACE) inhibitors have been shown to be effective in the same situation, and more recently angiotensin 2 receptors antagonists in the LIFE study.[23] All these treatments have an identical effect on the fall in BP and in the percentage of responders.[24,25] The same drugs lead to a modest reduction in coronary events, of the order of 20%. Although it has not been definitively proven, the regression in LVH by antihypertensive treatment allows improvement in myocardial perfusion thereby reducing the risk of CAD. In this context, ACE inhibitors may have a more marked effect than the other therapeutic classes as regards to regression in LVH.[26] As regards to secondary prevention, the only therapeutic classes which have been proven to prevent recurrence of coronary events, whether associated with hypertension or not, are beta blockers.[27]

Morphological data, obtained *in vivo* from the analysis of coronary angiographic patterns, are lacking for large populations. In a sample of patients with effort angina,[28] angiographic study showed that coronary atherosclerosis was not more severe in hypertensive than in normotensive patients; only in older patients (> 60 years) was the prevalence of triple-vessel disease 20% higher amongst hypertensives. In another study,[29] although patients with angiographic evidence of coronary atherosclerosis had higher prevalence of hypertension than the control population, the only variables significantly associated with the degree of atherosclerosis were total and HDL cholesterol. Therefore, the assumption that hypertension related IHD risk is due to a more severe atherosclerotic involvement of the coronary arteries is not fully supported by the available data.[30] Indeed, much attention should be devoted to factors other than atherosclerotic narrowing, such as impaired coronary reserve[31] microcirculatory abnormalities,[32] increased ventricular mass,[33] which could explain the higher incidence of IHD in patients with hypertension.[34]

Conclusion:

Based on the findings of the study, it can be concluded that hypertension alone is not associated with

development of atherosclerosis and CAD, but it is frequently associated with severity of lesion in terms of site of lesion (proximal and mid parts are generally involved in hypertensives), significant lesion (> 70% lesion is more common in hypertensives) and number of vessels affected (TVDs are more common in hypertensives). The mechanisms by which hypertension favors the development of CAD are multiple and are not simply limited to the presence of atheroma in the coronary arteries. So, hypertension as a major risk factor for CAD, can be partially reversed by anti-hypertensive treatment. However, as hypertension is often associated with severe CAD, blood pressure control may reduce the severity of the disease to some extent.

Conflict of Interest - None.

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Correlation of *N-Terminal pro-Brain Natriuretic Peptide* (NT-proBNP) with Echocardiographic Parameters of Left Ventricular Volume Load in Children with Patent Ductus Arteriosus

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Abstract:

Background: Natriuretic peptides are secreted by the human heart in response to myocyte stretch. Plasma NT-pro BNP rises in volume overload of varying aetiology including left-to-right shunts. Therefore, estimation of plasma NT-pro BNP may have a role in assessing the haemodynamic load and severity of shunt in PDA.

Objective: The study was carried out to compare the plasma NT-pro BNP level in children with PDA who have echocardiographic evidence of left ventricular volume overload with those who do not have echocardiographic evidence of left ventricular volume overload.

Methods: In this cross sectional study, 60 infants and children with PDA were divided into two groups on the basis of echocardiographic evidence of LV volume overload: group I consisted of 30 patients with LVEDD and LVESD >+2 Z score, and group II consisted of 30 patients with LVEDD and LVESD <+2 Z score. Plasma NT-pro BNP was measured in both groups and then correlated with echocardiographic parameters of volume load in PDA.

Results: The mean NT-proBNP level was significantly more elevated in group I than in group II (818.07±698.07 pg/mL vs. 244.69±283.55 pg/mL, p<0.001). Also, compared to the group II, significantly more patients in group I had elevated NT-proBNP. Haemodynamically significant shunt defined as Qp:Qs >1.5 was more common in group I than in group II. Mean ductal size (r=0.32, p=0.01), Qp/Qs ratio (r=0.67, p<0.001), LVEDD (r=0.71, p<0.001), LVESD (r=0.56, p<0.001), and LAD/AoD ratio (r=0.32, p=0.01) significantly correlated with elevated plasma NT-proBNP.

Conclusion: In infants and children with PDA, plasma NT-Pro BNP correlates with severity of shunt and left ventricular volume status. So, as a noninvasive test, plasma NT-Pro BNP may help identifying PDA patients with volume overload and requiring timely intervention.

Keywords: Patent Ductus Arteriosus, Cardiac Volume, Echocardiography, NT-proBNP

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Introduction:

The clinical significance of a patent ductus arteriosus (PDA) is primarily determined by the volume of blood shunting across it. PDA causes left to right shunting of the high aortic pressure blood into low pressure pulmonary artery, in both systole and diastole. In Large PDA the magnitude of the shunt is determined by relationship of the systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR).[1] Left-to-right shunting through the PDA results in pulmonary over-circulation and left heart volume overload. Increased pulmonary flow from the ductal shunting leads to increased pulmonary fluid volume, and in patients with moderate or large shunts, this causes decreased lung compliance. Increased flow returning to the left heart results in increased left atrial and left ventricular end-diastolic pressures. The left ventricle compensates by increasing stroke volume and eventually may hypertrophy.[1]

Natriuretic peptides, including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are produced

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and secreted by the human heart in response to myocyte stretch.[2] The measurement of circulating BNP and NT-pro BNP is now recommended by international guidelines as a biomarker for diagnosis, prognosis, and therapeutic monitoring in adult patients with cardiac diseases , especially those with acute and chronic heart failure[3] However, in children with congenital heart diseases, the primary complaints are ventricular volume load and pulmonary hypertension, not cardiac dysfunction.

Previous studies in children with CHD showed that NT proBNP is increased in shunt lesions with volume overload, specially in children with PDA.[4] These studies suggests that the measurement of BNP level in blood samples is a useful noninvasive indicator of volume overload in children with CHD involving left to right shunt[5] A normal NT-proBNP value cannot preclude any pathology but reûects a compensatory status of the heart in children with PDA. Measurement of NT-proBNP cannot replace echocardiography but provide independent, low-cost and complimentary information for the evaluation of hemodynamic load and clinical status.[6] To the best of our knowledge no studies related to plasmaNT-proBNP and haemodynamics in PDA were carried out in children in Bangladesh. So, the study was planned to see the role of NT-proBNP in quantifying the shunt severity of PDA, and thereby deciding upon timely intervention in these patients.

Methods:

This cross-sectional study was conducted in the Department of Pediatric Cardiology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Children with PDA between 1 month and 12 years of age were initially approached and selected as a case who fulfilled the inclusion and exclusion criteria for this study. Informed written consent was obtained from all parents. Meticulous history and clinical examination was done and pulse oximetry was checked in both upper and lower limbs as routine. Complete blood count (CBC), C-reactive protein (CRP), liver function test, serum creatinine, chest x-ray, and ECG were done.Transthoracic echocardiography (TTE) including two-dimensional (2-D), M-mode and Doppler was done by Vivid 7 (GE Healthcare, 9900 Innovation Drive, Wauwatosa, WI 53226, USA) following the standard protocol.[7,8] Some PDA children required sedation for echocardiography examination. Pediatric probe 7S and also adult probe MS3 were used. The patent ductus arteriosus diameter was measured in high left parasternal short-axis view (ductal view). The minimal diameter of the PDA was the narrowest inner echocardiographic measurement measured.[9] The left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD) were obtained from the parasternal long axis view. End-diastole was defined as frame at which mitral valve (MV) closes and end-systole as the frame preceding MV opening.[7] Children with PDA having LVEDD> +2 Z score and LVESD > +2 Z score were considered as group I and those having LVEDD and LVESD ≤2 Z score were considered as group II.

After echocardiography, 3 ml of venous blood was taken from each patient and sent for serum NT pro-BNP assay in the Department of Biochemistry, BSMMU.The values of NT pro-BNP were compared with age speciûc normal values of serum NT Pro-BNP in infants and children.

Results:

This cross-sectional study was done in the Department of Pediatric Cardiology, BSMMU, Dhaka. The study was conducted with the aim to find out the correlation between plasma NT-proBNP and echocardiographic parameters of left ventricular volume overload in children with PDA.

Baseline demographic and clinical characteristics did not differ significantly between the two groups except for transverse diameter of cardiac shadow in CXR and haemoglobin (Hb). (Table I). Majority of the patients aged less than 5 years in both groups. Female predominance was observed in both groups. (Table II)

The Table 3 compares serum NT-proBNP and magnitude of shunt between the groups. The mean NT-proBNP level was significantly more elevated in group I than in group II (818.07±698.07 pg/mL vs. 244.69±283.55 pg/mL, p<0.001). Also, compared to the Group II, significantly more patients in group I had elevated NT-proBNP. Haemodynamically significant shunt defined asQp:Qs >1.5 was more common in Group I than in group II. (Table III)

Multivariate logistic regression analysis for determinants of elevated NT-proBNP level as a marker of LV volume overload revealed Qp/Qs ratio, ductal diameter, LVEDD, LVESD, LA/AOD ratio being independent predictors. (Table IV)

Mean ductal size (r=0.32, p=0.01), Qp/Qs ratio (r=0.67, p<0.001), LVEDD (r=0.71, p<0.001), LVESD (r=0.56, p<0.001), and LAD/AoD ratio (r=0.32, p=0.01) significantly correlated with elevated plasma NT-proBNP. (Figure 1 and Figure 2) On the other hand, no significant correlation was found between elevated plasma NT-proBNP and LVEF, E/A and E/e'. (Figure 2)

Table-I

Demographic and clinical characteristics of the patients (n= 60).

Characteristics	Group I (n = 30)		Group II (n = 30)		p value
Age (yrs) mean ± SD	3.6±3.9		3.9±3.8		
Range (min – max)	(5 months – 12)		(6 months - 12)		0.77^{ns}
	No.	%	No.	%	
Gender					
Male	13	43.3	8	26.7	0.17^{ns}
Female	17	56.7	22	73.3	
Height (cm) mean ± SD	84.6 ± 30.2		90.3 ± 24.2		0.44^{ns}
Weight (kg) Mean ± SD	12.4 ± 8.6		13.7 ± 6.8		0.50^{ns}
Presentation	No.	%	No.	%	
Poor feeding	19	63.3	13	43.3	0.12^{ns}
Prolonged feeding	19	63.3	14	46.7	0.19^{ns}
H/o of suck rest suck cycle	19	63.3	15	50.0	0.29^{ns}
Recurrent RTI	21	70.0	17	56.7	0.28^{ns}
H/o hospitalization	14	46.7	10	33.3	0.29^{ns}
Dyspnoea	7	23.3	4	13.3	0.32^{ns}
Left atrial enlargement	7	23.3	4	13.3	0.32^{ns}
Transverse diameter of heart	19	63.3	9	30.0	0.01^{s}
Haemoglobin (%) mean±SD	10.5±2.1		11.6±1.2		0.02^{s}

Group I: PDA patients with LV volume overload
Group II: PDA patients without LV volume overload
s = Significant (p <0.05), ns=Not significant (p >0.05); unpaired t-test and chi square/Fisher's exact test applied for quantitative and qualitative variables respectively; RTI = respiratory tract infection

Table-II

Comparison of echocardiographic parameters between two groups (n=60).

Variable	Group I (n = 30) Mean ± SD	Group II (n = 30) Mean ± SD	p value
Ductal diameter (mm)	4.3±1.3	3.5±1.4	0.02^{s}
LVEDD (z-score), cm	4.6±1.9	0.9±1.2	$<0.001^{s}$
LVESD (z-score), cm	3.7±1.6	0.8±1.1	$<0.001^{s}$
LAD (mm)	19.9±8.5	15.5±7.1	0.03^{s}
AOD (mm)	14.5±6.4	12.2±5.5	0.15^{ns}
LAD/AOD ratio	1.2±0.3	1.2±0.3	0.54^{ns}
Qp:Qs	1.8±0.7	1.3±0.4	0.003^{s}
TR (m/sec)	2.1±1.4	2.1±0.9	0.99^{ns}
PASP (mmHg)	31.5±17.2	28.9±16.7	0.55^{ns}
E/A ratio	2.1±2.8	1.5±0.3	0.32^{ns}
E/e2 ratio	8.2±2.5	8.1±2.4	0.94^{ns}
LVEF (%)	66.4±5.4	66.2±7.2	0.91^{ns}

Group I: PDA patients with LV volume overload
Group II: PDA patients without LV volume overload
s = Significant (p<0.05), ns= Not significant (p >0.05); unpaired t-test was applied.
Here, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, LAD =left atrial diameter, AOD = aortic diameter. TR = tricuspid regurgitation peak velocity, PASP = pulmonary artery systolic pressure, LVEF = left ventricular ejection fraction.

Table-III

Comparison of plasma NT-proBNP and shunt between two groups (n=60).

Variables	Group I (n = 30)		Group II (n = 30)		*p* value
NT-proBNP (pg/mL) mean±SD	818.07±698.07		244.69±283.55		<0.001[s]
NT-proBNP	No.	%	No.	%	
Elevated	22	73.3	6	20.0	<0.001[s]
Not elevated	8	26.7	24	80.0	
Shunt (Qp:Qs >1.5)	No.	%	No.	%	
Present	18	60.0	6	20.0	0.002[s]
Absent	12	40.0	24	80.0	

s = Significant (p<0.05); unpaired t-test and chi square test were applied for quantitative and qualitative variables respectively.
Group I: PDA patients with LV volume overload
Group II: PDA patients without LV volume overload

Table-IV

Multivariate logistic regression analysis for determinants of elevated plasma NT-proBNP level as a marker of LV volume overload (n=60).

Variables of interest	Regression coefficient (β)	p value	OR	95% CI
Ductal diameter	0.383	0.04[S]	1.33	1.104 – 3.937
LVEDD (z-score)	1.361	0.01[S]	3.90	1.288 – 11.811
LVESD (z-score)	0.512	0.004[S]	1.67	1.177 – 2.366
LAD	0.169	0.04[S]	1.07	1.077 – 1.487
Qp:Qs	2.054	0.001[S]	7.80	2.404 – 25.310
E/A ratio	0.218	0.64[NS]	1.24	0.491 – 3.147
e/e2 ratio	-0.162	0.37[NS]	0.85	0.594 – 1.218
LVEF	0.121	0.07[NS]	1.12	0.013 – 1.258

Dependent variable: elevated plasma NT-proBNP;
Independent variables: ductal diameter, LVEDD (z-score), LVESD (z-score), LAD, Qp:Qs, E/A ratio, e/e2 ratio and LVEF.
S = Significant, NS = Not significant
Here, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, LAD =left atrial diameter, AOD = aortic diameter. TR = tricuspid regurgitation peak velocity, PASP = pulmonary artery systolic pressure, LVEF = left ventricular ejection fraction.

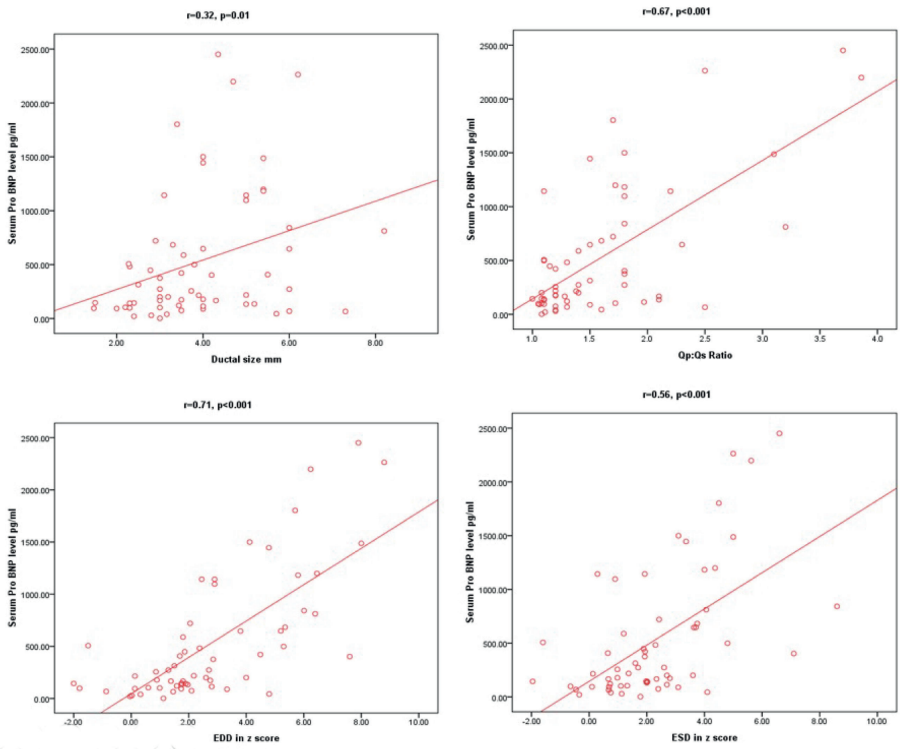


Fig.-1. *Correlations between plasma NT-proBNP level and ductal size, Qp:Qs, LVEDD and LVESD. The scatter plot shows significant positive correlation between elevated plasma NT-proBNP and mean ductal size, Qp/Qs ratio, LVEDD, and LVESD.*

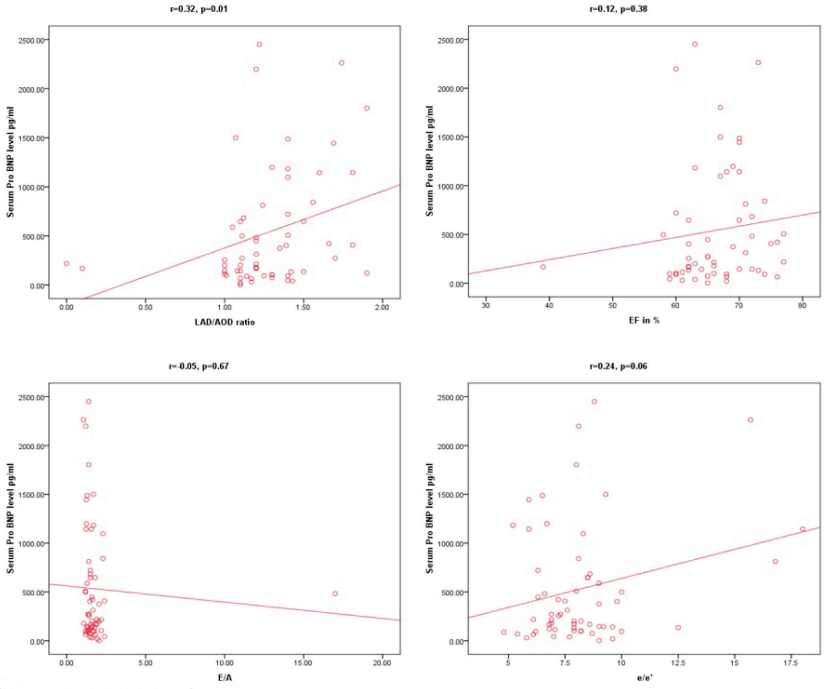


Fig.-2. *Correlations between plasma NT-proBNP level and LAD/AoD, LVEF, E/A and E/e'. The scatter plot shows significant positive correlation between elevated plasma NT-proBNP level and LAD/AoD, but no significant correlation of plasma NT-proBNP level with LVEF, E/A and E/e'.*

Discussion:

The present study was carried out to find out the role of plasma NT-Pro BNP level in predicting the severity of left to right shunt, and to see whether there is any correlation between the plasma NT-Pro BNP level and the echocardiographic parameters of ventricular volume overload in infants and children with PDA. For this, significant shunt was defined as the Qp/Qs ratio >1.5. For assessing the volume status in the patients with PDA, the echocardiographic parameters studied include LVEDD, LVESD, LA/AOD ratio, peak TR velocity, and PASP. Also studied are LVEF, E/A ratio, and e/e'. Children with PDA having LVEDD >+2 Z score and LVESD >+2 Z score were considered as group I and those having LVEDD and LVESD ≤+2 Z score were considered as group II.

In the present study, the PDA patients with volume overload had larger shunt than those without volume overload (Qp:Qs 1.8±0.7 vs. 1.3±0.4, p=0.003). The mean plasma NT-proBNP in those with volume overload was significantly higher than in those without volume overload (818.07±698.07 pg/ml vs. 244.69±283.55 pg/ml, p <0.001). These findings correlate with those of Kavga et al.[10] Kavga et al. determined the plasma B-type natriuretic peptide (BNP) levels in children with left-to-right shunt, and correlated with the shunt volume. Plasma BNP level was found higher in children with left-to-right shunt than in healthy children, and also in those with Qp/Qs >1.5 than in those with Qp/Qs <1.5. Plasma BNP values were similar among patients with atrial septal defect (ASD) and ventricular septal defect (VSD), but were significantly higher in patients with PDA. In the present study, a strong positive correlation was found between Qp/Qs ratio and plasma NT-Pro BNP (r=0.67, p <0.001). (Figure 1). In a more recent cross-sectional study involving 60 infants and children with left-to-right shunt, Jamei Khosroshahi et al.[11] demonstrated a significant positive correlation between plasma NT-Pro BNP and Qp/Qs ratio (p=0.0001). The cut-off point of plasma NT-Pro BNP level demonstrating a Qp/Qs ratio >1.5 was 40.36 pg/mL, with a sensitivity and specificity of 92% and 79%, respectively. In an older study by Holmgren et al.[5] plasma BNP levels were elevated in children with congenital heart disease than in healthy controls, and were significantly higher in those with left ventricular volume overload as compared to those with right ventricular volume overload or pressure overload determined by echocardiography and/ or cardiac catheterization.

The mean ductal diameter in group I was significantly larger than group II (4.3±1.3 mm vs. 3.5±1.4 mm, p= 0.02), and there was a weak positive correlation between ductal diameter and plasma NT-Pro BNP level (r=0.32, p =0.01). (Figure 1) Jeong et al. found similar positive correlation between ductal diameter and plasma BNP level in preterm infants (r=0.368, p <0.001).[12] In the present study, in group I with LVEDD and LVESD >+2Z score, plasma NT-Pro BNP level was significantly higher than in group II with LVEDD and LVESD <+ 2Z score. In the study by Holmgren et al.[5], the highest LVEDD Z score was found in the LV volume overload group and plasma BNP correlated significantly with LVEDD Z score (r= 0.38, p <0.005). In the present study, both LVEDD and LVESD significantly correlated with elevated level of plasma NT-Pro BNP (r=0.71, p <0.001; r=0.56, p <0.001, respectively). The correlations between the parameters are rather stronger in the present study than in the study by Holmgren et al. In a more recent study, Kusmira et al. found significant positive correlation between LVEDD and LVESD and plasma NT-Pro BNP before and after transcatheter closure of PDA and VSD. Plasma NT-Pro BNP level along with LVEDD and LVESD significantly reduced after closure of the VSD and PDA.[13] LAD/AOD correlated positively with plasma NT-Pro BNP level (r=0.32, p =0.01) in the present study, though the correlation was rather weak. (Figure 1) In their study, Jeong et al. found similar weak positive correlation between LAD/AOD and plasma BNP level (r=0.412, p <0.001) in preterm infants.[12]

In the present study, statistically significant correlation was not found between plasma NT-Pro BNP level and LVEF, peak TR velocity, PASP, E/A ratio, and e/e'. Koch et al., in their study, found positive correlation between plasma BNP and right ventricular systolic pressure (r= 0.69; p <0.001) and to mean pulmonary arterial pressure (mPAP) (r=.66, p <0.001) in addition to Qp/Qs (r= 0.66; p < 0.001).[4] Plasma natriuretic peptide levels generally correlate with mPAP and pulmonary vascular resistance in patients with pulmonary arterial hypertension due to heterogeneous aetiology (ASD, chronic thromboembolic disease, and scleroderma).[14] This apparent disparity may be due to the fact that Koch et al.'s study included heterogeneous congenital heart disease patients including left-to-right shunt, left or right heart obstruction, tetralogy of Fallot, functionally univentricular heart, and impaired left ventricular function. E/A ratio, and e/e' are, in general, markers of diastolic dysfunction. Plasma natriuretic peptides generally rise in diastolic dysfunction. According to a recent meta-analysis, the diagnostic performance of

natriuretic peptides for the detection of diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF) is reasonable; they may be used to rule out diastolic dysfunction or HFpEF, and not for the diagnosis of diastolic dysfunction or HFpEF.[15] Further studies are needed to explore the correlation between echocardiographic parameters of RV function and ventricular diastolic function in the context of congenital heart disease including PDA.

The study was a single-centre study involving relatively small number of patients likely precluding generalization of findings and making any concrete recommendation. Also, right ventricular volume status and its correlation with plasma NT-Pro BNP were not addressed adequately.

Conclusion:

For PDA, plasma NT-Pro BNP rises more in patients with significant shunt and volume overload compared to those with insignificant shunt and without volume overload. Plasma NT-Pro BNP correlates positively and significantly with Qp/Qs ratio, ductal diameter, LVEDD and LVESD, and LA/AOD ratio. So, as a noninvasive test, plasma NT-Pro BNP may help identifying PDA patients with volume overload and requiring timely intervention.

Conflict of Interest - None.

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ORIGINAL ARTICLE

Association Between Angiographic Severity of Coronary Artery Disease and High Density Lipoprotein Cholesterol Level

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Abstract

Background: HDL has long been known as the anti-atherosclerotic factor. There is an inverse relationship between plasma levels of HDL-C and CAD. Even the HDL levels are normal or high, significant vascular residual risk still exist. Hence, we evaluate association between angiographic severity of CAD and HDL-C Level in this study.

Methods: This is a hospital based, prospective, observational study conducted in Shahid Gangalal National Heart Centre (SGNHC), Kathmandu, Nepal. Our Study included 102 patients who had undergone coronary angiography and HDL-C measurement from August 2021 to January 2022.

Results: We had enrolled 102 patients. 82 (80.2%) were males and 20 (19.6%) were females. The mean age of patients was 59.4±11.4 years. HDL-C was normal in 43 (42.2%) and abnormal in 59 (57.8%) patients. Single, double, and triple vessels disease was found in 22 (21.6%), 26 (25.5%) and 22 (21.6%) patients respectively. Similarly, mild, moderate and severe CAD was found in 26 (25.5%), 59 (57.8%) and 7 (6.9%) patients. Results has shown that there was significant association with serum HDL-C level between double and triple vessels disease than single vessel disease (P value =0.03). Moderate to severe CAD was higher in abnormal HDL-C than mild disease but statistically not significant (p value=0.11).

Conclusion: Serum HDL-C level has significant association between DVD and TVD than SVD. According to friesinger score, Severity has no statistically significant association with HDL-C level.

Key words: Coronary artery disease (CAD), High density lipoprotein cholesterol (HDL-C), Single vessel disease (SVD), Double vessels disease (DVD), Triple vessels disease (TVD)

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Introduction

Coronary artery disease (CAD) is one of the major cause of morbidity and mortality[1]. It is responsible for about 30% of deaths worldwide.[2,3] By 2020, it is predicted that coronary artery disease will claim 25 million lives annually and that coronary artery disease (CAD) will surpass infectious disease as the world´s number one cause of death and disability[4].

Atherosclerosis is the major contributing factor. The circulating lipoproteins continuously bathe vascular endothelial cells and contribute causally to the pathogenesis of human atherosclerosis. There is an inverse relationship between plasma levels of HDLC and the presence of CAD. HDL promotes reverse cholesterol transport and can prevent lipoprotein oxidation and exert anti- inflammatory actions[5,6].

The proportion of cardiovascular disease burden is highest amongst the South Asian countries like Pakistan, Sri-Lanka, Bangladesh, India and Nepa.l.[7,8] Estimates from the Global burden of Disease Study suggests that by the year 2020 this part of the world will have more individuals with atherosclerotic cardiovascular disease than any other region.[9]

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Dyslipidemias, including high low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) concentrations and low high-density lipoprotein cholesterol (HDL-C) concentration, are risk factors for CHD.[10]

HDL has long been known as the "anti-atherosclerotic factor" However, in clinical work, it is found that although the HDL levels are normal or even high, significant vascular residual risk still exist[11],[12].That is the reason when patient with normal HDL-C level (Male>40mg/dl and female >50mg/dl) still develop cardiovascular events. Therefore, HDL of patients with CAD has not only amount problems, but also quality problems. There are different measuring ways of HDL-C functional state like inflammatory action by inhibiting chemotaxis of monocytes by oxidized LDL of atherosclerotic plaque hence improving HDL-C function may be more important than raising its level. [14]

Increased plasma HDL-C is protective for myocardial infarction (MI) which has been shown in studies by examining the relationship between genetic variations associated with elevated levels of plasma HDL-C and the risk of MI.[13]

Currently available blood assays cannot determine the functionality of HDL cholesterol (HDL-C) but can only quantify it in plasma. They may in future be replaced by assays that can assess the composition and functionality of HDL-C.

According to Adult Treatment Panel III guideline, an HDL-C level of 60 mg/dl or greater is a negative (protective) risk factor.[15] On the other hand, a high-risk HDL-C level is described as being below 40 mg/dl. Low levels of HDL predict increased cardiovascular risk, particularly in healthy individuals with no history of cardiovascular events. The relationship between HDL and CHD risk is complex. HDL-C and cardiovascular disease have nonlinear relationship.

There are some studies done around the globe about relationship between HDL-C and CAD but not clearly defined severity of CAD and level of HDL-C.

Hence, the present study aim to examine population of CAD with different severity with different serum level of HDL-C so that they can be identified and prompt intervention can be done prior to future CV events.

Materials and Methods:

This is a Hospital based, cross-sectional, prospective study conducted at Shahid Gangalal National Heart Centre (SGNHC), Kathmandu, Nepal from August 2021 to january 2022. Informed written consent was taken prior to enrolment in the study. After approval from Institutional review board (IRB) of National Academy of Medical Sciences (NAMS), Bir hospital, 102 patients who fulfilled inclusion criteria were enrolled in our study. HDL-C level was measured. Normal HDL-C were taken as group B (Male -≥40mg/dl, female-≥50mg/dl) and abnormal HDL-C were Group A (<40mg/dl in male and <50mg/dl in female) and associated with vessel and friesinger scores. Vessel score is the number of vessels with a significant stenosis (for left main coronary artery 50% or greater and for others 70% or greater reduction in luminal diameter). Score ranges from 0 to 3, depending on the number of vessels involve i.e score 0 is normal vessel, score 1,2 and 3 are single, double and triple vessel disease respectively. Left main coronary artery was scored as single vessel disease. Similarly, severity of CAD was calculated from friesinger score which ranges from 0 to 15. Each of the three main coronary arteries is scored separately from 0 to 5 i.e. score 0: no arteriographic abnormality, score 1: trivial irregularities (lesion from 1-29%), score 2: localized 30-68% luminal narrowing, score 3: multiple 30-68% luminal narrowing of same vessel, score 4: 69-100% luminal narrowing without 100% occlusion of proximal segments, score 5: total obstruction of a proximal segment of a vessel. Coronary artery is normal, If score is 0, mild, moderate and severe coronary artery disease if score ranges from 1-4, 5-11, 12-15 respectively.

Inclusion Criteria

All patients with coronary artery disease with age > 18 years

Exclusion criteria

1. All patients with prior coronary revascularization either CABG or angioplasty, congenital heart diseases, valvular heart diseases, cardiomyopathy
2. Patient refuses to undergo CAG
3. Patients taking statin therapy
4. Subjects not willing to give consent

Statistical Methods

All data were entered into an electronic spread sheet (Microsoft Excel, Redmond) and the statistical analysis was done by using the SPSS version 20 software. All categorical variables were expressed in

frequency and percentage. For numerical data, normality was checked by using Sapiro wilk test. All normal numerical data were presented in a mean±SD. For association, Pearson's chi. square test was applied. Processing of all available information and statistical analysis of their significance was done. For the purpose of this study a 95% confidence interval was accepted.

Results:

Among 102 patients majority were males 82 (80.4%) and 20 (19.6%) were females. Mean age of patients was 59.4±11.4 years (Table 1). Minimum HDL-C level was 30 mg/dl and maximum was 89mg/dl. Mean HDL-C was 42.17±10.01mg/dl. Normal HDL-C (group B) was found in 43(42.2%, mean ±SD=51±10) patients and abnormal (Group A <40mg/dl in male and <50mg/dl in female) was in 59 (57.8%, mean ±SD= 36±4) patients (Table 2). According to vessel score, no vessel involvement, single, double and triple vessels disease were found in 32 (31.4%), 22 (21.6%), 26 (25.5%) and 22 (21.6%) patients respectively (Table 3). There was significant association with serum HDL-C level between double and triple vessels disease than single vessel disease (P value =0.03) (Table 5). Similarly, according to friesinger score, no vessels involvement, mild, moderate and severe coronary artery disease was found in 10 (9.8%), 26 (25.5%), 59 (57.8%), 7 (6.9%) patients respectively (Table 4). Moderate to severe CAD was higher in abnormal HDL-C level patients than mild disease however it was not significant statistically (p value=0.11) (Table 5).

Table-I

Age and sex wise distribution

Age (years)	Male (%)	Female (%)	Mean±SD
18-40	5(4.9%)	0	59.4±11.4
41-50	15(14.7%)	2(1.9%)	
51-60	25(24.5%)	8(7.8%)	
60-70	26(25.4%)	8(7.8%)	
>70	11(10.7%)	2(1.9%)	
Total	82(80.4%)	20(19.6%)	

Table-II

HDL-C level

HDL	Frequency	Percentage	Mean ±SD
Normal (Group B)	43	42.2	51±10
Abnormal (Male <40mg/dl, Female <50mg/dl (group A)	59	57.8	36±4

Table-III

Vessel score

Vessel score	Frequency	Percentage
Normal vessel	32	31.4
SVD	22	21.6
DVD	26	25.5
TVD	22	21.6

Table-IV

Friesinger score

Friesiner score (severity of CAD)	Frequency	Percentage
Score 0 (Normal)	10	9.8
Score 1-4 (Mild)	26	25.5
Score 5-11 (Moderate)	59	57.8
Score 12-15 (Severe)	7	6.9

Discussion:

Table-V

Vessel and friesinger scores association with HDL-C

Score	HDL-C level				
Vessel score	Normal (%) (Group B)	Abnormal (%) (Group A)	Total	Chi-square value	P-value
0: No vessel involvement	18(56.3%)	14(43.8%)	32	8.78	0.032
1: Single Vessel disease(SVD)	12(54.5%)	10(45.5%)	22		
2: Double vessels disease(DVD)	8(30.85)	18(69.2%)	26		
3: Triple vessels disease(TVD)	5(22.7%)	17(77.3%)	22		
Friesinger score					
0: Normal	5(50%)	5(50%)	10	4.27	0.118
1-4: Mild	15(57.7%)	11(42.3%)	26		
5-11: Moderate, 12-15: Severe	23(34.8%)	43(65.2%)	66		

Low HDL-C level is a strong risk factor for CAD and is associated with poor cardiovascular outcome. The Framingham study and others observational data suggest that each incremental increase in HDL cholesterol of 10 mg/dl is associated with 2% to 3% decrease in risk of total CVD. High-density lipoprotein cholesterol (HDL-C) has been dubbed the good cholesterol because it is thought to reflect the ability of HDL particles to transport excess cholesterol molecules from peripheral cells including those in atherosclerotic plaques to the liver. HDL-C has frequently been assumed to be a biomarker of HDL functions, consistent with the inverse relationship in observational studies between plasma levels of HDL-C and risk of coronary artery diseases. 16 Patients with angiographically proven CAD more often have low levels of HDL-C than high levels of low density cholesterol.

Park GM et al had evaluate the association between HDL-C and obstructed CAD in 1,114 diabetic patients who achieved optimal glycemic control (OCG). They underwent coronary computed tomographic angiography and found that the patients with a high HDL-C level (e 40 mg/dL and e 50 mg/dL in males and females, respectively) showed a lower prevalence of obstructive CAD than those with a low HDL-C level in the OGC group (8.9% vs. 14.4%; p = 0.046).[17]

Similarly, in our study patients underwent coronary angiography and HDL-C was measured in each patient and compared with invasive angiographic findings. Those patients who had low level of HDL-C (d 40 mg/dL and d 50 mg/dL in males and females, respectively), 18 had double (69.2%) and 17 had triple vessels (77.3%) disease rather than Single vessel disease (P value=0.03). Moderate to severe CAD was higher in low HDL-C level patients than mild disease however it was not significant statistically (p value=0.11).

Ahmed MI et al studied 100 patients with coronary artery diseases and divided into two groups. 50 patients with low HDL-C (<40 mg/dl) were taken in study group (Group-A) and 50 patients with normal HDLC (>40 mg/dl) were taken in control group (Group-B). SVD [11 (22.0%) vs 25 (50.0%); p=0.020] were significantly fewer in group A than that of group-B. while DVD [14 (28.0%) vs 5 (10.0%); p=0.039] and TVD [22 (44.0%) vs 6 (12.0%); p=0.002] were significantly higher in group-A than that of group-B. Moderate [20(40.0%) vs 9 (18.0%); p=0.041] and severe Friesinger score [21 (42.0%) vs 6 (12.0%); p <0.004] were significantly higher in group-A than that of group-B. Mild disease were significantly fewer in group A than that of group-B. Moderate to severe CAD were higher in group B. They concluded that low HDL-C level is associated with angiographically more severe coronary artery disease.[18]

Our results, according to vessel score, no vessel involvement, SVD, DVD and TVD were found in 32 (31.4%), 22 (21.6%), 26 (25.5%) and 22 (21.6%) patients respectively. Amongst 22(21.6%) patients with SVD, 10 (45.5%) had low HDL-C level. Similarly 18(69.2%) DVD and 17 (77.3%) TVD patient had low HDL-C level. These findings were significantly higher than the study conducted by Ahmed et.al. According to friesinger score, mild, moderate and severe coronary artery disease were found in 26 (25.5%), 59 (57.8%), 7 (6.9%) patients respectively. Moderate to severe CAD was higher in abnormal HDL-C level patients than mild disease however it was not significant statistically (p value=0.11). Our results according to vessels score were similar to the results of this study but results of friesinger score were although similar but statistically not significant.

Similarly, Sáez Y et al. conducted a clinical study of HDL-C and APo-A1 level with presence and severity of coronary obstruction in to investigate the relationship between different lipids parameters with presence and severity of coronary obstruction. They angiographically evaluated 897 patients (629 men and 268 women) and blood extracted to determine concentrations of lipid markers like total cholesterol, HDL-C, triglycerides, LDL cholesterol, apolipoprotein A1, apolipoprotein B100 and their ratios. Multivariate analysis revealed that low HDL-C levels were independently associated with the presence of coronary obstruction. In relation to severity of coronary stenosis, only apoA1 levels and apoB/apoA1 ratio were independent predictors. Their study demonstrated that HDL-C was the only lipid parameter negatively and significantly associated with the presence of coronary obstruction, whereas apoA1 levels and apoB/apoA1 ratio were independent predictors of stenosis severity.[16]

Our results are also similar to the study by Sáez Y et al. According to vessel score, CAD is associated with low HDL-C level. However, there is no statistically significant relation of severity of CAD with HDL-C

according to friesinger score.

With the reviews of different literatures we evaluated the patients CAD association with HDL-C level by using vessel and friesinger score. Our results showed us the double and triple vessels disease were higher with lower level of HDL-C (<40mg/dl in male and <50mg/dl in female) and was statistically significant. Severity of coronary artery disease according to friesinger score was also higher in low HDL-C level but statistically not significant.

Study Limitations

Invasive coronary artery angiography and visual estimation of stenotic lesions may be different between different operators so biasness was major limitation for the assessment of the severity of coronary artery disease in our study.

Conclusion:

Serum HDL-C level has significant association between double and triple vessels disease than single vessel disease. According to friesinger score, Severity has no statistically significant association with HDL-C level .

Conflict of Interest - None.

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Impact of pre-treatment with intracoronary adenosine on the incidence of myonecrosis after elective percutaneous coronary intervention

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Abstract

Background: Creatine Kinase-Myocardial band (CK-MB) elevation after successful Percutaneous Coronary Intervention (PCI) is common. There is a growing interest on the role of pharmacotherapy to prevent peri-procedural myocardial injury during elective PCI. In this study, we investigated the impact of prophylactic intracoronary (IC) adenosine administration during elective percutaneous coronary intervention.

Method: In this case control study total sixty (60) patients undergoing elective coronary intervention were included in this study from October 2006 to October 2007 at National Institute of Cardiovascular Diseases (NICVD), Dhaka, approved by the ethical committee of NICVD. The Patients were divided into adenosine receiver and placebo group randomly (Group I and group II respectively) with thirty (30) patients in each group. In adenosine group, 50 microgram of adenosine was administered through guide catheter into target vessels prior to wiring of each lesion whereas placebo group did not receive any medication. For multi-vessel PCI another 50 micrograms of adenosine was given prior to intervention of subsequent vessels. Primary end point of post coronary intervention, peri-procedural myonecrosis was assessed by measuring abnormal CK-MB levels, angiographic coronary flow assessed by Thrombolysis in Myocardial Infarction (TIMI). Secondary end points were peri-procedural Myocardial Infarction, cumulative incidence of in-hospital death and urgent target vessel revascularization.

Result: The mean age of were 46.43±10.2 and 47.33±8.73 years respectively in between the groups. Post-PCI myonecrosis occurred more frequently without adenosine than with adenosine treated group (40% vs 16.7%; p=0.046). The mean post-procedural CK-MB level was significantly lower in patients pre-treated with adenosine (22.6±10.3U/l vs. 28.9±12.7U/l, p=0.039). Incidence of myocardial infarction was 3.3 % and 13.3 % in adenosine and placebo group respectively, which were not statistically significant. In hospital events including death and urgent target vessel revascularization were not observed in either group.

Conclusion: Intracoronary administration of adenosine in patients undergoing percutaneous coronary Intervention is associated with decreased post procedural complication and hospital stay.

Key words: Adenosine, Myonecrosis, Elective PCI.

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Introduction

Coronary heart disease is one of the leading causes of death in developed as well as in developing countries. A population based study showed the prevalence of ischemic heart disease is 6.5 per thousand population of Bangladesh[1].The use of percutaneous coronary intervention in patients with ischaemic coronary artery disease has expanded dramatically over the last two decades. Percutaneous coronary intervention (PCI) is well accepted and established treatment modality of myocardial revascularization for coronary artery disease[2].

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Ever since the introduction of coronary stents, success rates have increased and the outcomes of PCI have improved. Yet, the incidence of cardiac enzyme elevation after PCI has not changed significantly.[3,4] Several studies have showed that cardiac enzyme elevation after PCI might be associated with increased post procedural long- term mortality.5-10 Possible causes of cardiac enzyme elevation after PCI are distal embolization of thrombotic or atherosclerotic debris, platelet activation and thrombus formation, neurohormonal activation, microvascular spasm, oxidative stresses, inflammation, and occlusion of a side-branch at the site of PCI.[11-16] Numerous strategies have been introduced to prevent this phenomenon, including medical and interventional therapies e.g. dual antiplatelet and lipid-lowering therapies, use of anticoagulant and direct stenting are some of the proposed strategies.[17,18]

Adenosine with the activation of vascular smooth muscle A2-receptors dilates coronary arteries a function that is not endothelial-dependent. The effects are more relevant on the vessels smaller than 100 ìm; and, hypothetically, it can prevent myonecrosis with preconditioning and improve microcirculation during ischemic episods.[19,20] Several studies have shown the beneficial effects of intracoronary (IC) Adenosine in the setting of primary and elective PCI in patients with ST-elevation myocardial infarction (STEMI) in terms of reducing no-reflow, infarct size, and mortality.[21-23] Different PCI guidelines give a class I recommendation for the measurement of cardiac biomarkers (the MB fraction of creatine kinase [CK-MB], cardiac troponin, or both) in patients who have signs or symptoms suggestive of myocardial infarction during or after PCI and for those who have undergone complicated procedures.[24]

A number of key pathophysiological processes in combination, are believed to be responsible for this complication such as distal embolization of atherothrombotic debris, thrombus formation, and endothelial dysfunction of the distal arteriolar and capillary bed, including endothelial desquamation and microcirculatory vasospasm. It can lead to myonecrosis, elevation of cardiac enzymes, and in some instance increased long-term mortality.[25] Short term and late adverse outcomes of PCI seems partially related to the presence and extent of the release of creatine kinase MB or other marker[26]. After successful percutaneous coronary intervention 24-44% of patients suffer some myocardial damage as indicated by a significant change in the

concentration of CK-isoenzyme[27]. Elevations of CK-MB after PCI predict adverse outcome, the greater the elevation, more the adverse prognosis. This has not consistently been the case with cardiac troponins[28]. Patients who has transient elevation in cardiac markers such as CK and CK-MB fractions, has higher cardiac mortality during extended follow up than those who did not and is independent of other predictors of mortality[7].

Several reports have identified NSTEMI with CK-MB elevations of 3 to 5 times the upper limit of normal having clinical significance, one report suggests that a greater than 5 times increase in CK-MB is associated with worse outcome after PCI[24]. Therefore procedural CK-MB elevations during PCI should be prevented. Recently, different studies address an important question relating to the possibility of further improving interventional outcome using pre-procedure adenosine therapy. In a prospective randomized trial by Lee et.al. evaluated the incidence of myonecrosis after non-urgent PCI with and without pre-treatment with intracoronary adenosine. The results showed that, the incidence of myonecrosis was reduced from 39 to 13% with adenosine pre-treatment[29].

Adenosine induced hyperemia can potentially ameliorate the deleterious effects of distal embolization associated with non-urgent PCI through dilatation of the microvasculature, which may also work through cardio protective mechanisms including replenishment of high-energy phosphate stores, ischemic pre conditioning, free radical suppression, and platelet and neutrophil inhibition[30]. This study was carried out in patients undergoing elective PCI to to evaluate the effect of prophylactic IC Adenosine in preventing the elevation of cardiac enzymes as a marker of myonecrosis after PCI in Bangladeshi population.

Methods:

This prospective observational case control study was conducted in the department of cardiology, National Institute of Cardiovascular Diseases (NICVD) Dhaka, from October 2006 to October 2007. The study protocol conformed to the principles of the declaration of Helsinki and was approved by NICVD Ethics Committee. Informed written consent was obtained from all patients. Purposive sampling method was used and samples were collected on the basis of inclusion and exclusion criteria with matched case and control groups. Patients selected for elective PCI in native coronary artery with baseline normal creatine kinase-myocardial band (CK-MB) were the study population. Patients with heart rate below 50 beats per minute, history of recent myocardial infarction and history of bronchial asthma were excluded from the study. The Patients were divided into adenosine receiver and

placebo group (Group I and group II respectively) with thirty (30) patients in each group.

Detailed history was taken and meticulous clinical examination was done. ECG, echocardiography, blood biochemistry, CBC and virologcal markers were tested. The first blood sample of CK-MB was collected at the beginning of the procedure and subsequently sample taken at 8-12 hours after the procedure and CK-MB level > 25 u/L were considered abnormal. The primary efficacy outcome of this study was post-PCI myonecrosis, defined as an elevation in CK.MB greater than the upper limit of normal > 25 IU/L. Secondary end point was safety of IC Adenosine administration in the setting of PCI in patients undergoing PCI.

Coronary angiographic findings were recorded before balloon dilatation and after stent placement. Lesion was quantified in percentage by visual estimation, and TIMI flow was recorded. According to ACC/AHA PICA guidelines lesions were classified as type A, type B and type C lesion31. Coronary angiography was followed by PCI with stenting as per American College of Cardiology (ACC) /American Heart Association (AHA) guideline for PCI24. Stenting was done as an elective procedure. All the procedures were done through the right femoral approach. In most cases Judkins type guide catheter (6F/7F) was used. Patients selected to the adenosine group were given 50 microgram of adenosine (diluted in 5 ml normal saline) rapidly through the guiding catheter into the target coronary artery prior to guide wire advancement. For multi vessel stenting, another 50 micro gram of adenosine was given prior to intervention of the subsequent vessel. Procedural complications e.g. no flow, slow flow, side branch occlusion, peri-procedural MI, coronary dissection, in- stent thrombosis, coronary spasm, bronchospasm, ventricular arrhythmia, cardiogenic shock and need for urgent CABG and failed PCI were noted. Patients were followed up thoroughly during intervention and hospital stay after the procedure. Chest pain, hypotension, heart failure, vascular access site complications and major events as mentioned above if any were monitored.

The numerical data obtained from the study were analyzed and significance of difference was estimated by using the statistical methods. Data were expressed in frequency, percentage, mean and standard deviation as applicable. Comparison between groups was done by unpaired student's test, chi-square test, and Fisher's exact test as applicable. Data were analyzed by using computer based SPSS program (version 16). Probability less than 0.05 was considered significant.

Result:

In this study, baseline parameters like age, sex, body mass index, risk factors for coronary artery disease, prior pattern of coronary artery disease, baseline ECG, CK- MB and left ventricular ejection fraction showed no statistically significant differences between the two groups (Table I).

Angiographic parameters of the study groups were also similar as shown in the table II. Among Group I subjects, 5 (16.7%) had CK-MB level above 25U/1, whereas among Group II subjects, CK-MB level above 25 U/L in 12 (40.0%) patients. But the mean level of CK-MB was significantly higher among the patients of Group II (28.9±12.7) U/L than that of Group I patients

Table I

Demographic and clinical characteristic of the patients in between the groups

Variables	Group I(n=30)	Group II(n=30)	p value
Age (Mean ±SD)	46.43±10.2	47.33±8.73	0,437ns
BMI (kg/m2)	26.3±3	25.9 ±2.5	0.567ns
Smoking (n, %)	19 (63.3%)	21 (70.0%)	0.704ns
Hypertension (n, %)	15 (50.0%)	13 (43.4%)	0.987ns
Diabetes mellitus (n, %)	14 (46.7%)	11 (36.7%)	0.463ns
Dyslipidaemia (n, %)	9 (30.0%)	6 (20.0%)	0.378ns
Family H/O CAD (n, %)	6 (20.0%)	4 (13.3%)	0.563ns
Category of ACS·	Stable Angina (n, %)	9 (30%)	6 (20.0%)
0.667ns			
· Unstable angina (n, %)	7 (23.3%)	6 (20.0%)	0.857ns
· STEMI (n, %)	11 (36.7%)	14 (46.7%)	0.785ns
· NSTEMI (n, %)	3 (10.0%)	4 (13.3%)	0.750ns
SBP in mmHg (Mean ±SD)	124.8±18.7	123.6±16.5	0.321ns
DBP in mmHg (Mean ±SD)	78.8±11.4	79.5±10.5	0.447ns
EF% (Mean ±SD)	55.4+3.9	56.1+4.1	0.395ns

Table II

Angiographic and procedural characteristics in between the groups

Variables	Group I	Group II	p value
Number of vessel involved (n, %)·			
Single	22, 73.3%	23, 76.7%	0.766ns
· Multiple	8, 26.7%	7, 23.3%	0.072ns
Lesion Classification (n, %)			
· A	9, 30.0%	7, 23.3%	0.87ns
· B	13,43.3%	15, 50%	0.83ns
· C	2, 6.7%	3, 10.0%	0.68ns
· Mixed	6, 20.0%	5, 16.7%	0.77ns
Number of stents implanted (n, %)			
· Single	22, (73.4%)	23, (76.6%)	0.383ns
· Multiple	8, (26.6%)	7, (23.4%)	0.425ns
TIMI flow before PCI (n, %)			
1	4, (13.7%)	3, (10.0%)	
· 2	18, (60.0%)	20, (66.7%)	0.854ns
3	8, (26.3%)	7, (23.3%)	
·TIMI flow after PCI (n, %)			
· 1	2 (6.7%)	3 (10.0%)	
· 2	3 (10.0)	5 (16.6%)	0.673ns
· 3	25, (83.3%)	22, (73.3%)	
Distribution of patients according to CK-M Level after PCI (n, %)			
B·			
<25 u/L	25, (83.3%)	18, (60.0%)	0.046s
· >25u/L	5, (16.7%)	12, (40.0%)	0.041s
· > 3 times ULN	1 (3.3%)	4 (13.3%)	0.245ns
Pre & post PCI CK-MB Changes (u/L)			
· Base Line (Mean ±SD)·	18.8±4.7	19.3±3.2	0.632ns
· After PCI (Mean ±SD)	22.6±10.3	28.9±12.7	0.039ns
PCI related Parameters			
PTCA balloon inflation pressure (ATM)	9.6±1.8	9.8±1.5	0.574ns
Post Stent inflation pressure (ATM)	13.7±2.67	13.6±2.86	0.754ns
Total inflation time (Seconds)	28.1 ± 4.8	29.0 ± 3.5	0.276ns
Diameter of Stent (mm)	3.11 ± 1.15	3.04 ± 1.03	0.594ns
Length of Stent (mm)	20.86 ± 4.21	21.32 ± 4.60	0.639ns
Duration of hospital stay (Mean ± SD) in days	3.2 ± 2.6	3.4±1.8	0.730ns

(22.6 ± 10.3) at 8 to 12 hours after the procedure (p=0.039). PCI procedure related parameters were similar among the groups and there was no peri-procedural flow related complications or side branch occlusion in both the groups.

Analysis indicates that, acute MI, hypotension was more common in Group II patients than in Group I (Table III). Whereas vascular access-site complications were more common in Group I. There were no statistically significant differences between the two groups in terms of in-hospital complications.

Table IV shows the logistic regression analysis of rise of CK-MB with selected variables. It was found that CK-MB was negatively correlated with prior medication with adenosine ($p<0.05$) and positively correlated with type C lesion ($p<0.05$) but no statistically significant correlation with other variables such as vessel involvement, target vessel and balloon inflation pressure.

Table-III

Distribution of patients by in-hospital post PCI complications (N=60).

Complications	Group I		Group II		p value
	n=30	%	n=30	%	
Hypotension	2	6.7	3	10	0.37ns
Acute MI	1	3.3	4	13.3	0.18ns
Heart Failure	1	3.3	1	3.3	0.00ns
Arrhythmia	1	3.3	2	6.7	0.50ns
Hemorrhage	2	6.7	1	3.3	0.50ns

Table-IV

Logistic regression analysis of rise of CK-MB with selected variables (N=60)

Variables	Coefficient	p value
Study subjects (adenosine vs. placebo)	0.29	0.029s
Type of lesion (type C vs. others)	0.53	0.041s
Vessel involvement (Multi vessel vs. single vessel)	0.33	0.061ns
Target PCI vessel (Multi-vessel vs. single vessel)	0.13	0.901ns
Balloon inflation pressure	0.19	0.342 ns

Discussion:

The main objective of the study was to evaluate the effect of prior adenosine therapy on peri-procedural myonecrosis by measuring serum CK MB level after coronary intervention and to asses, in-hospital outcome of PCI with IC adenosine pre- treatment.

In this case control study mean age and gender was similar among the groups. The age structure was consistent with Rahman et al. but Desmet et.al. had a study on which patients older then this study[32, 27]. Subsets of patients with coronary artery disease who underwent interventional procedure were myocardial infarction (36.7% vs. 46.7%), non ST segment elevated MI (10.0% vs. 13.3%), unstable angina (23.3% vs. 20.0%) and stable angina (30.0% vs. 20.0%) and there were no statistically significant differences in incidence of coronary artery diseases between the two groups (p>0.05).

In this study incidence of CK-MB rise following PCI was 40.0% without adenosine pretreatment and 16.6% with adenosine pretreatment which was statistically significant (p<0.05). Without adenosine pretreatment 4 (13.3%) patients had CK-MB elevation >3 times the upper limit normal (ULN) in comparison to 1 (3.3%) patient with adenosine pretreatment (p>0.05). Above results were similar to those of the study done by Lee et al., which showed CK-MB elevation in 13% cases with adenosine pre-treatment and 39% cases without adenosine pre-treatment[29]. In a study, Desmet et al. showed patients with intracoronary adenosine infusion had lower CK-MB level than patients without adenosine infusion (16.7% vs. 50%; p=0.04)[27]. Kizilirmak et.al. in their study found CK-MB levels were similar in both groups (11 % vs. 19 %, p: 0.263). Post-procedural TFCs in the adenosine group were significantly lower than the placebo group (24 ± 4 vs. 27 ± 5, p: 0.004)[33].

The mean post-procedural CK-MB level was 22.6 ± 10.3 U/L in group I and 28.9±12.7 U/L in the group II, which was statistically significant (p<0.05). Sanati et.al. in their study showed there were no differences in the mean serum cardiac biomarkers between the study groups (meanCK.MB level of 29.5 ± 14.5 IU/L in the placebo group and 31.5 ± 18.5 IU/L in the control group; p value = 0.41)[25].

In hospital complications following PCI were more commonly observed in patients without adenosine pre-treatment. Post-procedural acute myocardial infarction occurred in 5 patients which were diagnosed on the basis of CK-MB elevation more than 3 times of the normal values. The incidence of myocardial infarction was 3.3% (n=l) in Group I and 13.3% (n=4) in Group II (p= >0.05). This finding is consistent with that of Lee et al. They found myocardial infarction in 6% of adenosine treated and 16% of adenosine untreated group[29].

side branch (SB) involvement (3.6% in the placebo vs. 3% in the Adenosine group)[25].

In this study, there was no incidence of SB involvement, post procedural TIMI 1 and Hypotension developed in 6.7% and 10.0% of Group I and Group II patients respectively. Vascular access-site complications in the form of bleeding and haematoma were observed in 3.3% of patients in both groups. Only, two patients experienced significant sinus bradycardia, which were transient and resolved spontaneously within seconds. No patients of any group developed bronchospasm and none needed to undergo repeat PCI or CABG. Sanati et.al., found that, procedural complications were equally distributed in the two groups, excluding the TIMI 2 flow was detected cumulatively in 16.5% and 26.6% cases in group I and II respectively (p =<0.05).

Logistic regression analysis found that CK-MB was negatively correlated with prior medication with adenosine ($p<0.05$) and positively correlated with type C lesion ($p<0.05$) but no statistically significant correlation with other variables such as vessel involvement, target vessel and balloon inflation pressure ($p>0.05$).The mean duration of post procedural hospital stay was 3.2 ± 2.6 days for Group I patients and 3.4±1.8 days for Group II patients. There was no statistically significant difference in between the two groups in terms of post procedural hospital stay. Gustavsson et.al. observed in their study, that CK-MB and troponin do not provide comparable information in PCI patients when used according to present recommendations and they consider it too early to abandon CK-MB as a marker of myonecrosis or MI in the setting of PCI[34]. Overall in this study, the use of IC Adenosine was safe and without permanent complications.

Conclusion:

In this study, procedural and clinical outcome were better in patients received intracoronary adenosine. This observational study suggests that pre-treatment with adenosine during percutaneous coronary intervention may have cardio protective effect and reduces myonecrosis. However the sample size was relatively small. Apart from that, other factors e.g. contrast injection, catheter manipulations, and distal embolism of the air and microscopic particles may cause release of cardiac biomarkers. So, larger randomized trial of adenosine administration before percutaneous coronary intervention is needed to assess this apparent beneficial effect.

Conflict of Interest - None.

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REVIEW ARTICLE

Cell Membrane Cholesterol Content Determines Infectivity of Enveloped Viruses: a Link between Statin and COVID-19 Virus

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Abstract:

The severity of the recent Coronavirus pandemic was not uniform worldwide. The reason for these differences may be explained in terms of either the difference in the immunity of different populations or the difference in the virulence of the virus in different parts of the world.

Enveloped viruses, like Coronavirus, enter their host cells, by first coming in contact with their specific receptors, and then fusion of their envelope with the plasma membrane of host cells. After replicating inside, they exit from their host cells by incorporating part of their host cell plasma membrane, and they further infect other cells. Both entry and exit take place in special areas of the plasma membrane known as lipid rafts which are micro-domains rich in cholesterols and sphingomyelins, and which act as scaffolds for various signal transduction molecules and various receptors. It has been shown in virology labs that a change in cholesterol content of lipid rafts on the cell membrane of the host cell can affect viral infectivity. Experiments have shown that various inhibitors of the cholesterol biosynthesis pathway results in either decrease or increase in the content of cholesterol of lipid raft and non-raft fractions of cell membrane depending upon the conditions of media in which the cell cultures are grown.

This article aims to explain how statin, widely used for primary and secondary prevention of cardiovascular diseases, could result in increased content of cholesterol in the raft and non-raft fractions of the plasma membrane, which in turn can influence viral infectivity of enveloped viruses like Coronavirus.

Keywords: Coronavirus, enveloped virus, lipid rafts, cholesterol, statin, sterol regulatory element-binding proteins (SREBP), low-density receptor (LDL-R)

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Background :

The Coronavirus disease (COVID-19) pandemic caused by SARS-CoV-2 (severe acute respiratory syndrome corona virus-2), started in December 2019. In the last two years, it was observed that the severity of the pandemic was not uniform worldwide. This pandemic hit certain parts of the globe more severely, with a greater death toll, particularly in Europe and America. Countries like India, Bangladesh, and Pakistan, despite having a very high human density, and their inability to maintain social distancing, were relatively less affected in terms of mortality. According to the WHO data, out of the total population of 334,805,269 in the USA[1] there was a total death of 1,009,906 due to COVID-19[2], giving a mortality rate of 0.30%, while in India, with a population of 1,406,631,776 the total death was 525,343 giving a mortality rate of 0.04%, in the period of 3 January 2020 to 8 July 2022, showing a much higher mortality rate for the disease in the US.

The explanation for this has to be made in terms of either the difference in the immunity of different populations or the difference in the virulence of the virus in different parts of the world.

Statins have been used extensively for primary and secondary prevention of cardiovascular diseases in the past two decades, with the US and Europe having the highest consumption rate[3]. It is a well-known fact that statins decrease cholesterol levels in the blood

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plasma, however, how it decreases and where this cholesterol goes have not been explicitly explained or studied. Moreover, there is ambiguity about whether these cholesterol-reducing agents decrease or increase the cholesterol content of the plasma membrane. Some studies do show that cholesterol content of the plasma membrane is decreased by statins[4,5] and other cholesterol-reducing agents when cells are grown in the presence of such agents, in an in-vitro experiment, where the growth media have not been enriched with LDL-cholesterol. These studies do not seem to have taken into account that, in-vivo, our cells exist in a cholesterol-rich medium, i.e. LDL-cholesterol. However, some studies did show that the cholesterol content of the plasma membrane was increased by some cholesterol biosynthesis inhibitors when the growth medium for the cells were enriched with cholesterol[6]. Considering the importance of cholesterol in maintaining the fluidity and integrity[7] of the cell membrane and the lipid rafts that have multiple functions in maintaining the homeostasis of a cell including their function as a scaffold for various receptors on the cell membrane[8] any substance that would decrease the cholesterol content of cell membrane and lipid rafts would not be beneficial to any cell.

Our perspective is that prolonged intake of statin increases cholesterol content of raft and non-raft fractions of cell membranes which facilitates entry of enveloped viruses like Coronavirus and also the viruses budding out of such cholesterol-rich membranes acquire more cholesterol in their envelope making them more sturdy and durable in the external environment. The virion envelope, which is derived from its host cell membrane is very much similar structurally to its host cell membrane, made up of a bilayer of phospholipids interspersed with cholesterol and proteins. It is a known fact that cholesterol is extremely important in the maintenance of the integrity and fluidity of the phospholipid bilayer. Depletion of the cholesterol content of the cell membrane results in increased fluidity in hot temperatures and increased rigidity in cold temperatures, both of which could result in breakage of the cell membrane. Biswas A et al have shown in their experiment that cholesterol depletion increases membrane tension, making cells prone to rupture on hypo-osmotic shock[7].

Razin S[9]) reported that cholesterol increased the tensile strength of the mycoplasma membrane and permitted the survival and growth of these organisms without the protection of cell walls. Bacterial cells, Lactobacillus acidophilus that was grown in the presence of cholesterol micelles and bile salts were more resistant to lysis by sonication than were those grown in their absence[10].

Perspective

The SARS-CoV-2 (severe acute respiratory syndrome corona virus-2) is an RNA (ribonucleic acid) enveloped virus. Enveloped viruses derive their covering from their host cell membrane which structurally is a bilayer of phospholipids. This bilayer of phospholipids is fragile and is easily destroyed outside the body. The proper fluidity and rigidity of such a phospholipid membrane are maintained by cholesterol molecules interspersed regularly within the membrane. The importance of cholesterol cannot be overemphasized regarding maintaining the integrity of phospholipid bilayer that in its absence the phospholipid molecules would behave like oil at high temperatures and like butter at lower temperatures. Therefore, cholesterol has a very important role in the stability of enveloped viruses in the external environment. Non-enveloped viruses, however, with their covering of protein capsid can survive in the external environment for a much longer duration of time[11]. Despite being an enveloped virus, COVID-19 viruses do seem to survive for a relatively much longer duration of time in the external environment, unlike other enveloped viruses. World Health Organization has stated that COVID-19 viruses may persist on different surfaces for a few hours to several days. Survival of these viruses may not only depend on the type of surface, temperature, or humidity of the environment but also the stability and integrity of the viral envelope[11,12,13]. It is a well-known fact that the stability and integrity of bilayer phospholipid of eukaryotic cells depend upon the cholesterol content of the cell membrane and this has also been shown to be true for the enveloped viruses[13].

Statins decrease cholesterol in the plasma, but in what way it does is not realized by many. Statin inhibits 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG Co-A reductase), a key enzyme in the Mevalonate pathway, present in all the nucleated cells of the body, resulting in either very low or no production of endogenous cholesterol by human cells. Cholesterol homeostasis is maintained by a complex network of intracellular organelles, proteins, and enzymes which involves cholesterol synthesis, import, export,

esterification, and metabolism[14]. In the endoplasmic reticulum (ER) membrane, sterol regulatory element-binding proteins (SREBP), are critical regulators of the genes involved in cholesterol biosynthesis and uptake of exogenous cholesterol[15]. Because cholesterol is so important for the integrity of cell membrane that there exist mechanisms that either derive cholesterol from the exogenous source from low-density lipoprotein cholesterol (LDL-C) of blood plasma or de novo cholesterol synthesis[16,17]. ER cholesterol acts as a sensor of intracellular cholesterol concentration. In the natural state, these mechanisms are very tightly controlled to maintain an adequate amount of cholesterol in the cell membrane. However, statins often prescribed lifelong, create a chronic deficiency of endogenous cholesterol. The decrease in ER cholesterol induces the translocation of SREBP from the ER to the Golgi and then to the nucleus for the transcriptional activation of the target genes, including those involved in cholesterol uptake and biosynthesis resulting in the upregulation of LDL-R in the cell membrane[18]. This constant upregulation of LDL-R in the cell membrane leads to more cholesterol being incorporated into the cell through LDL-C (the exogenous cholesterol that comes in the plasma either through the foodstuffs we ingest or from the liver). This is how statins decrease cholesterol in the blood plasma.

Studies have found that there are multiple areas in the eukaryotic cell membrane with a very high concentration of cholesterols and sphingolipids. These microdomains are known as lipid rafts (because they float like rafts on the water surface), and it has been shown that these are the areas where enveloped viruses fuse with their host cell membrane after coming in contact with their specific receptors on their host cell membrane[11]. Lipid rafts are extremely important microdomains in the plasma membrane because they act as scaffolds for various signal transduction molecules and receptors[8]. Angiotensin-converting enzyme-2 (ACE-2) has been found as the specific receptor on the respiratory epithelium for the COVID-19 virus. Experiments have shown that the depletion of cholesterol by methyl beta-cyclodextrin (MβCD) from the host cell membrane inhibits the fusion of the viral envelope with the host cell membrane[19]. There is strong evidence that enveloped viruses select lipid rafts for their assembly as well as budding[13,20]. Because viruses bud out from such cholesterol-rich microdomains, cholesterol depletion results in a reduced amount of cholesterol on the viral envelope, which in turn decreases viral stability in the external environment[12,13]. Whereas, the viruses that bud out from the host cell membrane rich in cholesterol may also have envelopes rich in cholesterol that make their envelope more stable and survive in the external environment for a longer duration of time. Compounds affecting cell membrane cholesterols (e.g., methyl β-cyclodextrin, amphotericin B methyl ester, statins) or sphingolipids (e.g., L-cycloserine, Lysenin) were shown to interfere with viral infectivity at different stages of virus replication[21].

The role of cholesterol in the plasma membrane of the host cell and the envelope of some respiratory viruses have been very well documented in the laboratory experiments done by Bajimaya et al[13]. They have interestingly shown that depletion of cholesterol from host cells disrupted lipid raft integrity on the cell membrane and inhibited virus assembly and virus particle production[22]. They have used cholesterol-reducing agents such as gemfibrozil and lovastatin. However, in their experiment, the host cells were not grown in a medium containing an excess of lipoprotein-rich plasma. This experiment gives the impression that statin reduces infectivity of enveloped viruses, but we would like to point out that the effect of a statin (Lovastatin in this study) would have been different in vivo. In vivo, when the cholesterol level goes down inside a cell the SREBP system would be activated as a negative feedback process and increase the intracellular cholesterol synthesis and upregulation of LDL-R on the cell membrane, resulting in increased uptake of LDL-C from the circulating plasma, whereas, in vitro, the upregulated LDL-R would not come in contact with an adequate amount of LDL-C unless the culture medium (Fetal calf serum) they used were enriched with LDL-C and Apoprotein E (ApoE) (4, 5). It is also to be noted that ApoE of humans and that of bovine serum are different and the cell line they used was the cancer cell line. Wandelmer JS et. al. (6) have shown in their experiment that in cells treated with cholesterol biosynthesis inhibitors, simultaneous supplementation with cholesterol prevented the reduction of cholesterol levels in both raft and non-raft fractions of the membrane. However, in the result of the experiment, it can be seen that the cholesterol content of both raft and non-raft fractions of the membrane has increased compared to the controls. This experiment supports our argument that when statin, a cholesterol biosynthesis inhibitor, is used in

vivo, the condition would be similar to that of using various cholesterol inhibitors in vitro along with cholesterol supplementation as the human plasma is already rich in cholesterol content. Therefore, unlike other cholesterol-reducing agents from the cell membrane, statins, ironically, may increase the cholesterol content of lipid rafts on the cell membrane making easy access for enveloped viruses like Coronaviruses, and also, because the viruses that bud out from such cholesterol-enriched cell membranes may acquire more cholesterol in their envelope, this may give them greater stability in the external environment.

It is probably because of this mechanism that viral load in humans and viral survival in the external environment have been particularly high in areas of the globe where statins are prescribed extensively. A 2004 article in BMJ showed that France, Germany, Italy, Spain, and the UK of the European continent were the countries with the highest rate of statin intake [23]. Another article published in BMJ states that there was an increase in statin utilization of 121% in Belgium to 1263% in Denmark within a period of twelve years, from 2000 to 2012[24]. The USA is another country where statins are extensively prescribed. In 2014, 13.5% (43 million out of 318 million) Americans were taking it (3). These are the parts of the globe with the highest numbers of COVID-19 infections at present. However, statin utilization in India is far below compared to Europe and America[25] and the situation in the surrounding countries could be similar. A recent study in China has shown significantly lower levels of serum cholesterol, HDL-cholesterol, and LDL-cholesterol among patients with COVID-19 infection compared to healthy controls[26,27]. The lower levels of serum cholesterol in these COVID-19 patients could be because of prolonged intake of statins, however, this data has not been provided in the study.

Conclusion:

We would thus like to conclude by putting forward our perspective that statins create a constant deficiency of endogenous cholesterol content of cells leading to constant upregulation of LDL-R, in turn leading to excessive incorporation of exogenous cholesterol into the cells and their cell membranes. This process leads to multiple lipid rafts on the cell membrane and enhances accessibility by Coronaviruses. At the same time, the viruses that bud out from such a cell membrane will also have a higher content of cholesterol on their envelope making them more stable and less destructible in the external environment. This will need to be tested in Virology labs by looking for whether there is a significant difference in Coronavirus infectivity of cells of patients taking statin and cells of individuals not taking a statin, and also look for whether viruses budding out from statin-treated individuals survive longer in the external environment compared to viruses budding out from statin non-treated individuals.

Abbreviations

SREBP (sterol regulatory element-binding proteins)

LDL-R (low-density lipoprotein receptors)

LDL (low-density lipoprotein)

COVID-19 (Coronavirus disease 2019)

SARS-CoV-2 (severe acute respiratory syndrome corona virus-2)

RNA (ribonucleic acid)

HMG Co-A reductase (3-hydroxy-3-methyl-glutaryl-CoA reductase)

ER (endoplasmic reticulum)

ACE-2 (Angiotensin-converting enzyme-2)

MâCD (methyl beta-cyclodextrin)

ApoE (Apoprotein E)

Declaration of Competing Interest

The author declares that there were no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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"With ECMO Death doesn't mean Death!!" — Our First ECMO Survivor from Cardiotoxic Drug Overdose.

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Abstract:

Extracorporeal membrane oxygenation (ECMO) use in cardiotoxic drug overdose is increasing. Calcium channel blockers along with â-blockers constitute more than 65% of deaths from cardiovascular medications[1]. The authors report here a case of ECMO use in amlodipine, metoprolol and some other unknown sedative tablet overdose, where ECMO was used to salvage the patient's life as a life-saving intervention.

Keywords: calcium channel blocker poisoning; Beta blocker poisoning; extracorporeal membrane oxygenation; refractive shock

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Introduction:

Calcium channel blocker (CCB) constitutes 34% of cardiovascular drug-related deaths.[2] When multiple cardiovascular drugs with synergistic mechanisms are ingested together, the management of such patients becomes more challenging and refractive to most medical management. Extracorporeal membrane oxygenation (ECMO) can become a lifesaving intervention in such a situation, when not responding to other medical management.

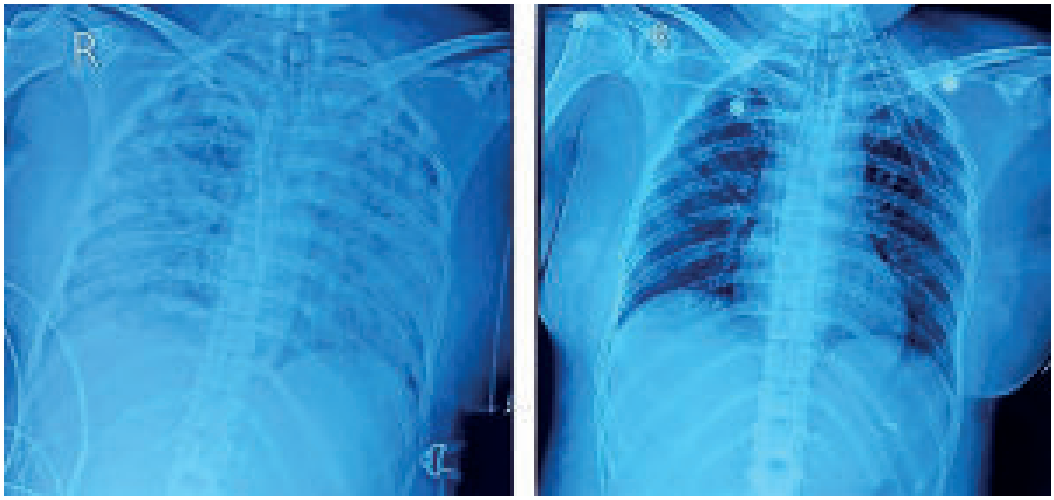


Figure 1: *Bilateral Pulmonary Oedema on X-ray Chest A/P view Before (left) and After (right) initiation of VA ECMO.*

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Case Report:

A 36-year-old female patient was brought to the hospital with alleged history of consumption of amlodipine 200 mg, metoprolol 500 mg and some other unknown sedative tablets in a suicide attempt. She was brought to the hospital after 3 hours of ingestion of these tablets. At the time of admission, she was conscious but drowsy, oriented and responding to verbal commands. Her vitals were as follows: heart rate 105 beats/min, blood pressure (BP) 70/50 mm Hg, and Spo2 97% at room air. Her cardiovascular and respiratory examinations were normal. The patient was initially managed with activated charcoal via nasogastric tube, normal saline infusion bolus, Inj. noradrenaline started at 0.1 μg/kg/min, and Inj. calcium gluconate. She was shifted to intensive care unit, and her BP continued to decrease. Inj. noradrenaline increased to 0.5 μg/kg/min, and Inj. adrenaline 0.5 μg/kg/min, Inj. vasopressin 5.8 U/h, and Inj. phenylephrine 14 μg/kg/min were also added. Calcium gluconate 10% infusion at 10 mL/h were also initiated. In spite of these aggressive medical managements, her BP never showed any improvement rather deteriorated rapidly. The patient was intubated considering her hemodynamic disturbances. Her arterial blood gas (ABG) showed severe metabolic acidosis with PH 7.10, and she went into severe vasoplegic state with very low urine output and low oxygen saturation. Transthoracic echocardiography showed very poor left ventricular function, normal functioning valves, and ejection fraction 20%. Chest Xray showed development of gross bilateral pulmonary oedema "Figure 1". Considering her failure to show any improvement for aggressive medical management, the decision was made to support the patient with VA ECMO. Peripheral VA ECMO established through right groin (fem-fem) cannulation with antigrade femoral cannulation for distal limb perfusion "Figure 3". The VA ECMO circuit consisted of Centrimag centrifugal pump (Abbott), Paragon (Chalice) ECMO oxygenator, 23F venous cannula in the right femoral vein, 19F arterial cannula in the right femoral artery, and 6F arterial cannula in the same artery distally for distal lower limb perfusion "Figure 2 and 3". The flow was

Table-I

Laboratory values on ECMO

Days	Hb (g/dl)	TLC (cells/mm^3)	Platelets (thous/mm^3)	Na (mEq/L)	K (mEq/L)	Urea (mg/dl)	Creatinine (mg/dl)
1	15.2	26,500	450	150	3.5	7.5	1.4
2	12.3	22,000	250	144	3.8	9.0	1.2
3	12.5	15,100	200	143	4.0	11.0	0.8



Fig.-2: *ECMO Console with Centrimag Pump head*



Fig.-3: *Right Groin Cannulation (fem-fem) with*

maintained at 3.8 L/min and sweep gas flow rate of 2.5 L/min with Fio2 80%. Activated clotting time was maintained between 180 and 200 seconds with heparin infusion, and the patient was ventilated with synchronous intermittent mandatory ventilation (SIMV) mode with tidal volume 200 mL, respiratory rate10 breaths/min, positive end-expiratory pressure 5 mm Hg, and Fio2 40%. She was supported with VA ECMO for 3 days, and vasopressors and inotropes were gradually weaned with ongoing VA ECMO support. Her laboratory values were shown in "Table 1". On third day after initiating VA ECMO, repeat ECHO showed improved LVEF to 55%, Chest Xray improved (Figure 1) and she was successfully weaned from VA ECMO and decannulated. Then after another two days, she was weaned from ventilator and extubated. She was discharged on 15th day, and follow-up after 1 month showed favorable outcome.

Discussion:

CCB and beta blocker overdose can cause serious mortality and morbidity. Half-life of amlodipine and metoprolol are 34 to 50 hours, 3 to 7 hours respectively.[3] The overdose of these drugs can cause profound refractory hypotension, bradyarrhythmias, and shock. The combination of these drugs may blunt the sympathetic and vasoconstrictive responses and worsen CCB toxicity.[4] These drugs are not dialyzable because they are highly protein bound with large volume of distribution.[5]

The medical management of CCB drug overdose includes general and specific measures. General measures include stomach wash via nasogastric tube with activated charcoal. Special measures include administration of vasoconstrictors, intravenous calcium gluconate, Inj. glucagon that acts by increasing intracellular cyclic adenosine monophosphate (cAMP). Hyperinsulinemia-euglycemia therapy involves infusion of high dose of insulin along with 25% dextrose to maintain euglycemia. Insulin has positive inotropic action, increases plasma levels of ionized calcium, and improves the myocardial use of carbohydrates instead of free fatty acids.[6] Lipid emulsion forms an expanded lipid phase in blood and helps in redistribution and trapping of tissue bound drug.[7] Methylene blue helps in scavenging the nitric oxide.[8]

In this patient, all these drugs were used except glucagon and methylene blue because of non-availability of the drug and these medical managements did not show any improvement.

Toxicology consultation has shown that ECMO is still rarely used in poisoned patients; 10 out of 26,271 patients were reported over a 3-year period.[9] Because this patient did not show any improvement to medical management, along with refractory shock and impending acute renal and respiratory failure, the authors decided to go ahead with VA ECMO. The goal of the VA ECMO was to temporarily support the hemodynamics and respiration until the drug got metabolized from her body. Even though ECMO has disadvantages such as not readily available and high cost, it can be a lifesaving intervention when medical management fails.

Conclusion:

When medical therapy is ineffective for cardiotoxic drug overdose, ECMO may be a lifesaving intervention.

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