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INSTRUCTION TO AUTHORS

A. Introduction

Bangladesh Heart Journal is the official journal of Bangladesh Cardiac Society, and accepts articles for publication from home and abroad. This is a biannual, peer-reviewed journal and aims to publish work of the highest quality from all sub-specialties of cardiology and cardiovascular surgery. The aim of the publication is to promote research in Bangladesh and serve as platform for dissemination of scientific information in cardiology.

B. Categories of Articles

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

Original Research:

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. Three 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). Numberof references should be limited to 50.

Review Articles:

Generally review articles are by invitation only. But unsolicited reviews will be considered for publication on merit basis. Following types of articles can be submitted under this category: Newer drugs, new technologies and review of a current concept.The manuscript should not exceed 5000 words (including tables and figures). A review article should include an abstract of up to 250 words describing the need and purpose of review,methods used for locating, selecting, extracting and synthesizing data, and main conclusions. The number of references should be limited to 50.

Case Reports:

Only case reports of exceptional quality will be published in the case report format. The text should not exceed 1500 words and is arranged as introduction, case report and discussion. Include a brief abstract of about 150 words. Number of tables/figures should be limited to 3. Include up to 10 most recent references. The patient's written consent, or that of the legal guardian, to publication must be obtained.

Cardiovascular Images:

Only clinical photographs with or without accompanying skiagrams, pathological images, echocardiographic images, angiographic images etc. are considered for publication. Image should clearly identify the condition and have the classical characteristics of the clinical condition. Clinical photographs of condition which are very common, where diagnosis is obvious, or where diagnosis is not at all possible on images alone would not be considered. Photographs should be of high quality, usually 127 × 173 mm (5 × 7 in) but no larger than 203 × 254 mm (8 × 10 in). A short text of up to 250 words depicting the condition is needed. Figures should be placed exactly at a logical place in the manuscript. The submitted images should be of high resolution (>300 dpi). The following file types are acceptable: JEPG and TIFF. The number of authors should not exceed 3. The authors should ensure that images of similar nature have not been published earlier. Authors must obtain signed informed consent from the patient, or the legal guardian.

Letter to the Editor:

Letters commenting upon recent articles in Bangladesh Heart Journal are welcome.Such letters should be received within 16 weeks of the article's publication. Letters should be up to 250 words; should contain no more than 1 figure/table and upto 5 most recent references. The text need not be divided into sections. The number of authors should not exceed 3.

C. Criteria for Acceptance

All manuscripts should meet the following criteria: the material is original, study methods areappropriate, data are sound, conclusions are reasonable and supported by the data, and the information is important; the topic has general cardiology interest; and that the article is written in reasonably good English. Manuscripts which do not follow the guidelines of Bangladesh Heart Journal are likely to be sent back to authors without initiating the peer-review process. All accepted manuscripts are subject to editorial modifications to suit the language and style of Bangladesh Heart Journal and suggestions may be made to the authors by the Editorial Board to improve the scientific value of the journal.

D. Editorial Process

The Bangladesh Heart Journal commits to high ethical and scientific standards. Submitted manuscripts are considered with the understanding that they have not been published previously in print or electronic format (except

in abstract or poster form) and are not under consideration by another publication or electronic medium. Statements and opinions expressed in the articles published in the Journal are those of the authors and not necessarily of the Editor. Neither the Editor nor the Publisher guarantees, warrants, or endorses any product or service advertised in the Journal. Bangladesh Heart Journal follows the guidelines on editorial independence produced by the International Committee of Medical Journal Editors (ICMJE). All manuscripts correctly submitted to the Bangladesh Heart Journal are first reviewed by the Editors. Manuscripts are evaluated according to their scientific merit, originality, validity of the material presented and readability. Some manuscripts are returned back to the authors at this stage if the paper is deemed inappropriate for publication in the Bangladesh Heart Journal, if the paper does not meet the submission requirements, or if the paper is not deemed to have a sufficiently high priority. All papers considered suitable by the Editors for progress further in the review process, undergo peer review by at least two reviewers. If there is any gross discrepancy between the comments of two reviewers, it is sent to a third reviewer. Peer reviewers' identities are kept confidential; authors' identities are also not disclosed to the reviewers. Accepted articles are edited, without altering the meaning, to improve clarity and understanding. Decision about provisional or final acceptance is communicated within 8 weeks.

E. Cover Letter

The cover letter should outline the importance and uniqueness of the work. It should include the signed declaration from all authors on:

1. Category of manuscript (original research, review article, case report, cardiovascular image, letter to the Editor)
2. Statement that the material has not been previously published or submitted elsewhere for publication (this restriction does not apply to abstracts published in connection with scientific meetings.)
3. Transfer of copyright to the Bangladesh Heart Journal upon the acceptance of the manuscript for publication
4. All authors have reviewed the article and agree with its contents
5. Information of any conflicts of interest (of any) of the authors.
6. Sources of research support, if any, including funding, equipment, and drugs.

The cover letter should also include the mailing address, telephone and fax numbers, and e-mail address of the corresponding author.

F. Manuscript Preparation

The manuscripts should comply with the prescribed guidelines. It should be well organized and written in simple and correct English under appropriate headings. The abbreviations and acronyms should be spelled out when they occur first time.

The Introduction should address the subject of the paper. The Methods section should describe in adequate detail the laboratory or study methods followed and state the statistical procedures employed in the research. This section should also identify the ethical guidelines followed by the investigators with regard to the population, patient samples or animal specimens used. A statement should be made, where applicable, that their study conforms to widely accepted ethical principles 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.

a. Title page information

- Title. Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations where possible.
- Author names and affiliations. Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower case superscript letter immediately after the author's name and in front of the appropriate address. Provide the e-mail address of each author.
- Corresponding author. Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.

b. Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. References should be avoided. Also, non-standard or uncommon abbreviations should be

avoided, but if essential they must be defined at their first mention in the abstract itself.

c. Keywords

Immediately after the abstract, provide a maximum of 5 keywords. Keywords should be the listed terms in the Medical Subject's Headings (MeSH) of the National Library of Medicine (NLM), available at https://www.nlm.nih.gov/mesh.

d. Abbreviations

Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

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.

g. Figures and graphics

- For graphics, a digital picture of 300 dpi or higher resolution in JPEG or TIFF format should be submitted.
- Figures should be numbered consecutively according to the order in which they have been first cited in the text, if there is more than 1 figure. Each figure should be cited in the text.
- Each figure/illustration should be provided with a suitable legend that includes enough information to permit its interpretation without reference to the text.
- All photomicrographs should indicate the magnification of the prints.
- When symbols, arrows, numbers or letters are used to identify parts of the illustrations, each one should be explained clearly in the legend.

h. Tables

Tables should be placed next to the relevant text in the article.

- Number tables consecutively in accordance with their appearance in the text. Each table should be cited in the text in Arabic numerals.
- Titles should be brief and a short or abbreviated heading for each column should be given.
- Explanatory matter should be placed in footnotes and not in the heading.
- Abbreviations in each table should be explained in footnotes.
- The data presented in a table should not be repeated in the text or figure.

i. References

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (ICMJE recommendations), available at: http://www.icmje.org/recommendations/. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journals that are not indexed should be written in full.

- References should be numbered consecutively in the order in which they are first mentioned in the text.
- References in text, tables and legends should be identified by superscript Arabic numerals at the end of the sentence outside any punctuation. If several different studies or papers are cited within one sentence, the number should be placed where it will accurately identify the correct study.
- The names of authors in the text should concur with the reference list.
- References cited only in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.
- 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).
- In general: All authors/editors should be listed unless the number exceeds six, when you should give six followed by "et al."

Examples of correct forms of references are given below:

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;42Suppl 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;66Suppl 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. ProcNatlAcadSci 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

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.

Article with document number in place of traditional pagination:

Williams JS, Brown SM, Conlin PR. Videos in clinical medicine.Blood-pressure measurement. N Engl J Med. 2009 Jan 29;360(5):e6. PubMed PMID: 19179309.

Article with a Digital Object Identifier (DOI):

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: PMC2615549.

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/.

G. Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The submission has not been previously published elsewhere, is original and has been written by the stated authors.
2. The article is not currently being considered for publication by any other journal and will not be submitted for such review while under review by the Bangladesh Heart Journal.
3. The submission file is in Microsoft Word file format, and the figures are in JEPG or TIFF format.
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.

H. Submission

Papers should be submitted to the Editor. Three copies of manuscript should be submitted duly signed by all authors with a copy of CD, to:

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House No. 17, Road No 8, Dhanmondi, Dhaka 1205
Bangladesh.

Papers can also be submitted via the email using the following address:

Email: bangladeshheartj@yahoo.com

Original Article

Obesity Paradox in Short-Term Clinical Outcomes After Percutaneous Coronary Interventions

Mohammad Khalilur Rahman Siddiqui[1], Pradip Kumar Karmakar[2], Nur Alam[3], Md. Mizanur Rahman[4], Pranob Karmaker[5], Mohammad Morshedul Ahsan[6], Anup Kumar Howlader[7], Fahdia Afroz[8], Chowdhury Md. Kudrat-E-Khuda[9], Abhijit Roy[10]

Abstract

Background: The "obesity paradox", a counterintuitive decrease in morbidity and mortality with increasing body mass index (BMI), has been shown in patients when acute cardiovascular decompensation occurs. However, whether this phenomenon exists in patients undergoing percutaneous coronary intervention (PCI) is not well known. The existence of obesity paradox and its impact on short-term clinical outcomes after PCI have not been thoroughly investigated, especially in Bangladesh.

Methods: This cross-sectional observational study was conducted at National Institute of Cardiovascular Diseases, Dhaka, in 100 patients who underwent PCI. They were divided in two groups on the basis of BMI of Asian ethnicity: Group I (BMI < 23 kg/m^2) and Group II (BMI ≥23.0 kg/m^2). Short-term in-hospital outcomes after PCI were observed and recorded.

Results: Acute left ventricular failure (LVF) was found to be statistically significant between groups (p < 0.01) being higher in Group-I. The difference of mean duration of hospital stay (LOS) after PCI was higher in the same group which was statistically significant (p < 0.01). Diabetes mellitus and dyslipidemia were found to be the independent predictors for developing adverse in-hospital outcome (OR= 1.68 and 1.46; 95% CI = 1.25 – 2.24 and 1.16 – 1.83; p = 0.018 and 0.040, respectively). BMI was inversely associated with in-hospital outcomes after PCI (OR = 0.95; 95% CI = 0.91 – 0.98; p = 0.007).

Conclusion: The results of the study uphold the phenomenon of the "obesity paradox" following PCI. The underweight and normal weight people are at greater risk to experience short-term in-hospital adverse clinical outcomes than overweight and obese people after PCI.

Key words: *obesity paradox, reverse epidemiology, percutaneous coronary interventions*

(Bangladesh Heart Journal 2021; 36(1): 1-8)

Introduction:

The relationship of obesity with cardiovascular disease and mortality in general population was found to be existing in a good number of epidemiological studies.[1–4] At present, the conventional way to categorize obesity is

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by the body mass index (BMI).[5] BMI, also known as the Quetelet index [i.e., ratio of weight (kg) to height squared (m^2)] and other adjusted measures of weight (such as for height) are the commonly used parameters to quantify changes in body mass adjusted for height, and the association between body mass and outcome.[4,6] In some studies of normal adults, a J or U curve effect has been observed in which those individuals with a low BMI also demonstrated an increased mortality, although not as high as obese individuals.[1,2,7] The term ''obesity paradox'' refers to the observations that, although obesity is a major risk factor in the development of cardiovascular and peripheral vascular disease, when acute cardiovascular decompensation occurs, for example, in myocardial infarction or congestive heart failure, obese patients may have a survival benefit.[8]

This counterintuitive discovery in the relationship between obesity and various clinical issues, explained by the existence of obesity paradox, is denoted as "reverse epidemiology" by some authors. The concept of reverse epidemiology appears at first to be confusing, especially because hypertension, obesity, and high levels of serum cholesterol, creatinine, and homocysteine are established risk factors for ischemic heart disease in the general population.[9] All these traditional risk factors of a poor clinical outcome and mortality in the general population are also found to be related to various outcomes but in an opposite direction.[10] The paradox becomes even more paramount when it is recognized that it is not a question of the existence or lack of an association between these risk factors and the clinical outcomes, but often the complete reversal and indeed the opposite direction of this relationship.[9]

Despite marked disparity in values, there seems to be a rising prevalence of coronary artery disease (CAD) in Bangladesh.[11] Globally, 30% of all deaths can be attributed to cardiovascular disease, of which more than half are caused by CAD.[12] With the combination of sophisticated equipment, experienced operators, and modern drug therapy, coronary angioplasty has evolved into an effective nonsurgical modality for treating patients with CAD.[13] The number of PCIs is expected to grow modestly (1% to 5%) over the next decade as a result of the aging population and an increased frequency of diabetes and obesity.[14]

Institute for Health Metrics and Evaluation at University of Washington reported 17% of adults of Bangladesh as overweight or obese.[12] The complex interplay between abdominal obesity and insulin resistance appears to be a prime candidate in explaining this excess cardiovascular risk of South Asian people. The recognition and adoption of ethnic-specific BMI cutoffs represent a major step forward in refining risk stratification in different ethnic groups, including South Asians.[15,16] There are limited data, however, on the relationship of BMI as a prognostic risk factor for outcomes following revascularization procedures such as PCI.[17]

Methods

In the Department of Cardiology, National Institute of Cardiovascular Diseases and Hospital, Dhaka, this cross-sectional observational study was conducted, and by purposive sampling technique total 100 patients who underwent PCI were selected. Study subjects were divided on the basis of their BMI in accordance with Asian ethnicity into two equal groups each containing 50 patients: Group I (BMI<23 kg/m^2) and Group II (BMI ≥23.0 kg/m^{-2}). Patients with chronic kidney diseases, chronic liver disease, chronic obstructive pulmonary disease, valvular heart disease, congenital heart disease, cardiomyopathy, previous history of revascularization were excluded from the study. Patients undergoing primary PCI, transradial interventions were not included, also. No ethical violation was made in conducting the study.

After having matched the inclusion and exclusion criteria the patients were selected for this study. Weight and height were measured and recorded in all participants by a standard medical scale and stadiometer, respectively. Self-reported weight or height was not accepted. BMI was calculated, categorized and recorded accordingly. PCI was done by transfemoral approach. Following PCI patients were monitored at Coronary Care Unit for at least 24 hours. Post-PCI development of in-hospital left ventricular failure along with common adverse outcomes were observed and recorded, i.e., bleeding, stroke, vascular access site complications, post-PCI ischemic chest pain, myocardial infarction with PCI, significant arrhythmia, acute stent thrombosis, repeat revascularization, contrast induced nephropathy, cardiogenic shock, cardiovascular death.

To adjust for the potential confounders in predicting the association between BMI and in-hospital outcomes, logistic regression analysis was performed. Univariate logistic regression analysis was performed to specify the odds ratio (OR) for overall adverse in-hospital outcomes. Multivariate logistic regression analysis was then performed by using SPSS 23.0 to investigate independent predictors for adverse in-hospital outcomes. Variables yielding p values ≤0.05 in univariate analysis were selected for multivariate model. Statistical significance was assumed if p≤0.05 throughout the study.

Results:

Out of 100 studied patients 84% were male and 16% were female. Male to female ratio was 4.5:1. No significant association (p>0.05) was found between the groups in terms of sex distribution. The mean age of the patients was 51.1 ± 9.57 years and the mean age difference between two groups was not statistically significant (p>0.05). In both of the groups the highest percentages of patients were in the age range of 41-50 years (Table-I).

Table II shows that among the different risk factors dyslipidemia, hypertension and diabetes mellitus were significantly more in group II (<0.05). The other risk factors i.e., smoking and family history of CAD were not significantly different between the groups (p >0.05).

The difference of means of height was insignificant (p>0.05) across the groups. But that of weight was found to be significant (p=0.001). BMI was significantly (p=0.001) higher in group II than group I. The

Table - I

Comparison of the study groups by their demographic characteristics (N = 100).

Age in years	BMI				Total (N =100)		p-value
	Group I (n = 50)		Group II (n = 50)				
	Number	%	Number	%	Number	%	
≤40	4	8.0	5	10.0	9	9.0	[a]0.11[NS]
41-50	23	46.0	25	50.0	48	48.0	
51-60	17	34.0	14	28.0	31	31.0	
> 60	6	12.0	6	12.0	12	12.0	
Mean ± SD	51.2 ± 11.4	50.9 ± 9.1	51.1 ± 9.57	[b]0.91[NS]			
Sex							
Male	43	86.0	41	82.0	84	84.0	[a]0.92[NS]
Female	7	14.0	9	18.0	16	16.0	

Group I = Patients with BMI <23 kg/m^2
Group II = Patients with BMI ≥23 kg/m^2
NS= Not Significant (p>0.05)
[a]p-value reached from chi-squared (χ^2) test and Fisher exact test
[b]p-value reached from unpaired t-test

Table-II

Comparison of the study groups according to their risk factors (N=100)

Risk factors	BMI				Total (N =100)		p-value
	Group I (n = 50)		Group II (n = 50)				
	Number	%	Number	%	Number	%	
Smoking	20	40.0	24	48.0	44	44.0	0.587[NS]
DM	9	18.0	21	42.0	30	30.0	0.038[S]
Hypertension	11	22.0	23	46.0	34	34.0	0.048[S]
Dyslipidemia	7	14.0	20	40.0	27	27.0	0.022[S]
Family history of CAD	14	28.0	14	28.0	28	28.0	0.931[NS]

Group I = Patients with BMI < 23 kg/m^2
Group II = Patients with BMI ≥23 kg/m^2
DM = Diabetes Mellitus
CAD = Coronary Artery Disease
S = Significant (p< 0.05)
NS = Not Significant (p > 0.05)
p-value reached from chi-squared (χ^2) test

breakdown of total patient would be 81 in Group I and 19 in Group II with statistically significant difference (p = 0.001) of mean BMI across the group had their conventional non-Asian BMI cut-off value been used (Table III).

The difference of means of height between the two sex groups was significant (p=0.001). The difference of means of weight across these groups was also significant (p<0.01). BMI was higher in female patients than in male but the difference between them was not statistically significant in any group (p>0.05) (Table IV).

Table V compares the distribution of clinical presentations between the groups. The percentage of STEMI was the highest in both groups. No statistically significant difference was noted between the two groups (p > 0.05).

Table VI shows that the baseline LV function measured by echocardiography between the two study groups was not statistically significant (p > 0.05). The difference of mean LVEF was also insignificant statistically (p > 0.05) between the groups. Post-PCI echocardiography to assess LV function was not done routinely.

Table VII shows that the difference of mean length of hospital stay was statistically significant (p < 0.01). The difference of frequency distributions of the patients in this two study groups according to hospital stay time was also significant (p < 0.05).

The adverse in-hospital outcomes were significantly (p<0.01) higher in Group I than Group II. Among all adverse in-hospital outcomes, only acute LVF was found to be statistically significant between the two study groups (p< 0.01) (Table VIII).

Table – III

Comparison of the study groups by their height, weight and BMI (N=100).

Parameters	BMI		Total(N =100)	*p*- value
	Group I (n = 50)	Group II (n = 50)		
	Mean ± SD	Mean ± SD	Mean ± SD	
Height(in meter)	1.61 ± 0.07	1.63 ± 0.06	1.62 ± 0.06	0.26^{NS}
Weight(in kilogram)	55.5 ± 5.5	65.7 ± 5.9	63.4 ± 7.2	0.001^{S}
BMI cutoff value 23 kg/m^2	21.3 ± 1.4	24.7 ± 1.4	23.9 ± 1.9	0.001^{S}
	*Group I (n=81)	*Group II (n= 19)		
BMI cutoff value 25 kg/m^2	23.3 ± 1.5	26.7 ± 1.3	23.9 ± 1.9	0.001^{S}

Group I = Patients with BMI <23 kg/m^2
Group II = Patients with BMI ≥23 kg/m^2
* = Had non-Asian BMI category been used in this study
S= Significant (p<0.05)
NS= Not Significant (p>0.05)
p-value reached from unpaired t-test

Table – IV

Comparison of height, weight and BMI within each study groups by sex of the patients (N = 100).

Study group	Male (n= 84)		Female (n= 16)		Mean ± SD	*p*-value
	Number	Mean ± SD	Number	Mean ± SD	(N =100)	
Height in meter	84	1.64 ± 0.04	16	1.51 ± 0.06	1.62 ± 0.06	0.001^{S}
Weight in kilogram	84	64.5 ± 6.3	16	56.4 ± 8.6	63.4 ± 7.2	0.006^{S}
Group I(n = 50)	43	21.2 ± 1.4	7	21.9 ± 0.8		0.436^{NS}
Group II(n = 50)	41	24.6 ± 1.3	9	25.3 ± 1.9		0.169^{NS}
	84	23.9 ± 1.9	16	24.5 ± 2.3	23.9 ± 1.9	0.294^{NS}

Group I = Patients with BMI <23 kg/m^2, Group II = Patients with BMI ≥23 kg/m^2.
S= Significant (p<0.05)
NS= Not Significant (p>0.05)
p-value reached from unpaired t-test

Smoking and family history of CAD were not included in multivariate model as univariate analysis yielded them as statistically insignificant in the current study (OR = 1.29 and 1.10; 95% CI = 0.82– 1.78 and 0.46 – 1.75; *p*=0.273 and 0.087, respectively). Hypertension and left ventricular ejection fraction (LVEF) that were significant (OR = 1.51 and 1.53;95% CI = 1.05 – 2.10 and 1.32 – 1.78; *p*=0.026 and 0.049, respectively) in univariate analysis were found to be insignificant (OR = 1.36 and 1.15; 95% CI = 0.92 – 1.95 and 0.98 – 1.35; *p*=0.114 and 0.087, respectively) in multivariate regression analysis. Diabetes mellitus and dyslipidemia were found to be the independent predictors for developing adverse in-hospital outcome after PCIs (OR= 1.68 and 1.46; 95% CI = 1.25 – 2.24 and 1.16 – 1.83; *p*=0.018 and 0.040, respectively). BMI was inversely associated with adverse in-hospital outcome after adjustment by multivariate logistic regression analysis (OR = 0.95; 95%CI = 0.91–0.98; *p*=0.007) (Table IX).

Table-V

Comparison of the study population by clinical presentations (N = 100)

Diagnosis	BMI				Total (N =100)		*p*-value
	Group I (n = 50)		Group II (n = 50)				
	Number	%	Number	%	Number	%	
CSA	6	12.0	5	10.0	11	11.0	0.27^{NS}
UA	6	12.0	7	14.0	13	13.0	
NSTEMI	9	18.0	11	22.0	20	20.0	
STEMI	29	58.0	27	54.0	56	56.0	

Group I = Patients with BMI < 23 kg/m^2
Group II = Patients with BMI ≥23 kg/m^2
CSA = Chronic Stable Angina
UA = Unstable Angina
NSTEMI = Non-ST-segment Elevation Myocardial Infarction
STEMI = ST-segment Elevation Myocardial Infarction
NS = Not Significant (*p* >0.05)
p-value reached from chi-squared (χ^2) test

Table-VI

Comparison of the study groups according to their LVEF (N = 100)

LVEF	BMI				Total (N =100)		*p*-value
	Group I (n = 50)		Group II (n = 50)				
	Number	%	Number	%	Number	%	
<50	23	46.0	29	58.0	52	52.0	$^{a}0.79^{NS}$
>50	27	54.0	31	62.0	58	58.0	
Mean ± SD	53.4 ± 8.2		52.1 ± 8.1		53.3 ± 8.1		$^{b}0.69^{NS}$

Group I = Patients with BMI < 23 kg/m^2
Group II = Patients with BMI ≥23 kg/m^2
LVEF = Left Ventricular Ejection Fraction
NS = Not Significant (*p* > 0.05)
[a]*p*-value reached from chi-squared (χ^2) test
[b]*p*-value reached from unpaired t-test

Table-VII

Comparison of the study groups by length of hospital stay after PCI (N = 100)

Length of stay	BMI				Total (N =100)		*p*-value
	Group I (n = 50)		Group II (n = 50)				
	Number	%	Number	%	Number	%	
< 72 hours	27	54.0	36	72.0	63	63.0	[a]0.036[S]
72 - 96 hours	11	22.0	12	24.0	23	23.0	
> 96 hours	12	24.0	2	4.0	14	14.0	
Mean ± SD	70.9 ± 34.3		56.0 ± 16.7		59.3 ± 22.5		[b]0.005[S]

Group I = Patients with BMI < 23 kg/m^2
Group II = Patients with BMI ≥23 kg/m^2
S = Significant ($p < 0.05$)
[a]*p*-value reached from chi-squared (χ^2) test and Fisher exact test
[b]*p*-value reached from unpaired t-test

Table-VIII

Comparison of the study groups by in-hospital outcomes after PCI (N=100)

Length of stay	BMI				Total (N =100)		*p*-value
	Group I (n = 50)		Group II (n = 50)				
	Number	%	Number	%	Number	%	
Adverse outcomes	11	22.0	3	6.0	14	14.0	0.006[S]
Chest pain	2	4.0	1	2.0	3	3.0	0.630[NS]
Arrhythmia	2	4.0	0	0.0	2	2.0	0.058[NS]
Access site complications	1	2.0	1	2.0	2	2.0	0.630[NS]
Acute LVF	4	8.0	0	0.0	4	4.0	0.007[S]
Shock	2	4.0	0	0.0	2	2.0	0.058[NS]
Death	0	0.0	1	2.0	1	1.0	0.594[NS]

Group I = Patients with BMI < 23 kg/m^2
Group II = Patients with BMI ≥23 kg/m^2
S = Significant (p <0.05)
NS = Not Significant (p > 0.05)
p-value reached from chi-squared (χ^2) test and Fisher exact test

Table-IX

Univariate and multivariate logistic regression analyses of variables associated with adverse in-hospital outcomes.

Variables of interest	Univariate analysis		*p*- value	Multivariate analysis		*p*- value
	OR	95% CI of OR		OR	95% CI of OR	
Smoking	1.29	0.82 - 1.78	0.273			
Hypertension	1.51	1.05–2.10	0.026	1.36	0.92 – 1.95	0.114
Diabetes	1.97	1.61 – 2.41	0.011	1.68	1.25 – 2.24	0.018
Dyslipidemia	1.54	1.11 – 1.72	0.034	1.46	1.16 – 1.83	0.040
Family history	1.10	0.46 – 1.75	0.087			
LVEF	1.53	1.32 – 1.78	0.049	1.15	0.98 – 1.35	0.087
BMI	0.89	0.87 – 0.92	0.004	0.95	0.91 – 0.98	0.007

Discussions:

In the general population, obesity is associated with increased risk of adverse outcomes. However, studies of patients with chronic disease suggest that overweight and obese patients may paradoxically have better outcomes than lean patients.[8] A number of studies have shown that the lean patients and those with normal BMI are at a higher risk for adverse in-hospital outcomes and post-PCI complications than overweight and obese patients. This is contrary to the common clinical

perception that overweight and obese patients would be at a higher risk of adverse outcomes following PCI. This unexpected phenomenon was explained by "obesity paradox".[17] To date, there is not a complete understanding of this complex effect.

A number of studies have shown that lean patients (<20 kg/m^2) and those with normal BMI (20–24.9 kg/m^2) are at a higher risk for adverse in-hospital outcomes and post-PCI complications than overweight (25–29.9 kg/m^2) and obese (≥30 kg/m^2) patients.[17–19] In the current study, in-hospital adverse outcomes after PCI was significantly higher in Group I also. Compared with normal-weight individuals, overweight and obese patients had shorter mean length of hospital stay (LOS) after PCI. Among all the adverse in-hospital outcomes, only LVF was found to be significantly more in Group-I. A study on 1,203 individuals with class IV heart failure found that higher BMI was associated with better survival, and multivariate analysis showed an inverse association between BMI and mortality.[20] BMI was inversely associated with post-PCI adverse in-hospital outcome after adjustment by multivariate logistic regression analysis in this study. Gruberg et al. noticed that very lean patients (BMI <18.5) and those with normal BMI are at the highest risk for in-hospital complications and cardiac death.[17] Patients at the extremes of BMI (<18.5 and >40kg/m^2) were also at increased risk of adverse outcomes after PCI.[21] Park et al. found that low BMI was associated with increased risks of adverse in-hospital outcomes and death.[22] They also found no excess risks of these events to be associated with a high BMI. A Japanese real-world multicenter registry analysis reported that lean patients, rather than obese patients were at greater risk for in-hospital complications during and after PCI.[22] Although obesity via its negative impact on systolic and diastolic function predisposes to overt heart failure, clinical evidence suggests that overweight/obese patients with heart failure paradoxically seem to have a better clinical prognosis than do their lean counterparts with clinical heart failure. An analysis based on 43,334 maintenance hemodialysis (MHD) patients, also showed an improved survival in those with higher BMI values.[23]

Finally, in a study by Lavie et al., a cohort of 529 patients in a cardiac rehabilitation program was evaluated. Survival analysis demonstrated that 20 patients with a BMI of more than 35 had the lowest mortality risk.[24] This study further demonstrated that this relationship persisted with respect to body composition, whereby patients with the highest baseline percent body fat had a lower mortality risk when compared with patients with a normal baseline body fat (2.8% vs 10.6%, respectively). Fonarow and colleagues demonstrated a linear reduction in in-hospital mortality as the BMI increased.[25] His findings showed a 10% reduction in mortality for every 5-unit increase in BMI.[5] Even, obesity was associated with better coronary flow after percutaneous coronary intervention and the number of lesions was lower in obese patients compared to non-obese elderly patients treated for STEMI.[26]

In essence, obesity is a risk factor for developing cardiovascular diseases, insulin-resistant diabetes, etc.; but after the onset of complications, obesity is a positive predictor for survival in various instances. The existence of this obesity paradox has led physicians to question whether obesity should be treated when associated with adverse clinical outcomes.[20]

Conclusion:

The underweight and normal weight people were at greater risk to experience in-hospital adverse outcomes than overweight and obese people following PCI. Though obesity is a recognized risk factor for cardiovascular diseases, once cardiovascular disease is developed, this obesity seems to play protective roles and provide some benefits. This 'Obesity Paradox' leads us to the necessity of reshuffling and reorganizing our plans whether we should take aggressive attempts or schemes to lose weight of an obese patient once he or she develops coronary artery disease.

Limitations of the study

There are some facts to be considered which might have affected the result of the current study.

- The study population was heterogeneous, including patients with different severities of CAD, ranging from chronic stable angina to myocardial infarction.
- The complexity of the lesions, procedural complications, use of anticoagulants and antiplatelets were not recorded which might have affected the incidence of complications in each of the BMI groups.

Conflict of interest- None.

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Original Article

Association of Obesity and C-Reactive Protein with Coronary Artery Disease

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Abstract:

Background: Obesity is now becoming a global epidemic. It is most of the times associated with hypertension, diabetes mellitus (DM), metabolic syndrome and dyslipidemia which are known risk factors for coronary artery disease (CAD). Coronary arteriosclerosis comprises a series of inflammatory responses at cellular and molecular level, whose reactions are stronger in obese patients. The objective of this study was to observe the association of obesity and raised inflammatory markers with CAD.

Method: This cross-sectional study was carried out in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka, Bangladesh, involving 668 patients of ischemic heart disease who underwent coronary angiography (CAG) from January 2017 to December 2017. Obesity was defined as body-mass index (BMI) ≥30.0 kg/m². C-reactive protein (CRP) was measured as the inflammatory marker, and was considered as high if >10 mg/L. CAD was classified on the basis of CAG findings: insignificant if stenosis is <50% and significant if stenosis is ≥50%; and single-vessel, double-vessel, triple-vessel disease and normal coronaries according to number of vessels involved. Chi square test was used to analyze the categorical variables, and Pearson's correlation coefficient was used to test the relationship between CRP and BMI in CAD patients. p values of <0.05 were considered as statistically significant.

Results: Demographic characteristics like age, sex and educational status did not differ significantly between obese and non-obese patients. Risk factors for CAD were similar between obese and non-obese, as well as, between high-CRP (>10 mg/L) and non-high CRP (≤10 mg/L) groups, however, DM, hypertension and dyslipidaemia were significantly more common in obese and high-CRP groups than in non-obese and non-high CRP groups. Raised CRP was significantly more common in obese than in non-obese patients (56.9% vs. 47.9%, p=0.04). Significant positive correlation was found between CRP and BMI (r=0.228; p=0.001). Triple-vessel CAD was found significantly more commonly in obese group than in non-obese group (29.3% vs 24.4%, p=0.04), whereas normal coronaries were more common in non-obese than in obese counterpart. Obesity, high CRP (>10 mg/L), DM, and high HbA1c (≥6.5%) were found significant predictors of severe CAD (p <0.5) in multivariate logistic regression analysis.

Conclusion: Obesity is associated with raised inflammatory marker in patients with CAD, and a significant positive association exists between obesity and inflammation and CAD. Future studies are needed to explore the impact of type of obesity and inflammation on CAD.

Keywords: *Obesity, Body Mass Index, Inflammation, C-Reactive Protein, Coronary Artery Disease.*

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Introduction:

Ischaemic heart disease (IHD) or coronary artery disease (CAD) is an important cause of mortality and morbidity of Mankind, and is the leading cause of death over decades.[1,2] IHD affects around 126 million individuals (1,655 per 100,000), which is approximately 1.72% of the world's population. The current prevalence rate of IHD has been estimated to be 1,655 per 100,000 population is expected to exceed 1,845 by the year 2030.[1] Nine million deaths are caused by IHD globally.[1] On the other hand, IHD is the biggest killer, and accounts for 16% of the world's total deaths.[3] Since 2000, the largest increase in deaths has been for this disease, rising by more than 2 million to 8.9 million deaths in 2019.[3] A number of risk factors are now known to be associated with IHD, including diabetes mellitus (DM), hypertension, smoking, hyperlipidemia, obesity, homocystinuria, and psychosocial stress.[4] Among these, obesity is common, an important public health issue, and is currently considered as a global epidemic.[5] Its magnitude is on the rise. According to a systematic review of prevalence of overweight and obesity in children and adults during 1980-2013, the situation has worsened significantly in adults, as well as, in children, in developed, as well as, in developing countries.[6] Worldwide, the proportion of adults with a body-mass index (BMI) of ≥25 kg/m2 increased between 1980 and 2013 from 28·8% to 36·9% in men, and from 29·8% to 38·0% in women. Prevalence has increased substantially in children and adolescents in developed countries; 23·8% of boys and 22·6% of girls were overweight or obese in 2013. The prevalence of overweight and obesity has also increased in children and adolescents in developing countries, from 8·1% to 12·9% in 2013 for boys and from 8·4% to 13·4% in girls.

Obesity is now considered an independent risk factor of CAD.[7] The interplay between obesity, inflammation and CAD is complex, but important in the pathophysiology of CAD. Adipose tissue was traditionally thought to be metabolically inert, however, it is now known that fat, specially the abdominal fat is a highly active endocrine and paracrine organ It also secrets a number of biological molecules including the inflammatory mediators.[8] The proinflammatory cytokines released from the visceral fat of obese persons, e.g., tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), leptin and visfatin have a potential of causing atherosclerosis.[9] In obese individuals, macrophages first accumulate within the adipose tissue, leading to local inflammation. As the obesity increases, proinflammatory factors, including IL-1, IL-6 and TNF-±, are produced in the adipose tissue. Macrophage accumulation and the subsequent local inflammation result in systemic inflammation. Endothelial dysfunction occurs during the early stages of atherosclerosis and is responsible for the pathophysiological changes in subclinical atherosclerosis, which include changes in a variety of mediators, surface proteins, and in autacoids that are involved in vasomotion, coagulation and inflammation.[10-2] Obesity also can increase systemic oxidative stress independently of blood glucose and diabetes.[11] The association between obesity and clinically significant CAD is blatant in the Framingham Heart Study[13] and the Nurses' Health Study[14]. Each unit of change in BMI was associated with 9% increase in ischemic cardiac events in the Asia Pacific Cohort Studies Collaboration.[15]

C-reactive protein (CRP) is an acute-phase reactant, and also is one of the strongest markers of chronic inflammation. Besides diagnostic potential, it appears to have significant role in the aetiopathogenesis of coronary atherosclerosis.[16] More than 20 prospective epidemiologic studies have demonstrated that high-sensitivity CRP is an independent predictor of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death, even in apparently healthy individuals[17,18] On the other hand, CRP mRNA has been shown to be expressed in human adipose tissue, indicating that adipose tissue may be an important source of circulating CRP.[19] Two recent studies have demonstrated that exercise training in conjunction with weight reduction significantly affected the CRP levels, body composition, and human left ventricular growth.[20,21]

Both CAD and obesity are common public health issues in Bangladesh. Like other South Asians, Bangladeshis appear unduly prone to develop CAD, which is often premature in onset, follows a rapidly progressive course and angiographically more severe.[22] On the other hand, according to the 2011 Bangladesh Demographic and Health Survey, the prevalence of overweight and obesity in adults aged 35–70 years was 18.9% (male 17.4% and female 18.4%) and 4.6% (male 3.0% and female 6.0%) respectively.[23] Like many other aspects, the relationship between obesity, inflammation and CAD in Bangladeshi ethnicity has not been adequately studied.

Methods:

This cross-sectional study was carried out in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka, Bangladesh, involving 668 patients of ischemic heart disease who underwent coronary angiography (CAG) from January 2017 to December 2017. Patients with infections, connective tissue disease and trauma were excluded. Also, patients with secondary

obesity like hypothyroidism were excluded. The patients' demographic variables, such as age, sex, waist and hip circumferences were recorded, and body-mass index (BMI) was calculated. BMI of ≥30.0 kg/m^2 was considered as obese.[24] Blood samples were collected for investigation before CAG. In this study, CRP was measured to assess inflammatory activity. CRP was assayed by turbidimetric assay using Beckman Coulter, model AU480 (250 S. Kraemer Blvd. Brea, CA 92821, USA). CRP values were divided into normal (<6 mg/L), borderline (6-10 mg/L) and high (>10 mg/L).[25] CAG was done as per institutional protocol, and CAG was analyzed by 2 independent interventional cardiologists. CAD was classified on the basis of CAG findings: insignificant if stenosis is <50% and significant if stenosis is ≥50%; and single-vessel, double-vessel, triple-vessel disease and normal coronaries according to number of vessels involved.

Categorical variables were expressed as proportions (percentages) and numerical data were expressed as mean (standard deviation) and range. Chi square test was used to analyze the categorical variables, and Pearson's correlation coefficient was used to test the relationship between CRP and BMI in CAD patients. Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows was used to analyze the data. p values <0.05 were considered as statistically significant.

The study was approved by the Ethical Review Board of Dhaka Medical College. Written informed consent was provided by the participants. Data were collected and analyzed by the investigators.

Results:

In the present cross-sectional study, almost 2/3rds (65.0%) of the patients belonged to age group 41-60 years. The mean age was 51.4±10.7 years, ranging from 25-85 years. Majority (82.3%) of the study patients were male. Among the risk factors, hypertension was the commonest (40.0%), followed by DM (31.3%), smoking (30.5%), history of IHD (28.3%) and dyslipidemia (22.6%). Demographic characteristics like age, sex and educational status did not differ significantly between obese and non-obese patients. (Table I) Risk factors for CAD were similar between obese and non-obese, however, DM, hypertension and dyslipidaemia were significantly more common in obese group than in non-obese group. (Table 2). In the present study, raised CRP was significantly more common in obese than in non-obese patients (56.9% vs. 47.9%, p=0.04), (Table 3) and a significant positive correlation was found between CRP and BMI (r=0.228; p=0.001) (Figure 1). Again, risk factors for CAD were similar between high-CRP (>10 mg/L) and non-high CRP (≤10 mg/L) groups, however, DM, hypertension and dyslipidaemia were significantly more common in high-CRP group than in non-high CRP group. (Table 4) Triple-vessel CAD was found significantly more commonly in obese group than in non-obese group (29.3% vs 24.4%, p=0.04). (Figure 2) Obesity, high CRP (>10 mg/L), DM, and high HbA1c (≥6.5%) were found significant predictors of severe CAD (p <0.5) in multivariate logistic regression analysis (Table V).

Most (65.0%) of the patients belonged to age 41-60 years. The mean age was found 51.4±10.7 years with range

Table-I

Association between obesity and demographic characteristics (N=668)

Demographic characteristics	Obesity		p value
	Yes (n=58)n (%)	No (n=610) n (%)	
Mean age (years)	49.8±12.0	51.5±10.6	0.249^{ns}
Range (min-max)	28-76	25-85	
Sex			
Male	45 (77.6)	505 (82.8)	0.321^{ns}
Female	13 (22.4)	105 (17.2)	
Educational status			
Illiterate	39 (67.2)	351 (57.5)	
Primary	7 (12.1)	103 (16.9)	
Secondary	5 (8.6)	106 (17.4)	0.261^{ns}
Higher	4 (6.9)	33 (5.4)	
Graduate and above	3 (5.2)	17 (2.8)	

Data were analyzed by chi-square test and unpaired t-test, ns= not significant

from 25-85 years. Majority (82.3%) patients were male and 390 (58.4%) patients were illiterate. In risk factors, highest 267 (40.0%) patients had hypertension followed by 209 (31.3%) diabetes mellitus, 204 (30.5%) smoker, 189 (28.3%) H/O ischemic heart disease, 151 (22.6%) dyslipidemia and 58 (8.7%) obesity. Mean age was little bit lower in obese group than non obese (49.8±12.0 vs 51.5±10.6 years), female patients were higher in obese group than non obese (22.4% vs 17.2%) but these results were not statistically significant (p>0.05) (Table I). Among the risk factors, diabetes mellitus, hypertension and dyslipidemia were found significantly higher in obese group than non obese (Table I). High CRP was found higher in obese than non obese (56.9% vs 47.9%) (Table III). Positive correlation (r= 0.228; p=0.001) was found between CRP and BMI (Figure 1). Among the risk factors, diabetes mellitus, hypertension and dyslipidemia were found significantly higher in high CRP group than normal and borderline group (Table IV). Triple vessel CAD was found significantly higher in obese group than non obese (29.3% vs 24.4%) and normal CAD was found significantly higher in non obese group than obese (Figure 2). Multi variable logistic regression was found high HbA1c, high CRP, diabetes mellitus and obesity were statistically significant (p<0.05) in severe CAD (Double and triple vessel) patient (Table V).

Table-II

Association between obesity with clinical risk factors (n=668)

Risk factor	Obesity		p value
	Yes (n=58)n (%)	No (n=610) n (%)	
Diabetes mellitus	41 (70.7)	168 (27.5)	0.001^{s}
Hypertension	32 (55.2)	235 (34.5)	0.013^{s}
Dyslipidemia	20 (34.5)	131 (21.5)	0.024^{s}
Smoking	22 (37.9)	182 (29.8)	0.200^{ns}
Smokeless tobacco	12 (20.7)	85 (13.9)	0.163^{ns}
Alcohol	1 (1.7)	1 (0.2)	0.166^{ns}
Family history of CAD	5 (8.6)	26 (4.3)	0.121^{ns}
H/o ischemic heart disease	19 (32.8)	170 (27.9)	0.429^{ns}
Previous PTCA	2 (3.4)	9 (1.5)	0.246^{ns}
Previous CABG	1 (1.7)	9 (1.5)	0.599^{ns}

Data were analyzed by chi-square test, s= significant, ns= not significant

Table-III

Association between obesity and CRP of the study population (N=668)

CRP	Obesity		p value
	Yes (n=58) n (%)	No (n=610) n (%)	
Normal (<6 mg/L)	0 (0.0)	56 (9.2)	
Borderline (6-10 mg/L)	25 (43.1)	262 (43.0)	0.045^{s}
High (>10 mg/L)	33 (56.9)	292 (47.9)	

Data were analyzed by chi-square test, s= significant

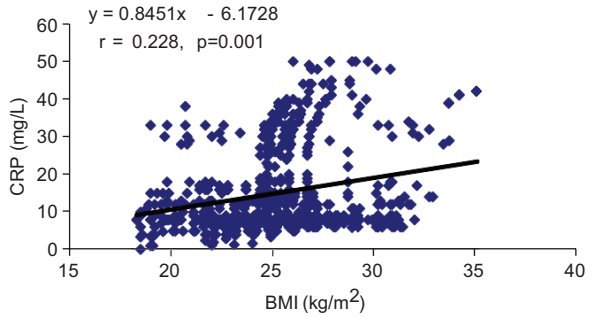

Fig.-1: *Scatter diagram showing correlation between CRP and BMI.*

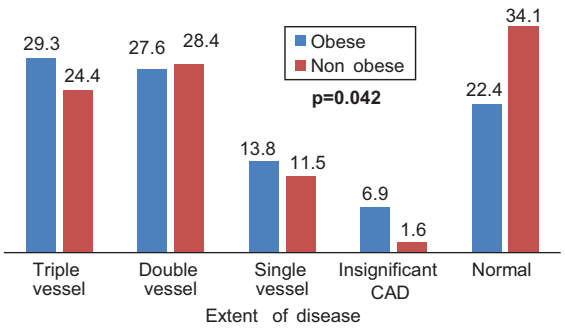

Fig.-2: *Bar diagram showing obesity and extent of coronary artery disease of the study population*

Table-IV

Association between CRP and clinical risk factors (N=668)

Risk factor	CRP		p value
	High (>10 mg/L) (n=325)n (%)	Not high (≤10 mg/L) (n=343)n (%)	
Diabetes mellitus	149 (45.8)	60 (17.5)	0.001^{s}
Hypertension	146 (51.1)	121 (29.4)	0.011^{s}
Dyslipidemia	88 (27.1)	63 (18.4)	0.048^{s}
Smoking	101 (31.1)	103 (30.0)	0.769^{ns}
Smokeless tobacco	50 (15.4)	47 (13.7)	0.537^{ns}
Alcohol	1 (0.3)	1 (0.3)	0.737^{ns}
Family history of CAD	16 (4.9)	15 (4.4)	0.736^{ns}
H/o ischemic heart disease	99 (30.5)	90 (26.2)	0.226^{ns}
Previous PTCA	6 (1.8)	5 (1.5)	0.693^{ns}
Previous CABG	6 (1.8)	4 (1.2)	0.343^{ns}

Data were analyzed by chi-square test, s= significant, ns= not significant

Table-V

Multivariable logistic regression analysis for severe CAD

	Adjusted	95% CI		P
	OR	Lower	Upper	Value
HbA1c (≥6.5)	0.261	0.025	0.882	0.023^{s}
CRP (>10 mg/L)	30.222	8.874	99.389	0.001^{s}
Diabetes mellitus	0.103	0.011	0.953	0.045^{s}
Obesity	0.396	0.195	0.967	0.048^{s}
Hypertension	1.059	0.268	4.181	0.935^{ns}
Dyslipidemia	0.698	0.146	3.346	0.653^{ns}
Smoking	0.547	0.143	2.092	0.378^{ns}
Constant	0.007	-	-	0.001^{s}

Data were analyzed by multivariable logistic regression, s= significant, ns= not significant, CAD= Coronary artery disease

Discussion:

In the present cross-sectional study, almost 2/3rds (65.0%) of the patients belonged to age group 41-60 years. The mean age was 51.4±10.7 years, ranging from 25-85 years. Majority (82.3%) of the study patients were male. Among the risk factors, hypertension was the commonest (40.0%), followed by DM (31.3%), smoking (30.5%), history of IHD (28.3%) and

dyslipidemia (22.6%). In the present study, 58 out of 668 patients were obese, hence the prevalence of obesity was 9.51%, which is higher than the national prevalence of 4.6%.[23] This disparity is presumably due to the patients having clustering of CAD risk factors included in the study. Similar observation was found by Khan et al.[26] Risk factors for CAD were similar between obese and non-obese, however, DM, hypertension and dyslipidaemia were significantly more common in obese group than in non-obese group. This is logical because risk factors of CAD tend to cluster together.

In the present study, raised CRP was significantly more common in obese than in non-obese patients (56.9% vs. 47.9%, p=0.04), and a significant positive correlation was found between CRP and BMI (r=0.228; p=0.001). A systematic review and meta-analysis involving various populations, obesity was associated with elevated levels of CRP and the association is stronger in women and North Americans/Europeans.[27] Another meta-analysis found significant correlation between CRP and obesity in Chinese adults and children.[28] Previously, in the study by Kao et al., higher BMI, as well as, central obesity were independently associated with higher levels of CRP.[29] Also, in a Mediterranean population, CRP concentrations increased significantly with increasing cardiovascular risk factors. Men and women with metabolic syndrome showed significantly higher levels of CRP than their counterparts, even after adjustment for BMI and age.[30] Again, risk factors for CAD were similar between high-CRP (>10 mg/L) and non-high CRP (≤10 mg/L) groups, however, DM, hypertension and dyslipidaemia were significantly more common in high-CRP group than in non-high CRP group. In an international multicentre study of 13,874 patients, among underweight, normal weight, overweight, and obese individuals, there was increasing prevalence of diabetes (7 vs.10% vs. 12 vs. 19%), hypertension (37 vs. 40% vs. 46 vs. 59%), and hyperlipidaemia (48 vs. 52% vs. 56 vs. 56%; P < 0.001 for trend).[31] Other studies demonstrated positive association between DM and metabolic syndrome with CRP.[32,33] Triple-vessel CAD was found significantly more commonly in obese group than in non-obese group (29.3% vs 24.4%, p=0.04). These findings correlate well with those of Khan et al. depicting higher presence of triple-vessel disease in obese patients compared to the non-obese counterparts.[26] In the present study, Obesity, high CRP (>10 mg/L), DM, and high HbA1c (≥6.5%) were found significant predictors of severe CAD (p <0.5) in multivariate logistic regression analysis. In the study by Labounty et al., higher BMI was independently associated with increased risk of myocardial infarction (hazards ratio: 1.28 per +5 kg/m(2), 95% CI: 1.12-1.45, P < 0.001).[31]

The study has got some limitations. This was a single-centre study. No distinction was made between generalized and visceral obesity. Only CRP was evaluated as a marker of inflammation. Also, CAD severity in CAG was determined by visual assessment, hence, intar- and inter-observer variability could not be ruled out.

Conclusion:

Obesity is associated with raised CRP in patients with CAD, and a significant positive association exists between obesity and inflammation and CAD. Future studies are needed to explore the impact of type of obesity and inflammation on CAD. Also, role of lifestyle modification and pharmacological management in reducing obesity and inflammation in the context of CAD may be evaluated.

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Original Article

Effect of Balloon Embedded Bifurcating Stenting with Single Stent Strategy for Side Branch Protection

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Abstract:

Background: Intervention for bifurcation lesions is associated with increased risk of adverse events and includes acute side branch (SB) occlusion during main branch (MB) stenting. This acute occlusion of side branch can often be catastrophic for the patient. We here in describe our experience in National Institute of Cardiovascular Diseases and Hospital (NICVD), Dhaka, Bangladesh with a technique which can be incorporated into bifurcation stenting to reduce or almost eliminate the incidence of side branch occlusion or catastrophe.

Methods: A prospective, observational, non-blinded study in patients from a single tertiary referral cardiac center National Institute of Cardiovascular Diseases & Hospital (NICVD), Dhaka, Bangladesh. Patients with an indication for percutaneous coronary intervention(PCI) of a denovo bifurcation lesion were screened. The study included 51 patients who underwent coronary angiogram in our institution and had bifurcation lesions suitable for single stent strategy between March 2017 to September2018.

Results: 51 patients with bifurcation lesion were included in the study and underwent a balloon embedded bifurcation stenting with a semi inflated balloon placed across the SB ostium.

Angiographic success was achieved in all the patients but procedural success was achieved in 88.2% of the patients. TIMI 3 flow of main branch (MB) was achieved 96.08% and side branch

(SB) was achieved 88.2%. Incidence of dissection was 5.9%, acute occlusion of SB was 2.0% and MACE was 3.9%. Mean fluoroscopy time and contrast volume was similar to that of conventional bifurcation stenting. The jailed SB balloon and wire could be successfully removed in all patients.

Conclusion: The present study suggests that balloon embedded bifurcation stenting with a semi inflated balloon to protect the SB is feasible, with minimal procedural adverse events and successful in minimizing or almost eliminating the incidence of acute side branch occlusion or dissection as well as MACE.

Keywords: *Bifurcation lesions, Percutaneous coronary intervention, Balloon embedded stenting, medina classification, MACE.*

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Introduction:

Bifurcation lesions account for 15–20% of interventions undertaken in a catheterization laboratory and is defined as "a coronary artery narrowing occurring adjacent to, and/or involving, the origin of a significant side branch(SB). A significant SB is a branch, whose loss is of consequence to a particular patient (symptoms, location of ischemia, viability of the supplied myocardium, collateralizing vessel, left ventricular function)."[1,14] Main branch(MB) stenting with provisional stenting of side branch is considered to be the gold standard strategy for bifurcation lesions currently.[13] During provisional approach, residual ostial stenosis or total occlusion of SB frequently occurs immediately after main vessel (MV) stenting.[8,12,20,21]

This strategy may however cause plaque shift, change in the bifurcation angle or ostial occlusion of the side branch resulting in side branch compromise in many cases.[8,11,19] Several techniques have been devised to decrease the risk of SB occlusion of which jailed guidewire technique1is widely used nowadays, but is associated with increased risk of wire entrapment and doesn't eliminate the incidence of SB occlusion. In a recently described jailed balloon technique,2a small balloon (diameter 1.5–2 mm) is kept uninflated in the SB during MB stent deployment, which helps to reduce the risk of SB occlusion but can't prevent it completely. If critical stenosis or occlusion of SB develops, rewiring of SB is attempted trying to SB salvage. But, the ability of rewiring of SB and restoring SB flow after MB stenting can be difficult.[5]

We here in intend to describe a technique in which a partially inflated balloon placed in the SB, extending from the SB to proximal MB can help in maximum side branch protection.

Material and methods

A prospective, observational, non-blinded study in patients from a single tertiary referral cardiac center (National Institute of Cardiovascular Diseases Institute & Hospital-NICVD). Patients with an indication for percutaneous coronary intervention(PCI) of a denovo bifurcation lesion were screened. The study included 51 patients who underwent coronary angiogram in our institution and had bifurcation lesions suitable for single stent strategy between March 2017 to September2018. Patients with severe calcified lesions and proximal tortuosity were excluded. Bifurcation lesions were classified according to Medina class.[15]

Inclusion criteria

(1) Patients were eligible for the studies if they were 18 to75 years old with true coronary bifurcation lesions undergoing PCI.

(2) The true bifurcation lesion consisted at least one major SB, bifurcation classifications were made according to Medina classification[14]; Medina 1,1,1 1,0,1 and 0,1,1 coronary bifurcation lesions with an SB diameter ≥2.0mm based on visual estimation were included in the training and study groups.

Exclusion criteria

(1) The bifurcation lesion was categorized as complex bifurcation lesions according to the DEFINITION[4], defined as Medina 1,1,1 and 0,1,1 coronary bifurcation lesions with each major criterion (left main vessel with ostial SB lesion length ≥10mm and diameter stenosis (DS) ≥70%; non-left main vessel with ostial SB lesion length ≥10mm and DS ≥90%) plus any 2 minor criteria (moderate to severe calcification; multiple lesions; bifurcation angle >45; main vessel RVD<2.5mm; thrombus-containing lesions; MV lesion length ≥25mm)

(2) Subject with renal failure (serum creatinine >2.0mg/dl)

(3) Subject exhibited severe left ventricular dysfunction (left ventricular ejection fraction < 35%)

(4) Subject with a serious comorbidity or with life expectancy <1 year

(5) Subject exhibited contraindications to aspirin or clopidogrel

Study procedure

a) Patients admitted in the Department of Cardiology in NICVD, Dhaka, Bangladesh with ischaemic heart diseases and elective PCI were considered for the study and those who had true coronary bifurcation lesion[4] with fulfilled inclusion, exclusion criteria and agreed to enter the study protocol.

b) Informed written consent was taken from each patient or legal guardian before enrollment.

c) A schematic diagram of the steps used in the technique is shown in Fig-I.

The steps include:

1. Wiring of both the main branch and side branch.
2. Predilatation of main vessel, predilatation of side branch when there is flow limiting obstruction.

3. Side branch balloon of 1:1 diameter was retained across the ostium with 1/3rd to 1/2 of the balloon in the main branch. (depending on the length of side branch lesion)
4. Stent was placed across the side branch ostium into the main branch and side branch balloon was inflated to 4–6 atmosphere.
5. The stent was deployed at nominal pressure jailing the partially inflated side branch balloon.
6. If the stent had a waist, main branch balloon was inflated to a higher pressure.
7. A check angiogram was done following removal of both balloons.
8. Side branch wire was removed and rewired across the MB stent.
9. POT(proximal optimisation technique) was done for the MB stent.
10. Final check angio was done and if it showed TIMI 3 flow in both branches, procedure was completed.
11. If SB showed<3 TIMI flow, SB was dilated across MB stent and final simultaneous dilation was done.

d) Angiographic success was defined as attainment of a residual diameter stenosis of 20% or less with TIMI 3 flow in both the main and side branches which was the primary end point.

e) Procedural success was defined as angiographic success without the occurrence of major complications(death, MI, stent thrombosis or CABG) before discharge.

f) Following PCI, all patients were monitored for post procedural complications.

g) ECG was taken immediate post procedure and 12 h after that.

h) Cardiac troponin and creatine kinase MB were measured on all patients before procedure and 12 h post intervention.

i) Elevation of 3 the upper limit of normal was considered significant.

Statistical Analysis:

Statistical analysis was performed using SPSS Statistical Software (version 22, SPSS Inc., Chicago, Illinois, USA). Continuous parameters were expressed as mean±SD

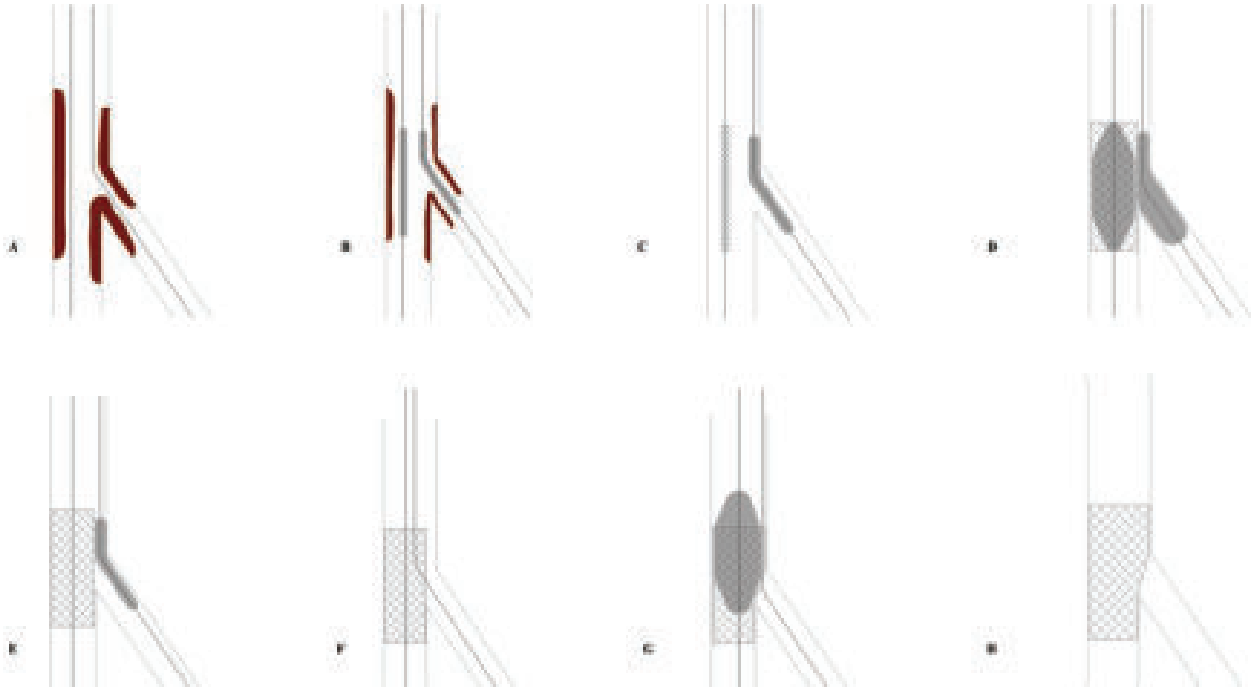

Figure-I. Schematic diagram showing steps used in the technique. A- Wiring of both the branches. B- Predilatation of both the branches. C- Stent in the main branch with an uniflated balloon across the side branch. D- Deploying the main branch stent while retaining the partially inflated balloon across the side branch. E- Deflating both the balloons. F- Rewiring the side branch across the main branch stent. G- POT for the main branch stent. H- Final result.

and categorical parameters as frequency and percentage.

Results:

This study included 51 patients of which 36 were males. Mean age of patients was 56.33 ± 11.24 years. History of an acute coronary syndrome(ACS) was present in 38 patients while the remaining 13 had a history of exertional angina grade II–III. (Table-I)

Out of 51 patients, majority (29) had lesions at bifurcation between left anterior descending(LAD) and diagonal(D) artery. Eight patients had significant obstruction between left main coronary artery (LMCA) and LAD artery, whereas six patients had lesion at left circumflex-obtuse marginal(LCX-OM) bifurcation. (Table-II)

Data regarding medina class, main vessel stent size, length, sidebranch balloon size, length and inflation pressure of each system is as shown in Table-III.

Procedural success rate was 88.2%. There was one SB loss and three side branch dissection and. The jailed SB balloon and wire could be successfully removed in all patients. (Table-IV)

Table-I

Baseline clinical characteristics (n = 51).

Characteristics	Results
Age, years(mean ± SD)	56.33 ± 11.24
Male	36(70.6%)
Diabetes Mellitus	27(52.9%)
Hypertension	39(76.5%)
Smokers	33(64.7%)
Family history of CAD	16(31.4%)
Dyslipidemia	42(82.4%)
History of ACS	38(74.5%)
history of exertional angina grade II–III	13(25.5%)

Table-II

Distribution of lesion in patients (n=51).

Site of Lesions	Number(%)
left main coronary artery and left anterior descending artery (LMCA-LAD)	08(15.7)
left anterior descending artery and diagonal artery (LAD-D).	29(56.9)
left circumflex artery and obtuse marginal artery (LCX-OM)	06 (11.8)
Right coronary artery and posterior descending artery/ posterior left ventricular artery (RCA-PDA/PLV)	04 (07.8)
Post percutaneous transluminal coronary angioplasty (PTCA)-instent restenosis (ISR)	01 (02)
Left main coronary artery (LMCA) trifurcation	01 (02)
Sequential left anterior descending artery and first diagonal artery (LAD-D1) followed by left main coronary artery and left anterior descending artery (LMCA-LAD)	01 (02)
Combined case of balloon embedded bifurcationculotte stenting at left anterior descending artery and first diagonal artery (LAD-D1) and balloon embedded left main coronary artery and left anterior descending artery (LMCA-LAD)	01(02)

Table-III

Procedure details of all the cases (n=51).

Characteristics	Results
Medina classification	
1,1,1	39(76.5%)
1,1,0	08(15.7%)
1,0,1	03(04.9%)
0,1,1	01(2.0%)
MB stent	
Mean Diameter (mm)	3.12 ± 0.49
Mean Length (mm)	21.32 ± 5.62
Inflation pressure of MB stent (atm)	10 to 16
Jailed balloon	
Mean Diameter (mm)	2.25 ± 0.29
Mean Length (mm)	10.63 ± 2.31
Inflation pressure of MB stent (atm)	4 to 8
Balloon used for POT	
Mean Diameter (mm)	3.07± 0.53
Mean Length (mm)	11.41 ±1.99
Inflation pressure of balloon used for POT	14 to 20

Table-IV

Immediate procedural and clinical outcomes (n=51).

Characteristics	Results
Angiographic Success(%)	51(100)
Procedural Success (%)	45 (88.2)
Procedural time (min)	63±13
Fluoro time (min)	31±09
SB loss	01(02%)
Dissection in the side branch	03(5.9%)
Per procedural MI	00(00%)
Entrapment of the Jailed balloon or wire	00(00%)
MACE in hospital	02(3.9%)
TIMI 3 flow	
Main Branch (MB)	49(96.08%)
Side Branch (SB)	45 (88.2%)

Discussion:

The study included 51 patients of which 70.6% were male. Mean age of patients was 56.33 ± 11.24 years. Risk factors included Diabetes Mellitus (52.9%), hypertension (76.5),smokers (64.7), dyslipidemia(82.4%) and positive family history of coronary artery disease(CAD)(31.4%). History of an acute coronary syndrome(ACS) was present in 74.5% patients while the remaining 25.5% had a history of exertional angina grade II–III that was similar to the most of the studies.1,4,8,12,20,21

Our study shown, out of 51 patients, majority (56.9%) had lesions at bifurcation between left anterior descending(LAD) and diagonal(D) artery. 15.7% patients had significant obstruction between left main coronary artery (LMCA) and LAD artery, whereas 11.8% patients had lesion at left circumflex-obtuse marginal(LCX-OM) bifurcation. Few cases of special mention include a case with combined balloon embedded culotte stenting for LAD-D1lesion and balloon embedded stenting with single stent for LMCA-LAD lesion a case where the technique was used for LMCA trifurcation and a patient with post percutaneous transluminal coronary angioplasty(PTCA) who presented with instent restenosis(ISR) that was similar to the most of the studies.4,8,14,21Procedural success rate was 88.2%. TIMI 3 flow of main branch (MB) was achieved 96.08% and side branch (SB) was achieved 88.2%. Incidence of dissection was 5.9%, acute occlusion of SB was 2.0% and MACE was 3.9%.The mean procedural time was 63/ ±/ 13 min and mean fluoro time was 31±09min which was comparable with the time taken for conventional bifurcation stenting done by the same operator team. All the patients were discharged on the third or fourth day and are under regular follow up.

Several studies have consistently demonstrated that a single-stent provisional strategy of stenting just the main branch (MB) has better clinical outcomes compared to double-stent techniques for bifurcation lesions. However, approximately 35% of patients require crossover to two stent strategy due to compromise of the side branch which often occurs due to plaque or carinal shift.6Side branch(SB) rewiring is difficult and time consuming in such cases and can cause prolonged impairment of flow leading to peri procedural MI. A strategy is thus needed which can improve the safety of SB during provisional approach. Provisional approach reduces adverse cardiovascular events, procedural time, radiation, and contrast administration as compared with elective two stent strategies.[6,9,10,13,17,18]

In the jailed guidewire technique1,the jailed wire in the SB can provide assistance to the other wire which passes through the struts in the MB but it does not prevent plaque or carinal shift in the SB. In the jailed balloon technique,2a small uninflated balloon is kept in the SB during MB stent deployment which helps in preventing carinal or plaque shift. Burzotta et al.2 showed that the rate of SB loss was 15% with this technique. Cayli et al.3 described an extention of jailed balloon technique, in which they placed a semi inflated balloon at the SB ostium, during MB stent deployment. This semi inflated balloon

technique prevented SB occlusion in 100% of cases and can be very useful in patients with complex bifurcation lesion with high risk of SB occlusion. However, there is very limited clinical experience with this technique and no such study in Indian population to our knowledge.

In this pilot study in NICVD, we used a semi inflated balloon placed at the side branch ostium to prevent carina or plaque shift during MB stenting. The study showed that this technique is safe and offers high procedural success with minimal complications. The technique was employed for both LMCA and non LMCA lesions and was associated with excellent SB protection in both type of lesions. Further 39(76.5%) of the patients included in the study had true bifurcation lesion with ostial involvement of the SB. Such patients are at high risk of SB occlusion during MB stenting due to plaque or carinal shift. However, there was no need for conversion to a two stent strategy as TIMI 3 flow was achieved in SB in all the cases. Decreasing or almost eliminating the crossover in provisional strategy can also prove to be cost effective by decreasing the number of stents required and decreasing the volume of contrast used for each procedure.

Potential risks and Limitations:

Although most of the result of this study have come up with the statistically significant findings, there are some facts to be considered which might affect the result. These are

a) Although adequate number of study population was used in our study, we believe that it is still limited in number to generalize the results.

b) It was conducted in a single center.

c) Short follow up period

d) The technique may be difficult when there are more than one significant side branches (may resort to a double catheter technique which has not been tried).

e) Rewiring the main branch before POT carries a risk of going behind the MB stent struts.

f) There is a potential risk of side branch balloon trapping, and deformation or polymer damage of main vessel stent.

g) OCT or IVUS was not used and hence dissections were assessed angiographically only.

h) Quantitative coronary angiography was not used in the study.

i) The study was performed in a single centre and all the cases were done by the same operator.

j) This was an observational study to assess the feasibility and safety of the technique, so the follow up was not included.

k) This study was planned as a prospective observational study, hence no control arm.

Conclusion:

SB occlusion is usually associated with ostial SB disease, and the mechanism for closure is likely plaque or carinal shift during MB stenting. Thus, balloon embedded stenting using a semi inflated balloon may be applied to bifurcation lesions with SB involvement to allow for an improved procedural result by protecting the SB. This however being an ovservational study, a randomized controlled trial(RCT) is needed to further validate the technique.

Recommendations:

Plaque shift is prevented or reduced. Need of bail out stenting is reduced/ abolished. Better TIMI flow is achieved in side branch. None of cases showed dissection in the SB. Can be practiced even in small side branches. Additional fluoroscopic exposure or procedure time is not required. Nevertheless, further studies with large number of patients with multicenter approach are needed to assess this comparison of the GRACE and TIMI risk score in predicting of in-hospital MACE of patients with ACS.

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Original Article

Evaluation of Safety and Efficacy of Combined Low Dose Aspirin and Warfarin Following Mechanical Heart Valve Replacement for Mitral Valve Disease

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Abstract:

Introduction: Warfarin is recommended following mechanical valve replacement to prevent thromboembolic complications. A combination of warfarin and aspirin may further reduce thromboembolic events in these patients. This study was designed to evaluate safety and efficacy of combined low dose aspirin and warfarin therapy following mechanical mitral valve replacement.

Materials and Methods: Purposively selected 99 patients who underwent mechanical mitral valve replacement were divided into two groups. Patients of Group A (n=50) received combined low dose aspirin (75mg) and warfarin. Patients of Group B (n=49) received conventional dose of warfarin alone. International normalized ratio (INR) was targeted 1.8-2.4 for group A Patients and 2.5-3.5 for group B Patients. Post-operatively INR, thromboembolic events, anti-coagulation related haemorrhage and other morbidity and mortality were registered in both groups.

Result: Patients were followed up postoperatively for 9 months. The mean dose of warfarin in group A and group B was 4.36 ± 0.31 mg and 5.57±0.52 mg respectively (p<0.001). The overall mean INR of two groups of patients were statistically different (P<0.001) with low INR in group A (2.19±0.13) patients compared to group B (3.03±0.31). The thromboembolic events in group A (0.02/patient year) were lower than those in group B (0.08/Patient year). There was no statistically significant (p=0.362) difference in bleeding episodes between two groups but data indicate proportion of minor bleeding manifestations were higher in patients treated with warfarin plus aspirin group.

Conclusion: Following mechanical mitral valve replacement, a combination of aspirin (75mg) and low dose warfarin with an aim to maintain INR between 1.8 and 2.4 (lower than recommended 2.5-3.5) may provide satisfactory outcomes in term of thrombosis, embolism and bleeding without increase in mortality.

Keywords: *Warfarin, Aspirin, Mitral valve replacement, Thromboembolism, Anticoagulation related haemorrhage.*

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Introduction:

Mitral valve diseases (stenosis and regurgitation) are surgically correctable mechanical problems of the heart. Surgical options are repair and replacement with either bioprosthetic or mechanical prosthetic valves. The most common mitral valve surgery is the replacement of the valve with the mechanical prosthetic valve.[1] Cardiac

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prostheses can cause peripheral and cerebral thromboembolism or can develop valve thrombosis; all are devastating complications.[2] In last 20 years, there were dramatic improvements in the reduction of morbidity of patients with prosthetic heart valves. However, thromboembolism still occurs in up to 2% of patients per year.[3]

Valvular thrombosis is not unique to mechanical prostheses, and it probably has a multifactorial etiology. With surgical technique, patient related factors, anticoagulation control and prosthesis design all playing a part; prosthesis design however, is perhaps the most important factor. These same factors also may influence the incidence of thromboembolic events, many of which are probably attributable to embolization of platelet aggregates rather than thrombus.[4] It is well recognized that with artificial devices in the bloodstream particularly prosthetic heart valves, platelet survival time decreases significantly and correlates closely with increased platelet activation and deposition. However, for the mitral prostheses, slow flow across the valve and large left atrium leading to stasis and prolong contact of coagulation factors with the prostheses is the primary cause of thromboembolism whereas platelet factors are the secondary contributory factor.[2]

Oral anticoagulation therapy plays an important role in the prevention of thromboembolic events. So, warfarin is prescribed lifelong following mechanical valve replacement.[1] However, the risk is reduced but not eliminated by the long-term administration of standard-intensity oral anticoagulant therapy.[5] Moreover it itself carries a significant bleeding hazard.[6] The incidence of bleeding complication varies with the quality and range of anticoagulation control.[4] Warfarin therapy is maintained following the prothrombin time (PT) and international normalized ratio (INR).[7]

A combination of warfarin and an antiplatelet agent such as aspirin may further reduce thromboembolic complications in patients with prosthetic heart valves. Though the risk of thromboembolism is lower in patients receiving combined aspirin and oral anticoagulation therapy, the risk of major bleeding is higher than in patients receiving anticoagulation therapy alone. This increased bleeding risk seems to be related to the dose of aspirin, as lower dose of aspirin is associated with a reduced risk of major bleeding when used together with warfarin.[1]

American College of Chest Physicians guidelines 2001 recommended an INR of 2.5 to 3.5 for patients with mechanical prosthetic valves and of 2.0 to 3.0 for those with bioprosthetic valves and low risk patients with bileaflet mechanical valves (such as the St. Jude Medical device) in aortic position. Similar guidelines have been promulgated conjointly by the American College of Cardiology and American Heart Association.[8]

Different comparative studies that analyzed anticoagulant intensities has revealed that thromboembolic and hemorrhagic complications are less prevalent with an intensity of oral anticoagulation below the recommended therapeutic ranges. However, the safety and efficacy of lower intensity anticoagulant have not proven so far.[6]

Because of uncertainty about the true intensity of anticoagulation, some patients were being anticoagulated at unnecessary high intensity and exposed to greater risk of bleeding. Although not fully worked out, for all types of mechanical and thrombotic risk factors, because of lack of data, there is now widespread acceptance of the principle that the target INR should be both prosthetic specific and patient specific. In general, there has been a lowering of recommended INR for low thrombogenicity prosthesis in recent years with an associated reduction in the risk of serious bleeding.[9]

As a means of improving the efficacy of antithrombotic therapy after cardiac valve implantation, anticoagulation has been augmented with an antiplatelet agent. Although the results of some of the trials have been encouraging, showing improved effectiveness with no substantial increase in bleeding risk, the results are far from consistent.[6]

Butchart et al.[4] in a review of embolism in prosthetic heart valves concluded that valves vary in susceptibility to thrombosis due to subtle design differences, that optimal INR range is often uncertain, and further research is needed.

American College of Cardiology / American Heart Association (ACC/AHA) guidelines 2001 had given messages that the addition of low dose aspirin (80 to 100 mg) to warfarin therapy not only decreases the risk of thromboembolism but also decreases mortality due to other cardiovascular diseases if INR is maintained within the target range with aspirin though there might be slight increase in the risk of bleeding with this combination.[8]

With higher INR levels the risk of bleeding related complication increases in ever increasing ratio. If addition of aspirin allows us to reduce the INR levels without sacrificing safety and efficacy of prosthetic valve, it will render us greater safety margin and thus reduce morbidity

and cost of treatment. This study is designed to evaluate safety and efficacy of combined low dose aspirin and warfarin following prosthetic mechanical heart valve replacement in mitral position.

Materials and Methods:

This prospective cohort study was conducted in the Department of Cardiac Surgery, National Institute of Cardiovascular Diseases, during the time period from July 2015 to March 2018. 99 adult patients who underwent mitral valve replacement were purposively selected. Patients having history of thromboembolic events, preoperative atrial fibrillation, major non-cardiac progressive diseases and aspirin hypersensitivity were excluded from the study. They were divided into two groups: a) Group A: Patients receiving combined low dose aspirin (75mg) and warfarin (target INR 1.8-2.4) and b) Group B: Patients receiving conventional dose of Warfarin (target INR 2.5 -3.5)

Demographic variables (e.g. age, sex), clinical variable (e.g. NYHA class), haematological parameters, chest x-ray and echocardiographic were taken into account for evaluation of all patients. Coronary angiography was done in selective cases to exclude coronary artery occlusion in patients having symptoms of angina, strong positive family history and age more than 40.

All the patients were operated in the Department of Cardiovascular Surgery, National Institute of Cardiovascular Diseases. Through a standard median sternotomy, cardiopulmonary bypass was instituted using ascending aortic and bicaval cannulations vent passed. Patient's temperature was cooled to 32 degree centigrade. Following which, aorta was cross-clamped. Then antegrade cardioplegia was given and heart was arrested. Left atriotomy was done. Mitral leaflets were excised so as to remove the scarred and calcified tissue. A valve sizer was used to determine the proper diameter of the prosthetic valve. Supra-annular pledgeted mattress sutures were placed sequentially around the mitral annulus. The valve sutures were passed sequentially through the sewing ring of the prosthetic valve. The valve was seated and sutures are tied. The most recent FDA approved least thrombogenic St. Jude Medical bi-leaflet mechanical valve was used in all patients. Then the valve leaflets were gently opened with valve tester to inspect proper opening of prosthetic valve. Left atriotomy was closed with 4/0 round body polypropylene and air was vented and patient weaned gradually off the Cardiopulmonary Bypass. After ensuring meticulous hemostasis, drain tubes were placed in the retrosternal and retro-cardiac part of the pericardial cavity. If required, separate pleural chest drain was placed and chest was closed in layers.

Post-operative evaluation:

Following the surgical procedure all the patients were brought to the cardiovascular intensive care unit where they were monitored until the patients were extubated and till stabilization of the respiratory and hemodynamic status. Aspirin and warfarin were commenced within 48 hours of the surgery, when patients were stabilized and chest drainage fluid volume was < 50 ml. Then the patients were transferred to the ward for the routine care. Prothrombin time and INR were done on the 3rd morning after starting warfarin. Then they were repeated twice weekly until target INR was achieved before discharge. The patients were then discharged from the ward and advised for subsequent follow up.

Patients attended at follow up clinic on the 1st, 2nd, 3rd, 6th and 9th month after discharge with INR results. During follow up, patients were evaluated clinically. Warfarin doses were adjusted to achieve target. Echocardiographic evaluations were done on 1st, 3rd and 9th month to determine the functional status of valve, paravalvular leakage, and prosthetic valve endocarditis and valve thrombosis.

Data collection

All data were collected from each patient using pre-designed questionnaire and collection form. Data were analyzed and verified with statistical program for social sciences (SPSS) using student's t test, fisher's exact test, chi-square test, where appropriate. The descriptive statistics used here were frequency, mean and standard deviation (SD) and compared using student's t test. Categorical data were expressed as percentages and evaluated using Chi-square or Fischer's exact probability test. The level of significant was 0.05. Any p-value <0.05 was considered as significant.

Result:

Age distribution of the study population

The mean age of the group A patients was 35.18 ± 10.59 years and that of group B patients was 32.94 ± 8.81 years. However, analysis revealed no statistically significant mean age difference between two groups (p>0.05).

Sex distribution of the study population

In group A 58% were female and 42% were male. But the sex distribution of group B showed a male (53.1%) predominance. Analysis found no statistically significant sex difference between two groups (p>0.05).

Distribution of the study population according to diagnosis

Both the groups showed similar pattern of disease, mostly mitral stenosis (50% vs. 49%), followed by mitral regurgitation (26% vs. 28.6%) and then combined pathology (24.0% vs. 22.4%).

Distribution of Post-operative INR at Follow Up

The mean INR of Group A the patients at the time of discharge was 2.25 ± 0.44. Subsequently it was 2.13 ± 0.39 at 1st month, 2.10 ± 0.37 at 2nd month, 2.20 ± 0.46 at 3rd month, 2.13 ± 0.38 at 6th month and 2.34 ± 0.46 at 9th month. Repeated measure analysis of variance indicated that overall mean INR remained unchanged and was not statistically significant (p>0.05). The mean INR of Group B at the time of discharge was 3.02 ± 0.46. Subsequent measurements were 2.96 ± 0.69 at 1st month, 2.99 ± 0.59 at 2nd month, 3.07 ± 0.61 at 3rd month, 3.03 ± 0.59 at 6th month and 3.10 ± 0.52 at 9th month. Overall mean INR remained unchanged and statistically not significant. Similar pattern of INR was observed in group B patients but the difference in inter follow up period in both the groups were statistically not significant (p>0.05). But there is significant difference throughout the follow up period between the two groups.

Distribution of Prescribed Warfarin Dose of the Study Population

The mean doses of warfarin prescribed for the patients in group A at the time of discharge was 4.48 ± 0.72 mg, at 1st month 4.32 ± 0.57 mg, at 2nd month 4.26 ± 0.51 mg, at 3rd month 4.36 ± 0.59 mg, at 6th month 4.45 ± 0.59 mg and at the 9th month 4.29 ±0.55 mg. Overall mean doses of warfarin remained unchanged and was not statistically significant (p>0.05). Similar pattern of warfarin doses were observed in group B patients with a little higher dose but the difference in inter follow up period was not statistically significant (p>0.05). There is significant difference between two groups at all follow up.

Analysis of Post-operative Complications:

In group A there were 8 (16%) events of minor bleeding from nose, gum and skin. In group B that were 5 (10%). One patient of group B died at the 3rd month of follow-up due to intracranial hemorrhage. Chi-square test showed no statistically significant difference in bleeding episodes between two groups but data indicate that proportion of bleeding manifestation was higher in patients treated with warfarin plus aspirin group. One patient of group A developed transient ischemic attack. Among the three thromboembolic episodes of group B one manifested as transient ischemic attack, one developed peripheral thromboembolism and third one developed ischemic stroke with left sided hemiparesis. Analysis showed that no statistically significant difference between two treatment strategy but data indicate that proportion of thromboembolic manifestation was higher in patients treated with warfarin alone. In group A there were 0.02/ patient-year and in group B 0.08 / patient- year of thromboembolic events. One patient from group B had died during the study at the 3rd month of follow-up due to intracranial hemorrhage. Two patients of group B developed surgical site infection. They did not

Table-I

Distribution of study subjects according to age (n=99)

Age (years)	Group A(n=50)	Group B(n=49)	p-value
≤20	4 (8.0)	4 (8.2)	
21 - 30	16 (32.0)	20 (40.8)	
31 - 40	18 (36.0)	17 (34.7)	
>40	12 (24.0)	8 (16.3)	
Mean ± SD#	35.18 ± 10.59	32.94 ± 8.81	0.292ns

Un-paired t test was done to measure the level of significance, ns= non-significant.

Table-II

Distribution of study subjects according to sex (n=99)

Gender¶	Group A(n=50)	Group B(n=49)	p-value
Male	21 (42.0)	26 (53.1)	0.270ns
Female	29 (58.0)	23 (46.9)	
Total	50 (100.0)	49 (100.0)	

¶ Chi-square test was done to measure the level of significance, ns= non-significant.

require any surgical intervention but prolonged the hospital stay. One patient of group B had mild paravalvular leakage. He was asymptomatic and was maintaining well. 3 patients in the group A had episodes of mild epigastric pain which relieved with two weeks course of proton pump inhibitor.

Table-III

Distribution of study subjects according to diagnosis in two groups (n=99)

Diagnosis¶	Group A(n=50)	Group B(n=49)	p-value
MSR	12 (24.0)	11 (22.4)	0.956^{ns}
MS	25 (50.0)	24 (49.0)	
MR	13 (26.0)	14 (28.6)	
Total	50 (100.0)	49 (100.0)	

¶ Chi-square test was done to measure the level of significance, ns= non-significant.

Table-IV

Distribution of Post-operative INR at Follow Up

INR range#		Group A(n=50)	Group B(n=49)	p-value
	<1.8	3 (6.0)	2 (4.1)	
	1.8 – 2.4	40 (80.0)	4 (8.2)	
INR at discharge	2.5 – 3.5	3 (6.0)	38 (77.5)	
	>3.5	4 (8.0)	5 (10.2)	
	Mean ± SD	2.25 ± 0.44	3.02 ± 0.46	<0.001^{s}
	<1.8	7 (14.0)	3 (6.1)	
	1.8 – 2.4	37 (74.0)	13 (26.5)	
INR at 1st month	2.5 – 3.5	4 (8.0)	27 (55.1)	
	>3.5	2 (4.0)	6 (12.2)	
	Mean ± SD	2.13 ± 0.39	2.98 ± 0.69	<0.001^{s}
	<1.8	8 (16.0)	2 (4.1)	
	1.8 – 2.4	38 (76.0)	9 (18.4)	
INR at 2nd month	2.5 – 3.5	2 (4.0)	34 (69.3)	
	>3.5	2 (4.0)	4 (8.2)	
	Mean ± SD	2.10 ± 0.37	2.99 ± 0.59	<0.001^{s}
	<1.8	5 (10.0)	3 (6.1)	
	1.8 – 2.4	40 (80.0)	6 (12.3)	
INR 3rd month	2.5 – 3.5	1 (2.0)	34 (69.3)	
	>3.5	4 (8.0)	6 (12.3)	
	Mean ± SD	2.20 ± 0.46	3.07 ± 0.61	<0.001^{s}
	<1.8	11 (22.0)	2 (4.1)	
	1.8 – 2.4	36 (72.0)	10 (20.4)	
INR at 6th month	2.5 – 3.5	2 (4.0)	33 (67.3)	
	>3.5	1 (2.0)	4 (8.2)	
	Mean ± SD	2.13 ± 0.38	3.03 ± 0.59	<0.001^{s}
	<1.8	2 (4.0)	2 (4.1)	
	1.8 – 2.4	39 (78.0)	4 (8.2)	
INR at 9th month	2.5 – 3.5	5 (10.0)	39 (79.5)	
	>3.5	4 (8.0)	4 (8.2)	
	Mean ± SD	2.34 ± 0.46	3.10 ± 0.52	<0.001^{s}

Un-paired t test was done to measure the level of significance, s= significant.

Table-V

Distribution of Prescribed Warfarin Dose (mg) of the Study Population (n=99)#

Group	At discharge(mg)	1st month(mg)	2nd month(mg)	3rd month(mg)	6th month(mg)	9th month(mg)
Group A	4.48 ± 0.72	4.32 ± 0.57	4.26 ± 0.51	4.36 ± 0.59	4.45 ± 0.59	4.29±0.55
Group B	5.87 ± 1.12	5.83 ± 1.10	5.61 ± 0.93	5.42 ± 0.69	5.38 ± 0.68	5.33±0.51
p value	<0.001s	<0.001s	<0.001s	<0.001s	<0.001s	<0.001s

Un-paired t test was done to measure the level of significance, s=significant.

Table-VI

Post-operative Complications (n=99)

Complications	Group A(n=50)	Group B(n=49)	p-value
Bleeding episodes¶	8 (16.0)	5 (10.2)	0.392ns
Embolic episodes¥	1 (2.0)	3 (6.1)	0.362 ns
Infection¥	0 (0.0)	2 (4.1)	0.242 ns
Epigastric pain¥	3 (6.2)	0 (0.0)	0.117 ns
Paravalvular leakage¥	0 (0.0)	1 (2.04)	0.494 ns
Death¥	0 (0.0)	1 (2.04)	0.494 ns

¶ Chi-square test, ¥ fisher's exact test, s= significant.

Discussion:

In this study, a total of 99 patients were included to observe the safety and efficacy of combined low dose warfarin and aspirin in patients with mechanical mitral valve. Group A received warfarin in combination with 75mg aspirin. Group B received warfarin alone.

The age range of this study population was 18 to 58 years with similar mean ages in two groups (35.18 ± 10.9 years for group A and 32.94 ± 8.81 years for group B). In study conducted by Hayashi et al.[10] patients who underwent mitral valve surgery had a mean age of 49.2 ± 11.8 years. This difference may due to different etiological factors. In our country rheumatic mitral valve disease is still prevalent and usually occurs earlier than the degenerative valvular diseases which are more prevalent in western countries. Among the study population 47 (47.47%) were male and 52 (52.53%) were female. In a similar study between warfarin plus aspirin and warfarin conducted by Turpie et al.[11] had male population of 52% and female population of 48% for all valve cases. Hayashi et al.[10] in his study of mitral valve surgery had found 53.33% patients were suffering from MS, 27.77% from MR and 18.89% from MSR; not very different from our study. For group A 76% of INR values were within the target range and for group B those were 69.67%. Kontozis et al.[12] in his series, with target of INR 2.5 to 3.5, had been able to maintain target INR with 77% of time. Saour et al.[13] in a trial of different intensities of anticoagulation in patients with prosthetic heart valves had reported that he had been able to maintain target INR of 2.3-2.7 at 86% of the visits.

Most of the minor bleeding occurred when the INR values were below 3.5. In group A, two patients had bleeding episode when INR was within target range (1.8-2.4), four patients had episode when INR was below 3.5 and two patients had bleeding episode when INR was above 3.5. In group B there were 5 bleeding episodes of minor bleeding out of which two had occurred when INR was within target range (2.5-3.5) and two bleeding had occurred when INR was 3.6 to 4.9 and one had occurred when INR was unstable. The incidence of bleeding events in our study was 0.24 /patient year for group A and 0.133 / patient year for group B. In the study reported by Yamak et al.[14] the incidence of bleeding was 1.2%/ patient year where the mean INR was 1.47± 0.9 (range 0.6-5.8) and 100 mg of aspirin and dyprimadole had been given to the patients along with warfarin. In the series reported by Kontozis et al.[12] bleeding episodes were 1.3%/ patient year, where target INR was 2.0-2.5, mean INR was 1.88 ± 0.54 with mean warfarin dose of 5.8 ± 1.8 mg. Considering bleeding episodes as major or minor there were no uniformity among the studies. In combination therapy the bleeding episode is directly related to the dose of aspirin. In the study conducted with the aspirin doses of 500 mg and higher had higher incidences of bleeding episodes.[15] The study conducted regarding the effective dose of Aspirin had showed conclusion that for the prevention of vascular thromboembolic events low

dose aspirin (around 100mg) is sufficient. Prescribing the larger doses only may precipitate unwanted major bleeding.

Thrombosis and embolism were also taken as the parameters for the outcome analysis in this study. Within the study period, total of 1 and 3 thromboembolic events occurs in group A and group B respectively. The linearized rate of thromboembolic events for Group A was 0.02 / patient year and for group B was 0.08/patient year (p=0.362). The risk of embolism was 3.22 times higher in group B patients compared to group A patients. In both the group there were embolic events when the INR was within the target range. In Yamak[14] series, the incidence of thromboembolism following MVR was 0.6%/patient year where the mean INR was 1.47 ± 0.9 (range 0.6-5.8) and 100 mg of aspirin and dyprimadole had been given to patients along with warfarin. In our study there was no single episode of valve thrombosis. But in the study conducted by Yamak et al.[14] (1999) the mean INR at time of valve thrombosis was 1.54 ± 0.3 (range 1.02-3.96).

Only one group B patient (2%) developed paravalvular leak during 9 months of follow up. The incidence of paravalvular leakage, in large series, in isolated mitral valve is in the range of 0.2% to 0.5%. [16] There was no single prosthetic valve endocarditis in this series. However, in the study conducted by Banbury et al.[16] the occurrence of endocarditis in isolated mitral valve was in the range of 0.5 to 1.0 %.

One patient had severe intolerance to aspirin, manifested with acute epigastric pain while in hospital. He was then treated with warfarin alone regime and included in Group B. During follow up period 3 patients from group A had complain of intermittent mild pain of gastritis. Their symptoms relived with two weeks of proton pump inhibitor. They were continued as group A population. There was no single episode of severe gastrointestinal bleeding in this study population.

Conclusion:

Our study showed that following the implantation of mechanical heart valve prosthesis in mitral position, a combination of low dose of warfarin and 75 mg aspirin with an aim of target INR 1.8-2.4 provides satisfactory result in term of thrombosis, embolism and bleeding. This is important from two standpoints. First it has the potential to improve the care of the patients with prosthetic heart valves by reducing the thromboembolic events and second less intense anticoagulant regime plus low dose aspirin (75mg) is efficacious as high-intensity anticoagulant regime but with reduction in major bleeding events. Although to validate this conclusion a larger sample of patients and early and long-term outcome should be included in a study.

Study Limitations:

Several limitations of this study should be addressed-

- The number of study population was limited
- The short duration of the study period
- It was a single center study

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I have no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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Original Article

Management of Vascular Injury in a Vascular Center of a Developing Country

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Abstract:

In surgical practice management of vascular injuries are challenging. Vascular injuries are well addressed in developed countries but there is scarcity of vascular surgeons in developing countries like us and a large number of victims fail to reach specialist in time with consequent loss of limbs or lives. To observe the pattern and outcome of management of vascular injury in a developing country this retrospective study was conducted at the department of vascular surgery, National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh. All patients with vascular injury arrived alive were included in the study. Date in terms of age, sex, cause of injury, segment of vessel involved, associated injuries, time elapsed after injury, vascular procedures done and postoperative complications were taken from records of the department and were analyzed. Out of 2174 patients with vascular injury 11 patients died at resuscitation & 52 did not come back after referral to other hospitals for management of associated injuries. Most of the patients were young male & road traffic accidents was the most common cause (91.50%). Majority (53.60%) of the patients presented after 6 hours. Majority of the cases lower limb vessels were injured (64.05%). Among the associated injuries combine orthopedic & soft tissue injuries were most common (60.58%). Among the vascular procedures antilogous venous graft (42.39%) followed by end to end anastomosis (27.79%) were in majority of the cases. In case of extremity vascular injury limb amputation rate was 35.40%. This morbidity can be reduced by improvement of road safely measures, encouraging doctors to vascular surgery specialty and effective training of orthopedic & general surgeons in the management of extremity vascular injury till the availability of vascular surgeons for provision of vascular services in remote areas.

Key words: *Vascular injuries, Extremity, Vascular surgeon, Time elapsed after vascular injury, Developing country.*

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Introduction:

Injury is the leading cause of death and disability in the first four decades of life and is the third most common cause of death overall. Among the causes of injury road traffic accidents (RTA) are commonest[1]. In case of polytrauma about 10% patients have associated vascular injury and these causes significant mortality & morbidity. Major uncontrolled bleeding is an important cause of preventable death in trauma victims. Peripheral arterial

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injuries are approximately 40-75% of all vascular injury. Risk factors, diagnosis and management of vascular injury depends on the vessel involved. A high degree of suspicion of vascular injury with early diagnosis & intervention are important for optimum outcome.[2-4]

Trauma including vascular injury is a national health problem in developing countries like us due to limited resource facilities with inadequate emergency health care services. Vascular injury are frequently associated with orthopedic & complex soft tissue injury. A surgeon have to be prepared to asses these urgently and decides the best management option depending on the individual patients condition.[5-7]

In the field of surgery vascular injury comprises one of the most fascinating conditions. Vascular surgeon's arc trained in the management of diseases affecting all parts of the vascular system except that of the heart & its vessels and the brain. Previously vascular surgery was a field within general surgery but now it is considered a specialty on its own right. But with limited resource facilities in developing countries and in areas & situations lacking the availability of vascular surgeons to deal with emergency cases of vascular injury in extremities & or the abdomen to save the life and limbs of patients- the general as well as orthopedic surgeons need to have an adequate training and good expertise in vascular surgcry.[8.9]

Methods:

This retrospective study was done at the department of vascular surgery, National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh from July 2017 to September 2018. Consecutive 2174 patients with vascular injury either isolated or associated with other injury presented in the emergency or outpatient department of the vascular surgery were included in this study; brought dead patients with vascular injury were excluded from the study.

Information's regarding age & sex of patients, cause of injury, time elapsed after injury, site & type of vascular injury, associated injury, treatment done and result of treatment including limb salvage & complication if any were recorded from patients file, ward, operation theatre & intensive care unit registers.

Patients with extremity vascular injury whose limbs were viable (warm, positive distal pulses, >90% oxygen saturation and intact neurological signs) with repairable soft tissues and skeletal injuries were considered salvaged. Patients with associated head injury or major orthopedic injury of extremity with unstable wounds were referred to other hospitals for neurocare and stabilization of fracture & or dislocation site first. Patients with extremity vascular injury with acute abdomen were also referred to other hospitals for management of acute abdomen first. Data were entered into a computer and data tile was constructed. Data were decribed as percentage (%) & mean±SD (standard deviation) as appropriate.

Results:

Out of 2174 patients of vascular injury of this study, 11 patients died during resuscitation and in 442 cases advised amputation of affected portion of extremity at presentation. 167 patients were referred to other hospitals for management of associated injuries as a priority basis and from them 115 patients came back for vascular injury management after treatment of associated injuries, it was advised amputation of affected part of limb in 39 cases of returned patients. But the treatment modality & outcome of rest 52 patients those not came back were lacking. Vascular procedures were done in total 1630 patients.

Age of the patients ranged from 03 — 83 years with mean age of 36.77±9.86 years. Majority (69.30%) of the patients were in the age group of 26 to 45 years. 93.20% of the patients were male & 6.80% were female. Road traffic accidents was the most common (91.50%) cause of vascular injury followed by assault (5.50%). 46.40% patients presented within 6 hours & 53.60% patients presented after 6 hours following injury (Table I).

In 64.05% cases lower limb, 35.45% cases upper limb, 00.30% cases abdominal and 00.20% cases neck vessels were involved (Table II). In 2148(98.80%) cases had associated injuries. Among the associated injuries majority (60.58%) were combined orthopedic & soft tissue injury (Table III). Time elapsed from injury to vascular procedures were 6 hours or less in 44.17% cases & more than 6 hours in 55.83% cases (Table IV). Among the vascular procedures end to end anastomosis in 27.79%, autologous vein interposition/patch in 42.39%, PTFE graft in 03.57%, ligation of bleeding vessels in 22.79% and vessel release in 3.46% cases were done (Table V). In patients with associated injuries of limb veins venous repair was done for popliteal, femoral and subclavian veins: rest of the veins were ligated. Fasciotomy were done in 37.45% (610) cases. Following vascular procedures- 548 (33.62%) patients developed postoperative complications (Table VI). In 265 patients' amputation were advised after vascular procedures due to failed repair, graft thrombosis, sepsis, renal failure & inadequate soft tissue coverage. In case of extremity vascular injury total 746 (35.40%) patients were advised for amputation with limb salvage rate of 64.60%.

Table-I

Base line characteristics of study patients (N=2174).

Variables	Number of Patients	Percentage
Age (in years)		
<15	71	03.30
16 - 25	331	15.20
26 - 35	805	37.00
36 - 45	703	32.30
46 - 55	176	08.10
56 - 65	45	02.10
>65	43	02.00
Mean± SD		
Range		
Sex		
Male	2026	93.20
Female	148	06.80
Cause of injury		
RTA		
Assault	1990	91.50
Industrial accidents	120	05.50
Explosive	43	02.00
Iatrogenic	15	00.70
	6	00.30
Time elapsed to reach hospital after injury (in hours)		
< 6	1009	
> 6	1165	46.40
		53.60

SD Standard deviation, RTA= Road traffic accident.

Table-II

Segments of vessel involved (N2 174).

Variables	Number of Patients	Percentage
Upper limbs	771	35.45
Subclavian	61	02.80
Axillary	24	01.10
Brachial	245	11.25
Radial/Ulnar	441	20.30
Lower Limbs	1390	6405
Femoral	339	15.60
Popliteal	685	31.50
Anterior Tibial/ Posterior tibial	366	16.95
Abdominal (Combined intra & retroperitoneal)	9	00.30
Neck vessels	4	00.20

Table-III

Associated injuries among the study population (n=2148)

Injury Type	Number of Patients	Percentage
Orthopedic injury (Fracture/dislocation)	54	02.50
Soft tissue (Muscle & or tendon) injury	378	17.60
Orthopedic + Soft tissue injury	1331	60.58
Nerve injury	337	15.70
Abdominal organs	6	00.30
Head injury	72	03.32

Table-IV

Time elapsed from injury to vascular procedures (n-1630)

Injury Time	Number of Patients	Percentage
< 06	720	44.17
07-12	436	26.76
13-24	362	22.25
> 24	112	06.82

Table-V

Vascular procedures done (n=1630)

Procedure	Number of Patients	Percentage
End to end anastomosis	453	27.79
Autologous vein interposition/patch	691	42.39
PTFE graft	58	03.57
Ligation of bleeding vessel	371	22.79
Vessel release	56	03.46

Table-VI

Postoperative complications after vascular procedure (n=548).

Complications	Number of Patients	Percentage
Wound infection	452	82.48
Compartment syndrome	09	01.64
Graft thrombosis	47	08.58
Hemorrhage	17	03.10
Renal failure	13	02.37
Respiratory failure	07	01.28
Cerebrovascular accident	03	00.55

Discussion

Vascular trauma involves injury to artery or vein or both. Among the vascular injuries arterial injury are more challenging condition in surgical practice. Venous injuries can cause bleeding profusely & may be complicated by air embolism particularly when the central veins are involved. Thin wall of veins make them difficult to handle. Control of hemorrhage and restoration of perfusion are key to the resolution of vascular injury. When patients fail to reach the specialist in time many of them end up with losing limbs or livcs.[10,11]

Vascular surgery is a specialty of surgery in which diseases of the vascular system are managed by medical therapy, catheter procedures and surgical reconstruction. As many as 50% of patients with vascular disease present urgently or as an emergency and in the past often been managed by general surgeons. Training programs in vascular surgery are slightly different in different parts of the world ranging from 1-6 years.[9] In Bangladesh post graduate students in general surgery as well as some other specialties like orthopedic & plastic surgery are either not exposed or if exposed then only for a relatively short time (1-3 months) to vascular surgery training. This period is very short for the candidate to grasp the decision-making and technical skill of vascular surgery.

It is needed to focus on common emergencies like acute limb ischemia due to vascular injury as well as abdominal vascular injuries. All trauma surgeons should be able to make an early diagnosis of 'vascular injuries on clinical bases, order and use bed-side procedures like portable Doppler examination, start an effective initial management to stop bleeding, treat shock and stabilize fractures &/or dislocations and initiate definitive management to repair the vessels or if not capable to do so then refer the patient to a vascular surgical centre as soon as possible.[9]

In our study it shows vascular injury occurred mostly in male young persons. It is because male young persons are more active and mobile in the society. Similar results were found in other studies.[10.12.13] In majority of the cases vascular injury was caused by RTA. This finding is consistent with some studies[24.14] but not with some other studies [3.5.15] in western world. Higher percentage of patients with RTA in our study reflects increased mobilization of people by the use of vehicle with the pace of industrialization and urbanization in the developing economy of the country. Relatively more cases with assault in western countries coincide with the level of domestic and civil violence's of those countries. In our study lower limb vessels injury was more common in comparison to upper limb or abdominal vessels. Among the lower limb vessels political artery injury was the most common site of injury. These findings are consistent with some similar studies. Among the associated injuries orthopedic & soft tissues injuries were most common as it showed in some other studies. Associated injuries are important factors for the outcome specially rate of amputation (in case of limb vessel injury) & mortality of vascular trauma victims. Majority of the patients presented after the golden period of six hours following trauma, so vascular procedures were done after 6 hours in majority of the cases. This finding is consistent with some studies) Time of presentation is an important prognostic marker of limb salvage and overall survival. Again vascular procedures were not done immediately after arrival at the hospital due to referral of some patients to other hospitals because of unavailability of orthopedic, neuro & general surgeons for stabilization of associated major fractures and management of life saving conditions like acute abdomen &/or head injuries as priority basis. These reflects countrywide hick of availability of effective ambulatory services, vascular expertise and trauma team with consequent deficiencies in trauma management. Our study hospital is a tertiary level hospital for vascular care but here there is no trauma team.

Satisfactory outcomes after trauma require the practiced, coordinated action of doctors from different specialties, nurses & radiographers. A team approach is required to achieve smooth resuscitation. The trauma team should have a leader responsibly for co-ordination and at least one member should be a trained general surgeon.

Among the vascular procedures autologous reverse vein graft were in majority of the cases followed by end to end anastomosis. This finding is consistent with some studies. Number of patients needed fasciotomy in our study is consistent with some other studies. Prophylactic ally fasciotomy should be done in patients with delayed presentation & low threshold for the procedure to reduce the risk of adverse limb outcomes. In patients with delayed fasciotomics had double the rate of major amputation and threefold the rate of mortality. Following vascular procedures 33.62% patients developed post-operative complications. Among the complications wound infection was commonest followed by graft thrombosis, hemorrhage, renal failure, compartment syndrome, respiratory failure & ccrcbrovascular accidents. These findings also mimics with an another study.

In case of extremity vascular injury limb salvage rate (64.60%) of our study is consistent with some studies in developing countries. Multiple factors are involved in the

prognosis of affected limb following traumatic vascular injury. Among the factors- delayed presentation & time elapsed before vascular procedures and associated injury mostly soft tissue deficits are important. High rate (35.40%) of amputation of our study reflects delayed presentation of patients & time elapsed after referral to other hospitals for priority management of associated injuries in some cases. Amputation after vascular procedures were advised for failed repair, graft thrombosis, sepsis, renal failure & inadequate soft tissue coverage of affected limb. Mortality of our study could not assessed as some of the patients referred to other hospitals for associated injuries did not came back and those patients referred to other hospitals after vascular procedures for management of complications were not followed up.

Conclusion:

In developing countries like us vascular injury is a major public health problem. Most ours of the victims are young males in their productive life period and road traffic accidents are the most common cause. Lack of availability of vascular specialist along with delayed presentation are major contributors of high rate of limb loss. Doctors should be encouraged to become vascular surgeon. Vascular surgeons should be available in trauma centers and at least one general surgeon should be available in a vascular center. Till the availability of vascular surgeons, the general as well as the orthopedic surgeons should be adequately trained and have a good expertise in vascular surgery to deal with emergency cases of vascular trauma in extremities &/or abdomen to save life and limbs of vascular trauma victims. Improvement in educational, socioeconomic & awareness condition of people and implementation of road safety measures are important for the prevention of injury.

Conflict of interest:

There are no conflicts of interest.

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Original Article

Association of Aortic Pulse Wave Velocity with the Severity of Coronary Artery Disease in Patients with Non-ST-Segment Elevation Myocardial Infarction

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Abstract:

Background: Noninvasive assessment of arterial stiffness with aortic pulse wave velocity (PWV) may serve as a useful adjunct to the cardiovascular risk stratification and risk management. The aim of this study was to evaluate the association between aortic PWV and severity of coronary artery disease (CAD) in patients with non-ST-segment elevation myocardial infarction (NSTEMI).

Methods: This cross sectional analytical study was conducted over 100 NSTEMI patients who were purposively selected and agreed to do coronary angiogram during index hospital admission. PWV was assessed noninvasively using the SphygmoCor® system on the day before coronary angiogram (CAG). Study subjects were divided into two groups on the basis of PWV. In group I: PWV was ≤10 m/sec and in group II: PWV was > 10 m/sec. Fifty patients in each group. Angiographic severity of CAD was assessed by vessel score, Friesinger score and Leaman score.

Results: Vessel score 2 and 3 were significantly (p<0.05) higher in group II and vessel score 0 and 1 were significantly (p<0.05) higher in group I. The mean PWV in the group with normal angiographic results was 8.21±1.8 m/sec, and in patients with single-vessel disease it was 9.88±2.02 m/sec. In those with double and triple vessel disease the mean PWV was found 11.95±2.61 m/sec and 14.37±2.96 m/sec respectively. There was a significant difference of the mean value of PWV among the vessel involvement group (p=0.001). Normal and low Friesinger score were significantly (p<0.05) higher in group I patients. Intermediate and high Friesinger score were significantly (p<0.05) higher in group II patients. Increased PWV was significantly associated with the presence and severity of CAD in NSTEMI. This association showed a positive linear relation between the values of PWV and vessel score (r=0.65, p=0.01), Friesinger score (r=0.61, p=0.01), and Leaman score (r=0.36, p=0.01).

Conclusion: From this study it may be stated that arterial stiffness, as measured by the aortic PWV, is an independent predictor of the presence and extent of CAD. Measurements of aortic PWV in NSTEMI can detect high risk patients requiring an early invasive strategy over a delayed invasive strategy.

Keywords: *Pulse wave velocity (PWV), NSTEMI, Coronary artery disease (CAD)*

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Introduction:

Increased arterial stiffness has been associated with increased risk of MI, stroke, congestive heart failure and overall mortality.[1] Increased arterial stiffness correlates with coronary risk factors as well as measures of arterial stiffness correlate with the presence of angiographic CAD.[2] Noninvasive assessment of arterial stiffness may serve as a useful adjunct to the cardiovascular risk stratification and risk management.[3]

Among the different noninvasive methods used to assess arterial stiffness the carotid femoral pulse wave velocity (PWV) has emerged as a gold standard due to its accuracy, reproducibility, relative easy measurement, and low costs.[4] PWV increases as arterial stiffness rises and it is an independent predictor of cardiovascular event over and above the existing risk factors.[5] Studies concerning pulse wave velocity and severity of coronary artery disease in non-ST-segment elevation myocardial infarction (NSTEMI) have been carried out predominantly in the developed countries, but there was no adequate data from Bangladesh addressing PWV as an independent risk assessment tool for predicting the severity of CAD.

Because a noninvasive approach clearly would be of value for the examination of a large population at risk, this noninvasive tool for the prediction of severity and extent of CAD in NSTEMI patients, this study was designed to demonstrate in detail the association between aortic pulse wave velocity and severity of CAD.

Materials and methods:

This cross sectional analytical study was conducted in the National Institute of Cardiovascular Diseases (NICVD), Dhaka from March 2013 to November 2013. Patients were purposively selected with NSTEMI and agreed to do coronary angiography (CAG) during index hospital admission. Total 100 patients were included in the study. Assessment of PWV was performed noninvasively with the commercially available SphygmoCor® system (SphygmoCor Vx pulse wave velocity system Model SCOR-Mx DCN: 100521 P/N: 1-00418, Rev: 9.0/0-0m, SphygmoCor Software Version: 8, AtCor Medical Pty Ltd. Sydney, Australia) using applanation tonometry with a high-fidelity micro manometer (Millar Instruments). Patients with STEMI and UA, valvular heart disease, congenital heart disease, cardiomyopathy, myocarditis or pericarditis, major non cardiovascular disorder such as severe renal impairment, patients with moderate to severe left ventricular systolic dysfunction, and patients known to have clinically evident peripheral artery disease (PAD), coarctation of aorta, aortic aneurysm, and aortic dissection were excluded from the study. Study protocol was approved by the Ethical Review Committee of NICVD.

Noninvasive assessment of pulse wave velocity:

The SphygmoCor® Vx pulse wave velocity system were used for the study to measure the velocity of ECG-gated blood pressure waveform between two superficial artery sites (carotid and femoral) using applanation tonometry. For the study the distance from the suprasternal notch to the distal measurement site (femoral), as well as, to the proximal measurement site (carotid) were measured. Subtracting the proximal measurement distance from the distal measurement distance determined the PWV distance. The mean time difference between R-wave of the QRS complex of ECG and the pressure wave on a beat by beat basis was calculated by SphygmoCor Vx Software process from each set of pressure pulse and ECG waveform data. The PWV was calculated using the mean time difference and the arterial path length between two recording sites. All PWV measurements were taken in a quiet, temperature-controlled room (22±1ºC) after a brief period (at least 5 minutes) of rest, most often on the day before cardiac catheterization by a doctor not involved in performance or interpretation of the angiograms.

Assessment of angiographic pattern and severity of CAD:

Coronary angiography was done during same hospital stay. Interpretation of coronary angiogram was done by visual estimation by two cardiologists to assess the severity of CAD. Severity of coronary stenosis was graded according to the number of major epicardial vessel with significant stenosis (vessel score), Friesinger score and Leaman score.

A. Vessel score: [6]

This 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 ranged from 0 to 3, depending on the number of vessel involved.

Score 0 = no vessel involvement.

Score 1 = single vessel involvement.

Score 2 = double vessel involvement.

Score 3 = triple vessel involvement.

B. Friesinger score: [6]

The Friesinger index is a score ranges from 0 to 15. Each of the three main coronary arteries was scored separately from 0 to 5.

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.

C. The Leaman score: [7]

A coronary scoring system to determine the severity of the underlying CAD. The 'Leaman score' is based on the severity of luminal diameter narrowing and weighted according to the usual blood flow to the left ventricle in each vessel or vessel segment.

Statistical Methods:

Data were collected by using a pre designed data sheet. Data were presented as frequency and percentage for categorical variables and as mean with standard deviation for quantitative variables. Categorical variables were analyzed by chi-square test. Quantitative variables were analyzed by t-test or ANOVA. Correlations between pulse wave velocity and angiographic severity was measured by Pearson's and Spearman's correlation test. To identify independent effects of risk factors on coronary artery disease multivariate regression analysis was done. P value less than 0.05 was considered as significant. Statistical analyses were performed with the SPSS (Ver. 17.0 for Windows). Chicago, IL: SPSS Inc.

Results:

This study was done with an aim to find out the association between the aortic pulse wave velocity and the angiographic severity of coronary artery disease in patients with non-ST-segment elevation myocardial infarction. On the basis of PWV, study subjects were categorized into two groups: 50 patients of NSTEMI with normal PWV (≤10 m/sec) were considered as group I and 50 patients of NSTEMI with increased PWV (>10 m/sec) were considered as group II.

Table I shows the risk factors among the studied patients. Highest percentage had history of smoking (58%) followed by hypertension (47%), diabetes mellitus (40%), dyslipidaemia (33%), family history of premature CAD (30%). Smoking, diabetes mellitus, hypertension, dyslipidemia and family history of premature CAD were higher in group II than in group I. It was observed that all risk factors were insignificantly greater in Group II (p>0.05).

Table-I

Risk factors of the study patients (n=100)

Risk Factors	Group I (n= 50)		Group II (n=50)		Total (n=100)		p value
	Number	%	Number	%	Number	%	
Smoking							
Yes	25	50.0	34	68.0	58	58.0	0.07^{ns}
No	25	50.0	16	32.0	42	42.0	
Hypertension							
Yes	20	40.0	29	58.0	47	47.0	0.06^{ns}
No	30	60.0	21	42.0	53	53.0	
Diabetes mellitus							
Yes	17	34.0	23	46.0	40	40.0	0.22^{ns}
No	33	66.0	27	54.0	60	60.0	
Dyslipidaemia							
Yes	13	26.0	20	40.0	33	33.0	0.14^{ns}
No	37	74.0	30	60.0	67	67.0	
Family H/O of premature CAD							
Yes	13	26.0	17	34.0	30	30.0	0.38^{ns}
No	37	74.0	33	66.0	70	70.0	

Group I: Patients with PWV ≤10 m/sec
Group II: Patients with PWV > 10 m/sec
p value reached from Chi Square test
s= Significant (p<0.05), ns = Not significant (p>0.05)

Table-II

Distribution of the study patients according to vessel score (n=100)

Vessel Score	Group I (n= 50)		Group II (n=50)		p value
	Number	%	Number	%	
Score – 0	10	20.0	3	6.0	0.04[s]
Score – 1	24	48.0	13	26.0	0.02[s]
Score – 2	11	22.0	17	34.0	0.04[s]
Score – 3	5	10.0	17	34.0	0.003[s]

Group I: Patients with PWV ≤10 m/sec
Group II: Patients with PWV > 10 m/sec
s=Significant
p value reached from Chi Square test.

Table II shows the vessel score of the study patients. It was found that among group II, highest percentage was of 3 and 2 vessel score (34%) followed by 1 vessel score 26%. Six percent patients had 0 vessel score. On the contrary, among group I, highest percentage was of 1 vessel score (48%). 22% and 10% belonged to 2 and 3 vessel score and 20% patient had 0 vessel score. No vessel involvement and single vessel involvement was found significantly higher in group I (p=0.04 and p=0.02), double and triple vessel involvement was also found significantly higher in group II (p=0.04 and p=0.003)

Table III shows the mean PWV (m/sec) of study patients according to the number of vessels involvement. The mean PWV of subjects with normal angiographic findings was 8.21±1.8 m/sec. The mean PWV of single, double and triple vessel disease were 9.88±2.02, 11.95± 2.61 and 14.37±2.96 (m/sec) respectively. The PWV increased in proportion with the number of vessel involved and the differences were statistically significant (p=0.001).

Table IV shows that normal Friesinger score (0) was found in 3 (6%) patients in group II and 10 (20%) patients in group I. Low Friesinger score (1-4) was found in 4 (8%) and 19 (38%) patients in group II and group I respectively. It was observed that normal and low Friesinger score was greater in group I with statistically significant difference (p=0.03 and p=0.001 respectively). Intermediate (5-10) and high Friesinger score (11-15) was found in 25 (50%) and 18 (36%) patients in group II and 17 (34%) and 4 (8%) patients in group I. Intermediate and high Friesinger score was significantly higher in group II (p=0.04 and p=0.002 respectively).

Table V shows the mean level of PWV (m/sec) was observed 12.6±3.1 and 9.5±2.2 in significant and insignificant CAD respectively. The difference of mean PWV between the insignificant and significant CAD groups was statistically significant (p=0.001).

Table-III

Association between PWV and number of vessels involved (n=100)

No. of vessel involved	PWV(m/sec)		p value
	Mean	SD	
No vessel involvement (n=13)	8.21	1.86	
Single (n=39)	9.88	2.02	0.001[s]
Double (n=48)	11.95	2.61	
Triple (n=54)	14.37	2.96	

p value reached from ANOVA test
s = Significant

Table-IV

Distribution of the study patients according to Friesinger score (n=100)

Friesinger Score	Group I (n= 50)		Group II (n=50)		p value
	Number	%	Number	%	
Normal (0)	10	20.0	3	6.0	0.03[s]
Low (1 – 4)	19	38.0	4	8.0	0.001[s]
Intermediate (5 – 10)	17	34.0	25	50.0	0.04[s]
High (11 – 15)	4	8.0	18	36.0	0.002[s]

Group I: Patients with PWV ≤10 m/sec
Group II: Patients with PWV > 10 m/sec
s=Significant; ns=Not significant
p value reached from Chi Square test and Fisher's exact test.

Table-V

Mean status of PWV of the study patients according to significant coronary artery disease defined by Friesinger index (n=100)

PWV m/sec	Insignificant CAD (n=46) Significant CAD (n=54)	(Friesinger score 0-4) (Friesinger score e"5)	p value
Mean ± SD	9.5±2.2 m/sec	12.6±3.1 m/sec	0.001[s]

s=Significant
p value reached from unpaired t test.

The figure shows that there was a positive correlation between PWV and coronary artery disease severity in terms of vessel score (r=0.65). It was observed that the Spearman's rank correlation was statistically significant (p=0.01) by correlation test.

The figure shows that there was a positive correlation between PWV and coronary artery disease severity in terms of Friesinger score (r=0.61). It was observed that the Spearman's rank correlation was statistically significant (p=0.01) by correlation test.

The figure shows that there was a positive correlation between PWV and coronary artery disease severity in terms of Leaman score (r=0.36). It was observed that the Pearson's correlation was statistically significant (p=0.01) by correlation test.

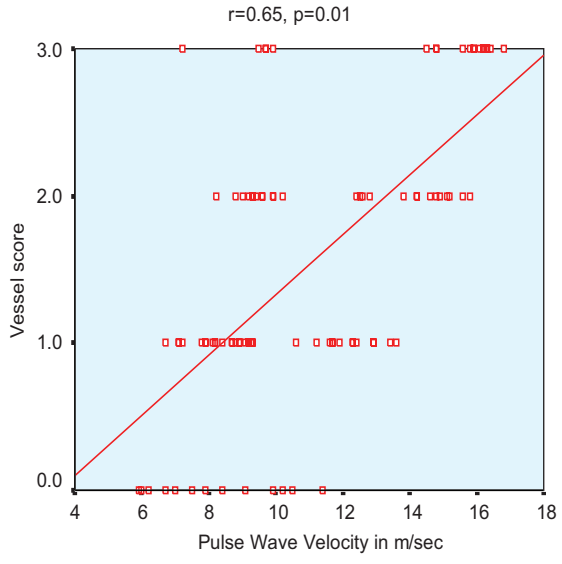

Fig.-1: *Correlation between PWV and vessel score*

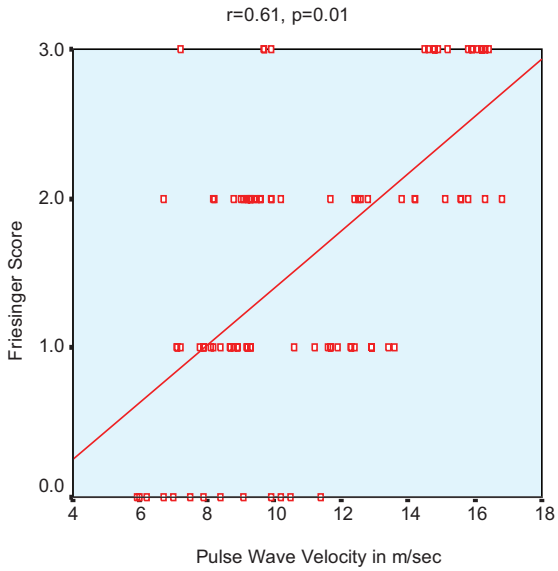

Fig.-2: *Correlation between PWV and Friesinger score*

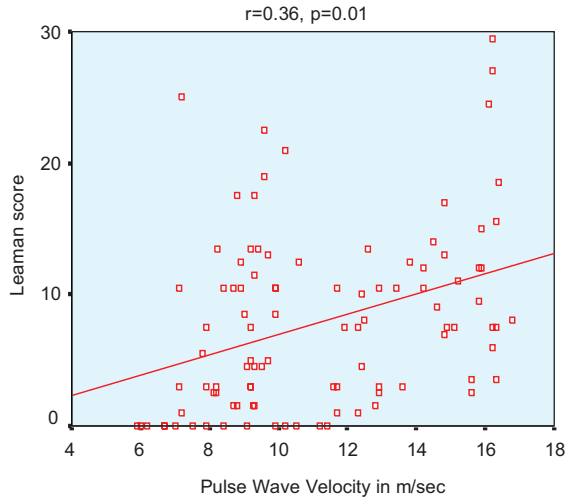

Fig.-3: *Correlation between PWV and Leaman score*

Table VI demonstrates the binary logistic regression analysis of odds ratio (OR) for characteristics of the subjects likely to cause coronary artery disease. The variables revealed to be significantly associated with severe CAD by univariate analysis. Of the 6 variables diabetes mellitus, hypertension and PWV were found to be the independently significant predictors of severe CAD with odds ratios being 2.12, 2.53 and 1.48 respectively.

Table VII demonstrates the binary logistic regression analysis of odds ratio (OR) for characteristics of the subjects likely to cause coronary artery disease severity. The variables revealed to be significantly associated with severe CAD by multivariate analysis were entered into the model directly. Of the 6 variables diabetes mellitus, hypertension and PWV were found to be the independently significant predictors of severe CAD with odds ratios being 2.10, 2.19 and 1.47 respectively.

Table-VI

Univariate analysis of determinants of CAD (by Friesinger score).

Variables of interest	B	S.E.	p value	OR	95% CI
Smoking	0.278	0.407	0.49	1.32	0.595 – 2.930
Diabetes mellitus	0.753	0.421	0.03[S]	2.12	1.061 – 4.849
Hypertension	0.927	0.414	0.02[S]	2.53	1.122 – 5.691
Dyslipidemia	0.223	0.391	0.23	0.60	0.258 – 1.386
Family history of CAD	0.230	0.396	0.60	0.80	0.337-1.873
PWV	0.389	0.087	0.001[S]	1.48	1.244 – 1.750

Dependent variable: CAD;
Independent variables: smoking, diabetes mellitus, hypertension, dyslipidemia, family history of CAD and PWV
s = Significant

Table-VII

Multivariate logistic regression of determinants of CAD (by Friesinger score).

Variables of interest	B	S.E.	p value	OR	95% CI
Smoking	0.260	0.399	0.92	0.95	0.362 – 2.501
Diabetes mellitus	0.658	0.401	0.04[s]	2.10	1.042 – 4.242
Hypertension	0.785	0.507	0.03 [s]	2.19	1.031 – 5.923
Dyslipidemia	0.211	0.291	0.25	0.58	0.075 – 0.830
Family history of CAD	0.241	0.399	0.62	0.77	0.264-1.543
PWV	0.388	0.097	0.001[s]	1.47	1.219 – 1.781

Dependent variable: CAD;
Independent variables: smoking, diabetes mellitus, hypertension, dyslipidemia, family history of CAD and PWV
s= Significant

Discussion:

This study was done with an aim to find out the association between the aortic pulse wave velocity and the angiographic severity of coronary artery disease in patients with non-ST-segment elevation myocardial infarction. A total of 100 patients with NSTEMI who agreed to undergo coronary angiography were included in the study. Coronary angiogram was done during index hospital admission. On the basis of pulse wave velocity (PWV), study subjects were categorized into two groups: 50 patients of NSTEMI with normal PWV (d"10 m/sec) were considered as group I and 50 patients of NSTEMI with increased PWV (>10 m/sec) were considered as group II.

The distribution of common risk factors for coronary artery disease in the present study revealed that smoking habit was found in 58 (58%) followed by hypertension 47 (47%), diabetes mellitus 40 (40%), dyslipidaemia 33 (33%), family history of premature CAD 30 (30%). It was observed that all risk factors were insignificantly greater in Group II than in Group I (p>0.05). Khan, et al.[8] found that smoking was the highest prevalent risk factor. This distribution of risk factors in study population is consistent with those found by Matsushima, et al.[9] and Wang, et al.[10]. However different studies carried out abroad demonstrated different patterns. This may be due to ethnic and cultural differences among the study populations. Mulders, et al.[11] found that first degree relatives with patients with premature coronary artery disease had higher PWV compared with unrelated controls. Similar to these findings, proportion of patients with positive family history of CAD was higher in group II of the present study.

In this study it was found that among group II, highest percentage was of 3 vessel score and 2 vessel score (34%) followed by 1 vessel score (26%). Six percent patients had 0 vessel score. On the contrary among group I, highest percentage was of 1 vessel score (48%). 22% and 10% belonged to 2 and 3 vessel score and 20% patient had 0 vessel score. 0 vessel and 1 vessel involvement was found significantly higher in group I (p=0.04 and p=0.02), double and triple vessel involvement was also found significantly higher in group II (p=0.04 and p=0.003 respectively).

The mean PWV of subjects with normal angiographic findings was 8.21±1.8 m/sec. The mean PWV of single, double and triple vessel disease were 9.88±2.02, 11.95± 2.61 and 14.37±2.96 (m/sec) respectively. The PWV increased in proportion with the number of vessels involved and the differences were statistically significant (p=0.001). Alarhabi, et al.[12] found that the mean PWV in the group with normal angiographic results was 8.14±1.25 m/sec and in patients with single-vessel disease it was11.13±0.91 m/ sec. In those with double vessel disease mean PWV was 15.22±1.11 m/sec, and in the multiple-vessel disease group it was 19.30±2.05 mD sec. There was statistically significant difference of PWV between the groups involving coronary arteries (P<.001). So, these findings of the present study are similar to the findings of the study done by Alarhabi, et al.[12]

Study conducted by Fukuda, et al.[13] found that patients with 3 vessel disease group had significantly higher PWV than the patients with normal coronary artery group (p<0.01), the 1 vessel disease group (p<0.01) and the 2 vessel disease group (p<0.05).Furthermore, PWV was significantly correlated with the number of diseased vessel (normal coronary artery group vs. 1 vessel disease group vs. 2 vessel disease group vs. 3 vessel disease group : 14.81 m/sec vs. 15.05 m/sec vs. 15.7 m/sec vs. 17.27 m/sec). PWV values of Fukuda, et al.[13] differ from the values of the present study as because ankle-brachial PWV was measured instead of carotid femoral PWV in the former study.

Ouchi, et al.[14] found PWV was significantly greater in triple vessel disease group (14.06±.88 m/sec) than in normal group (8.9±1.2 m/sec). So, in the above mentioned studies it was found that the PWV increased with increase in number of vessels involved which is similar to this present study.

In the present study, analysis of Friesinger score revealed that normal Friesinger score (0) was found in 3 (6%) patients in group II and 10 (20%) patients in group I. Low Friesinger score (1-4) was found in 4 (8%) and 19 (38%) patients in group II and group I respectively. Intermediate Friesinger score (5-10) was found in 25 (50%) patients in group II and in 17 (34%) patients in group I. High Friesinger score (11-15) was found in 18 (36%) patients in group II and 4 (8%) patients in group I. Normal and low Friesinger score were significantly higher in Group I (p=0.03 and p=0.001 respectively). Intermediate and high Friesinger score were significantly higher in group II. (p=0.04 and p=0.002 respectively).

Friesinger score 0-4 was defined as insignificant CAD whereas Friesinger score ≥5 was defined as significant CAD. The mean PWV was observed 12.6±3.1 m/sec and 9.5±2.2 m/sec in significant and insignificant CAD respectively. The difference of mean PWV between the significant and insignificant CAD groups was statistically significant (p=0.001), hence, PWV was significantly higher

in patients with significant CAD. Lee, et al.[15] found that the carotid radial PWV was higher in the complex lesion than in the simple lesion (9.55±1.5 m/sec vs. 8.99±1.5 m/sec respectively, p <.05). This finding is consistent to our study but differ in value as because Yamashina, et al.[16] noted that carotid femoral PWV is greater than carotid radial PWV but smaller than brachial ankle PWV.

In his study Covic, et al.[17] found that the patients with normal angiogram had significantly less arterial stiffness (as reflected by lower aortic PWV velocity, 8.2±1.53 m/sec) compared with the patients with obstructive coronary disease at angiography (13.21±1.15 m/sec). Moreover as more coronary vessels were affected, PWV increased proportionately. There was a statistically significant linear relationship between the atherosclerotic burden and measures of arterial stiffness and the result is closely related to the present study.

In this study there was a positive correlation between aortic PWV and coronary artery disease severity in terms of vessel score, Friesinger score and Leaman score (r=0.65, r=0.61 and r=0.36 respectively, p =0.01).

Hope, et al.[18] found in his study that he stenosis score were independently associated with aortic PWV (r=0.58, p< .001) whereas, Lee, et al.[15] found that the modified stenosis score had a positive correlation with PWV (r=0.55, p<0.001).These findings are consistent with those of the present study.

The binary logistic regression analysis of odds ratio (OR) for characteristics of the subjects likely to cause coronary artery disease, the variables revealed to be significantly associated with severe CAD by univariate analysis. Of the 6 variables diabetes mellitus, hypertension and PWV were found to be the independently significant predictors of severe CAD with ORs being 2.12, 2.53 and 1.48 respectively.

The odds ratio of aortic PWV for CAD was 1.38, found in the study done by Laurent, et al.[19], which is similar to our study. Blacher, et al.[5] found that the odds ratio of PWV for MI was 3.5 which differ from this study because they determined the odds ratio considering the value of PWV >13.5 m/sec as an independent variable.

The binary logistic regression analysis of odds ratio (OR) for characteristics of the subjects likely to cause coronary artery disease severity, the variables revealed to be significantly associated with severe CAD by multivariate analysis were entered into the model directly. Of the 6 variables diabetes mellitus, hypertension and PWV were found to be the independently significant predictors of severe CAD with odds ratios being 2.10, 2.19 and 1.47 respectively.

In their study, Kullo, et al.[20] found hypertension and aortic PWV to be independently associated with CAD, whereas, Alarhabi, et al.[10] found dyslipidemia and PWV as independent predictor for CAD. In the more recently published study by Wang, et al.[8] diabetes mellitus and aortic PWV were independent predictors for CAD. So, the findings of the present study correlate well with those studies done abroad.

Conclusion:

In conclusion, from this study it may be stated that arterial stiffness, as measured by the aortic pulse wave velocity, is an independent predictor of the presence and extent of coronary artery disease. This noninvasive evaluation method may be used as a useful marker of end organ damage in arterial system and help to identify patients at high risk for coronary artery disease. Early screening may help in early diagnosis and treatment of underlying vascular conditions before development into more serious illness. Moreover, measurements of aortic pulse wave velocity in non-ST-segment elevation myocardial infarction can detect high risk patients requiring an early invasive strategy over a delayed invasive strategy.

Study limitation:

This was a single center study and purposive sampling was done instead of random sampling method. Study was conducted only with NSTEMI patients, so the findings may not be applicable to the general population. Angiographic severity of coronary artery disease was evaluated by visual estimation, so chance of interobserver and intraobserver variation remained.

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Original Article

The Impact of Preoperative Anaemia on Early Outcomes after Off-pump Coronary Artery Bypass Grafting

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Abstract:

Introduction: In cardiac surgery, anaemia itself or combined with other risk factors has been found to be a major predictor for adverse outcome both preoperatively and postoperatively and even during extracorporeal circulation, but data about the specific tolerance of Coronary Artery Bypass Graft (CABG) patients for anaemia are conflicting and may in part be confounded by the effects of bypass surgery.

Objectives: This study was performed in the National Institute of Cardiovascular Diseases (NICVD) to observe whether the early outcomes of Off-Pump CABG (OPCAB)were affected by pre-operative haematocrit levels.

Methods: A total of 200 patients who underwent isolated OPCAB between January 2015 and December 2020 were retrospectively selected and purposively allocated into two groups: a)100 patients having preoperative anaemia and b) 100 patients without preoperative anaemia. Pre-operative, per-operative and early post-operative variables were recorded, compiled and compared.

Results: Preoperative characteristics were homogenously distributed between two groups other than haemoglobin level. Female patients had lower haemoglobin in each group. More patients of anaemic group required intraoperative and postoperative blood transfusion. The amount of blood loss and transfused blood products was also higher in anaemic patients. The ventilation time, length of ICU and post-operative hospital stay were significantly higher among anaemic patients. Among the post-operative complications, only the incidence of renal dysfunction was significantly higher among anaemic patients.

Conclusion:This study has showed that anaemic patients undergoing OPCAB had an increased risk of post-operative adverse events. Importantly, the extent of pre-existing comorbidities substantially affected perioperative anaemia tolerance. Therefore, pre-operative risk assessment, optimization and subsequent therapeutic strategies, such as blood transfusion, should take into account both the individual level of preoperative haemoglobin and the extent of concomitant risk factors.

Key Words: *Anaemia, preoperative, OPCAB.*

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Introduction:

Coronary artery bypass surgery (CABG) is the most effective method for the treatment of ischemic heart disease.[1]The success of surgery depends to some extent on the elimination or improvement of risk factors

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or on taking measures against it. Some of these factors include advanced age, poor ventricular function, presence of diffuse coronary lesions, presence of poor respiratory or renal function, previous cardiac surgery, complicated surgery, and emergent surgical intervention.[2]

Low haemoglobin is progressively frequent sign in patients having coronary heart disease.[3]About 51.5% patients with acute coronary syndrome in Indian population are anaemic.[4] Similar prevalence of anaemia is expected in our population with ischemic heart disease. World Health Organization (WHO) defined anaemia as haemoglobin level <13 gm/dl for adult male and <12 gm/dl for adult female.[5]

Although anaemia is a potentially treatable condition prior to surgery, numerous studies have proved that low haemoglobin level is linked with higher rate of post-operative morbidity (specially renal and neurologic events) and mortality in patients suffering from congestive heart failure, ischemic heart disease particularly in acute coronary syndrome and in elderly population.[3,6,7] Diseased heart cannot raise cardiac output sufficiently; therefore, reduced level of haemoglobin, even when fully saturated, cannot supply enough oxygen throughout body. In theory, patients with coronary artery disease may tolerate anaemia well as long as the compensating mechanisms of the cardiovascular system are largely uncompromised and no extensive comorbidity exists.[6]The impact of anaemia is confounded by blood transfusion during and after cardiac surgery. Blood transfusion increases postoperative morbidity and mortality. Anaemic patients need more blood transfusion.[8]Several studies have found that, compared to non-anaemic patients, anaemic patients have significantly higher rate of operative mortality, prolonged ventilation, post-operative atrial fibrillation, post-operative renal dysfunction, stroke, deep sternal wound infection, perioperative blood transfusion, longer ICU stay and longer hospital stay after cardiac surgery.[7,8,9,10,11]

The commonly applied preoperative risk stratification models in cardiac surgery like EuroSCORE, STS, ACEF, do not realize preoperative low haemoglobin level as a possible predictor of unfavorable outcomes and two out of nineteen models of risk stratification admit anaemia as an unconventional predictor of mortality.[3,12,13,14]Data from previous reports have disclosed preoperative anaemia to be self-sufficient predictor of unlucky outcomes in the form of morbidity and in-hospital death after coronary artery bypass graft (CABG) or valve surgery.[3,8,15]

Use of cardiopulmonary bypass during coronary artery bypass graft surgery has many adverse effects. Moreover, cardiopulmonary bypass increases the effect of anaemia and blood transfusion.[16] Blood transfusion is usually required to increase haematocrit after weaning from cardiopulmonary bypass. Off-pump coronary artery bypass graft (OPCAB) surgery is a technique that avoids the adverse effects of cardiopulmonary bypass. There is evidence that OPCAB significantly reduces blood transfusion than on-pump coronary artery bypass grafting.[17] So, in case of OPCAB surgery, impact of preoperative low haemoglobin level is minimally affected by blood transfusion and not affected by cardiopulmonary bypass.

The aim of this study was to investigate whether the routinely measured preoperative haematocrit level, affectsearly postoperative outcomes after OPCAB surgery.

Materials and Methods:

This retrospective observational study was performed in the department of Cardiac Surgery, National Institute of Cardiovascular Diseases (NICVD) from January 2015 and December 2020. 200 purposively selected patients who underwent elective off pump coronary artery bypass (OPCAB) graft surgery were allocated into two groups:

Group A: 100 patients having preoperative anaemia (haemoglobin level 9 to 13 gram/dl for male and 9 to 12 gram /dl for female).

Group B: 100 patients without preoperative anaemia (haemoglobin level 13 to 16 gram/dl for male and 12 to 15 gram /dl for female).

Technique of OPCAB:

Haemoglobin estimation was done within one week prior to surgery. All patients underwent standard off pump coronary artery bypass (OPCAB) graft surgery through median sternotomy.The internal thoracic artery, the radial artery, and the saphenous vein were harvested as appropriate with standard techniques. Then intravenous heparin (100IU/ kg) was given to maintain an ACT of 300 second before starting distal anastomoses. Regional myocardial immobilization was achieved with a suction stabilizer (Octopus) and apical suction device (Star Fish). Intracoronary shunts were used in most patients to maintain coronary flow, thereby reducing myocardial ischemia and at the sametime minimizing bleeding from the coronary arteriotomy. The left anterior descending (LAD) artery was revascularized first using left internal mammary/ thoracic artery (LIMA/ LITA). Proximal

anastomoses were performed on the partially clamped ascending aortausing 6-0 continuous Prolene suture. Distal anastomoses were performed with continuous 7-0 or 8-0 polypropylene (Prolene) monofilament suture. After the procedure, heparin therapy was reversed with protamine sulfate in a 1:1 ratio. The leg, forearm, and chest wounds were closed and the patients were shifted to ICU. Total operation time and number of grafts were recorded.

Postoperative Management:

After surgery, all patients were transferred to the intensive care unit (ICU). Cardiac, respiratory, renal function and hourly blood loss were monitored meticulously. Extubation was done as early as possible while the patients fulfill the extubation criteria. Arterial blood gas, serum electrolytes and hematocrit estimation were done as per standard protocol. Haemodynamic and other parameters were managed according to the standard protocol. Blood transfusion trigger was haematocrit of <26% or according to unit protocol. The amount of transfused blood or blood products were recorded. Serum creatinine was measured daily up to third postoperative day. Patients were on continuous ECG monitoring for 5 days and a check ECG was done prior to discharge to detect any arrhythmia. Neurological assessments were done on the first and second postoperative day.

Data Collection:

Data were collected using predesigned questionnaire and collection form. Data were analyzed and verified with statistical program for social sciences (SPSS) using student's t test, chi-square test, fisher's exact test where appropriate. The descriptive statistics used here were frequency, mean and standard deviation (SD) and compared using student's t test. Categorical data were expressed as percentages and evaluated using chi-square or Fisher's exact probability test. The level of significance was 0.05. Any p-value <0.05 was considered significant.

Results:

Patient characteristics are shown in the Table-1. The mean ages of the study sample were 60.3±7.86 years for the group A (with anaemia) and 58.9±6.79 years for the group B (without anaemia) showing no a significant difference (p=0.2986; >0.05) in age distribution. In the study both sexes were homogenously distributed between the two groups but with clear male predominance (86% vs. 88%; p=0.766). The mean BMI were almost similar (26.98±2.3vs. 27.2±2.14kg/m^2, p = 0.5885; >0.05).The mean haemoglobin level among group A males was significantly lower than that among group B (11.7±1.18 vs. 13.6±0.55; p=<0.0001). The same was true for females (10.2±0.58 vs. 12.2±0.21; p=<0.0001). In our study, the commonest co-morbid factor was smoking in both groups (48% vs. 51%; p= 0.6716). It was followed by hypertension (43% vs. 47%; p=0.5697), diabetes mellitus (38% vs. 41%; p=0.6642) and dyslipidemia (34% vs. 35%; p=0.882). Other co-morbid factors were family history of CAD (10% vs. 8%), past history of CVA (4% vs. 3%), COPD (11% vs. 9%), history of MI (45% vs. 47%), PVD (9% vs. 8%) and renal dysfunction (10% vs. 14%). All were almost identically distributed between the groups (p > 0.05). In the study the mean left ventricular ejection fraction (LVEF) was almost similar inboth groups (46± 5.7% vs. 47± 7.2; p = 0.2775). Pre-operative angiographic study demonstrated that majority of the patients had triple vessel diseases (TVD) in each group (76%and 72% respectively). The rest had double vessel diseases (DVD) and left main diseases (LMD) which were similarly distributed among the two groups (p>0.05).The distribution of NYHA and CCS angina classes between the two groups were also homogenous (p>0.05).

The mean operating times were similar in two groups (268.5 ± 33.5vs. 259.3 ± 34.8; p=0.06). All the patients of both groups received left internal mammary artery (LIMA) and saphenous vein (SVG) as conduit. Radial artery was also used in some patients of both groups as second arterial conduit (24% vs. 28%; p=0.5190). It is important to mention that all the left anterior descending arteries (LAD) of both groups were anastomosed to LIMA. Intra-operatively 74% anaemic and 56% non-anaemic patients required blood transfusion (p=0.0076). Intra-operative hemoglobin level was significantly lower in group A than group B (9.1±1.1 vs. 10.7± 1.2; p=<0.000).

Post-operative transfusion of blood products was significantly higher among group A (56% vs. 28%; p=0.00006). The mean amount of transfused blood products was also higher in group A(1085 ± 45 vs. 690 ± 30; p=<0.0001). Although the 30 days mortality was similar among two groups, other post-operative variables like mechanical ventilation time, total bleeding, length of ICU stay, length of post-operative hospital stay were significantly higher among anaemic patients. Two patients of group A and one of group B required IABP post-operatively. Among the post-operative complications renal dysfunction was higher among anaemic patients (21% vs. 7%; p=0.0043). Other complications like low output syndrome (LOS) (6% vs. 2%; p=0.279), re-exploration for bleeding (3% vs.1%; p=0.6212), arrhythmia

Table-I

Pre-Operative Characteristics of Patients with and without Anaemia

Variables	Group A(n=100)	Group B (n=100)	*p* Value
Age, years#	60.3±7.86*	58.9±6.79*	0.2986ns
Male, n (%)¥	86(86)	88(88)	0.766ns
BMI (kg/m²)#	26.98±2.3*	27.2±2.14*	0.5885ns
Haemoglobin (gram/dl)			
Male	11.7±1.18*	13.6±0.55*	<0.0001s
Female	10.2±0.58*	12.2±0.21*	<0.0001s
Hypertension, n (%)¥	43(43)	47(47)	0.5697ns
Diabetes mellitus, n (%)¥	38(38)	41(41)	0.6642ns
Smoking, n (%)¥	48(48)	51(51)	0.6716ns
Dyslipidemia, n (%)¥	34(34)	35(35)	0.882ns
Family H/O CAD, n (%)¥	10(10)	8(8)	0.6212ns
Past H/O CVA, n (%)¶	4(4)	3(3)	1.000ns
COPD, n (%)¥	11(11)	9(9)	0.6373ns
History of MI, n (%)¥	45(45)	47(47)	0.7766ns
PVD, n (%)¥	9(9)	8(8)	0.7798ns
Renal dysfunction, n (%)¥	10(10.0)	14(14)	0.2841ns
Arrhythmia, n (%)¥	6(6)	7(7)	1.000ns
LVEF (%)#	46± 5.7*	47± 7.2*	0.2775ns
NYHA class II or III, n (%)¥	16(16)	14(14)	0.6921ns
CCS angina class III or IV, n (%)¥	43(43)	39(39)	0.5652ns
LMD¥	10(10)	12(12)	0.6513ns
DVD¥	14(14)	16(16)	0.6921ns
TVD¥	76(76)	72(72)	0.519ns

* Data are presented as the mean ± SD for continuous variable.
# Student's t-Test, ¥ Chi-square (χ^2) Test, ¶ Fisher's Exact Test, s= significant, *ns* = Non-significant
CCS: Canadian Cardiovascular Society Angina Class; COPD: Chronic Obstructive Pulmonary Disease; CVA:Cerebrovascular Accident; DVD: Double Vessel Disease; LMD: Left Main Disease; MI: Myocardial Infarction; NYHA: New York Heart Association;PVD: Peripheral Vascular Disease; TVD: Triple Vessel Disease.

Table-II

Operative Data of Patients with and without Pre-operative Anaemia

Variables	Group A (n=100)	Group B (n=100)	*p* Value
Total operating time, minutes#	268.5 ± 33.5*	259.3 ± 34.8*	0.06ns
Conduit used¥			
LIMA, n (%)	100(100)	100(100)	1.000ns
Radial artery, n (%)	24(24)	28(24)	0.5190ns
SVG, n (%)	100(100)	100(100)	1.000 ns
Graft distribution¥			
LAD territory, n (%)	100(100)	100(100)	1.000 ns
Circumflex territory, n (%)	93(93)	97(97)	0.1944 ns
RCA territory, n (%)	85(85)	83(83)	0.6997ns
Intra-operative transfusion of blood products, n (%)¥	74(74)	56(56)	0.0076s
Intra-operative lowest hemoglobin (gram/dl) #	9.1±1.1	10.7± 1.2	<0.0001s

* Data are presented as the mean ± SD for continuous variable.
# Student's t-Test, ¥ Chi-square (χ^2) Test, s= significant, *ns* = Non-significant
LAD: Left Anterior Descending Artery; LIMA: Left Internal Mammary Artery; RCA: Right Coronary Artery; SVG: Saphenous Venous Graft.

Table-III

Post-operative of Patients with and without Pre-operative Anaemia Data

Variables	Group A(n=100)	Group B (n=100)	*p* Value
Post-operative transfusion of blood products¥	56(56)	28(28)	0.00006s
Amount of blood products needed (ml) #	1085 ± 45*	690 ± 30*	<0.0001s
30 days mortality, n (%)¶	4(4)	2(2)	0.6827ns
Ventilation time, hours#	11.4±2.3*	8.6±3.5*	<0.0001s
LOS or Prolonged inotropic support¶	6(6)	2(2)	0.279ns
Postoperative IABP¶	2(2)	1(1)	1.000ns
Total bleeding (ml) #	602 ± 85*	378 ± 75*	<0.0001s
Length of ICU stay (days) #	4.8± 2.5	3.4± 2.2	<0.0001s
Length of post-operative hospital stay(days) #	10.3 ± 1.3*	8.2 ± 1.2*	<0.0001s
Re-exploration for bleeding¶	3(3)	1(1)	0.6212ns
Stroke¶	3(3)	1(1)	0.6212ns
Pulmonary complication¶	4(4)	2(2)	0.6827ns
Perioperative MI¶	2(2)	2 (2)	1.000ns
Arrhythmia¥	10(10)	8(8)	0.6212ns
Surgical site infection¶	6(6)	4(4)	0.7475ns
Renal dysfunction¥	21(21)	7(7)	0.0043s

* Data are presented as the mean ± SD for continuous variable.

Student's t-Test, ¥ Chi-square (χ^2) Test, ¶ Fisher's Exact Test, s= significant, *ns* = Non-significant

IABP: Intra-aortic Balloon Pump; ICU: Intensive Care Unit; LOS: Low Output Syndrome; MI: Myocardial Infarction.

(10% vs. 8%; p=0.6212), peri-operative MI (2% vs. 25; p=1.000), stroke(3% vs.1%; p=0.6212), pulmonary complications (4% vs. 2%; p=0.6827), surgical site infection (6% vs. 4%; p=0.7475) were homogenously distributed among the two groups.

Discussion:

This study is unique in evaluating the effect of pre-operative anaemia on post-operative outcomes in patients undergoing exclusively isolated off-pump CABG. Previous studies have reported several advantages of off-pump CABG compared with conventional CABG, including less intra-operative haemodilution. During CABG with cardiopulmonary bypass, the crystalloid priming solution and cardioplegia solution may decrease the haemoglobin concentration, increase haemodilutional anaemia, and result in worse post-operative outcomes. The associated morbidities may occur more frequently in patients with pre-operative anaemia. Moreover, although the pre-operative anaemia may allow for a period of adaptation, haemodilutional anaemia causes a sudden change in tissue oxygenation. All these factors render patients with anaemia at higher risk of adverse events when they undergo CABG with cardiopulmonary bypass. In patients undergoing off-pump CABG, the effects of haemodilution with crystalloid priming solution and cardioplegic solution are eliminated.

According to the pre-operative characteristics the groups were comparable other than haemoglobin concentrations. Female patients had lower haemoglobin than male patients in each group. Kumar et al.[2] and Karkouti et al.[6] in their studies showed similar findings. However, Matsuda et al.[19] in their retrospective observational study showed that patients with pre-operative anaemia had more comorbidities than patients without pre-operative anaemia; patients with pre-operative anaemia were older and more likely to be female, and had a smaller body surface area, lower left ventricular ejection fraction, and greater renal dysfunction.

Although total operative time and graft distribution were similar among anaemic and non-anaemic groups, more patients of anaemic group required intra-operative blood transfusion (74% vs. 56%) as their mean haemoglobin level was lower. The ventilation time, length of ICU and post-operative hospital stay were significantly higher

among anaemic patients. Kumar et al.[2]in their study found that post-operative drainage, the need for blood and blood product transfusion, and length of ICU and hospital stay were statistically higher in low-haematocrit group Matsuda et al.[19] found that in the post-operative period more patients with pre-operative anaemia required blood transfusion and the amount of blood loss and blood products transfused were also higher in those patients.It has been suggested that peri-operative RBC transfusion negatively affects outcomes after cardiac surgery. More recently, Zhang and colleagues[20] demonstrated that in patients who underwent CABG within 21 days of myocardial infarction, pre-operative anaemia was not associated with mortality or major adverse events; however, intraoperative RBC transfusion predicted major adverse events. In a study by Surgenor et al.[21] 36% of patients received one to two units of packed cell transfusion; among them, 43% were transfused intra-operatively, and the rest were post-operatively transfused, and the mortality rate was found to be 16% higher in patients receiving transfusion compared to those who did not receive it.

Matsudaet al.[19] showed that patients with intra-operative RBC transfusion had worse outcomes than patients without intra-operative RBC transfusion. The primary purpose of RBC transfusion is to increase oxygen delivery, which is determined by cardiac output and arterial oxygen saturation, the latter being dependent on the haemoglobin level. However, the Transfusion Requirements after Cardiac Surgerytrial conducted by Hajjar et al.[22] compared a restrictive transfusion strategy (<24%) with a liberal transfusion strategy (<30%), reported no difference in the primary end point (combined outcome of 30-day mortality and severe morbidity) between the groups. The restrictive transfusion strategy did not result in reduced oxygen availability to cells, as demonstrated by similar lactate levels in both groups. The adverse effects of RBC transfusion include acute haemolytic and non-haemolytic reactions; transmission of viral and bacterial diseases, transfusion-related acute lung injury, transfusion-related acute kidney injury, transfusion-related circulatory overload and immunosuppression. The decision to transfuse should be individualized and based on a rational approach that accounts for physiologic variables in addition to the haemoglobin level.

Among the post-operative complications, we found the incidence of renal dysfunction was higher among anaemic group. Although the actual incidences of operative mortality, stroke, peri-operative MI, arrhythmia, pulmonary complications and infective complications were higher among anaemic patients these were not statistically significant. A large study with greater sample size might show actual findings. Karkoutiet al.[6] found that renal dysfunction was an important peri-operative pathophysiological factor for adverse outcome, being both a cause for and a result of pre-operative anaemia. It appears that the renal system especially with history of dysfunction was more sensitive than other organs to a temporary relative haemoglobin deficiency, thereby acting as a particularly sensitive and early indicator of pending ischemic injury to vital organs. Ranucci et al.[8] found that patients with pre-operative haematocrit levels <35% developed more than three-fold of major morbidities when compared to patients with pre-operative haematocrit levels of >42% circulation Karkoutiet al.[6] showed that pre-operative anaemia was associated with an increase of all post-operative adverse events, starting at haemoglobin level <11 gm/dl in a dose-dependent fashion.Specially low pre-operative haemoglobin was an independent predictor for post-operative renal and central nervous system outcome, and the association with increased cardiac adverse events was caused by concomitant risk factors prevalent in anaemic patients. The extent of comorbidities substantially amplified the adverse effects of low pre-operative haemoglobin, which in turn was a significant marker for severe underlying diseases and comorbidities. Matsuda et al.[19] in their study showed that patients with pre-operative anaemia had higher rates of low output syndrome, haemodialysis requirement, and the composite adverse outcome after isolated off-pump CABG than patients without pre-operative anaemia. Patients with pre-operative anaemia also tended to have a higher rate of operative death, but this difference was not statistically significant. However, multivariate analyses showed that pre-operative anaemia was not an independent predictor of these post-operative outcomes. Rather old age was the only independent predictor of mortality; however, old age, high serum creatinine, prior myocardial infarction, and low ejection fraction were found to be significant independent predictors of mortality.

Conclusion:

The present study found that patients with preoperative anaemia had poorer outcomes after isolated off-pump CABG than patients without preoperative anaemia. Though the mortality among the anaemic patients was not significantly higher, a large scale study might have shown the exact scenario. The adverse outcomes might be related to associate comorbidities including age, smaller body surface area, lower glomerular filtration rate, congestive heart failure, non-elective surgery, and intraoperative blood transfusion. Cardiac surgery population is aging, and thus comorbid renal and central nervous system complications warrant increased

attention because they play an important role in the decision to proceed with CABG. Awareness and optimization of risk factors prior to operation is essential for better outcomes and early recovery.

Study Limitations:

The present study has several limitations and those are as follows:

1. Sample size was small and patients were selected purposefully. There was possible selection bias in patients selected for off-pump CABG rather than CABG with cardiopulmonary bypass.
2. They were not randomly assigned to either group.
3. Intra-operative and post-operative blood transfusion was at the discretion of the surgeon or anaesthesiologist. So the relative importance of pre-operative anaemia and intra-operative transfusion remained unclear.
4. The duration of follow up of this study was limited. Clinical outcomes were restricted to 30-days mortality. Patients were not followed up for medium and long-term results.
5. As a single institutional study the conclusions may not be applicable in general because of differences in practice patterns of other centres.

Other factors such as variations in surgical skill, patient difference in extent or distribution of coronary artery disease and echocardiography reports although unavoidable should also be considered.

Recommendations:

Despite the advances in cardiovascular medicine and cardiac surgical techniques, morbidity and mortality are still a problem after CABG. With increasing life expectancy, morbidity and mortality rates have also increased in elderly individuals. Due to this reason, preoperative assessment is extremely important to determine the risk factors. This study showed that anaemic patients undergoing OPCAB had an increased risk of postoperative adverse events. Importantly, the extent of pre-existing comorbidities substantially affected perioperative anaemia tolerance. By using risk stratification systems, operating surgeons, cardiac anaesthetists, ICU teams, patients' relatives, and the patients themselves become aware of what awaits them. We believe that preoperative haemoglobin level should be added to the risk scoring systems, which could be used to evaluate the patients' postoperative mortality risk and to predict the length of hospital stay and cost-efficacy.

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Review Article

The Anesthesia & Anesthetists of the First Open Heart Surgery of Bangladesh

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Abstract:

Although a few closed heart operations were performed in the late 1960s, well organized approach to open heart surgery began in Bangladesh only after establishment of Institute of Cardiovascular Diseases (ICVD) in 1978. A Japanese team of surgeons, anesthetists, nurses and technicians provided extensive support in capacity building of the local human resources. Ultimately the first open heart surgery of Bangladesh, the direct closure of Atrial Septal Defect of an 18 year old college student, was performed on 18th September 1981. It was great news of that time. People came to know about the success story of the ICVD director then Colonel M Abdul Malik, a renowned cardiologist cum team leader and the Bangladeshi surgeon duo Dr M Nabi Alam Khan and Dr S R Khan. But somehow the anesthetists, an important part of the team were out of focus and have been forgotten over time. Led by Prof Khalilur Rahman, the anesthetist team of the day included Dr Nurul Islam, Dr Abdul Hadi, Dr Delowar Hossain, Dr A Y F Ellahi Chowdhury and Dr Monir Hossain. This article is an attempt to remind their contribution and expressing respect and gratitude to the anesthetists of that pioneering team.

Key Words: *Anesthesia, Anesthetist, Bangladesh, first open heart surgery, Pioneer.*

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Introduction:

Although a few cases of finger fracture closed mitral commissurotomies were performed in the Dhaka Medical College Hospital and in the then TB hospital at Mahakhali during late 1960s and early 1970s, full-fledged cardiac surgical services began in Bangladesh only after the establishment of Institute of Cardiovascular Diseases (ICVD) at Dhaka in 1978. First ever open heart surgery of the world using heart lung machine and utilizing cardiopulmonary bypass was performed by Dr John Gibbon in USA on the 6th May 1953[1]. Twenty-eight years later the first open heart surgery in Bangladesh was performed on the 18th September 1981. There were no experienced or trained Bangladeshi cardiac surgeons or anesthetists in those days. A Japanese team of cardiologists, surgeons, anesthetists, nurses and technicians was deployed at ICVD to help capacity building of the local human resources. But for some obscure reason, the events of those early days of cardiac surgery in Bangladesh have never been properly published. The objective of this study is to draw a pen-picture of that important cardiac anesthetic episode of medical history of Bangladesh mainly based on the reminiscence of the pioneering team members. The surgical aspect of the event would be covered in a follow up article of this series.

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Materials and Methods:

It is difficult to figure out the exact details of such an extraordinary event almost four decades later. The memory of the persons concerned has been the primary source. Most of the pioneer surgeons, physicians and anesthetists are still alive and present in Bangladesh. The persons listed in table 1 were interviewed for obtaining information related to that operation. They were either part of the pioneering team or working at ICVD during that period. A standard set of questionnaires was prepared for the interview. Average interview time was 53 minutes.

In addition, some other persons who were not at ICVD that time but might possess some important clues have also been contacted. The ICVD records and documents have been checked. The books and memoirs written by some of the above have also been good source of information. Pub med and internet search engines were also utilized in search of information related to the operation. Finally, the principal author had an opportunity to have an over the telephone discussion with the first patient himself. The issues of that discussion have been reflected in the article. However, the contact with the first patient was later lost and his latest whereabouts couldn't be reestablished at the time of finalizing this paper.

The Historic Episode

Colonel M Abdul Malik was the founder Director of ICVD. The Government of Bangladesh took initiative to start specialized medical services of various sub-specialty in the late 1970s & early 1980s. Indoor services of ICVD began on August 1978. Initially it was cardiology services only. Prof M Nabi Alam Khan was the first surgeon to join ICVD. Prof S R Khan had literally driven his own car back home from UK and joined chest Hospital. He also had an attachment 3 days a week to ICVD. Prof Khalilur Rahman was the chief anesthetist of the hospital during that period.

OT-1 of ICVD was commissioned on the 14th June 1980. Interestingly the first few cases of ICVD OT were not cardiac, rather included a wide variety including incision

Table-I

List and designation of the persons interviewed.

Name	Designation at that time	Role
Brig. (Rtd) Prof M Abdul Malik	Director cum Professor, ICVD	Team Leader
Prof S R Khan	Professor of Surgery, ICVD	Surgeon
Prof Khalilur Rahman	Professor of Anesthetist, ICVD	Chief Anesthetist
Prof M Nazrul Islam	Assistant Professor of Cardiology, ICVD	Observer
Prof AKM Mahibullah	Assistant Registrar, Cardiology, ICVD	Observer
Prof A Y F Elahi Chowdhury	DA student, IPG MR	Visiting anesthetist
Prof Nasiruddin Ahmed	Assistant Registrar, Cardiac Surgery, ICVD	Observer
Mrs Anima Boiragi	Senior Staff Nurse, ICVD	OT Nurse

Fig.-1: *The Daily Observer reporting the event. (spelling of "Dhaka" was "Dacca" on those days)*

and drainage of abscess, cholecystectomy, vagotomy & gastro-jejunostomy, pyelolithotomy, appendicectomy, excisional biopsy and what not! The first true cardiac case was a closed mitral valvotomy performed by Prof M Nabi Alam Khan on the 9th July 1980. The anesthetist was Prof Khalilur Rahman. He was assisted by Dr Zaheda. This may be described as the first cardiac operation at ICVD or in other words the first well organized, definite and documented cardiac surgical procedure of Bangladesh. Dr Khalilur Rahman and Dr Zaheda hence are the anesthetists of the first reported cardiac operation in Bangladesh as per the NICVD records.

A few other anesthetists also took part in the ICVD cardiac operations in those days. They include Dr Hadi, Dr Hafiz and Dr AYF Ellahi Chowdhury. Some of these anesthetists were not NICVD staff, rather they were students Diploma in Anesthesiology (DA) course at IPGMR. They used to attend the ICVD operations at the invitation of their teacher and mentor Prof Khalilur Rahman.

The Final Preparation

The first open heart operation of any country is a matter of great celebration. In the summer of 1981, all were set for the beginning. The Japanese team was ready to provide logistics support and capacity building for this noble move. Finally, a suitable patient was found for the first open heart surgery. Mr Md Mustafizur Rahman, an 18-year-old college student from Sitakunda, Chittagong diagnosed with ASD secundum patient was the first candidate of the journey through cardiopulmonary bypass in Bangladesh. There were some preparatory meetings and mock trials before the D-day. The Japanese anesthetist attending was Dr Yishibashi Kishi. To ensure adequate support in the OT and ICU Prof Khalilur Rahman invited 2 Diploma in Anesthesiology students from IPGMR to join the ICVD anesthetist team. They were Dr A Y F Ellahi Chowdhury and Dr Monir Hossain. These two young anesthetists had no previous idea about open heart surgery. But being part of this history making event was quite an experience for them.

The D day

On 18th September 1981 history was made when the first ever open heart operation of Bangladesh was performed at ICVD. The 18-year-old college student was taken to the OT. The first obstacle came when inexperienced anesthetists were having difficulty in putting the arterial line. Late Prof M Nabi Alam Khan then came with help and performed the radial artery cannulation using his vascular surgery experience. Rest of the anesthetic procedure ran smoothly. The surgical team comprised of Dr Kome Saji of Japan, Prof M Nabi Alam Khan, Prof S R Khan and Dr Minhaz. The role of perfusionist was performed by another Japanese surgeon Dr Tomino and Dr Fazlur Rahman, the then resident surgeon of ICVD. Led by Prof Khalilur Rahman, the anesthetist team (Table 2) included Dr Nurul Islam, Dr Abdul Hadi, Dr Delowar Hossain, Dr A Y F Ellahi Chowdhury and Dr Monir Hossain. The actual operation turned out to be an easy one. It was a small atrial septal defect, managed by direct closure. Cross clamp time was 27 minutes. Rest of the operation went smoothly

Table-II

The Anesthesia Team

Name	Position in 1978-81	Current Whereabouts (2018)
Dr. Khalilur Rahman	Associate Consultant Anesthetist (Associate Professor), ICVD)	Legendary Professor of Anesthesia, retired from professional activities, but engaged in academic sessions
Dr Nurul Islam	Anesthetist, ICVD	Deceased
Dr Abdul Hadi	Anesthetist, ICVD	Working in Medina Saudi Arabia for the 35 years
Dr Delawar Hossain	Junior Anesthetist, ICVD	Deceased
Dr A Y F Elahi Chowdhury	DA student, IPGMR	Legendary Professor of Anesthesia & Former Director of NICVD. Now Professor & in charge of ICU, National Heart Foundation Hospital Dhaka
Dr Monir Hossain	DA student, IPGMR	Working in Riyadh, Saudi Arabia

and the patient was transferred to ICU by 2.30 PM. The patient was put on an IKA R120 ventilator for mechanical ventilation support. The ICVD ICU was equipped and Nehon Coden invasive cardiac monitors at that time. These were huge bulky monitors requiring a number of dry cell batteries for power support.

The Anesthetic Course of Action

The cardiac anesthesia available at NICVD in 1981 was almost completely different from what we see today. The induction in those days used to be done by a combination of morphine, diazepam and thiopental sodium. For maintenance of anesthesia, a mixture of halothane-nitrous oxide-oxygen, together with incremental doses of morphine and diazepam were used. There was no fentanyl. Pancuronium bromide (Pavulon) and gallamine triethiodide (Flaxedil) were the only two neuromuscular blocking agents available. Pancuronium was used for muscle relaxation in open heart surgery and gallamine for closed heart cases. In those days, closed mitral commissurotomy (CMC), ligation and division of patent ductus arteriosus (PDA), Blalock-Taussig shunt for palliation of tetralogy of Fallot's (TOF) and repair of coarctation of aorta used to be branded as closed heart surgery. No proper intravenous vasodilator, not even glyceryl trinitrate was available. Interestingly, chlorpromazine hydrochloride (Largactil) prepared as a 1mg/ml solution was used incrementally to achieve vasodilatation.

The Near Disaster

There is an old proverb in cardiac surgery. "Mistakes are waiting to happen, keep them waiting". This pristine operation could have turned into a disaster despite the highest level of precautions. As one of the team members recalled that soon after the patient was shifted to the ICU, a nurse had rushed to the doctors and informed that probably half a bag of mismatched blood had been transfused to the patient. This was a real emergency nobody was prepared for. In those days even Mannitol was a rare item in Bangladesh. Prof A Y F Ellahi Chowdhury clearly recalled the events even after 37 years. Prof Khalilur Rahman had sent him to Chankherpul

Fig.-3: *Report on the Daily Sangbad, 25th September 1981*

medical market, where only a handful of stores kept Mannitol solution. It was a memorable ambulance ride for the young anesthetist with siren playing from ICVD to Chankerpul and back. With this invaluable Mannitol and other available medications, the aftermath of mismatch transfusion was managed successfully. The remainder of ICU stay of the patient was smooth and uneventful.

However, the incident of mismatched transfusion was taken seriously. An enquiry committee was formed headed by Prof Mujibur Rahman, head of the ICVD Blood bank. After thorough investigation the committee didn't find any malafide intention or sabotage. The committee concluded that human error was responsible for this mistake.

The Legacy and Aftermath

The World's era of open heart surgery began in 1953 with the invention of heart lung machine by Dr John Heysham Gibbon[3]. Before that only a few cases of open heart operations were performed in 1952 using deep hypothermic arrest technique by John Lewis at the University of Minnesota. Dr Gibbon closed the atrial septal defect of an 18-year-old girl using his heart lung machine on 6th May 1953. This operation was reported a year later. But due to death of the next patients, Dr Gibbon gave up using his heart lung machine except for contributing in its research and further development[4]. John Kirklin and his coworkers at Mayo clinic actually developed the first truly commercialized heart lung machine, known as the Mayo-Gibbon device based on the original design of Dr Gibbon[5].

The first open heart surgery of the subcontinent was performed by Dr K N Dastur at Bombay on 16th February 1961[6,7]. Even 20 years later, the first open heart operation in 1981 was considered a real heroic act in Bangladesh. The news was not disclosed to public for a couple of days. The ICVD authority had held a press conference on 24th September, six days after the operation. The newspapers flashed the news of this great achievement the next day[8]. The people of Bangladesh welcomed this news with euphoria. There was discussion everywhere regarding this huge achievement. The only TV channel in those days Bangladesh Television also gave huge coverage. There was a special episode in a popular TV variety show "যদি কিছু মনে করেন" covering this unique achievement.

The team leader Colonel Abdul Malik drew the highest media attention. Some media described that he himself had performed the operation. The two Bangladeshi surgeons Prof M Nabi Alam Khan and Prof S R Khan also had fair share of the glory, if not right at that moment, but later over the years. But the anesthetists are mostly forgotten, so are the Japanese volunteers. Hardly anybody today knows the names of the anesthetist members of the team, or those of the Japanese volunteers. Bangladesh postal department published a commemorative stamp and a first day cover in 2011 on the 30th anniversary of the operation[9].

Conclusion:

The first open heart surgery was quite like the feelings of Neil Armstrong, the first man on moon: 'a small step for a team, but a big leap for a nation'. It was a big boost in the cardiac care of Bangladesh. ICVD became the national institute and continued as a production unit of cardiac surgeons, cardiac anesthetists, cardiologists, cardiac nurses and technicians. It became the symbol of cardiac care and remained as the main cardiac care center for the nation for more than next two decades until the big private hospitals showed up after the beginning of the new century. The first operation of 18th September 1981 remains a day of celebration for the nation.

The Bangladeshi surgeons of the team Late Prof M Nabi Alam Khan and Prof S R Khan later on became heroes for their role in establishing cardiac and vascular surgery in the country. The timely introduction of postgraduate academic course helped creating legacy for the Khan duo. They have become the part of the history of medical science in Bangladesh. The anesthetists played a very important role in that pioneering operation. But unfortunately, their role didn't yield the glory they deserved. People have largely forgotten the names of the anesthetists. This article is an attempt to remind and highlight the glorious role of the anesthetists who were integral part of the pioneering cardiac surgical team on the 18th September 1981.

Acknowledgement:

Collecting and compiling information on an event that had happened 37 years ago was not easy. I had been working on the history of development of cardiac surgery in South Asia for quite some time. Many information of this article was collected as part of that effort. But the idea of recording the history of Bangladesh actually came while having a chat with promising young cardiologist Dr A K M Monwarul Islam, Prof Abdullah Al Shafi Majumder and Prof A K M Mohibullah, the two top office bearers of Bangladesh Cardiac Society. I'm grateful to them for their enthusiastic approach to encourage me for starting this difficult task. I pay tribute to former ICVD Professor of Anesthesia Dr Khalilur Rahman and 3 former NICVD Directors namely National Professor Brig (Rtd) Abdul Malik, Prof M Nazrul Islam and Prof A Y F Elahi Chowdhury as most of the information of this article came from them.

However some aspects of the early ICVD days I came to know while working there as an Assistant Registrar during 1996-97. I had the opportunity to listen to the cardiac surgery grand masters Prof S R Khan, Late Prof M Nabi Alam Khan, Prof M Alimuzzaman, Prof Nasiruddin Ahmed, Prof N A Kamrul Ahsan, Prof Asit baran Adhikary, Prof Faruque Ahmed, Dr Jahangir Kabir, Prof M Aftabuddin, Prof Abul Kashem, Dr SAM Abdus Sabur, Dr A A Solaiman, Dr Lutfor Rahman, Prof M Sharifuzzaman along with anesthetists Prof A T M Khalilur Rahman, Dr Ahsan Habib and many others. I thank them all.

1981 news clips from Daily Observer and Dainik Sangbad " দৈনিক সংবাদ" have been used in the article. We express our gratitude to those dailies along with Mr Syed Badrul Ahsan, the Associate Editor of Daily Obsrver and Mr Khandaker Muniruzzaman, the Editor in charge of Dainik Sangbad. I also thank my friends Dr Bilquis Ferdous Ara and Ms Nihad Kabir in this regard.

Finally may I offer special thanks to all the pioneers of the early days for their invaluable contribution to development of cardiac surgery in Bangladesh.

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Case Report

Anomalous Origin of Left Main Coronary Artery from Right Coronary Artery in A Patient Presenting with Inferior Wall Myocardial Infarction: A Case Report

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Abstract:

Anomalous origin of the coronary arteries is a very rare phenomenon and is seen only in less than 1% of the general population. Single coronary artery (SCA) is a congenital anatomic abnormality identified by a single coronary ostium giving rise to one coronary artery. Our case presented at 40 years with intermittent chest discomfort, effort intolerance and a history of getting Streptokinase one month back due to AMI (Inferior). Diagnosis was confirmed with elective conventional coronary angiography and coronary CT angiography as an extremely rare variant of the left main coronary artery (LMCA) branching off from the right coronary artery (RCA) and then following a pre-pulmonic course. We did Off Pump CABG surgery with four grafts and discharged the patient uneventfully with guideline-directed medical therapy with a beta-blocker, statin, and dual antiplatelet agents and the patient is on follow up.

Key words: *Single coronary artery, Coronary artery anomaly, Pre-pulmonic, Anomalous left main coronary artery, CABG*

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Introduction:

The term 'coronary artery anomaly' (CAA) is used when the observed coronary pattern is seen in less than 1% of the general population.1 The overall incidence of CAA has been estimated between 0.9% and 5.6%.2–4 Based on the origin and course of the anomalous artery, CAA can either represent a benign incidental finding or can have severe cardiovascular sequelae. Coronary computed tomography angiography (CTA) is a reliable non-invasive tool for diagnosing CAA. The management varies based on the nature of symptoms. Here, we present a case of inferior wall ST-elevation myocardial infarction due to distal right coronary artery (RCA) occlusion with incidental findings of anomalous left main coronary artery (LMCA) branching off the RCA.

Case

A 40-year-old hypertensive and diabetic lady presented to our facility for elective CAG with a h/o AMI (Inferior) approximately one and half months back. Other relevant medical history included effort fatiguability and occasional

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left sided chest pain for two months with a positive family history. On presentation, the patient was haemodynamically stable and physical examination including cardiovascular auscultation was unremarkable. Electrocardiograms (EKG) displayed Q-wave and inverted T-wave in the leads II, III, and AVF (Figure 1A). The patient was admitted under Cardiology department and transferred to the cardiac catheterization lab where she underwent coronary angiogram. After an initial failed attempt to first cannulate the left coronary ostium to evaluate for concomitant left anterior descending (LAD) and circumflex disease with the suspected culprit being the RCA based on EKG, the right coronary ostium was engaged instead, which revealed a large caliber RCA descending through the coronary sulcus to the crux, giving rise to left anterior descending and obtuse marginal branches before giving rise to an early posterior descending artery (Early PDA) and continued to a postero-lateral vessel (PLV). Contrast injection into the RCA also showed the anomalous origin of the LMCA stemming from the proximal segment of the RCA. RCA was dominant, good size vessel having 98-99 stenosis at its proximal segment and 70-80 stenosis at its distal segment. The aberrant LMCA reached the left side of the heart anterior to the pulmonary artery and trifurcated into a small caliber LAD, ramus intermedius (RI), and left circumflex (LCX) artery that ends into a bifurcated obtuse marginal system (Figure 2). Patient was then referred back to Cardiac Surgery department for CABG operation. After proper pre operative evaluation among which Transthoracic echocardiogram (TTE) showed an ejection fraction (EF) between 45% and 50%, basal segment of inferior and inferolateral wall akinesis and no valvular abnormalities (Figure 1B). A coronary CTA confirmed the findings of coronary angiogram and a potential malignant course of anomalous LMCA was ruled out (Figure 3). Off-Pump Coronary Artery Bypass Surgery with four grafts (OPCAB×04 grafts) done with Left Internal Mammary Artery (LIMA) to LAD and Reverse Saphenous Vein Graft (RSVG) to OM, Early PDA & Poster-lateral Vessel (PLV) (Figure 4). Her immediate post-op and further hospital stay remained uneventful, and the patient was discharged home on guideline-directed medical therapy with a beta-blocker, statin, and dual antiplatelet agents. At 1-month follow-up visit, the patient remained asymptomatic and a repeat TTE showed no new findings.

Course of management:

Day	Timing	Events
Day 1	17.08.2020	Patient presents with chest pain in a peripheral hospital. Diagnosed as having AMI (Inferior). Treated with Inj. Streptokinase and LMWH. Started on dual antiplatelet, statin therapy and released with advice for early CAG.
Day 43	30.09.2020	Elective CAG done at our center. Which revealed 98-99% stenosis at the proximal segment of LAD, 70-80% stenosis at the proximal segment of LCX, 98-99% stenosis at the proximal segment of RCA and 70 -80% stenosis at its distal segment right coronary artery (RCA) lesion and anomalous origin of left main coronary artery (LMCA) from RCA. Transthoracic echocardiography is performed which shows mild to moderately reduced ejection fraction.
Day 44	01.10.2020	Patient is scheduled for coronary computed tomography (CT) angiography and Evaluation for CABG. Coronary CT angiography (on 21.10.2020) demonstrates benign prepulmonic course of aberrant LMCA.
Day 74	01.11.2020	Off Pump CABG Surgery with 04 Grafts done.
Day 83	10.11.2020	Patient discharged on aspirin, clopidogrel, atorvastatin, metoprolol and furosemide with advice for follow up.

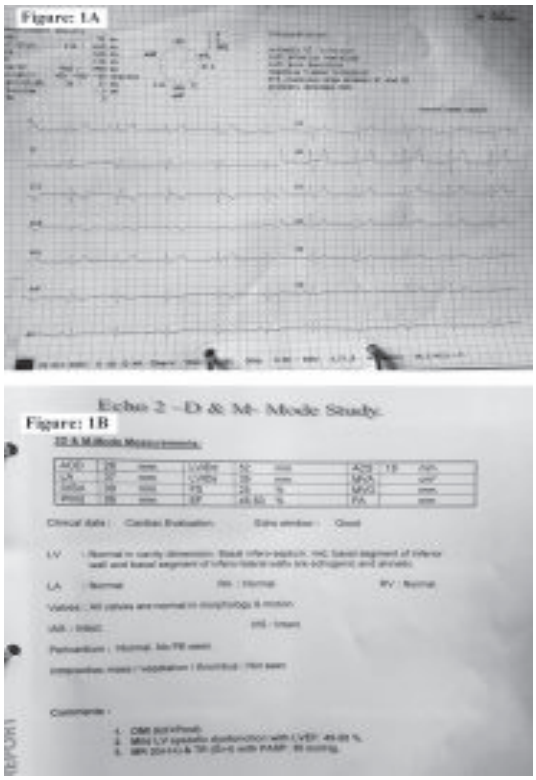

Fig.-1: *(A) Electrocardiograms (EKG) displayed Q-wave and inverted T-wave in the leads II, III, and AVF (B) Transthoracic echocardiogram (TTE) showed an ejection fraction (EF) between 45% and 50%, basal segment of inferior and inferolateral wall akinesis and no valvular abnormalities.*

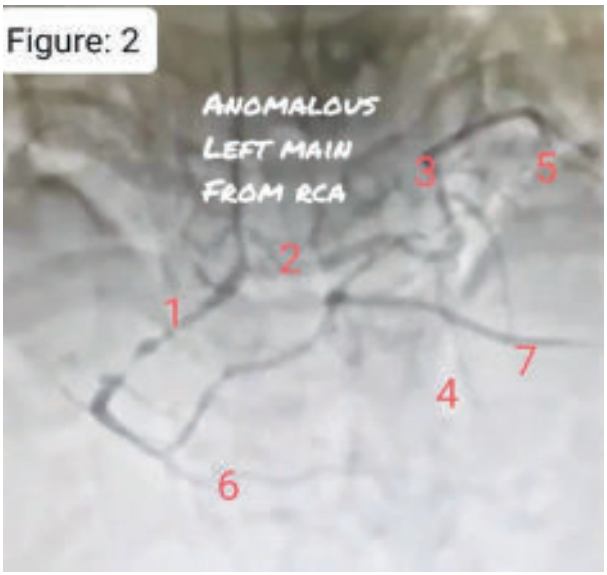

Fig.-2: *Contrast injection into the RCA showed the anomalous origin of the LMCA stemming from the proximal segment of the RCA. RCA was dominant, good size vessel having 98-99 stenosis at its proximal segment and 70-80 stenosis at its distal segment. The aberrant LMCA reached the left side of the heart anterior to the pulmonary artery and trifurcated into a small caliber LAD, ramus intermedius (RI), and left circumflex (LCX) artery that ends into a bifurcated obtuse marginal system. 1, right coronary artery; 2, left main coronary artery; 3, left circumflex artery; 4, left anterior descending artery; 5, obtuse marginals; 6, early posterior descending artery; 7, postero lateral vessel*

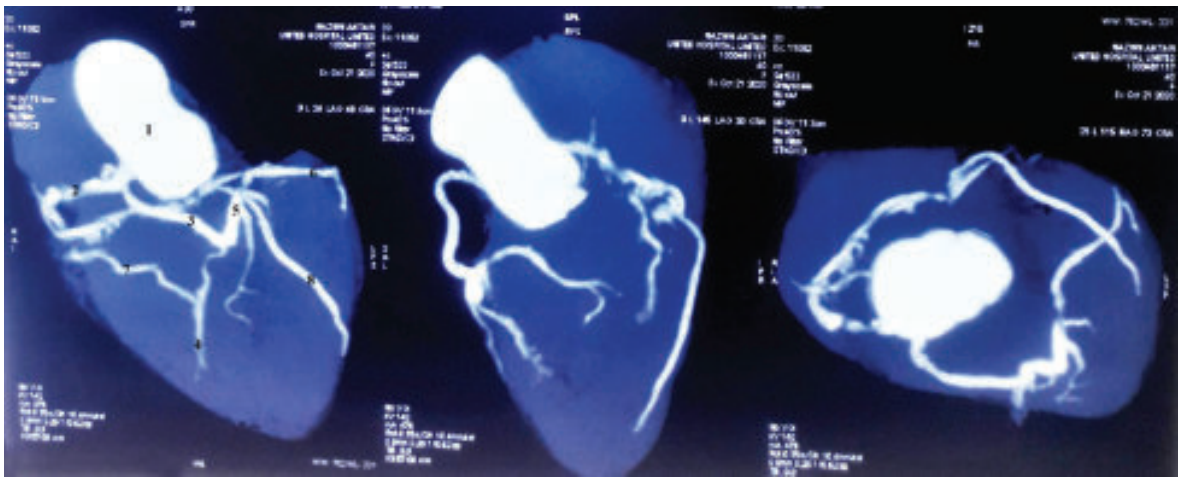

Fig.-3: *Computed tomography image of the heart (left) showing the right coronary artery giving rise to the left main coronary artery and the latter's course anterior to the main pulmonary trunk. 1, ascending aorta; 2, right coronary artery; 3, left main coronary artery; 4, left anterior descending artery; 5, left circumflex artery; 6, obtuse marginal branches; 7, early posterior descending artery; 8, postero-lateral vessel.*

Table-I

Lipton's classification for single coronary artery

Ostia location	Anatomic distribution subtypes
Right sinus of Valsalva (R)	
	RI—SCA follows the course of a normal RCA
	RII—SCA from the right sinus gives off an anomalous transverse branch that crosses the base to reach the contralateral side
	RIII—SCA from the right sinus, with LAD and LCx separate coronary trunks instead of single trunk
Left sinus of Valsalva (L)	
	LI—SCA follows the course of a normal LMCA
	LII—SCA from the left sinus gives off an anomalous transverse branch that crosses the base to reach al side

LAD, left anterior descending artery; LCx, left circumflex artery; LMCA, left main coronary artery; RCA, right coronary artery

Table-II

Subtypes of type II single coronary artery based on the course of the aberrant vessel

Anatomic distribution	SCA subtypes based on course of anomalous transverse branch
RII or LII Type A	—courses anterior to the pulmonary trunk
Type B	—courses between pulmonary artery and aorta
Type P	—courses posterior to the aorta
Type S	—septal type courses above the interventricular septum
Type C	—combined

Discussion:

Single coronary artery anomaly (SCA) is a congenital anatomic abnormality identified by a single coronary ostium giving rise to all arteries supplying the heart. Single CAA is uncommon and seen in only 0.024–0.06% of cases.5 In 1979, Lipton et al.6 provided the angiographic classification of SCA based on the site of ostial location, the anatomical course of the single vessel and relationship of the aberrant transverse branch with respect to the great arteries of the heart. This was further modified by Yamanaka et al.3 in 1990. Single CAA can either be right (R) or left (L) sided corresponding to the ostial location in the right or left sinus of Valsalva. Single CAA are classified into three groups from I to III with Group II consisting of various subtypes based on the course of the aberrant vessel (Tables 1 and 2). Villa et al.7 in 2016 classified CAA functionally as (i) anomalies with obligatory ischaemia, (ii) anomalies without ischaemia, and (iii) anomalies with episodic ischaemia that occasionally cause severe events but are otherwise compatible with normal life. In our case, the patient had congenital SCA; however, her acute presentation was unrelated to the aberrant vessel pathology. Based on the Lipton anatomic classification, the patient illustrated SCA type RIIA with the prepulmonic course of the aberrant vessel (LMCA). Potentially LMCA, RCA, and LAD can all branch from the SCA and take an aberrant course. Type II SCA involving the LMCA is fairly common and is seen in 5% of patients with tetralogy of

Fallot which can often complicate valve repair. As the vessel crosses the right ventricular outflow tract anteriorly, there are no significant haemodynamic consequences, however, isolated cases of angina have been reported.8 The aberrant vessel can also take an interarterial,

retroaortic, or septal (sub-pulmonic) route before reaching the left side of the heart. The five potential paths of the aberrant vessel before reaching the perfusion territory, correlate directly with the risk of SCA. Inter-arterial branch coursing between the pulmonary trunk and aorta has an aberrant intramural course within the aortic wall resulting in hypoplasia and lateral compression.9 Inter-arterial course can lead to sudden cardiac death (SCD). The mortality rates of left interarterial arteries (LAD or LMCA) are higher (57%) compared to right interarterial arteries such as RCA (25%). In the retroaortic subtype, the aberrant branch courses between the posterior aorta and the interatrial septum which can often complicate aortic valve surgery. This anomaly

usually arises from RCA and is not haemodynamically significant. In the subpulmonic type of SCA, the aberrant branch travels anteriorly and inferiorly through the interventricular septum before coursing through septal myocardium. The subpulmonic type has a lower position, is surrounded by septal myocardium and does not have slit like orifice differentiating it from interarterial course. When diagnosing suspected CAA, it is imperative that an exact anatomical course is established to assess the risk of SCD. The role of TTE in diagnosing CAA is limited. Inclusion of two new screening views by Thankavel et al.10 improved the diagnostic ability of TTE in anomalous coronary artery from opposite sinus from 0.02% to 0.22%. Currently, coronary CTA and magnetic resonance angiography are Class I indications for diagnosing congenital CAA11 Cardiac

CTA allows for improved, non-invasive visualization of CAA albeit at the expense of radiation and contrast exposure. Superiority of coronary CTA was depicted by Shi et al.12 in a report that showed conventional angiography was diagnostic in only 53% of CTA proven CAA cases. Magnetic resonance angiography is an alternative that can simultaneously assess structural abnormalities without requiring contrast or harmful radiation exposure however the use remains limited. Coronary angiography remains a useful test to diagnose and classify CAA and is the gold standard for identifying associated coronary artery disease. Traditional angiography offers limited visualization of the coronary ostia, proximal course, and surrounding structures. Ali et al.13 recommended looking for the presence of two signs that should raise suspicion for coronary anomaly (i) the unperfused myocardium sign where the vessel supplying that myocardial territory is not visualized. (ii) The 'aortic root' sign where the vessel appears to cross the aorta and the pulmonary artery at the level of aortic root. In cases with difficult LMCA cannulation, a cuspogram can be performed to visualize the partly opacified artery. When the cuspogram is unsuccessful, right, and non-coronary sinus should be engaged to look for the anomalous origin of LMCA. The 'dot and eye method' was tested by Ishikawa et al.14 to determine the true course of CAA radiologically. The role of non-invasive functional testing to assess the haemodynamic effect of SCA on myocardial perfusion remains controversial.

Both exercise treadmill and stress myocardial perfusion scan can yield false-positives and false-negative results. The use of fractional flow reserve (FFR) and intravascular ultrasound (IVUS) to guide therapy is increasingly gaining attention. Fractional flow reserve can help assess the haemodynamic flow of the aberrant vessel and IVUS can provide an insight on the ostial anatomy. Intravascular ultrasound can help identify slit like or stenosed orifice, acute angle takeoff, and intramural aortic segment (coursing through aortic wall) all of which can increase risk of SCD. Together FFR and IVUS can helps establish the need for intervention especially when the presenting symptoms are atypical.15

Treatment options include observation with conservative medical management, percutaneous intervention, or surgical repair. Proximal stenosis in cases with SCA can be devastating if adequate collaterals do not exist. The 2008 guidelines for adults with congenital heart disease recommend revascularization or surgical repair of interarterial course regardless of symptoms due to higher rates of myocardial infarction and surgical revascularization on follow-up11 Aberrant vessels with prepulmonic, retroaortic, or transseptal courses have excellent prognosis. Asymptomatic patients with high risk anatomic features and absence of ischaemia on stress testing need multidisciplinary approach.

Conclusion:

We report a rare case of an incidentally identified SCA with Lipton type RIIA pattern. Although the majority of the patients are asymptomatic further evaluation with coronary CTA is warranted to rule out potential malignant pathology. The risk of SCD is highest with the interarterial course of the aberrant vessel. Stress testing is often not reliable in assessing the functional status of the patient. The optimal approach involves risk stratification, multidisciplinary management, and surgical intervention in appropriate patients.

Conflict of interest: None

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We Mourn

Professor Abul Hossain Khan Chowdhury
(18/02/1954-20/07/2020)

Professor Abdul Hossain Khan Chowdhury was a dedicated interventionist and an excellent tutor.

After a lengthy battle against Covid-19, he took his last breath at the age of 66 years. Faridpur was his birthplace and he later obtained M.B.B.S from Dhaka Medical College in 1976 and F.C.P.S in 1987 and trained in interventional cardiology from Australia in 1997.

Over the course of his long career, he produced substantial advances in cardiology, and he was at the forefront of early works on coronary interventional treatments and significant research investigations. He was well-known for his unwavering commitment to the education and growth of doctors. He highly appreciated the doctors who worked under him and always stood by their side.

He was the Director of National Institute of Cardiovascular Diseases (NICVD) for a short time in 2010, the last year before he retired. During the short time he was there, despite all the constraints, primary PCI was started in a limited way in the NICVD. His dedication to study was demonstrated by the fact that he sat in the front row of practically every national cardiology conference even after retirement.

He disliked sticking to the traditional office schedule and often stayed at the hospital past office hours. Moreover, his lively nature and unique personality added to his popularity.

I, as an Assistant Professor then along with others and trainees used to find clinical round and cathlab tiring, but at the end of the day, we found that those activities and efforts were beneficial for trainee doctors and care of the patients.

His passing is a significant loss for the cardiology community. We convey our sorrow and grief over the loss of our beloved teacher.

Prof. Dr. Md. Khalequzzaman
Professor of Cardiology
Jeshore Medical College