Isfahan Cardiovascular Research Institute

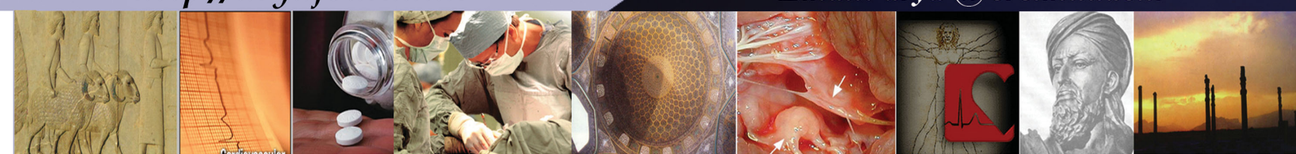
ARYA Atherosclerosis

ARYA Atherosclerosis has been licensed as a scientific & research journal by the Iranian commission for medical publications, ministry of health and medical education

Indexed by:
- *PubMed*
- *PubMed Central*
- Scopus
- Islamic World Science Citation (ISC)
- WHO/EMRO/Index Medicus
- NLM Catalog
- Directory of Open Access Journals (DOAJ)
- Index Copernicus
- Academic Search Complete EBSCO Publishing databases
- Scientific Information Database
- Open J Gate
- Google Scholar
- Barakatkns
- Magiran

Serial Issue: 55 *Volume 12, Issue 5, September 2016* *Print ISSN: 1735-3955*
Online ISSN: 2251-6638

http://aryajournal.ir *Email: arya @ crc.mui.ac.ir*



ARYA Atherosclerosis

Official Journal of the Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences

Publisher: Isfahan University of Medical Sciences
Email: publications@mui.ac.ir

Copy Edit, Layout Edit, Design, Print and Online Support: Farzanegan Radandish Publications
Tel: +98-31-32224335, +98-31-32224382
http://www.farapub.com Email: farapublications@gmail.com

Circulation: 500
Distribution: International
Language: English
Interval: Bimonthly
Print ISSN: 1735-3955, **Online ISSN:** 2251-6638

Address: ARYA Journal Office, Isfahan Cardiovascular Research Institute, Seddigheh Tahereh Research Complex, Khorram Ave. Isfahan, Iran

PO. Box: 81465-1148 Tel: +98-311-3377883 Fax: +98-311-3373435
Email: arya@crc.mui.ac.ir Web: www.aryajournal.ir

ARYA Atherosclerosis

INSTRUCTIONS FOR AUTHORS

MANUSCRIPTS

Manuscripts containing original material are accepted for consideration if neither the article nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the *Journal*. This restriction does not apply to abstracts or press reports published in connection with scientific meetings. Copies of any closely related manuscripts must be submitted along with the manuscript that is to be considered by the *Journal*. Authors of all types of articles should follow the general instructions given below. Please see Types of Articles for specific word counts and instructions.

SUBMISSION

- Only online submission is acceptable. Please submit online at: http://www.aryajournal.ir
- Manuscripts should be divided into the following sections: (1) Title page, (2) Abstract and Keywords, (3) Introduction, (4) Methods, (5) Results, (6) Discussion, (7) Acknowledgements, (8) Authors contribution, (9) References, (10) Figures' legend, (11), Tables and (12) Appendices. Figures should be submitted in separate files using JPEG or TIF format.
- Prepare your manuscript text using a Word processing package (save in .doc or .rtf format NOT .docx). Submissions of text in the form of PDF files are not permitted.

COVER LETTER

A covering letter signed by corresponding author should provide full contact details (include the address, telephone number, fax number, and Email address). Please make clear that the final manuscript has been seen and approved by all authors, and that the authors accept full responsibility for the design and conduct of the study, had access to the data, and controlled the decision to publish. There should also be a statement that the manuscript is not under submission elsewhere and has not been published before in any form.

AUTHORSHIP

As stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, credit for authorship requires substantial contributions to: (a) conception and design, or analysis and interpretation of data; (b) the drafting of the article or critical revision for important intellectual content and (c) final approval of the version to be published. Authors should meet conditions a, b and c. All authors must sign authorship form attesting that they fulfill the authorship criteria. Your submitted manuscript will not be processed unless this form is sent. There should be a statement in manuscript explaining contribution of each author to the work. Those contributors who did not fulfill authorship criteria should be listed in acknowledgments.

Any change in authorship after submission must be approved in writing by all authors.

ASSURANCES

In appropriate places in the manuscript please provide the following items:

- If applicable, a statement that the research protocol was approved by the relevant institutional review boards or ethics committees and that all human participants gave written informed consent
- The source of funding for the study
- The identity of those who analyzed the data
- Financial disclosure or a statement indicating "None" is necessary.

TITLE PAGE

With the manuscript, provide a page giving the title of the paper; titles should be concise and descriptive (not declarative). Title page should include an abbreviated running title of 40 characters, the names of the authors, including the complete first names and no more than two graduate degrees, the name of the department and institution in which the work was done, the institutional affiliation of each author. The name, post address, telephone number, fax number, and Email address of the corresponding author should be separately addressed. Any grant support that requires acknowledgment should be mentioned on this page. Word count of abstract and main text as well as number of tables and figures and references should be mentioned on title page. If the work was derived from a project or dissertation, its code should also be stated. For clinical trials, a registry number like Iranian Registry of Clinical Trials (IRCT) should also be provided.

Affiliation model: Academic Degree, Department, Institute, City, Country

Example: Associate Professor, Department of Cardiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Provide on a separate page an abstract of not more than 300 words. This abstract should consist of four paragraphs, labeled **Background, Methods, Results, and Conclusion**. They should briefly describe the problem being addressed in the study, how the study was performed, the salient results, and what the authors conclude from the results, respectively. Three to 10 keywords may be included. Keywords are preferred to be in accordance with MeSH terms. Find MeSH terms: http://www.ncbi.nlm.nih.gov/mesh

CONFLICT OF INTEREST

Authors of research articles should disclose at the time of submission any financial arrangement they may have with a company whose product is pertinent to the submitted manuscript or with a company making a competing product. Such information will be held in confidence while the paper is under review and will not influence the editorial decision, but if the article is accepted for publication, a disclosure will appear with the article.

Because the essence of reviews and editorials is selection and interpretation of the literature, the *Journal* expects that authors of such articles will not have any significant financial interest in a company (or its competitor) that makes a product discussed in the article.

REVIEW AND ACTION

Submitted papers will be examined for the evidence of plagiarism using some automated plagiarism detection service. Manuscripts are examined by members of the editorial staff, and two thirds are sent to external reviewers. We encourage authors to suggest the names of possible reviewers, but we reserve the right of final selection. Communications about manuscripts will be sent after the review and editorial decision-making process is complete. After acceptance, editorial system makes a final language and scientific edition. No substantial change is permitted by authors after acceptance. It is the responsibility of corresponding author to answer probable questions and approve final version.

COPYRIGHT

JOURNAL STYLE

Use normal page margins (2.5 cm), and double-space throughout.

Tables

Double-space tables and provide a title for each.

Figures

Figures should be no larger than 125 (height) x 180 (width) mm (5 x 7 inches) and should be submitted in a separate file from that of the manuscript. The name of images or figures files should be the same as the order that was used in manuscript (fig1, fig2, etc.). Only JPEG, TIF, GIF and EPS image formats are acceptable with CMYK model for colored image at a resolution of at least 300 dpi. Graphs must have the minimum quality: clear text, proportionate, not 3 dimensional and without disharmonic language. Electron photomicrographs should have internal scale markers.

If photographs of patients are used, either the subjects should not be identifiable or the photographs should be accompanied by written permission to use them. Permission forms are available from the Editorial Office.

Medical and scientific illustrations will be created or recreated in-house. If an outside illustrator creates the figure, the *Journal* reserves the right to modify or redraw it to meet our specifications for publication. The author must explicitly acquire all rights to the illustration from the artist in order for us to publish the illustration. Legends for figures should be an editable text as caption and should not appear on the figures.

References

The Vancouver style of referencing should be used. References must be double-spaced and numbered as superscripts consecutively as they are cited. References first cited in a table or figure legend should be numbered so that they will be in sequence with references cited in the text at the point where the table or figure is first mentioned. List all authors when there are six or fewer; when there are seven or more, list the first six, then "et al." In the following some examples are listed:

1. McLaughlin TJ, Aupont O, Bambauer KZ, Stone P, Mullan MG, Colagiovanni J, et al. Improving psychologic adjustment to chronic illness in cardiac patients. The role of depression and anxiety. J Gen Intern Med 2005; 20(12): 1084-90.
2. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Health Sciences; 2007. p. 1976, 1981, 1982.

3. Gaston M. The psychological care of patients following a myocardial infarction [Online]. 2003; Available from: URL: http://www.nursingtimes.net/the-psychologicalcare-of-patients-following-a-myocardialinfarction/199464.article/

Units of Measurement

Authors should express all measurements in conventional units, with Système International (SI) units given in parentheses throughout the text. Figures and tables should use conventional units, with conversion factors given in legends or footnotes. In accordance with the Uniform Requirements, however, manuscripts containing only SI units will not be returned for that reason.

Abbreviations

Except for units of measurement, abbreviations are discouraged. Consult Scientific Style and Format: The CBE Manual for Authors, Editors, and Publishers (Sixth edition. New York: Cambridge University Press, 1994) for lists of standard abbreviations. Except for units of measurement, the first time an abbreviation appears, it should be preceded by the words for which it stands.

Drug Names

Generic names should generally be used except for studies on comparative effects of different brands. When proprietary brands are used in research, include the brand name and the name of the manufacturer in parentheses in the Methods section.

For any more detail about the writing style for your manuscripts refer to:

http://www.icmje.org

Try to prepare your manuscript in accord with the scientific writing checklists available in EQUATOR Network:

http://www.equator-network.org

AFTER YOUR SUBMISSION

When a manuscript arrives to ARYA office, a staff member checks it to make sure that all materials required for submission are included. If everything is present, the article is registered in office and referred to the managing editor.

The first step the manuscript makes on its editorial journey is on the desk of the editor-in-chief, who reviews each submission (in his absence this is done by the managing editor) and decides on the basis of its general content whether it is appropriate even for consideration for publication. Each of the remaining scientific manuscripts is assigned to an associate editor with expertise in the subject area covered by the study, who makes an independent assessment of the value and validity of the paper. If the associate editor believes that even with favorable reviews the paper would not be published because it lacks novelty or importance, or if he/she spots a major flaw in experimental design, performance or statistical analysis the manuscript is returned to the authors.

If, on the other hand, the associate editor believes that the paper may merit publication, it is sent to two of our outside **reviewers**. They are asked to provide a frank evaluation of the *scientific validity of the manuscript, insight into its freshness, clinical impact, and timeliness, and an overall opinion* of its worthiness for publication. This is the key step in manuscript evaluation. As editors, we are grateful to all our reviewers for their continued contribution to the rating process. We are careful not to refer to them as "referees," which would suggest that the decision to publish a paper rests entirely with them. It does not. The reviewers provide critiques and advice that the editorial staff uses in making decisions. But we, **ARYA editorial board**, make the decisions. When both outside reviews are returned, the associate editor then assesses the manuscript again, along with the comments of the reviewers. She may seek additional opinions from other reviewers, or may discuss the manuscript at a meeting of the entire editorial staff. At this meeting a decision is made either to reject the paper or to proceed further editorial consideration, including, if appropriate, a formal review of the statistical or experimental methods. In some cases, the editorial staff may recommend additional review by outside reviewers. On completion of this process, the manuscript is usually returned to its authors along with a letter inviting them to revise it and to respond to certain questions. When all the requested information has been received, the manuscript is reconsidered by an associate editor, and it may be discussed again with other members of the editorial staff. We then make our final decision to *accept* or *reject* the paper.

We recognize that the peer-review process is not perfect, but we earnestly believe that it is the best way to select and publish the most important medical research. Peer review is labor-intensive and sometimes *time-consuming*, but without it physicians themselves would have to assess the validity of new medical research and decide when to introduce new treatments into practice.

We do all our efforts to finalize this process in a *3 to 4 months* period for each manuscript.

We understand the importance of a submitted manuscript to its authors. **We invite you to submit your best research to us; we will treat it with respect, and you can follow it on its journey**.

Type of Articles Considered to be Published in *ARYA Atherosclerosis Journal*

ARYA Atherosclerosis is a bimonthly peer-reviewed scientific Journal providing academically sound, clinically practical information for physicians, medical scientists and health care providers. ARYA Atherosclerosis is published by Isfahan Cardiovascular Research Institute. Journal editors review articles in fields of atherosclerosis, its risk factors and related diseases.

ORIGINAL RESEARCH

- **Original Articles** are scientific reports of the results of original clinical research. The text is limited to 3000 words (excluding abstracts and references), with a structured abstract, a maximum of 5 tables and figures (total), and up to 30 references.
- **Special Articles** include data and generally focus on areas such as economic policy, ethics, law, or health care delivery. The text is limited to 3000 words, with an abstract, a maximum of 5 tables and figures (total), and up to 30 references.
- **Qualitative Researches** focus to clear underlying reasons, opinions, and motivations. It helps to develop ideas or hypotheses for potential quantitative research. The text is limited to 3500 words, with an abstract, a maximum of 5 tables and figures (total), and up to 30 references.
- **Short Communication Articles** are short scientific entities often dealing with methodological problems or with byproducts of larger research projects and are suitable for the presentation of research that extends previously published research. A short communication is for a concise, but independent report representing a significant contribution to cardiology. Short communication is not intended to publish preliminary results. It should be no more than 1000 words, and could include 2 figures or tables. It should have at least 15 references. Short communications are also sent to peer review.

CLINICAL CASES

- **Brief Reports** usually describe one to three patients or a single family. The text is limited to 1000 words, a maximum of 5 tables and figures (total), and up to 15 references. It does not include an abstract.
- **Clinical Problem-Solving** manuscripts consider the step-by-step process of clinical decision making. Information about a patient is presented to an expert clinician or clinicians in stages (in the manuscript this is indicated in **boldface** type) to simulate the way such information emerges in clinical practice.
The clinician responds (regular type) as new information is presented, sharing his or her reasoning with the reader. The text should not exceed 2500 words, and there should be no more than 20 references. The use of clinical illustrative materials, such as x-ray films, is encouraged.

REVIEW ARTICLES

All review articles undergo the same peer-review and editorial process as original research reports. The text is limited to 7000 words, with unlimited number of figures, tables, and references.

- **Conflicts of Interest:** Because the essence of review articles is selection and interpretation of the literature, the **ARYA Atherosclerosis Journal** expects that the authors of such articles will not have a significant financial association with a company (or its competitor) that makes a product discussed in the article.
- **Clinical Practice** articles are evidence-based reviews of topics relevant to practicing physicians, both primary care providers and specialists. Articles in this series should include the following sections: clinical context, strategies and evidence, areas of uncertainty, guidelines from professional societies, and recommendations from the authors. The text does not include an abstract.
- **Current Concepts** articles focus on clinical topics, including those in specialty areas but of wide interest.
- **Drug Therapy** articles detail the pharmacology and use of specific drugs or classes of drugs, or the various drugs used to treat particular diseases.
- **Mechanisms of Disease** articles discuss the cellular and molecular mechanisms of diseases or categories of diseases.
- **Medical Progress** articles provide scholarly, comprehensive overviews of important clinical subjects, with the principal (but not exclusive) focus on developments during the past five years. Each

article details how the perception of a disease, disease category, diagnostic approach, or therapeutic intervention has evolved in recent years.

OTHER SUBMISSIONS

- **Editorials** usually provide commentary and analysis concerning an article in the issue of the *Journal* in which they appear. They may include an illustration or table. They are nearly always solicited, although occasionally, unsolicited editorials may be considered. Editorials are limited to 1200 words, with up to 15 references.
- **Perspectives** are also nearly always solicited, but we are willing to consider unsolicited proposals. Perspectives provide background and context for an article in the issue in which they appear. Perspectives are limited to 800 words and usually include an illustration. There are no reference citations.
- **Sounding Board** articles are opinion essays. They are similar to editorials but not tied to a particular article. They often present opinions on health policy issues and are normally unsolicited. The text is limited to 2000 words.
- **Clinical Implications of Basic Research** articles discuss single papers from preclinical journals. The purpose is to explain the findings and comment on their possible clinical applications in fewer than 1000 words. There may be one figure and up to four references. We do not consider unsolicited manuscripts in this category.
- **Images in Clinical Medicine** are classic images of common medical conditions. Visual images are an important part of much of what we do and learn in medicine. This feature is intended to capture the sense of visual discovery and variety that physicians experience. Images in Clinical Medicine are not intended as a vehicle for case reports.
- **Special Reports** are miscellaneous articles of special interest to the medical community. They are limited to 2700 words.
- **Legal Issues in Medicine** are nearly always solicited, but *Journal* is willing to consider unsolicited manuscripts or proposals for manuscripts.
- **Health Policy Reports** are nearly always solicited, but *Journal* is willing to consider unsolicited manuscripts or proposals for manuscripts.
- **Occasional Notes** are accounts of personal experiences or descriptions of material from outside the usual areas of medical research and analysis.
- **Book Reviews** are generally solicited.
- **Letters to the Editor:** Letters to the Editor are considered for publication (subject to editing and abridgment) provided they do not contain material that has been submitted or published elsewhere. The text, not including references, must not exceed 250 words if it is in reference to a recent *Journal* article, or 500 words in all other cases. A letter must have no more than 5 references and 1 figure or table. It must not be signed by more than three authors. Letters referring to a recent *Journal* article must be received within three weeks of its publication.

The publication fees of ARYA Atherosclerosis Journal

Type of the article	Permitted word count*	The payment fee in Iranian Rial (IRR)	The payment fee for each 500 excess words (IRR)
Letter to the Editor	500	-	-
Clinical Case	1000	2,000,000	1000,000
Short Communication	1000	2,000,000	1000,000
Original Article	3000	3,500,000	1000,000
Qualitative Research	3500	3,500,000	1000,000
Review Article	7000	3,500,000	1000,000

* All the words of the article containing the references; each table is considered as 300 words.

There will be a 50% discount of publication fee if both the first and the corresponding author are affiliated to Isfahan University of Medical Sciences (IUMS).

Table of Contents

The prevalence of low physical activity in an urban population and its relationship with other cardiovascular risk factors: Findings of a community-based study (KERCADRS) in southeast of Iran

Hamid Najafipour[1], Mansoor Moazenzadeh[2], Mahdi Afshari[3], Hamid Reza Nasri[2], Mohammad Khaksari[4], Afsaneh Forood[2], Ali Mirzazadeh[5]

Original Article

Abstract

BACKGROUND: The low physical activity (LPA) more or less affects every community. Because of high prevalence of cardiovascular diseases in Iran and their relationship with LPA, this study aimed to measure precisely the epidemic size of LPA and determine its relationship with six other coronary artery disease (CAD) risk factors among an urban population aged 15 to 75 years in Kerman, Iran.

METHODS: Using household survey, 5895 adults were randomly recruited through single-stage cluster sampling from 250 postal codes. Demographic characteristics, blood pressure, blood glucose, cholesterol, triglyceride, smoking, opium use, mental status and physical activities at work, rest and recreation were assessed and ranked as low, moderate and intense. Adjusted odds ratio (AOR) was reported as a measure of the relationship between LPA and other CAD risk factors.

RESULTS: The prevalence of low, moderate, and intense physical activity were 42.1% (40.3-43.9), 45.0% (43.6-47.4) and 12.4% (11.1-13.9), respectively. LPA showed a sudden rise from 36.8% to 45.4% after the age of 25 years. On average, women had less physical activity than men (45.1% vs. 39.2%, P = 0.01). Participants with low physical activity compared to those without physical activity had significantly higher chance of anxiety [odds ratio 1.39; confidence interval (95% CI) 1.08-1.79; P = 0.01], hypertension (1.59; 1.08-2.35; P = 0.02), hyper-cholesterolemia (1.37; 1.06-1.76; P = 0.02), cigarette smoking (1.52; 1.07-2.11; P = 0.01), opium addiction (1.47; 1.07-2.02; P = 0.02) and overweight/obesity (1.34; 1.05-1.71; P = 0.02).

CONCLUSION: LPA was very common in the studied population and almost half of the adults were at risk for CAD because of insufficient level of physical activity. Such risky life-style pattern makes the emerging of CAD epidemic unavoidable, if effective interventions not being in place timely to this community.

Keywords: Physical Activity, Coronary Artery Disease, Urban Population, Kerman, Iran

Date of submission: 18 May 2015, ***Date of acceptance:*** 20 Aug 2016

Introduction

According to the report from World Health Organization (WHO), cardiovascular diseases account for almost 30% of overall deaths all around the world.[1] In developing countries, 80% of deaths are because of cardiovascular diseases mostly due to change in life style, increase in urbanism and lack of intervention plans in these countries.[2] Although Iran is not among countries with highest cardiovascular mortality rates, the change in life style and aging might lead to a huge increase in cardiovascular diseases in the near future. In a national project that measured the burden of diseases in 2003, ischemic heart diseases accounted for the most burden of diseases in Iranian population.[3]

1- Professor, Cardiovascular Research Center AND Department of Physiology, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
2- Associate Professor, Physiology Research Center AND Department of Cardiology, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
3- Assistant Professor, School of Public Health, Zabol University of Medical Sciences, Zabol, Iran
4- Professor, Endocrinology and Metabolism Research Center AND Department of Physiology, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
5- Assistant Professor, Global Health Sciences, University of California, San Francisco, CA, USA
Correspondence to: Mansoor Moazenzadeh Email: mmoazenzadeh170@gmail.com

Based on the definition of WHO, physical activity is any type of body movement produced by skeletal muscles that requires energy expenditure. Physical activity does not inclusively mean doing a sport. In fact, all kind of activities including a body movement such as working, playing, training, housekeeping and recreational activities should be accounted.[4] Low physical activity is accounted as the fourth cause of mortality and morbidity in the world. It also accounts for 27% of diabetes and 30% of ischemic heart diseases. Regular physical activity in adults decreases hypertension, coronary artery diseases (CAD), strokes, diabetes, and colon and breast cancers.[4]

Unlike some cardiovascular risk factors which have mostly genetic basis and are not modifiable (e.g. hypertension and hyperlipidemia), low physical activity could be decreased and removed by a proper planning, change in attitude and behavior. In a research carried out to measure the lipid and glucose of Tehran's population, Iran, only 30% of the participants had enough physical activity.[5] Based on the findings of the third round of CAD surveillance of risk factors conducted in 2006, 40% of Iranian adults had low physical activities.[6]

With a population of 2,990,000 (based on a census carried out in 2011), Kerman province constitutes 3.9% of Iran's population.[7] According to the data given by the third national surveillance of risk factors of non-communicable diseases (NCDs), obesity and overweight increased from 39% in 2003 to 42% in 2006 in this province.[6] Only a few studies have examined the relationship between CAD risk factors and physical activity in Iran.[5] In a study carried out on cardiovascular risk factors in Semnan, Iran, physical activity was not taken into consideration.[8] Few researches focused on the physical activity of their participants, and they were only limited to specific hours instead of the whole day. For example, in a large study performed on the glucose and lipid of Tehran's population, only physical activity in leisure time was addressed.[5]

Here, we included all types of physical activities at work, daily commute, recreational and sport-related activities. We also addressed less routine CAD risk factors including anxiety, depression and opium use along with ordinary risk factors of obesity, hypertension, hyperlipidemia, high blood glucose and smoking status in the study. None of the previous cross sectional studies at local or national level assessed psychological status or opium addiction as CAD risk factor.

The objective of this paper was to comprehensively describe the prevalence and pattern of low physical activity by age, sex, education and occupation subgroups, and also to estimate the association of other CAD risk factors with individual level of physical activity.

Materials and Methods

The present paper is a sub-analysis of data collected in a study which focused on the risk factors of CADs (i.e. Kerman Coronary Artery Disease Risk Factor Study; KERCADRS). It was carried out on 5895 individuals ranging between 15 to 75 years of age in 2010-2011 on an urban population in southeast of Iran. The ethics committee of the Kerman University of Medical Sciences approved the study protocol (ethic code 88/110KA). A written informed consent was obtained from all participants in the study. Kerman is the biggest city in the southeast of Iran that, according to the 2012 census, has a population of about 750,000. More details about the city conditions and sampling and data collection methods are previously published at IJPH.[9]

One stage cluster sampling method was applied for sample selection. The primary units of sampling were households who have been living in Kerman for at least one year prior to the interview. Using the zip code in the mail office, we marked 250 areas and approached households in the area to recruit 5895 individuals in twelve strata of age and sex. The eligible people (6200 subjects) were invited to complete the informed consent and participate in the research, from which close to 95% responded to the invitation. They were referred to the clinical study site located in city downtown where they went through several steps of in-person interview to disclose their demographic characteristics, CAD risk behaviors and past medical history, mental status (anxiety and depression), and to provide fasting blood sample (after 12-14 hours fasting) for serum lipid and glucose level measurement. They were also asked to report their smoking status, opium use and physical activity level. The sample size was calculated as of 5910 based on prevalence of 50% to be efficient for all NCD risk factors considering the precision at the level of 5%, and response rate 78%, which was corrected according to eight age-sex strata.

Daily physical activities at home and work place were recorded using WHO Global Physical Activity Questionnaire (GPAQ).[10] To evaluate the intensity of physical activity, metabolic equivalent (MET) was used. MET is the use of energy in an adult individual while he/she is sitting (equivalent to 3.5 ml oxygen consumption per kg body weight in a

minute). Moderate physical activity is considered as consuming energy four times, and intense physical activity equal to or more than eight times in proportion to sitting. In other words, a combination of walking and other physical activities with at least 3000 METs per week was assigned to intense physical activity. Subjects with less than 1500 METs were regarded as low physical activity.

Anthropometric measurements were height (a tape stadiometer with a minimum measurement of 0.1 cm in a standing position, without shoes) and weight [light clothing without shoes measured by a calibrated standard weighing balance (Seca, model 707, Germany) with an accuracy of 100 g]. Laboratory measurements were blood pressure (measured in sitting position after at least 10 minutes at rest, if abnormal, was measured once again about one hour after the first measurement),[11] with standard manometer (RISHTER mercury manometer, Germany), fasting blood glucose (KIMIA Kit, code 890410, Iran), triglyceride (TG) (KIMIA Kit, code 890201, Iran), and total cholesterol (KIMIA Kit, code 890303, Iran). Cholesterol and TG values more than 200 mg/dl were considered as over normal values.[12] Depression was measured by a valid-translation of the 21-question BECK-BDI questionnaire,[13] and anxiety score was measured by a valid-translation of the 21-question BECK Anxiety questionnaire,[13] both conducted by a face to face interview. Both questionnaires had a score range of 0-63. For depression, score of more than 30 and for anxiety, score of more than 26 were identified as disease state. Opium addiction was defined according to DSM-IV criteria. A physician asked the participants to disclose whether they have ever used any type of drug. "Occasional users" were not dependent but irregularly used opium (mostly for entertainment) and "dependents" were regular opium consumers.[14,15]

All interviewers were trained before data collection and the validity of their collected data was checked by gold standards (chief researcher). Because the most of required information were objective and we used trained interviewers, we did not measure the agreement indices. However, strict quality control was performed during the study conduction to minimize any error. We tried to track all non-response households twice and replace participants who were not found at the end by their neighborhoods.

Continuous variables were reported as mean ± standard deviation (SD) and non-continuous variables as n (%). We did a survey analysis keeping household as primary sampling unit (clusters). People were assigned into three subgroups; having low, moderate and intense physical activity and the prevalence of different CAD risk factors was reported for every subgroup. Because of non-proportionate to size sampling method, the total estimates were standardized based on the real age distribution of the target population (national consensus of Kerman population size for 2006). We weighted the estimates by non-responses. We also assessed the correlations by applying chi-square test. A logistic regression model was applied to evaluate the relationship between the different levels of physical activity and other CAD risk factors. To control any potential confounders, we adjusted the estimates controlling for age, sex, smoking status, education, occupation and body mass. Using likelihood ratio test, we observed a statistically significant dominancy of the effect of categorical age variable ($P = 0.013$) and no trend effect of age as a continuous variable was found. All the statistical procedures were performed in Stata Statistical Software, Release 11.0 (Stata Corporation, College Station, TX, USA) under survey data analysis. $P < 0.05$ was considered as significant.

Results

This analysis was carried out on 5895 individuals including 2659 (45.1%) males and 3236 (54.9%) females with age of 45.4 ± 16.4 years.

About 42.1% (n = 2476) of the participants [confidence interval (95% CI) 40.3%-43.9%] had low physical activity. The most frequent (47.7%) and the least frequent low physical activity (36.8%) was observed among elderly people and those with 15-24 years of age respectively (Table 1). Physical activity decreased as age increased from 15 to 75 years ($P < 0.001$). Overall, the prevalence of intense physical activity was less than 20%.

Surprisingly, the level of physical activity was almost constant among people with different education status (36.2%-41.6%). In terms of occupation, the lowest physical activity was observed in unemployed people and housewives (49.7%). Women were less physically active compared to men (45.1% vs. 39.2%) ($P < 0.001$) (Table 2).

Individuals with low physical activity, had significantly higher rates of hypertension (11.4% vs. 10.1%, $P = 0.009$), obesity (15% vs. 11.5%, $P = 0.001$), occasional opium consumption (5.6% vs. 4.6%, $P = 0.001$), anxiety (79.1% vs. 76.1%, $P = 0.03$), depression (37% vs. 33.4%, $P = 0.01$) and hypertriglyceridemia (16% vs. 12.6%,

Table 1. The standardized prevalence of different levels of physical activities by age groups (total participants = 5895)

Age range (year)	The level of physical activity					
	Low (n = 2496)		Moderate (n = 2700)		Intense (n = 504)	
	Raw [n (%)]	Standardized % (95% CI)	Raw [n (%)]	Standardized % (95% CI)	Raw [n (%)]	Standardized % (95% CI)
15-24	309 (37.2)	36.8 (35.4-38.2)	374 (45.9)	45.7 (44.2-47.3)	129 (16.9)	17.5 (16.3-18.7)
25-34	493 (45.5)	45.4 (44.6-46.3)	476 (43.8)	43.3 (42.4-44.1)	104 (10.8)	11.3 (10.8-11.9)
35-44	478 (45.9)	46.4 (45.8-47.0)	473 (44.9)	43.3 (42.7-43.8)	100 (9.2)	10.3 (10.0-10.7)
45-54	522 (43.2)	43.7 (43.2-44.1)	593 (50.1)	48.7 (48.3-49.1)	83 (6.7)	7.6 (7.4-7.9)
55-64	441 (42.9)	42.7 (42.5-42.9)	516 (51.2)	51.2 (51.0-51.4)	60 (6.0)	6.1 (6.0-6.2)
65-75	253 (47.2)	47.7 (47.5-47.9)	268 (47.3)	47.1 (46.9-47.3)	28 (5.4)	5.2 (5.1-5.3)
Total	2496 (43.6)	42.1 (40.3-43.9)	2700 (47.5)	45.5 (43.6-47.4)	504 (8.9)	12.4 (11.1-13.9)

P < 0.001 for effect of age; 95% CI: Confidence interval
To reduce the number of rows in the table, age ranges were reported by divisions of 10-year

P = 0.004) compared to those with moderate and intense physical activities. Conversely, prevalence of dependent opium use (4.6% vs. 6.9%, P = 0.001) and hypercholesterolemia (27.2% vs. 31.4%, P < 0.001) among low physically active subjects were significantly lower than hyperactive individuals (Table 3).

After adjusting for sex, age, education, occupation, smoking status and body mass, low physical activity compared to intensive activity, increased the odds ratio (OR) of anxiety, hypertension, hypercholesterolemia, cigarette smoking, opium addiction and overweight/obesity to 1.39 (P = 0.01), 1.59 (P = 0.02), 1.37 (P = 0.02), 1.52 (P = 0.01), 1.47 (P = 0.02) and 1.34 (P = 0.02) respectively. In addition, we did not observe any significant adjusted odds ratios for diabetes/high FBG (OR 1.21; P = 0.3), depression (OR 1; P > 0.999) and hypertriglyceridemia (OR 1.35; P = 0.07) (Table 4).

Table 2. The prevalence of low physical activity in the participants by sex, education and occupation groups (total participants = 5895)

Variable	Number and prevalence of low physical activity [n (%)] 95% CI	P
Education		
Illiterate	420 (36.2) (28.9-44.3)	0.200
Less than Diploma	1715 (41.6) (39.5-43.8)	
More than Diploma	472 (41.4) (37.7-45.2)	
Occupation		
Unemployed, housewife	1638 (49.7) (42.9-56.5)	< 0.001
Employee	781 (35.4) (27.8-43.7)	
Soldier, student	176 (36.1) (31.6-40.9)	
Other jobs	12 (18.0) (12.7-24.7)	
Gender		
Male	1091 (39.2) (37.9-40.6)	< 0.001
Female	1518 (45.1) (43.8-46.4)	

95% CI: Confidence interval

Table 3. The prevalence confidence interval (95% CI) of coronary artery disease (CAD) risk factors among people with different physical activity levels (total participants = 5895)

Risk factor	Physical activity status (95% CI)		P
	Low [n (%)] 95% CI	Moderate and intense [n (%)] 95% CI	
Hypertension (n = 1333)	638 (11.4) (10.2-12.6)	695 (10.1) (9.3-11.1)	0.009
Obesity (n = 1048)	522 (15.0) (13.2-17.0)	526 (11.5) (10.3-12.9)	0.001
Occasional opium use* (n=366)	187 (5.6) (4.6-6.9)	179 (4.6) (3.8-5.6)	0.001
Dependent† (n = 484)	256 (6.9) (5.9-8.1)	228 (4.6) (3.9-5.4)	0.001
Smoking (n = 657)	322 (11.8) (10.2-13.6)	335 (8.6) (7.6-9.8)	0.002
Anxiety (n = 4531)	2051 (79.1) (76.6-81.5)	2480 (76.1) (74.0-78.1)	0.030
Depression (n = 2304)	1127 (37.0) (34.1-39.9)	1177 (33.4) (31.1-35.7)	0.010
Triglyceride > 200 mg/dl (n = 1119)	545 (16.0) (14.1-18.1)	574 (12.6) (11.4-14.0)	0.004
Cholesterol > 200 mg/dl (n = 2352)	1112 (31.4) (29.0-34.0)	1240 (27.2) (25.4-29.0)	< 0.001

*Occasional use: Irregularly used opium mostly for entertainment; †Dependent: Regularly consumed opium; 95% CI: Confidence interval

Discussion

The findings of this study showed that low physical activity was a widespread phenomenon, and almost half of the community did not have enough physical activity efficient to prevent coronary artery diseases and the corresponding risk factors. Physical activity decreased after the age of 15 years. Higher education had no positive association with physical activity.

Table 4. The association of physical activity with other coronary artery disease (CAD) risk factors (total participants = 5895)

Risk factor	The level of physical activity	Crude odds ratios		Adjusted odds ratios	
		Amount (P)	95% CI	Amount	95% CI
Blood glucose > 126 mg/dl or old diabetes	Intense	1	---	1.00	---
	Moderate	1.95 (< 0.001)	1.35-2.82	1.30	0.86-1.96
	Low	1.97 (< 0.001)	1.36-2.86	1.21	0.80-1.83
Depression	Intense	1	---	1.00	---
	Moderate	1.24 (0.070)	0.98-1.56	0.82	0.63-1.06
	Low	1.59 (< 0.001)	1.26-2.01	1.00	0.77-1.29
Anxiety	Intense	1	---	1.00	---
	Moderate	1.69 (< 0.001)	1.34-2.15	1.25	0.98-1.61
	Low	1.94 (< 0.001)	1.53-2.47	1.39	1.08-1.79
Hypertension	Intense	1	---	1.00	---
	Moderate	2.32 (< 0.001)	1.68-3.20	1.41	0.96-2.07
	Low	2.59 (< 0.001)	1.87-3.57	1.59	1.08-2.35
Triglyceride > 200 mg/dl	Intense	1	----	1.00	---
	Moderate	1.39 (0.030)	1.02-1.89	1.16	0.84-1.60
	Low	1.63 (0.002)	1.20-2.21	1.35	0.98-1.88
Cholesterol > 200 mg/dl	Intense	1	---	1.00	---
	Moderate	1.73 (< 0.001)	1.37-2.20	1.19	0.92-1.54
	Low	1.99 (< 0.001)	1.57-2.52	1.37	1.06-1.76
Smoking	Intense	1		1.00	
	Moderate	0.60 (< 0.001)	0.41-0.78	1.00	0.72(1.40)
	Low	0.81 (0.200)	0.60-1.11	1.52	1.09(2.11)
Addiction	Intense	1		1.00	
	Moderate	0.70 (0.020)	0.52-0.94	0.92	0.66-1.27
	Low	1.08 (0.600)	0.81-1.45	1.47	1.07-2.02
Overweight/obesity	Intense	1		1.00	
	Moderate	1.80 (< 0.001)	1.42-2.21	1.12	0.88-1.42
	Low	1.97 (< 0.001)	1.58-2.46	1.34	1.05-1.71

The odds ratios are adjusted based on sex, age, education, occupation, smoking status and body mass; 95% CI: Confidence interval

Housewives and unemployed individuals were significantly less physically active than the rest of the participants. Compared with moderate/intense physically active participants, the prevalence of hypertension, obesity, opium use, smoking, anxiety and depression were significantly higher in individuals with less physical activity. The level of TG and cholesterol were also higher in people with low physical activity. Low physical activity had a significant positive association with anxiety, high blood pressure, high level of cholesterol, cigarette smoking, opium use and overweight/obesity status.

Overall, we found 42.1% of adult population had low physical activity. In a study carried out by Bergman et al. on 1470 Swedish males and females, the prevalence of low physical activity was reported to be 37.1%.[16] In another study by Hallal et al. on 3128 individuals over 20 years in Brazil, the prevalence of low physical activity was 41.1%.[17] In another study in Tehran, the prevalence of low physical activity was estimated as 69.8%.[5] However they only measured exercise during non-working time. In a similar study in Yazd, Iran, on the population over 20 years of age, the prevalence of low physical activity was found to be 65.8%.[18] The existing difference in results could be ascribed to the different age range of the studied population, different questionnaire, and the different definitions of physical activity levels.[5,18,19] The results of the prevalence of low physical activity in this study are in line with the findings of the third national surveillance of risk factors of NCDs.[6]

We found the prevalence of low physical activity was higher in females than in males. In other studies such as the third national surveillance of risk factors of NCDs, the same result was attained.[2] This is mainly because the majority of women in our population were housewives, which led to reduced physical activity in comparison with men.

Among the age ranges, the highest and lowest rate of low physical activity belonged to the oldest and youngest groups respectively. In the age group of 15 to 24 years old which was expected to be the most active group, only 17.5% had intense physical activity. This is an important issue to be taken into account. This figure decreased by 6.5% among the next age group (25 to 34 years). Unfortunately, this measure was added to the low physical activity group (Table 1). The prevalence of low physical activity related to age has been shown in Yazd and other cities and countries as well.[16,18,20]

Many people mention busy life and long working hours as excuses for not being physically active. However, our results showed that unemployed people had a 49.7% low physical activity rate, which proved the busy life is not a reason for having low physical activity. Basically this attitude needs to change in a way that people do not consider physical activity as leisure, but more to improve their health and incorporate it in their daily life.

It is believed that there would be a decrease in the level of physical activity among people after their marriage. Considering the average marriage age (25-30 years) in Iran, one of the reasons for sudden rise in low physical activity after the age of 25 could be marriage.

It appears that the current national education system does not have much influence on people's attitude and performance on daily activities. People with high education level who have higher level of socio-economic status do not have more physical activity. This is a challenge and needs specific attention and intervention strategies.

In the present study, the depression and anxiety among the low physical activity group has been more than the moderate or intense ones. In the multivariate analysis, after adjusting the confounding variables, it was shown that low physical activity increased the odds of anxiety to 39%. This finding is in agreement with the positive effect of physical activity on reducing depression and anxiety found in other studies.[21-23] This can be due to the fact that exercising increases endorphin release in the brain. Endorphins have been proven to cause feelings of happiness.[24] On the other hand, anxiety increases sympathetic activity that may cause reduction of synovial blood flow because of sympathetic innervation and the presence of adrenergic receptors in the joint blood vessels.[25,26] Joint blood flow reduction may worsen the negative impact of low physical activity on the joints' health.

We observed a positive association between smoking and low physical activity. Mensink et al.[27] and Salimzadeh et al.[28] report have also verified such results. Low physical activity was also reported to be associated with hypertension, high cholesterol and high triglyceride.[29,30] We also observed such clustering among the other CAD risk factors and physical activity in our study.[14,31] It has been shown that opium in long term increases the risk of hypertension and causes reduction of plasma high density lipoprotein (HDL) cholesterol.[32]

Although univariate analyses showed significant associations between low physical activity and diabetes mellitus, depression and hypertriglyceridemia, controlling for potential

confounders did not show any relationship. It indicates that the observed effects of low physical activity are due to other factors such as sex, age, education, occupation, smoking status and body mass.

We acknowledge the limitation of our study as a cross-sectional survey. Beside, our study benefited from a relative large sample size, random sampling from a general population, high response rate (close to 95%) and including all aspects of physical activity and numerous risk factors including psychological status and opium addiction. For further studies, we recommend monitoring physical activity both at individual and community level by a longitudinal prospective cohort study. It is required to assess the efficacy of local and national intervention programs in managing and control of the epidemic of low physical activity.

Conclusion

The findings of this study showed that almost half of the population lack sufficient physical activity to effectively prevent coronary artery diseases and their risk factors. Low physical activity was associated with higher prevalence of unemployment, anxiety, smoking, opium use, and hyperlipidemia. Without effective and timely interventions, current risk profile would significantly increase the burden of cardiovascular diseases in this community in near future.

Acknowledgments

We would like to acknowledge Nadia Ghazanfari-Moghaddam for proof-reading of this manuscript and Dr. Maryam Shahrokhi from University of Illinois, USA, for editing of the Manuscript.

Conflict of Interests

Authors have no conflict of interests.

References

1. World Health Organization. Cardiovascular diseases (CVDs) [Online]. [cited 2011]; Available from: URL: http://www.who.int/mediacentre/factsheets/fs317/en
2. Fuster V, Kelly BB, Vedanthan R. Global cardiovascular health: urgent need for an intersectoral approach. J Am Coll Cardiol 2011; 58(12): 1208-10.
3. Naghavi M, Abolhassani F, Pourmalek F, Lakeh M, Jafari N, Vaseghi S, et al. The burden of disease and injury in Iran 2003. Popul Health Metr 2009; 7: 9.
4. World Health Organization. Physical activity [Online]. [cited 2012]; Available from: URL: http://www.who.int/topics/physical_activity/en
5. Momenan AA, Delshad M, Mirmiran P, Ghanbarian A, Azizi F. Leisure Time Physical Activity and Its Determinants among Adults in Tehran: Tehran Lipid and Glucose Study. Int J Prev Med 2011; 2(4): 243-51.
6. Esteghamati A, Khalilzadeh O, Rashidi A, Kamgar M, Meysamie A, Abbasi M. Physical activity in Iran: results of the third national surveillance of risk factors of non-communicable diseases (SuRFNCD-2007). J Phys Act Health 2011; 8(1): 27-35.
7. Statistical Center of Iran. National Census of Population and Housing of Iran [Online]. [cited 2011]; Available from: URL: http://www.amar.org.ir/Default.aspx?tabid=133. 2016.
8. Rashidy Pour A, Malek M, Eskandarian R, Ghorbani R. Prevalence of Obesity and Some Related Factors in 30-70 year-old Population of Semnan Province, Iran. J Isfahan Med Sch 2009; 10(1): 516-28. [In Persian].
9. Najafipour H, Mirzazadeh A, Haghdoost AA, Shadkam M, Afshari M, Moazenzadeh M, et al. Coronary Artery Disease Risk Factors in an Urban and Peri-urban Setting, Kerman, Southeastern Iran (KERCADR Study): Methodology and Preliminary Report. Iran J Public Health 2012; 41(9): 86-92.
10. World Health Organization. Cancer control: Knowledge into action: WHO guide for effective programmes. Geneva, Switzerland: World Health Organization; 2007.
11. Najafipour H, Nasri HR, Afshari M, Moazenzadeh M, Shokoohi M, Foroud A, et al. Hypertension: diagnosis, control status and its predictors in general population aged between 15 and 75 years: a community-based study in southeastern Iran. Int J Public Health 2014; 59(6): 999-1009.
12. Arnett DK, Jacobs DR Jr, Luepker RV, Blackburn H, Armstrong C, Claas SA. Twenty-year trends in serum cholesterol, hypercholesterolemia, and cholesterol medication use: the Minnesota Heart Survey, 1980-1982 to 2000-2002. Circulation 2005; 112(25): 3884-91.
13. Kaviani H, Mousavi S, Mohit A. Psychological Interviews and Tests. Tehran, Iran: Sana Publications; 2001. p. 169-79. [In Persian].
14. Najafipour H, Masoomi M, Shahesmaeili A, Haghdoost AA, Afshari M, Nasri HR, et al. Effects of opium consumption on coronary artery disease risk factors and oral health: Results of Kerman Coronary Artery Disease Risk factors Study a population-based survey on 5900 subjects aged 15-75 years. Int J Prev Med 2015; 6: 42.
15. Yousefzadeh G, Shokoohi M, Najafipour H, Eslami M, Salehi F. Association between opium use and metabolic syndrome among an urban population in Southern Iran: Results of the Kerman Coronary

Artery Disease Risk Factor Study (KERCADRS). ARYA Atheroscler 2015; 11(1): 14-20.
16. Bergman P, Grjibovski AM, Hagstromer M, Bauman A, Sjostrom M. Adherence to physical activity recommendations and the influence of socio-demographic correlates - a population-based cross-sectional study. BMC Public Health 2008; 8: 367.
17. Hallal PC, Victora CG, Wells JC, Lima RC. Physical inactivity: prevalence and associated variables in Brazilian adults. Med Sci Sports Exerc 2003; 35(11): 1894-900.
18. Motefaker M, Sadrbafghi SM, Rafiee M, Bahadorzadeh L, Namayandeh SM, Karimi M, et al. SuicEpidemiology of physical activity: a population based study in Yazd cityide attempt and its relation to stressors and supportive systems: a study in Karaj city. Tehran Univ Med J 2007; 65(4): 77-81. [In Persian].
19. Kelishadi R, Ghatrehsamani S, Hosseini M, Mirmoghtadaee P, Mansouri S, Poursafa P. Barriers to Physical Activity in a Population-based Sample of Children and Adolescents in Isfahan, Iran. Int J Prev Med 2010; 1(2): 131-7.
20. Sodergren M, Sundquist J, Johansson SE, Sundquist K. Physical activity, exercise and self-rated health: a population-based study from Sweden. BMC Public Health 2008; 8: 352.
21. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ 2006; 174(6): 801-9.
22. Peluso MA, Guerra de Andrade LH. Physical activity and mental health: the association between exercise and mood. Clinics (Sao Paulo) 2005; 60(1): 61-70.
23. Najafipour H, Banivaheb G, Sabahi A, Naderi N, Nasirian M, Mirzazadeh A. Prevalence of anxiety and depression symptoms and their relationship with other coronary artery disease risk factors: A population-based study on 5900 residents in Southeast Iran. Asian J Psychiatr 2016; 20: 55-60.
24. Strohle A. Physical activity, exercise, depression and anxiety disorders. J Neural Transm (Vienna) 2009; 116(6): 777-84.
25. Najafipour H, Ferrell WR. Sympathetic innervation and alpha-adrenoceptor profile of blood vessels in the posterior region of the rabbit knee joint. Br J Pharmacol 1993; 108(1): 79-84.
26. Najafipour H, Ferrell WR. Sympathetic innervation and beta-adrenoceptor profile of blood vessels in the posterior region of the rabbit knee joint. Exp Physiol 1993; 78(5): 625-37.
27. Mensink GB, Loose N, Oomen CM. Physical activity and its association with other lifestyle factors. Eur J Epidemiol 1997; 13(7): 771-8.
28. Salimzadeh H, Najafipour H, Mirzaiepour F, Navadeh S, Shadkam-Farrokhi M, Mirzazadeh A. Prevalence of active and passive smoking among adult population: findings of a population-based survey in Kerman (KERCADRS), Iran. Addict Health 2016; 8(1): 16-24.
29. Bassett DR, Jr., Fitzhugh EC, Crespo CJ, King GA, McLaughlin JE. Physical activity and ethnic differences in hypertension prevalence in the United States. Prev Med 2002; 34(2): 179-86.
30. Raitakari OT, Taimela S, Porkka KV, Telama R, Valimaki I, Akerblom HK, et al. Associations between physical activity and risk factors for coronary heart disease: the Cardiovascular Risk in Young Finns Study. Med Sci Sports Exerc 1997; 29(8): 1055-61.
31. Najafipour H, Yousefzadeh G, Forood A, Karamouzian M, Shadkam M, Mirzazadeh A. Overweight and obesity prevalence and its predictors in a general population: A community-based study in Kerman, Iran (Kerman coronary artery diseases risk factors studies). ARYA Atheroscler 2016; 12(1): 18-27.
32. Joukar S, Najafipour H, Malekpour-Afshar R, Mirzaeipour F, Nasri HR. The effect of passive opium smoking on cardiovascular indices of rabbits with normal and ischemic hearts. Open Cardiovasc Med J 2010; 4: 1-6.

How to cite this article: Najafipour H, Moazenzadeh M, Afshari M, Nasri HR, Khaksari M, Forood A, et al. **The prevalence of low physical activity in an urban population and its relationship with other cardiovascular risk factors: Findings of a community-based study (KERCADRS) in southeast of Iran.** ARYA Atheroscler 2016; 12(5): 212-9.

Relationship between metabolic syndrome and angiographic severity of coronary artery disease

Reza Miri[1], Amir Sajjadieh[2], Mohammad Parsamahjoob[1], Bahareh Hajibaratali[3], Masood Shekarchizadeh[4], Ali Asghar Kolahi[5], Mehran Sadeghi[6], Zahra Ahmadi[7], Hamedreza Farmanara[8], Mansoureh Shekarchizadeh-Esfahani[9]

Original Article

Abstract

BACKGROUND: There are a few literature data on the correlation between metabolic syndrome (MetS) and coronary disease among Iranian population. This study aimed to find relationship between MetS and severity of coronary artery disease (CAD) in presence of diabetes.

METHODS: Total of 192 patients were consecutively enrolled in the study who were admitted to coronary care unit because of acute coronary syndrome (ACS) and then underwent coronary angiography. MetS was defined by Iranian criteria. A coronary atherosclerosis score was used to quantify the extent of atherosclerotic involvement. The relationship between MetS and angiographic CAD severity or clinical presentation was compared between them after adjusting for diabetes.

RESULTS: Individuals with MetS (n = 125) had a higher prevalence of ST-elevation myocardial infarction (71% vs 30%, P < 0.001), multi-vessel disease (50% vs. 34%, P = 0.003), decreased ejection fraction (P = 0.001) and more severe angiographic stenosis based on both modified Gensini (P = 0.081) and syntax (P = 0.008) scores, compared to those without MetS. Syntax score showed statistically significant difference between two groups before (P = 0.021) and after adjustment for diabetes (P = 0.005).

CONCLUSION: MetS was related to the severity of CAD both clinically and by angiographic scores but diabetes was a challenging factor and may independently increase the severity of CAD.

Keywords: Metabolic Syndrome, Angiography, Severity, Coronary Artery Disease

Date of submission: 13 June 2015, ***Date of acceptance:*** 17 Aug 2016

Introduction

Metabolic syndrome (MetS) is considered as a major health problem in recent years and recognized by a cluster of risk factors related to diabetes and amplified risk of coronary artery disease (CAD).[1,2] Previous studies have shown that Asians have additional risk for development of MetS since the prevalence of abdominal obesity and diabetes are greater among them.[3] Despite important controversy, the increased risk of cardiovascular diseases in subjects suffering from MetS has been established.[4,5] Recent epidemiological and clinical studies have confirmed the association between MetS and increased risk of CAD,[6,7] which is the leading cause of mortality. Morbidity and mortality from CAD are greater in patients with MetS; consequently, early evaluation of the risk of CAD in patients with MetS is necessary since it could lead to

1- Associate Professor, Department of Cardiology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2- Associate Professor, Department of Cardiology, Isfahan University of Medical Sciences, Isfahan, Iran
3- Associate Professor, Department of Cardiology, Shahid Labbafinejad Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4- Internist, Fellow of Cardiology, Rajaei Cardiovascular Research Center AND Department of Cardiology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5- Associate Professor, Social Determinants of Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
6- Resident, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran
7- Resident, Department of Cardiology, Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
8- Resident, Department of Sports Medicine, Iran University of Medical Sciences, Tehran, Iran
9- Internist, Department of Internal Medicine, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Correspondence to: Masood Shekarchizadeh, Email: masoodshekarchi@sbmu.ac.ir

change in lifestyle behavior and reducing CAD risk factors. Diabetes is considered as one of the complications of obesity and a strong risk factor for CAD.[8-10] There is evidence that shows the duration of diabetes is associated with greater risk of acute coronary syndrome (ACS) and CAD.[11-14] So this study was conducted to evaluate whether MetS could be associated with the coronary artery disease severity and to see whether the severity of coronary lesion was different in MetS patients with or without type 2 diabetes.

Materials and Methods

This cross-sectional study was done from February 2012 to March 2015 in Shahid Beheshti University of Medical Sciences, Tehran, Iran. Totally 192 patients were enrolled in the study, who were admitted to coronary care unit (CCU) due to chest pain, and subsequently underwent coronary angiography. Patients entered the study after obtaining written informed consent. Positive family history of coronary artery disease, current smoker or ex-smoker, subjects with high low-density lipoprotein-cholesterol (LDL-C) (LDL level > 160 mg/dl and or under treatment for high LDL) and prior coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) were considered as exclusion criteria. Data on social, demographic, personal and family medical history, and lifestyle (physical activity, smoking, alcohol intake, and diet) were obtained from either physical and laboratory examinations (anthropometric testing, blood sample laboratory analysis, and blood pressure measurements) or questionnaires. Triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C) and fasting blood sugar (FBS) levels were measured by enzymatic methods (Pars Azmon commercial kits, Iran) based on previously published methods.[15]

Blood pressure was measured twice in sitting position after five minutes resting. Waist circumference was measured with a flexible tape placed on a horizontal plane at the level of the iliac crest as seen from the anterior view.[16]

Extent of coronary artery disease was assessed by modified Gensini and syntax scoring systems.

On quantitative analyses of coronary angiograms (Quantcor QCA, version 4.0; Pie Medical Imaging, Maastricht, The Netherlands), the presence of stenosis ≥ 50% in diameter of major epicardial vessels was characterized as CAD (Gensini score > 1).

The extent of CAD was quantified using the number of vessels with ≥ 50% stenosis and a coronary atherosclerosis score as mentioned below.[17,18]

The syntax score system used to show the severity of CAD quantitates the complexity and the extent of CAD to aid clinicians in assessing early and late outcomes of PCI and CABG in patients with multivessel CAD and has become the preferred risk assessment tool for grading lesion complexity.[19]

All statistical analyses were performed by SPSS (version 22.0, SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test and Q-Q plot were used to examine normality of data. Qualitative variables were expressed as numbers (percentages) and quantitative data was showed by mean and standard deviation (SD). Multiple logistic regression was used to compare the types of (ACS) and angiographic recommendations after adjustment for diabetes. P-values were considered significant at a level of < 0.05.

Results

Among 192 patients, 138 (71.9%) patients were male, and 125 (65%) patients fulfilled the criteria of MetS. Patients without MetS were significantly older than MetS group ($P < 0.001$). The prevalence of diabetes was 47%. Table 1 shows summary of clinical characteristics based on the presence of the MetS. Blood pressure, waist circumference, FBS, cholesterol (CHL), HDL-C, LDL-C, creatine phosphokinase-MB (CPK-MB) and troponin were significantly different in subjects with MetS compared to those free of MetS ($P < 0.001$). Table 2 shows among patients with MetS, low HDL-C (95%) was the most frequent component followed by increased waist circumference (82%), elevated FBS (76%), hypertension (HTN) (71%), and elevated TG (39%). The frequency of MetS components in all the subjects was as follows: Low HDL-C (80%), diabetes (70%), increased waist circumference (63%), HTN (50%), elevated TG (26%). Similar to the MetS group, low HDL-C was the most frequent finding (80%) in all the cases without MetS. Table 2 shows regardless of existing MetS, diabetic patients had significantly different Gensini scores ($P < 0.001$) and syntax scores ($P = 0.007$) compared to non-diabetic patients. Among hypertensive patients, only the syntax score was significantly different ($P = 0.030$) compared with normotensive patients while Gensini score ($P = 0.900$) showed no significant difference (data not shown).

Table 1. Demographic and biochemical parameters in the study patients

Variable	Total	MetS		P
		Yes	No	
Number	192	125 (65.0)	67 (35.0)	
Age				
Mean ± SD	65.00 ± 11.00	63.0 ± 11.00	68.00 ± 10.00	0.007†
Median (range)	63 (44.00-85.00)	61 (44.00-85.00)	70 (46.00-82.00)	
Diastolic blood pressure				
Mean ± SD	81.00 ± 13.00	84.0 ± 14.00	75.00 ± 9.00	0.001†
Median (range)	80 (40.00-140.00)	80 (40.00-140.00)	80 (60.00-90.00)	
Waist Circumference				
Mean ± SD	98.00 ± 11.00	102.0 ± 10.00	92.00 ± 9.00	< 0.001†
Median (range)	98 (71.00-123.00)	102 (71.00-123.00)	89 (79.00-113.00)	
CPK				
Mean ± SD	1156.00 ± 1342.00	1509.0 ± 1462.00	499 ± 721	< 0.001‡
Median (range)	642 (46.00-6400.00)	1222 (57.00-6400.00)	250 (46.00-2982.00)	
CPK-MB				
Mean ± SD	137.00 ± 154.00	170.0 ± 161.00	75.00 ± 117.00	< 0.001‡
Median (range)	67 (15.00-696.00)	121 (20.00-696.00)	36 (15.00-510.00)	
Troponin				
Mean ± SD	0.96 ± 0.93	1.2 ± 0.92	0.51 ± 0.78	< 0.001‡
Median (range)	0.87 (0.02-3.16)	1.17 (0.02-3.16)	0.03 (0.02-2.48)	
Fasting blood pressure				
Mean ± SD	136.00 ± 63.00	141.0 ± 61.00	126.00 ± 66.00	0.003‡
Median (range)	118 (60.00-370.00)	129 (60.00-369.00)	101 (72.00-370.00)	
TG				
Mean ± SD	129 ± 75	143.0 ± 85.00	101.00 ± 38.00	< 0.001‡
Median (range)	105 (57.00-511.00)	124 (57.00-511.00)	91 (60.00-189)	
HDL-C				
Mean ± SD	36.00 ± 7.00	34.0 ± 7.00	39.00 ± 7.00	< 0.001†
Median (range)	36 (21.00-52.00)	35 (21.00-52.00)	41 (23.00-49.00)	
LDL-C				
Mean ± SD	97.00 ± 33.00	102.0 ± 33.00	88.00 ± 29.00	0.005†
Median (range)	94 (11.00-208.00)	97 (29.00-208.00)	89 (11.00-124.00)	
Systolic blood pressure				
Mean ± SD	134.00 ± 28.00	141.0 ± 29.00	121.00 ± 22.00	<0.001†
Median (range)	130 (70.00-240.00)	140 (70.00-240.00)	120 (85.00-190.00)	
Cholesterol				
Mean ± SD	162 ± 33	166.0 ± 38.00	154.00 ± 22.00	0.015†
Median (range)	161 (90.00-280.00)	171 (98.00-280.00)	157 (90.00-183.00)	
Acute coronary artery disease				
STEMI [n (%)]	109 (56.8)	89 (71.2)	20 (29.9)	< 0.001*
Non STEMI [n (%)]	16 (8.3)	16 (12.8)	0 (0.0)	
USA [n (%)]	67 (34.9)	20 (16.0)	47 (70.1)	
Diabetes				
Yes [n (%)]	91 (47.4)	71 (56.8)	20 (29.9)	< 0.001*
No [n (%)]	101 (52.6)	54 (43.2)	47 (70.1)	
Sex				
Male [n (%)]	138 (71.9)	79 (63.2)	59 (88.1)	< 0.001*
Female [n (%)]	54 (28.1)	46 (36.8)	8 (11.9)	
Hypertension				
Yes [n (%)]	97 (50.5)	89 (71.2)	8 (11.9)	< 0.001*
No [n (%)]	95 (49.5)	36 (28.8)	59 (88.1)	

* Based on chi-square test; † Based on Student's t-test; ‡ Based on Mann-Whitney test

MetS: Metabolic syndrome; STEMI: ST-elevation myocardial infarction; CPK: Creatine phosphokinase; TG: Triglyceride; LDL-C: Low-density lipoprotein-cholesterol; HDL-C: High-density lipoprotein-cholesterol; USA: Unstable angina; SD: Standard deviation

Table 2. Relationship between metabolic syndrome and angiographic severity of coronary artery disease

Variable		Total	MetS		P	Model 1	Model 2
			Yes	No			
Gensini score	Mean ± SD	6.7 ± 2.8	7.1 ± 2.6	5.9 ± 2.9	0.004*	0.137£	0.081§
Syntax score	Mean ± SD	13.7 ± 7.7	14.9 ± 6.6	11.5 ± 8.9	0.008*	0.020£	0.005§
Ejection fraction	Mean ± SD	45.5 ± 8.7	44.6 ± 8.8	47.4 ± 8.4	0.032*	0.018£	0.002§
Angiographic results	SVD [n(%)]	26 (13.5)	10 (8.0)	16 (23.9)	< 0.001**	0.006£	0.003£
	2VD [n(%)]	77 (40.1)	53 (42.4)	24 (35.8)			
	3VD [n(%)]	85 (44.3)	62 (49.6)	23 (34.3)			
	LMS [n(%)]	4 (2.1)	0 (0.0)	4 (6.0)			
Medical treatment	Medical treatment [n(%)]	7 (3.6)	3 (2.4)	4 (6.0)	0.363**	0.101£	0.187£
	PCI [n(%)]	100 (52.1)	64 (51.2)	36 (53.7)			
	CABG [n(%)]	85 (44.3)	58 (46.4)	27 (40.3)			

Model 1: Adjusted for diabetes; Model 2: Adjusted for diabetes, age and sex; * Based on Student's t-test; ** Based on Fisher exact test; § Based on analysis of covariance; £ Based on multinomial logistic regression; MetS: Metabolic syndrome; SVD: Single-vessel disease; 2VD: Two-vessel disease; 3VD: Three-vessel disease; LMS: Left main stem; PCI: Percutaneous coronary angiography; CABG: Coronary artery bypass graft; SD: Standard deviation

ST-elevation myocardial infarction (STEMI) was more frequent in MetS group (P < 0.001). The frequency of multi-vessel disease was higher in patients with MetS compared to those without it (P < 0.001 and after adjustment P < 0.003).

However, syntax score showed statistically significant difference between two groups before (P = 0.008) and after adjustment for diabetes (P = 0.020) and age and sex (P = 0.005). Concerning the ejection fraction, the same result was observed after adjustment for diabetes status and age and sex (P = 0.032, P = 0.018, P = 0.002, respectively) (data not shown).

Discussion

This study showed significant relationship between MetS and CAD severity according to angiography documents in Iranian subjects. In addition, we showed that presence of diabetes has significant effect on the CAD severity among subjects with MetS.

Numerous studies have shown that MetS is able to predict cardiovascular events and diabetes, but there is argument about the role of MetS in cardiovascular risk among diabetic patients.[20-23] Yoon et al. showed there is no relationship between MetS and coronary atherosclerosis in diabetic subjects.[21] In addition, Sarrafzadegan et al. showed among symptomatic Korean population, MetS was independently associated with the presence and severity of CVD only in the non-diabetic subjects, and there was no significant difference between MetS group and non-MetS group regarding their age.[24]

Similar to our results, Solymoss et al. showed that MetS was significantly related to more severe coronary angiographic alterations and higher frequencies of unstable angina, myocardial infarction, PCI, and CABG.[18] Another important finding in our study was the 1.5 to 3 fold increased risk of new onset CVD in patients with MetS without diabetes.[14]

In our study, there was significant difference between modified Gensini score and syntax score. This comparison showed that patients with MetS had more severe atherosclerosis in coronary arteries by both scores.

After adjusting the effect of diabetes, syntax score was significantly associated with MetS, however the modified Gensini score did not have any significant association with MetS. Another important point is the effect of age. Patients without MetS were significantly older than other group; Gensini score had non-significant relationship with MetS whereas syntax score was significantly related to the MetS. So apparently modified Gensini score, which was used in this study, was a better predictor; also, the syntax score was more complete than modified Gensini score.[18]

The syntax index assigns a heavier weight to the more severe luminal narrowing. Weights are also assigned to each segment depending on vessel size and importance; segments serving larger regions of myocardium are more heavily weighted.[23-25] Another probable cause, as mentioned earlier, is a semantic argument about the effects of diabetes on metabolic syndrome, which might have affected our results.[23]

Also in MetS group, the patients had more multi-vessel disease and more acute events (STEMI versus unstable angina); although they were younger in comparison to MetS patients.

Conclusion

MetS is strongly related to the severity of ACS presentation, documented clinically and angiographically in younger subjects. As such, control of MetS components is necessary in Iranian population. We recommend more studies with more participants and multicenter design and evaluation of Iranian lifestyle and MetS components, also utilizing complete Gensini score and other angiographic scores with larger samples.

Acknowledgments

We would like to acknowledge the patients for their participation and staffs of CCU centers. We also thank Mrs. Ghodsi Najjari nurse of Imam Hossein Hospital CCU, Dr. Alireza Ebadi Associate Professor of Endocrinology, and Dr. Mehdi Yaseri, Assistant Professor of Biostatistics for their cooperation.

Conflict of Interests

Authors have no conflict of interests.

References

1. Timoteo AT, Mota Carmo M, Cruz Ferreira R. Does metabolic syndrome predict significant angiographic coronary artery disease? Rev Port Cardiol 2012; 31(12): 769-78.
2. Richelsen B, Pedersen SB. Associations between different anthropometric measurements of fatness and metabolic risk parameters in non-obese, healthy, middle-aged men. Int J Obes Relat Metab Disord 1995; 19(3): 169-74.
3. Koh KK, Han SH, Quon MJ. Inflammatory markers and the metabolic syndrome: insights from therapeutic interventions. J Am Coll Cardiol 2005; 46(11): 1978-85.
4. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991; 14(3): 173-94.
5. Lindsay RS, Howard BV. Cardiovascular risk associated with the metabolic syndrome. Curr Diab Rep 2004; 4(1): 63-8.
6. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988; 37(12): 1595-607.
7. St-Onge MP, Janssen I, Heymsfield SB. Metabolic syndrome in normal-weight Americans: new definition of the metabolically obese, normal-weight individual. Diabetes Care 2004; 27(9): 2222-8.
8. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. Diabetes 1998; 47(5): 699-713.
9. Conus F, Allison DB, Rabasa-Lhoret R, St-Onge M, St-Pierre DH, Tremblay-Lebeau A, et al. Metabolic and behavioral characteristics of metabolically obese but normal-weight women. J Clin Endocrinol Metab 2004; 89(10): 5013-20.
10. Yang RF, Liu XY, Lin Z, Zhang G. Correlation study on waist circumference-triglyceride (WT) index and coronary artery scores in patients with coronary heart disease. Eur Rev Med Pharmacol Sci 2015; 19(1): 113-8.
11. Srinivasan MP, Kamath PK, Bhat NM, Pai ND, Bhat RU, Shah TD, et al. Severity of coronary artery disease in type 2 diabetes mellitus: Does the timing matter? Indian Heart J 2016; 68(2): 158-63.
12. Talaei M, Sadeghi M, Marshall T, Thomas GN, Kabiri P, Hoseini S, et al. Impact of metabolic syndrome on ischemic heart disease-a prospective cohort study in an Iranian adult population: Isfahan Cohort Study. Nutr Metab Cardiovasc Dis 2012; 22(5): 434-41.
13. Kasai T, Miyauchi K, Kubota N, Tamura H, Kojima T, Yokoyama K, et al. The relationship between the metabolic syndrome defined by various criteria and the extent of coronary artery disease. Atherosclerosis 2008; 197(2): 944-50.
14. Kasper DL, Fauci AS, Hauser S, Longo D, Jameson L, Loscalzo J. Harrison's Principles of Internal Medicine. 19th ed. Philadelphia, PA: McGraw Hill Professional; 2015. p. 2449-54.
15. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. Lancet 2005; 366(9491): 1059-62.
16. Delavari A, Forouzanfar MH, Alikhani S, Sharifian A, Kelishadi R. First nationwide study of the prevalence of the metabolic syndrome and optimal cutoff points of waist circumference in the Middle East: the national survey of risk factors for noncommunicable diseases of Iran. Diabetes Care 2009; 32(6): 1092-7.
17. Gharipour M, Sadeghi M, Dianatkhah M, Bidmeshgi S, Ahmadi A, Tahri M, et al. The cut-off values of anthropometric indices for identifying subjects at risk for metabolic syndrome in Iranian elderly men. J Obes 2014; 2014: 907149.
18. Solymoss BC, Bourassa MG, Campeau L, Sniderman A, Marcil M, Lesperance J, et al. Effect of increasing metabolic syndrome score on atherosclerotic risk profile and coronary artery disease angiographic severity. Am J Cardiol 2004; 93(2): 159-64.
19. Mann DL, Zipes DP, Braunwald E, Libby P, Bonow RO. Braunwald's heart disease: A textbook of cardiovascular medicine. 10th ed. Philadelphia, PA: Elsevier/Saunders; 2015.
20. Gharipour M, Sadeghi MM, Sadeghi M, Farhmand N, Sadeghi PM. Detrimental predictive effect of

metabolic syndrome on postoperative complications in patients who undergoing coronary artery bypass grafting. Acta Biomed 2015; 86(1): 86-91.
21. Yoon SE, Ahn SG, Kim JY, Park JS, Shin JH, Tahk SJ, et al. Differential relationship between metabolic syndrome score and severity of coronary atherosclerosis as assessed by angiography in a non-diabetic and diabetic Korean population. J Korean Med Sci 2011; 26(7): 900-5.
22. Gensini GG. Coronary arteriography. Austin, TX: Futura Pub. Co; 1975. p. 261.
23. Ringqvist I, Fisher LD, Mock M, Davis KB, Wedel H, Chaitman BR, et al. Prognostic value of angiographic indices of coronary artery disease from the Coronary Artery Surgery Study (CASS). J Clin Invest 1983; 71(6): 1854-66.
24. Sarrafzadegan N, Gharipour M, Sadeghi M, NouriF, Asgary S, Zarfeshani S. Differences in the prevalence of metabolic syndrome in boys and girls based on various definitions. ARYA Atheroscler 2013; 9(1): 70-6.
25. Sadeghi M, Pourmand K, Sanei H, Heidari R, Talaei M. Which major atherosclerosis risk factors represents the extent of coronary artery disease? ARYA Atheroscler 2012; 7(Special Issue): 63-9.

How to cite this article: Miri R, Sajjadieh A, Parsamahjoob M, Hajibaratali B, Shekarchizadeh M, Kolahi AA, et al**. Relationship between metabolic syndrome and angiographic severity of coronary artery disease.** ARYA Atheroscler 2016; 12(5): 220-5.

Myocardial iron load measured by cardiac magnetic resonance imaging to evaluate cardiac systolic function in thalassemia

Masoumeh Kahnooji[(1)], Hamid Reza Rashidinejad[(2)], Mohammad Shahram Yazdanpanah[(3)], Nahid Azdaki[(4)], Ahmad Naghibzadeh-Tahami[(5)]

Original Article

Abstract

BACKGROUND: The assessment of cardiac iron overload in thalassemia major has been considered as an important predictive factor of heart injury. The magnetic resonance imaging (MRI)-derived relaxation time parameter (T2*) varies inversely with iron level, and elevated myocardial iron levels by T2* are associated with depressed left ventricular (LV) ejection fraction (EF). We compared echocardiographic (ECHO) indices of systolic function to myocardial T2* in these patients.

METHODS: A cross-sectional database review identified 200 consecutive patients with thalassemia who underwent both ECHO and MRI T2* assessment.

RESULTS: There was a negative correlation between T2* measurement and ECHO EF ($r = -0.389$, $P < 0.001$). Using a cutoff value of 50% for differentiating LV normal and abnormal function by ECHO, T2* MRI had a sensitivity of 57.1%, a specificity of 89.9%, and an accuracy of 86.5% for predicting LV dysfunction. Receiver operating characteristic analysis showed that cardiac iron measurement had an acceptable value for discriminating normal and abnormal LV function (area under the curve = 0.769, 95% confidence interval: 0.653-0.885). With respect to the relationship between serum ferritin level and cardiac iron value, the level of serum ferritin was positively correlated with the level of cardiac iron load ($r = 0.257$, $P < 0.001$).

CONCLUSION: Myocardial iron load assessed by MRI T2* is associated with deterioration of the LV function assessed by ECHO with a high specificity and moderate sensitivity. It is important to identify the thalassemic patients with a risk of iron overloaded cardiomyopathy and heart failure.

Keywords: Thalassemia, Iron Overload, Magnetic Resonance Imaging, Ferritin, Accuracy

Date of submission: 23 Jan 2016, ***Date of acceptance:*** 17 Aug 2016

Introduction

Anemia simultaneous with marrow expansion is main competing factor of cardiac injuries in thalassemia major. They can be an increase in cardiac outlet that lead to increasing of hearth function.[1,2]

Further, the cardiac iron sediment leads to decreasing hearth function in people with certain background.[3] Iron is too a risk factor for myocardium. Iron can be accumulate in cells as hemosiderin, ferritin. Free iron is the most toxic form that stimulates production of free radicals.[4,5] Furthermore, evaluation of cardiac iron overload as predictive factor of heart injury is important in thalassemia major. We have different way to evaluation of cardiac iron overload including measurement of plasma ferritin level, liver biopsy, cardiac echocardiographic (ECHO)-Doppler studies, and recently magnetic resonance imaging (MRI).[6]

MRI as a reliable, valid, and robust method can provide indirect assessment of cardiac iron overload.[7] Even, it has been advised to determination the degree of cardiac iron overload.[8] The reciprocals of T2 and T2*, known as R2 and R2*, are directly proportional to iron and demonstrate the most promising results.[9,10] In this

1- Assistant Professor, Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
2- Associate Professor, Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
3- Cardiologist, Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
4- Assistant Professor, Atherosclerosis and Coronary Artery Research Center, Academic Status, Birjand University of Medical Sciences, Birjand, Iran
5- PhD Candidate, Research Center for Modeling in Health, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
Correspondence to: Ahmad Naghibzadeh-Tahami, Email: anaghibzadeh61@gmail.com

method, the MRI-derived relaxation time parameter, T2*, changes inversely with iron level and thus elevated myocardial iron levels by T2* have been shown to be associated with depressed left ventricular ejection fraction (LVEF).[11,12]

Although this technique is progressively applied in different clinical settings and even prefers using ECHO, its diagnostic performance has been already unclear in thalassemia major patients. We therefore sought to directly compare echocardiographic indices of systolic function to myocardial T2* in these patients and determine the value of cardiac MRI for discriminating LV dysfunction measured basically by tissue Doppler ECHO.

Materials and Methods

In this analytical cross-sectional study, 200 patients with major thalassemia aged between 10 and 20 were selected from Samen Alhojaj Center (Charity Foundation for Special Diseases) by census method from August 2013 to November 2014. A retrospective database review identified 200 consecutive patients with thalassemia who underwent both ECHO done at Shifa Hospital in Kerman University of Medical Sciences, Iran, and MRI T2* assessment in a private center in Tehran, Iran.

Medical Center in Samen Alhojaj permission for a database and medical record review was granted by the Kerman University of Medical Sciences Committee on Clinical Investigation. This database included baseline characteristics of the patients as well as medical history, medications, and laboratory data of consecutively enrolled patients. All patients were prescribed chelation therapy with deferoxamine typically beginning before the age of 7 years. The conventional chelation treatment was subcutaneous infusion of deferoxamine in a daily dose 30-50 mg/kg, 5-6 times/week. Chelation therapy was monitored by frequent estimation of ferritin.

MRI examinations were routinely performed within 10 days of transfusion. MRI was performed 2 weeks after ECHO. MRI measurements were performed using a 1.5-T clinical MRI scanner.

Myocardial T2* was assessed from a single midpapillary ventricular short-axis slice using a cardiac-gated, segmented, multi ECHO gradient ECHO sequence obtained in a single breath-hold, as previously described.[11]

Iron in the myocardium was quantified by measuring T2* (1/R2*), an MR relaxation parameter that has been shown to vary inversely with tissue iron concentration.[12-14,15] The T2* values were calculated using custom written software developed in MATLAB (MathWorks Inc, Natick, MA).

Two-dimensional M-Mode and tissue Doppler imaging (TDI) (six segments of LV) was performed to assess LV function, conducted by Vivid 3 ECHO devices with 3 and 5 MHz probes. Systolic dysfunction was defined as mild if the EF was 41% to 50%, moderate if 31% to 40%, and severe if ≤ 30%.

Results were presented as mean ± standard deviation for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Correlation between the quantitative variables was examined using the Pearson's correlation coefficient test.

The diagnostic performance of MRI T2* according to the results of TDI was measured by the quantity of true positives, true negatives, false positives, and false negatives. In this regard, a cutoff point of 4 for 1/R2* (1-3 indicated normal value to moderate abnormal level and 4 or more indicated severe abnormal level) was measured by MRI T2*, and a cutoff 50% for differentiating LV normal and abnormal function by ECHO was considered. In the prediction system, the total prediction accuracy, sensitivity, and specificity were calculated.[16]

A receiver operating characteristic (ROC) curve was used to identify the best cutoff point, by which to maximize the sensitivity and specificity of discriminating LV normal and abnormal function. For the statistical analysis, the statistical software SPSS software for Windows (version 19.0, SPSS Inc., Chicago, IL, USA) was used. P values of 0.050 or less were considered statistically significant.

Results

A total of 200 patients (93 males, mean age of 17.87 ± 6.27 years) were identified with thalassemia undergoing both ECHO and MRI T2* assessment. The mean duration of transfusion was 16.66 ± 7.26 months with a mean pre-transfusion hemoglobin level of 9.18 ± 1.39 g/dl, and the average serum ferritin level was 3023.55 ± 2258.41 ng/ml (Table 1).

The mean LVEF was 56.59 ± 5.78% (ranged 35-65%) that 10.0% of patients had EF < 50%. Systolic function as measured by ECHO EF was classified as normal in 96 cases (48.0%), mild dysfunction in 94 cases (47.0%), and moderate dysfunction in 10 cases (5.0%).

There was a significant negative correlation between 1/R2* measurement and ECHO EF ($r = -0.389$, $P < 0.001$). Furthermore, with respect to the relationship between serum ferritin level and cardiac iron value, the level of serum ferritin was

positively correlated with the level of cardiac iron load (r = 0.257, P < 0.001).

Table 1. Baseline characteristics and clinical data of the study subjects (n = 200)*

Variables	N (%)
Gender (Male)	93 (46.50)
Age (year)	17.87 (6.27)
Family history of thalassemia	59 (29.50)
Duration of transfusion (mo)	16.66 (7.26)
Serum BUN	26.60 (9.26)
Serum creatinine	0.62 (0.16)
Serum hemoglobin	9.18 (1.39)
Serum ferritin	3023.55 (2258.41)
Serum platelet	295.27 (153.33)
Serum ALT level	61.72 (85.99)
Serum AST level	48.09 (46.63)
Serum ALP level	437.80 (225.75)
Serum T3 level	141.27 (103.51)
Serum TSH level	2.54 (1.39)

* For qualitative variables, relative and absolute frequencies, and for quantitative variables, mean and standard deviation were used to present the statistics.
AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase, TSH: Thyroid-stimulating hormone, BUN: Blood urea nitrogen

Only 7.0% of the patients had normal level of cardiac iron, 41.5% had mild abnormal value, and 36.0% had moderate abnormal value of cardiac iron. In this parallel, severe abnormal value of iron was observed in only 15.5% of them. Using a cutoff point of 4 for 1/R2* (1-3 indicated normal value to moderate abnormal level and 4 or more indicated severe abnormal level) measured by MRI T2* and a cutoff 50% for differentiating LV normal and abnormal function by ECHO, T2* MRI had the sensitivity of 57.1%, specificity of 89.9%, positive predictive value of 40.0%, negative predictive value of 94.7%, and accuracy of 86.5% for predicting LV dysfunction. In this study to evaluate LV function in patients, tissue Doppler method was compared to MRI. It was shown tissue Doppler sensitivity of 57.1%, specificity 89.9%, and positive predictive value 94.7%.

ROC analysis was used to explore the sensitivity and specificity of threshold values of T2* for ventricular dysfunction, and the results of this analysis are presented in figure 1. Cardiac iron measurement had an acceptable value for discriminating normal and abnormal LV function (area under the curve = 0.769, 95% confidence interval: 0.653-0.885).

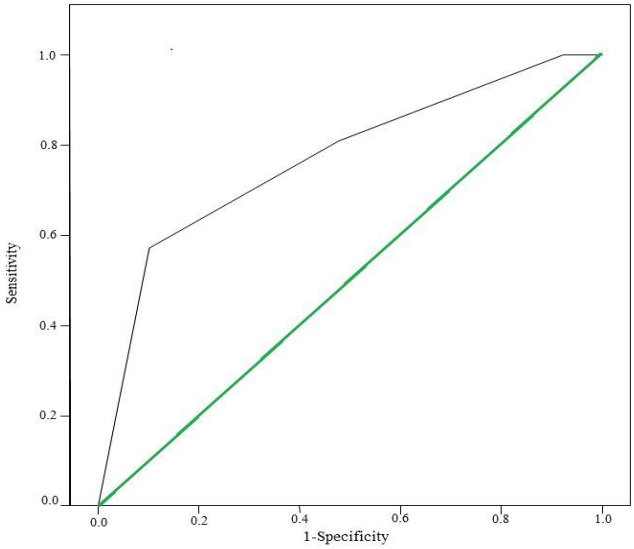


Figure 1. Receiver operator characteristic curves were constructed to investigate the diagnostic power of cardiac iron overload for predicting left ventricular dysfunction

Discussion

The present study assesses diagnostic performance of myocardial T2* measured by cardiac MRI compared with ECHO to predict LV systolic function. We could show a mild to moderate adverse correlation between increased myocardial iron as measured by T2* and LVEF measured by ECHO. In this context, MRI T2* had a high specificity but a moderate sensitivity to predict LV dysfunction. In the literature, there are some available ECHO studies evaluating cardiac systolic function as well as volumetric parameters in thalassemic patients; however, detection of myocardial iron overload as an applicable indicator of systolic function has been recently described. In support of our study, some other studies demonstrated that MRI findings can be a good predictor of future cardiac dysfunction.[17-19]

In addition, in a study by Liguori et al.,[20] relationship between myocardial T2* values and cardiac volumetric and functional parameters in β-thalassemia patients was evaluated by cardiac magnetic resonance in association with serum ferritin levels. In our study, myocardial iron loading was found in 93.0% of our patients that was higher than that reported in Caucasian populations.[21]

The mean LVEF of our study population was 56.0% that only 10.0% of them had EF < 50%. In fact, thalassemic patients have greater LVEFs than normal subjects.[5] These patients have impaired LV function at higher values of EF than previously

thought.[5,19] This factor is important in the interpretation of the impaired EF. This fact is the main reason to consider higher cutoff point value (50.0%) for discriminating normal and abnormal LV systolic function in this study.

Serum ferritin levels are used as a main diagnostic indicator for identifying and monitoring of iron overload. In our study, the level of serum ferritin was positively correlated with the level of cardiac iron load. Contrarily, some studies in the literature have shown that the relationship between the cardiac T2* value and the serum ferritin level is either non-significant or weak.[22] It is suggested that myocardial iron levels can be also predicted using this parameter but weaker than the measurement of cardiac iron level.

The presented data were analyzed retrospectively, which is a limitation of our study. In addition, for assessing LV systolic function, we did not assess other variables such as strain and strain rate that should be considered in future studies. The main strength of this study was its large sample size. As far as the author is aware, no study has been done with the large sample size and it seems that this is the first study with a larger sample size which possibility of the establishment of random relations to minimize and suggests that the results are real.

Conclusion

The current study demonstrates that myocardial iron load assessed by MRI T2* is mild to moderate associated with deterioration of the LV function assessed by ECHO with a moderate sensitivity and high specificity. It is important to identify the thalassemic patients with a risk of iron overloaded cardiomyopathy and heart failure.

Acknowledgments

This study was supported by the Kerman Charity Samen-Alhojaj. We wish to thank charity for their sincere cooperation.

Conflict of Interests

Authors have no conflict of interests.

References

1. Olivieri NF. The beta-thalassemias. N Engl J Med 1999; 341(2): 99-109.
2. Aessopos A, Farmakis D, Deftereos S, Tsironi M, Tassiopoulos S, Moyssakis I, et al. Thalassemia heart disease: a comparative evaluation of thalassemia major and thalassemia intermedia. Chest 2005; 127(5): 1523-30.
3. Walker JM. The heart in thalassemia. Eur Heart J 2002; 23(2): 102-5.
4. Hershko C, Link G, Cabantchik I. Pathophysiology of iron overload. Ann N Y Acad Sci 1998; 850: 191-201.
5. Pourmoghaddas A, Sanei H, Garakyaraghi M, Esteki-Ghashghaei F, Gharaati M. The relation between body iron store and ferritin, and coronary artery disease. ARYA Atheroscler 2014; 10(1): 32-6
6. Wood JC, Enriquez C, Ghugre N, Otto-Duessel M, Aguilar M, Nelson MD, et al. Physiology and pathophysiology of iron cardiomyopathy in thalassemia. Ann N Y Acad Sci 2005; 1054: 386-95.
7. Hazirolan T, Eldem G, Unal S, Akpinar B, Gumruk F, Alibek S, et al. Dual-echo TFE MRI for the assessment of myocardial iron overload in beta-thalassemia major patients. Diagn Interv Radiol 2010; 16(1): 59-62.
8. Bluemke DA, Liddell RP. Can MR imaging provide a noninvasive "biopsy" of the heart to measure iron levels? Radiology 2005; 234(3): 647-8.
9. Stark DD, Bass NM, Moss AA, Bacon BR, McKerrow JH, Cann CE, et al. Nuclear magnetic resonance imaging of experimentally induced liver disease. Radiology 1983; 148(3): 743-51.
10. Papakonstantinou O, Kostaridou S, Maris T, Gouliamos A, Premetis E, Kouloulias V, et al. Quantification of liver iron overload by T2 quantitative magnetic resonance imaging in thalassemia: impact of chronic hepatitis C on measurements. J Pediatr Hematol Oncol 1999; 21(2): 142-8.
11. Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J, et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. Circulation 2009; 120(20): 1961-8.
12. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J 2001; 22(23): 2171-9.
13. Westwood M, Anderson LJ, Firmin DN, Gatehouse PD, Charrier CC, Wonke B, et al. A single breath-hold multiecho T2* cardiovascular magnetic resonance technique for diagnosis of myocardial iron overload. J Magn Reson Imaging 2003; 18(1): 33-9.
14. Wood JC, Otto-Duessel M, Aguilar M, Nick H, Nelson MD, Coates TD, et al. Cardiac iron determines cardiac T2*, T2, and T1 in the gerbil model of iron cardiomyopathy. Circulation 2005; 112(4): 535-43.
15. Wood JC, Enriquez C, Ghugre N, Tyzka JM, Carson S, Nelson MD, et al. MRI R2 and R2* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia

and sickle cell disease patients. Blood 2005; 106(4): 1460-5.
16. Matthews BW. Comparison of the predicted and observed secondary structure of T4 phage lysozyme. Biochim Biophys Acta 1975; 405(2): 442-51.
17. Leonardi B, Margossian R, Colan SD, Powell AJ. Relationship of magnetic resonance imaging estimation of myocardial iron to left ventricular systolic and diastolic function in thalassemia. JACC Cardiovasc Imaging 2008; 1(5): 572-8.
18. Vogel M, Anderson LJ, Holden S, Deanfield JE, Pennell DJ, Walker JM. Tissue Doppler echocardiography in patients with thalassemia detects early myocardial dysfunction related to myocardial iron overload. Eur Heart J 2003; 24(1): 113-9.
19. Tanner MA, Galanello R, Dessi C, Smith GC, Westwood MA, Agus A, et al. Combined chelation therapy in thalassemia major for the treatment of severe myocardial siderosis with left ventricular dysfunction. J Cardiovasc Magn Reson 2008; 10: 12.
20. Liguori C, Pitocco F, Di Giampietro I, de Vivo AE, Schena E, Cianciulli P, et al. Relationship between myocardial T2 values and cardiac volumetric and functional parameters in beta-thalassemia patients evaluated by cardiac magnetic resonance in association with serum ferritin levels. Eur J Radiol 2013; 82(9): e441-e447.
21. Anderson LJ, Westwood MA, Holden S, Davis B, Prescott E, Wonke B, et al. Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. Br J Haematol 2004; 127(3): 348-55.
22. Wood JC, Tyszka JM, Carson S, Nelson MD, Coates TD. Myocardial iron loading in transfusion-dependent thalassemia and sickle cell disease. Blood 2004; 103(5): 1934-6.

How to cite this article: Kahnooji M, Rashidinejad HR, Yazdanpanah MS, Azdaki N, Naghibzadeh-Tahami A. **Myocardial iron load measured by cardiac magnetic resonance imaging to evaluate cardiac systolic function in thalassemia.** ARYA Atheroscler 2016; 12(5): 226-30.

Relationship between high-sensitivity C-reactive protein serum levels and the severity of coronary artery stenosis in patients with coronary artery disease

Seyed Masoud Seyedian[(1)], Farzaneh Ahmadi[(2)], Razieh Dabagh[(3)], Hannaneh Davoodzadeh[(4)]

Original Article

Abstract

BACKGROUND: High-sensitivity C-reactive protein (hs-CRP) inflammatory biomarker is one of the best informative markers of prognosis of coronary artery disease (CAD) that has been studied. Some studies have found that hs-CRP has a direct correlation with CAD. The aim of this study was to determine the relationship between serum levels of hs-CRP and the severity of coronary artery stenosis in patients with stable and unstable angina.

METHODS: In a cross-sectional study, 150 patients undergoing coronary angiography in Golestan Hospital Ahvaz, Iran in 2012, were studied in three groups of stable angina (n = 50), unstable angina (n = 50), and normal coronary angiography (n = 50). Hs-CRP levels were measured in patients before angiography by enzyme-linked immunosorbent assay method, were compared between the three groups and its correlation with the degree of stenosis was evaluated.

RESULTS: The mean levels of hs-CRP in the stable angina group, unstable angina group and the group with normal coronary angiography were 2.46 ± 1.79, 4.84 ± 3.38, and 2.95 ± 2.57 mg/L, respectively. The results show that the mean levels of hs-CRP in patients with unstable angina was significantly higher compared to patients with stable angina ($P < 0.050$) and patients with normal coronary angiography ($P < 0.001$). However, a statistical difference between the mean CRP levels in patients with stable angina and patients with normal angiography results was not seen ($P > 0.050$). A significant relationship between arterial stenosis points and hs-CRP levels in patients with stable angina was not seen ($P = 0.985$).

CONCLUSION: The findings suggest that it seems hs-CRP level in patients with unstable angina were significantly higher than those in patients with stable angina and patients with normal coronary angiography. It also appears that the level of hs-CRP in patients with unstable angina is associated with the severity of coronary stenosis. Given the finding of consistent results, the use of hs-CRP as a prognostic factor in these patients may be useful.

Keywords: Coronary Artery Disease, High-sensitivity C-reactive Protein, Stable Angina, Unstable Angina

Date of submission: 31 Aug 2014, ***Date of acceptance:*** 27 July 2016

Introduction

Coronary artery disease (CAD) is one of the leading causes of mortality in the world.[1,2] CAD is the most common form of cardiovascular disease with a prevalence of 6.9% in men and 6% in women. It is currently the leading cause of morbidity and mortality in people older than 38 years in Iran. Death from heart disease in this country ranges from 28% to 48%, and the incidence of ischemic heart disease is highly reported.[3] Studies show that risk factors for cardiovascular disease may differ in different societies. Even in cases where the relationship between these risk factors and CAD among different populations appears to be identical, the prevalence of these risk factors may differ, as the prevalence rate in Iran has been reported differently than in other countries.[4,5] Many risk factors for cardiovascular disease can be regulated by specific preventive measures.[6,7] These risk factors include smoking, dyslipidemia, hypertension,

1- Assistant Professor, Atherosclerosis Research Center AND Department of Cardiology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
2- Assistant Professor, Echocardiography Fellowship, Atherosclerosis Research Center AND Department of Cardiology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
3- Cardiologist, Atherosclerosis Research Center AND Department of Cardiology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
4- Clinical Research Development Unit, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz AND Department of Toxicology, Shahreza Branch, Islamic Azad University, Shahreza, Iran
Correspondence to: Farzaneh Ahmadi, Email: ahmadithc@yahoo.com

diabetes, abnormal obesity, lack of daily consumption of fruits and vegetables, regular alcohol consumption, and lack of regular physical activity.[8,9] Although other factors such as older age and male gender are listed as risk factors for CAD, these factors alone cannot predict the relative risk of the disease and the discovery of new markers may help identify patients at risk.[10,11] Because atherosclerosis is the main focus of CAD researchers, the study of the factors influencing the process of atherosclerosis is highly valuable. Fundamental research shows that inflammation is involved in all stages of the process of atherosclerosis[12,13] and is followed by clinical complications. Furthermore, inflammation is the main initiator of plaque formation and plays a role in incomplete endothelial function, plaque instability, and plaques rupture.[14,15] High-sensitivity C-reactive protein (hs-CRP) is one of the best studied inflammatory biomarkers in CAD.[16,17] Hs-CRP, a marker of systemic inflammation, rises in response to injury, infection, and other inflammatory stimuli.[18,19] Unlike other inflammatory phase reactants, serum hs-CRP remains high for a long time, even in the absence of stimuli.[20-22] Furthermore, a number of studies have shown a stable relationship between hs-CRP levels and an increased risk of cardiovascular events such as myocardial infarction and cardiovascular death.[23-26] However, the mechanisms responsible for the association between hs-CRP and cardiovascular disease remain unclear.[27] Although some studies have found that hs-CRP was poorly correlated with the severity of CAD, other studies have suggested a strong association between hs-CRP and the severity of stenosis.[28,29] On the other hand, less attention has been paid to the relationship between hs-CRP, the activation of plaque and the incidence of unstable angina, and warnings of hs-CRP for ischemic events. Therefore, the aim of this study was to determine the relationship between serum levels of hs-CRP and the severity of coronary artery stenosis in patients with stable and unstable angina.

Materials and Methods

A total of 150 patients undergoing coronary angiography participated in this cross-sectional study in Educational Governmental Golestan Hospital, Ahvaz city, Khuzestan, South West of Iran, in 2012. Among all of patient that visited during 2012, 150 patients (that have stable or unstable form of angina, without any inflammatory diseases or any immunosuppresses drug and have not any problem to test serum levels of hs-CRP) obtained randomly in this study. Written informed consent from all participants and approval from the Ethics Committee of the Medical University of Ahvaz was obtained. Patients with a history of infectious disease, connective tissue disease, acute myocardial infarction, heart failure, left ventricular ejection fraction < 30%, smoking, surgery 3 months before the study, and factors affecting the level of CRP were excluded from the study.

Questionnaires including questions about age, gender, history of hypertension, history of diabetes, and dyslipidemia were completed. The patients' blood pressure and pulse rate were measured while resting. The electrocardiogram was gathered from all patients. Furthermore, the level of white blood cells, blood sugar, triglycerides, cholesterol, and blood creatinine were each measured and recorded in Hospital Laboratory, glucose oxidase test, and cholesterol oxidase-peroxidase, respectively. Before angiography, 5 ml of venous blood sample was taken from fasting patients. The samples were transported to the laboratory, where hs-CRP levels were measured by enzyme-linked immunosorbent assay. Coronary angiography was performed by Judkins method. To determine the degree of stenosis genesis scoring was performed in which eight major coronary vessels including left main, left anterior descending, diagonal, first septal, left circumflex coronary artery, obtuse marginal, patent ductus arteriosus, and right coronary artery were studied. The degree of stenosis was reported on a scale from 0 to 4, with 0 meaning no narrowing, Grade 1 stenosis of < 50%, Grade 2 stenosis of 50-75%, Grade 3 stenosis of 75-99% and Grade 4 was considered as complete obstruction. Based on this method vessels can achieve a score of 0-32. Patients were divided into three groups of 50 persons that were enrolled consecutively: patients with stable angina who have angiographic lesions (Group I), patients with unstable angina who had angiographic lesions (Group II), and patients with stable or unstable angina who had normal coronary angiographies (Group III).

According to previous studies[28] and the formula, 150 patients entered in three groups. For describing data, the mean and standard deviation were used. The primary assumption of normality was checked using Kolmogorov–Smirnov test. The nonsignificant results of this test ($P = 0.198$, $P = 0.124$) suggesting no violation of the assumption of normality for hs-CRP and severity of coronary stenosis. Hence, both variables appear to

be reasonably normally distributed. The chi-square goodness of fit test was used to test whether all categories contain the same proportion of values. One-way analysis of variance (ANOVA) followed by Tukey multiple comparison tests was utilized to compare the means of hs-CRP and severity of coronary stenosis among the three groups. The relationship between hs-CRP level and arterial stenosis was investigated using Pearson product-moment correlation coefficients. Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 22.0; IBM Corp., Armonk, NY, USA). A statistically significant result is one in which the observed P value is < 0.05.

Results

Out of 150 patients examined in this study, 50 patients had unstable angina, 50 patients had stable angina, and 50 patients had normal angiograms. 61 of the participants were male and 89 were female. The mean age for male participants was 56.6 ± 10.6 and the mean age for female participants was 55.5 ± 12.4 years, which did not have a statistically significant difference ($P = 0.577$). In addition, 37.7% of men and 46.1% of women had hypertension, 32.8% of men and 34.8% of women suffered from dyslipidemia, and 29.5% of men and 40.4% of women had Type II diabetes, of which, none showed statistically significant differences ($P = 0.115$, $P = 0.468$ and $P = 0.198$, respectively) in three groups.

As shown in table 1, the male to female ratios were 0.28, 1.38, and 0.72 for normal angiography, stable angina, and unstable angina groups, respectively, where showed a statistically significant difference ($P < 0.001$).

The percentages of patients with hypertension were 34%, 42%, and 52% for normal angiography, stable angina, and unstable angina groups, respectively. The percentages of patients who suffered from dyslipidemia were 32%, 40%, and 30% in three groups, respectively. In normal angiography group, 24% had Type II diabetes. Moreover, 42% of patients in stable angina group and 36% of patients in unstable angina groups had Type II diabetes.

A chi-squared test was conducted to test whether three categories contain the same proportion of patients. The results indicated that there were not statistically significant differences between the proportion of patients with hypertension, dyslipidemia, and Type II diabetes in unstable angina, stable angina, and normal angiography groups ($P = 0.190$, $P = 0.536$, $P = 0.096$).

Furthermore, the mean hs-CRP level and vasoconstriction amount were evaluated based on gender, hypertension status, dyslipidemia and diabetes, of which hs-CRP levels and vasoconstriction amount only showed significant differences between the two gender groups. ($P < 0.001$) (Table 2).

Table 2 showed the mean and standard deviations for hs-CRP, and severity of coronary stenosis for patients in normal angiography, stable angina, and unstable angina groups. The results are presented as mean ± standard deviation (SD).

A one-way ANOVA was done to see whether there are significant differences between the mean of hs-CRP levels and severity of coronary stenosis among three groups. Primary assumption testing was conducted to check for normality and homogeneity of variance. The results showed that the two assumptions were met. The results of ANOVA test indicated a statistically significant difference in the mean of the CRP levels among three groups ($P < 0.001$). The results of Tuckey pairwise comparison tests showed that the mean of CRP level for unstable angina group was significantly higher than the other two groups ($P < 0.001$). However, the results did not show a statistically significant difference between the mean of hs-CRP levels in patients with stable angina and patients with normal angiograms ($P > 0.050$). The ANOVA test also revealed that there was not a statistically significant difference in the mean severity of coronary stenosis among the three groups. As depicted in table 2, the same results were obtained where the analysis was separately conducted on male and female patients.

Table 1. Patients' characteristics

Characteristics	Normal angiography	Stable angina	Unstable angina	Total	P
Number of patients	50	50	50	150	-
Male: female raito	0.28 (11.39)	1.38 (29.21)	0.72 (21.29)	0.68 (61.89)	< 0.001
Patients with hypertension (%)	17.00 (34.00)	21.00 (42.00)	26.00 (52.00)	64.00 (42.70)	0.190
Patients with dyslipidemia (%)	16.00 (32.00)	20.00 (40.00)	15.00 (30.00)	51.00 (34.00)	0.536
Patients with Type II diabetes (%)	12.00 (24.00)	21.00 (42.00)	18.00 (36.00)	51.00 (34.00)	0.096

Table 2. Comparison of high-sensitivity C-reactive protein (hs-CRP) and severity of coronary stenosis among normal angiography, stable angina and unstable angina groups

Variable	Normal angiography		Stable angina		Unstable angina		P
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	
hs-CRP level							
Male	11	3.09 ± 2.05	29	2.90 ± 2.14	11	6.25 ± 4.14	< 0.001
Female	39	2.91 ± 2.73	11	1.85 ± 0.84	29	3.82 ± 2.28	< 0.001
Total	50	2.95 ± 2.57	50	2.46 ± 1.79	50	4.84 ± 3.38	< 0.001
Severity of coronary stenosis							
Male	11	-	29	12.28 ± 4.90	11	10.05 ± 4.51	0.108
Female	39	-	11	8.95 ± 6.28	29	9.07 ± 4.47	0.939
Total	50	-	50	10.88 ± 5.70	50	9.48 ± 4.47	0.663

hs-CRP: High-sensitivity C-reactive protein; SD: Standard deviation

Furthermore, the mean hs-CRP level and vasoconstriction amount were evaluated based on gender, hypertension status, presence of dyslipidemia and diabetes, of which the mean of hs-CRP levels and vasoconstriction amount only showed significant differences between the two gender groups ($P < 0.001$).

The relationship between hs-CRP level and arterial stenosis was investigated using Pearson product-moment correlation coefficients. Preliminary analyses were performed to ensure no violation of the assumptions of normality and linearity. As shown in table 3, for unstable angina group, a correlation coefficient of 0.518 indicates that there was a significant moderate linear relationship between hs-CRP level and severity of arterial stenosis ($P < 0.001$). In addition, the correlation coefficient of 0.105 showed that there was not a significant linear relationship between hs-CRP level and arterial stenosis for stable angina group ($P = 0.958$).

Table 3. Correlations between high-sensitivity C-reactive protein (hs-CRP) level and arterial stenosis in stable angina and unstable angina groups

Variable	N	Correlation coefficient (r)	P
Stable angina			
Male	29	0.114	0.887
Female	21	0.101	0.960
Total	50	0.105	0.922
Unstable angina			
Male	21	0.531	< 0.001
Female	29	0.509	< 0.001
Total	50	0.518	< 0.001

hs-CRP: High-sensitivity C-reactive protein

Since this study was designed to determine, whether, an increase in one variable caused an increase in the value of a second variable it would seem logical to say that in unstable angina, severity of coronary stenosis is more likely to increase when hs-CRP increases.

Discussion

The previous studies suggest an association between serum hs-CRP levels and cardiovascular disease.[30-32] However, in these studies, the predictive potential of hs-CRP on cardiovascular events has been studied, but the degree of arterial stenosis or the relationship with arterial lesion type has not been vastly evaluated.[33-35] The results of this study suggest that hs-CRP levels in patients with coronary artery lesions and unstable angina were higher compared to patients with stable angina and patients with normal angiograms. A significant difference was not seen between the serum levels of hs-CRP in patients with stable angina and patients with normal coronary angiography. Although this statistical relationship was present in all CAD patients, later analysis showed that this relationship is simply due to the linear relationship between hs-CRP levels and vasoconstriction points in patients with unstable angina and this relationship was not seen in patients with stable angina. The results of previous studies are consistent with our findings. In 2011 in India, Masood et al. studied 80 patients in a similar study which also showed a statistically significant relationship between hs-CRP levels and the extent of vascular stenosis.[36] Furthermore, Assadpour Piranfar et al.,[37] in 2012, in a study titled evaluation of serum hs-CRP with the severity of vascular stenosis showed that levels of hs-CRP in patients with moderate and severe stenosis was significantly more than patients with mild stenosis. Consistent results were also found in a study of Luo[38] in 2010 in China. The results of their study also showed that there was a significant relationship between the serum levels of hs-CRP and severity of

coronary stenosis. In our study and the three previously mentioned, the relationship between serum hs-CRP levels and the severity of CAD was assessed using the Gensini score and comparison of the same variables with the same index in the above studies indicate the results of these studies are consistent. Another strength of this study was a large sample size compared to other studies. Moreover, patients were studied in three groups: patients with stable angina, patients with unstable angina, and patients with normal coronary angiographies. Furthermore, the mean hs-CRP level and vasoconstriction points were evaluated based on predisposing factors such as hypertension status, dyslipidemia, and diabetes. Similar studies with opposite or conflicting results are inevitable in the field of research therefore, some studies with conflicting results have also been found. For example, in a study by Avanzas et al.,[29] in 2004 in London, the relationship between hs-CRP levels and the severity of coronary stenosis showed that a significant relationship between arterial stenosis points and hs-CRP levels in patients with stable angina was not seen. Another study conducted in Iran by Kojouri et al.[27] in 2010 also suggest that a significant correlation between serum hs-CRP levels and the degree of stenosis in patients with stable angina was not seen. The lack of consistent results in different studies can be due to many reasons. One of these reasons can be the assessment of patients in different research communities or the genetic susceptibility of individuals. In this study, the mean serum hs-CRP level and arterial stenosis in male participants were higher than in female participants. In a study by Kojouri et al.,[27] mean serum hs-CRP levels in male participants with stable angina was higher than in female participants. The baseline hs-CRP is an important factor in the outcome of the research. The median hs-CRP level is 1.5-2.2 mg/dl.[39] But in our study, the overall mean hs-CRP level in patients was 2.84 ± 3.42, 2.95 ± 2.57 mg/l in the normal angiography group, 2.46 ± 1.79 mg/l in the stable angina group and 4.84 ± 3.38 mg/l in the unstable angina group, which shows the high biodiversity of hs-CRP. In this study, patients' medications, their habits and diet, level of physical activity, body mass index and body fat distribution was not considered. As these factors could also influence the results of the study, it is recommended that they be addressed in future studies. It seems hs-CRP level in patients with unstable angina were significantly higher than those in patients with stable angina and patients with normal coronary angiography. It also appears that the level of hs-CRP in patients with unstable angina is associated with the severity of coronary stenosis. Other studies with a larger volume of patients, consideration of contributing factors and multiple hs-CRP measurement is recommended.

Acknowledgments

This study is the result of thesis number d/534 from Ahvaz Jundishapour University of Medical Sciences. The authors would like to thank all colleagues who contributed to this study and the Golestan Clinical Research Development unit especially Ms. Caroline Kheradmand for English translation and editing of this paper.

Conflict of Interests

Authors have no conflict of interests.

References

1. Gupta S, Saxena SK, Lalchandani A, Chandra R, Gupta AC, Mishra MP. Significance of platelet volume indices in patients of coronary artery diseases (CAD) and acute myocardial infarction (mi): a new predictor for Ihd. Indian J Cardiolo 2012; 15(22-25).
2. Zheng L, Luo G, Zhang J, Mu Q, Shi Y, Berggren-Soderlund M, et al. Decreased activities of apolipoprotein m promoter are associated with the susceptibility to coronary artery diseases. Int J Med Sci 2014; 11(4): 365-72.
3. Vahedian Azimi A, Alhani F, Ahmadi F, Kazemnejad A. Effect of family-oriented empowerment model on the life style of myocardial infarction patients. Iran J Crit Care Nurs 2010; 2(4): 127-32.
4. Shibata R, Ouchi N, Kikuchi R, Takahashi R, Takeshita K, Kataoka Y, et al. Circulating omentin is associated with coronary artery disease in men. Atherosclerosis 2011; 219(2): 811-4.
5. Nesar Hosseini V, Taghipour M, Sharifian R, Hamta A, Feyzi S. Prevalence of coronary artery diseases risk factors in Sari-Iran (2005-10). J Gorgan Uni Med Sci 2013; 15(4): 96-100.
6. Carlsson AC, Wandell PE, Gigante B, Leander K, Hellenius ML, de Faire U. Seven modifiable lifestyle factors predict reduced risk for ischemic cardiovascular disease and all-cause mortality regardless of body mass index: a cohort study. Int J Cardiol 2013; 168(2): 946-52.
7. Wilson PW, D'Agostino R Sr, Bhatt DL, Eagle K, Pencina MJ, Smith SC, et al. An international model to predict recurrent cardiovascular disease. Am J Med 2012; 125(7): 695-703.

8. Keramati MR, Nezafati MH. Multivariate predictors of blood transfusion in patients undergoing coronary artery bypass graft in Mashhad, Iran. Iran Red Crescent Med J 2008; 10(2): 79-83.
9. Shemirani H, Separham KH. The relative impact of smoking or Hypertension on severity of premature coronary artery disease. Iran Red Crescent Med J 2007; 9(4): 177-81.
10. Sharoni E, Kogan A, Medalion B, Stamler A, Snir E, Porat E. Is gender an independent risk factor for coronary bypass grafting? Thorac Cardiovasc Surg 2009; 57(4): 204-8.
11. Trubnikova OA, Tarasova IV, Artamonova AI, Syrova ID, Barbarash OL. Age as a risk factor for cognitive impairments in patients undergoing coronary bypass. Neurosci Behav Physiol 2013; 43(1): 89-92.
12. Hansson GK, Hermansson A. The immune system in atherosclerosis. Nat Immunol 2011; 12(3): 204-12.
13. Libby P, Okamoto Y, Rocha VZ, Folco E. Inflammation in atherosclerosis: transition from theory to practice. Circ J 2010; 74(2): 213-20.
14. Cimmino G, Ragni M, Cirillo P, Petrillo G, Loffredo F, Chiariello M, et al. C-reactive protein induces expression of matrix metalloproteinase-9: a possible link between inflammation and plaque rupture. Int J Cardiol 2013; 168(2): 981-6.
15. Kals J, Kampus P, Kals M, Pulges A, Teesalu R, Zilmer K, et al. Inflammation and oxidative stress are associated differently with endothelial function and arterial stiffness in healthy subjects and in patients with atherosclerosis. Scand J Clin Lab Invest 2008; 68(7): 594-601.
16. Ghodke SS, Padalkar RK, Bhagat SS, Ghone RA, Patil SM. hs- CRP: A "golden marker" of inflammation and coronary artery disease. Int J Health Sci Res 2012; 2(6): 42-6.
17. Deshmukh A, Deshmukh A, G, Garg PK. Study of coronary artery disease risk factors and value of CRP in coronary risk determination in semi urban population of western U.P. India. Indian J Public Health Res Deve 2011; 2(1): 1-3.
18. Wilson AM, Ryan MC, Boyle AJ. The novel role of C-reactive protein in cardiovascular disease: risk marker or pathogen. Int J Cardiol 2006; 106(3): 291-7.
19. Biasucci LM, Koenig W, Mair J, Mueller C, Plebani M, Lindahl B, et al. How to use C-reactive protein in acute coronary care you have access. Eur Heart J 2013.
20. Zakynthinos E, Pappa N. Inflammatory biomarkers in coronary artery disease. J Cardiol 2009; 53(3): 317-33.
21. de Torres JP, Pinto-Plata V, Casanova C, Mullerova H, Cordoba-Lanus E, Muros de Fuentes M, et al. C-reactive protein levels and survival in patients with moderate to very severe COPD. Chest 2008; 133(6): 1336-43.
22. Rao AD, Milbrandt EB. To JUPITER and beyond: statins, inflammation, and primary prevention. Crit Care 2010; 14(3): 310.
23. Tiongco RH, Te CG, Punzalan FE, Gonda VM. High sensitivity CRP and short-term cardiovascular risk among patients with acute myocardial infarction: A two-center study. Acta Med Philipp 2012; 46(3): 64-8.
24. Choi JH, Cho DK, Song YB, Hahn JY, Choi S, Gwon HC, et al. Preoperative NT-proBNP and CRP predict perioperative major cardiovascular events in non-cardiac surgery. Heart 2010; 96(1): 56-62.
25. Salminen M, Kuoppamaki M, Vahlberg T, Raiha I, Irjala K, Kivela SL. Does high sensitive CRP improve cardiovascular risk prediction in metabolic syndrome among the aged? Scand Cardiovasc J 2013; 47(4): 210-6.
26. Kablak-Ziembicka A, Przewlocki T, Sokolowski A, Tracz W, Podolec P. Carotid intima-media thickness, hs-CRP and TNF-alpha are independently associated with cardiovascular event risk in patients with atherosclerotic occlusive disease. Atherosclerosis 2011; 214(1): 185-90.
27. Kojouri J, Karimi A, Pourafshar N, Vosoughi AR. Association between serum levels of hs-crp and ldl-c with degree of coronary artery stenosis in patients with stable angina pectoris. Iran Red Crescent Med J 2010; 12(4): 396-405.
28. Nyandak T, Gogna A, Bansal S, Deb M. High sensitive c-reactive protein (hs-CRP) and its correlation with angiographic severity of coronary artery disease (CAD). J Indian Acad Clin Med 2007; 8(3): 217-21.
29. Avanzas P, Arroyo-Espliguero R, Cosin-Sales J, Quiles J, Zouridakis E, Kaski JC. Multiple complex stenoses, high neutrophil count and C-reactive protein levels in patients with chronic stable angina. Atherosclerosis 2004; 175(1): 151-7.
30. Rensburg MA, Matsha T, Hoffmann M, Hassan MS, Erasmus RT. Distribution and association of hs-CRP with cardiovascular risk variables of metabolic syndrome in adolescent learners. Afr J Lab Med 2012; 1(1): 6.
31. Poon PY, Szeto CC, Kwan BC, Chow KM, Li PK. Relationship between CRP polymorphism and cardiovascular events in Chinese peritoneal dialysis patients. Clin J Am Soc Nephrol 2012; 7(2): 304-9.
32. May EB, Scirica B, Bonaca M, Murphy S, Braunwald E, Morrow D. Prognostic value of high-sensitivity CRP for cardiovascular outcomes in Tra 2°p-timi 50. J Am Coll Cardiol 2013; 61(Suppl): 1162-6.
33. Hamirani YS, Pandey S, Rivera JJ, Ndumele C, Budoff MJ, Blumenthal RS, et al. Markers of

inflammation and coronary artery calcification: a systematic review. Atherosclerosis 2008; 201(1): 1-7.
34. Khera A, de Lemos JA, Peshock RM, Lo HS, Stanek HG, Murphy SA, et al. Relationship between C-reactive protein and subclinical atherosclerosis: the Dallas Heart Study. Circulation 2006; 113(1): 38-43.
35. Kazemi-Bajestani SM, Ghayour-Mobarhan M, Ebrahimi M, Moohebati M, Esmaeili HA, Ferns GA. C-reactive protein associated with coronary artery disease in Iranian patients with angiographically defined coronary artery disease. Clin Lab 2007; 53(1-2): 49-56.
36. Masood A, Jafar SS, Akram Z. Serum high sensitivity C-reactive protein levels and the severity of coronary atherosclerosis assessed by angiographic gensini score. J Pak Med Assoc 2011; 61(4): 325-7.
37. Assadpour Piranfa M, Beyranvand M R, Fartookzadeh S, Valaei N. Relation between hs-CRP level and severity of coronary artery stenosis. Pajouhesh Dar Pezeshki 2012; 36(3): 139-42. [In Persian].
38. Luo JG. Relationship between serum IL-8 hsCRP, TNF-alpha and coronary lesions in CHD patients. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 2010; 26(8): 789-91.
39. Woloshin S, Schwartz LM. Distribution of C-reactive protein values in the United States. N Engl J Med 2005; 352(15): 1611-3.

How to cite this article: Seyedian SM, Ahmadi F, Dabagh R, Davoodzadeh H**. Relationship between high-sensitivity C-reactive protein serum levels and the severity of coronary artery stenosis in patients with coronary artery disease.** ARYA Atheroscler 2016; 12(5): 231-7.

Pentoxifylline and prevention of contrast-induced nephropathy: Is it efficient in patients with myocardial infarction undergoing coronary angioplasty?

Ali Eshraghi[(1)], Roya Naranji-Sani[(2)], Hourak Pourzand[(3)], Mohammad Vojdanparast[(4)], Negar Morovatfar[(5)], Javad Ramezani[(1)], Ramin Khamene-Bagheri[(1)], Pouya Nezafati[(6)]

Original Article

Abstract

BACKGROUND: Contrast-induced nephropathy (CIN) is a major concern following procedures with applying iodinated contrast media. The basis prevention of CIN is hydration and to avoid hypovolemia. We aimed to evaluate the efficacy of pentoxifylline (PTX) for the prevention of CIN in patients with myocardial infarction (MI) undergoing coronary angioplasty.

METHODS: This prospective, single-blind, randomized clinical trial study was performed on 175 (127 men) of MI patients undergoing routine treatment. Patients were assigned randomly to the control (n = 84) and study groups (n = 91). In our study group, patients received 400 mg/3 times a day from 24 hours before to 24 hours after coronary angiography. In addition, before the procedure and after 48 hours from the procedure, serum creatinine was measured.

RESULTS: CIN occurred in 14 patients (8.0%); 8 controls (9.5%) and 6 patients (6.6%) in the PTX group (P = 0.475) showing PTX to have no significant effect on CIN [P = 0.750, odds ratio = 0.82 (confidence interval = 0.24-2.8)] though a significantly different volume of contrast was used between the groups (231.29 ± 105.10 mm^3 and 190.88 ± 75.82 mm^3; P = 0.005, respectively).

CONCLUSION: There was no significantly different occurrence of CIN on patients with MI, undergoing coronary angioplasty, but its relatively lower rate in PTX group would recommend the prophylactic oral use of PTX for CIN prevention.

Keywords: Pentoxifylline, Myocardial Infarction, Contrast Media, Angioplasty, Nephropathy, Creatinine

Date of submission: 1 Jan 2016, ***Date of acceptance:*** 6 Aug 2016

Introduction

Coronary angioplasty as a non-surgical procedure is widely used in patients with known indications, and the contrast dye is used to guidewires through the vessels. A known side effect in performing this procedure occurs by means of contrast-induced nephropathy (CIN), which is the third leading cause of new onset renal failure in hospitalized patients. CIN is defined as a > 25% increase in baseline serum creatinine or > 0.5 mg/dl absolute increase in serum creatinine above baseline within 48 hours of exposure.[1] CIN is recognized as one of the complications of contrast media after coronary angiography and angioplasty.[1-4] Its incidence ranges from 2% to 50% in low- and high-risk populations, respectively.[5] Moreover, CIN incidence is 13% in non-diabetic patients and 20% in diabetics.[1]

Morbidity, mortality, length of hospitalization, and risk of progression toward end-stage renal disease are increased due to CIN. Dialysis is needed

1- Assistant Professor, Atherosclerosis Prevention Research Center AND Department of Cardiology, Imam Reza School of Medicine, Imam Reza Hospital, Mashhad, University of Medical Sciences, Mashhad, Iran
2- Resident, Department of Cardiology, Imam Reza School of Medicine, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
3- Associate Professor, Atherosclerosis Prevention Research Center AND Department of Cardiology, Imam Reza School of Medicine, Imam Reza Hospital, Mashhad, University of Medical Sciences, Mashhad, Iran
4- Cardiologist, Atherosclerosis Prevention Research Center, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
5- Assistant Professor, Imam Reza Clinical Research Units, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
6- General Practitioner, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medicine Sciences, Isfahan, Iran
Correspondence to: Hourak Pourzand, Email: pourzandh@mums.ac.ir

for about 1% of CIN patients and remains permanent in half of these patients.[1,5-9] There are some risk factors in developing this complication including, volume and type of contrast media, underlying diseases such as chronic kidney disease, diabetes mellitus, and congestive heart failure, and also individual factors such as sex, advanced age, anemia, and reduced effective circulation volume;[10] CIN pathophysiological mechanism is believed to be related to the changes in renal hemodynamics and damages on tubular cells caused by free radicals or direct toxic effect of the contrast media.[11]

A recent agent in preventing CIN is pentoxifylline (PTX), a methylxanthine derivative with multiple hematologic properties.[11] According to some of its anti-inflammatory properties, PTX is commonly used to treat peripheral vascular diseases. Furthermore, there is evidence that PTX reduces nitric oxide deterioration and scavenging of free radical. However, beneficial effects of PTX in CIN are not fully showed in trials, especially in patients undergoing angioplasty.

Spargias et al.[12] found that the parenteral use of PTX in patients with septic shock could reduce the serum levels of some inflammatory cytokines. Furthermore, plasma level of PTX peaks within 2-3 hours after drug ingestion and its oral absorption is nearly complete.

Due to the anti-inflammatory and antioxidant effects of PTX, we hypothesized that its oral administration before contrast media use might be effective in preventing CIN. The purpose of this study is to investigate the efficacy of PTX to prevent CIN in patients with myocardial infarction (MI) who are subjected for coronary angioplasty.

Materials and Methods

In view of other trials on risk of nephropathy and CIN prevention,[13] we calculated sample size of study as 87 in each group considering the significance level of 0.05 to evaluate the efficacy of PTX on prevention of CIN.

Patients with ST elevation MI and above 18 years of age who referred for emergency angioplasty to the Interventional Cardiology Department at Imam Reza Hospital, between October 2013 and July 2014, were enrolled into this study. All procedures were performed by a single interventional cardiologist.

Exclusion criteria were serum creatinine more than 1.5 mg/dl, heart failure, history of end-stage renal failure or being on dialysis, use of N-acetylcysteine, theophylline, aminoglycosides, and non-steroidal anti-inflammatory medicines, and intravenous contrast media administration within the last 2 days. Besides, patients with pulmonary edema, multiple myeloma, and uncontrolled hypertension were excluded from the study. This study protocol was approved by Ethics Committee of Mashhad University of Medical Sciences and conforms to the standards currently applied by the Iranian Registry of Clinical Trial (IRCT2014092819316N1). Written informed consent was obtained from all patients.

This was a prospective, single-blind, randomized clinical trial study. The patients were randomly allocated to treatment (PTX) or control group. Paraclinical tests were done in a single hospital laboratory, and laboratory personnel were blinded to the study protocol.

In this study, no placebo was administered for the control group. Similar routine preparation for angioplasty, including hydration with normal saline before and after the protocol, was received in both groups before and after the protocol.

Normal saline 1-1.5 cc/kg was administered from 6 hours before to 6 hours after procedure. PTX was administrated at a dose of 400 mg 3 times a day from referral day until 24 hours after the procedure in the treatment group.

Serum creatinine level was measured for both groups in referral time and after 48 hours of protocol. Serum creatinine was measured with Beckman Coulter SYNCHRON CX5® PRO Clinical System during study protocol.

Iso-osmolar nonionic contrast media iodixanol (Vesipaque 320, GE Healthcare, Cork, Ireland) was used for performing coronary angioplasties. Mehran et al.[14] introduced a risk prediction score for the development of CIN which we used this to predict the risk of CIN in all patients. Our primary end point was considered as either a minimum of 0.5 mg/dl or 25% increase in serum creatinine above the baseline, 48 hours after exposure to contrast media, which we defined as the occurrence of CIN.

The data were analyzed using SPSS software for Windows (version 16, SPSS Inc., Chicago, IL, USA). Normality distribution of quantitative data was checked by Kolmogorov–Smirnov test. Continuous data were expressed as mean ± standard deviation. The Chi-square test was applied for comparison of qualitative data between the two groups. Quantitative data were checked if normality distributed in each group using the Kolmogorov–Smirnov test. Then, the independent sample t-test or Mann–Whitney U-test was applied for comparison of data between the two

groups. Logistic regression was used to control of effect of sex, age, history of hypertension, smoking, diabetes history, and contrast volume on CIN occurrence. All significance tests were two-tailed. $P < 0.050$ considered as significant level.

Results

In this study, we recruited a total of 175 patients (127 men and 48 women); 91 patients received PTX, and 84 were in the control group (Figure 1). The demographic data and some paraclinical characteristics are presented in table 1. Besides the history of hypertension and the level of hematocrit which were significantly higher in the PTX group than control group (52% vs. 32%; P = 0.020, 43.0 ± 6.7 vs. 41.0 ± 6.6; P = 0.020, respectively), no significant difference was found between the two groups regarding age, sex, body mass index, and biochemical markers including high-density lipoprotein, low-density lipoprotein, and triglyceride.

Vesipaque was the type of contrast media used both in the control and PTX groups.

Statistical analysis showed that there was a significant difference between volume of contrast used (P = 0.005). We found that CIN occurred in 14 patients (8%); 8 controls (9.5%) and 6 patients (6.6%) in the PTX group, which was not significantly different between the two groups (P = 0.475) (Table 1).

Regression analysis by backward method with CIN as dependent variable and sex, age, history of hypertension, smoking, diabetes history, and contrast volume as independent variables showed that none of them had significant independent effects on CIN occurrence across the two groups of study. Mean level of hematocrit had nearly significance effect [P = 0.051, odds ratio (OR) = 0.92 (confidence interval (CI) = 0.85-1.00)]. Moreover, the use of PTX had no significant effect on CIN occurrence [P = 0.750, OR = 0.82 (CI = 0.24-2.8)] (Table 2).

Our studied patients did not require any renal replacement therapy; moreover, there was not any hospital mortality in the control and PTX groups.

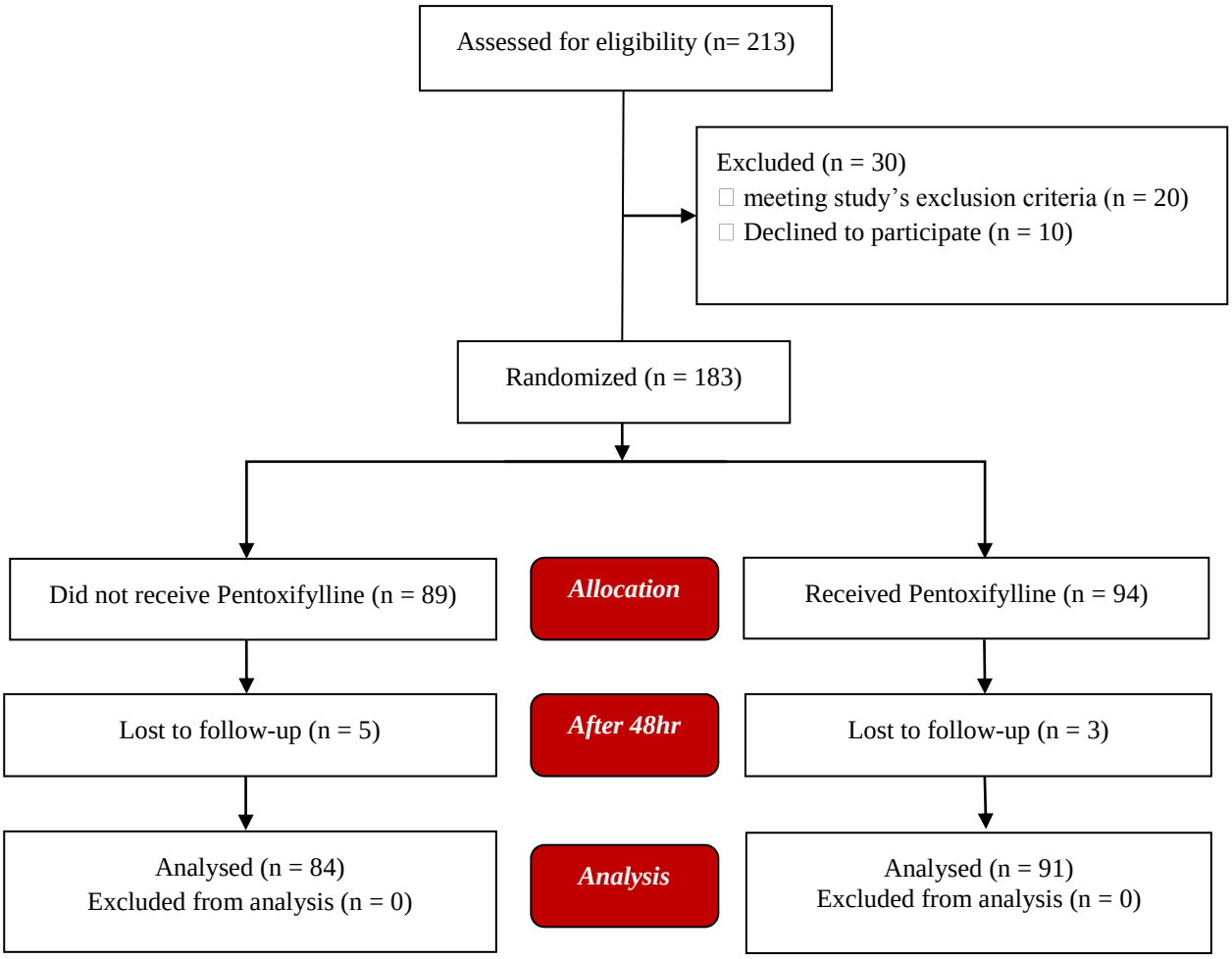


Figure 1. Flowchart of the study

Table 1. Demographic, clinical, and laboratory data of patients in the two groups

Variables	Control group (n = 84)	PTX group (n = 91)	P
Age (mean ± SD)	57.90 ± 14.27	60.46 ± 14.03	0.270
Height (cm) (mean ± SD)	165.00 ± 15.10	167.38 ± 8.70	0.679
Weight (kg) (mean ± SD)	71.72 ± 15.61	72.53 ± 13.87	0.233
BMI (kg/m^2) (mean ± SD)	25.06 ± 3.13	25.35 ± 5.25	0.726
Hematocrit(mean ± SD)	42.75 ± 6.70	41.33 ± 6.60	0.020
Hemoglobin (mean ± SD)	14.25 ± 1.83	13.60 ± 2.34	0.051
HDL (mean ± SD)	37.43 ± 13.76	40.25 ± 26.01	0.430
LDL (mean ± SD)	113.20 ± 44.10	113.20 ± 39.42	0.997
TG (mean ± SD)	127.90 ± 78.37	113.10 ± 59.08	0.216
Volume of contrast use mm^3 (mean ± SD)	231.29 ± 105.10	190.88 ± 75.82	0.005
Baseline creatinine (mg/dl) (mean ± SD)	1.12 ±0.26	1.147 ±0.424	0.670
Creatinine after procedure (mg/dl) (mean ± SD)	1.21 ± 0.36	1.214 ± 0.425	0.990
Difference in creatinine (mg/dl) (mean ± SD)	0.09 ± 0.02	0.066 ± 0.011	0.380
Sex (male) [n (%)]	66 (79.0)	61 (67.0)	0.087
Diabetes [n (%)]	29 (35.0)	41 (45.0)	0.076
Hypertension [n (%)]	27 (32.0)	47 (52.0)	0.024
Incidence of CIN [n (%)]	8 (9.5)	6 (6.6)	0.475

BMI: Body mass index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride; CIN: Contrast-induced nephropathy; PTX: Pentoxifylline; SD: Standard deviation

Table 2. Regression analysis showing the effect of multiple variables on contrast-induced nephropathy CIN) occurrence after administrating pentoxifylline (PTX)

Variables	OR (95% CI)	P
Sex	0.695 (0.19-2.59)	0.588
Age	1.019 (0.98-1.07)	0.399
Hypertension	0.586 (0.18-1.96)	0.386
Diabetes history	0.830 (0.17-4.00)	0.817
Hematocrit	0.924 (0.85-1.00)	0.051
Smoking	1.437 (0.33-6.26)	0.629
Baseline creatinine	0.304 (0.042-2.19)	0.237
Volume of contrast use	1.005 (0.99-1.01)	0.083
PTX use	0.822 (0.24-2.78)	0.750

OR: Odds ratio; CI: Confidence interval; PTX: Pentoxifylline

Discussion

The key finding of this study is that although CIN occurrence was shown to be less in the group with prophylactic oral PTX, this reduction was not significantly different (P = 0.475). There is not any animal study about the preventive effect of PTX in CIN. However, there is only one clinical study about this preventive effect by Firouzi et al. in 2012.[15] Similarly, they also found that PTX could reduce, though not significantly, the occurrence of CIN in patients undergoing angioplasty.

Our study was single blind, and laboratory staffs that measured the serum creatinine were blinded to the treatment status of the patients. Our patients' demographic data and baseline risk factors for CIN were similar in the two groups, except for the significantly higher prevalence of hypertension and hematocrit in the PTX group. There was a significant difference in volume of Vesipaque between control and PTX group; however, this was not correlated significantly with the occurrence of CIN which could be the result of selecting patients with normal renal function in this study.

Busch et al.[5] revealed that the incidence of CIN is significantly lower in low-risk population after coronary angioplasty, and as we excluded patients with creatinine level of more than 1.5 mg/dl, the low incidence of CIN in both groups was predictable. Moreover, we reported the overall incidence of CIN in the control group to be 9.5%. This was recorded 13.69% in Firouzi et al. study,[15] which was comparable to the reported incidence of CIN in unselected populations.[1]

Prophylactic oral administration of PTX showed a trend toward non-significant reduction of CIN occurrence (8 patients in control and 6 patients in PTX group). However, our two groups were not exactly comparable with each other, and after performing the logistic regression analysis, the PTX independent role in reducing CIN was found to be not significant (P = 0.750).

In our study, low rate of CIN in both groups and a non-significant difference between the groups could be due to the selection of low-to-moderate risk patients and excluding patients at higher risk. Hence, it is possible that the selection of patients

with higher risk would have shown the efficacy of PTX more prominently. In addition, adding PTX to N-acetylcysteine and its synergistic effects in preventing CIN could also be tested which might reduce the probability of CIN.

Conclusion

The authors recommend that oral administration of PTX in patients with myocardial infarction and low-to-moderate risk of CIN undergoing coronary angioplasty has a non-significant reduction effect on CIN. Performing larger trials in higher risk patients is suggested to determine the probable protective role of PTX.

Acknowledgments

The authors would like to thank all participating patients for their cooperation and for their permission to publish this article.

Conflict of Interests

Authors have no conflict of interests.

References

1. McCullough P. Renal complications of contrast media. In: King SB 3rd, Yeung AC, Editors. Interventional Cardiology. New York, NY: McGrawHill Medical; 2007.
2. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997; 103(5): 368-75.
3. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002; 105(19): 2259-64.
4. Best PJ, Lennon R, Ting HH, Bell MR, Rihal CS, Holmes DR, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol 2002; 39(7): 1113-9.
5. Busch SV, Jensen SE, Rosenberg J, Gogenur I. Prevention of contrast-induced nephropathy in STEMI patients undergoing primary percutaneous coronary intervention: a systematic review. J Interv Cardiol 2013; 26(1): 97-105.
6. Pyxaras SA, Sinagra G, Mangiacapra F, Perkan A, Di Serafino L, Vitrella G, et al. Contrast-induced nephropathy in patients undergoing primary percutaneous coronary intervention without acute left ventricular ejection fraction impairment. Am Cardiol 2013; 111(5): 684-8.
7. Chiou YL, Shieh JJ, Lin CY. Blocking of Akt/NF-kappaB signaling by pentoxifylline inhibits platelet-derived growth factor-stimulated proliferation in Brown Norway rat airway smooth muscle cells. Pediatr Res 2006; 60(6): 657-62.
8. Yavari V, Ostovan MA, Kojuri J, Afshariani R, Hamidian Jahromi A, Roozbeh J, et al. The preventive effect of pentoxifylline on contrast-induced nephropathy: a randomized clinical trial. Int Urol Nephrol 2014; 46(1): 41-6.
9. Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. Ann Intern Med 2008; 148(4): 284-94.
10. Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, et al. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. JAMA 2008; 300(9): 1038-46.
11. Roozbeh J, Hamidian Jahromi A, Sharifian M, Pakfetrat M, Afshariani R. Protective effect of pentoxifylline on contrast induced nephropathy. Saudi J Kidney Dis Transpl 2008; 19(6): 985-6.
12. Spargias K, Alexopoulos E, Kyrzopoulos S, Iokovis P, Greenwood DC, Manginas A, et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. Circulation 2004; 110(18): 2837-42.
13. Zhang J, Fu X, Jia X, Fan X, Gu X, Li S, et al. B-type natriuretic peptide for prevention of contrast-induced nephropathy in patients with heart failure undergoing primary percutaneous coronary intervention. Acta Radiol 2010; 51(6): 641-8.
14. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 2004; 44(7): 1393-9.
15. Firouzi A, Eshraghi A, Shakerian F, Sanati HR, Salehi N, Zahedmehr A, et al. Efficacy of pentoxifylline in prevention of contrast-induced nephropathy in angioplasty patients. Int Urol Nephrol 2012; 44(4): 1145-9.

How to cite this article: Eshraghi A, Naranji-Sani R, Pourzand H, Vojdanparast M, Morovatfar N, Ramezani J, et al. **Pentoxifylline and prevention of contrast-induced nephropathy: Is it efficient in patients with myocardial infarction undergoing coronary angioplasty?** ARYA Atheroscler 2016; 12(5): 238-42.

Echocardiographic characteristics of isolated left ventricular noncompaction

Afsoon Fazlinezhad[(1)], Mohammad Vojdanparast[(2)], Shadi Sarafan[(3)], Pouya Nezafati[(4)]

Case Series

Abstract

BACKGROUND: Although isolated left ventricular noncompaction (ILVNC) has been described almost two decades ago, our knowledge about its diagnosis, presentation, echocardiographic features and clinical outcome is sparse. We aimed to assess the echocardiographic and clinical characteristics of ILVNC in a group of patients referred to our center.

METHODS: Patients who were referred to a tertiary referral center, affiliated with Mashhad University of Medical Sciences, with primary diagnosis of dilated cardiomyopathy underwent comprehensive echocardiographic evaluation. The diagnosis of ILVNC was made based on the presence of two-structural layer in myocardium; ratio of noncompacted to compacted layers more than 2, and excessive trabeculation in the left ventricle.

RESULTS: Final diagnoses of ILVNC were made in 42 patients. Mean age of patients was 32.9 ± 15.6 years (ranging from 9 to 70 years). Females comprised a higher proportion of patients (61.9%) and shortness of breath was the most reported symptom among patients (47.6%). Non-compacted layers were detected in inferior and lateral segments of apex in 97.6% of patients. A total of 26 (61.9%) patients had left ventricle (LV) dysfunction (defined as ejection fraction less than 50%). The only factor that showed significant association with LV dysfunction was the number of affected segments with noncompaction (P = 0.008). Reduced ejection fraction was not associated with either age or sex (P = 0.437 and P = 0.206, respectively).

CONCLUSION: Based on the result of the current study, it can be suggested that apex of the heart is the most common site of noncompaction and increasing numbers of affected segments might be associated with LV dysfunction.

Keywords: Isolated Left Ventricular Noncompaction, Characteristic, Echocardiography

Date of submission: 10 Nov 2015, ***Date of acceptance:*** 25 Apr 2016

Introduction

Left ventricular noncompaction (LVNC) is described as the presence of pronounce trabeculation and deep intertrabecular recesses communicating with the ventricular cavity.[1,2] Histopathologic findings of isolated LVNC (ILVNC), obtained intra vitam by endocardial biopsy or postmortem are nonspecific. Either they are reported as normal or as subendocardial fibrosis/fibroelastosis, myocardial fibrosis, myocardial disorganization, myocardial hypertrophy and degeneration, scarring of the myocardium, or signs of inflammation.[3] This phenomenon was initially considered as a concomitant pathology occurring along with other congenital heart abnormalities such as pulmonary and aortic atresia, and ventricular septal defects.[3-5] Therefore, ILVNC, in the absence of other cardiac anomalies, was thought to be very rare and the prevalence of the isolated form has been reported to be as low as 0.3% in the adult population.[6] It appears that ILVNC is a morphologic abnormality with genetic heterogeneity, which involves the mutation of G4.5 gene encoding a protein. In recent decades, owing to the availability of modern imaging modalities, ILVNC has been visualized by computed tomography and magnetic resonance imaging in addition to echocardiography.[4] However, echocardiography is the most commonly used imaging modality for the diagnosis of LVNC. It has been postulated that the malformation is caused by intrauterine arrest of physiologic processes involved in the morphogenesis of myocardium that leads to an alteration of myocardial wall.[7,8]

1- Professor, Cardiovascular Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
2- Cardiologist, Cardiovascular Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
3- General Practitioner, Department of Medical Sciences, Mashhad Branch, Islamic Azad University, Mashhad, Iran
4- General Practitioner, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan AND Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran
Correspondence to: Pouya Nezafati, Email: pouya.nezafati@gmail.com

Although the ILVNC was first described in eight cases by Chin et al.,[7] still there is no consensus among researchers and cardiologists about its classification, diagnosis, and definition. In this regard, the Word Health Organization and the European Society of Cardiology categorized LVNC as an unclassified cardiomyopathy in 1995 and 2008, respectively.[9,10] American Heart Association, on the other hand, has considered it as a distinct primary cardiomyopathy in its statement published in 2006.[8] Currently, there are three different echocardiographic diagnostic criteria available that might not lead to single diagnosis in one patient suspected for having the disease.[7,11-13]

Based on the available data, our knowledge about this disease and its clinical features is sparse. Therefore, this study was conducted to assess the clinical and echocardiographic characteristics of patients with ILVNC.

Materials and Methods

A cross-sectional descriptive study was conducted to assess all patients with ILVNC between 2010 and 2013 in Mashhad, Iran. Study recruitment was performed among patients with suspected diagnosis of dilated cardiomyopathy who were referred to a tertiary referral center affiliated with Mashhad University of Medical Sciences. All participants were asked to fill a questionnaire regarding the demographic information, their symptoms, and family history of heart disease. In addition, all patients underwent electrocardiogram (ECG). Patients who had no exclusion criteria were enrolled and underwent echocardiography to diagnose cases with ILVNC. Exclusion criteria were as follows: history of coronary heart disease, hypertension, systemic illnesses, and primary organ failure. Study protocol was in accordance with the latest declaration of Helsinki for investigating on human subjects and it was approved by local ethics committee. Written informed consent was obtained from all patients prior to enrollment.

All patients underwent comprehensive transthoracic two-dimensional and Doppler echocardiography using a System Five or Vivid 7 echocardiograph (GE Medical Systems) by a single expert cardiologist. Biplane area length method was employed to calculate left ventricular ejection fraction (LVEF). Measurements of left ventricular end-diastolic (LVED) and left ventricular end-systolic (LVES) dimension were obtained in accordance with the recommendations of the American Society of Echocardiography.[4] Also, right ventricle (RV) function was obtained from Tricuspid Annular Plane Systolic Excursion (TAPSE). RV dysfunction was considered as TAPSE less than 16 mm.

Diagnostic criteria for ILVNC

Patients were considered to have ILVNC if all the following conditions were fulfilled: two-layer myocardial structures were detected with the thin compacted layer and a think non-compacted layer, absence of co-existing cardiac structural abnormalities, more than three excessively prominent trabeculations and deep intratrabecular recesses, and the ratio of end systolic diameter of noncompacted to compacted layer at parasternal short axis views > 2 in adults and > 1.4 in children.[11]

SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA) was employed to perform all statistical analyses. Descriptive data were demonstrated as mean and standard deviation, while categorical variables were presented as percentage. Chi-square test was employed to compare categorical variables. Normality of data was checked by Kolmogorov-Smirnov test (K-S test). The number of affected segments' differences between the two groups of normal LV function and low LV function was evaluated using Mann-Whitney test. Significance level was considered as P value lower than 0.05 in all the tests.

Results

Among 4540 subjects who underwent echocardiography, final diagnoses of ILVNC were made in 42 patients. Mean age of patients was 32.9 ± 15.6 ranging from 9 to 70 years. Study group comprised of 26 (61.9%) men and 16 (38.1%) women. The most common symptom was shortness of breath that was reported by 20 (47.6%) of patients, while 11 (26.2%) were asymptomatic. Based on New York Heart Association (NYHA) classification, 25 (59.5%) participants were considered as NHYA class I/II. Only four patients had documented history of left ventricular noncompaction disease in their first-degree family members. Baseline characteristics and ECG of the study sample are demonstrated in table 1.

Thirty-six (85.7%) had an abnormal ECG. Abnormalities included left bundle branch block (LBBB) (n = 18, 43%), poor R wave progression (n = 7, 17%), ST-segment change (n = 6, 14%) and T-wave inversion (n = 5, 12%). Also, four patients were in atrial fibrillation at the time of diagnosis.

Table 1. Demographic and clinical characteristics of study group

Variables	N = 42
Mean age (mean ± SD)	32.9 ± 15.6
Gender [n(%)]	
Male	26 (61.9)
Female	16 (38.1)
NYHA class [n(%)]	
I/II	25 (59.5)
III/IV	17 (40.5)
Symptoms [n(%)]	
Asymptomatic	11 (26.2)
Shortness of breath	20 (47.6)
Chest pain	11 (26.2)
Abnormal ECG [n(%)]	36 (85.7)
Family history of heart disease [n(%)]	
Positive	4 (9.5)
Negative	38 (90.5)

NYHA: New York Heart Association; ECG: Electrocardiogram; SD: Standard deviation

Ten (23.8%) patients had ventricular tachyarrhythmia, which were candidates to receive implantable cardioverter defibrillators (ICDs). Moreover, no embolic events were detected.

Table 2. Echocardiographic features of study participants

Variables	Mean ± SD
Ejection Fraction (%)	38.4 ± 14.70
Left ventricle	
End-systolic volume (cc/m^2)	32.0 ± 18.60
End-systolic diameter (mm/m^2)	21.2 ± 5.75
End-diastolic volume (cc/m^2)	53.0 ± 18.10
End-diastolic diameter (mm/m^2)	27.4 ± 5.29
Pulmonary artery pressure (mmHg)	38.7 ± 16.20
Left atrium size (mm)	43.8 ± 15.90
Right ventricle diameter (mm)	30.0 ± 2.32
TAPSE (mm)	18.5 ± 3.61
S' (cm/sec)	11.8 ± 2.24

SD: Standard deviation; TAPSE: Tricuspid annular plane systolic excursion; S': Peak systolic annular velocity

Echocardiographic features including end-systolic diameter (ESD), end-systolic volume (ESV), end-diastolic diameter (EDD) and end-diastolic volume (EDV) of left ventricle, pulmonary artery pressure (PAP), and left atrium and right ventricle sizes are shown in table 2. Details regarding valvular regurgitations and insufficiencies and their severity are presented in table 3. The most common site of noncompacted layers were the lateral and inferior segments of apex (97.6%) (Figure 1).

A total of 16 (38.1%) patients had normal or near normal LV function (LVEF > 50%) and 26 (61.9%) had LVEF lower than 50%. No significant differences were observed between patients with and without LV dysfunction regarding age (30.3 vs. 34.4, P = 0.4) and sex distribution (male to female ratio 3:1.16, P = 0.2). Mean value of LVEF was 38.4 ± 14.7 ranging from 15 to 60 percent. The factor that showed significant association with LV dysfunction was the number of affected segments of the heart by noncompacted layers. Patients with normal LV function (EF > 50) had a mean of 3.37 ± 1.62 affected segments, while the corresponding figure in the other group (EF < 50) was 6.76 ± 2.01 (P = 0.008). Also, RV dysfunction was revealed in eight (19%) patients.

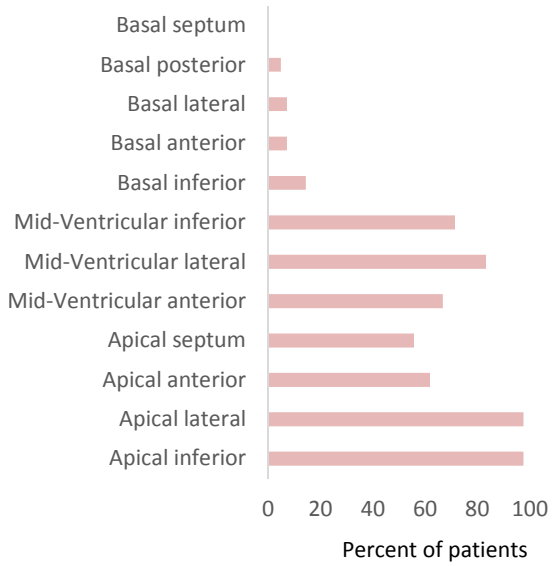


Figure 1. Distribution of the noncompacted segments

Table 3. Frequencies and severities of valvular regurgitation and insufficiency among study population

Severity of valvular regurgitation	Mitral regurgitation	Tricuspid regurgitation	Aortic insufficiency	Pulmonary insufficiency
Severe	9 (21.40)	1 (2.4)	0 (0.0)	1 (2.4)
Moderate	4 (9.52)	14 (33.3)	3 (7.1)	4 (9.5)
Mild	20 (47.60)	26 (61.9)	2 (4.8)	33 (78.6)
Trace	8 (19.00)	1 (2.4)	7 (16.7)	0 (0.0)
Absence	1 (2.39)	0 (0.0)	30 (71.4)	4 (9.5)

Data are shown as number (percent)

Discussion

In the current study, clinical and echocardiographic characteristics of a group of patients with ILVNC was reported. Subjects were patients with suspected dilated cardiomyopathy who were referred to our center for diagnosis, management and follow-up. The study group was mostly comprised of female patients and the most common symptom was shortness of breath. Mild valvular insufficiencies or regurgitations were observed in most of the patients. Shortness of breath was the most common symptom and 59.5% of patients were categorized as NYHA I/II. Similar findings were demonstrated by Oechslin et al. that reported 65% of patients with ILVNC had dyspnea classified as NYHA I/II.[14]

It is worth noting that prominent trabeculation can be seen in 68% of healthy hearts, but the ratio between noncompacted and compacted parts never reaches 2.[15] As suggested in previous studies, we used the cut-off value of 2 and 1.4 for adults and children, respectively to correctly identify patients with ILVNC.[11]

The most frequent site of trabeculation was the apex of LV (97.6%), which is in accordance with the results of previous articles published on this subject.[14,16,17] Additionally, this emphasizes the accuracy of considering the presence of trabeculation in apex of the heart as the diagnostic criteria. In contrast, diffuse trabeculation of myocardial wall indicates secondary pathologies such as arterial hypertension or valvular disease, compared to segmented trabeculation and noncompaction that can be seen in ILVNC.

Controversial results have been reported regarding the association between the number of affected segments with noncompaction and the prevalence of LV dysfunction. In a study conducted by Habib et al., a total of 105 patients with ILVNC were reviewed and no correlation was found between the numbers of affected segments and lower LVEF.[16] The same finding was reported by Fazio et al.[17] In contrast to previous reports, Aras et al. showed that the number of segments affected with noncompaction can be an independent predictor of LV dysfunction.[18] The same results were observed in the current study. It can be postulated that with the increasing number of segments incapable of performing normal contraction, the risk of LV dysfunction can increase.

Conclusion

In conclusion, this report of a series of cases with ILVNC showed that the disease has distinct echocardiographic patterns and comprehensive evaluation of patients with shortness of breath and cardiomyopathy can lead to a definite diagnosis. Echocardiographic evaluation showed that the apex of the heart is the most common site of noncompacted layers. Additionally, highly affected segments may compromise the heart function and reduce LVEF.

Acknowledgments

The authors would like to thank all the patients for their cooperation and permission to publish this paper.

Conflict of Interests

Authors have no conflict of interests.

References

1. Ichida F. Left ventricular noncompaction. Circ J 2009; 73(1): 19-26.
2. Malla R, Sharma R, Rauniyar B, Kc MB, Maskey A, Joshi D, et al. Left ventricular noncompaction. JNMA J Nepal Med Assoc 2009; 48(174): 180-4.
3. Stollberger C, Finsterer J. Left ventricular hypertrabeculation/noncompaction. J Am Soc Echocardiogr 2004; 17(1): 91-100.
4. Nugent AW, Daubeney PE, Chondros P, Carlin JB, Cheung M, Wilkinson LC, et al. The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med 2003; 348(17): 1639-46.
5. Stollberger C, Finsterer J. Trabeculation and left ventricular hypertrabeculation/noncompaction. J Am Soc Echocardiogr 2004; 17(10): 1120-1.
6. Ritter M, Oechslin E, Sutsch G, Attenhofer C, Schneider J, Jenni R. Isolated noncompaction of the myocardium in adults. Mayo Clin Proc 1997; 72(1): 26-31.
7. Chin TK, Perloff JK, Williams RG, Jue K, Mohrmann R. Isolated noncompaction of left ventricular myocardium. A study of eight cases. Circulation 1990; 82(2): 507-13.
8. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 2006; 113(14): 1807-16.
9. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the

Definition and Classification of cardiomyopathies. Circulation 1996; 93(5): 841-2.
10. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008; 29(2): 270-6.
11. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. Heart 2001; 86(6): 666-71.
12. Stollberger C, Finsterer J, Blazek G. Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. Am J Cardiol 2002; 90(8): 899-902.
13. Kohli SK, Pantazis AA, Shah JS, Adeyemi B, Jackson G, McKenna WJ, et al. Diagnosis of left-ventricular non-compaction in patients with left-ventricular systolic dysfunction: time for a reappraisal of diagnostic criteria? Eur Heart J 2008; 29(1): 89-95.
14. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. J Am Coll Cardiol 2000; 36(2): 493-500.
15. Boyd MT, Seward JB, Tajik AJ, Edwards WD. Frequency and location of prominent left ventricular trabeculations at autopsy in 474 normal human hearts: implications for evaluation of mural thrombi by two-dimensional echocardiography. J Am Coll Cardiol 1987; 9(2): 323-6.
16. Habib G, Charron P, Eicher JC, Giorgi R, Donal E, Laperche T, et al. Isolated left ventricular non-compaction in adults: clinical and echocardiographic features in 105 patients. Results from a French registry. Eur J Heart Fail 2011; 13(2): 177-85.
17. Fazio G, Novo G, Casalicchio C, Di Gesaro G, Sutera L, Grassedonio E, et al. Left ventricular non-compaction cardiomyopathy in children: Is segmental fibrosis the cause of tissue Doppler alterations and of EF reduction? Int J Cardiol 2009; 132(2): 278-80.
18. Aras D, Tufekcioglu O, Ergun K, Ozeke O, Yildiz A, Topaloglu S, et al. Clinical features of isolated ventricular noncompaction in adults long-term clinical course, echocardiographic properties, and predictors of left ventricular failure. J Card Fail 2006; 12(9): 726-33.

How to cite this article: Fazlinezhad A, Vojdanparast M, Sarafan S, Nezafati P. **Echocardiographic characteristics of isolated left ventricular noncompaction.** ARYA Atheroscler 2016; 12(5): 243-7.

Is herbal therapy safe in obesity? A case of Apium graveolens (Celery) induced hyperthyroidism

Hojjat Rouhi-Boroujeni[1], Masih Hosseini[2], Mojgan Gharipour[3], Hamid Rouhi-Boroujeni[4]

Case Report

Abstract

BACKGROUND: Apium graveolens is one of the well-known herbs used for the treatment of different; however, allergic reactions have been reported after its use. This report aimed to demonstrate the A. graveolens induced hyperthyroidism after its oral consumption for weight loss.

CASE REPORT: Mr. A, 48-year-old, with no history of any thyroid diseases, was diagnosed with hyperthyroidism due to daily consumption of 4 g of dried celery leaves for 45 days. After cessation of consumption and treatment with methimazole, the symptoms remitted. Then, the medication was discontinued when the lab tests and ultrasound were normal and indicated the patient's definite recovery. In 2 months follow up of, he was normal and thyroid-stimulating hormone (TSH), T4, T3, anti-TSH receptor, anti thyroperoxidase and antithyroglobulin were in normal ranges.

CONCLUSION: Hyperthyroidism may be induced by consumption celery. Although many studies have reported side effects such as allergic reactions for this herb, this is the first report of hyperthyroidism induced by celery in which the patient recovered after discontinuing the medication. Therefore, it can be assumed that celery induces hyperthyroidism as a side effect of this herb if it is used for a long term.

Keywords: Hyperthyroidism, Celery, Obesity, Case Report

Date of submission: 09 Feb 2015, ***Date of acceptance:*** 29 June 2016

Introduction

Medicinal herbs have long been ensued in the treatment of diseases. Human frustration with chemical drugs due to their relatively high side effects and peoples' believing that medicinal herbs have no side effects even if they have no benefits, led to an increased tendency toward medicinal herbs and herbal products.[1]

Celery, scientifically known as Apium graveolens, is one of the aromatic herbs belonging to Apiaceae family. Celery is known for its diuretic, laxative, sedative, antispasmodic, antifungal, lipid-lowering, antihypertensive, and anti-obesity effects.[2,3] In addition, it has strong antioxidant properties, increases breast milk secretions and reduces the toxicity of many drugs and all these effects have been proved,[4,5] so far central nervous system complications, abortion, allergic reactions and the risk of anaphylactic shock, especially if it is used with renin-angiotensin converting enzyme inhibitor drugs have been reported as the clinical side effects of this herb and animal studies have reported its role in increasing thyroid function tests.[6-8]

This report suggests the possibility of another important clinical side effect of this herb.

Case Report

Mr. A, who is 48-year-old, is 88 kg and has a body mass index of 26.3, began taking 4 g/day of celery powder that purchased from the sale of medicinal herbs center and checked and approved by the Medicinal Plants Research Center, for 45 days to lose weight. His medication history showed losartan 25 mg/bid. Five days before taking the herb, checkup testing was performed, and all components of the test were reported normal. After 45 days,

1- Member of Student Research Committee, Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran
2- Medical Plants Research Center AND Department of Anatomy, School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran
3- PhD Candidate, Department of Molecular and Cellular Biology, Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Internist, Associate Professor, Department of Internal Medicine, School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran
Correspondence to: Hamid Rouhi-Boroujeni, Email: dr_rohib@yahoo.com

patient's weight reduced from 88 to 84.5 kg. The patient went to the physician for a check-up. According to the patient's physical conditions, including weight loss, exophthalmos, and sweating, the physician prescribed thyroid function tests for him. The test report read thyroid-stimulating hormone (TSH) value and T4 level as 0.011 mlU/l and 13.1, respectively. Then, for differential diagnosis of hyperthyroidism anti thyroperoxidase, antithyroglobulin, anti TSH receptor and thyroid scan performed and all of them was normal and thyroiditis, graves diseases, and drug-induced thyrotoxicosis ruled out. The patient began taking methimazole 5 mg/bid daily. After 15 and 30 days, TSH values reached 0.059 mIU/l and 0.125 mIU/l, respectively, and T4 level became normal. Then, the dosage of methimazole was reduced to 5 mg/day and after 15 days, TSH value and T4 level reached 0.35 mIU/l and 4.49 mIU/l, respectively. Then, the result of thyroid ultrasound and TSH concentration were reported normal and 15 days after discontinuation of methimazole, the patient's recovery was confirmed. He had normal thyroid function tests in 2 months follow-up.

Discussion

According to patient's previous state and his normal thyroid function tests, we suppose that patient's hyperthyroidism is associated with celery consumption. Furthermore, patient's subsequent weight loss can be attributed to this side effect. Celery is used in formulations of herbal anti-obesity products.[9]

Furthermore, the patient reported that skin eruptions appeared all over his body while he was using this herb, which may be attributed to its allergic reactions.[10] According to experimental studies, celery affects thyroid function tests[11] which is consistent with this study. Therefore, we recommend that celery not be used in patients with hyperthyroidism and that the thyroid function tests be taken into consideration carefully.

Acknowledgments

This article has been derived from the Ph.D. thesis of the first author and financially supported by the Research Deputy of Shahrekord University of Medical Sciences, Iran.

Conflict of Interests

Authors have no conflict of interests.

References

1. Traditional Medicine Programme. Guidelines for the assessment of herbal medicines. Geneva, Switzerland: WHO Programme on Traditional Medicines; 1991.
2. Atta AH, Alkofahi A. Anti-nociceptive and anti-inflammatory effects of some Jordanian medicinal plant extracts. J Ethnopharmacol 1998; 60(2): 117-24.
3. Ahmed B, Alam T, Varshney M, Khan SA. Hepatoprotective activity of two plants belonging to the Apiaceae and the Euphorbiaceae family. J Ethnopharmacol 2002; 79(3): 313-6.
4. AbdEl-Fattah SA. Biochemical and nutritional impact of celery and turnip leaves on induced obese by high fat diet (HFD). J Nutr Food Sci 2014; 2(6): 285-302.
5. Rouhi-Boroujeni H, Rouhi-Boroujeni H, Heidarian E, Mohammadizadeh F, Rafieian-Kopaei M. Herbs with anti-lipid effects and their interactions with statins as a chemical anti- hyperlipidemia group drugs: A systematic review. ARYA Atheroscler 2015; 11(4): 244-51.
6. Moneret-Vautrin DA, Kanny G. Food-induced anaphylaxis. A new French multicenter survey. Ann Gastroenterol Hepatol (Paris) 1995; 31(4): 256-63.
7. Ballmer-Weber BK, Hoffmann A, Wuthrich B, Luttkopf D, Pompei C, Wangorsch A, et al. Influence of food processing on the allergenicity of celery: DBPCFC with celery spice and cooked celery in patients with celery allergy. Allergy 2002; 57(3): 228-35.
8. Rouhi-Boroujeni H, Rouhi-Boroujeni H, Gharipour M, Mohammadizadeh F, Ahmadi S, Rafieian-Kopaei M. Systematic review on safety and drug interaction of herbal therapy in hyperlipidemia: a guide for internist. Acta Biomed 2015; 86(2): 130-6.
9. Tuetun B, Choochote W, Kanjanapothi D, Rattanachanpichai E, Chaithong U, Chaiwong P, et al. Repellent properties of celery, Apium graveolens L., compared with commercial repellents, against mosquitoes under laboratory and field conditions. Trop Med Int Health 2005; 10(11): 1190-8.
10. Sausenthaler S, Koletzko S, Schaaf B, Lehmann I, Borte M, Herbarth O, et al. Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. Am J Clin Nutr 2007; 85(2): 530-7.
11. Kooti W, Ali-Akbari S, Asadi-Samani M, Ghadery H, Ashtary-Larky D. A review on medicinal plant of Apium graveolens. Advanced Herbal Medicine 2015; 1(1): 48-59.

How to cite this article: Rouhi-Boroujeni H, Hosseini M, Gharipour M, Rouhi-Boroujeni H. **Is herbal therapy safe in obesity? A case of Apium graveolens (Celery) induced hyperthyroidism.** ARYA Atheroscler 2016; 12(5): 248-9.

Study of the involved vascular territories in patients with ischemic stroke in Kerman, Iran

Hossein Ali Ebrahimi[(1)], Mohammad Saba[(2)], Behnaz Sedighi[(3)], Hoda Kamali[(4)]

Short Communication

Abstract

BACKGROUND: The races show different cerebrovascular involvements, for example, the involvement of intracranial arteries are higher among Asians than Caucasians. The aim of this study was to investigate the cerebrovascular stenosis pattern by computed tomography angiography (CTA), which is unprecedented in Iran.

METHODS: In this study, patients with brain stroke (thrombosis), confirmed by CT scanning and cardiac assessments, who referred to Shafa Hospital in Kerman, Iran, underwent brain and cervical arteries CT angiography to assess involved cerebrovascular territories and also its risk factors from June 2012 to June 2013.

RESULTS: We did CTA for 100 patients. Eighty-four cases had cerebral artery stenosis. Intracranial vessel involvement alone was observed in 47.6% of patients, simultaneous intracranial and extracranial artery stenosis in 26.2%, and extracranial artery stenosis in 26.2%. Posterior cerebral artery territory showed the highest degree of vascular stenosis. Posterior cerebral artery stenosis alone was observed in 51.3% of the cases; 27.4% of the cases suffered from anterior artery stenosis, and 21.6% had simultaneous anterior and posterior cerebral artery stenosis. Smokers showed higher extracranial artery involvement compared to non-smokers; 44% of smokers and 14% of non-smokers had extracranial vertebral involvement.

CONCLUSION: Our findings showed that intracranial artery involvement was the most prevalent finding in patients with thrombotic stroke in Kerman. Also posterior cerebral artery stenosis was more prevalent than anterior artery stenosis. Hypertension was the most common risk factor. Furthermore, smoking was considered as an important risk factor for extracranial artery stenosis, especially in the posterior cerebral artery.

Keywords: Thrombosis, Stroke, Computed Tomography, Angiography, Risk Factors

Date of submission: 26 Nov 2014, ***Date of acceptance:*** 07 May 2016

Introduction

Stroke is a sudden neurological deficit, due to the disturbance of blood and oxygen supply.[1] Stroke is one of the main causes of morbidity and is the third leading cause of mortality after heart disease and cancer, and the second most common cause of mortality in developing countries.[2]

One of the most important causes of ischemic stroke is intracranial atherosclerosis,[3] which is defined as the skull base large-artery atherosclerosis with a poor prognosis.[4] The prevalence of intracranial atherosclerosis is different in different countries.[5] In the past two decades, many studies have pointed to different intracranial arteries stenosis and related risk factors in different races.[5-9]

Numerous methods can be done for cerebrovascular assessment. Brain and cervical computed tomography angiography (CTA) have high sensitivity and specificity (98%) for detecting intracranial stenosis, providing reliable and fast-produced information regarding the location of obstruction, the segment involved, and the presence or absence of collateral arteries,[10] with a high negative predictive value, unlike Doppler ultrasound and magnetic resonance angiography (MRA).[11]

Because CTA highlights intracranial artery thrombosis in patients with mild symptoms of acute stroke, and that this thrombosis increases recurrent strokes and worsens the patient's clinical symptoms,[7] application of CTA is rising. CTA is a

1- Professor, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran
2- Assistant Professor, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran
3- Associate Professor, Neurology Research Center AND Department of Neurology, Kerman University of Medical Sciences, Kerman, Iran
4- Resident, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran
Correspondence to: Hossein Ali Ebrahimi, Email: hebrahimi@kmu.ac.ir

rapidly developing technology with great potentials. This is particularly true for evaluating neurovascular diseases.[12] CTA has been advanced by the development of improved multi-detector CT (MDCT) and workstations that post-process the data.[13,14]

Materials and Methods

Sampling: In this cross-sectional study, we evaluated 100 patients with thrombotic stroke. The patients with suspected stroke, who referred to the Neurological Emergency Department of Shafa Hospital in Kerman, Iran, underwent physical examination by a neurologist from June 2012 to June 2013. After that, brain CT scan or Magnetic resonance imaging (MRI) was conducted for the suspected patients to confirm thrombotic stroke diagnosis.

Exclusion criteria were hemorrhagic stroke, embolic stroke, unstable hemodynamic status, impaired renal function or sensitivity to the radio-contrast agent and those who did not consent.

Based on a population-based study, risk factors for atherosclerosis were defined as hypertension, diabetes mellitus and hypercholesterolemia.[15] Patients with daily dependence on cigarettes and opium were considered smoker and opium-addict, respectively.

Performing CTA: As a part of the diagnosis program, brain and cervical CTA (with contrast medium 370 mg/ml) were conducted for patients with confirmed thrombotic stroke, and without the mentioned exclusion criteria (non-invasive method).[16-18] Findings such as 3-dimention images, were assessed by a radiology faculty member to determine the involved vascular territories. We used descriptive and Student's t-test for data analysis.

Results

Prevalence of the involved vascular territory: Eighty-four patients (male = 45, female = 39) had visible cerebral artery stenosis. As for the 16 cases with no evidence of cerebral and cervical artery stenosis in the CTA, the pertaining clinical and radiographic symptoms indicated the involvement of intracranial small artery. Concerning risk factors analysis (sex, mean age of patients, rate of smoking, opium addiction, hypertension, diabetes and hyperlipidemia), no significant relationship was observed between the two groups, with small and large artery stenosis. The involvement of middle cerebral artery was more than twice of anterior cerebral artery.

Investigation of risk factors: Seventy-three percent of the cases were hypertensive. Extracranial artery involvement was significantly higher in men than in women (40 vs. 10%) (P = 0.003), while, women showed higher simultaneous intra- and extracranial artery stenosis (P = 0.003).

Intracranial vertebral artery involvement was significantly higher in women (38.5%) than in men (13.3%) (P = 0.008). Whereas, extracranial vertebral artery involvement was higher in men (P = 0.030).

About 44% of smokers and 14% of non-smokers had extracranial vertebral involvement, which was statistically significant (P = 0.030).

There was no significant relationship between age, hyperlipidemia, diabetes mellitus, opium-dependence, and intra- and extracranial artery involvement.

As for risk factor analysis in the two groups, concerning the involvement of posterior and anterior cerebral circulation, hypertension was observed in 62% and smoking in 53% of ischemic stroke patients, within the territory of posterior cerebral circulation. Involvement of posterior cerebral circulation was significantly higher in smokers, than in non-smokers (P = 0.040). However, no significant relationship was observed between gender, age, high blood cholesterol, diabetes, opium-dependence, and anterior/posterior cerebral circulation involvement.

Discussion

Intracranial atherosclerosis is a major cause of ischemic stroke. Frequency of atherosclerosis is different in different races. Intracranial artery involvement is more common in Asian races. Information on ischemic stroke patients in Iran, according to the findings of Doppler ultrasound, indicated that extracranial artery involvement was higher than that of intracranial artery.[19-21] Of the studied cases, 16% had no involvement, which might be due to small artery disorders. In general, CTA may slightly underestimate stenosis.[13]

The present study reported an intracranial artery involvement of 47.6%, which confirms the results of the majority of studies conducted in Asia. In a study in South Korea, the intracranial artery involvement was reported in 26.4% of the cases, simultaneous intra- and extracranial artery involvement in 39%, and extracranial artery involvement in 12.2% of the cases.[22] Another study in China reported 29% intracranial artery involvement, 9% extracranial, 43% simultaneous and no stenosis in 19% of cases.[23]

A study in Netherlands showed an exceeding 30% intracranial artery stenosis in 36% of the cases, mostly present in posterior cerebral circulation

(67%), which matches our findings in terms of the territory of the involved arteries, but against with some studies in Europe, as well as a study in Iran.[19,21] Paciaroni et al.[24] studied the correlation between the potential causes of stroke (TOAST etiological groups) and the involvement of different vascular territories seen on CT scans in patients with ischemic stroke. Large artery disease was the main cause of entire middle cerebral artery (MCA) territory infarcts (40.9%), superficial MCA territory infarcts (35.7%), and watershed infarcts (68.2%).[24] Chung et al.[25] studied a consecutive series of 2702 acute ischemic stroke patients whose stroke lesions were confirmed by diffusion weighted imaging and who underwent a thorough etiological investigation. Large artery atherosclerosis (37.3%) was the most common stroke subtype, and MCA (49.6%) was the most frequently involved territory. Large-artery atherosclerosis was the most common subtype for anterior cerebral, middle cerebral, vertebral, and anterior and posterior inferior cerebellar artery territory infarctions.[25] Maybe different conclusions are due to different methodologies; for example studies done in Iran used Doppler ultrasound, which has a lower sensitivity in finding intracranial stenosis, especially those of posterior cerebral circulation.[10,11]

Our finding of higher prevalence of stenosis in the territory of posterior cerebral circulation is against reported results by other studies in Asia, which similarly employed CTA.[11] These studies reported the middle and carotid cerebral arteries as the most common involved arteries,[22,23,26] which may be a result of racial differences. Smokers, in our study, suffered from a higher extracranial artery involvement, which is supported by a study in China.[27]

The most common risk factors for patients with posterior cerebral artery stroke were hypertension (62%), followed by smoking (53%). The study by Mousavi and Hoseini showed similar risk factors, where smoking was reported more common in patients with posterior, rather than anterior cerebral artery involvement.[28] Against our findings, Lee et al. reviewed consecutive patients with acute posterior cerebral artery territory infarction who underwent diffusion-weighted MRI (DWI) and MRA within 7 days after onset. In this study, hypertension (n = 144, 70.2%) was the most prevalent risk factor, followed by diabetes (n = 74, 36.1%), smoking (n = 60, 29.3%), hyperlipidemia (n = 46, 36.1%), previous stroke (n = 35, 17.1%), heavy alcohol drinking (n = 29, 14.1%), and other potential risk factors (n = 21, 10.2%).[29]

Our study has limitations. First, vascular evaluation was performed by CTA, but not conventional angiography. Second, transesophageal echocardiography and longtime Holter monitoring were performed in a limited number of patients. As discussed earlier, this might have underestimated the frequency of cardiac emboli. However, we attempted to document the source of embolism whenever an embolism was suspected.

Conclusion

Our findings showed that intracranial artery involvement was the most prevalent finding in patients with thrombotic stroke in Kerman. Also, posterior cerebral artery stenosis was more prevalent than anterior artery stenosis and hypertension was the most common risk factor. Furthermore, smoking was considered as an important risk factor for extracranial artery stenosis, especially in the posterior cerebral artery.

Acknowledgments

This study was approved by the Neurology Research Center of Kerman University of Medical Sciences, and is a part of residency thesis of Hoda Kamali.

Conflict of Interests

Authors have no conflict of interests.

References

1. Riebau D, Hermann L. Secondary management of ischemic stroke. Virtual Mentor 2009; 11(10): 772-7.
2. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics-2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008; 117(4): e25-146.
3. Jeng JS, Tang SC, Liu HM. Epidemiology, diagnosis and management of intracranial atherosclerotic disease. Expert Rev Cardiovasc Ther 2010; 8(10): 1423-32.
4. Arenillas JF. Intracranial atherosclerosis: current concepts. Stroke 2011; 42(1 Suppl): S20-S23.
5. De Silva DA, Woon FP, Lee MP, Chen CP, Chang HM, Wong MC. South Asian patients with ischemic stroke: intracranial large arteries are the predominant site of disease. Stroke 2007; 38(9): 2592-4.
6. Moussouttas M, Aguilar L, Fuentes K, Anyanwu B, Manassarians H, Papamitsakis N, et al. Cerebrovascular disease among patients from the Indian subcontinent. Neurology 2006; 67(5): 894-6.

7. Puetz V, Dzialowski I, Coutts SB, Hill MD, Krol A, O'Reilly C, et al. Frequency and clinical course of stroke and transient ischemic attack patients with intracranial nonocclusive thrombus on computed tomographic angiography. Stroke 2009; 40(1): 193-9.
8. Wong KS, Huang YN, Gao S, Lam WW, Chan YL, Kay R. Intracranial stenosis in Chinese patients with acute stroke. Neurology 1998; 50(3): 812-3.
9. Ali Ebrahimi H, Hamzeaie Moghadam A, Aredestani E. Evaluation of patent foramen ovale in young adults with cryptogenic stroke. ARYA Atheroscler 2011; 7(2): 74-7.
10. Rorick MB, Nichols FT, Adams RJ. Transcranial Doppler correlation with angiography in detection of intracranial stenosis. Stroke 1994; 25(10): 1931-4.
11. Graf J, Skutta B, Kuhn FP, Ferbert A. Computed tomographic angiography findings in 103 patients following vascular events in the posterior circulation: potential and clinical relevance. J Neurol 2000; 247(10): 760-6.
12. Homburg PJ, Plas GJ, Rozie S, van der Lugt A, Dippel DW. Prevalence and calcification of intracranial arterial stenotic lesions as assessed with multidetector computed tomography angiography. Stroke 2011; 42(5): 1244-50.
13. Enterline DS, Kapoor G. A practical approach to CT angiography of the neck and brain. Tech Vasc Interv Radiol 2006; 9(4): 192-204.
14. Camargo EC, Furie KL, Singhal AB, Roccatagliata L, Cunnane ME, Halpern EF, et al. Acute brain infarct: detection and delineation with CT angiographic source images versus nonenhanced CT scans. Radiology 2007; 244(2): 541-8.
15. Feigin VL, Wiebers DO, Nikitin YP, O'Fallon WM, Whisnant JP. Risk factors for ischemic stroke in a Russian community: a population-based case-control study. Stroke 1998; 29(1): 34-9.
16. Willinsky RA, Taylor SM, TerBrugge K, Farb RI, Tomlinson G, Montanera W. Neurologic complications of cerebral angiography: prospective analysis of 2,899 procedures and review of the literature. Radiology 2003; 227(2): 522-8.
17. Marler JR, Goldstein M, Grady PA, Toole JF, Baker WH. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995; 273(18): 1421-8.
18. Josephson SA, Dillon WP, Smith WS. Incidence of contrast nephropathy from cerebral CT angiography and CT perfusion imaging. Neurology 2005; 64(10): 1805-6.
19. Ghandehari K, Shoueyb A. Comparison of the topography of carotid territory stenosis in North American and Iranian stroke patients. J Shaheed Sadoughi Univ Med Sci 2007; 14(4): 20-3. [In Persian].
20. Caplan LR, Gorelick PB, Hier DB. Race, sex and occlusive cerebrovascular disease: a review. Stroke 1986; 17(4): 648-55.
21. Iranmanesh F, Farahmand H, Gadari F. Doppler sonography of extracranial and intracranial vessels in patients with thrombotic stroke. J Res Med Sci 2006; 11(6): 391-5.
22. Kim YD, Choi HY, Cho HJ, Cha MJ, Nam CM, Han SW, et al. Increasing frequency and burden of cerebral artery atherosclerosis in Korean stroke patients. Yonsei Med J 2010; 51(3): 318-25.
23. Biswas M, Sen S, Simmons J. Etiology and risk factors of ischemic stroke in Indian-American patients from a hospital-based registry in New Jersey, USA. Neurol Asia 2009; 14(2): 81-6.
24. Paciaroni M, Silvestrelli G, Caso V, Corea F, Venti M, Milia P, et al. Neurovascular territory involved in different etiological subtypes of ischemic stroke in the Perugia Stroke Registry. Eur J Neurol 2003; 10(4): 361-5.
25. Chung JW, Park SH, Kim N, Kim WJ, Park JH, Ko Y, et al. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification and vascular territory of ischemic stroke lesions diagnosed by diffusion-weighted imaging. J Am Heart Assoc 2014; 3(4).
26. Zarei H, Ebrahimi H, Shafiee K, Yazdani M, Aghili K. Intracranial stenosis in patients with acute cerebrovascular accidents. ARYA Atheroscler 2008; 3(4): 206-10.
27. Leung SY, Ng TH, Yuen ST, Lauder IJ, Ho FC. Pattern of cerebral atherosclerosis in Hong Kong Chinese. Severity in intracranial and extracranial vessels. Stroke 1993; 24(6): 779-86.
28. Mousavi SA, Hoseini T. Difference between risk factors of anterior and posterior circulation strokes. J Res Med Sci 2007; 12(4): 161-4.
29. Lee E, Kang DW, Kwon SU, Kim JS. Posterior cerebral artery infarction: diffusion-weighted MRI analysis of 205 patients. Cerebrovasc Dis 2009; 28(3): 298-305.

How to cite this article: Ebrahimi HA, Saba M, Sedighi B, Kamali H**. Study of the involved vascular territories in patients with ischemic stroke in Kerman, Iran.** ARYA Atheroscler 2016; 12(5): 250-3.