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01

Journal of Invasive and Clinical Cardiology

INSTRUCTION TO AUTHORS

A. Introduction

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

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. 3 to 5 keywords to facilitate indexing should be provided in alphabetical order below the abstract. The text should be arranged in sections on INTRODUCTION, METHODS, RESULTS, and DISCUSSION. The typical text length for such contributions is up to 3000 words (including title page, abstract, tables, figures, acknowledgments and key messages). Number of references should be limited to 50.

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 15 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 Journal of Invasive and Clinical Cardiology 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 up to 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 are appropriate, 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 Journal of Invasive and Clinical Cardiology 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 Journal of Invasive and Clinical Cardiology and suggestions may be made to the authors by the Editorial Board to improve the scientific value of the journal.

D. Editorial Process

Journal of Invasive and Clinical Cardiology 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. Journal of Invasive and Clinical Cardiology follows the guidelines on editorial independence produced by the International Committee of Medical Journal Editors (ICMJE). All manuscripts correctly submitted to Journal of Invasive and Clinical Cardiology 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 Journal of Invasive and Clinical Cardiology, 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 Journal of Invasive and Clinical Cardiology 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 lowercase 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 U.S. 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*

The authors are responsible for the accuracy and completeness of the references and their citations in the text.

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.
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- Abstracts as references may be used; "unpublished observations" and "personal communications" may not be used as references, although references to written, not oral, communications may be inserted (in parentheses) in the text.
- Papers accepted but not yet published may be included as references by adding "In press" after the journal name. Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses).
- 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;42 Suppl 2:S93-9.

5. *Issue with supplement*

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

6. *Type of article indicated as needed*

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

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

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

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

Books and Other Monographs

1. *Personal author(s)*

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

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

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

3. *Organization(s) as author*

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

4. *Chapter in a book*

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

5. *Conference proceedings*

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

6. *Dissertation or thesis*

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

Other Published Material

Newspaper article

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

Unpublished Material

In press or Forthcoming

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

Electronic Material

1. *Journal article on the Internet*

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

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.

8.

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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Transcatheter Aortic Valve Implantation (TAVI) in 2019: Is Simplification a Strong Argument to Support TAVI in All Symptomatic Aortic Stenosis?

Thomas Cuisset*

J Invasive Clin Cardiol 2019; 1(1): 1-2

Introduction:

Since its introduction in 2002, Transcatheter aortic valve implantation (TAVI) has evolved dramatically and has emerged as the gold standard therapeutic option for patients with symptomatic severe aortic stenosis who are ineligible for conventional surgical aortic valve replacement (SAVR) or at high- or intermediate-operative risk[1]. This has been possible with combination of scientific evidence, improved operator experience, innovation of transcatheter heart valves and delivery catheters, the expanded use of 3-dimensional (3D) imaging including multislice computed tomography (MSCT), and the extension of TAVI technology to younger and lower risk patients.

Simplification of TAVI: make it simple but not simpler!

Simplification of the procedure also modified the perception of both physicians and patients. Main modifications aiming to simplify TAVI during last decade are summarized in Figure 1.

Conscious Sedation.

A major change has been to perform routinely TAVI under conscious sedation and not general anesthesia anymore. Potential advantages of general anesthesia are patient's procedural comfort, possibility of using transesophageal echocardiography (TOE) and rapid conversion to surgery when complications occur, which are clearly counterbalanced by issues related to general anesthesia such as hemodynamic instability, higher need for inotropic drugs, higher risk of bleeding, increased risk of pulmonary infection, extubation difficulty or delay in patients with chronic pulmonary disease, late complications dentification such as stroke or aortic complications and finally, longer procedural duration, hospital stay and global costs. Use and expertise of operators in Multislice CT (MSCT) has also been key to allow shift from general anesthesis to local sedation by obviating the need for TOE during the procedure.

Vascular Access.

Over the past decade, sheath diameter has been gradually reduced to 14–16 French with the last generation percutaneous heart valves and therefore a move from surgical cut-down to real percutaneous approach using closure device for preclosing was observed for TAVI procedures. This, together, with

Simplification of TAVI

2000-2005 < Surgical Like>	2015-2020 < PCI Like>
General Anesthesia	Conscious sedation
Routine use of TOE	No TOE
Central venous line	No central venous line
Surgical cut-down	Percutaneous / Preclosing
Contralateral femoral access	Contralateral femoral access
Routine use of Predilatation	Very selective use of predilatation
Pacing on RV lead	Pacing on LV wire
Post surgical unit after TAVI	Intensive care unit after TAVI
Hospital stay 8 days	Hospital stay 3-5 days
Rehabilitation program	Discharge at home

Fig.-1: *Simplification of TAVI in the last*

* Head of the Cathlab & Interventional Cardiology Unit, Central University Hospital (CHU), La Timone, Marseille, France.

ultrasound-guided puncture decreased the rate of vascular complications during TAVI. Thus, percutaneous transfemoral access is as safe as the surgical approach and feasible in the majority of cases with a very high rate of success after the learning phase. Most vascular complications can be managed percutaneously. It is an essential component of TAVI's simplification process allowing conscious sedation and early discharge. Also, the use of radial approach for contralateral access during TAVI has been promoted to reduce access-site bleeding complications. This radial access allows angiography before puncture if angio-guided, aortography for valve positioning as well as final angiography after femoral artery closure and management of complications if needed.

Pacing during valve deployment

Using balloon expandable TAVI, rapid ventricular pacing is mandatory. Rapid pacing is also indicated during predilatation, postdilatation and selected cases of self-expandable valves. Rapid pacing is usually performed through a venous access with temporary pacemaker implantation. However, this technique may be challenging in anatomic variations and may lead to increased X-ray exposure and complications such as hematoma, arterio-venous fistula, or right ventricle perforation with tamponade. Recently, rapid ventricular pacing through the left ventricle guide wire has been described as a way of simplifying the procedure by eliminating the need for additional vascular access during TAVI. This approach is now the standard of care in our center like many others with very high success rate and low incidence of complications, if any.

Valve implantation without predilatation: "direct TAVI"

In the early days of TAVI, balloon aortic valvuloplasty (BAV) was considered a mandatory step. However, BAV have been shown to be associated with a higher risk of cerebral embolization, and severe acute aortic regurgitation may occur after predilatation in up to 3% of cases with possible hemodynamic instability. TAVI without BAV was initially evaluated in small series and recently, an analysis from the French TAVI registry performed by our group showed that direct TAVI is feasible with reduced rate of complications such as tamponade and simplified procedure with less X-ray and contrast. Accordingly, nowadays, more than 90% of TAVI in our center are performed without BAV and only selected cases with extreme AS and/or difficult access to valve (tortuosity, calcified access) still require BAV prior to valve implantation.

Conclusion:

Procedure simplifications and decrease in complications rates significantly improved TAVI results and allowed simpler post-procedure management and shorter hospital stay. Also, scientific evidence in last decade validated indication of TAVI in patients unable to undergo surgery, in high-risk and then in intermediate risk patients. However, before TAVI can be proposed to all patients with AS, we still have to solve different challenges. First one, to come in 2019, will be the results of clinical studies testing TAVI versus surgery in low surgical risk patients. Second, efforts will have to be made to reduce further some complications, still higher with TAVI compared to surgery such as paravalvular leak or conduction abnormalities post TAVI. Third, although we already have reassuring data on long-term durability of TAVI bio prosthesis, more data are needed to definitely address this issue. Finally, with a worldwide perspective, cost issue will have to be addressed to allow diffusion of the technique in low-income country where national health care system cannot afford the current prices of the device.

References:

1. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-91.

ORIGINAL ARTICLE

Mitral Annular Calcification May Predict Significant Atherosclerotic Coronary Artery Disease in Young Patients with Ischemic Heart Disease

Mohammad Arifur Rahman[1], Afzalur Rahman[2], Md. Zillur Rahman[3], Tariq Ahmed Chowdhury[4], Farhana Ahmed[5], Md. Delwar Hossain[6], Ishrat Jahan Shimu[7], Md. Nazmul Islam[8], Ashiqur Rahman[9], Afifa Rahman[10]

Abstract

Background: Mitral annular calcification (MAC) is degenerative, fibrous calcification of the mitral valve annulus. It is more common in people over 70 years old. It is a marker of increased cardiovascular risk which occurs in a graded fashion by MAC severity. The aim of this study was to evaluate the association of Mitral annular calcification with significant atherosclerotic coronary artery disease (CAD) in patients under 65 years old.

Methods: This study was conducted in National Institute of cardiovascular Diseases (NICVD), Dhaka during January 2015 to July 2016.. 140 patients aged <65 years with IHD were enrolled and grouped into MAC and Non MAC group. MAC was defined as intense echo-producing structure at junction of the atrioventricular groove and posterior mitral leaflet on parasternal long axis and apical 4-chamber views, measured in millimeters from the leading anterior to the trailing posterior edge and quantified as mild to moderate (1 to 4mm) and severe (>4mm).Angiographic severity of CAD was assessed by Vessel, Friesinger and Leaman score.

Results: Smoking and family history of IHD were higher in MAC group. Left main and triple vessel disease (TVD) were significantly higher in MAC group (p=0.001, p=0.01). Intermediate and high Friesinger score (e"5) were significantly higher in MAC group. There was significant (p=0.01) positive correlation between MAC and CAD severity in terms of vessel score (r=0.76) Friesinger score (r=0.75) and Leaman score(r=0.42). Regression analysis showed MAC as independent predictors of significant CAD (p=0.002, OR= 2.84). ROC curve analysis for prediction of presence of CAD demonstrated that the area under the curve (AUC) for MAC was 0.836 with 87.142% sensitivity, 81.43% specificity, 82.43% positive predictive value and 86.36% negative predictive value.

Conclusion: Echocardiographically detected mitral annual calcification (MAC) in patients under 65 years may be an independent predictor of significant coronary artery disease (CAD). Left main disease and TVD were significantly higher in MAC group. Cheap, available, portable and radiation free nature of the echocardiographic detection of MAC may be a marker of significant atherosclerotic CAD.

Key wards: Mitral annular calcification, Severity of coronary artery disease.

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Introduction:

Mitral annular calcification (MAC) was initially thought to represent a degenerative process that progressed with advancing age.[1] More recent studies showed that this calcification was also considered as part of generalized atherosclerosis especially in elderly population.[2] Patients with aortic valve sclerosis (AVS) undergoing coronary angiography had shown to have a higher prevalence of coronary artery disease (CAD).[3] A highly significant association of mitral annular calcification (MAC) was reported with atherosclerosis of the vascular system including CAD.[4] Another study showed that aortic arch calcification was independently associated with older age and increased risk of CAD.[5] Very few studies tested the clinical significance and relation of MAC with severity and pattern of coronary artery atherosclerosis.

Cardiovascular diseases (CVDs) are leading cause of mortality and morbidity in industrialized countries, and they are also emerging as a prominent public health problem in developing countries.[6] There is a common clinical perception that myocardial infarction

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is uncommon in young population. Epidemiological survey from many countries indicates its increasing incidence in young patients. The clinical picture of coronary artery disease does not differ between young and elderly patients.[7]

The prevalence of MAC has been reported to be as high as 15% in population-based studies [8] and up to 35% in patients with severe CAD.[9] MAC is more common in women and in people over 70 years old. MAC is associated with several cardiovascular disorders and events, including CAD, [10] carotid and aortic atherosclerosis, stroke, heart failure, and atrial fibrillation. MAC has also been shown to be associated with mortality in the Framingham heart study and in a study of patients less than 61 years old.[11] MAC patients have a higher prevalence of coronary artery disease[12] and a higher incidence of new coronary events than patients without MAC.[13]

Despite being an everyday practice guiding tool, echocardiography alone is not the best method for detection and/or quantification of MAC because of its low specificity in distinguishing between calcification and dense collagen. Recently, computed tomography was employed to determine the presence, extent and also calculate selective and total score of the coronary as well as extracoronary calcification[14]. In Bangladesh the proportion of population <65 years is 96.8% and e"65years is only 3.2%[14]. As the economic burden is increasing steeply for the diagnosis and management of ischemic heart disease (IHD) a cheap and available tool is necessary for the prediction of severity of CAD. The objectives of our study were to examine the association between mitral annular calcification with severity and pattern of atherosclerosis involving the coronary arteries.

Materials and methods:

This Cross sectional, analytical study was conducted in the department of Cardiology, NICVD during January 2015 to July 2016. Objectives of the study were to find out the association of MAC with severity and pattern of atherosclerosis involving coronary arteries. Total 140 patients under 65 years old with IHD were selected purposively. They were grouped into MAC group and non MAC group on the basis of presence or absence of MAC respectively. The study protocol was approved by the ethical review board.

Angiographic pattern and severity of CAD

After all routine investigation Coronary Angiogram were done during same hospital stay. Interpretations of coronary angiogram were done by visual estimation by two cardiologists to assess the severity of coronary artery disease. Severity of coronary stenosis was graded according to Vessel score, Friesinger score and Leaman score.

A. Vessel score: 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).[15] Score ranges from 0 to 3, depending on the number of vessel involved. Left main coronary artery was be scored as single vessel disease.[16]

Score 0 = no vessel involvement.

Score 1 = single vessel involvement.

Score 2 = double vessel involvement.

Score 3 = triple vessel involvement.

B. Friesinger score: Friesinger score ranges from 0 to 15. Each of the three main coronary arteries is scored separately from 0 to 5.[17]

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. Leaman score: A coronary scoring system to determine the severity of the underlying CAD. Leaman score is based on the severity of luminal diameter narrowing and weighed according to the usual blood flow to the left ventricle in each vessel or vessel segment.[18]

Statistical Methods:

Data obtained from the study were analyzed and significance of differences were estimated by using statistical methods. Variables were analyzed by chi-square test and t-test where applicable. Correlations were done by Pearson's correlation and Spearman's correlation t-test where applicable. Multivariate logistic

regression analysis was done. P value P<0.05 were considered as significant. Statistical analyses were performed with SPSS, version 16.0 (SPSS Inc).

Results:

The mean age of the MAC patients were 50.8±8.5 years ranging from 30 to 64 years and the mean age of the non MAC patients were 48.2±8.6 years ranging from 30 to 64 years (Table- I).

Among the studied patients, highest percentage had history of smoking (85.7%) followed by dyslipidaemia (74.3%), family history of IHD (60%), diabetes mellitus (55.7%) and hypertension (50%) in the MAC group. Smoking (p=0.001) and Family history of IHD (p=0.03) were found significantly higher in MAC group (Table- II).

Among the MAC group 15 (21.4%), 12 (24.2%) and 33(47.1%) had SVD, DVD and TVD respectively. Left main CAD was significantly higher in MAC group (p=0.01). TVD (p=0.001) and Left main CAD (p=0.01) were significantly higher in MAC group whereas SVD and normal coronary arteries were higher in non MAC group. The sequence of number of vessels involved with MAC by mean score was normal, SVD, DVD and TVD being 2.80, 3.40, 4.51 and 6.09 respectively. Differences were statistically significant (p=0.001) (Table III).

Friesinger score 0, 1-4, 5-9 and 10-15 was 5 (7.1%), 4 (5.7%), 25 (35.7%) and 36 (51.4%) in MAC group whereas it was 27 (38.6%), 30 (42.9%), 12 (17.1%) and 1 (1.4%) in non MAC group respectively. Friesinger scores were significantly higher in MAC group (Table IV).

There was strong positive correlation between mitral annular calcification (in mm) and coronary artery disease severity in terms of Friesinger score (r=0.75, p=0.01) (Figure 1).

Multivariate logistic regression analysis of odds ratio (OR) for characteristics of the subjects likely to cause CAD severity showed that among the 7 variables MAC (p=0.002), family history of CAD (p=0.003), smoking (p=0.005), and dyslipidemia (p=0.005), were found to be the independently significant predictors of severe CAD with ORs being 2.84, 2.69, 2.68 and 2.67 respectively (Table V)

Table-I

Age distribution of the study population (n=140)

Age(Years)	MAC (n= 70)		Non MAC (n=70)		Total (n=140)		P value
	Number	%	Number	%	Number	%	
d" 40	5	7.1	19	27.1	24	17.1	
41 – 50	24	34.3	25	35.7	49	35.0	0.08 ^{ns}
51 – 60	29	41.4	20	28.6	49	35.0	
> 60	12	17.1	6	8.6	18	12.9	
Mean ± SD	50.8±8.5		48.2±8.6		49.5±8.6		

Table-II

Risk factors of the study patients (N=140)

Risk Factors	MAC(n= 70)		Non MAC(n = 70)		Total (N=140)		p value
	Number	%	Number	%	Number	%	
Smoking	60	85.7	43	61.4	103	73.6	0.001^{S}
Hypertension	35	50.0	28	40.0	63	45.3	0.23^{NS}
Diabetes mellitus	39	55.7	33	47.1	72	51.4	0.39^{NS}
Dyslipidemia	52	74.3	44	62.9	96	68.6	0.14^{NS}
Family H/O of IHD	42	60.0	29	41.4	71	50.7	0.03^{S}

Table-III

Distribution of the study population according to vessel score (N=140)

Vessels	Group		p value
	MAC(n=70)	non-MAC (n=70)	
SVD	15 (21.4)	21 (30.0)	0.13 ns
DVD	17 (24.2)	19 (27.1)	0.24 ns
TVD	33 (47.1)	2 (2.9)	0.001S
Normal	5 (7.1)	28 (40.0)	0.001S
Left main	8 (11.4)	3 (4.3)	0.01S

Table-IV

Distribution of the study population according to Friesinger score (N=140)

FriesingerScore	MAC(n= 70)		Non MAC(n =70)		p value
	Number	%	Number	%	
0	5	7.1	27	38.6	0.001S
1 – 4	4	5.7	30	42.9	0.001S
5 – 9	25	35.7	12	17.1	0.01S
10 – 15	36	51.4	1	1.4	0.001S

Table-V

Multivariate logistic regression of determinants of significant CAD.

Variables of interest	²	S.E.	*p* value	OR	95% CI
Sex (Male)	0.279	0.344	0.32NS	1.29	0.692-2.262
Age(>50 yrs)	0.220	0.412	0.36NS	1.60	0.629-4.095
Smoking	0.743	0.332	0.005S	2.68	1.313-7.451
Hypertension	0.099	0.447	0.72NS	1.08	0.556-2.114
Dyslipidemia	0.725	0.379	0.005S	2.67	1.277-5.587
Family history of CAD	0.799	0.312	0.003S	2.69	1.395-5.340
MAC in mm	0.833	0.132	0.002S	2.84	1.625 – 5.129

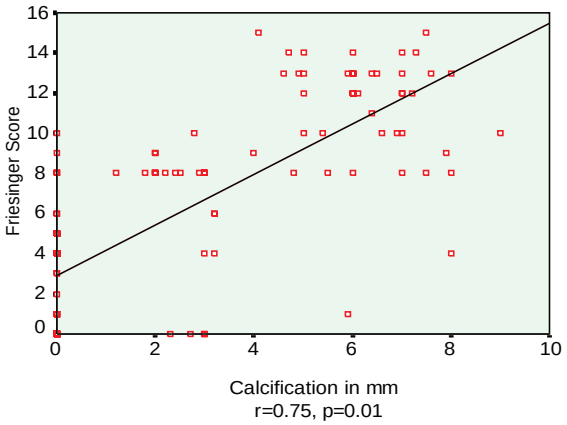


Fig.-1: *Correlation between MAC and Friesinger score*

Table VI

Sensitivity, specificity, positive and negative predictive values of the MAC for prediction of severity of coronary artery disease.

Validity test	Percentage
Sensitivity	87.142%
Specificity	81.43%
Positive predictive value	82.43%
Negative predictive value	86.36%

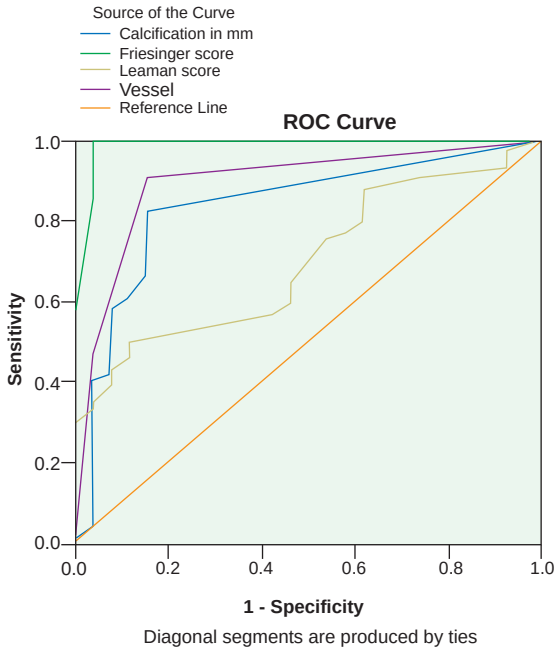


Fig.-2a: *ROC curve analysis showing the area under the curve (AUC) for different variables used in prediction of coronary artery disease.*

Fig.-2b: *Area Under the Curve*

Test Result Variable(s)	Area
Calcification in mm	0.836
Friesinger Score	0.989
Leaman score	0.699
Vessel score	0.895

ROC curve analysis for prediction of presence of significant CAD demonstrated that the area under the curve (AUC) for MAC was 0.837 (Figure 2a, 2b) with 87.142% sensitivity, 81.43% specificity, 82.43% positive predictive value and 86.36% negative predictive value (Table VI).

Discussion:

The mean age of the MAC patients were 50.8±8.5 years ranging from 30 to 64 years and non MAC patients were 48.2±8.6 years ranging from 30 to 64 years (Table- I). According to Adler, et al. mean age 74.36 years; range 47 to 89 years for MAC group and mean age 73.66 years; range 61 to 96 years for non MAC group. Calcification was more common in elderly population.[19]

Male patients were 84.3% and 85% in MAC group and non MAC group respectively. On the contrary female patients were 15.7% and 14.3% in MAC group and non MAC group respectively. Male : female ratio was 5.7:1.there was no significant sex difference between two groups. In The Framingham Heart Study found that, the baseline examination, subjects with MAC were older, more likely to be female. [20] In present study lower female percentage might be due to social circumstances that restrict women seeking medical help outside the home even in face of serious illness.

Smoking (85.7%) was the commonest risk factor followed by dyslipidaemia (74.3%), family history of IHD (60%), diabetes mellitus (55.7%) and hypertension (50%) in the MAC group. Smoking (p=0.001) and Family history of IHD (p=0.03) were found significantly higher in MAC group (Table-II). Fox, et al., (2004) in The Framingham Heart Study found that, 68.7% of MAC and 60.9% non-MAC were hypertensive, 27.6% of MAC and 24.1% of non- MAC group were diabetic with no significant difference between groups. According to Atar, et al. hyperlipidemia was found among 37% of MAC patients and 45% of non-MAC group without statistical significance.[9] In Alder et al. study 27% of MAC and 25% of non MAC patients had higher level of total cholesterol. [21] The findings of the present study are comparable with the above mentioned studies.

Among the MAC group 11(15.7%), 21(30.0%) and 33(47.1%) had SVD, DVD and TVD respectively. TVD (p=0.001) and Left main CAD (p=0.01) were significantly higher in MAC group whereas SVD and normal coronary arteries were higher in non MAC group (Table-III). Aronow, found that, the prevalence of TVD was 45% in persons with versus 24% in persons without MAC (p= 0.001). The prevalence of left main CAD was 13% in persons with versus 5% in persons without MAC (p = 0.009).[22]

Friesinger score 0, 1-4, 5-9 and 10-15 was 5 (7.1%), 4 (5.7%), 25 (35.7%) and 36 (51.4%) in MAC group whereas it was 27 (38.6%), 30 (42.9%),12 (17.1%) and 1 (1.4%) in non MAC group respectively. Friesinger scores were significantly higher in MAC group (Table-IV). There was statistically significant (p=0.01) positive correlation between MAC and CAD severity in terms of vessel score (r=0.76), Friesinger score (r=0.75) (Figure 1) and Leaman score(r=0.42).

Multivariate regression analysis showed among 7 variables MAC (p=0.002), family history of CAD (p=0.003), smoking (p=0.005) and dyslipidemia (p=0.005) were found to be the independently significant predictors of severe CAD with ORs being 29.71, 2.69, 2.68 and 2.67 respectively (Table V).

Corciu, et al. observed, hypercholesterolemia (OR=3.74; p=0.002), diabetes (OR=2.84; p=0.036), gender and MAC (OR=1.20; p=0.038) were individually significant predictors of CAD status (p=0.05) [23].

ROC curve analysis for prediction of presence of significant CAD demonstrated that the area under the curve (AUC) for MAC was 0.837 (Figure 2a, 2b) with 87.142% sensitivity, 81.43% specificity, 82.43% positive predictive value and 86.36% negative predictive value (Table VI).

Study limitations:

It was a single centre study and the number of study population was limited. This study was done in patients who underwent both echocardiography and coronary angiography for various indications. This may have caused a bias in selecting patients with a high pretest likelihood of having CAD. However, both groups were selected in the same way and were similarly affected by the selection bias, yet showed a highly significant difference in their angiographic findings.

Conclusion:

Echocardiographically detected mitral annual calcification (MAC) in patients under 65 years may be an independent predictor of significant coronary artery disease (CAD). Left main disease and TVD were significantly higher in MAC group. Cheap, available, portable and radiation free nature of the echocardiographic detection of MAC may be a marker of significant atherosclerotic CAD.

Conflict of Interest - None.

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Prevalence of Anaemia among Patients with Heart Failure in a Tertiary Care Cardiac Centre of Bangladesh.

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Abstract

Background: Heart failure (HF) is a frequent cause of hospitalisation in Cardiology. Anaemia is frequently found among patients with HF, often compounding its prognosis. This study aimed to determine the prevalence of anaemia among patients with heart failure, as well as the aetiology of anaemia and peripheral blood film patterns.

Methods: This prospective observational study was carried out in the Department of Cardiology in Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh from 1st of April 2018 to 30th of September 2018. Patients admitted with the clinical diagnosis of HF based on validated clinical criteria were included. Anaemia was defined as a haemoglobin level < 13 g/dl for men and < 12 g/dl for women. Data pertaining to patient demographics, serum iron profiles, peripheral blood films, correction of anaemia during hospitalization and in-hospital outcomes were recorded. Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 16.0 (Chicago, Illinois, USA). P< 0.05 was considered statistically significant.

Results: Mean age was 63.8 ±10.5 years. 81.5% of the patients were male. 35 (64.8%) of HF patients had anaemia. Overall, 83.3% of the patients were in NYHA functional class III- IV. 75.9% had chronic kidney disease (CKD). 92.6% had coronary artery disease (CAD). 87% of patients were on aspirin. 74.1% were on dual anti-platelet therapy. 3.7% were on oral anticoagulation. Only 2 patients (3.7%) had a prior history of gastro-intestinal bleeding. 61.4% and 80% of male and female patients had anaemia respectively (p= 0.26). Mean levels of haemoglobin were 10.4 ±1.8 and 14.2±1.6 g/dl for the anaemic and non-anaemic patients, respectively (p <0.001). Anaemic patients were significantly older than non-anaemic ones, aged 65.9 ± 10.0 years vs. 59.9±10.4 years respectively (p =0.045). The majority (51.4%) of anaemic patients had iron deficiency anaemia (IDA). 20% of anaemic patients had absolute iron deficiency, while 62.9% had functional iron deficiency. 31.4% of anaemic patients received blood transfusions during hospital stay, while 22.9% of patients were given IV iron supplementation. A single in-hospital mortality was observed, from the anaemic group.

Conclusion: This preliminary study showed a high prevalence of anaemia among HF patients, most notably due to iron deficiency and mechanisms related to CKD. Further large-scale studies investigating their effects on outcomes in HF patients are warranted.

Key words: Anaemia, Heart Failure, Iron Deficiency

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Introduction:

Anaemia is a frequent co-morbidity among heart failure (HF) patients and is associated with poor outcomes. Anemia in heart failure is considered to develop due to a complex interaction of iron deficiency (ID), kidney disease, and cytokine production, although micronutrient insufficiency and blood loss may contribute.[1] Although the reports of prevalence of anemia vary widely, it is unequivocal that anemia is prevalent in patients with heart failure regardless of the clinical setting. Overall, the prevalence of anemia is known to vary widely, ranging from 14% to 56% in outpatient registries to 14% to 61% in hospitalized patients.[2,3] The severity of anaemia is also known to be greater among females.[1,4] In 2012, the European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic HF recognized ID as a comorbidity in HF.[5] There is a paucity of data on the prevalence and aetiology of anaemia among HF patients in Bangladesh. The aim

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of this study was to determine the prevalence of anaemia among patients with HF, as well as the aetiology of anaemia and peripheral blood film patterns.

Methods:

Patient population and definitions: This prospective observational study was carried out in the Department of Cardiology in Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh from 1st of April 2018 to 30th of September 2018. Patients admitted with the clinical diagnosis of HF (i.e. left or biventricular heart failure) based on validated clinical criteria were included. Patients admitted for exclusively right heart failure, or a cause other than heart failure, as well as for sickle anaemia, were excluded. Anaemia was defined as a haemoglobin level < 13 g/dl for men and < 12 g/dl for women, based on WHO definition.[6] Although generally accepted serum ferritin cutoff level to diagnose absolute ID is 30 µg/L, in HF, both intracellular iron accumulation and inflammation stimulate the tissue expression of ferritin and increase its blood level. In such cases, for the diagnosis of absolute ID, a higher serum ferritin cut-off value is used (e.g. 100 mg/L).[7] In our study, absolute ID was taken as serum ferritin < 100 µg/L and functional ID was defined as normal serum ferritin (100– 300 µg/L) with low TSAT (<20%).[7,8]

Data collection & statistical analysis: Data pertaining to patient demographics, clinical and echocardiographic parameters, including type of heart failure (left or biventricular),NYHA (New York Heart Association) functional class, the use of aspirin and/or oral anticoagulation, serum iron profiles, peripheral blood films, renal function (estimated by glomerular filtration rate using the Cockroft– Gault equation; considered to be chronic kidney disease [CKD] if GFR < 60 ml/min). treatment modalities for correction of anaemia during hospitalization and in-hospital mortality were recorded. Patients were divided into two groups according to anaemic status: anaemic (n = 35) and non-anaemic patients (n = 21). Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 16.0 (Chicago, Illinois, USA). P< 0.05 was considered statistically significant. Continuous variables were expressed as mean ± standard deviation, and compared using the student's t-test and ANOVA statistics. Categorical variables were expressed as number with corresponding percentage, and compared using the chi-square test. A p value < 0.05 was considered statistically significant.

Ethical approval: The study complied with the Declaration of Helsinki and ethical approval was obtained by the ethical review committee of ICHRI, Dhaka, Bangladesh.

Results:

A total of 54 patients were evaluated, including 44 men (81.5%) and 10 women (18.9%), with a mean age of 63.8 ±10.5 years (range 41 – 92). Table I demonstrates the chief characteristics of the overall study population 75.9% had chronic kidney disease (CKD). 92.6% had coronary artery disease (CAD). Overall, 83.3% of the patients were in NYHA functional class III- IV (Table II). Heart failure was mostly left ventricular (87%) and biventricular in 7 cases (13%). 87% of patients were on aspirin. 74.1% were on dual anti-platelet therapy. 3.7% were on oral anticoagulation. Only 2 patients (3.7%) had a prior history of gastro-intestinal bleeding.

Table-I

Characteristics of study population

Parameters	Patients (n=54)
Male gender, *n* (%)	44 (81.5%)
Age (years), SD (range)	63.8 ±10.5 (41 – 92)
Haemoglobin (g/dl), SD (range)	11.9±2.6 (6.2 -18.8)
Anaemia, *n* (%)	35 (64.8%)
Absolute Iron deficiency (ID), *n* (%)	8(14.8%)
Functional Iron deficiency (ID), *n* (%)	39 (72.2%)
eGFR (ml/min)	45.0 ± 20.9 (7.6 - 93.4)
LVEF (%), SD (range)	38.3 ± 11.0 (20 – 65)
NYHA III–IV, *n* (%)	45 (83.3%)
Prior history of heart failure, *n* (%)	25 (46.3%)
Biventricular heart failure, *n* (%)	7 (13%)
Only left ventricular failure (LVF), *n* (%)	47 (87%)
Diabetes, *n* (%)	42 (77.8%)
Hypertension, *n* (%)	35 (64.8%)
Smoking, *n* (%)	21 (38.9%)
Alcohol abuse, *n* (%)	1 (1.9%)
Coronary artery disease (CAD), *n* (%)	50 (92.6%)
Prior MI, *n* (%)	23 (42.6%)
Prior PCI, *n* (%)	13 (24.1%)
Prior CABG, *n* (%)	9 (16.7%)
Chronic kidney Disease, *n* (%)	41 (75.9%)
Primary valvular heart disease	2 (3.7%)
Secondary mitral regurgitation	21 (38.9%)
Hospitalisation stay (days), SD	7.6 ± 4.1 (2 – 18)
Mortality rate, *n* (%)	1 (1.9%)
Medications	
Aspirin, *n* (%)	47 (87.0%)
P2Y12 inhibitor, *n* (%)	45 (83.3%)
Dual antiplatelet therapy (DAPT) , *n* (%)	40 (74.1%)
Oral anticoagulation, *n* (%)	2 (3.7%)

Table-II
Distribution of study population according to NYHA functional class (n=54)

NYHA functional class	Number	Percentage (%)
I	1	1.9
II	8	14.8
III	12	22.2
IV	33	61.1

The prevalence of anaemia was 64.8%, with an average haemoglobin level of 11.9±2.6 g/dl (6.2 - 18.8). 61.4% and 80% of male and female patients had anaemia respectively (p= 0.26). Table 3 demonstrates a comparison of characteristics between anaemic and non-anaemic groups. Mean levels of haemoglobin were 10.4 ±1.8 and 14.2±1.6 g/dl for the anaemic and non-anaemic patients, respectively (p <0.001). Anaemic patients were significantly older than non-anaemic ones, aged 65.9 ± 10.0 years vs. 59.9±10.4 years respectively (p =0.045). Average left ventricular ejection fraction was 39.7±10.5 in anaemic and 36 ±11.6 in non-anaemic patients (p= 0.23). Mean eGFR was numerically lower among anaemic patients (44.2 ±22.3 ml/min vs 48.1±19.5 ml/min for anaemic and non-anaemic subjects respectively, p= 0.51). The average duration of hospital stay was 7.8±4.4 days vs.7.1 ±3.5 days for anaemic and non-anaemic subjects respectively (p= 0. 0.54). A single in-hospital mortality was observed, from the anaemic group.

Table IV shows the aetiological classification among anaemic subjects (n=35). The majority (51.4%) of anaemic patients had iron deficiency anaemia (IDA), followed by normocytic normochromic anaemia (28.6%). 20% of anaemic patients had absolute ID in comparison to 5.3% of non-anaemic subjects, while 62.9% vs 89.5% of anaemic and non-anaemic subjects respectively, had functional ID. The most predominant peripheral blood film picture among study subjects was on a non-specific morphology (48.1%), followed by mirocytic hypochromic anaemia (37%) and combined deficiency anaemia (9.3%) [Table V].

In terms of measures taken for correction of anaemia, 31.4% of anaemic patients received blood transfusions during hospital stay, while 22.9% of patients were given IV iron supplementation (Table VI).

Table-III
Comparison between anaemic and non-anaemic patients

Parameters	Anaemic patients (n=33)	Non- anaemic patients (n=21)	*p* value
Age (years)	65.9 ± 10.0	59.9±10.4	0.045
Haemoglobin (g/dl),	10.4. ±1.8	14.2±1.6	<0.001
Absolute Iron deficiency (ID), *n* (%)	7 (20.0%)	1 (5.3%)	0.145
Functional Iron deficiency (ID), *n* (%)	22 (62.9%)	17 (89.5%)	0.037
eGFR (ml/min)	44.2 ±22.3	48.1±19.5	0.51
LV Ejection fraction (%)	39.7±10.5	36 ±11.6	0.23
Hospital stay (days)	7.8±4.4	7.1 ±3.5	0.54
Mortality, *n* (%)	1(2.9%)	0 (0%)	0. 457
Male gender, *n* (%)	27 (77.1%)	17 (89.5%)	0.265
LV systolic dysfunction, *n* (%)	32 (91.4%)	18(94.7%)	0.658
LV diastolic dysfunction, *n* (%)	17 (48.6%)	14 (73.7%)	0.075
Primary valvular heart disease, *n* (%)	1 (2.9%)	1 (5.3%)	0.655
Secondary mitral regurgitation, *n* (%)	13 (37.1%)	8 (42.1%)	0.721
Aspirin, *n* (%)	30 (85.7%)	17 (89.5%)	0.694
P2Y12 Inhibitor, *n* (%)	29 (82.9%)	16 (84.2%)	0.899
Oral anticoagulation, *n* (%)	1 (2.9%)	1 (5.3%)	0.655

Table-IV

Distribution of anaemic patients according to aetiology (n=35)

Aetiology of anaemia	Number	Percentage (%)
Iron deficiency anaemia (IDA)	18	51.4
Combined deficiency anaemia	7	20.0
Normocytic normochromic anaemia	10	28.6

Table-V

Distribution of study population according to peripheral blood film study (n=54)

Peripheral blood film type	Number	Percentage (%)
Microcytic hypochromic anaemia	20	37.0
Combined deficiency anaemia	5	9.3
Normocytic normochromic anaemia	3	5.6
Non-specific morphology	26	48.1

Table-VI

Distribution of anaemic according to management measures taken to correct anaemia (n=35)

Management measure	Number	Percentage (%)
Blood transfusion	11	31.4
Oral iron supplementation	6	17.1
Intravenous iron supplementation	8	22.9

Discussion:

The findings from this study highlight a remarkably high prevalence of anaemia in HF patients among Bangladeshi population (64.8%). Overall, the prevalence of anemia is known to vary widely, ranging from 14% to 56% in outpatient registries to 14% to 61% in hospitalized patients.[2,3] However, a prevalence of 64.8% still remains higher than most registries such a STAMINA-HFP (Study of Anemia in a Heart Failure Population) registry (34%)[9] and a Canadian population-based cohort (17%).[10] A recent registry found a prevalence of anaemia of 41% in multi-ethnic Asian patients with heart failure with reduced ejection fraction, with a wide range across ethnicities (33-54%).[11] This large variability may be explained by methodological differences, possibly also to the definition of anaemia. Most publications use the definition of anaemia by the World Health Organisation (anaemia is a haemoglobin concentration < 13 g/dl in men and < 12 g/dl in postmenopausal women).[6] However, other cut-offs exist, resulting in such variability of prevalence.

The anaemic patients in our study were significantly older than their non-anaemic counterparts, but the mean age was comparable to Indian subjects with iron deficiency anaemia.[12] Our anaemic subjects are relatively younger (~65.9 years,) in comparison to Western studies, where the median age is ~70 years,[13, 14] but older than African anaemic subjects with heart failure.[15] Studies have also demonstrated that, overall, patients with HF and anemia tend to be older than their nonanemic counterparts.[16] Furthermore, elderly patients with anemia often have significant comorbidities, including heart failure and chronic kidney disease.[17]

In chronic HF, factors associated with a high prevalence of anaemia include concomitant kidney disease, advanced age, female gender, African American ethnicity, diabetes, hypertension, and lower estimated glomerular filtration rates.[1,18, 19] Our study concurs with these observations, with a majority of women being found to have anaemia. Anaemic subjects also had lower eGFR.

Regarding aetiology, mechanisms of anaemic in HF are multi-factorial: iron and other haematological deficiencies, renal insufficiency (related to erythropoetin production and resistance), the role of haemodilution, chronic diseases and 'inflammation', and the renin–angiotensin system. [1,20]

As in our study, iron deficiency appears to be the most common cause of anaemia in HF.[21,22] This is particularly relevant in an Asian context, where in fact, iron deficiency is prevalent in HF patients even without anemia, which is already an established poor prognostic factor.[12] A more detailed analysis into the presence of absolute and functional ID among HF patient with and without anaemia is warranted. The high prevalence of CKD (75.9%) may also be responsible for the relatively higher overall prevalence of anaemia among our study subjects.

31.4% of anaemic patients received blood transfusions during hospital stay, while 22.9% of patients were given IV iron supplementation during hospital stay. As this was an observational study, the effect of iron supplementation on improvement of HF and NYHA class could not be analyzed. Various studies with beneficial effect of Iron supplementation in HF have been published. [23,24] Apart from NYHA class and walking distance, Iron supplementation has been shown to improve echocardiographic parameters of myocardial performance.[25,26] Such trials among Bangladeshi subjects are also warranted.

A large number of studies have confirmed that anaemia is an independent predictor of increased mortality rate and hospitalisation stay in patients with systolic and diastolic dysfunction, new-onset HF, and severe chronic HF. [21,27,28] In our study, we found numerically higher mortality rates and longer hospital stay in the anaemic patients compared to non-anaemic subjects, however statistical significance could not be demonstrated owing to the smaller sample size of the study.

Limitations:

This study is a single-center study conducted at a tertiary care center in Dhaka with a small sample size. As such, it is difficult to generalize these findings necessitating multicenter larger studies. Secondly, this was an observational study, not designed to elucidate anaemia as a predictor of poor outcomes, nor the underlying detrimental mechanisms of ID in patients with HF. As such, further detailed analyses regarding absolute and functional ID and their impact on prognosis of HF are needed.

Conclusion:

This preliminary study showed a high prevalence of anaemia among HF patients, most notably due to iron deficiency and mechanisms related to CKD. Our study also sheds light on the yet underestimated and neglected burden of ID in HF patients in Bangladesh, suggesting the necessity of further large-scale studies.

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Comparison of Prevalence of Metabolic Syndrome between Young and Older Patients with Non-ST Elevation Myocardial Infarction

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Abstract

Background: The incidence of non-ST elevation myocardial infarction (NSTEMI), in comparison, to ST elevation myocardial infarction (STEMI) is increasing, probably as a result of demographic changes in population. Evidence reveals that increased cardiovascular risk starts to develop at young age. Metabolic syndrome is considered one of the important factors that increase the cardiovascular risk. Data on prevalence of metabolic syndrome in young and older patients with NSTEMI are very limited.

Objectives: This study was conducted to compare the prevalence of metabolic syndrome between young and older patients with NSTEMI.

Methods: The cross-sectional study was done in the Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh from July, 2016 to July, 2017. The patients with NSTEMI were divide into young and older groups considering age. Age ≤45 years was considered as young and age >45 years was considered as older. The International Diabetes Federation (IDF) and the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) criteria were used to define metabolic syndrome. According to NCEP ATP III criteria, MS was diagnosed as having three or more of abdominal obesity (WC >102 cm for male and >88 cm for female), dyslipidemia (TG ≥150 mg/dl or HDL< 40 mg/dl in male and < 50mg/dl in female), hypertension (BP ≥130/85 mm Hg) and impaired fasting glucose or diabetes (FPG ≥ 5.5 mmol/L). The IDF criteria differs from the NCEP ATP III criteria. It included central obesity as an essential component of metabolic syndrome and the WC cutoffs were fixed as race and gender specific (WC ≥90 cm for male and ≥80 cm for female in Asian-Indian population). Presence of central obesity with any two of dyslipidemia, hypertension, impaired fasting glucose or diabetes were described for the diagnosis of MS by the IDF criteria. Dyslipidemia, hypertension, impaired fasting glucose or diabetes were defined as of NCEP ATP III criteria. Presence of metabolic syndrome was compared between young and older patients.

Result: Out of 372 patients, 102 were young and 270 were older. According to IDF criteria, 32 of the young and 52 of the older group were found to have metabolic syndrome respectively and it was observed that the prevalence of metabolic syndrome in young patients was 31.4% and in older patients, 19.3%. According to NCEP-ATP III criteria, 29 of the young and 40 of the older group were found to have metabolic syndrome respectively and it was observed that the prevalence of metabolic syndrome in young patients was 28.4% and in older patients, 14.8%. Thus, the difference in prevalence of metabolic syndrome, diagnosed by both IDF and NCEP-ATP III criteria was found higher in young than older patients which was statistically significant (p= 0.01 and p= 0.003 respectively).

Conclusion: Our study demonstrated that, the prevalence of metabolic syndrome according to both IDF and NCEP-ATP III criteria was more in young patients than in older presenting with NSTEMI, when they were compared.

Key words: Metabolic Syndrome, Non-ST Elevation Myocardial Infarction, Young Adults, Bangladesh.

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Introduction:

Coronary artery disease (CAD) is the leading cause of cardiovascular mortality, responsible for about 30% of deaths worldwide. It has been projected that cardiovascular mortality will increase to 24.2 million by the year 2030[1]. Age standardized death rates for CAD are increasing in developing and transitional countries like Bangladesh as a result of demographic changes, urbanization, and lifestyle changes[2]. The exact prevalence of coronary artery disease in

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Bangladesh is not known. More recent data indicates that CAD prevalence is 1.85% to 3.4% in rural population and 19.6% in an urban population[3]. The incidence of non-ST elevation myocardial infarction (NSTEMI), in comparison, to ST elevation myocardial infarction (STEMI) is increasing, probably as a result of demographic changes in population. NSTEMI currently accounts for about 50% of all myocardial infarctions[4]. Young patients with CAD are specific subset of population requiring attention. The cut off age of 45 years has been used in most studies to define young patients with CAD and myocardial infarction[5]. These patients have different risk factor profiles, and prognosis than older patients[6,7]. Older patients had higher frequencies of diabetes, hypertension, dyslipidemia, but less history of smoking, obesity, and family history of CAD, which were high among younger patients[8].

Studies have suggested that the risk of myocardial infarction is mostly due to modifiable risk factors like smoking, physical inactivity, poor diet, psychosocial stress, hypertension, diabetes mellitus, dyslipidemia and increased waist-hip ratio[9-10]. Many of these risk factors are grouped or are seen at the onset of metabolic syndrome (MS). Although there are different criteria for the identification of metabolic syndrome, they all tend to agree that the core components are obesity (waist circumference), pre-diabetes or diabetes, dyslipidemia, and hypertension[11].The International Diabetes Federation (IDF) released a global consensus definition[12] for MS, along with race- and gender-specific waist circumference (WC) cutoffs. This definition identified central obesity as an essential component of MS. The National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) criteria[13] differs from the IDF criteria. It did not include central obesity as an essential component of metabolic syndrome and the WC cutoffs were fixed only as gender but not as race specific. Some studies have analyzed the prevalence of MS in patients with the acute coronary syndrome (ACS) with mix populations including both STEMI and NSTE-ACS, also all age groups[14-16]. Data on prevalence of metabolic syndrome in patients with NSTEMI are very limited. The prevalence of MS in young patients, in comparison to older with NSTEMI has not been studied in Bangladesh, to our knowledge. Understanding the prevalence of metabolic syndrome in patients with NSTEMI in younger and older age group is important for developing public health policy towards prevention and management. Hence this study was undertaken to know the prevalence of metabolic syndrome in patients with NSTEMI using both the IDF Bangladeshi and NCEP-ATP III criteria and to compare it between young and older age group. To the best of our knowledge, such type of comparison in the Bangladeshi population is the first study.

Methods:

Participants and study design

This cross-sectional study was done in the Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh from July, 2016 to July, 2017. Total 372 patients with non-ST elevation myocardial infarction were studied. The patients with history of prior myocardial infarction, valvular heart diseases, congenital heart diseases, cardiomyopathy, suspected myocarditis or pericarditis and who underwent prior PCI or CABG were excluded from the study. The study protocol was approved by ethical review committee of the National Institute of Cardiovascular Diseases, Dhaka, Bangladesh.

Procedure

After enrollment, all patients with suspected non-ST elevation acute coronary syndrome were evaluated clinically at first presentation. Demographic data such as age, sex and occupation were recorded. Risk factors including diabetes, smoking, hypertension, dyslipidemia, family history (premature CAD at 55 and 65 years of age in male and female first-degree relatives, respectively[17]) and history of using antihypertensive, antidiabetic and lipid lowering drugs were noted. General and systemic physical examinations including cardiovascular system were done thoroughly. Three readings of BP were recorded in both arms at 5 minutes interval for an average of three values. A 12-lead resting ECG was done on admission at a paper speed of 25 mm/s and 10mm standardization. Cardiac troponin I was measured to confirm the diagnosis of NSTEMI from the sample taken during admission. Troponin I concentration was measured by immunometric assay in our institute and the level of more than 1ng/ml was considered as positive. Random blood sugar and serum creatinine were also measured from the first sample. In the following morning after an overnight fast blood sample was taken for fasting lipid profile like, total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) and at day-5, for fasting plasma glucose (FPG). Waist

circumferences (WCs) were measured in all patients at the level midway between the lowest rib and the iliac crest before discharge.

Definition

The patients admitted with NSTEMI were divide into young and older groups considering the age. Age ≤45 years was considered as young and age >45 years was considered as older[18]. The International Diabetes Federation (IDF) global consensus definition and the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) criteria were used to define metabolic syndrome. According to NCEP ATP III criteria[14], MS was diagnosed as having three or more of abdominal obesity (WC >102 cm for male and >88 cm for female), dyslipidemia (TG ≥ 150 mg/dl or HDL< 40 mg/dl in male and < 50mg/dl in female), hypertension and impaired fasting glucose or diabetes. According to IDF criteria[13], MS was diagnosed by the presence of central obesity (identified by race and gender specific WC ≥ 90 cm for male and ≥ 80 cm for female in Asian-Indian population) with any two of dyslipidemia (TG ≥ 150 mg/dl or HDL< 40 mg/dl in male and <50mg/dl in female), hypertension, impaired fasting glucose or diabetes. Hypertension was defined as the BP during admission ≥ 130/85 mm Hg or if a previous diagnosis of hypertension had been made and/or treatment had already been prescribed. Impaired fasting glucose or diabetes was said when fasting plasma glucose (FPG) ≥ 5.5 mmol/L or if a previous diagnosis of diabetes had been made and/or treatment had already been prescribed. These definitions of hypertension and impaired fasting glucose or diabetes were used in both the criteria.

Statistical analysis

Continuous variables were expressed as mean and standard deviation and categorical variables as frequency and percentage. Quantitative variables were analyzed by unpaired t-test. Categorical variables were analyzed by chi-square test. The chi square test was also used to compare the prevalence of metabolic syndrome between young and older age group. P value of less than 0.05 was used as a cut off for statistical significance. Statistical analysis was performed by using SPSS statistical software (version 19, SPSS Inc., Chicago, Illinois, USA)

Results:

Minimum age of the study population was 26 years and maximum age was 75 years. Out of 372 patients 102 (27%) patients were young and 270 (73%) patients were older. The mean age of young and older were 40.7±5.2 and 55.9±6.3 years respectively. Mean age difference between the two age groups was statistically significant with p value <0.001(Table I). Male patients were predominant in the study (80%). Male-female ratio was 4.2:1. In young, 87.3% were male and 12.7% were female. In older, 78.1% were male and 21.9% were female (Table II).

Table-I

Age distribution of the study population (n=372).

Age group (years)	Young (n=102)		Older (n=270)		Total (n=372)		p- value
	Number	%	Number	%	Number	%	
≤ 30	7	6.9	0	0.0	7	1.9	
31 – 40	30	29.4	0	0.0	30	8.1	
41 – 50	65	63.7	80	29.6	145	39.0	
51 – 60	0	0.0	135	50.0	135	36.3	
e” 60	0	0.0	55	20.4	55	14.8	
Mean ± SD	40.7±.5.2		55.9±6.3		51.7±9.1		<0.001

Table-II

Sex distribution of the study population (n = 372)

Sex	Young(n=102)		Older (n=270)		Total (n=372)		p- value
	Number	%	Number	%	Number	%	
Male	89	87.3	211	78.1	300	80.6	0.05
Female	13	12.7	59	21.9	72	19.4	

Among the other risk factors, patients with history of smoking was higher in older (77%) than young (67%) with statistically significant association, in comparison to young patients (p value is 0.04). On the other hand, dyslipidemia was found higher in young (46%) patients than in older patients (31%) with significant association (p=0.009). Individually, hypertension (Young = 62%, Older = 72%), diabetes mellitus (Young = 53%, Older = 59%) and family history of premature CAD (Young = 48%, Older = 40%) showed no statistically significant difference between young and older patients in this study.

Abdominal obesity was identified by the waist circumference of the study population. The mean waist circumference, according to IDF criteria was 93.6 ±6.8 cm in young patients (Male = 92.5 cm and female = 81.8 cm) and 84.8 ± 4.9 cm in older patients (Male = 93.9 cm and female = 83.7 cm). It showed waist circumference was higher in young than older patients with statistically significant difference of p value < 0.05 (Table III and Fig.-1).

Table-III

As per IDF criteria, mean waist circumference between young and older age group of the study population (n = 372).

Variables	Young (n=102)	Older (n=270)	P value
	Mean ± SD	Mean ± SD	
Waist circumference cm	93.6±6.8	84.8±4.9	0.01

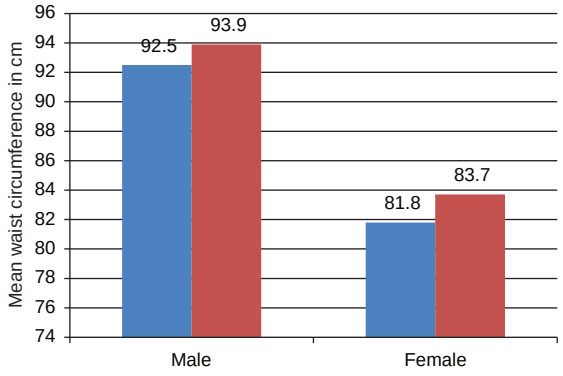


Fig.-1: *Mean waist circumference of young and older male - female patients as per IDF criteria (n=372).*

The mean waist circumference, according to NCEP-ATP III criteria was 95.9 ±7.8 cm in young patients (Male = 103.6 cm and female = 89.7 cm) and 87.6 ± 6.4 cm in older patients (Male = 104.2 cm and female = 90.6 cm). It showed waist circumference was higher in young than older patients with statistically significant difference of p value < 0.05 (Table IV and Fig.-2).

Table-IV

As per NCEP-ATP III criteria, mean waist circumference between young and older age group of the study population (n = 372).

Variables	Young (n=102)	Older (n=270)	P value
	Mean ± SD	Mean ± SD	
Waist circumference cm	95.9±7.8	87.6±6.4	0.01

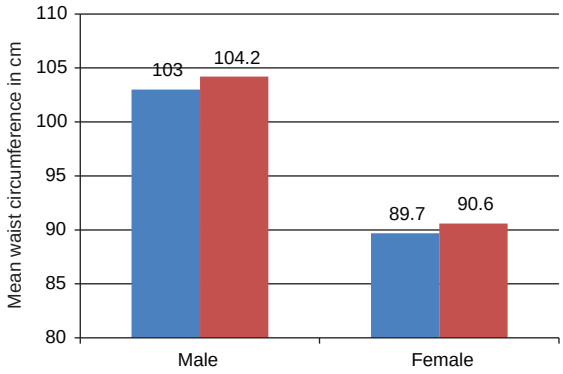


Fig.-2: *Mean waist circumference of young and older male - female patients as per NCEP-ATP III criteria (n=372).*

Finally, according to IDF criteria, prevalence of total metabolic syndrome was 22.6% in the study population comprising 31.4% in young patients and 19.3% in older patients. The difference was significantly higher in young than in older patients with p value 0.01(Table V and Fig.-3).

Table-V

Prevalence of metabolic syndrome between young and older patients by IDF criteria (n = 372).

Metabolic Syndrome	Young (n=102) No. (%)	Older (n=270) No. (%)	Total (n=372) No. (%)	P value
Present	32 (31.4)	52 (19.3)	84 (22.6)	0.01
Absent	70 (68.6)	218 (80.7)	288 (77.4)	

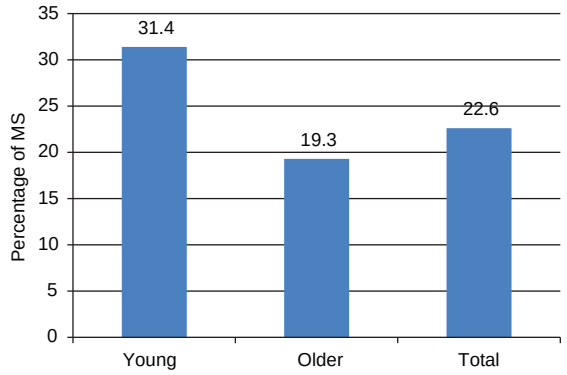


Fig.-3: *Prevalence of metabolic syndrome between young and older patients according to IDF criteria.*

According NCEP-ATP III criteria, prevalence of total metabolic syndrome was 18.5% comprising 28.4% in young patients and 14.8% in older patients. The difference was also significantly higher in young than in older patients with p value 0.003(Table VI and Fig.- 4).

Table-VI

Prevalence of metabolic syndrome between young and older patients by NCEP-ATP III criteria (n = 372).

Metabolic Syndrome	Young (n=102) No. (%)	Older (n=270) No. (%)	Total (n=372) No. (%)	P value
Present	29 (28.4)	40 (14.8)	69 (18.5)	0.003
Absent	73 (71.6)	230 (85.2)	303 (81.5)	

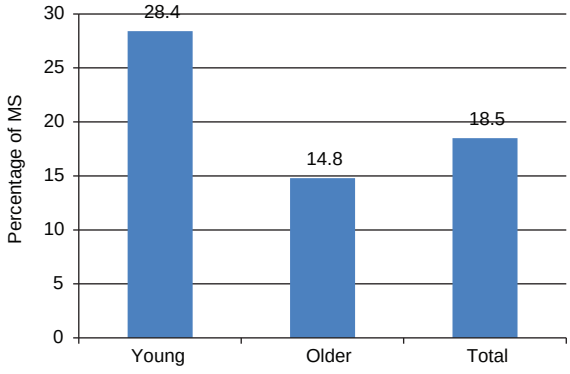


Fig.-4: *Prevalence of metabolic syndrome between young and older patients according to NCEP-ATP III criteria.*

Discussion:

Age standardized death rates for coronary artery Disease (CAD) are increasing in developing and transitional countries like Bangladesh as a result of demographic changes, urbanization, and lifestyle changes. The incidence of non-ST elevation myocardial infarction (NSTEMI), in comparison, to ST elevation myocardial infarction (STEMI) is also increasing. Risk factors for CAD are now well recognized and modification of these factors can prevent acute coronary syndrome (ACS) and prolong life. Dyslipidemia, cigarette smoking, hypertension, positive family history, age and diabetes mellitus are the major risk factors of CAD. Age, male sex and family history are the non-modifiable risk factors. Smoking, hypertension, diabetes mellitus, sedentary lifestyle, obesity and dyslipidemia are the modifiable risk factors[19].

Metabolic syndrome (MS) is characterized by a constellation of risk factors such as raised triglyceride, low high-density lipoprotein (HDL), glucose intolerance, hypertension and abdominal obesity that may lead to the development of CAD. South Asians are more prone to develop MS because of their high percentage of body fat, abdominal obesity and insulin resistance[20]. Moreover, Asian Indians have a different distribution of body fat, with abdominal obesity or a higher body fat content, even in the presence of normal body mass index[21].

Data on the prevalence of metabolic syndrome in patients with NSTEMI are very limited. The prevalence of MS in young patients with NSTEMI, in comparison to older has not been studied in Bangladesh, to our knowledge. Understanding the prevalence of metabolic syndrome in patients with NSTEMI in younger and older age group is important for developing public health policy towards prevention and management. We aimed to know the prevalence of metabolic syndrome in patients with NSTEMI and to compare the prevalence between young and older patients. To best of our knowledge, such type of comparison in the Bangladeshi population is the first study. This cross-sectional study was done in the Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh from July, 2016 to July, 2017 and total 372 patients with NSTEMI were studied.

There are different criteria for the diagnosis of metabolic syndrome. The International Diabetes Federation (IDF) released a global consensus definition[12] for MS, along with race- and gender-specific waist circumference (WC) cutoffs (WC ≥ 90 cm for male and ≥ 80 cm for female in Asian-

Indian population). This definition identified central obesity as an essential component of MS. The National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) criteria[13] differs from the IDF criteria. It did not include central obesity as an essential component of metabolic syndrome and the WC cutoffs were fixed only as gender but not as race specific (WC >102 cm for male and >88 cm for female). We have applied both IDF and NCEP-ATP III criteria to diagnose the MS. The cut off age of 45 years has been used to define young patients in this study. Sundaramoorthy, et al. in 2017 and Oz, et al. in 2018 used the cut off age 45 years to define young adult and older patients in their study to see the prevalence of MS in young patients with STEMI and CAD respectively[22,23].

We found 27% young and 73% older patients. Ayub and Anwar, 2017 studied 300 patients with NSTEMI in Pakistani population and found 17% young and 83% older patients[24].

According to IDF criteria, the prevalence of total metabolic syndrome was 22.6% in our study population comprising 31.4% in young and 19.3% in older patients. The difference was significantly higher in young than in older patients with p value 0.01. According NCEP-ATP III criteria, the prevalence of total metabolic syndrome was 18.5% comprising 28.4% in young and 14.8% in older patients. The difference was also significantly higher in young than in older patients with p value 0.003. Dhakhada V, et al. 2013 in their study of 100 patients of Indian population, found 59% prevalence of metabolic syndrome in ACS patients using IDF criteria. As they included all patients of ACS in all age group, the prevalence they found high[25]. In Turkey, Oz, et al, in 2018 studied 141 patients with STEMI and the total prevalence of metabolic syndrome using NCEP-ATP III criteria was 46% in young patients. It might be explained by the geographic variation of patient characteristics, subset of ACS and the criteria used to diagnose metabolic syndrome[23]. The total prevalence of metabolic syndrome in patients with NSTEMI in our study was lower when used NCEP-ATP III criteria than when used the IDF criteria but the prevalence of it in young is more than in older patients for both the criteria. Although NCEP-ATP III criteria is widely used in studies related with metabolic syndrome, we have used IDF criteria also mainly because for looking at Asian phenotype of obesity and as for many patients with metabolic syndrome could be underestimated by applying the NCEP-ATP III criteria.

Study limitations

Though adequate number of study population was used, we believe that it is still limited to generalize the results and it was conducted in a single center.

Conclusion

The prevalence of metabolic syndrome was more in young patients with NSTEMI than in older patients in Bangladeshi population when they were compared according to both IDF and NCEP-ATP III criteria. Total prevalence of metabolic syndrome, diagnosed by IDF criteria in all patients with NSTEMI was found more than diagnosed by the NCEP-ATP III criteria. So, primary prevention of metabolic syndrome may help in preventing NSTEMI in young adult age group. Nevertheless, further studies with large number of patients with multicenter approach are needed to assess this comparison between young and older patients with NSTEMI.

Conflict of Interest - None.

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REVIEW ARTICLE

Role of Echocardiography in Non-Coronary Cardiovascular Interventions

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Abstract:

As structural heart disease interventions continue to evolve to a sophisticated level, accurate and reliable imaging is required for pre-procedural selection of cases, intraprocedural guidance, post-procedural evaluation, and long-term follow-up of patients.

A major advantage of echocardiography over other advanced imaging modalities (magnetic resonance imaging, computed tomographic angiography) is that echocardiography is mobile and real time. Echocardiograms can be recorded at the bedside, in the cardiac catheterization laboratory, in the cardiovascular intensive care unit, in the emergency room—indeed, any place that can accommodate a wheeled cart. This tremendous advantage allows for the performance of imaging immediately before, during, and after various procedures involving interventions. This article provides information on the selection of patients for interventions, monitoring during the performance of interventions, and assessing the effects of interventions after their completion.

The use of imaging techniques to guide even well-established procedures enhances the efficiency and safety of these procedures.

Key Words: Echocardiography, Cardiovascular, Interventions

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Introduction:

Traditionally, percutaneous cardiovascular interventions have predominantly used angiographic and fluoroscopic guidance, which is limited when interventions involve the myocardium, pericardium, and cardiac valves. There is a great role of echocardiography in guiding a wide variety of interventional and electrophysiological procedures. So, here is a discussion about the critical echocardiographic aspects of these procedures and delineation of the intraprocedural differences between echocardiographic modalities, comparing transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and intracardiac echocardiography (ICE). ICE is a new echocardiographic modality. which echo-cardiography has had an important impact in the procedures being performed and their outcomes. As percutaneous therapy for heart disease continues to advance at a rapid pace, it is inevitable that echocardiographic procedural guidance will continue to evolve rapidly as well. Similarly, other modalities, such as magnetic resonance imaging and combined multiple imaging modalities (eg, reconstructed 3D computerized tomography with superimposed real-time echocardiography) will continue to evolve and develop roles in guiding these complex procedures as well.

Currently, percutaneous interventional procedures that are performed under echocardiographic guidance include[1-3]:

1. Closure of congenital and acquired septal defects
   a. Atrial septal defect (ASD)
   b. Patent foramen ovale (PFO)

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c. Ventricular septal defect (VSD), especially post infarction VSD

2. Valvular heart disease
   a. Balloon mitral valvuloplasty
   b. Mitral valve repair (edge to edge repair with a mitral clip)
   c. Aortic valve implantation
   d. Prosthetic paravalvular leak closure
   e. Valve in valve implantation for a degenerative bioprosthetic valve
   f. Tricuspid valve repair (functional tricuspid regurgitation with use of the Mitralign System)
3. Left atrial appendage device occlusion
4. Pulmonary vein ablation for atrial fibrillation.
5. Ventricular pseudoaneurysms, post-infarction
6. Pericardiocentesis
7. Myocardial biopsy
8. Alcohol septal ablation
9. Suction of right heart clots
10. Placement of percutaneous left ventricular support devices
11. Laser lead extraction of pacemaker and defibrillator leads
12. A diverse array of other congenital heart diseases
    a. Patent ductus arteriosus closure with coil
    b. Stenting of aortic coarctation
    c. Valvulopasty for congenital aortic and pulmonary stenosis
    d. Narrowed baffles opening

Use of different modalities of echo in interventional cardiology[4]

Use of Transthoracic Echo

TTE is widely available and portable and offers excellent image quality; as such, it has been used widely in guiding percutaneous noncoronary interventional and electrophysiologic procedures. Most currently available ultrasound systems, including handheld and portable ultrasound systems, offer sufficient 2-dimensional (2D) and Doppler capabilities to guide a variety of interventions, such as echocardiography-guided pericardiocentesis, alcohol septal ablation for hypertrophic cardiomyopathy, percutaneous transvenous mitral commissurotomy (PTMC), and myocardial biopsy. The advent of Doppler tissue imaging has made TTE essential in the optimization of biventricular pacemakers.[4]

Use of Transesophageal Echo

TEE has been widely used as an alternative to TTE in guiding complex procedures. TEE offers superior image resolution to TTE and can be used to monitor a variety of interventions, such as percutaneous transcatheter closure (PTC) of septal defects, PTMC, transseptal catheterization, and many others. Compared with TTE, it excels at assessing intraprocedural anatomy and physiology, monitoring catheter position and contact, and excluding thrombus, pericardial effusion, and other complications.[4]

Intracardiac Echo[4]

A more recent application of cardiac ultrasound, ICE has also demonstrated great potential for monitoring and guiding interventions. Experimental and clinical studies have demonstrated the utility of ICE in monitoring left ventricular and right ventricular function, delineating anatomy, guiding transseptal punctures and therapy, and biopsy of cardiac masses.[7-13]

ICE offers imaging that is comparable with or superior to TEE. ICE has been shown to provide significant benefits when used for radiofrequency ablation of atrial fibrillation (AF) and transcatheter atrial septal closure procedures and has become the imaging standard during these procedures at many centers.[14-20] In the catheterization laboratory during these procedures, an advantage over TEE is that ICE obviates the need for general anesthesia and for additional echocardiography physician support. Compared with guidance using TEE, ICE has been shown to improve patient comfort, shorten both procedure and fluoroscopy times, and offer comparable cost with TEE-guided interventions.[15-16] Additional uses of ICE may include guidance of transseptal catheterization, the placement of LAA occluder devices, the placement of percutaneous left ventricular assist device cannulas, the performance of PBMV, and many others.[8,9,28-29] Diagnostic intracardiac imaging may be considered as an alternative to TEE in selected patients with absolute contraindications to TEE (eg, esophagectomy) or to

potentially evaluate anatomic regions that TEE may not be able to visualize well because of shadowing from other structures (eg, ascending aortic evaluation, which is not well seen on TEE because of tracheal shadowing in the "TEE blind spot").

Use of Echocardiography in Transseptal Catheterization[4]

Transseptal catheterization is performed when procedural access to the left atrium is required and is used for PTMC, anterograde aortic balloon valvuloplasty, radiofrequency ablation of AF and other left-sided arrhythmias, transseptal PFO closure, the placement of percutaneous left ventricular assist device cannulas in the left atrium, balloon or blade atrial septostomy, the measurement of complex hemodynamics (such as evaluation of a mechanical aortic valve prosthesis or critical aortic stenosis in which the valve itself cannot be crossed), and, most recently, investigational applications such as the placement of LAA occlusion devices and percutaneous mitral valve repair.[28-33] Traditionally, transseptal catheterization has relied on fluoroscopic guidance, in which anatomic structures are not directly visualized.

Observational studies have suggested that TTE or TEE may be helpful in performing this procedure by allowing direct visualization of the transseptal catheter and its relationship to the fossa ovalis. Although echocardiographic imaging is not invariably required for the successful performance of transseptal catheterization, it offers potential advantages over traditional anatomic and fluoroscopic guidance.[9,24,34-42] Anatomic variability in the position and orientation of the fossa ovalis and its surrounding structures may present specific challenges to even those interventional cardiologists with significant transseptal experience, and imaging offers increased safety, with a lower risk for cannulating other spaces adjacent to the fossa. Inadvertent puncture of the intrapericardial aorta is a serious complication of transseptal catheterization, and echocardiographic imaging reduces this risk. Similarly, imaging may decrease the time required for the transseptal puncture to be performed and minimizes the fluoroscopy time required for the procedure. In patients undergoing PBMV who are pregnant, radiation exposure can be reduced with echocardiographic guidance of the procedure, including the transseptal puncture.[36] Imaging may also assist those operators without significant transseptal experience who are learning the procedure.

Early studies of TTE-guided transseptal puncture demonstrated that TTE can delineate the aorta and interatrial septum and the characteristic bulging (or tenting) of the fossa ovalis at a satisfactory location that occurs before transseptal puncture.[41] Saline contrast echocardiography with TTE may help confirm needle position in the right atrium before puncture and in the left atrium after puncture. TTE does not always offer sufficient imaging resolution to guide transseptal catheterization, and as such, TEE and more recently ICE have been used when imaging is required. TEE and ICE also provide the ability to choose the exact site of transseptal puncture, which is important in performing advanced mitral valve interventions for mitral regurgitation (MR) because the catheters are more difficult to manipulate and position if the transseptal crossing point is too close to the plane of the mitral valve orifice. Because ICE can be performed without additional sedation or general anesthesia, as well as with minimal additional patient risk and discomfort, it has become the standard at many centers if imaging is required only for the transseptal catheterization aspect of a procedure.[9,24,35-43]

With ICE during a transseptal procedure, recognition of tenting of the interatrial septum identifies the location of the transseptal sheath before puncture . The possibility of perforation of the aorta, pulmonary artery, and atrial wall exists during transseptal catheterization. The injection of a small amount of microbubbles or contrast into the left atrium after the needle has crossed the septum is used to confirm left atrial access . Finally, a guidewire is passed into the left atrium under guidance with ICE to establish stable left atrial access.

Use of Echocardiography-Guided Pericardiocentesis[4]

Fluoroscopic guidance and electrocardiographic needle monitoring have been used to improve the safety of pericardiocentesis,[44,45] but complications, including damage to the liver, myocardium, coronary arteries, and lungs, have been reported.[46]

Safety and Efficacy of Echocardiography-Guided Pericardiocentesis

In a Mayo Clinic series, echocardiography-guided pericardiocentesis was successful in withdrawing

pericardial fluid or relieving tamponade in 97% of the procedures.[47] Major complications including chamber laceration, intercostal vessel injury, pneumothorax requiring a chest tube, sustained ventricular tachycardia (VT), bacteremia, and death occurred in 1.2% of patients, and minor complications including transient cardiac chamber entry, transient arrhythmia, minor pneumothorax, and vasovagal reactions were noted in 3.2%.[47] The safety and efficacy of echocardiography-guided pericardiocentesis had been shown in various subgroups, including pediatric patients, patients who were hemodynamically very unstable after cardiac perforation secondary to invasive percutaneous procedures, postoperative patients, and patients with malignancies or connective tissue diseases.[48]

Technique of Echocardiography-Guided Pericardiocentesis

Two-dimensional and Doppler studies are performed to assess the size, distribution, and hemodynamic impact of the effusion and to identify the ideal entry site and needle trajectory for pericardiocentesis. The ideal site of needle entry is the point at which the largest fluid collection is closest to the body surface and from which a straight needle trajectory avoids vital structures. Because ultrasound does not penetrate air, the lungs are effectively avoided. Safety is ensured by using sheathed needles and withdrawing the steel needle upon entering the fluid space.

The left chest wall is often the location selected for entry.[47]The subcostal route involves a longer path to reach the fluid, passes anterior to the liver capsule, and is directed toward the right chambers of the heart.

The position of a catheter introduced into the pericardial space can be confirmed by the injection of agitated saline, and this is performed if bloody fluid has been aspirated or if the catheter position is in question. The appearance of contrast in the pericardial sac confirms its position . If the catheter is not in the pericardial space, it should be repositioned, or another needle passage should be attempted.

Precautions and Contraindications

The contraindications to echocardiography-guided pericardiocentesis are few, and even these should be evaluated on a case-by-case basis. In theory, pericardiocentesis is contraindicated in the setting of myocardial rupture or aortic dissection because of the potential risk for extending the rupture or dissection with decompression.[49]

Use of Echocardiography to Guide Myocardial Biopsy[4]

Endomyocardial biopsies are typically performed in the right ventricle to diagnose a wide variety of myocardial disorders, including infiltrative cardiomyopathy and cardiac transplant rejection. Although endomyocardial biopsy is often performed with fluoroscopic guidance alone, some centers use 2D TTE to complement or replace fluoroscopy.[50-54] Similarly, others have reported using TEE or ICE to guide biopsies of masses in the right heart and aorta in selected patients.[55-57]

With echocardiographic guidance, it is possible to provide a wider choice of biopsy sites. In addition to the ventricular septum, both the right ventricular apex and free wall can be biopsied. Moreover, this approach improves the yield of the biopsy by reducing the number of fibrotic samples due to “bites” in the same site (midventricular septum). This approach may also reduce the likelihood of perforation and damage to the tricuspid valve.[54]Other potential advantages of echocardiography-guided endomyocardial biopsy include the reduction of radiation exposure and portability.

Optimal views on TTE for guiding right ventricular biopsies include the apical 4-chamber view and the subxiphoid 4-chamber view . The transducer may be positioned more medially (midclavicular line) to optimally visualize the right ventricle during biopsy. Optimal views on TEE include the midesophageal 4-chamber view, as well as the transgastric short-axis and long-axis views. ICE from either the right atrium or the right ventricle can be used for the guidance of right ventricular biopsy. Note, however, that the tip of a catheter cannot always be visualized with certainty.

Other limitations to the use of echocardiography for guiding myocardial biopsy include the difficulty in performing TTE in patients in the catheterization laboratory who are in the supine position and the difficulty in imaging patients such as those with chest tubes and bandages, obesity, or chronic lung disease. TEE and ICE overcome these limitations in image quality, although with the need for additional echocardiography physician support and sedation (for TEE), as well as additional cost and attendant vascular risks (for ICE).

Echocardiography, particularly TTE, is useful as an adjunctive imaging modality in patients undergoing intracardiac and intravascular biopsy procedures. Although TEE and ICE may offer improved imaging over TTE, the additional risk and cost must be outweighed by significant procedural benefits, and the modalities are recommended for use only in highly selected patients.

Echocardiographic Guidance of Percutaneous Transvenous Mitral Commissurotomy[4]

General Imaging Considerations

PTMC is performed with fluoroscopic guidance alone at many centers, but radiographic anatomic landmarks can mislead even experienced operators. Kronzon et al[41] recommended 2D TTE (in the apical 4-chamber and parasternal short-axis views) as a useful adjunct to fluoroscopy during transseptal cardiac catheterization during PTMC. Pandian et al[58] advocated the use of subcostal views to assist PTMC as well. Disadvantages of TTE include that it interrupts the flow of the procedure, potentially interferes with sterile technique, and provides inadequate imaging in some patients.

TEE is an alternative to TTE for guiding PTMC[59-62]. The role of TEE before and during balloon mitral valvuloplasty is well established. TEE can be used for patient selection[63,64] and for all aspects of online procedural guidance[59-62]. It is used to guide the transseptal catheterization and is generally superior to TTE in this regard. TEE is also superior to TTE when it is used to exclude left atrial and LAA thrombus, and it facilitates wire and balloon position before and during inflation . TEE is used to measure transmitral gradients and mitral valve area and to assess the degree of MR immediately after each balloon inflation. Finally, TEE can be used to look for complications of PTMC, such as severe MR, pericardial effusion or tamponade, dislodgement of thrombus, and residual ASD. Moreover, some authors have suggested that the use of online TEE can both reduce fluoroscopic and procedure time and improve results[59-62]

ICE provides another alternative for online guidance of PTMC.[26,40,65] It provides an excellent view of the fossa ovalis and can be used to guide the transseptal puncture.[40] Newer phased-array intracardiac echocardiographic catheters provide pulsed-wave, continuous-wave, color flow Doppler, and Doppler tissue imaging. Thus, like TEE and TTE, ICE can facilitate the immediate assessment of the results of the valvuloplasty, including the transmitral gradient, the mitral valve area, the presence or worsening of MR, and the detection of complications, such as cardiac perforation, tamponade, or a torn mitral valve. Like TEE, ICE does not interfere with the catheterization process and can be used for each of the sequential tasks needed to perform mitral valvuloplasty.[26,65]The relative value of ICE compared with TTE and TEE has yet to be determined. Cost is a significant consideration, because a phased-array intracardiac echocardiographic catheter costs approximately $2,500 to $3,000, for a catheter that may only be used up to 3 times. Visualization of left-sided structures on ICE may be inferior or superior to that provided by TEE or TTE, depending on the chamber from which the catheter is providing images. In particular, the LAA may not be well visualized when intracardiac echocardiographic images originate only from the right atrium, and the presence or absence of an intracardiac thrombus cannot be confirmed. Imaging from the left atrium or pulmonary artery may overcome this limitation. On the other hand, ICE visualizes the mitral valve structures, especially the subvalvular structures of chordae tendineae and papillary muscles, with superior spatial resolution compared with TEE or TTE.[65] Images should be transmitted to a monitor that is easily viewed by the catheterization operator, usually adjacent to the fluoroscopic monitor.

Immediate Assessment of Results

Online echocardiography during the procedure is ideally suited for the immediate assessment of the results of PTMC.[9] The adequacy of valvulotomy can be determined by evaluating the maximal mitral leaflet separation and by continuous-wave Doppler determination of the mean mitral gradient and mitral valve area. With TEE and ICE in addition, the pulmonary venous flow profile can be assessed, with a more rapid diastolic deceleration expected after successful PTMC.[66]Finally, new or worsening MR is sought by color Doppler. Decisions about the adequacy of the procedure versus the need for further dilation should be made on the basis of both echocardiographic and hemodynamic data.

Early Detection of Complications

Although uncommon, serious complications do occur with PTMC. The majority of these (eg, the development of severe MR, cardiac perforation and tamponade,

ASDs) can be identified accurately and quickly by online echocardiography during the procedure. An increase in the degree of MR occurs in approximately half of patients after PTMC[42,58,67,68]. In most, this increase is mild, but the reported incidence of the development of severe MR is 1% to 6%.[74] Acute, severe MR may be caused by tear or rupture of the mitral leaflets, by ruptured chordae tendineae, or rarely by avulsion of a papillary muscle.[69] Each of these can be detected readily by echocardiography, particularly by TEE or ICE. Moreover, the presence and severity of MR can be determined without the need for ventriculography.

The incidence of cardiac tamponade during PTMC has been reported to be between 0% and 9%.[70] Perforation of the atrial free wall at the time of transseptal puncture is the most common cause of bleeding into the pericardial space. Echocardiographic detection of such fluid is immediate and permits rapid pericardiocentesis before major hemodynamic compromise occurs. Perforation of the left ventricle, especially with the double-balloon technique, has also been reported. Online TEE can lead to rapid detection and treatment of this potentially life threatening complication.[70]

The reported incidence of ASD resulting from PTMC is highly variable depending on the technique used for its detection. A left-to-right shunt at the atrial level is detected by oximetry in only 8% to 25% of patients.[61] TTE can detect an atrial shunt after PBMV in 15% to 60% of patients. TEE, a more sensitive technique, has been reported to detect shunts in as many as 90% of patients. ICE, with its excellent visualization of the fossa ovalis, should offer comparable sensitivity. Because the defects are usually small and because left atrial pressure in these patients is high, the small left-to-right shunting jets are easily detected by transesophageal echocardiographic or intracardiac echocardiographic color Doppler imaging. The creation of a small ASD should be considered an expected consequence rather than a true complication in the majority of patients.

Limitations

Several investigators have pointed out that immediately after PTMC, Doppler evaluation of mitral valve area by the pressure half-time method should be interpreted with caution because of a reduced correlation with hemodynamic measurements obtained by cardiac catheterization. This discrepancy may be related in part to acute alterations in left atrial and left ventricular compliance and a reduced initial peak mitral valve gradient.

Effect on Outcomes

The use of echocardiographic guidance during the procedure may improve the procedural success and complication rates.[71,72] Online imaging can provide more precise targeting of the transseptal needle toward the fossa ovalis region of the atrial septum, thereby minimizing the likelihood of perforation.[62,70,73,74] In addition, imaging not only has the potential to reduce the risk for procedural complications but may also allow immediate identification of these complications should they occur, permitting more prompt correction. Moreover, echocardiographic guidance may reduce procedural and fluoroscopic time[70]. Park et al[70] evaluated fluoroscopic guidance only (n = 64) and patients who underwent PTMC with online transesophageal echocardiographic guidance (n = 70). The procedural time was significantly shorter in the latter group (99 ± 48 vs 64 ± 22 minutes; *P*< .0001). The average fluoroscopic time was also shorter in the TEE-guided group (30 ± 17 vs 19 ± 15 minutes), but this was not statistically significant (*P* = .25). Echocardiographic guidance may also reduce the risk for worsening MR as a result of the better assessment of the number of balloon inflations required and better positioning of the balloon catheter. Further studies are required to validate the incremental safety and efficacy of echocardiographic guidance to supplement or replace fluoroscopic guidance of PTMC.

Echocardiographic Guidance of Atrial Septal Defect and Patent Foramen Ovale Closure[4]

Introduction

Percutaneous transcatheter closure of ASDs and PFO is an increasingly attractive alternative to surgical repair. These procedures are widely performed for hemodynamically significant left-to-right shunting, to prevent recurrent paradoxical embolism, and for the platypnea-orthodeoxia syndrome. A variety of different approaches are used to guide PTC of ASDs and PFO, each with unique advantages and disadvantages. These include primary fluoroscopic guidance and echocardiographic guidance with TTE, TEE, and, most recently, ICE.[15,16,19,75-77]

Echocardiographic Modalities

TTE, TEE, and ICE are used to evaluate and guide the percutaneous closure of PFOs and ASDs. TTE has the advantage of offering multiple planes to evaluate the device and atrial septum, but it has limited ability to interrogate the lower rim of atrial septal tissue above the inferior vena cava after device placement, because the device interferes with imaging in virtually all planes. In addition, because the septum is relatively far from the transducer (relative to TEE or ICE), color imaging is suboptimal in larger patients. Some centers, however, use TTE for monitoring in all patients. In adult patients, TTE typically provides more limited imaging of the interatrial septum and surrounding structures, and as such, most adult centers typically use TEE or ICE to guide PTC.

Transesophageal echocardiographic guidance has been described extensively in adult patients and offers the advantages of providing real-time, highly detailed imaging of the interatrial septum, surrounding structures, catheters, and closure device.[15,19] TEE requires either conscious sedation, with attendant aspiration risk in a supine patient, or general anesthesia, with an endotracheal tube to minimize this risk. This approach also requires a dedicated echocardiographer to perform the TEE while the catheterization operator performs the closure procedure, as well as anesthesia support personnel if general anesthesia is used.

ICE provides imaging of the interatrial septum and surrounding structures that is comparable with TEE but does not require additional sedation or general anesthesia to perform. Currently available intracardiac echocardiographic systems provide a single-use 8Fr to 10Fr mechanical or phased-array intracardiac ultrasound–equipped catheter and require additional 8Fr to 11Fr venous access. The development of newer, smaller caliber catheters has allowed the use of ICE in smaller pediatric patients. In addition to obviating the need for general anesthesia in adults, ICE offers the potential to reduce the need for additional echocardiographic support, because the operator performing the percutaneous closure can also manipulate the catheter. At some centers, however, additional echocardiography expertise is used to assist in ICE during these procedures. This is particularly helpful in patients with large defects, for whom the risk for misplacement or embolization is greater. In these patients, continuous evaluation with echocardiography during device placement can prevent complications of the procedure.

Additional advantages of ICE in the guidance of PTC compared with TEE include shorter procedure and fluoroscopy times, improved imaging, and the addition of supplementary incremental diagnostic information, and as such, it is emerging as the standard imaging modality for evaluation of the interatrial septum and for guiding PTC.[15,16,75] ICE can be used as the primary imaging modality, without supplemental TTE or TEE. Recently, ICE has been shown to offer comparable cost with TEE-guided PTC when general anesthesia is used for those undergoing TEE-guided closure.[15,16,19,75, 76, 78]

General Procedural Considerations

A number of different devices are currently in use for PTC, and the method of implantation is variable and unique to each device. The mechanism of closure of all devices ultimately involves stenting the defect, with subsequent thrombus formation and neoendothelialization along the interatrial septum.

Preprocedural assessment of the interatrial septum includes evaluation of the entire interatrial septum and surrounding structures. A PFO is defined as any anatomic communication through the foramen ovale, and a stretched PFO is defined when resting or intermittent left-to-right flow on color Doppler imaging is seen . Right-to-left shunting through a PFO is typically demonstrated by the injection of agitated saline microbubbles at rest and with provocative maneuvers such as the Valsalva maneuver. An atrial septal aneurysm is typically defined as 11 to 15 mm of total movement of a 15-mm base of atrial septal tissue.

Echocardiography offers the ability to define ASD type (ostium secundum, ostium primum, sinus venosus, or coronary sinus), maximum ASD diameter, and defect number if multiple defects are present. Presently, only ostium secundum ASDs are amenable to PTC, and an interatrial septum that contains multiple small fenestrations may not be suited to PTC with currently available devices. Defects up to 40 mm in diameter have been closed successfully via PTC, as have multiple ASDs and those associated with atrial septal aneurysms. Associated abnormalities of the pulmonary veins, inferior vena cava, superior vena cava, coronary sinus, and atrioventricular valves should be excluded. Consideration of the size of the

atrial septal rim of tissue surrounding the defect is important in evaluating patients for successful PTC, and a surrounding rim of 5 mm is generally considered adequate. The inferior and superior rims may be particularly important for successful PTC, although small series have reported success in patients with deficient rims.[77]In smaller patients, assessment of total septal length is an important additional consideration, because this may limit the size of the device that can be placed successfully.[79]

Echocardiographic Guidance of Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy[4]

Introduction and Indications[4]

Surgical myectomy for severely symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM) has been performed for >40 years but is performed at only a relatively small number of experienced centers with acceptable morbidity and mortality.[80,81] Atrial-ventricular sequential pacing is an alternative to surgical myectomy, but after initial enthusiasm, randomized controlled trials reported less favorable results, with incomplete gradient reduction and a lack of sustained symptomatic improvement.[82] A second alternative to surgery is the more recently developed alcohol septal ablation technique.[83] This technique involves the introduction of alcohol into a target septal perforator branch of the left anterior descending coronary artery for the purpose of producing a myocardial infarction within the proximal ventricular septum.

This procedure, which results in a localized septal infarction, was referred to as nonsurgical septal reduction therapy by Sigwart,[83] who first described the procedure in 1995. Since the introduction of this procedure by Sigwart, a number of other groups have applied and modified this technique with good results.[84-88] Perhaps the most important modification has been the use of myocardial contrast echocardiography to delineate the vascular distribution of the individual septal perforator branches of the left anterior descending artery. In fact, the use of contrast echocardiography is paramount to the success of this procedure.

TTE is the conventional approach for intraprocedural echocardiographic monitoring of transcoronary ablation of septal hypertrophy for HOCM. Some laboratories prefer TEE because it provides more precise imaging of the subaortic anatomy of the left ventricle than TTE.[103] ICE is a third imaging alternative for use during this procedure.

Methods for Guidance[4]

Because the septum is perfused through a number of septal perforators, with significant individual variation and overlap in distribution, exact delineation of the vascular territory of each perforator artery is important to determine the vessel or vessels that should receive the alcohol injection. To determine that the presumed target septal perforator was correctly selected, intraprocedural myocardial contrast echocardiography should be performed. After verification of the correct balloon position and the hemodynamic effect of balloon occlusion, 1 to 2 mL of diluted echocardiographic contrast agent followed by a 1-mL to 2-mL saline flush is injected through the inflated balloon catheter under continuous TTE or TEE. The echocardiographic contrast agent should be diluted with normal saline to optimize myocardial opacification and to minimize attenuation. Details of the dilution vary with the contrast agent used. Agitated radiographic contrast can be used instead of an ultrasound contrast agent.

The optimal target territory of the basal septum should include the color Doppler–estimated area of maximal flow acceleration and the area of systolic anterior motion–septal contact without contrast opacification of any other cardiac structures. After myocardial contrast echocardiography confirms that the presumed target septal perforator perfuses the desired region of the basal septum, alcohol can be administered.

If TTE is used, apical 4-chamber and 3-chamber (long-axis) views should be used. These views may be supplemented with parasternal long-axis and short-axis views. If TEE is used, the apical 4-chamber view (at 0°) and the longitudinal view (usually 120°-130°) should be used. These views may be supplemented by the transgastric short-axis view to help ensure that no erroneous perfusion of the papillary muscles occurs. The deep transgastric view, which resembles an apical 4-chamber transthoracic view, is useful for measuring the intracavitary gradient with TEE.

Immediate Assessment of Results[4]

Intraprocedural echocardiography is also useful for evaluating the results of the procedure in the catheterization laboratory.[89-90]The region of the basal

septum, which is infarcted by the infused alcohol, is typically intensely echo dense. In addition, this region of the septum should have reduced thickening and contractility.[89]There should also be resolution or improvement of the degree of systolic anterior motion of the anterior mitral leaflet and usually reduction in the degree of MR. In addition, there should be elimination or reduction of the intracavitary gradient. This is readily measured by TTE and can often be measured by TEE with a deep transgastric view or midesophageal long-axis view.

Outcome Data

Several studies have suggested a favorable impact of echocardiographic monitoring during this procedure.[91] Echocardiographic monitoring of percutaneous transluminal septal myocardial ablation has resulted in the reduction of the amount of injected alcohol and the number of occluded septal branches. Online echocardiography may also reduce the need for repeat interventions with occlusions of several septal branches, thus avoiding unnecessary enlargement of the septal scar with all of the associated potential negative consequences for left ventricular systolic and diastolic function.

Another important advantage of myocardial contrast echocardiography during the procedure is that opacification of myocardium distant from the intended target septal area can prevent erroneous instillation of alcohol into unwanted territory, such as the papillary muscle, left ventricular free wall, or right ventricle .

A recent American College of Cardiology and European Society of Cardiology consensus document on HOCM stated that “myocardial contrast echocardiography guidance is important in selecting the appropriate septal perforator branch.”[92, 93] Nevertheless, a randomized multicenter study with respect to this issue does not exist.

Intracardiac Echocardiography guided cardiac interventions[5]

Use of intracardiac echocardiography in LAA closure

The introduction of percutaneous left atrial appendage (LAA) closure into clinical practice has

stirred considerable interest to reduce the risk of thromboembolism in patients with atrial fibrillation, with several clinical trials demonstrating high procedural success rates and noninferiority to warfarin for preventing embolic stroke [94]. The procedure is fairly intricate with echocardiographic guidance being an essential tool at all stages of this procedure. Pre-procedural echocardiography is required to screensuitable candidates and to define LAA morphology

and dimension. Periprocedural echocardiography has amajor role in guiding and deployment of the device as well as for screening for complications and assessment of procedural success. Post-procedural echocardiography is important in the surveillance and monitoring of long-term outcome, including complications. TEE is widely considered the gold standard tool in visualizing

the LAA and is typically used to guide implantation of the LAA device. To obviate the need for endotracheal and esophageal intubation, there has been increased interest in performing the procedure under ICE guidance only. Over the past decade, there have been several reports discussing the utilization of ICE in guiding LAA closure; however, to date, comparative studies between the 2 imaging modalities in guiding LAA closure are lacking [95-96]. Berti et al. [97] report the short-term and mid-term results from 121 patients with mean age of 77 years, who

underwent ICE-guided percutaneous LAA occlusion using Amplatzer Cardiac Plug I and II devices (St. Jude Medical, St. Paul, Minnesota). All patients had nonrheumatic atrial fibrillation with high stroke risk and absolute contraindication for oral anticoagulation. The ICE catheter was positioned either in the right atrium or coronary sinus. From those positions, the LAA

dimension was defined and followed by implantation of the appropriate device size. The LAA dimensionobtained by ICE correlated well with those obtained by angiography and, to a lesser degree, with preprocedural TEE. In the majority of cases, the initial device size selected based on ICE measurements wasimplanted successfully. Excellent technical (96.7%)and procedural outcomes (93.4%) were achieved with 4 patients having major adverse events. These data

support the pre-existing literature reporting the feasibility of ICE imaging in guiding LAA device closure as an acceptable alternative to TEE [98].

Use of intracardiac echocardiography in cardiac electrophysiology[4]

Anatomy-Dependent Arrhythmias

Catheter-based ICE has been applied extensively in cardiac electrophysiology laboratories to guide ablative procedures. To a large degree, this early adoption has occurred because of the critical dependence of specific cardiac arrhythmias on underlying anatomy. For example, accessory atrioventricular pathways bridge from atrial to ventricular tissue across the mitral or tricuspid annulus, requiring selective energy delivery at a specific anatomic location to successfully eliminate related supraventricular tachycardias. In addition, clarification of the pathophysiology of typical atrial flutter demonstrated that the cavotricuspid isthmus was a critically important component of the underlying reentrant circuit.[99,100] Because of this, the nomenclature of this arrhythmia was changed to "isthmus-dependent, counterclockwise atrial flutter." It follows that the ability to visualize specific anatomic structures should be of substantial importance in the nonpharmacologic treatment of these arrhythmias.

Phased-Array Imaging

The application of phased-array technology with a transesophageal probe was shown in early studies to be useful for imaging during VT ablation[101] and the treatment of accessory pathway–mediated tachycardias. [102,103] The miniaturization of this technology and application via intracardiac catheters allowed deeper penetration and standard 2D visualization and Doppler imaging of both right-sided and left-sided structures from within the right heart. Long-axis imaging with phased-array technology has been particularly suited for the electrophysiology laboratory environment. Within the context provided by forward imaging, intracardiac ultrasound frequently has been used to guide the insertion of catheters into specific cardiac chambers, across the cardiac valves into the ventricles, and to guide transseptal catheterization into left-heart structures, from a single imaging viewpoint or with minimal catheter rotation. Intracardiac ultrasound has been preferable to transesophageal imaging because it does not require prolonged esophageal intubation, accompanying patient discomfort, or the risk for aspiration. It is also routinely performed by a single interventionist, without the need for other personnel for further image acquisition and interpretation.

Ultrasound-Guided Anatomic Ablation

Intracardiac ultrasound has been applied to guide the positioning of ablation catheters near specific cardiac structures for ablation of the related arrhythmia. The value of such intracardiac echocardiographic imaging extends to establishing a clear-cut relationship between the catheter tip and underlying tissue, a critically important determinant of ablation success. In many cases, the lesion produced in the delivery of ablation energy can be visualized in tissue adjacent to the catheter tip. This observation is of theoretical importance, because the identification of each individual lesion could facilitate the juxtaposition of subsequent energy deliveries, as required in linear ablation. This utility has also been documented in linear ablation studies from several centers.[20,104-106] However, the visualization of an evolving lesion is a function of the imaging frequency, the distance of the ablation site from the transducer, the catheter tip—tissue contact, the delivered energy, and the thickness of the underlying tissue. Therefore, the lesions formed by the ablation of ventricular myocardium are more readily seen than with atrial ablation.[107-109] Furthermore, continued energy delivery in the ablation of atrial tissue to the point of lesion visualization is not necessary for a successful outcome and may be excessive. In short, lesion visualization with B-mode imaging is insufficiently sensitive for establishing an end point for ablation. Other means of enhancing lesion detection are currently being studied.[110]

Avariety of studies have tested the utility of intracardiac ultrasound in the setting of atrial tachycardias,[111] atrioventricular nodal reentrant tachycardia,[112] sinus tachycardia,[113] ventricular arrhythmias,[114] atrial flutter,[99,108,115,116] and AF.[12,20,22,117] Ablation of the cavotricuspid isthmus has been found to be 95% to 98% successful in eliminating atrial flutter simply through the identification of the anatomic site of origin of that arrhythmia.[99,100] Recent studies[118,119] have also shown the utility of imaging the left ventricular scar that results from myocardial infarction in ablation of postinfarct VT. Typically, stable VT arises within the border zone of an infarct. In such cases, intracardiac ultrasound can be used to guide ablation and create lesion bridges from the center of the scar, across the infarct border zone, on to a neighboring electrically inert cardiac structure such as the mitral annulus. Such lesions interrupt the VT circuit that passes

through the spared tissue immediately around the infarct, such as the submitral valve isthmus in the setting of inferior wall infarction.[120] Linear ablation along the border of an infarction, such as is required for ablation of fast, unstable VT, has also been facilitated by direct imaging.[118] Such left ventricular imaging is best conducted from below the tricuspid valve from a venue near the right ventricular outflow tract. From this position, both long-axis and short-axis images of the left ventricle can be created.

Ablation of AF

ICE has been used most consistently for the guidance of ablation of AF. This approach establishes the number and position of pulmonary veins and determines whether a left pulmonary vein antrum, formed by the confluence of the left superior and inferior pulmonary veins, is present. ICE also clarifies the branching patterns of the right pulmonary vein, guides the positioning of interventional catheters, verifies catheter tip–tissue contact, assesses underlying pulmonary vein physiology, helps in the positioning of balloon-type catheters for ablative interventions, and monitors for excessive tissue heating as manifested by the occurrence of microbubbles. Furthermore, ultrasound establishment of the venoatrial junction has recently been shown in preliminary studies to be more accurate than is possible with contrast venography.[121,122] Given its position in relationship to the left pulmonary veins, the location of the vein of Marshall, relevant in AF ablation, can also be identified from imaging of the "Q-tip" ridge, seen between the LAA and those pulmonary veins.[123]

Not only does the ultrasound beam allow identification of the underlying pulmonary vein and other relevant structures, it also enables positioning of guidance catheters, such as the circular Lasso catheter, to a position immediately at the orifice of the pulmonary vein. This is particularly critical because these catheters have a tendency to drift into the vein, providing a false sense of the true orifice of the vessel.Ablation too far into a vein increases the risk for pulmonary vein stenosis and decreases the efficacy of AF ablation.[124] Several studies[17,117,125,126] have shown the utility of intracardiac ultrasound to guide ablation at or outside the pulmonary vein orifice, which results in increased efficacy for AF ablation.

Monitoring for Ablation-Related Complications

Microbubble formation has also been widely observed with intracardiac ultrasound imaging.[20,127,128] This phenomenon may be even more accurate than catheter-tip temperature monitoring for the assessment of heat generation during the ablation of cardiac tissue.[128,129] Nevertheless, although this finding has been proposed as an end point to guide ablation, recent studies have demonstrated that microbubble appearance frequently reflects excess tissue heating to substantially greater temperatures than reflected by catheter-tip temperature monitoring.[125,127] This inadvertent tissue overheating, in turn, may lead to clot, char, or crater formation; intracardiac thrombus; or even pulmonary vein stenosis. Therefore, ultrasound visualization of microbubbles is most useful for prompting discontinuation of energy delivery when microbubbles are seen.

Along this same line, intracardiac ultrasound is useful in monitoring for potential complications of ablative intervention. In addition to the observation of the untoward results of tissue overheating, several studies have recently demonstrated the utility of ultrasound for detecting thrombus formation on the interventional catheter, which could lead to either a stroke or a peripheral thromboembolic event.[130,131] Ongoing surveillance of the pericardium during an interventional case is useful for the early detection of an effusion , before its physiological relevance is manifested by tamponade physiology. Imaging from an intracardiac venue also facilitates the catheter-based treatment of the effusion.

Doppler imaging likewise has contributed in the surveillance process. Pulsed-wave Doppler imaging, available with phased-array imaging over the course of an ablation, reveals an increase in flow velocity with pulmonary vein narrowing. An increment to a level in excess of 1.6 m/s has been found to be predictive of subsequent stenosis. In contrast, veins with lower flow velocities, $\leq$1.0 m/s, are unlikely to progress to any significant degree.[132]It is noteworthy, however, that these intracardiac Doppler flows are highly dependent on the presence of AF or catecholamines.

Percutaneous mitral valve repair[6]

Several percutaneous techniques have been developed totreat mitral regurgitation in patients who are at highsurgical risk. These techniques can be

classified into four general categories, and most of them are under developmentand/or in early stages of clinical trials4:(i) Indirect annuloplasty-coronary sinus techniques(ii) Direct annuloplasty(iii) Leaflet repair(iv) Ventricular remodeling. To date, the most commonly used technique is leafletrepair based on mitral clipping. The Percutaneous MitralClip system is currently the only mitral valve procedure

approved by the FDA, and it mimics the Alfieri surgicaltechnique, creating edge to edge repair. It delivers a twoarmed,V-shaped clip that grasps the tips of the middleportions of the anterior and posterior mitral leaflets, createsa double orifice mitral valve and restores coaptation toreduce the degree of MR.4Everest I and II trials and a continued access Realismregistry have published the clinical results of thisprocedure.[133-134]Echocardiography is the key imaging modality to firstselect patients who are amenable for this treatment, thenguide the procedure and finally evaluate post proceduralmitral regurgitation.

a. Pre-procedural Transcatheter edge to edge repair(TEtoE) imaging

A basic factor for a successful outcome is appropriatecase selection, which heavily relies on echocardiography asthe MV leaflets are not visible by fluoroscopy. The echostudy has to determine the mitral regurgitation mechanism,severity, and suitability for clipping.This method is applicable in two categories ofpatients [2,133-135]:

1. Those with degenerative MR (prolapse or flail of the A2and/or P2 scallops) Carpentier type II. The flail gap mustbe <10 mm and flail width <15 mm, and there must beno calcification of the grasping area.
2. Those with functional MR, either due to dilated cardiomyopathyor to ischemic LV remodeling, provided thatthe regurgitant jet arises from the A2-P2 portion. Thecoaptation length must be at least 2 mm and coaptationdepth <11 mm.Another essential role of pre-procedural echo imaging isto quantitate the severity of mitral regurgitation using parameters based on current guidelines.Carpentier Classification is used to assess the mitralvalve anatomy to optimize communication regarding the MV morphology among echocardiologists and interventional cardiologists.

Some worthwhile views that may help identify whichleaflet is moving abnormally include the Zero-degree viewsin which the A1 and P1 segments can be seen in the superiorposition, A2 and P2 segments in a more central position,and A3 and P3 segments in an inferior position of theprobe. The Inter commissural (60-70) views make the P1,A2, and P3 scallops visible, whereas an anterior (clockwise)rotation of the probe exposes the A1, A2, and A3 segmentsof the anterior leaflet and a posterior (counter clockwise)rotation presents the P1, P2, and P3 segments of the posteriorleaflet. A long-axis or LVOT view (90) shows the A2and P2 segment. In the transgastric short-axis views, allsegments of the anterior and posterior leaflets can be

identified.8,15Moreover, with 3D TEE, putting the aortic valve at 12o'clock, the left atrial appendage can be seen at 9o'clock, anterior commissure can be seen at 9 o'clock with

the adjacent A1 & P1 mitral segments and posteriorcommissure can be seen at 3 o'clock (A3 & P3 segments).With 3D imaging, all mitral segments can be illustratedmore precisely and accurately than 2D TEE, and 3D TEEhas the unique advantage of identifying prolapse of the mitral commissure, which is a rare occurrence.

Procedural monitoring

The procedure is complex and has 5 steps that requirereal-time echocardiographic guidance complemented with fluoroscopy.Standardized 2D planes can be used as the primary imaging

method for guidance during the Mitral Clip procedure.

Step 1: Transseptal puncture

The target area for crossing is thefossa ovalis with a posterior mid-approach and in a posteriorand superior direction, facilitating the clip deliverysystem to reach the middle of the mitral orifice parallel tothe antegrade mitral flow. The site of optimal puncturevaries among degenerative and functional regurgitation andcan be assessed with the 4 Ch (0) imaging plane. Indegenerative MR, the puncture site must be 4-5 cm abovethe mitral annulus, whereas functional MR requires apuncture site 3.5 cm above the annular plane due toextensive tethering.[135]

Step 2: Advancement of the Clip DeliverySystem (CDS) towards the mitral valve.

Once the correct transseptal crossing has been achieved,the delivery catheter is turned down and

monitoring withTEE begins towards the mid portion of the mitral leaflets(A2-P2), avoiding contact with the left atrial appendageand left atrial wall.The inter-commissural (55-75º) view and LV outflow(100-160º) view are particularly helpful at this step byshowing the medial-lateral alignment and posterior anterior alignment, respectively. A single 3D en faceview (3D zoom) shows whether the approaching clip isdirected optimally.[135]

Step 3: Positioning the mitral clip above themitral leaflets

The clips' arms need to be placed perpendicular to thecommissure line, above the largest regurgitant jet, asindicated by the PISA effect. Using the RT3D surgeon's viewis valuable in this step, and where 3D is not available, thetransgastric 2D short axis view is recommended as analternative.[2,135]

Step 4: Advancement of the Clip DeliverySystem (CDS) into the left ventricle

The CDS system crosses the mitral leaflets, passes into the left ventricle under fluoroscopy and TEE guidance, and can be viewed from the LVOT position (100-160). Advancement of the CDS can be monitored best in X-plane imaging based simultaneously on LVOT using an inter-commissural view. A rapid reassessment of the perpendicular clip orientation and position using the transgastric 2D short axis or 3D en face views is mandatory to be sure that the CDS system has not rotated as it is advanced in the LV.[2,135]

Step 5: Grasping of the leaflets and evaluating adequate leaflet insertion

Once the mitral clip is at an optimal position, the open device is pulled up to grasp the leaflets. Assessment of proper leaflet insertion into the clip is usually performed using 2D LVOT and inter-commissural views. 3D imaging has limited value at this step of the procedure. If either leaflet has not been adequately grasped, a replacement is necessary.[2,135]

Step 6: Clip release and assessment of the result

Once both leaflets are successfully clipped, the MitraClip can be closed and an evaluation is made of the residual MR. If the result is not sufficient, the clip is brought back into the LA and the process is repeated. Sometimes, a second Clip should be placed.

After implantation of the clip, it is essential to evaluate the grade of mitral regurgitation and mitral stenosis. Due to the newly created double mitral orifice, the estimation of residual regurgitation is not easy because there are many limitations to conventional parameters.

Currently, there are no recommendations for the best wayto evaluate the MR in the presence of a double orifice. Generally, utilization of multiple parameters is valuable in assessing the MR after mitral clip implantation. It is well-known that this procedure is very demanding on both the echocardiographer and interventionalist. Although 2D TEE is used primarily to guide the mitral clip procedure, 3D TEE can supplement 2D TEE and provide unique, additional, anatomic information. It is recommended for guidance of interventional mitral valve procedures.

10,11 With real-time 3D TEE, full volume data sets can be acquired, which allow en-face views of the MV, either from the atrial or left ventricle perspectives. These unique 3D views facilitate the precise assessment of the MV structure and pathology, which is crucial for the selection of patients. During the procedure, 3D TEE enables visualization of the mitral valve, left atrium, interatrial septum, delivery catheters, wires, and devices in a single view that is easily understandable in 3D space.[2,135]Notably, 2D TEE plays an essential role in transseptal puncture, optimal clip alignment and evaluation of mitral regurgitation pre- and post-clip implantation. Unfortunately, the lack of real-time 3D color and low frame rate limit the use of 3D TEE in the main procedural steps, such as the positioning of the delivery system to the origin of the regurgitant jet and grasping the leaflet.[2,135,136]As all imaging modalities have their own limitations, it has been demonstrated that the combined use of 2D TEE, 3D TEE and fluoroscopy facilitates the procedure and increases the likelihood of a successful result.

Transcatheter closure of periprosthetic regurgitation (TCPPR)[6]

Paravalvular regurgitation is a recognized complication that affects from 5% to 17% of all surgically implanted prosthetic heart valves. Most patients are asymptomatic, but sometimes

they present with heart failure, hemolytic anemia or both. In those patients who have a significant re-operative risk, percutaneous techniques may allow successful treatment of paravalvular

regurgitation.[2,137-143]The role of echocardiography is essential in this procedure and can be summarized as below:

1. Making a diagnosis of the periprosthetic defect and assessing the severity of paravalvular regurgitation. Evaluation of prosthetic valve regurgitation is technically more demanding than that of native valves, especially for aortic prosthetic PVR.
2. Localization of defects, describing the whole number and shape as well as providing accurate sizing of the hole. Realetime 3D TEE using 3D color Doppler is the preferred imaging modality for MV leaks, but it is not very helpful in aortic leaks.
3. Assessment of other structures (chambers, valves and pericardial space) and an analyses of the relationships between the defects, aortic valve, left atrial appendage and interatrial septum.
4. Ruling out the presence of thrombus, vegetation and significant dehiscence involving more than onefourth of the valve ring because these are considered to be contraindications for percutaneous repair.
5. Guiding access either antegrade, venous transseptal, or retrograde approach via aortic valve or transapical valve.
6. Guiding the wire across the defect and catheter placement.
7. Assessing the decrease in paravalvular regurgitation during balloon inflation.
8. Evaluating proper positioning and stability of the closure device.
9. Assessing possible complications (pericardial effusion, prosthetic leaflet entrapment).
10. Re-evaluating of the severity of residual paravalvular regurgitation and estimating whether a second occlusiondevice is needed.

Transcatheter aortic valve implantation(TAVI)[6]

Currently, transcatheter aortic valve implantation is considered to be an alternative therapy to conventional surgery for severe, symptomatic aortic valve stenosis (AS) in patients who are inoperable or at high surgical risk. At the moment, two devices with different characteristics, the Edwards SAPIEN and CoreValve, are approved prostheses for TAVI.[145]A multidisciplinary approach including interventional cardiology, cardiac surgery, vascular surgery, cardiac anesthesia and obviously cardiac imaging is needed for a successful outcome. Echocardiography, angiography, fluoroscopy, multislice computed tomography (CT) and, rarely, CMR are the imaging modalities for TAVI procedures.[146,147]Many studies, new guidelines for 3D echocardiography and TEE, and recent recommendations for interventional echocardiography have been published supporting the critical and expanding role of echocardiography either preimplantation, intra-procedural or post-TAVI implantation assessment.[2,144]

A. A comprehensive echo study prior to a TAVI procedure is important for patient selection and should include assessment of 4:

1. The severity of aortic stenosis:

Transthoracic echocardiography (TTE) is the primary imaging modality to estimate the severity of AS and provide a differential diagnosis between true severe AS and pseudo-severe AS.

2. The aortic annulus size:

The decision of the aortic prosthetic size is crucial, and it is related to the aortic valve annulus dimensions. Due to the elliptical shape of the annulus, accurate sizing is not always easy. It is well-known that both TTE and TEE undersize the annulus diameter, assuming annular circularity. The 3D echo overcomes the limitations of the annulus shape and provides a more accurate assessment of the LV outflow tract and annular diameter . Currently, CT has been recommended as the gold standard for aortic annulus evaluation.[2,144]

3. The aortic valve and root morphology:

Echocardiography has to describe the number of cusps, leaflet thickening and fusions, mobility and calcification, and geometry and symmetry of the aortic valve opening, sinus of Valsalva and sinotubular junction. A bicuspid aortic valve is a relative contraindication for TAVI due to the risk of severe paravalvular regurgitation, aortic dissection and embolization. Severe calcification is related to post-TAVI paravalvular regurgitation, coronary artery ostium compression and occlusion.[145]

4. The coronary ostium height:

Measuring the distance between the annular plane and coronary ostia is of paramount importance, and a minimum distance of 10-11 cm is required to minimize the risk of coronary occlusion. Usually, this measurement is performed by CT, but 3D echocardiography can also provide accurate sizing.[147]

5. The thoracic aorta:

A significant aneurismal dilatation is a contraindication for CoreValve, and severe aortic arch calcification leads to a transapical approach.

6. The additional structures:

Mitral regurgitation is a common finding in patients with AS, and the degree of MR usually decreases after the TAVI procedure. Aorto-mitral continuity was recently described with 3D TEE, and the anatomy and function of the mitral valve should be evaluatedeither pre- or post-TAVI because both valves areinterdependent. Additionally, the presence of the LVthrombus and significant LVOT obstruction due to basal septal hypertrophy should be excluded as they

are contraindications prior to TAVI. The existence of a patch in the LV and the presence of severe pericardial calcification discourage a transapical approach.[144,147]

A. Echocardiography during the TAVI procedure.

It is a well-established fact that fluoroscopy is the gold standard for procedure guidance, and the role of echocardiography is limited compared with its major role in the selection of patients for TAVI. The disadvantages of using peri-procedural TEE include the requirement of general anesthesia as well as the partially concealed and shackled fluoroscopic view caused by the TEE probe. Sometimes, to have a clearer view, the probe must be removed during prosthesis implantation and positioned post-deployment. Occasionally, some interventionalists prefer purely fluoroscopic guidance during TAVI.[144,146]However, echocardiography is the primary imaging modality for a wire's guidance and the assessment of complications. In addition, TEE may be helpful in cases in which the stenotic valve does not have much calcification and the fluoroscopic view alone is limited.

The most important procedural steps are:

1. Crossing the aortic valve.

Traditionally, passing a guidewire through the aortic valve is manipulated by fluoroscopy. Nevertheless, this step may be difficult in patients with aortic root distortion and dilatation. In such cases, the use of real-time 3D TEE can safely guide the wires through the aortic valve orifice . Additionally, 3D TEE, due to its better spatial resolution, provides sufficient imaging of the pacing wire and left ventricular stiff wire.[2,146-148]

2. Balloon dilatation and positioning

TEE, as a supplemental imaging method to fluoroscopy, confirms the optimal site for balloon inflation and provides information about the efficacy of inflation in aortic cusps as they are moved back towardthe coronary ostia. Accidentally, the balloon may not remain stable during inflation and may migrate, especially in cases with severe subaortic septal hypertrophy and a narrow sinotubular junction.[2,146-148]

3. During deployment of the prosthesis

Therefore, TEE in combination with fluoroscopy secures the ideal position of the valve. The appropriate localization for the Edwards SAPIEN valve is 2-4 mm below the aortic annulus, and the appropriate location for the CoreValve is 5-10 mm below the plane of the annulus. Immediately after deployment, it is important to ensure via TEE that the aortic cusps of new prosthesis function well, the valve stent has a circular configuration (3D TEE), there is no contact with adjacent structures (such as the anterior mitral leaflet) and severe paravalvular regurgitation is absent. Severe paravalvular regurgitation is related to an inappropriate position or undersized prosthesis and inadequate balloon inflation. In this case, the balloon may be re-inflated or a second prosthesis may be needed. It is well-known that a small degree of valvular regurgitation due to guidewires and mild paravalvular regurgitation is a common finding. [2,146-148]

The criteria for a successful implantation are assumed to be an optimal anatomical position of the prosthesis, aortic valve area >1.2 cm2, mean gradient <20 mmHg, Vmax <3 m/sec and absence of moderate or severe regurgitation.[147]

A. Echocardiography after the TAVI procedure.

Following the TAVI procedure, repeated echocardiograms must be performed. After the first

24 h, an echo study is recommended at 1, 6, and 12 months and then on an annual basis. Assessment of aortic prosthesis function,left ventricular function and evaluation of aortic regurgitation

is of paramount importance. Moreover, complications related to the TAVI procedure include migration or misplacement of the prosthesis, mitral valve damage, coronary ostium occlusion, cardiac tamponade secondary to left and/or right ventricular rupture, and dissection or tear of the aortic root.[149]

Tricuspid valve repair (Mitralign system)[6]

It is well known that uncorrected severe functional tricuspid regurgitation has serious long-term morbidity and mortality and is highly related to poor prognosis. Transcatheter tricuspid valve repair could become an attractive alternative treatment for high-surgical risk patients who do not respond to optimal medical therapy. Recently, the first-in-human transcatheter repair for functional tricuspid regurgitation was reported with the use of Mitralign's Percutaneous Tricuspid Valve Annuloplasty System (PTVAS).[150]This percutaneous tricuspid valve repair mimics a surgical repair procedure (Kay bicuspidization) based on tricuspid bicuspidization by plicating the annulus along the posterior leaflet using sutures.

The Mitralign system (Mitralign, Inc., Tewksbury, Massachusetts) plicates the tricuspid annulus by placing pledget sutures, effectively converting the insufficient trileaflet valve into a functioning bi-leaflet one. Echocardiography is the key imaging modality to first select patients who are candidates for this treatment, to then guide the procedure and to finally evaluate the post procedural tricuspid regurgitation and related complications.

TEE (2D and 3D) was performed at baseline and during and after the procedure. Operators advanced a delivery catheter through a trans-jugular vein across the tricuspid valve and into the right ventricle under echocardiographic guidance. Using the Mitralign system, they positioned 2 sutured pledgets, or anchoring pads, in the annulus around the posterior leaflet (either postero-anterior commisure or septo-posterior commisure). After that, a lock device was used to bring the pledgets together, thereby tightening the annulus. The result was successful "bicuspidization" of the tricuspid valve in a similar way achieved by a surgical technique.[150]

Accurate assessment of the guide catheter is of paramount importance for safe placement of the sutured pledgets. Both 2D and 3D TEE combined with fluoroscopy contribute to a successful outcome without complications, such as coronary or chamber perforation. Currently, the Mitralign System is being investigated and is not available for sale or distribution.

Future directions[6]

Despite the great evolution of echocardiography in recent years, especially with the introduction of a 3D echo in catheter laboratories, an ideal echocardiographic modality has not been established. 3D echo is not widely accepted among most echocardiographers and interventionalists due to existing techniquerelated limitations, such as a low frame rate, dropout artifacts, reverberations and shadowing caused from catheters and a lack of standardized protocols suggesting ways to acquire useful perspectives easily and quickly during the procedure. Furthermore, some interventionalists seem to be reluctant to introduce not only 3D TEE but even 2D TEE in the laboratory. They feel unfamiliar with the new imaging modalities because they received different training, rendering spatial orientation difficult. X-ray image and Echo image orientation are completely uncorrelated. What is perceived as right on the fluoroscopic view might be left on the Echo image, whereas what is perceived as down on the Echo image might be up on the fluoroscopy view. Each time the interventional cardiologist switches his view from fluoroscopy to echocardiography, he needs to mentally reorient

himself. The solution may be available by the recently introduced integrated 3D Echo-X-Ray navigation system (EchoNavigator,Philips Healthcare, Eindhoven, the Netherlands)whereby 3D TEE imaging is registered automatically in real- time with live 2-dimensional fluoroscopy images acquired from an X-ray imaging system.[148]

The EchoNavigator live image guidance tool (EchoNavigator), which received 510(k) clearance fromthe US Food and Drug Administration (FDA)at 3/13, provides an intelligently

integrated view of live X-ray and 3D ultrasound images. It automatically registers and aligns X-rayswith echo results and enables echocardiographers to identify anatomical targets and mark them as they appear on the X-ray image. The

EchoNavigator system currently has smart technology that automatically localizes and tracks the position of the TEE probe. Every time the interventionalist steps on the fluoro pedal, EchoNavigator will instantly and continuously detect the TEE probe in the image. The interventional cardiologist can view the 3D echo from any angle, without disturbing what is being seen by the operator of the Philips echo system. This process essentially means that with the EchoNavigator markers, the interventionist is aware at all times of the relation between the cardiac structures and catheter implants and thus can improve the control, appreciation and communication between invasive and non-invasive cardiologists, ultimately in an attempt to save valuable time and to enhance patient care.

It is likely that echo-navigation will be the standard method in the foreseeable future for the echo-guidance of interventions in the cath lab, although more experience to demonstrate its accuracy is required. Other future developments that will further extend the role of ICE in the cardiac laboratory may include a reduction in catheter size, improved catheter stability and handling, as well as enhanced image quality and development of real time 3D imaging.

Other potential advances include the integration of ICE into current electro-anatomical mapping systems and also coupling of ICE and ablative therapy into a single catheter. The recent development of a neonatal TEE probe that is small and flexible enough to allow transnasal insertion in adults may have a potential application in interventional cardiology. The transnasal approach, typically better tolerated by patients, may offer the distinct advantage of enabling some interventional procedures requiring TEE guidance to be performed without general anesthesia. However, acceptable image quality and good patient tolerance with this application are yet to be demonstrated in scientific evaluations.

Conclusion:

Rapid evolution in interventional cardiology demands detailed and accurate imaging of cardiac structures and the guidance of wires. The entrance of echocardiography in almost every stage of all procedures in catheterization laboratories is inevitable, suggesting an important step for echocardiographers. Despite recent progression in echocardiography, problems still arise, especially concerning the communication between the echocardiographer and interventional cardiologist. Moreover, the clear advantage of the X-ray demonstrating the catheters and implant devices must be merged with the clear advantage of echocardiography demonstrating the soft tissues. Finally, as technology progresses, it seems that the Echonavigator system and real-time fusion of live X-ray and live echo images will provide intuitive and successful guidance during structural heart disease interventions. More experimentation with this new system is required at the global scale before it becomes the standard method of care in percutaneous catheter-based procedures.

Echocardiography offers the potential for improved safety in performing transseptal catheterization, and although it is not invariably required in all procedures, its use is recommended. ICE offers the advantage of not requiring echocardiographic support when performing transseptal catheterization. Echocardiography-guided pericardiocentesis with extended catheter drainage can be performed safely and with efficacy at centers with staff members experienced in this technique. Using echocardiography to guide the procedureavoids the radiation associated with fluoroscopy and allows the procedure to be performed in the catheterization laboratory, at the bedside, or in the echocardiography laboratory. Increased safety and markedly lower cost compared with surgery ensure that echocardiography directed pericardiocentesis is a procedure of choice. Echocardiography, particularly TTE, is useful as an adjunctive imaging modality in patients undergoing intracardiac and intravascular biopsy procedures. Although TEE and ICE may offer improved imaging over TTE, the additional risk and cost must be outweighed by significant procedural benefits, and the modalities are recommended foruse only in highly selected patients. Echocardiography provides significant benefit in percutaneous balloon valvuloplasty for mitral stenosis and is recommended for the assessment of patient selection and to assess the adequacy of results. Online intraprocedural echocardiography offers significant advantages compared with fluoroscopic guidance, in monitoring procedural efficacy and monitoring for complications. TEE can also be used to guide the procedure. TTE is recommended for procedural guidance, monitoring for complications, and to assess the adequacy of

results, when preprocedural TEE has already been performed. ICE can be used for procedural guidance and provides imaging that is comparable with TEE.Echocardiography is recommended to guide PTC of PFO and ASDs. All modalities of echocardiography can be used, but ICE should be considered when suitable expertise is available. Numerous factors must be considered when choosing the ideal echocardiographic modality for procedure guidance, including the patient population, specific anatomy, and local expertise. Echocardiography is recommended in selecting the appropriate septal perforator during alcohol injection during septal ablation for HOCM. Both TTE and TEE can be used. They provide an assessment of immediate procedural results and allow monitoring for complications. ICE is recommended for radiofrequency ablation for AF. It is used to guide transseptal catheterization, as well multiple aspects of the procedure, to monitor for complications, and to assess pulmonary vein flow before and after ablation.

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REVIEW ARTICLE

Pharmaco-invasive Therapy as a Reperfusion Strategy – A Practical Alternative of Primary Percutaneous Coronary Intervention

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Abstract:

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy in patients with ST elevation myocardial infarction (STEMI), if it is performed by skilled operators in a timely fashion. However, this strategy has shown to be of limited access due to lack of adequate PCI capable hospital or delay in the first medical contact-to balloon time for logistic reasons in many parts of the world. This delay is more prominent in less advanced countries where emergency services and public awareness and education programs are not well established. Each minute's delay contributes to myocardial damage. It has been shown that the 1-year mortality increases by 7.5% for each 30-minute delay in treatment. Realizing these limitations of primary PCI pharmaco-invasive strategy was developed. In facts this strategy might be a better approach when the delay of primary PCI is anticipated. Pharmaco-invasive strategy has been endorsed by both the European Society of Cardiology and American College of Cardiology STEMI guidelines.

Key Words: STEMI, Primary PCI, Pharmaco-Invasive Strategy.

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Introduction:

Coronary artery disease (CAD) is the most common form of heart disease and single most important cause of premature death in most part of the world. IHD was the leading cause of all health loss globally, as well as in each world region. There were an estimated 7.29 million acute myocardial infarction and 110.55 million prevalent cases of IHD in 2015. There were an estimated 8.92 million death due to IHD in 2015, making IHD the leading cause of death in the world.[1] Cardiovascular disease burden has been increasing at an exponential pace in low and middle-income countries such as India, Bangladesh. At least three quarters of the world's deaths from CVDs occur in low- and middle-income countries.[2] So prevention of growth of coronary artery disease as well as early management is the major health issue around the world.

Among coronary artery disease acute ST elevation myocardial infarction (STEMI) is one of the severe form. It generally occurs due to sudden occlusion of a coronary artery by formation of thrombus at the site of fissured or ruptured atherosclerotic plaque.[3] The major aspect of treatment of STEMI is reperfusion of the infarct related artery. Reperfusion therapy aims at restoration of ante-grade flow in the occluded infarct related artery, which reduce infarct size and improves clinical outcome.[4] Early, effective and sustained reperfusion of the culprit artery is needed to salvage myocardium, maintain left ventricular function and reduce mortality.

Over the last two decades Primary Percutaneous Coronary Intervention (PPCI) has emerged as the preferred reperfusion strategy if it can be performed by a skilled operator in a timely fashion. Many STEMI patients however presented to hospitals without capability to perform PCI and not all PCI capable hospitals giving 24 hours PCI services. Even developed country like USA only 39% have

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catheterization facilities,[5] about one third hospitals have the capability to perform PPCI 24/7.[6] With this scenario even in developed countries many STEMI patients need to transfer to PCI center with too long transfer time specially who are residing in rural areas. But any significant delay may negate the benefit of primary PCI over fibrinolysis. Current guideline from the European Society of Cardiology and American College of Cardiology Foundation recommend Fibrinolysis if PCI cannot be performed within 120 minutes from the first medical contact.[7,8] Despite that recent data from the US National Cardiovascular Data Registry showed that only 51% of STEMI patients transferred to primary PCI achieved the recommended door to balloon time less than 120 min,[6] Data from Quebec,[9] where 65% of patients were transferred for primary PCI, found that 80% were not treated within the guideline recommended door to balloon time. In Denmark, which has an organized transfer system for STEMI, 65% of transferred STEMI patients experienced a system related delay of greater than 120 minutes, which was associated independently with increased mortality.[10] In the CREATE registry, which included majority of patients from cities in India with PPCI facilities available, median time from symptom onset to reach hospital was 300 minutes.[11]A study in Bangladesh[12] shows that pain to first medical contact (FMC) time is 4.6 ± 1.8 hours, FMC to balloon time is 1.9 ± 0.9 hours, and total Ischemic time is 6.8 ± 2.1 hours which is far away from the recommended time.

It is already proved that efficacy of primary PCI is highly time-dependent. In the Global Use of Strategies to Open Occluded arteries (GUSTO)-IIbsubstudy,[13] a strong inverse relationship between time to angioplasty and mortality was noted with 1.0% and 6.4% mortality rates when time to angioplasty was equal to or less than 60 minutes and equal to or greater than 90 minutes, respectively. Considering the availability of Fibrinolytic agents and to cover the myocardial damage due to delayed Primary PCI, Pharmaco-invasive Strategy was developed and it would be a better approach especially when the delay of primary PCI anticipated. Pharmaco-invasive strategy has been endorsed by both European Society and American Heart association STEMI guideline.[7,8] This article reviews pharmaco-invasive strategy as an option for STEMI patients who do not have timely access to primary PCI.

Pharmaco-invasive therapy:

The pharmaco-invasive approach involves initially administering fibrinolytic agents, and then systematically performing an angiography within 2 to 24 hours after the start of fibrinolytic therapy,[14] regardless of whether fibrinolysis results in successful reperfusion or not (Figure 1).

Do studies favours pharmaco-invasive therapy as a treatment option:

(Pharmaco-invasive Trails)

These are the following large radomized control trails comparing the early PCI after fibrinolysis to standard therapy in STEMI patients.

CARESS-in-AMI (2008):[16]

Inclusion Criteria: High-risk STEMI patients who were admitted to non-PCI hospitals in France, Italy, or Poland.

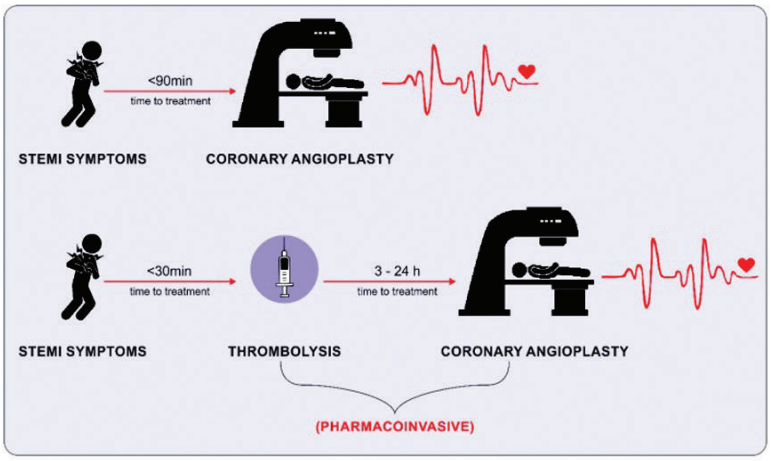


Fig.-1: *Pharmacoinvasive approach to STEMI care* [15]

Lytic agents: half-dose Reteplase,

Strategy: Randomized to immediate transfer for PCI or admission to the non-PCI hospital with transfer for rescue PCI if needed.

Primary end point: Composite of death, re-infarction, or refractory ischemia at 30 days

Result: The primary outcome occurred in 4.4% of the immediate PCI group compared with 10.7% in the standard care/rescue PCI group (hazard ratio, 0.4%; 95% CI, 0.21–0.76; P 5 .004).

TRANSFER-AMI (2009):[17](Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction)

Inclusion Criteria: Randomized high-risk STEMI patients presenting to non-PCI hospitals in Canada.

Lytic agents: Full-dose Tenectaplase

Strategy: Immediate transfer after tenectaplase for PCI versus tenectaplase and transfer for rescue PCI if the patient had persistent ST segment elevation, chest pain, or hemodynamic instability.

Primary end point: Combined death, re-infarction, recurrent ischemia, and new or worsening congestive heart failure or cardiogenic shock within 30 days.

Results: The primary endpoint, a composite of death, re-infarction, recurrent ischemia, and new or worsening congestive heart failure or cardiogenic shock within 30 days, was significantly decreased in patients receiving pharmaco-invasive PCI (11%) compared with patients receiving standard care/ rescue PCI (17%; P 5 .004).

NORDISTEMI trail (2010):[18] (NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction) trial.

Inclusion criteria: Acute STEMI patients living in rural areas with greater than 90-minute transfer times.

Lytic agents: Tenectaplase

Strategy: Patients with acute STEMI living in rural areas with greater than 90 minute transfer times were treated with standard dose tenectaplase, aspirin, enoxaparin, and clopidogrel and then randomized to transfer for PCI or to standard treatment at the non-PCI hospital with transfer only if indicated for rescue PCI.

Primary end point: A composite of death, re-infarction, stroke, or new ischemia at 12 months.

Results: Composite of death, re-infarction, stroke, or new ischemia at 12 months, did not show a significant difference. However, a composite of death, re-infarction, or stroke at 12 months was significantly reduced in the early invasive group compared with the conservative group (6% vs 16%; hazard ratio, 0.36; 95% CI, 0.16–0.81; P 5 .01). There were no difference in bleeding (P 5 0.68).

STREAM (2010) :[19](Strategic Reperfusion Early After Myocardial Infarction) trial.

Inclusion Criteria: STEMI patients who presented within 3 hours after symptom onset and who were unable to undergo primary PCI within 1 hour.

Lytic Agents: Tenecteplase

Strategy: Patient who were presented with STEMI with in 3 hours of onset of symptom selected randomly to undergo either primary PCI or receive tenectaplase, clopidogrel, and enoxaparin before transport to a PCI-capable hospital. Patients who received fibrinolysis had coronary angiography and PCI within 6 to 24 hours if there was resolution of ST elevation or rescue PCI if reperfusion failed to occur within 90 minutes.

Primary end point: A composite of death, shock, congestive heart failure or reinfarction up to 30 days.

Results: Combined death, shock, congestive heart failure or re-infarction up to 30 days, occurred in 12.4% in the fibrinolysis group compared with 14.3% in the primary PCI group (relative risk, 0.86; 95% CI, 0.68–1.09; P 5 .21) There were more intracranial hemorrhages in the fibrinolysis group than in the primary PCI group overall (1% vs 0.2%; P 5 .04).

A substudy of the STREAM trial examined 30 day clinical outcomes stratified according to PCI-related delay. They found that, as PCI-related delay increased, the outcomes (30-day death/congestive heart failure/shock/ MI) for the pharmaco-invasive strategy became superior to primary PCI.

A metaanalysis of early routine PCI after fibrinolysis compared with standard therapy in STEMI patients demonstrated a significant reduction in re-infarction and recurrent ischemia at 30 days with no significant increase in major bleeding events (Fig. 2).[20] The benefits of early PCI were maintained at 6 to 12 months with persistent reduction in re-infarction (odds ratio [OR], 0.64; 95% CI, 0.040–0.98; P 5 .01) and combined death/re-infarction (OR, 0.71; 95% CI, 0.52–0.97; P 5 .03).

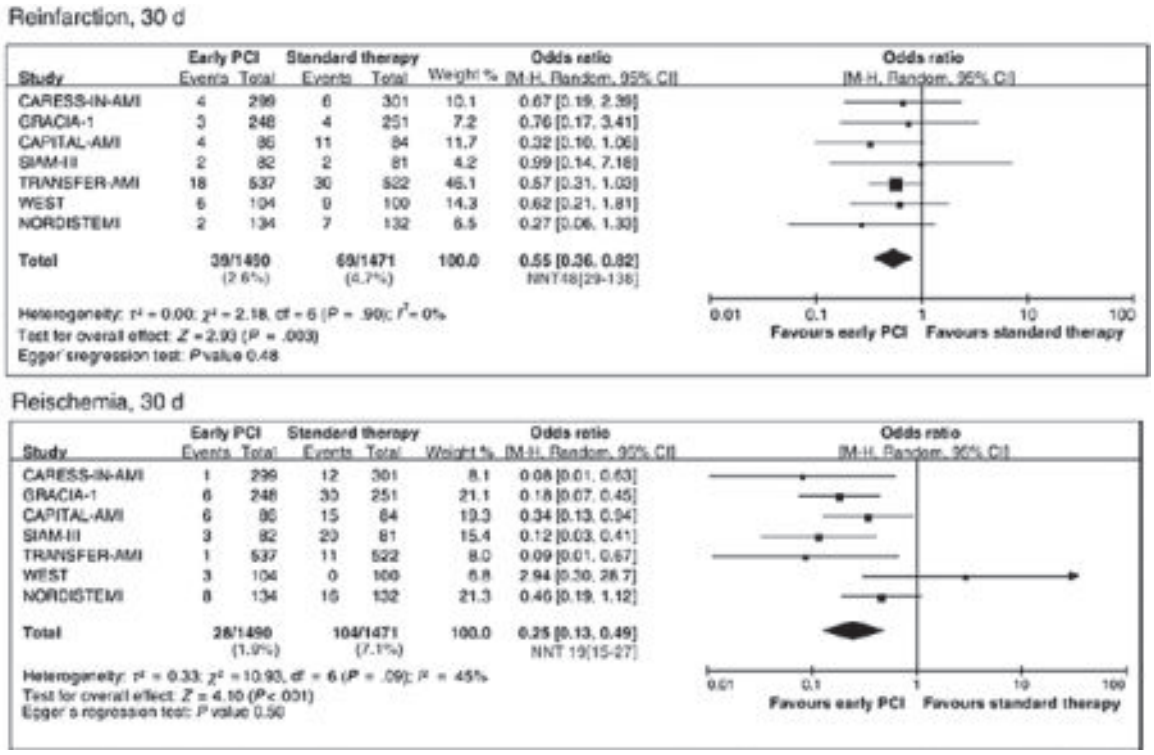


Fig.-2: *Results from a metaanalysis of early routine percutaneous coronary intervention (PCI) after fibrinolysis versus standard therapy in ST-segment elevation myocardial infarction (STEMI).*[20]

Another meta analysis published in The American Journal of Cardiology[21] whereall published randomized control trials (RCTs) or observational studies comparing PIT with PPCI in patients presenting with STEMI were included.

Meta-analysis suggests that no significant difference in all-cause mortality exists between PPCI and PIT in transfer patients and also did not find any significant difference in long-term mortality between the 2 groups (PPCI group and PIT group). Analysis also suggested that the risk of cardiogenic shock was significantly lower in the PIT group when compared with the PPCI group as the delay of reperfusion are a known risk factor of cardiogenic shock and early reperfusion is the key to prevent this complication. Meta-analysis of RCTs also finds significantly higher risk of developing intracranial hemorrhage; this was not surprising as intracranial bleeds are a known complication of fibrinolytic drugs.[21]

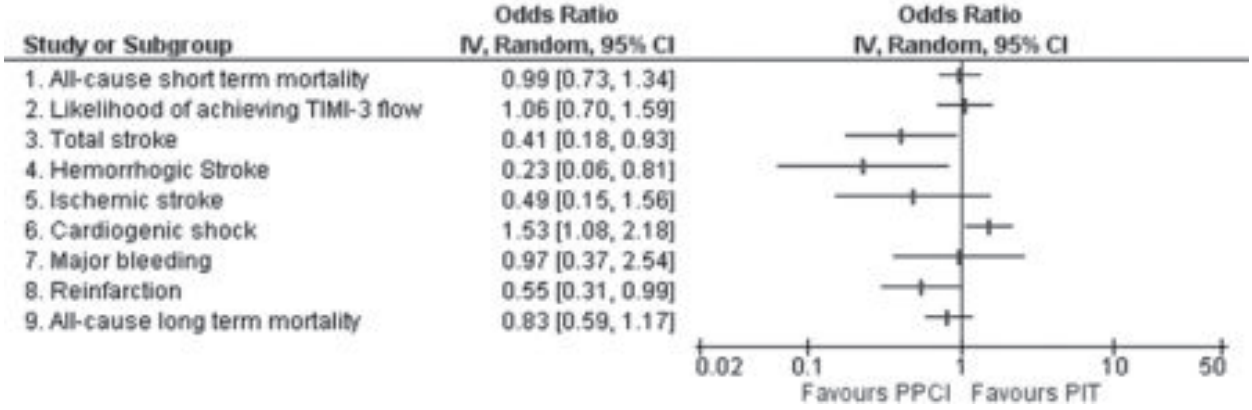


Fig.-3: *Summarized results of meta-analysis of randomized control trials. PIT = pharmaco- invasive therapy; PPCI = primary percutaneous coronary intervention.*[21]

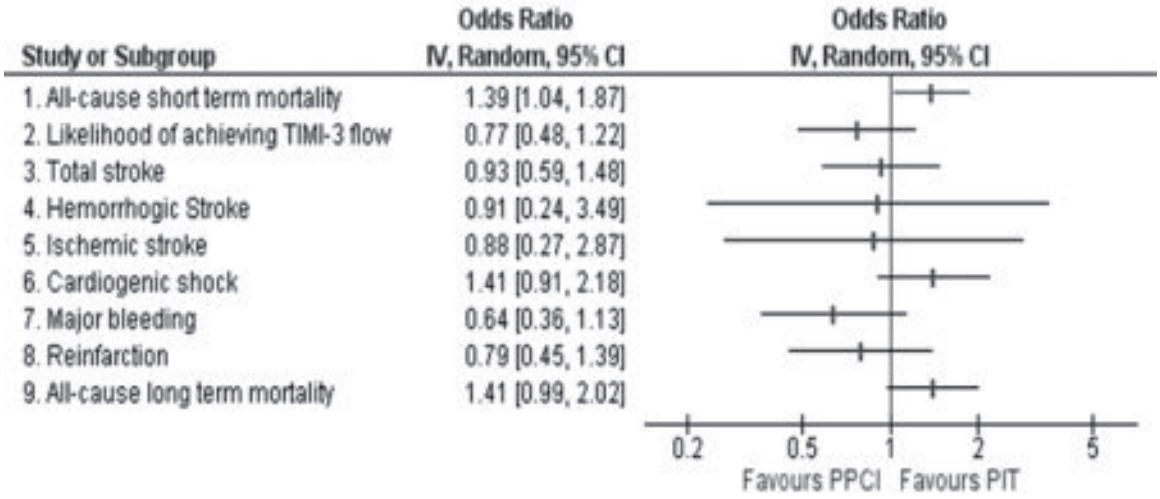


Fig.-4: *Summarized results of meta-analysis of observational studies. PIT= pharmaco- invasive therapy; PPCI=primary percutaneous coronary intervention.*[21]

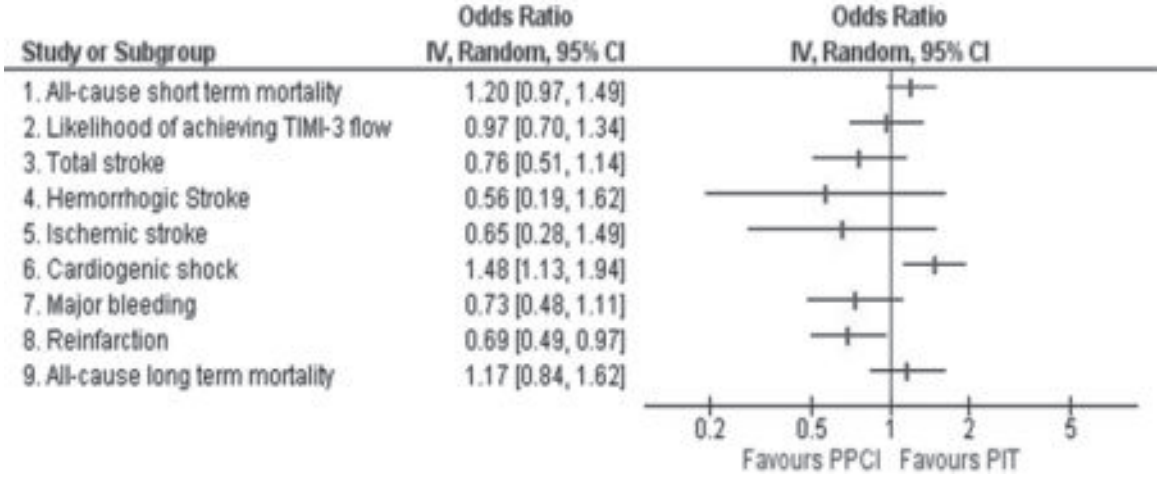


Fig.-5: *Summarized results of randomized control trials and observational studies pooled together. PIT = pharmaco-invasive therapy; PPCI = primary percutaneous coronary intervention.*[21]

Most of the trials and meta analysis was based on the study done in western world. Few studies were conducted in Asian context. One large scale study[22] done where data were collected from KAMIR (Korean Acute Myocardial Infarction Registry). Study showed in-hospital mortality was lower in pharmacoinvasive group; incidences of major bleeding and stroke during hospitalization were not different. Pharmacoinvasive group had lower rates of 12-month death and MACE. In propensity-matched cohort, there were no signicant differences in in-hospital adverse event rates. Twelve-month mortality and MACE were not different between pharmacoinvasive strategy and PPCI 4.4% versus 4.1% and 7.5% versus 7.8%, respectively. This study reflecting the out come in Asian population and the results was matched with the FASTMI2015 results in a European population and the STREAM results in a North American population.

The 'Tamilnadu ST segment elevation myocardial infarction (TN-STEMI) program[23] was designed with the aim of delivering timely reperfusion therapy for patients presenting with STEMI in the Indian set-up. The MACCE rates were similar in both PPCI group and PTI group except for fewer readmissions (29.8% vs. 12.6%, p = 0.0002) and target revascularizations at 1 year (4.8% vs. none, p = 0.002) in the post-implementation group.

STEPP-AMI, an observational, multicentred, prospective study of 200 people presented with

STEMI where followed up for 2 years. Study evaluated the efficacy and safety of a strategy of pharmaco-invasive therapy with primary PCI. Tenecteplase used as fibrinolytic agents. he primary endpoint of 30 day incidence of death, cardiogenic shock, reinfarction, repeat revascularization, and congestive heart failure, was similar in both groups, although there was a trend toward benefit in the primary PCI group (11.1% vs. 3.9%, p = 0.07, RR = 2.87; 95% CI: 0.92–8.97). At the end of 2-year follow- up, the initial benefit from primary PCI seemed to be narrowed as more events have occurred in the primary PCI group vs pharmaco-invasive group (17.8% vs. 13.6%, p = 0.47, RR = 1.31; 95% CI: 0.62–2.76).26Overall, the study concluded that fibrinolysis followed by an early coronary angiogram within 3–24 h with PCI, if appropriate, resulted in similar outcomes when compared to primary PCI in patients with STEMI at 2-year follow-up.[24]

Results of studies both from Western and Asian part is identical, the pharmaco-invasive approach has also been recommended by guidelines. [7, 8]

What fibrinolytics is appropriate for Pharmaco-invasive:

Fibrinolytics therapy lyses thrombotic occlusion associated with STEMI and restores the coronary flow. A range of thromlytic agents are available. But there is no head to head study comparing efficacy of different fibrinolytics in pharmaco-invasive therapy. In the western world second generation (Alteplase) and third generation (Tenecteplase, Reteplase) is mostly used as fibrinolytics. The scenario is different in the Asia specially India, Bangladesh, Pakistan where Streptokinase is most popular and frequently used drug due to its rapid availability and cost. In National Institute of Cardiovascular Diseases in Bangladesh Government provide Streptokinase in free of cost for treating patient with STEMI.[25] Most of the pharmaco-invasive trial like STEPP-AMI,[24] STREAM,[19] NORDISTEMI,[18] TRANSFER AMI [17] used Tenecteplase as fibrinolytic, CARESS-IN-AMI[16]and SIAM-III[26] used reteplase as fibrinolytic. The impact of Pharmaco-invasive strategy with newer generation thrombolytic agents has been established.[19]

On the other hand, there is no major data which have evaluated streptokinase as a part of pharmaco-invasive strategy. Few studies conducted in Asia region used streptokinase as fibrinilytic agents. The TN STEMI programme[23]is one of them and provide a unique data regarding this subset of patients.Timely restoration of IRA patency in STEMI is critical for myocardial salvage. Fibrinolytic agents and primary PCI are equally effective in the initial hours of STEMI.[27,28] Hence for thrombolytic to be effective reperfusion agents, shorter times-to-treatment is important, more so with agents like streptokinase.

Considering administration, third generation Reteplase have some advantage over other fibrinolytics; there is no need of dose adjustment based on body weight. Furthermore, administration of Reteplase is easy as it does not require infusion and therefore minimizes dosing errors. The safety and efficacy of Reteplase in patients with acute myocardial infarction has been evaluated in few international clinical studies. The INJECT trial was conducted to establish equivalence of Reteplase with Streptokinase in the reduction of mortality after acute myocardial infarction.[29]In this study, in which reteplase was associated with greater ST resolution and a trend towards lower mortality than streptokinase.the RAPID 1 and RAPID 2 studies validated the potential advantage of Reteplase over Alteplase.[30] Compared to Alteplase, Reteplase can result in earlier and more complete coronary patency.[31] The beneficial effects of Reteplase have been corroborated in the Indian context too. A phase-III prospective, multi-centric trial has found that Reteplase can be effective and safe in the treatment of patients with STEMI.[32] In addition, the RAPID 1, RAPID 2 and INJECT studies have shown that treatment with Reteplase is not associated with an increase in bleeding complications or other adverse events.

Why pharmaco-invasive therapy getting so importance:

The main objectives of patient with acute STEMI is reducing the total ischemic time. The pharmaco-invasive approach is beneficial in patient where very delay to primary PCI is expected.

Although primary PCI is regarded as a gold standard for reperfusion therapy, but having limited access. In India it is accessible to less than 10% STEMI patients.[33] InUSA only 39% have catheterization facilities,[5] About one third hospitals have the capability to perform PPCI 24/7.[6] So all the patient not getting chance to adhere into PCI facility immediately after STEMI. Pharmaco-invasive therapy is initiated to

minimize the delay of reperfusion at the same time to get same benefit of primary PCI.

Various factors are responsible for delay to primary PCI. Patient delay (Time from symptom to first medical contact) may occur due to lack of awareness in recognizing early sign and symptom of myocardial infarction; lack of transfer facility, prolong transfer time to hospital with PCI capability.This delay is more prominent in less advanced countries where emergency services and public awareness and education programs are not well established. Moreover, in third world country patient have no health insurance coverage or very limited coverage so financial constrain is a issue to take decision regarding primary PCI.

Beside patient related delay health system related delay is an important contributing factor. Not all the hospital have 24/7 primary PCI facility and some times non availability of PCI lab during busy time. Maximum expected delay from STEMI diagnosis to primary PCI to choose primary PCI over fibrinolysis is <120 minutes, and maximum time delay from STEMI diagnosis to PPCI in PCI capable hospital is <60 minutes.[7] But each minute delay contribute to myocardial damage, It has been shown that the 1-year mortality increases by 7.5% for each 30-minute delay in treatment.34 When door to balloon time is >120 min the primary PCI has no advantage over fibrinolysis in terms of short term mortality. On the other hand, fibrinolytic is available easily and can administered easily. So, the imminent myocardial damage which occurs due to the delay in instituting primary PCI, can be prevented by using fibrinolytic therapy.

To overcome the delay of primary PCI idea of facilitated PCI were developed initially by using pharmacological agents (i.e., fibrinolytic drugs or half-dose fibrinolytic therapy plus glycoprotein IIb/IIIa inhibitors[GPI]) in patients with long delays to PCI has anintuitive appeal. This so-called “facilitated PCI” is expected to increase the window of opportunity in which primary PCI can be performed, by enabling early reperfusion followed by rapid transfer to a PCI facility. Despite being attractive, this concept has been frustrated by at least two large randomized trials. In the Assessment of Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction (ASSENT-4) trial[35] was done but the trial was prematurely interrupted because of the observed increased risk of adverse events in the facilitated arm, including death or heart failure (primary endpoint), intracranial hemorrhages.

The Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) trial[36] were also found no benefit of facilitated PCI over primary PCI. In view of the above-mentioned data, it seems that the idea of a facilitated strategy in STEMI should be put aside and, in fact, this approach is not currently recommended by guidelines. Whereas safety and efficacy of Pharmaco-invasive therapy is already established.

Therefore, in our context pharmaco-invasive approach is a golden opportunity for the management of STEMI patients.This prolongs the window of opportunity to 24 hours and provide breathing space to relatives of the patient to arrange finances, gather manpower, complete insurance formalities if any.

Moreover, Meta-analysis of early routine PCI after fibrinolysis compared with standard therapy in STEMI patients demonstrated a significant reduction in re-infarction and recurrent ischemia at 30 days with no significant increase in major bleeding events and also did not find any significant difference in long-term mortality provided fibrinolytic therapy initiated in timely fashion.[20, 21]

Conclusion:

There is no conflict between on time PPCI and PIT. Primary PCI is always encouraged as gold standard management of STEMI. Pharmaco-invasive is a realistic alternative to primary PCI where the delay to PCI is anticipated. It can be a life saving option for the patient who come from rural area or patient presented in non-PCI capable hospital. Healthcare system improvement and patient education program is needed for successful STEMI management. Increase facility to initiate thrombolytic therapy early even in rural area is the key to success of pharmaco-invasive therapy.

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Infective Endocarditis after Coronary Angiography in a Middle-Aged Male - A Case Report

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Abstract:

Bacteremia following cardiac catheterization rarely leads to systemic or localized infection with adverse outcome. Here, we describe the case of a - 38 year -old male who presented with prolonged fever complicated by left sided weakness and difficulty in speech and swallowing. Later he was diagnosed as a case of infective endocarditis (IE) with ischaemic stroke. He had a history of coronary angiography 4 months before his presentation. During parenteral antibiotic therapy for IE, he developed acute kidney injury, and while on dialysis, he died. So, post-coronary angiography infective endocarditis should be kept in mind while dealing with patients present with prolonged fever after CAG and other cardiac invasive procedures.

Key word: Infective endocarditis, Coronary Angiography, Acute Kidney Injury.

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Introduction:

Diagnostic coronary angiography and percutaneous coronary intervention are most common procedures performed in cardiac catheterization laboratory. Infections are an inherent risk of any invasive procedure. A large retrospective study involving over 22,000 cardiac procedures found a bloodstream infection rate of 0.11%.[1] The factors influencing the pathogenesis of procedure related infections include the virulence of the pathogen, host response, and the properties of the device.[2]

Case Summary:

Mr. X a 36- year- old expatriate Bangladeshi male underwent coronary angiography for exertional chest pain through femoral cannulation which revealed normal findings. Baseline echocardiography was also normal. He developed fever with rigor two months after the procedure. He developed sudden weakness of left side of the body one month after onset of febrile illness. He visited several doctors as out-patient basis but as his condition did not improve he got himself admitted in a hospital.

He had mild anaemia and clubbing, pulse was 74/ min, regular, large volume, collapsing in nature and BP was 130/40 mm Hg. On precordial examination, apex beat was in left 5th inter-costal space 09 cm from midline and thursting in nature. A_2 was soft and a mid diastolic murmur of grade 3/6 was present in the 3rd and 4th intercostal space at left para- sternal area. Neurological examination revealed dysarthria, left sided upper motor facial palsy and left sided hemiparesis. ECG showed sinus tachycardia. Echocardiography demonstrated large vegetation attached to right coronary cusp of aortic valve causing grade 3 aortic regurgitation. Haemogram showed, total leucocyte count 13.5 x 10^9/L with neutrophil 82%. Two sets of blood culture were negative. Abdominal ultrasound revealed mild splenomegaly. CT scan of head showed right frontal lobe infarct. His renal function was normal. He was diagnosed as a case of culture negative infective endocarditis (IE), aortic regurgitation and ischaemic stroke. Management started with injectable ceftriaxone, gentamicin and

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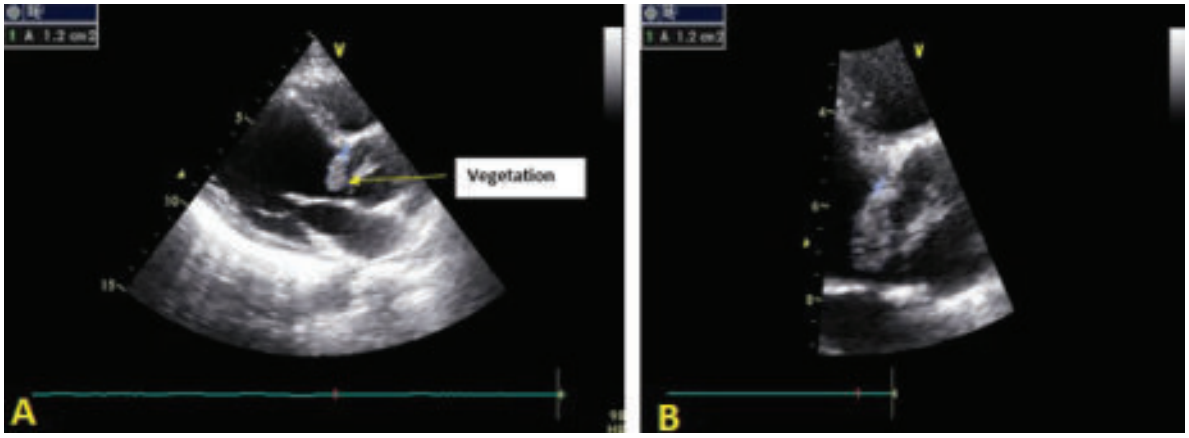


Fig.-1: *2D echocardiography parasternal long axis view. Panel A shows large vegetation attached to the right coronary cusp of aortic valve marked by yellow arrow, Panel B shows the same vegetation in zoomed view.*

flucloxacillin. Within 1 week he developed acute kidney injury. Nephrology consultation was taken; urgent dialysis was started and continued for 15 days. Despite all effort, his condition did not improve and he died while on dialysis.

Discussion:

With advancement of medical science, invasive diagnostic and therapeutic procedures are most preferred options for management of cardiac diseases. Bacteraemia following cardiac catheterization is a rare complication.[3] In a previous study, it is shown that only 0.4% of patients had positive blood culture after cardiac catheterizations and coronary interventions.[4] Our patient was suffering from prolonged fever after coronary angiography and visited several physicians as an out- patient basis and received antimicrobials before hospital admission.

Our patient fulfilled modified Duke's criteria for definite IE.[5] One major criteria is echocardiographic evidence of vegetation attached to aortic valve. Three minor criteria are fever, embolic phenomena i.e. ischaemic stroke and glomerulonephritis. Two sets of blood culture were negative in our patient and the probable cause behind this may be patient's recent exposure to antimicrobials.

Our patient had normal aortic valve morphology before coronary angiography. In most reported cases, aortic valve most commonly affected following cardiac invasive procedures. The possible cause for this is endocardial injury which increases the risk of development of infectious endocarditis.

Neurological complications are common manifestations and occur in 20 to 40% cases of IE.[4] Moreover most complications occur in blood culture positive infective endocarditis[2]. Blood culture negative infective endocarditis is not common, and few studies reported the correlation between culture-negative IE and neurological complications. Our patient presented with ischaemic stroke with left sided hemiparesis and CT scan of head revealed infarct in right frontal lobe and adjacent para-ventricular region.

The incidence of renal complications ranges from 2 to 60% in patients with infective endocarditis[6]. Patients with infective endocarditis can develop renal complications in several forms. It may be infection-related immune- complex mediated glomerulonephritis, renal infarction from septic emboli and renal cortical necrosis. In addition drugs like aminoglycoside can cause acute kidney injury which is used for treating infection[7]. Our patient developed acute kidney injury after starting injectable antibiotics. Initial urine routine examination showed proteinuria and hematuria. Initial serum creatinine was also normal (1.07mg/dl). But three days after starting treatment for IE, his renal function became compromised. This renal complication may be due to drug like gentamicin or may be a complication of infection itself. Nephrology consultation was done and hemodialysis was started. Despite all effort patient's condition did not improve and died while dialysis.

Conclusion:

Infectious complications of percutaneous cardiac procedures are rare but must be considered in any

patient presenting with prolonged fever with chills and rigor. There are several clinical and procedural related risk factors for infections. This case demonstrates that post CAG culture negative IE with its complications has lethal outcome. In an era of interventional cardiology, prevention of procedure related infection is of paramount importance.

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