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 in :

- 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
- Iranmedex
- Magiran

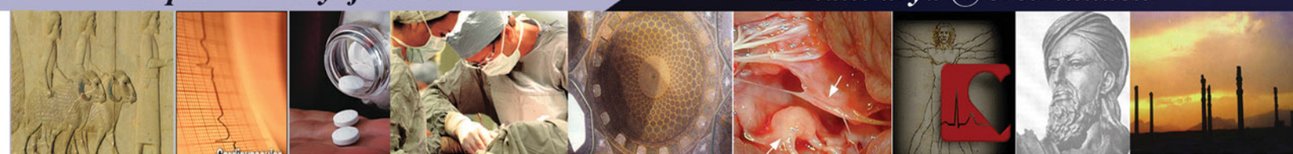
Serial Issue: 38 *Volume 10, Issue 1, January 2014* *Print ISSN: 1735-3955*
Online ISSN: 2251-6638

Original Article(s)

Case Report(s)

Short Communication(s)

http://www.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 and Print: Farzanegan Radandish Co.
Tel: +98-311-2241953
+98-311-2241876
Email: f.radandish@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

Address: ARYA Journal Office, Isfahan Cardiovascular Research Institute, Seddigheh Tahereh Research Complex, Khorram Ave. Isfahan, Isfahan, Iran
PO. Box: 81465-1148 Tel: +98-311-3377883 Fax: +98-311-3373435 E-mail: 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 quarterly 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 40 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 40 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 1500 words, and could include two figures or tables. It should have at least 8 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 2000 words, a maximum of 3 tables and figures (total), and up to 25 references. They do 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.

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 is limited to 2500 words, and a small number of figures and tables. They do not include an abstract.
- **Current Concepts** articles focus on clinical topics, including those in specialty areas but of wide interest. The text is limited to 2400 words, with a maximum of four figures and tables (total), and up to 50 references. They do not include an abstract.
- **Drug Therapy** articles detail the pharmacology and use of specific drugs or classes of drugs, or the various drugs used to treat particular diseases. The text is limited to 4000 words, with a maximum of six figures and tables (total), and up to 120 references. They do not include an abstract.
- **Mechanisms of Disease** articles discuss the cellular and molecular mechanisms of diseases or

categories of diseases. The text is limited to 3500 words, with a maximum of six figures and tables (total), and up to 100 references. They do not include an abstract.

• **Medical Progress** articles provide comprehensive, scholarly 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. The text is limited to 3500 words, with a maximum of six tables and figures (total), and up to 100 references. They do not include an abstract.

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 175 words if it is in reference to a recent *Journal* article, or 400 words in all other cases. A letter must have no more than five references and one 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.

Table of Contents

Combination of atorvastatin/coenzyme Q10 as adjunctive treatment in congestive heart failure: A double-blind randomized placebo-controlled clinical trial

Masoud Pourmoghaddas[(1)], Majid Rabbani[(2)], Javad Shahabi[(3)], Mohammad Garakyaraghi[(4)], Reza Khanjani[(2)], Pegah Hedayat[(5)]

Original Article

Abstract

BACKGROUND: Heart failure is one of the leading causes of mortality, is a final common pathway of several cardiovascular diseases, and its treatment is a major concern in the science of cardiology. The aim of the present study was to compare the effect of addition of the coenzyme Q10 (CoQ10)/atorvastatin combination to standard congestive heart failure (CHF) treatment versus addition of atorvastatin alone on CHF outcomes.

METHODS: This study was a double-blind, randomized placebo-controlled trial. In the present study, 62 eligible patients were enrolled and randomized into 2 groups. In the intervention group patients received 10 mg atorvastatin daily plus 100 mg CoQ10 pearl supplement twice daily, and in the placebo group patients received 10 mg atorvastatin daily and the placebo of CoQ10 pearl for 4 months. For all patients echocardiography was performed and blood sample was obtained for determination of N-terminal B-type natriuretic peptide, total cholesterol, low density lipoprotein, erythrocyte sedimentation rate, and C-reactive protein levels. Echocardiography and laboratory test were repeated after 4 months. The New York Heart Association Function Class (NYHA FC) was also determined for each patient before and after the study period.

RESULTS: Data analyses showed that ejection fraction (EF) and NYHA FC changes differ significantly between intervention and placebo group (P = 0.006 and P = 0.002, respectively). Changes in other parameters did not differ significantly between study groups.

CONCLUSION: We deduce that combination of atorvastatin and CoQ10, as an adjunctive treatment of CHF, increase EF and improve NYHA FC in comparison with use of atorvastatin alone.

Keywords: Coenzyme Q10, Atorvastatin, Clinical Trial, Congestive Heart Failure

Date of submission: 23 Jul 2013, ***Date of acceptance:*** 6 Aug 2013

Introduction

Heart failure (HF) is one of the leading causes of mortality in the world and is a final common pathway of several cardiovascular diseases such as hypertension, myocardial infarction, volume overload, and cardiomyopathies.[1,2]

For the vast majority of patients, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers, diuretics, and digoxin are the main treatment choices.[3]

Recent studies mentioned the role of oxidative stress and inflammation in the treatment of heart failure. Statins play an important role in lowering the pro-inflammatory markers in congestive heart failure (CHF) patients independent of their lipid lowering effect which triggered their use as an adjunctive therapy in CHF.[4] Coenzyme Q10 (CoQ10) is a vitamin-like agent which is structurally similar to vitamin K.[5] It was first isolated from beef mitochondria in 1957 and then found in other

1- Professor, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Resident, Hypertension Research Center, Isfahan Cardiovascular Research Institute , Isfahan University of Medical Sciences, Isfahan, Iran
3- Resident, Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Associate Professor, Heart Failure Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
5- Resident, Department of Pathology, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Javad Shahabi, Email: j.shahabi@yahoo.com

organs such as the heart, brain, and liver.[6] CoQ10 is a fat soluble quinon which enhances cell membrane stabilization and mitochondrial energy production, and also has antioxidant effects.[7,8] Recent studies have shown that statins have antioxidant activity, by means of activation of superoxide dismutase; moreover, some statins have been shown to reduce the endogenous CoQ10 levels through inhibition of 3-hdroxy 3-methyl glutaryl CoA reductase (HMG-CoA reductase).[9]

Previous studies showed that serum CoQ10 levels are lower in CHF patients than in the normal population which shows the importance of using its supplement in Patients with CHF.[10]

As mentioned above, statins and CoQ10 can be used as adjuncts in the treatment of CHF due to their anti-inflammatory and antioxidant effects, respectively. However, this matter remains a controversial issue.[9,11-13] The aim of the present study was to compare the effect of the addition of atorvastatin/CoQ10 combination to standard CHF treatment with that of the addition of atorvastatin alone on CHF outcomes.

Materials and Methods

Trial design and participants

This study was a single centre, double blind, randomized, placebo-controlled clinical trial with parallel design which was performed in Chamran Hospital, a tertiary referral centre in Isfahan, Iran. During a period of 7 months, May 2012 to February 2013, 62 consecutive patients who met the inclusion criteria were enrolled in the study. Eligibility criteria were documented CHF, ejection fraction (EF) of less than 40%, compensated heart failure without hospital admission during the previous 3 months, no change in type and dose of medications in the last months, and New York Heart Association Function Class (NYHA FC) 2 to 4. Patients were excluded if any of the following criteria were present: acute coronary syndrome developing in the last month; active myocarditis; active pericarditis; uncontrolled hypertension; hepatic failure (Child B, C); pulmonary or renal failure; and heart failure with KILLIP classification 3 and 4.

Written informed consents were obtained from all patients for authorized use of their medical records for research purposes. Moreover, the protocol was approved by the ethical committee of our university.

In this study, a sample size of 30 in each group was calculated using statistical formula considering $\alpha = 0.05$ and $\beta = 0.2$. This study was a double blind trial. For the purpose of blindness of patients, placebo was made with the same shape and size of the actual drugs, and for the blindness of physicians the drugs were delivered to patients by one of the study investigators who did not perform the echocardiography and determination of NYHA FC grade.

Intervention

Patients who enrolled in the study were randomly divided into 2 groups, using Random Allocation Software the sequence generation was performed by one of the study investigators who did not play a role in the clinical assessments and drug delivery to patients.[14] Patients in the first group (intervention) received 10 mg atorvastatin (Abidi, Iran) daily plus CoQ10 pearl supplement (USA, manufactured in Sobhan, Isfahan, Iran) with the dose of 100 mg twice daily for 4 months. In the other group (placebo), patients received 10 mg atorvastatin daily and the placebo of CoQ10 pearl, with the same shape and size of the drug, for 4 months. Placebo pearls were produced in the School of Pharmacology of Isfahan University of Medical Sciences. In both study groups, patients received standard CHF medication. The drugs were delivered to patients by one of the study investigators. The dose of drugs used in this study was determined according to previous studies performed in this field.[5]

Assessments and outcomes

In all patients, baseline data including age, sex, weight, history of diabetes and myocardial infarction, previous use of beta blockers, and ACEI were collected. In the first visit, for each patient, echocardiography was performed using Vivid 7, USA device by one of the study investigators (JS) who was blinded to the patients' group. EF and cardiac index (CI) were determined. Blood samples were taken and N-terminal B-type natriuretic peptide (NT-proBNP), total cholesterol (TC), low density lipoprotein (LDL), erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) levels were recorded. NYHA FC was also determined for each patient. Glomerular filtration rate (GFR) was calculated. After the study period (4 months), echocardiography was repeated by the same device and the same investigator, NYHA FC was calculated for the second time, and laboratory tests were checked again in the same laboratory in which previous tests had been performed. The primary outcome of this study was the effect of the addition of the atorvastatin and CoQ10 combination supplement to standard regiment on cardiac EF, in comparison with atorvastin and placebo. Secondary outcomes were the comparison

of change in NYHA FC, CI, NT-proBNP, TC, LDL, ESR, and CRP.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 16; SPSS Inc., Chicago, IL, USA). Student's t-test was used for parametric variables, chi-square test was used for nonparametric variables, and Man-Whitney test for data without normal distribution pattern. Statistical difference was considered significant if $P < 0.05$.

Results

During the period of the project a total number of 62 patients were enrolled in the study. Patients' enrolment, allocation, and follow up are shown in figure 1.

Demographic data in both study groups are shown and compared in table 1. There was no statistically significant difference in study parameters between the groups. All patients had used ACEI and beta blocker before the study began. After 4 months, all patients were alive and came back for follow up.

Data analyses showed EF and NYHA FC changed significantly before and after the study period in the intervention group; however, these changes were not significant in the placebo group ($P < 0.01$ for both parameters). Other parameter changes did not differ significantly between the study groups. Detailed data are shown in table 2.

Discussion

The aim of the present study was to compare the effect of the addition of the CoQ10/atorvastatin combination to standard CHF treatment with that of the addition of atorvastatin alone on CHF outcomes. Our study results showed that EF, as the primary outcome of the study, increased significantly in the intervention group in comparison with the placebo group. Among secondary outcomes, NYHA FC decreased significantly in the intervention group in comparison with the placebo group.

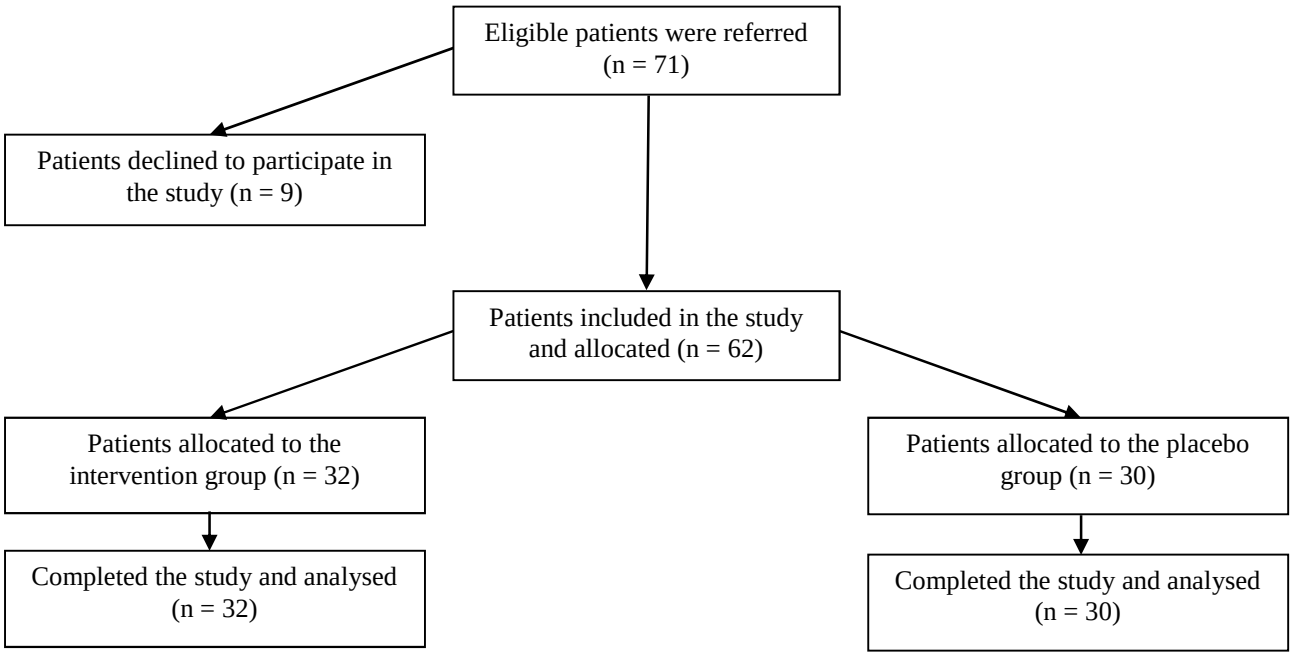


Figure 1. Patients' enrolment, allocation, and follow up

Table 1. Demographic data in the study groups

	Intervention group (n = 32)	Placebo group (n = 30)	P
Age	50.70 ± 12.5	54.47 ± 14.6	0.27
GFR (ml/minute)	72.29 ± 19.7	64.20 ± 20.7	0.12
Male	23 (71.9%)	22 (73.3%)	0.89
History of diabetes	7 (21.9%)	11 (36.7%)	0.20
History of MI	13 (40.6%)	14 (46.7%)	0.63

Data are presented as mean ± standard deviation and number (%); GFR: Glomerular filtration rate, MI: Myocardial infarction

Table 2. Comparison of parameters between study groups before and after the study period

	Intervention group		P	Placebo group		P	Mean's difference	Standard error	P
	Baseline	4 months		Baseline	4 months				
EF	18.7 ± 10.3	24.2 ± 14.5	0.003*	26.2 ± 9.1	25.8 ± 9.7	0.23	5.98	2.11	0.006*
CI	4.2 ± 1.7	4.4 ± 1.8	0.360	3.8 ± 1.4	4.0 ± 1.3	0.41	-1.56	1.74	0.370
NYHA FC	2.7 ± 0.7	2.3 ± 0.7	0.025*	2.9 ± 0.8	2.7 ± 0.7	0.17	-0.48	0.15	0.002*
CRP	3.7 ± 2.1	3.5 ± 2.3	0.130	4.6 ± 2.7	4.5 ± 3.3	0.22	-0.14	0.40	0.900
ESR	13.6 ± 13.3	11.6 ± 15.2	0.110	6.7 ± 5.1	6.3 ± 4.6	0.31	1.83	5.76	0.750
LDL	106.7 ± 32.8	93.4 ± 29.3	0.150	87.4 ± 15.7	88.1 ± 16.0	0.42	0.02	0.34	0.930
TC	120.2 ± 39.7	114.2 ± 44.2	0.130	146.0 ± 40.1	138.2 ± 40.8	0.35	-0.09	0.69	0.890
NT-proBNP	561.9 ± 293.7	541.6 ± 469.0	0.510	518.1 ± 218.5	484.6 ± 186.6	0.38	13.23	81.80	0.870

Data are presented as mean ± standard deviation; NYHA FC: New York Heart Association Functional Class; EF: Ejection fraction; CI: Cardiac index; CRP: C -reactive protein; ESR: Erythrocyte sedimentation rate; LDL: Low density lipoprotein; TC: Total cholesterol; NT-proBNP: N- terminal B-type Natriuretic Peptide

* P < 0.05 considered significant

Langsjoen and Langsjoen have evaluated heart failure outcome by the administration of CoQ10 supplement and found an increase in EF and notable clinical improvement by decrease in NYHA FC.[15] In line with this study and several other studies, including a recent meta–analysis performed by Sander et al[5], Okello et al[9] and Fotino et al.[16] in this field we found an increase in EF and decrease in NYHA FC. The effect of CoQ10 on EF can be explained in this way that CoQ10 reduces the reactive oxygen species which rise in heart failure; on other hand, CoQ10 reduces peripheral vascular resistance and improves the heart pomp to push blood.[17-20]

In a meta-analyses performed by sander et al., they mentioned that patients who use heart failure treatment, including ACEI, may not be gain benefit by using CoQ10 for EF improvement; however, in contrast with this study we found that in patients who are using ACEI drugs, EF increased by administration of CoQ10 supplement.[5]

Previous studies mentioned that CoQ10 supplement improves lipid profile. Shojaei et al., in their study, revealed that CoQ10 supplement reduces serum lipoprotein (a) level in patients using statin, but other serum lipids did not change significantly which can be due to the concomitant use of statin.[21] In line with this study, our results showed that although there is reduction in TC and LDL, the difference of this change between study groups was not significant.

About the other markers, such as BNP, ESR, and CRP, although there was a decrease in their level, the difference between the 2 groups was not significant. In line with our study, the study by Okello et al. showed a decrease in pro-inflammatory markers by the administration of CoQ10 as an adjunctive treatment of heart failure.[9]

Our study also had a limitation; the follow up in our study was 4 months. Furthermore, studies with longer follow up period are recommended in order to evaluate survival rate.

In conclusion, we deduce that the combination of atorvastatin and CoQ10 as an adjunctive treatment of heart failure increase EF and improve NYHA FC in comparison with single use of atorvastatin. We did not found a difference in other parameters such as ESR, CRP, LDL, TC, NT-proBNP, and CI.

Conflict of Interests

Authors have no conflict of interests.

References

1. Mishra P, Samanta L. Oxidative stress and heart failure in altered thyroid States. ScientificWorldJournal 2012; 2012: 741861.
2. Esfahani MA, Jolfaii EG, Torknejad M, Etesampor A, Amiz FR. Postprandial hypertriglyceridemia in non-diabetic patients with coronary artery disease. Indian Heart J 2004; 56(4): 307-9.
3. Pepe S, Marasco SF, Haas SJ, Sheeran FL, Krum H, Rosenfeldt FL. Coenzyme Q10 in cardiovascular disease. Mitochondrion 2007; 7(Suppl): S154-S167.
4. Sola S, Mir MQ, Lerakis S, Tandon N, Khan BV. Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. J Am Coll Cardiol 2006; 47(2): 332-7.
5. Sander S, Coleman CI, Patel AA, Kluger J, White CM. The impact of coenzyme Q10 on systolic

function in patients with chronic heart failure. J Card Fail 2006; 12(6): 464-72.
6. Tran MT, Mitchell TM, Kennedy DT, Giles JT. Role of coenzyme Q10 in chronic heart failure, angina, and hypertension. Pharmacotherapy 2001; 21(7): 797-806.
7. Molyneux SL, Florkowski CM, George PM, Pilbrow AP, Frampton CM, Lever M, et al. Coenzyme Q10: an independent predictor of mortality in chronic heart failure. J Am Coll Cardiol 2008; 52(18): 1435-41.
8. Shekelle P, Morton S, Hardy ML. Effect of supplemental antioxidants vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cardiovascular disease. Evid Rep Technol Assess (Summ) 2003; (83): 1-3.
9. Okello E, Jiang X, Mohamed S, Zhao Q, Wang T. Combined statin/coenzyme Q10 as adjunctive treatment of chronic heart failure. Med Hypotheses 2009; 73(3): 306-8.
10. Freeman LM, Roubenoff R. The nutrition implications of cardiac cachexia. Nutr Rev 1994; 52(10): 340-7.
11. Khatta M, Alexander BS, Krichten CM, Fisher ML, Freudenberger R, Robinson SW, et al. The effect of coenzyme Q10 in patients with congestive heart failure. Ann Intern Med 2000; 132(8): 636-40.
12. Berman M, Erman A, Ben-Gal T, Dvir D, Georghiou GP, Stamler A, et al. Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation: a randomized, placebo-controlled study. Clin Cardiol 2004; 27(5): 295-9.
13. Rosenfeldt F, Hilton D, Pepe S, Krum H. Systematic review of effect of coenzyme Q10 in physical exercise, hypertension and heart failure. Biofactors 2003; 18(1-4): 91-100.
14. Saghaei M. Random allocation software for parallel group randomized trials. BMC Med Res Methodol 2004; 4: 26.
15. Langsjoen PH, Langsjoen AM. Supplemental ubiquinol in patients with advanced congestive heart failure. Biofactors 2008; 32(1-4): 119-28.
16. Fotino AD, Thompson-Paul AM, Bazzano LA. Effect of coenzyme Q(1)(0) supplementation on heart failure: a meta-analysis. Am J Clin Nutr 2013; 97(2): 268-75.
17. Hodgson JM, Watts GF. Can coenzyme Q10 improve vascular function and blood pressure? Potential for effective therapeutic reduction in vascular oxidative stress. Biofactors 2003; 18(1-4): 129-36.
18. Pacher P, Schulz R, Liaudet L, Szabo C. Nitrosative stress and pharmacological modulation of heart failure. Trends Pharmacol Sci 2005; 26(6): 302-10.
19. Ferrari R, Guardigli G, Mele D, Percoco GF, Ceconi C, Curello S. Oxidative stress during myocardial ischaemia and heart failure. Curr Pharm Des 2004; 10(14): 1699-711.
20. van den Heuvel AF, van Veldhuisen DJ, van der Wall EE, Blanksma PK, Siebelink HM, Vaalburg WM, et al. Regional myocardial blood flow reserve impairment and metabolic changes suggesting myocardial ischemia in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2000; 35(1): 19-28.
21. Shojaei M, Djalali M, Khatami M, Siassi F, Eshraghian M. Effects of carnitine and coenzyme Q10 on lipid profile and serum levels of lipoprotein(a) in maintenance hemodialysis patients on statin therapy. Iran J Kidney Dis 2011; 5(2): 114-8.

How to cite this article: Pourmoghaddas M, Rabbani M, Shahabi J, Garakyaraghi M, Khanjani R. **Combination of atorvastatin/coenzyme Q10 as adjunctive treatment in congestive heart failure: A double-blind randomized placebo-controlled clinical trial.** ARYA Atheroscler 2014; 10(1): 1-5.

Comparison of competing risks models based on cumulative incidence function in analyzing time to cardiovascular diseases

Minoo Dianatkhah[(1)], Mehdi Rahgozar[(2)], Mohammad Talaei[(3)], Masoud Karimloua[(2)], Masoumeh Sadeghi[(4)], Shahram Oveisgharan[(5)], Nizal Sarrafzadegan[(6)]

Original Article

Abstract

BACKGROUND: Competing risks arise when the subject is exposed to more than one cause of failure. Data consists of the time that the subject failed and an indicator of which risk caused the subject to fail.

METHODS: With three approaches consisting of Fine and Gray, binomial, and pseudo-value, all of which are directly based on cumulative incidence function, cardiovascular disease data of the Isfahan Cohort Study were analyzed. Validity of proportionality assumption for these approaches is the basis for selecting appropriate models. Such as for the Fine and Gray model, establishing proportionality assumption is necessary. In the binomial approach, a parametric, non-parametric, or semi-parametric model was offered according to validity of assumption. However, pseudo-value approaches do not need to establish proportionality.

RESULTS: Following fitting the models to data, slight differences in parameters and variances estimates were seen among models. This showed that semi-parametric multiplicative model and the two models based on pseudo-value approach could be used for fitting this kind of data.

CONCLUSION: We would recommend considering the use of competing risk models instead of normal survival methods when subjects are exposed to more than one cause of failure.

Keywords: Competing Risks, Cumulative Incidence Function, Fine and Gray Model, Binomial Approach, Pseudo-value Approach, Cardiovascular Diseases

Date of submission: 28 Jul 2013, ***Date of acceptance:*** 23 Nov 2013

Introduction

Problems involving competing risks are common in medical researches, where (K > 0) competing causes of failure may occur. Occurrence of any of the risks causes failure or death and precludes the occurrence of other competing risks.[1,2] For such data one observes only the failure time and a cause of failure for each subject in the study. Methods for estimating the probability of failure for events that are subject to competing risks are not new. It is still quite common to see inappropriate methods used to estimate such probabilities for endpoints that suffer from competing risks.[1]

Generally, two types of analysis can be performed when competing risks are present; modeling cause-specific and sub-distribution hazard or cumulative incidence function.[3,4] The Cox regression modeling for each event is an example of the first type. In such a model a subject who has failed in other competing risks is treated as a censored subject. This method is valid if the censoring distributions are independent.[5] Multi-state models that do not require the existence of potential failure times and Aalen additive hazards model are

1- Department of Statistics and Computer Sciences, University of Social Welfare and Rehabilitation Sciences, Tehran AND Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Assistant Professor, Department of Statistics and Computer Sciences, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran
3- Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran AND Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore
4- Associate Professor, Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
5- Department of Neurology, Tehran University of Medical Sciences, Tehran, Iran
6- Professor, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Mehdi Rahgozar, Email: m_rahgozar2003@yahoo.com

other examples of the first type of modeling.[6,7] Klein modeled covariate effects using this method.[7] For the second type, we can find the Fine and Gray[8] method, the binomial approach suggested by Scheike and Zhang,[9] and the pseudo-value approach suggested by Klein and Andersen.[10,11] These approaches are introduced in section 3. We fitted these three methods to cardiovascular diseases (CVD) data of the Isfahan Cohort Study (ICS) introduced in section 2.4.[12,13] In section 3 We present the results, and in section 4 findings are discussed in brief.

Materials and Methods

The most common model for competing risks is in terms of potential failure times, where K is competing risks denoted by $D_1,\ldots,D_k$, and for each risk there is a potential failure time of X_i, i=1,…,K. One observes $T = \min(X_1,\ldots,X_k)$ and a variable $\varepsilon = j$, j = 1,…,K,

Where $T = X_j$ defines which of the risks caused the event to occur. Competing risk probabilities can be summarized by cumulative incidence function for the j^{th} competing risk. This function is defined as probability of experiencing risk j prior to time t in the presence of all competing risks. This quantity depends on all the cause-specific hazard rates ($h_j(t)$ = 1,…,k), not just the crude hazard rate of cause of interest.[1]

(1)

$$F_j(t) = P[T \le t, \varepsilon = j\,] = \int_0^t h_j(x)\exp\{-\sum_{i=1}^{k}\int_0^x h_i(u)$$

When there is a covariate, it is common in medical sciences to study the effect on competing risks quantities.[14-18] One solution is a direct regression modeling of cumulative incidence function. Here, we discuss three approaches that focus on this topic.

Fine and Gray Model

The first approach suggested by Fine and Gray[8] is a proportional sub-distribution hazards model with:

(2) $\gamma(t, Z) = \gamma_0(t)\exp[\beta' Z]$

Where γ and γ_0 are hazard and baseline hazard of the sub-distribution, Z and β are vectors of covariates and coefficients, respectively. The partial likelihood is given by:

(3) $L(\beta) = \prod_{i=1}^{r}\left(\frac{exp(\beta z_i)}{\sum_{j\epsilon R_i}\omega_{ij}exp(\beta z_j)}\right)$

$R_i = \{j; t_j \ge t_i$ or $(t_j \le t_i$ and the subject had competing risk event)$\}$

The risk set R_i is formed of those who did not experience an event by time t and those who experienced a competing risk event by time t. Thus, those who experienced other types of events remain in the risk set all the time. The weights are defined as:

(4) $\omega_{ij} = \frac{\hat{G}(t_i)}{\hat{G}(\min(t_i,t_j))}$

Where $\hat{G}$ is the Kaplan-Meier estimate of survivor function of the censoring distribution.[3] This model is valid if the proportionality assumption is established.

Binomial Approach

The second method is the direct binomial approach suggested by Scheike and Zhang[9] which models cumulative incidence function by a general class of models given by:

(5) $h\{F_1(t,z)\} = g\{\eta(t),\beta,z\}$

Where h and g are the known link and regression functions, respectively, $\eta(t)$ is the unknown regression function and β is the vector of regression parameters. We use the semi-parametric multiplicative model:

(6) c1n1n$\{1\text{-}F_1(t;x,z)\} = \eta(t)'x+\beta'z$

Where X is a (p+1) –dimensional ($X = (1,x_1,\ldots,x_p)$), and Z a q-dimensional covariate. These flexible models allow covariate X to have time-varying effects and the covariate Z to have constant effects:

(7) $E\left(\frac{\Delta_i N_i(t)}{G(T_i)}\right) = F_1(t; X_i, Z_i)$

The model suggests testing the hypothesis that a specific covariate x_j has a constant effect over time and define hypothesis H_0: $\eta_j(t) \equiv \eta$. This leads to a very useful goodness-of-fit test for model validation. The test shows exactly where non-proportionality is present. This approach is to start out with a model where all effects initially have parametric or non-parametric effects, and then reduce model complexity by successive testing to find an appropriate semi-parametric model that fits the data. In brief, for this approach, the model is chosen according to proportionality assumption.

Pseudo-value Approach

The third method of direct modeling of the cumulative incidence function is based on a pseudo-value approach.[11] For this model a grid of time points $\tau_1,\ldots,\tau_M$ is selected. At each grid point, the estimated cumulative incidence function is computed based on the complete data set $\hat{F}(\tau_h)$ and the estimated cumulative incidence function based on the sample of size n-1 obtained by deleting the i^{th} observation $\hat{F}^{(i)}(\tau_h)$ then the pseudo-value for the i^{th} subject at time τ_h is defined as:

(8) $\hat{\theta}_{ih} = n\hat{F}(\tau_h) - (n-1)\hat{F}^{(i)}(\tau_h), i = 1,\ldots,n,$ $h = 1,$ There are the pseudo-values known from jack-knife techniques. $n\hat{F}(t)$ is the number of events of type of interest occurring prior to t, When there

is no censoring. In this case $\hat{\theta}_i = (\hat{\theta}_{ih}, h = 1, \dots, M) = (I(T_i \leq \tau_1, \varepsilon_i = 1), \dots, I(T_i \leq \tau_M, \varepsilon_i = 1))$ and $\hat{\theta}_i's$ are independent. When we have censoring, because pseudo-values are close to the indicators they are approximately independent. This allows us to make use of results from generalized linear models to model the effects of covariates.

(9) $g(\theta_{ih})=\alpha_h+\gamma'Z_i=\beta'Z_{ih},\ i = 1,\dots,n,\ \ h = 1,\dots,M$

Where g(0) is a link function. The possible choices could be the logit link g(x) = log(x/(1-x)), or complementary log-log function g(x) = -log(-log(1-x)) on x. Unlike the Fine and Gray model, this approach does not need to establish proportionality assumption. To select the appropriate link function, one crude way, when the factor is categorical, is to look at plots of differences in transformed estimates of the cumulative incidence functions for each category from the baseline category.

For two categorical factors, the cumulative incidence functions for two groups (ignoring other covariates), is estimated separately. Then, $g(F_{1h}(t))-g(F_{10}(t))$ is plotted, here $F_{10}(t)$ and $F_{1h}(t)$ are the estimated cumulative incidence function for baseline and other categories, respectively, and g(0) is either the logit or complementary log-log transforms. If the link chosen for the plot is correct, then the curves should approximately be horizontal.

Data

To compare these three approaches, we used the data of the Isfahan Cohort Study. The ICS is a community-based, ongoing longitudinal study on 6504 adults aged 35 and older at baseline, aiming at Iranian cardiovascular disease risk chart. Participants lived in both urban and rural areas of three cities and their associated district villages in central Iran (Isfahan, Arak, Najafabad). Several risk factors for cardiovascular disease, like smoking status, lipids, blood pressure, and anthropometric measurements, were measured at baseline. They were followed for 5 years from January 1997 to September 2001. End of study for each subject was confirmed if one of the cardiovascular disease events (CVD) (non-fatal myocardial infarction, fatal myocardial infarction, non-fatal stroke, fatal stroke, sudden cardiac death, and unstable angina) occurred or the subject experienced unrelated CVD death. Finally, data of 5515 participants who had at least one follow-up time after baseline were included in analysis. There is one competing risk of CVD event (event of interest), and it has occurred when the subject experienced unrelated CVD death.[12-19]

Results

From 5515 (2815 females and 2700 males) cases in ICS data, 5.13% had one of the mentioned CVD and 1.5% experienced unrelated CVD death. The study consisted of patients with non-fatal myocardial infarction (n = 52), fatal myocardial infarction (n = 19), sudden cardiac death (n = 46), non-fatal stroke (n = 40), fatal stroke (n = 14), and unstable angina (n = 112). Moreover, 2133 subjects were 35 to 44 years old, 2449 between 45 to 64, and 933 were 65 and older at baseline.

To fit ICS data with R software, the 3 Fine and Gray, binomial, and pseudo-value competing risks approaches, which are directly based on cumulative incidence function were used.[3,5,20,21] As is common in medical literature, parametric models have been studied first. Table 1 shows the results. The Fine and Gray model has maximum number of significant covariates (8) and the lowest variances. On the contrary, multiplicative models have minimum number of significant covariates (6) and the most variances, and 7 covariates are significant in logit and complementary log-log models. In the Fine and Gray model, except for abdominal obesity (P = 0.76) and high low-density lipoprotein cholesterol (high LDL-C) (P = 0.20), other covariates are significant (P < 0.05). For the multiplicative model, age, abdominal obesity, hypertension, diabetes mellitus, and current smoking status are significant (P < 0.05). In logit and complementary log-log models, age, hypertension, high LDL-C, low high-density lipoprotein cholesterol (low HDL-C), diabetes mellitus, and current smoking status are significant (P < 0.05). Slight differences among the models are seen for parameter estimates. In addition, for the Fine and Gray logit and multiplicative models, we can interpret $\exp(\hat{b})$ as the odds in favor of the categories of a factor relative to the baseline category. Table 2 shows the results of fitting of non-parametric multiplicative model. These models differ from parametric models, because their coefficients have time-varying effects. This table also shows the results of testing goodness-of-fit or constant effect test. Age (65 years and older), abdominal obesity, and diabetes mellitus are significant (P < 0.05). This implies that Fine and Gray, parametric and non-parametric multiplicative models are not appropriate, because the proportionality assumption is violated. Therefore, fitting the semi-parametric model is necessary and allows the covariates with constant and non-constant effects to be presented simultaneously in

the model. We use this model later to predict cumulative incidence function for specific subjects. Table 3 shows semi-parametric model results. For this model, age (65 years and older), abdominal obesity, and diabetes mellitus do not have parameter estimates, because of their non-constant effects in time. Figure 1 shows goodness-of-fit plot for hypertension with two logit and complementary log-log transforms. The two plots are approximately horizontal; meaning that both are suitable. Because of differences in variance estimation between these two models, the complementary log-log model is preferred.

Table 1. Results of fitting parametric models on Isfahan Cohort Study (ICS) data

Covariate			Fine and Gary model	Logit model	Complementary log-log model on $1-F_1(t)$	Multiplicative model
Sex**		B	0.482	0.320	0.265	0.186
		SE (b)	0.146	0.191	0.180	0.221
		P	(0.001)*	(0.094)	(0.142)	(0.400)
Age***	45-64	B	0.828	0.790	0.770	1.190
		SE (b)	0.188	0.252	0.246	0.276
		P	(< 0.001)*	(0.002)*	(0.002)*	(< 0.001)*
	≥ 65	B	1.475	1.438	1.372	1.900
		SE (b)	0.198	0.259	0.251	0.278
		P	(< 0.001)*	(< 0.001)*	(< 0.001)*	(< 0.001)*
Abdominal obesity		B	-0.04	-0.165	-0.168	-0.460
		SE (b)	0.151	0.200	0.188	0.244
		P	(0.760)	(0.409)	(0.372)	(0.050)*
Hypertension		B	0.980	1.154	1.099	1.190
		SE (b)	0.129	0.158	0.150	0.202
		P	(< 0.001)*	(< 0.001)*	(< 0.001)*	(< 0.001)*
High LDL-C		B	0.455	0.412	0.381	0.194
		SE (b)	0.124	0.163	0.154	0.200
		P	(< 0.001)*	(0.012)*	(0.013)*	(0.313)
Low HDL-C		B	0.162	0.376	0.353	0.336
		SE (b)	0.153	0.168	0.157	0.210
		P	(0.200)	(0.025)*	(0.024)*	(0.109)
Diabetes mellitus		B	0.592	0.600	0.513	0.733
		SE (b)	0.153	0.191	0.177	0.225
		P	(< 0.001)*	(0.002)*	(0.004)*	(0.001)*
Hypertriglyceridemia		B	0.340	0.253	0.233	0.119
		SE (b)	0.137	0.177	0.167	0.224
		P	(0.013)*	(0.153)	(0.163)	(0.597)
Smoking		B	0.391	0.585	0.533	0.607
		SE (b)	0.153	0.198	0.184	0.233
		P	(0.010)*	(0.003)*	(0.003)*	(0.009)*

* Significant at α = 0.05 level; ** Females are reference group; *** Age between 35 and 44 are reference group
SE: Standard error; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol

Table 2. P-values for non-parametric model on Isfahan Cohort Study (ICS) data

Covariate		Multiplicative Model	
		H_0: η(t)=0	H_0: Constant effect
Sex		0.358	0.264
Age	45-64	< 0.001*	0.280
	> = 65	< 0.001*	< 0.001*
Abdominal obesity		0.002*	0.016*
Hypertension		< 0.001*	0.096
High LDL-C		0.170	0.508
Low HDL-C		0.118	0.490
Diabetes mellitus		< 0.001*	0.024*
Hypertriglyceridemia		0.240	0.578
Smoking		0.012*	0.084

* Significant at α = 0.05 level
LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol

Table 3. Results of fitting semi-parametric model on Isfahan Cohort Study (ICS) data

Covariate		Multiplicative Model		
		b	SE (b)	P
Sex		0.142	0.225	0.527
Age	45-64	1.090	0.225	< 0.001*
	≥ 65	-	-	< 0.001*
Abdominal obesity		-	-	< 0.001*
hypertension		1.190	0.201	< 0.001*
High LDL-C		0.213	0.202	0.292
Low HDL-C		0.375	0.225	0.081
Diabetes mellitus		-	-	< 0.001*
Hypertriglyceridemia		0.110	0.236	0.640
Smoking		0.635	0.234	0.006*

* Significant at α = 0.05 level;
SE: Standard error; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol

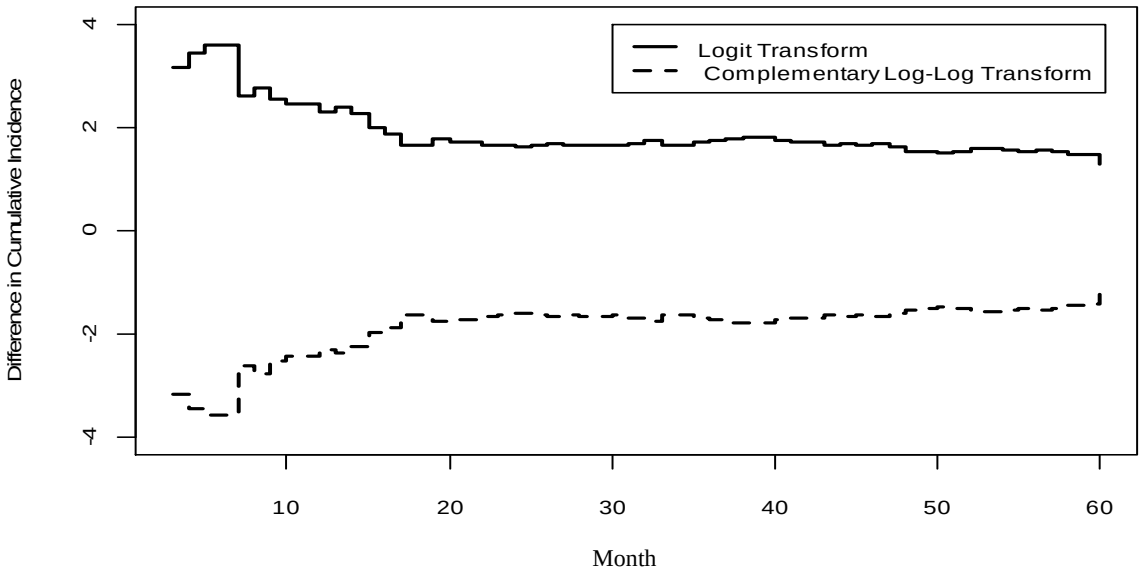


Figure 1. Difference in cumulative incidence function for logit and complementary log-log transform in hypertension

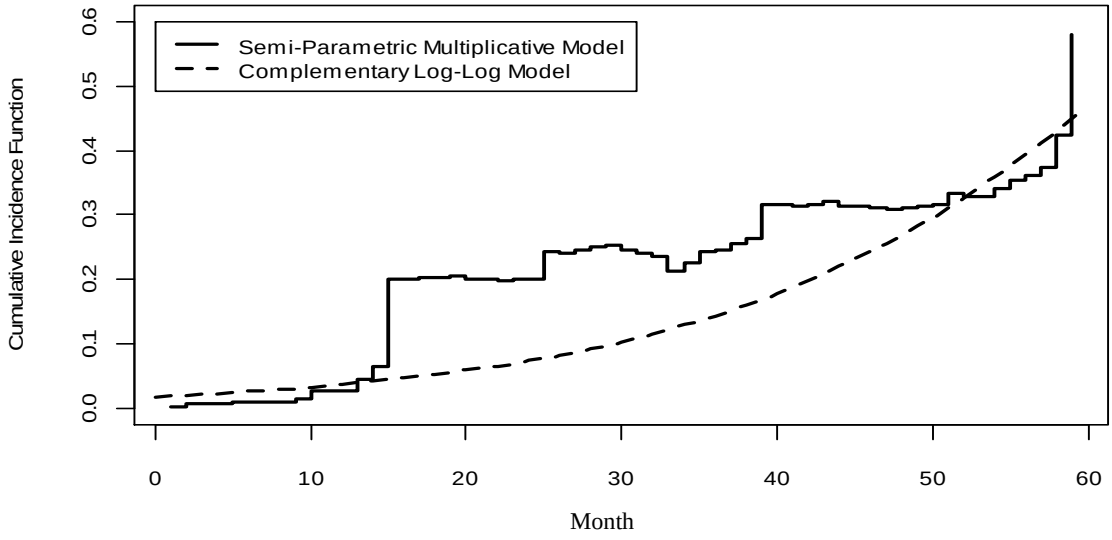


Figure 2. Predictions for cardiovascular diseases (CVD) cumulative incidence function for Isfahan Cohort Study (ICS) data using semi-parametric multiplicative and complementary log-log model

Sometimes it is important to get an idea of the cumulative incidence probability for specific patients. Therefore, computing the predicted cumulative incidence function for a given set value of covariates is very popular.[22,23] For example, suppose that physicians want to know the value of cumulative incidence function for male patients older than 65 with abdominal obesity, hypertension, high LDL-C, low HDL-C, diabetes mellitus, hypertriglyceridemia, and smoking. Figure 2 shows the predicted cumulative incidence function during 60 months for two appropriate complementary log-log and semi-parametric multiplicative models. The predicted values for the first model are less than the second model for about 35 months (between the 15th-58th months).

Discussion

Data from studies with competing risks outcomes present challenges to the data analyst. Some articles analyze such data with normal survival models. A criticism that can be leveled at these models is the assumption that upon removal of one cause of failure, the risk of failure from remaining causes is unchanged. In human studies this assumption is rarely true.[3-5] Here we have used three approaches (Fine and Gray, binomial, and pseudo-value approaches) which are based directly on the cumulative incidence function and their validity depends on proportionality assumption. This collection of models gives a rich variety, from which a user can choose an appropriate model for analyzing the data.

We saw that the Fine and Gray, parametric multiplicative model was not able to describe the cumulative incidence function for ICS data. This model's lacking flexibility was found using the goodness-of-fit approach. This showed that its non-proportionality can primarily be attributed to the effect of covariates. A similar conclusion was reached for the non-parametric multiplicative model. The semi-parametric multiplicative model could be a good choice for this data. With the pseudo-value approaches, two link functions were used in GLM model (logit or complementary log-log function). Unlike the Fine and Gray and multiplicative models, this is more flexible so that we do not need to assume proportionality. Goodness-of-fit plots showed that both link functions are suitable for hypertension groups, but they were different in variance estimation. Moreover, it seems the complementary log-log function is more appropriate. Predictions plot for ICS data using semi-parametric multiplicative and complementary log-log models were quite similar during 5 years, but slight differences in parameters regression were found between the two models.

Conclusion

Inappropriate statistical methods are not rare in binomial literature.[5] The competing risk problem is a critical issue in survival analysis. We would recommend considering competing risk models instead of simply using normal survival methods when subjects are exposed to more than one cause of failure. In future studies like ICS, using competing risks models is suggested, because a large number of unrelated CVD deaths will occur during years of follow-up and the use of normal survival functions can lead to incorrect or at least imprecise estimates. As we described, the two appropriate semi-parametric multiplicative and complementary log-log models are proposed for fitting of such data.

Acknowledgements

The authors appreciate the cooperation of Prof. Nizal Sarrafzadegan, Head of Isfahan Cardiovascular Research Institute, and would like to thank her colleagues for their valuable comments and suggestions.

Conflict of Interests

Authors have no conflict of interests.

References

1. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999; 18(6): 695-706.
2. Klein JP. Competing risks. Wiley Interdisciplinary Reviews: Computational Statistics 2010; 2(3): 333-9.
3. Pintilie M. Competing Risks: A Practical Perspective. New Jersey, NJ: John Wiley & Sons; 2006.
4. Pintilie M. Analysing and interpreting competing risk data. Stat Med 2007; 26(6): 1360-7.
5. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007; 26(11): 2389-430.
6. Andersen PK, Abildstrom SZ, Rosthoj S. Competing risks as a multi-state model. Stat Methods Med Res 2002; 11(2): 203-15.
7. Klein JP. Modelling competing risks in cancer studies. Stat Med 2006; 25(6): 1015-34.
8. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk.

Journal of the American Statistical Association 1999; 94(446): 496-509.
9. Scheike TH, Zhang MJ. Flexible competing risks regression modeling and goodness-of-fit. Lifetime Data Anal 2008; 14(4): 464-83.
10. Andersen PK, Klein JP, Rosthøj S. Generalised Linear Models for Correlated Pseudo-Observations, with Applications to Multi-State Models. Biometrika 2003; 90(1): 15-27.
11. Klein JP, Andersen PK. Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. Biometrics 2005; 61(1): 223-9.
12. Sarrafzadegan N, Talaei M, Sadeghi M, Kelishadi R, Oveisgharan S, Mohammadifard N, et al. The Isfahan cohort study: rationale, methods and main findings. J Hum Hypertens 2011; 25(9): 545-53.
13. 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.
14. Cox DR, Oakes D. Analysis of survival data. London, UK: Chapman & Hall; 1984.
15. Crowder MJ. Classical competing risks. New York, NY: Taylor & Francis; 2001.
16. David HA, Moeschberger ML. The Theory of Competing Risks. London, UK: Griffin Publishing Group; 1978.
17. Prentice RL, Kalbfleisch JD, Peterson AV, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. Biometrics 1978; 34(4): 541-54.
18. Klein JP, Moeschberger ML. Survival Analysis: Techniques for Censored and Truncated Data. New York, NY: Springer; 2003.
19. Sarraf-Zadegan N, Sadri G, Malek AH, Baghaei M, Mohammadi FN, Shahrokhi S, et al. Isfahan Healthy Heart Programme: a comprehensive integrated community-based programme for cardiovascular disease prevention and control. Design, methods and initial experience. Acta Cardiol 2003; 58(4): 309-20.
20. Crawley MJ. The R Book. New Jersey, NY: John Wiley & Sons; 2007.
21. Klein JP, Gerster M, Andersen PK, Tarima S, Perme MP. SAS and R functions to compute pseudo-values for censored data regression. Comput Methods Programs Biomed 2008; 89(3): 289-300.
22. Hyun S, Sun Y, Sundaram R. Assessing cumulative incidence functions under the semiparametric additive risk model. Stat Med 2009; 28(22): 2748-68.
23. Zhang MJ, Zhang X, Scheike TH. Modeling cumulative incidence function for competing risks data. Expert Rev Clin Pharmacol 2008; 1(3): 391-400.

How to cite this article: Dianatkhah M, Rahgozar M, Talaei M, Karimloua M, Sadeghi M, Oveisgharan Sh, et al. **Comparison of competing risks models based on cumulative incidence function in analyzing time to cardiovascular diseases.** ARYA Atheroscler 2014; 10(1): 6-12.

Stent underexpansion in angiographic guided percutaneous coronary intervention, despite adjunctive balloon post-dilatation, in drug eluting stent era

Mehrdad Taherioun[(1)], Mohammad Hassan Namazi[(2)], Morteza Safi[(2)], Habibolah Saadat[(3)], Hossein Vakili[(2)], Saeed Alipour-Parsa[(4)], Hasan Rajabi-Moghadam[(5)], Shamsedin Pedari[(1)]

Original Article

Abstract

BACKGROUND: Stent underexpansion is the most powerful predictor of long-term stent patency and clinical outcome. The purpose of this study was to evaluate the incidence and predictors of stent underexpansion despite adjunctive post-dilatation with non-compliant balloon.

METHODS: After elective coronary stent implantation and adjunctive post-dilatation with non-compliant balloon and optimal angiographic result confirmed by the operator, intravascular ultrasound (IVUS) was performed for all the treated lesions. If the treated lesions fulfilled the IVUS criteria, they are considered as the optimal stent group; if not, they are considered as the suboptimal group.

RESULTS: From 50 patients enrolled in this study 39 (78%) had optimal stent deployment and 11 (22%) had suboptimal stent deployment. In the suboptimal group 7 (14%) had underexpansion, 2 (4%) malposition, and 2 (4%) had asymmetry. There were no stent edge dissections detected by IVUS. We did not find any correlation between lesion calcification, ostial lesions, stent length, and stent underexpansion. Stent diameter ≤ 2.75 mm had a strong correlation with stent underexpansion.

CONCLUSION: Despite adjunctive post-dilatation with noncompliant balloon, using a relatively small stent diameter was a strong predictor for underexpansion. IVUS guided percutaneous coronary intervention (PCI) may be considered for drug eluting stent (DES) implantation in relatively small vessels.

Keywords: Stent, Percutaneous Coronary Intervention, Ultrasound, Post-dilatation

Date of submission: 16 May 2013, ***Date of acceptance:*** 5 Nov 2013

Introduction

Angiographic guided percutaneous coronary intervention (PCI) is a common practice for the treatment of coronary artery lesions and procedural success is usually determined by the operator visual estimation. However, such subjective estimation of the procedural result is thought to be of limited reliability. Undoubtedly, intravascular ultrasound (IVUS) analysis is more accurate than angiography in detecting suboptimal stent deployment.[1-4] In comparison with bare metal stents; drug eluting stents (DESs) have led to a dramatic reduction in the rate of stent restenosis and the need for repeated revascularization. Therefore, the importance of optimal stent deployment was less considered.[5-7] This has caused the decreased use of adjunctive post-dilatation with noncompliant balloon. The frequency of achieving optimum stent deployment varied in different studies depending on the IVUS criteria used. Although many IVUS criteria for suboptimal stent deployment have been described, a uniform and accepted definition of optimal expansion is still lacking. The fundamental concepts underlying them include stent underexpansion, incomplete stent apposition, edge dissection, and lesion under coverage. Adjunctive post-dilatation with non-compliant balloon can increase minimal stent area (MSA) and decrease

1- Cardiac Rehabilitation Research Centre, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Associate Professor, Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3- Professor, Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4- Assistant Professor, Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5- Assistant Professor, Kashan University of Medical Sciences, Kashan, Iran
Correspondence to: Morteza Safi, Email: mortezasaafi@yahoo.com

suboptimal stent deployment; therefore, it may reduce the frequency of target vessel revascularization (TVR) and stent thrombosis.[8]

This study was designed to evaluate the incidence and predictors of stent underexpansion despite adjunctive post-dilatation with non-compliant balloon. We also hypothesized that relatively small stent diameter might be a predictor of inadequate stent expansion.

Materials and Methods

The present study consisted of 50 patients who underwent stent implantation from April 2012 to March 2013 at Modarres Hospital, Tehran, Iran. All patients were pre-medicated with 325 mg of aspirin and loading dose of 300-600 mg of clopidogrel. Intravenous heparin was administered to maintain an activated clotting time of 250-300 s. The use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Inclusion criteria included coronary significant stenosis scheduled for elective coronary stent implantation. Exclusion criteria included a distal reference vessel diameter < 2.5 mm by visual estimation, acute myocardial infarctions (within 48 h), left main stenting, stent placement within an aneurysmal portion of a vessel, and allergies to aspirin, clopidogrel, or heparin. The study protocol was approved by the Institutional Ethics Committee, and a written informed consent was obtained from all the patients.

All the stents implanted were drug eluting stents and had received FDA approval or CE mark. Stents were deployed at nominal pressure and post-dilatation was done for all the treated lesions with non-compliant balloons, 0.25-0.5 mm larger than the stent delivery balloon at high pressure of 18-20 atmospheres (atm). The need for additional post-dilatation with larger non-compliant balloon depends on angiographic success and operator's decision. Angiographic success is defined as a final stent diameter stenosis of less than 10% of the distal reference vessel with the use of an automated edge detection system (QCA-CMS, Medis Medical Imaging Systems, Nuenen, Netherlands). If the patient fulfilled the angiographic success criteria, IVUS study was performed.

IVUS imaging and analysis

Intravascular ultrasound studies were performed with a commercially available system (Volcano Corporation, Rancho Cordova, CA, USA), incorporating an Eagle Eye catheter. After the administration of 100 to 200 μg of intracoronary nitroglycerine, ultrasound transducer was advanced 5 mm beyond the stent, and an image recording was performed to a point 5 mm proximal to the stent by manual pullback. All IVUS recordings were reviewed and quantitative parameters evaluated. These data consisted of MSA at the lesion, and at proximal and distal stent edges. Optimal stent deployment was defined as either MSA > 5.0 mm^2 or > 90% of the distal reference lumen area, complete apposition to the vessel wall, no edge dissection, and symmetry of stent.

Statistical Analysis

The statistical analysis was performed using SPSS for Windows (version 15; SPSS Inc., Chicago, IL, USA). The quantitative results were expressed as mean ± SD. Normality of data was evaluated with the Kolmogorov–Smirnov test, and statistical evaluation of data was performed using analysis of variance (ANOVA), followed by the Tukey's post-hoc test. The statistical significance of differences between proportions was determined by chi-square analysis with Yates' correction. Differences were considered significant if $P < 0.05$.

Results

All 50 patients enrolled in this study had adequate data for IVUS core laboratory analysis. Baseline clinical characteristics of patients in this analysis were similar in both groups. Baseline procedural and angiographic characteristics were also similar (Table 1). Of these 50 patients, 39 (78%) met the predefined IVUS criteria for optimum stent deployment, and the remaining 11 patients (22%), who did not meet the IVUS criteria, were classified as the suboptimum stent deployment group. There were no significant differences in baseline clinical, angiographic, and procedural characteristics between patients who met and did not meet the IVUS criteria for suboptimum stent deployment (Table 2).

The suboptimal group included stent underexpansion, stent malposition, asymmetry of stent, and edge dissection (Table 3). Calcification at target lesion, and vessel type were not predictors of stent underexpansion (Table 4). Of the procedural characteristics, stent length was not a predictor of sent underexpansion, but nominal stent diameter ≤ 2.75 mm was a strong predictor of stent underexpansion ($P = 0.002$), (Table 4). There were 22 stents (44% of total number of stents) with a diameter ≤ 2.75 mm implanted in this study, and about one third (7 out of 22) did not meet the IVUS criteria for optimum stent expansion. All implanted stents with a diameter > 2.75 mm had well

Table 1. Base line clinical characteristics

	All	Optimal stent deployment	Suboptimal stent deployment	P
Age (mean ± SD)	60.9 ± 11.8	61.0 ± 12.2	60.8 ± 10.9	0.910*
EF (mean ± SD)	47.7 ± 10.8	48.7 ± 10.7	44.1 ± 11.0	0.213**
DM	20	15 (75.0%)	5 (25.0%)	0.736*
HT	33	26 (79.0%)	7 (21.0%)	1.000*
HLP	30	23 (77.0%)	7 (23.0%)	1.000*
SM	18	15 (83.4%)	3 (16.6%)	0.734*
AMI	14	10 (71.4%)	4 (28.6%)	0.788*
Female	18	14 (88.0%)	4 (22.0%)	0.381*

* Chi-square test; ** ANOVA

EF: Ejection fraction; DM: Diabetes melitus; HT: Hypertension; HLP: Hyperlipidemia; SM: Smoker; AMI: Acute myocardial infarction

Table 2. Base line angiographic characteristics

Vessel	All	Optimal stent deployment	Suboptimal stent deployment	P
LAD	32	24 (75.0%)	8 (25.0%)	0.501*
LCX	11	9 (82.0%)	2 (18.0%)	0.501*
RCA	7	6 (85.7%)	1 (14.3%)	0.501*
Location				
Ostial	11	10 (90.9%)	1 (9.1%)	0.392*
Sent length (mean ± SD)	25.3 ± 8	25.3 ± 8	25.3 ± 8	0.581**

* Chi-square test; ** ANOVA

LAD: Left anterior descending artery; LCX: Left cicumflex atery; RCA: Right coronary artery

expanded in IVUS. Stent area at lesion was 4.4 ± 0.3 mm^2 in the underexpansion group, and 7 ± 2.1 mm^2 in the optimal stent group. No correlation was found between patients' previous medical history or their risk factors included in this study, and the result of expansion. Additionally, no further significant relations were found among the various variables examined using regression models.

Table 3. Prevalence of suboptimal stent deployment

Suboptimal stent deployment	N	%
Underexpansion	7	14
Mal apposition	2	4
Asymmetry	2	4
Edge dissection	0	0
Total	11	22

Table 4. Angiographic and procedural predictors of stent underexpansion

Angiographic characteristic	Met IVUS criteria for underexpansion	P*
Vessel	5	0.510
LAD, n = 32	2	
LCX, n = 11	0	
RCA, n = 7		
Calcification		0.337
Yes, n = 12	3	
No, n = 38	4	
Procedural characteristic		
Stent diameter		0.002
≤ 2.75 mm, n = 22	7	
> 2.75 mm, n = 28	0	
Stent length		0.660
< 23 mm, n = 16	3	
≥ 23 mm, n = 34	4	
Stent area at lesion (mean ± SD)	4.4 ± 0.3 mm^2	

* Chi-square test

LAD: Left anterior descending artery; LCX: Left cicumflex atery; RCA: Right coronary artery; IVUS: Intravascular ultrasound

Discussion

This study demonstrated that 22% of lesions, which had undergone angiographic guided DES implantation following adjunctive post-dilatation with noncompliant balloon, did not meet IVUS criteria for optimal stent deployment. We did find that 14% of all implanted stents had either MSA < 5.0 mm^2 or < 90% of the distal reference lumen area; they were classified as underexpansion subgroup. Nominal stent diameter ≤ 2.75 mm was a strong predictor of stent underexpansion in our study. It showed that despite adjunctive post-dilatation with noncompliant balloon, PCI on relatively small vessel or choosing an undersized stent could result in stent underexpansion.

It has been shown that post-dilatation with noncompliant balloons improved stent expansion and decreased the frequency of suboptimum stent deployment.[9,10] In the Bare Metal Stent (BMS) era, several studies demonstrated the beneficial effect of a larger MSA with adjunctive post-dilation balloon on post procedural angiographic results and stent restenosis during long-term follow up.[11-13] The importance of adjunctive balloon for post-dilatation has been shown in the post-dilatation clinical comparative study (POSTIT) trial; with optimal stent expansion defined as MSD ≥ 90% of the average reference lumen diameter, only 36% of patients undergoing coronary stenting met the IVUS criteria without adjunctive balloon post-dilatation.[9] In the angiography versus intravascular ultrasound-directed (AVID) study, optimum stent deployment (defined as MSA ≥ 90% of the average reference lumen area by blinded IVUS) was achieved in 57% of patients.[8] In comparison to our study, such a high incidence of underexpansion, despite adjunctive post-dilatation in AVID trial, was due to strict IVUS criteria used for optimizing BMSs.

In the DES era, in a substudy of the Sirius trial, the adequate DES patency was defined as a follow up IVUS MSA > 4.0 mm^2. When the adequate post-interventional MSA of sirolimus-eluting stents (SESs) was defined as > 5.0 mm^2, the positive predictive value of patency was 90%.[14] de Ribamar et al. found that without adjunctive balloon post-dilatation, 24% of SES and 28% of paclitaxel-eluting stent (PES) did not achieve a final MSA of 5 mm^2.[15] In comparison to our study, the higher rate of underexpansion observed by de Ribamar et al. indicated the importance of adjunctive balloon post-dilatation in DES implantation.

There are several potential reasons to the occurrence of suboptimal stent expansion despite post-dilatation with a larger noncompliant balloon. First, the inflated balloon pressure could be inadequate for optimal stent deployment. In the POSTIT trial, stent deployment at less than 12 atm was associated with a high frequency of suboptimal stent deployment. However, this did not appear to be the case in our study, since all stents were deployed at nominal pressure and post-dilated with larger noncompliant balloon at a high pressure of 18-20 atm. Second, selecting an undersized stent delivery balloon for the target lesion may usually cause stent underexpansion.[8] Since we did not perform IVUS before stent implantation, the operator could not assess whether the vessel was really a small vessel or just appeared as such at angiography.

This practice might result in stent underexpansion. Although the benefit of IVUS guidance is most important in complex lesion subsets, such as left main and bifurcation lesions, IVUS guided PCI even in relatively small vessels resulted in larger MSA. In health outcome and mortality evaluation (HOME) DES study all the IVUS guided PCI group had optimal stent expansion.[16]

Calcified vessels could affect final stent lumen area, preventing complete stent expansion even when higher pressures or larger balloons were applied.[17,18] However, vessel calcification was not a predictor of stent underexpansion in our study; this result was in accordance with the study of de Ribamar et al.[15]

The present study showed that about one third of implanted DESs with nominal diameter ≤ 2.75 mm met the IVUS criteria for underexpansion. In nominal diameter > 2.75 mm all implanted DESs with adjunctive post-dilatation had expanded well.

Study limitations

This was a single-center study with a relatively small sample size. Interobserver and intraobserver differences in interpretation may affect the results.

Conclusion

The present study showed that despite adjunctive post-dilatation with noncompliant balloon, stent diameter ≤ 2.75 mm was a strong predictor of DES underexpansion. IVUS guided PCI in relatively small vessels may prevent stent underexpansion. Angiographic guided PCI with adjunctive post-dilatation had acceptable IVUS results in DES implantation in stent diameter > 2.75 mm.

Conflict of Interests

Authors have no conflict of interests.

References

1. Nakamura S, Colombo A, Gaglione A, Almagor Y, Goldberg SL, Maiello L, et al. Intracoronary ultrasound observations during stent implantation. Circulation 1994; 89(5): 2026-34.
2. Blasini R, Neumann FJ, Schmitt C, Bokenkamp J, Schomig A. Comparison of angiography and intravascular ultrasound for the assessment of lumen size after coronary stent placement: impact of dilation pressures. Cathet Cardiovasc Diagn 1997; 42(2): 113-9.
3. Mudra H, Klauss V, Blasini R, Kroetz M, Rieber J, Regar E, et al. Ultrasound guidance of Palmaz-Schatz intracoronary stenting with a combined intravascular ultrasound balloon catheter. Circulation 1994; 90(3): 1252-61.
4. Laskey WK, Brady ST, Kussmaul WG, Waxler AR, Krol J, Herrmann HC, et al. Intravascular ultrasonographic assessment of the results of coronary artery stenting. Am Heart J 1993; 125(6): 1576-83.
5. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban HE, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002; 346(23): 1773-80.
6. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003; 349(14): 1315-23.
7. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004; 350(3): 221-31.
8. Russo RJ, Attubato MJ, Davidson CJ, DeFranco AC, Fitzgerald PJ, Iaffaldano RA, et al. Angiography versus intravascular ultrasound-directed stent placement: final results from AVID. Circulation 1999; 100(suppl I): I-234.
9. Brodie BR, Cooper C, Jones M, Fitzgerald P, Cummins F. Is adjunctive balloon postdilatation necessary after coronary stent deployment? Final results from the POSTIT trial. Catheter Cardiovasc Interv 2003; 59(2): 184-92.
10. Chieffo A, Latib A, Caussin C, Presbitero P, Galli S, Menozzi A, et al. A prospective, randomized trial of intravascular-ultrasound guided compared to angiography guided stent implantation in complex coronary lesions: the AVIO trial. Am Heart J 2013; 165(1): 65-72.
11. Gorge G, Haude M, Ge J, Voegele E, Gerber T, Rupprecht HJ, et al. Intravascular ultrasound after low and high inflation pressure coronary artery stent implantation. J Am Coll Cardiol 1995; 26(3): 725-30.
12. Fitzgerald PJ, Oshima A, Hayase M, Metz JA, Bailey SR, Baim DS, et al. Final results of the Can Routine Ultrasound Influence Stent Expansion (CRUISE) study. Circulation 2000; 102(5): 523-30.
13. Albiero R, Rau T, Schluter M, Di MC, Reimers B, Mathey DG, et al. Comparison of immediate and intermediate-term results of intravascular ultrasound versus angiography-guided Palmaz-Schatz stent implantation in matched lesions. Circulation 1997; 96(9): 2997-3005.
14. Sonoda S, Morino Y, Ako J, Terashima M, Hassan AH, Bonneau HN, et al. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the sirius trial. J Am Coll Cardiol 2004; 43(11): 1959-63.
15. de Ribamar CJ, Mintz GS, Carlier SG, Fujii K, Sano K, Kimura M, et al. Intravascular ultrasound assessment of drug-eluting stent expansion. Am Heart J 2007; 153(2): 297-303.
16. Jakabcin J, Spacek R, Bystron M, Kvasnak M, Jager J, Veselka J, et al. Long-term health outcome and mortality evaluation after invasive coronary treatment using drug eluting stents with or without the IVUS guidance. Randomized control trial. HOME DES IVUS. Catheter Cardiovasc Interv 2010; 75(4): 578-83.
17. Albrecht D, Kaspers S, Fussl R, Hopp HW, Sechtem U. Coronary plaque morphology affects stent deployment: assessment by intracoronary ultrasound. Cathet Cardiovasc Diagn 1996; 38(3): 229-35.
18. Vavuranakis M, Toutouzas K, Stefanadis C, Chrisohou C, Markou D, Toutouzas P. Stent deployment in calcified lesions: can we overcome calcific restraint with high-pressure balloon inflations? Catheter Cardiovasc Interv 2001; 52(2): 164-72.

How to cite this article: Taherioun M, Namazi MH, Safi M, Saadat H, Vakili H, Alipour-Parsa S, et al. **Stent underexpansion in angiographic guided percutaneous coronary intervention, despite adjunctive balloon post-dilatation, in drug eluting stent era.** ARYA Atheroscler 2014; 10(1): 13-7.

Relationship between legumes consumption and metabolic syndrome: Findings of the Isfahan Healthy Heart Program

Firouzeh Sajjadi[(1)], Mojgan Gharipour[(2)], Noushin Mohammadifard[(3)], Fatemeh Nouri[(4)], Maryam Maghroun[(5)], Hasan Alikhasi[(6)]

Original Article

Abstract

BACKGROUND: Epidemiologic studies have shown an inverse association between dietary fiber and metabolic syndrome (MetS). Therefore, the purpose of this study was to investigate the association between MetS and consumption of legumes in adults in Isfahan, Iran.

METHODS: This cross-sectional study was carried out on 2027 individuals who were a subsample of the 3rd phase of the Isfahan Healthy Heart Program (IHHP). Basic characteristics information such as age, sex, smoking status, and physical activity were collected using a questionnaire. A validated 48-item food frequency questionnaire was used to assess dietary behaviors. Blood pressure, waist circumference (WC), glucose, triacylglycerols, and high-density lipoprotein cholesterol were measured, and MetS was defined based on Adult Treatment Panel III guidelines. Multiple logistic regression models examined associations of frequency consumption of legumes with MetS occurrence and its components.

RESULTS: All MetS components were less prevalent among subjects with regular legume intake ($P < 0.01$). Legume intake was inversely associated with the risk of MetS, after adjustment for confounding factors in women. Life style adjusted odds ratio of Mets between highest and lowest tertile and no consumption (as reference category) of legume intake were 0.31 (0.13, 0.70), 0.38 (0.17, 0.87), respectively, in women ($P = 0.01$).

CONCLUSION: This study showed that age has a crucial role in MetS incidence; therefore, after further age adjustment to lifestyle adjusted model there was no significant difference in lower and higher tertile of legume intake and MetS.

Keywords: Legumes, Metabolic Syndrome, Iran

Date of submission: 23 Jul 2013, ***Date of acceptance:*** 23 Nov 2013

Introduction

The metabolic syndrome (MetS) may contribute to the increase in the risk of cardiovascular disease (CVD) and diabetes.[1] This condition affects at least one quarter of the population in developed countries, and its prevalence has steadily increased in recent years.[2] The prevalence of MetS, based on Adult Treatment Panel (ATP) III criteria, is more than 25% in developed countries.[3] However, it seems this figure is relatively higher in developing countries; for example, the prevalence of this syndrome has been reported to be 21.0% in Oman, 39.6% in Emirate, 22.5% in Iran, and 33.4% in Turkey.[4-6]

Many studies have revealed a clear relationship between diet and components of MetS.[7,8] Having a healthy food pattern, which includes cereals, fish, legumes, vegetables, and fruits, is inversely associated with waist circumference (WC), blood pressure (PB), triglycerides (TG), and positively

1- Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- PhD Candidate, Department of Metabolic Syndrome, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- PhD Candidate, Department of Nutrition, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
5- Hypertension Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
6- Department of Nutrition, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Mojgan Gharipour, Email: gharipour@crc.mui.ac.ir

linked with high density lipoprotein-cholesterol (HDL-C) levels, which are all well-known components of the MetS.[9] Epidemiologic studies have shown an inverse association between dietary fiber and MetS.[10-12] In this regard, Bazzano et al. reported a significant inverse relationship between legume intake and risk of CVD.[13] They reported that legume consumption of 4 times or more per week, compared with less than once a week, was associated with a 22% lower risk of coronary heart disease (CHD) and an 11% lower risk of CVD.[13] Additionally, the current findings indicate that a dietary pattern characterized by high consumption of fruit, vegetables, poultry, and legumes is associated with reduced risk of insulin resistance and the MetS in Iranian females.[14] Although many studies have been done to find the role of nutritional groups, especially fiber source foods, with Mets, to our knowledge, this study is the first to provide evidence related to the role of legumes according to sex and lifestyle factors.[15,16] Therefore, the purpose of this study was to investigate the association between MetS and consumption of legumes in adults in Isfahan, Iran.

Materials and Methods

This is a cross-sectional study based on data from the 3rd phase of the Isfahan Healthy Heart Program (IHHP) in 2007. Using a stralificated cluster random sampling, 2027 individuals were selected from Isfahan and Najafabad counties, according to age, sex, and rural and urban population distribution. In this survey, multistage, cluster random sampling design was used. The methodology has been previously published in detail elsewhere.[17,18] The samples were 19 years old, had no hemorrhagic diseases and mental retardation, had Iranian nationality, and were living at their current address for at least 6 months. Pregnant and breast-feeding women were excluded from the study.

To determine validity and reliability of the questionnaire 2 pilot studies have been performed on 200 adults who were not part of the final sample. Questioners were completed 2 times in 2 weeks.

The questionnaire's reproducibility was examined by pretest and posttest on 200 subjects. The final questionnaire was approved by the Medical Education Development Center, and Cronbach's alpha correlation coefficient was determined (Cronbach's alpha = 0.80).[19]

Demographic data, such as age and sex, nutritional knowledge, attitude and practice, and medical history, were obtained. Moreover, clinical and paraclinical examinations were conducted. Trained interviewers collected demographic information and information about the individuals and their nutritional practices.

We used updated ATP III definition for MetS. In this definition participants should meet at least 3 of the following criteria: WC ≥ 102 cm in men and ≥ 88 cm in women; HDL-C < 40 mg/dl in men and < 50 mg/dl in women or specific treatment for this lipid abnormality; TG ≥ 150 mg/dl or specific treatment for this lipid abnormality; systolic BP (SBP) ≥ 130 mmHg or diastolic BP (DBP) ≥ 85 mmHg or treatment of previously diagnosed hypertension; and fasting blood glucose (FBS) ≥ 110 mg/dl or using drug.[20] Serum total cholesterol (TC) and TG were measured with enzymatic colorimetric methods (Elan Auto Analyzer 2000). HDL_C was measured after the precipitation of other lipoproteins (with a heparin manganese chloride mixture) and low density lipoprotein-cholesterol (LDL) level was derived from the Friedewald et al. equation.[21] Serum glucose concentration was measured using an enzymatic reaction.[22] The variation coefficient was < 5% for all laboratory measurements.

All of the tests were performed at the Isfahan Cardiovascular Research Center laboratory which is under the qualitative control of the National Reference Laboratory [a WHO (World Health Organization) collaborating center]. BP was measured using a standard mercury sphygmomanometer on the right arm with subjects seated and after at least 10 minutes resting. WC was measured in the middle distance between the lowest rib and the highest end of the pelvis.[23]

Assessment of dietary intake

Dietary behaviors were assessed with validated qualitative 48-item food frequency questionnaire (FFQ).[19] As the present study is an interventional program similar to the countrywide integrated noncommunicable diseases intervention (CINDI) program, the FFQ was adapted from the CINDI program questionnaire.[24] For each food item, participants were asked to report frequency consumption during the previous year. Dietary intake on the FFQ questionnaire was first classified into 12 food groups as follows: (i) fruits; (ii) vegetables; (iii) dairy products; (iv) non-hydrogenated vegetable oils; (v) legumes; (vi) nuts; (vii) white meat; (viii) grains; (ix) hydrogenated vegetable oils; (x) red meat; (xi) processed meat; and (xii) sweets and pizza. We then quantified participants' intake from these groups and divided the participants into quintiles according to their intake. Individuals in the 2 highest intake quintiles

for fruits, vegetables, dairy products, non-hydrogenated vegetable oils, legumes, nuts, and white meat were classified as having a healthy diet and were given a score of 1 for each food group. However, those in the lowest, second, and third intake quintiles of these food groups were given a score of 0. For unhealthy food groups, like grains, hydrogenated vegetable oils, red meat and processed meat, and sweets and pizza, the opposite was done; individuals in the lowest and second quintiles were given a score of 1 and those in the three highest quintiles were given a score of 0. All grains were classified as unhealthy, because the ones ordinarily consumed in Iran are refined rather than whole. Pizza plus sweets were counted as a single unhealthy food group, because both are commonly consumed in Iran and contain harmful fats, such as trans-fats. It was not possible to separate low- and high-fat dairy products, because the distinction was not made in the consumption questionnaire; therefore, all dairy products were classified as a single, healthy food group. The total dietary score was calculated as the sum of the scores given for all 12 food groups. Thus, the total dietary score for each individual could vary from 0–12.[25] Data on physical activity and smoking behaviors were gathered by questionnaires. Physical activity, expressed as metabolic equivalent task (MET) minutes per week, were obtained through an oral questionnaire that included questions on 4 activity domains: job-related physical activity; transportation-related physical activity; housework and house maintenance activities; and recreation, sport, and leisure-time physical activity. We asked participants to think about all the vigorous and moderate activities they had performed in the last 7 days, considering the number of days a week and the time spent on these activities. Several questions on smoking behaviors were asked, with the following key questions used to categorize individuals: "Are you currently smoking (cigarettes, pipe, and hookah)?" and "What is the frequency of smoking in a day, week, or month?".[25] Quality of life was assessed using the world Health Organization Quality of Life Questionnaire BREF (WHOQOL-BREF). This is 26-item questionnaire that assesses life in the physical, psychological, social, and environmental domains.[26]

Statistical analysis

Data were analyzed by SPSS (version 15; SPSS Inc., Chicago, IL, USA). The results were presented as absolute frequencies and percentages for categorical variables and mean ± SD for continuous variables. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with the expected count of less than 5 were observed. Continuous variables were also compared using Student's independent t-test. Logistic regression was performed between participants without any MetS components, and MetS subjects as dependent variable and tertiles of legume as independent variables in 4 models based on sex. The crude model was unadjusted. The first model was adjusted by dietary score, second model was adjusted by lifestyle status (physical activity, dietary score, quality of life, and smoking status), the third model was adjusted by age and lifestyle status, and the forth was adjusted by body mass index (BMI), age, and lifestyle behavior. To solve the co-linearity problem between dietary score and legume intake in all models, we used residual of linear regression as dietary score adjusted legume intake, with dietary score as dependent variable and legume intake as independent variable. To determine P-value for trend across tertile of legume, we assigned the median consumption of legume to individual's variable as continuous variable in logistic regression for participants without any MetS components vs. MetS subjects. P-values < 0.05 were considered as statistically significant.

Results

In this study 982 (617 women and 365 men) subjects with MetS and 1045 (396 women and 649 men) without any MetS components were enrolled with an average of 40.58 ± 16.18 years. Demographic characteristics, such as age, sex, and obesity indices, and life style behavior variables, such as physical activity, dietary score, quality of life, and smoking status, are presented in table 1. Significant differences in all study parameters have been found between the groups ($P < 0.001$). The frequency of daily intakes of legumes in subjects with MetS was 2.41 ± 1.92 and in the group without any MetS components was 2.61 ± 1.92 ($P < 0.001$).

Frequency of MetS components based on legume consumption was shown in table 2. All MetS components are more prevalent among subjects without regular legume intake ($P < 0.001$). In other words, these results showed that higher consumption of legumes is related with lower prevalence in all components of MetS ($P = 0.01$).

Multiple logistic regressions were done to find adjusted odds ratio for having MetS across tertile of legume consumption as shown in table 3. We found a significant inverse relationship between legume intake and risk of MetS among females. Life style adjusted odds ratio of MetS between highest and lowest tertile vs. no (as reference category) legume intake were 0.31 (0.13, 0.70) and 0.38 (0.17, 0.87), respectively, in females (P-value for trend = 0.01).

Table 1. Characteristic of participants of the Isfahan Healthy Heart Program

	Number of components of metabolic syndrome		
	0 components*	≥ 3 components**	P
Number	1045	982	
Sex (female)§	396 (37.9)	617 (62.8)	< 0.001
Smoker§	240 (23.0)	124 (12.6)	< 0.001
BMI category§			
25 < BMI < 30	231 (23.6)	427 (44.1)	< 0.001
BMI ≥ 30	18 (1.8)	415 (42.8)	
Age category§			
< 40 (year)	843 (80.7)	286 (29.1)	
41-60 (year)	161 (15.4)	436 (44.4)	< 0.001
> 60 (year)	40 (3.8)	260 (26.5)	
Healthy dietary score*	150 (14.4)	188 (19.1)	0.004
Age (year)£	32.09 ± 12.03	49.59 ± 15.11	< 0.001
BMI£	22.77 ± 3.43	29.55 ± 4.33	< 0.001
Leisure time physical activity (minutes per week)£	200.47 ± 262.61	120.82 ± 194.14	< 0.001
Dietary Score§	5.38 ± 1.96	5.69 ± 1.98	< 0.001
Quality of life£	68.25 ± 12.24	63.71 ± 13.41	< 0.001

BMI: Body mass index

* Subjects without any MetS components; ** MetS subjects; § Indicates: P-value obtained from chi-square test; £ Indicates: P-value obtained from Student's t-test

Table 2. Frequency of metabolic syndrome components based on legumes consumption

Variables	Tertile of legume				P
	No consumption	Tertile 1 (< 2 times per week)	Tertile 2 (2-3 times per week)	Tertile 3 (≥3 times per week)	
High BP*	27 (43.5)	205 (38.2)	190 (31.0)	237 (31.3)	0.010
high FBS**	16 (24.6)	95 (17.1)	79 (12.7)	93 (11.9)	0.003
Low HDL$	41 (64.1)	246 (44.5)	247 (39.7)	317 (40.7)	0.001
High TG£	41 (64.1)	232 (41.8)	225 (36.1)	293 (37.6)	< 0.001
High WC§	37 (60.7)	240 (45.0)	209 (34.7)	279 (37.2)	< 0.001

* Blood presser ≥ 130/85 mmHg or treatment; ** Serum glucose ≥ 110 or treatment; $ Low high-density lipoprotein cholesterol < 40 mg/dl in makeanol < 50 in female or treatment; £ Serum triglyceride ≥ 150 mg/dl or treatment; § Waist circumference > 102 cm in males and > 88 in females
BP: Blood pressure; FBS: Fasting blood glucose; HDL: High density lipoprotein; TG: Triglycerides; WC: Waist circumference

Table 3. Adjusted odds ratio and 95% confidence interval for metabolic syndrome (≥ 3 components) vs. normal (0 components) across tertile of legume consumption of the Isfahan Healthy Heart Program

Models	Tertile of legume				P for trend
	No consumption	Tertile 1 (< 2 times per week)	Tertile 2 (2-3 times per week)	Tertile 3 (≥3 times per week)	
Crude					
Female	Ref	0.39 (0.17, 0.86)	0.31 (0.14, 0.68)	0.29 (0.13, 0.65)	0.005
Male	Ref	0.68 (0.27, 1.70)	0.45 (0.18, 1.13)	056 (0.23, 1.38)	0.180
Model 1*					
Female	Ref	0.39 (0.18-0.87)	0.31 (0.14, 0.70)	0.29 (0.13, 0.66)	0.004
Male	Ref	0.72 (0.29-1.81)	0.49 (0.19-1.25)	0.56 (0.23-1.38)	0.080
Model 2**					
Female	Ref	0.38 (0.17, 0.87)	0.31 (0.13, 0.71)	0.31 (0.13, 0.70)	0.017
Male	Ref	0.66 (0.25, 1.71)	0.47 (0.18, 1.21)	0.50 (0.19, 1.28)	0.060
Model 3***					
Female	Ref	045 (0.17, 1.19)	0.44 (0.17, 1.14)	055 (0.21, 1.41)	0.800
Male	Ref	0.73 (0.24, 2.26)	0.57 (0.19, 1.77)	0.68 (0.22, 2.07)	0.620
Model 4£					
Female	Ref	0.22 (0.05-0.93)	0.17 (0.04, 0.74)	0.21 (0.05, 0.89)	0.290
Male	Ref	0.43 (0.09, 2.07)	0.37 (0.08, 1.80)	0.41 (0.09, 1.97)	0.660

Ref: Reference category; * adjusted by dietary score; ** adjusted by life style (Physical activity, quality of life, dietary score, and smoking status); *** adjusted by life style and age; £ adjusted by life style, age, and body mass index (BMI)

Discussion

Our results showed an adverse relationship between legume consumption and MetS by potential confounder adjustment. Similar to our findings, another national study showed that increase in legume intake, from the first quartile to the latest quartile, causes significant changes in some components of MetS.[27] Our findings revealed that components of MetS improved by higher legume consumption in subjects with MetS. Moreover, 2 studies performed on diabetic patients revealed that higher consumption of legumes improved glycemic control and insulin resistance.[28,29]

International diabetes mellitus guidelines recommended the consumption of legumes (including beans, and chickpeas) and controlling of the glycemic index.[30] Results of an Italian National Research revealed that daily consumption of legumes decreases systolic blood pressure.[31] Alizadeh et al. demonstrated that the consumption of a legume-rich hypocaloric diet for 6 weeks reduced some anthropometric measures, such as waist and hip, among healthy premenopausal women with central obesity.[32] Our findings demonstrated that an increment in intake of legume from the lowest tertile to the highest decreased WC.

Several cross-sectional and prospective studies have also indicated the negative association between legume and fruit consumption and obesity and cardiovascular dieses.[33] In the present study, we found an adverse relationship between MetS and legume consumption in women after adjusting for confounding factors such as life style (physical activity, dietary score, quality of life, and smoking status). To date, few observational studies have examined the association of legume intake with MetS.[16] Lignin, as a major dietary insoluble fiber source, may control homeostasis of glucose and insulin sensivity as well as weight reduction; therefore, they might play a crucial role in controlling MetS.[34] Azizi et al. showed that intake of soluble fiber was associated with reduced risk of MetS. They showed that 5 g increment in intake of soluble fiber was associated with a reduction of 54% in risk of MetS.[35]

Several population studies have reported an increase in the prevalence of the MetS with age, regardless of definition, although some have reported a peak in the 7th decade and then a decline in both sexes.[36,37]

This was evident especially in women, with a sevenfold increase in prevalence from the 20-29 year olds age group to the 80-89 year olds age group.[38] This study showed that age has a significant relationship with prevalence of MetS; therefore, after age adjustment, there is no significant difference in lower and higher tertile of legume intakes. Findings from the third National Health and Nutrition Examination Survey show the percentage of people with MetS differs by age group. It is currently estimated that 13% of adolescents in the United States have metabolic syndrome. Approximately 24% of young to middle-aged adults and 40% of adults aged 70 years or older have MetS.[39,40] Another study evaluated the association between total dietary fiber and its types and sources with the risk of MetS. Among sources of dietary fiber, fruit fiber and legume fiber were significantly and inversely associated with the risk of having MetS. After further adjustment for age, gender, lifestyle, and dietary confounders, a substantial reduction in the risk of MetS was observed with increasing fruit fiber and legume fiber intake.[41] The strengths of this study are its large sample size consisting of participants with various socioeconomic and demographic characteristics, random sampling from two counties in central Iran, and control over a wide variety of potential confounders.

Limitation

These findings are limited due to the use of a cross-sectional design; therefore, we could not assess cause and effect relationship between MetS and legume. However, the evaluation of dietary intake of participants has a strong relationship with previous dietary intake. In addition, after adjustment for potential lifestyle confounders, unknown conditions may confound the relation between legume intake and MetS.

Conflict of Interests

Authors have no conflict of interests.

References

1. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001; 24(4): 683-9.
2. Jacobs M, van Greevenbroek MM, van der Kallen CJ, Ferreira I, Blaak EE, Feskens EJ, et al. The association between the metabolic syndrome and peripheral, but not coronary, artery disease is partly mediated by endothelial dysfunction: the CODAM study. Eur J Clin Invest 2011; 41(2): 167-75.
3. Executive summary of the third report of the national cholesterol education program (ncep) expert panel on detection, evaluation, and treatment

of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001; 285(19): 2486-97.
4. Al-Lawati JA, Mohammed AJ, Al-Hinai HQ, Jousilahti P. Prevalence of the metabolic syndrome among Omani adults. Diabetes Care 2003; 26(6): 1781-5.
5. Sarrafzadegan N, Gharipour M, Ramezani MA, Rabiei K, Zolfaghar B, Tavassoli AA, et al. Metabolic syndrome and health-related quality of life in Iranian population. J Res Med Sci 2011; 16(3): 254-61.
6. Ozsahin AK, Gokcel A, Sezgin N, Akbaba M, Guvener N, Ozisik L, et al. Prevalence of the metabolic syndrome in a Turkish adult population. Diabetes Nutr Metab 2004; 17(4): 230-4.
7. Mosca F, Stracqualursi A, Persi A, Calabro V, Zappala O. Gastric diverticulum. A case report with long-term follow-up and a review of the literature. Minerva Chir 2003; 58(4): 607-13.
8. Lennie TA. Cardiology patient page. The metabolic syndrome. Circulation 2006; 114(15): e528-9.
9. Panagiotakos DB, Pitsavos C, Chrysohoou C, Skoumas J, Tousoulis D, Toutouza M, et al. Impact of lifestyle habits on the prevalence of the metabolic syndrome among Greek adults from the ATTICA study. Am Heart J 2004; 147(1): 106-12.
10. Cabello-Saavedra E, Bes-Rastrollo M, Martinez JA, Diez-Espino J, Buil-Cosiales P, Serrano-Martinez M, et al. Macronutrient intake and metabolic syndrome in subjects at high cardiovascular risk. Ann Nutr Metab 2010; 56(2): 152-9.
11. Eshak ES, Iso H, Date C, Kikuchi S, Watanabe Y, Wada Y, et al. Dietary fiber intake is associated with reduced risk of mortality from cardiovascular disease among Japanese men and women. J Nutr 2010; 140(8): 1445-53.
12. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA 1997; 277(6): 472-7.
13. Bazzano LA, He J, Ogden LG, Loria C, Vupputuri S, Myers L, et al. Legume consumption and risk of coronary heart disease in US men and women: NHANES I Epidemiologic Follow-up Study. Arch Intern Med 2001; 161(21): 2573-8.
14. Esmaillzadeh A, Kimiagar M, Mehrabi Y, Azadbakht L, Hu FB, Willett WC. Dietary patterns, insulin resistance, and prevalence of the metabolic syndrome in women. Am J Clin Nutr 2007; 85(3): 910-8.
15. Feldeisen SE, Tucker KL. Nutritional strategies in the prevention and treatment of metabolic syndrome. Appl Physiol Nutr Metab 2007; 32(1): 46-60.
16. Babio N, Bullo M, Basora J, Martinez-Gonzalez MA, Fernandez-Ballart J, Marquez-Sandoval F, et al. Adherence to the Mediterranean diet and risk of metabolic syndrome and its components. Nutr Metab Cardiovasc Dis 2009; 19(8): 563-70.
17. Sarraf-Zadegan N, Sadri G, Malek AH, Baghaei M, Mohammadi FN, Shahrokhi S, et al. Isfahan Healthy Heart Programme: a comprehensive integrated community-based programme for cardiovascular disease prevention and control. Design, methods and initial experience. Acta Cardiol 2003; 58(4): 309-20.
18. Gharipour M, Sarrafzadegan N, Sadeghi M, Andalib E, Talaie M, Shafie D, et al. Predictors of metabolic syndrome in the Iranian population: waist circumference, body mass index, or waist to hip ratio? Cholesterol 2013; 2013: 198384.
19. Mohammadifard N, Kelishadi R, Safavi M, Sarrafzadegan N, Sajadi F, Sadri GH, et al. Effect of a community-based intervention on nutritional behaviour in a developing country setting: the Isfahan Healthy Heart Programme. Public Health Nutr 2009; 12(9): 1422-30.
20. British Hypertension Society. Technique of blood pressure measurement- a poster to illustrate recommended techniques. J Hypertens 1985; 3: 293.
21. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18(6): 499-502.
22. World Health Organization. WHO draft protocol and manual of operations population survey for cardiovascular disease risk factors in the Eastern Mediterranean Region? Alexandria, Egypt: World Health Organization; 1995. p. 1-35.
23. North American Association for the Study of Obesity, National Heart, Lung, and Blood Institute, National Institutes of Health. The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Washington, DC: National Institutes of Health, National Heart, Lung, and Blood Institute, NHLBI Obesity Education Initiative, North American Association for the Study of Obesity; 2000.
24. Leparki E, Nussel E. CINDI: countrywide integrated non-communicable diseases interventional programme: protocol and guidelines for monitoring and evaluation procedures. Berlin, Germany: Springer-Verlag p. 73-82; 1987.
25. Sarrafzadegan N, Kelishadi R, Esmaillzadeh A, Mohammadifard N, Rabiei K, Roohafza H, et al. Do lifestyle interventions work in developing countries? Findings from the Isfahan Healthy Heart Program in the Islamic Republic of Iran. Bull World Health Organ 2009; 87(1): 39-50.
26. Esfahani MA, Jolfaii EG, Torknejad M, Etesampor A, Amiz FR. Postprandial hypertriglyceridemia in

non-diabetic patients with coronary artery disease. Indian Heart J 2004; 56(4): 307-9.
27. Hosseinpour-Niazi S, Mirmiran P, Amiri Z, Azizi F. Dietary Legumes Intake and Metabolic Syndrome and Its Component in Adults. Int J Endocrinol Metab 2011; 12(6): 594-602.
28. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. Circulation 2008; 117(6): 754-61.
29. Mellen PB, Walsh TF, Herrington DM. Whole grain intake and cardiovascular disease: a meta-analysis. Nutr Metab Cardiovasc Dis 2008; 18(4): 283-90.
30. Jenkins DJ, Kendall CW, Augustin LS, Mitchell S, Sahye-Pudaruth S, Blanco MS, et al. Effect of legumes as part of a low glycemic index diet on glycemic control and cardiovascular risk factors in type 2 diabetes mellitus: a randomized controlled trial. Arch Intern Med 2012; 172(21): 1653-60.
31. Trevisan M, Krogh V, Farinaro E, Panico S, Mancini M. Calcium-rich foods and blood pressure: findings from the Italian National Research Council Study (the Nine Communities Study). Am J Epidemiol 1988; 127(6): 1155-63.
32. Alizadeh M, Daneghian S, Ghaffari A, Ostadrahimi A, Safaeiyan A, Estakhri R, et al. The effect of hypocaloric diet enriched in legumes with or without L-arginine and selenium on anthropometric measures in central obese women. J Res Med Sci 2010; 15(6): 331-43.
33. Aude YW, Mego P, Mehta JL. Metabolic syndrome: dietary interventions. Curr Opin Cardiol 2004; 19(5): 473-9.
34. Steemburgo T, Dall'Alba V, Almeida JC, Zelmanovitz T, Gross JL, de Azevedo MJ. Intake of soluble fibers has a protective role for the presence of metabolic syndrome in patients with type 2 diabetes. Eur J Clin Nutr 2009; 63(1): 127-33.
35. Azizi F, Esmaillzadeh A, Mirmiran P. Correlates of under- and over-reporting of energy intake in Tehranians: body mass index and lifestyle-related factors. Asia Pac J Clin Nutr 2005; 14(1): 54-9.
36. Jorgensen ME, Bjerregaard P, Gyntelberg F, Borch-Johnsen K. Prevalence of the metabolic syndrome among the Inuit in Greenland. A comparison between two proposed definitions. Diabet Med 2004; 21(11): 1237-42.
37. Athyros VG, Ganotakis ES, Elisaf M, Mikhailidis DP. The prevalence of the metabolic syndrome using the National Cholesterol Educational Program and International Diabetes Federation definitions. Curr Med Res Opin 2005; 21(8): 1157-9.
38. Hildrum B, Mykletun A, Hole T, Midthjell K, Dahl AA. Age-specific prevalence of the metabolic syndrome defined by the International Diabetes Federation and the National Cholesterol Education Program: the Norwegian HUNT 2 study. BMC Public Health 2007; 7: 220.
39. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005; 112(17): 2735-52.
40. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002; 287(3): 356-9.
41. Hosseinpour-Niazi S, Mirmiran P, Sohrab G, Hosseini-Esfahani F, Azizi F. Inverse association between fruit, legume, and cereal fiber and the risk of metabolic syndrome: Tehran Lipid and Glucose Study. Diabetes Res Clin Pract 2011; 94(2): 276-83.

How to cite this article: Sajjadi F, Gharipour M, Mohammadifard N, Nouri F, Maghroun M, Alikhasi H. **Relationship between legumes consumption and metabolic syndrome: Findings of the Isfahan Healthy Heart Program.** ARYA Atheroscler 2014; 10(1): 18-24.

Determinants of uncontrolled hypertension in an Iranian population

Somayeh Arabzadeh[(1)], Masoumeh Sadeghi[(2)], Katayoun Rabiei[(3)], Nizal Sarrafzadegan[(4)], Ladan Taheri[(1)], Jafar Golshahi[(2)]

Original Article

Abstract

BACKGROUND: Uncontrolled hypertension, a major concern among hypertensive patients, may be caused by various factors such as inadequate knowledge and inappropriate attitude, unhealthy lifestyle, and ineffective treatment. The present study tried to cast light on factors leading to uncontrolled hypertension.

METHODS: In this cross-sectional study, all hypertensive participants of the third phase of the Isfahan Healthy Heart Program were contacted and invited to take part in the study. A questionnaire including knowledge of and attitude toward hypertension and its control and treatment methods, and practice about lifestyle and pharmacological treatment was completed for all patients who consented to participate. The participants' anthropometric indices and blood pressure were then measured. Chi-square and Student's t-tests were used to compare the groups with controlled and uncontrolled blood pressure. The effect of each factor on uncontrolled blood pressure was assessed by employing stepwise logistic regression.

RESULTS: Of 114 participants, 43 (37.12%) and 71 (62.28%) individuals had controlled and uncontrolled blood pressure, respectively. Stepwise logistic regression revealed body mass index > 25 kg/m^2 to have the greatest effects on uncontrolled blood pressure [Odds ratio (OR) = 13.091, Confidence interval of 95% (95% CI): 1.437-116.352, P = 0.021). In addition, male gender increased the risk for uncontrolled blood pressure (OR = 8.475, CI95%: 1.276-56.313, P = 0.027), while inappropriate attitude decreased the mentioned risk (OR = 0.047, CI95%: 0.007-0.318, P = 0.002).

CONCLUSION: According to our findings, obesity is the most important cause of uncontrolled blood pressure. Therefore, weight has to be closely monitored and controlled in hypertensive patients.

Keywords: Uncontrolled Hypertension, Obesity, Attitude

Date of submission: 1 Oct 2013, ***Date of acceptance:*** 4 Dec 2013

Introduction

Hypertension (HTN) is currently identified as a major risk factor for death and loss of health; accounting for 13% of deaths and 6% of disability worldwide.[1,2] HTN is the 4th cause of premature death in developed countries and the 7th cause of death in developing countries.[3]

The seventh report of the Joint National Committee defines HTN as systolic and diastolic blood pressure of higher than 140 and 90 mmHg, respectively.[4] Despite treatment recommendations, research has shown the high prevalence of uncontrolled HTN. About 40% of hypertensive Americans are not treated and 2.3% of those under treatment never reach the desirable blood pressure level (< 140/90 mmHg).[5] Treatment was found to successfully control blood pressure in 37% of hypertensive patients in Saudi Arabia and only 19.88% of those in Romania.[6,7] This rate has been reported as low as 11.8% in China.[8] Unfortunately, no more than 6.6% of diagnosed cases of HTN in India have controlled HTN.[9]

Barriers to optimal control of HTN are categorized as either patient-related or physician-

1- Resident, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Associate Professor, Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Professor, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Masoumeh Sadeghi, Email: sadeghimasoumeh@gmail.com

related.[10,11] Unawareness about HTN and its pharmacological and non-pharmacological treatments, inappropriate attitude toward the risk and treatment of HTN, and lack of commitment to a healthy lifestyle, use of medicines, and risk factors such as diabetes and obesity may prevent the effective control of blood pressure.[12]

The third national risk factor surveillance in Iran declared the prevalence of HTN as 26.6% which is undoubtedly high.[13] On the other hand, Khosravi et al. found controlled hypertension in only 15.8% of Iranian hypertensive patients under treatment.[14] Thus, implementation of efficient health and medical policies in the country will require the identification of factors leading to uncontrolled HTN. Since insufficient research has been performed on factors preventing controlled HTN in Iran, the present study sought to shed light on this subject to facilitate the design of more effective blood pressure control methods.

Materials and Methods

In a cross-sectional study, all hypertensive participants of the third phase of the Isfahan Healthy Heart Program (IHHP) were evaluated. The IHHP was a three-phase community-based study in Isfahan and Najafabad as intervention areas and Arak as the reference area.[15,16] The third phase of the IHHP selected 12000 adults (age > 19 years) from the three mentioned cities (all in central Iran) through multistage random sampling and assessed their knowledge, attitude, and practice toward a healthy lifestyle and risk factors of cardiovascular diseases. The subjects were also examined for the presence of the risk factors and cardiovascular diseases. Blood pressure measurements were conducted while the questionnaires were completed.[17]

After extracting patient data from the available files, the individuals were phoned. In case of changed phone numbers, the emergency phone numbers in patient files were contacted. The subjects were excluded after 3 unanswered phone calls. Finally, for the persons who were reached the objectives and methods of the research were explained and they were asked to attend the Isfahan Cardiovascular Research Center (Isfahan, Iran) if they consented to participate.

After referring to the Isfahan Cardiovascular Research Center, the participants signed an informed consent form and completed a questionnaire including demographic characteristics (age, gender, and marital status), socioeconomic status (education and monthly income level, and occupation), history of hyperlipidemia, diabetes, and cardiovascular diseases, and knowledge, attitude, and practice toward HTN, blood pressure control methods, pharmacological and non-pharmacological treatments of HTN, and lifestyle. The subjects were inquired about their HTN control status, frequency of visits to the physician, the treatment regimen and used/discontinued medications, and non-pharmacological treatments. In order to assess lifestyle, a number of questions regarding diet, salt, fruit, and vegetable intake, physical activity, smoking, and stress management were asked. The participants were then classified as physically active (leisure time physical activity for at least 3 sessions of 30-minute duration per week) or inactive according to their weekly exercise pattern.[18]

The next step was to measure blood pressure and anthropometric indices. For each individual, right arm blood pressure was taken 3 times at 10-minute intervals and the mean value was recorded. Height and weight were measured using a Seca scale and a wall mounted measuring tape, respectively. Following the measurement of waist circumference at 2 cm above the iliac crest and hip circumference around the widest portion of the buttocks, waist to hip ratio was calculated. Body mass index (BMI) was also computed as weight divided by height squared.

HTN was confirmed based on the person's declaration of having a history of HTN, use of antihypertensive medications, or systolic/diastolic blood pressure ≥ 140/90 mmHg. Uncontrolled HTN was defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg in an individual with the history of HTN despite drug therapy.

Statistical analyses

Data were entered in SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL, USA). After using descriptive analysis (mean and standard deviation or crude and relative frequency), the two groups with controlled and uncontrolled HTN were compared in terms of demographics, socioeconomic status, knowledge, attitude, and practice about definition, control, and treatment of hypertension. Chi-square and Student's independent t-tests were applied to compare qualitative and quantitative variables, respectively. Then, the crude odds ratio (OR) of each variable was determined using logistic regression analysis. In the next stage, adjusted OR for each variable was calculated from stepwise logistic regression. In all analyses, $P < 0.05$ and confidence interval of 95% (95% CI) were considered significant.

Results

A total of 114 individuals participated in the present

study (mean age: 61.10 ± 9.91 years). Controlled and uncontrolled HTN was detected in 43 (37.72%) and 71 (62.28%) subjects, respectively. The mean systolic pressure was 12.89 ± 0.93 cmHg in persons with controlled HTN and 15.17 ± 1.59 mmHg in those with uncontrolled HTN (P < 0.001). The corresponding values for diastolic blood pressure were 8.07 ± 0.73 and 8.93 ± 0.69 cmHg, respectively (P < 0.001).

There were no statistically significant differences between the two groups with controlled and uncontrolled HTN regarding mean age, sex distribution, marital status, education level, monthly income, insurance coverage, and history of diseases. The groups were only significantly different in terms of mean waist circumference (i.e., the values were significantly lower in subjects with controlled HTN) (P = 0.013). Although mean BMI was also lower in the mentioned group, this difference was not statistically significant (P = 0.063) (Table 1).

Table 2 compares the knowledge, attitude, and practice of the two groups and shows a significantly higher frequency of individuals with adequate knowledge about avoiding tobacco products for hypertension treatment in the group with uncontrolled HTN. The frequency of subjects with favorable attitude was also significantly higher in the group with uncontrolled HTN than in those with controlled HTN (P = 0.002). The two groups were not significantly different in the frequency of desirable practice about lifestyle and use of medicines.

Table 3 shows the crude effects of all the studied factors (i.e., demographics, history of diseases, lifestyle, overweight or obesity (BMI > 25 kg/m^2), visits to the physician, and use of medicines) on uncontrolled HTN. As it is seen, only overweight and obesity had a significant effect on the incidence of uncontrolled HTN (OR = 4.469; CI95%: 1.431-13.955; P = 0.010). Stepwise logistic regression revealed that after adjustments for all variables, being male and BMI > 25 kg/m^2 increased the chance for uncontrolled HTN. In contrast, inappropriate attitude decreased the chance (Table 4).

Table 1. Demographic and socioeconomic characteristics and risk factors in individuals with controlled and uncontrolled Hypertension (HTN)

Variable	Controlled	Uncontrolled	P
Gender*	43 (37.7)	71 (62.3)	
Male	18 (41.9)	37 (52.1)	0.288
Female	25 (58.1)	34 (47.9)	
Education (year)*			
0-5	26 (60.5)	38 (53.5)	0.556
5-12	11 (25.6)	25 (35.2)	
> 12	6 (14.0)	8 (11.3)	
Marital status*			
Single	5 (11.6)	11 (15.5)	0.565
Married	38 (88.4)	60 (84.5)	
Household's monthly income (Iran Rial)*			
< 300,000 IRR	7 (16.7)	16 (22.9)	
300,00_ 500,000 IRR	19 (45.2)	26 (37.1)	0.749
500,00_ 800,000 IRR	9 (21.4)	18 (25.7)	
> 800,000 IRR	7 (16.7)	10 (14.3)	
Insurance coverage*	34 (79.1)	61 (85.9)	0.342
History of diabetes*	15 (34.9)	27 (38.0)	0.736
History of hyperlipidemia*	22 (51.2)	43 (60.6)	0.326
History of heart attack*	3 (7.0)	4 (5.6)	1.000
History of stroke*	0 (0)	6 (8.5)	0.082
Age (year)**	60.63 ± 12.10	60.75 ± 9.88	0.955
Night sleep (hour)**	5.36 ± 2.91	5.09 ± 3.22	0.718
Body mass index(kg/m^2)**	28.44 ± 4.10	30.05 ± 4.63	0.063
Waist/hip ratio (mean ± SD)**	0.91 ± 0.09	0.94 ± 0.06	0.064

* N (%); ** Values are n (%) or mean ± SD

Table 2. The comparison of knowledge, attitude, and practice about lifestyle between the two groups

	Controlled n (%)	Uncontrolled n (%)	P
Knowledge			
What is normal blood pressure?	5 (11.6)	9 (12.7)	0.869
What is hypertension?	15 (34.9)	34 (47.9)	0.174
Are regular blood pressure measurements necessary?	39 (90.7)	69 (97.2)	0.197
Can a person measure his/her blood pressure at home?	42 (97.7)	70 (98.6)	1.000
Does hypertension require pharmacological treatment?	38 (88.4)	68 (95.8)	0.151
Is diet modification necessary to control blood pressure?	41 (95.3)	68 (95.8)	1.000
Is physical activity necessary to control blood pressure?	40 (93.0)	71 (100.0)	0.051
Is avoiding tobacco products necessary to control blood pressure?	36 (83.7)	68 (95.8)	0.027
Is stress management necessary to control blood pressure?	40 (93.0)	70 (98.6)	0.150
Desirable knowledge score	24 (55.8)	46 (64.8)	0.340
Attitude			
Is hypertension a disease?	40 (93.0)	64 (90.1)	0.740
Is hypertension treatable?	36 (83.7)	64 (90.1)	0.311
Do herbal medicines suffice in the treatment of hypertension?	24 (55.8)	45 (63.4)	0.423
If you have hypertension, do you think your blood pressure is controlled?	7 (16.3)	11 (15.5)	0.911
Desirable attitude score	27 (62.8)	62 (87.3)	0.002
lifestyle			
Low-salt food	23 (53.5)	42 (59.2)	0.554
Daily intake of fruits	27 (62.8)	54 (76.1)	0.130
Daily intake of fresh vegetables	17 (39.5)	36 (50.7)	0.247
Not adding table salt	38 (88.4)	63 (88.7)	0.953
Adequate physical activity	22 (51.2)	32 (45.1)	0.528
Current smoker	3 (7.0)	5 (7.0)	1.000
Visits to the physician and pharmacological treatment			
At least one visit to the physician during the past six months	35 (81.4)	61 (85.9)	0.521
Receiving prescriptions from the physician	40 (93.0)	69 (97.2)	0.364
Regular use of the prescribed antihypertensive medicines	36 (90.0)	61 (88.4)	0.798
The physician's emphasis on medicine use during every visit	29 (74.4)	48 (71.6)	0.762
Family support in taking antihypertensive medicines	11 (27.5)	16 (23.2)	0.615
Discontinuation of antihypertensive medicines	4 (10.0)	9 (13.0)	0.637
Side effects of antihypertensive medicines	3 (7.7)	10 (14.7)	0.285
At least one visit to the physician during the past six months	35 (81.4)	61 (85.9)	0.521

Table 3. Crude effect of demographic and socioeconomic characteristics, risk factors, knowledge, attitude, and practice, lifestyle, and pharmacological treatment on blood pressure control

Variable	Odds ratio	Confidence interval	P
Male gender	1.510	0.704-3.245	0.289
Education level lower than high school diploma	1.270	0.411-3.968	0.627
Not being married	1.390	0.449-4.324	0.566
Income level < 500,000 Rials	0.920	0.421-2.024	0.842
No insurance coverage	0.619	0.229-1.672	0.344
History of diabetes	1.145	0.520-2.522	0.736
History of hyperlipidemia	1.466	0.683-3.148	0.327
History of heart attack	0.796	0.168-3.740	0.773
Body mass index > 25 kg/m^2	4.469	1.431-13.955	0.010
Undesirable knowledge	0.686	0.317-1.489	0.341
Undesirable attitude	0.245	0.096-0.623	0.003
Not using low-salt diet	0.794	0.370-1.704	0.554
No daily fruits intake	0.531	0.233-1.211	0.133
No daily fresh vegetables intake	0.636	0.295-1.371	0.248
Immobility (30-minute sessions of physical activity less than 3 times per week)	1.277	0.598-2.727	0.528
Smoking	1.010	0.229-4.456	0.989
No visits to the physician in the past six months	0.717	0.259-1.986	0.522
No prescription from the physician	0.386	0.062-2.412	0.309
Not taking the prescribed antihypertensive medicines regularly	1.180	0.332-4.199	0.798
The physician's lack of attention to emphasizing on regular use of medicines in every visit	1.148	0.470-2.806	0.762
Lack of family support in using antihypertensive medicines	1.256	0.515-3.063	0.616
Discontinuation of antihypertensive medicines	0.741	0.213-2.581	0.637
Side effects of antihypertensive medicines	0.483	0.125-1.875	0.293

Table 4. Factors leading to uncontrolled Hypertension (HTN) after stepwise logistic regression

	Odds ratio	Confidence interval	P
Male gender	8.475	1.276-56.313	0.027
Body mass index > 25 kg/m^2	13.091	1.437-116.352	0.021
Appropriate attitude	0.047	0.007-0.318	0.002

Discussion

The present study indicated that the two groups with controlled and uncontrolled HTN were similar in terms of gender, education and income level, insurance coverage, history of diseases, treatment type, frequency of visits to the physician, and family support. Furthermore, no significant difference in knowledge, attitude, and practice was observed between the two groups (except for appropriate knowledge about smoking which was significantly higher in subjects with uncontrolled HTN). Meanwhile, the frequency of desirable attitude was significantly higher in the group with uncontrolled HTN than in the other group. The mean BMI was also higher, but not significantly, in the mentioned group. After all analyses, BMI > 25 kg/m^2 and being male were confirmed to have significant effects on increasing the chance for uncontrolled HTN.

Previous studies about the effects of gender on uncontrolled HTN have reported contradictory results. Being female had no impact on BP control in Oman but in Canada women older than 60 years of age were more likely to have uncontrolled hypertension than men.[19,20] Keyhani et al. evaluated data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey in the United States and found higher frequency of women among subjects with uncontrolled HTN. Moreover, in logistic regression, 65-80 year old women had a lower chance of blood pressure control than their male counterparts.[21]

In contrast, the National Health and Nutrition Examination Survey in the United States rejected any difference in blood pressure control between the two sexes.[22] A systematic review on studies about blood pressure control in Africa concluded that women had better controlled HTN than men.[23] Cultural differences might have been responsible for such inconsistencies. In addition, according to recent studies, the higher prevalence of mortality and morbidity due to cardiovascular diseases in women has attracted physicians' attention toward the treatment of female patients.[24]

BMI > 25 kg/m^2 was another factor leading to uncontrolled HTN. Various studies have reported similar relations between overweight/obesity and uncontrolled HTN. In a study on hypertensive African-Belgians, Decoste et al. found uncontrolled HTN to be significantly related with obesity, diabetes, and a sedentary lifestyle.[25] Downie et al. identified overweight and obesity as a factor leading to uncontrolled HTN.[26] Lloyd-Jones et al. observed the significant effect of BMI > 30 kg/m^2 (as compared to BMI > 25 kg/m^2) on uncontrolled HTN.[27] In general, overweight and obesity are currently considered as a major barrier to blood pressure control.[5,28]

The effect of BMI > 25 kg/m^2 on uncontrolled HTN in the current study was much stronger than that in similar research. This is extremely important, since our groups had no significant differences in lifestyle, treatment regimen, or demographic and socioeconomic characteristics. Further investigation may help clarify the reason behind this difference. Iranian ethnicity and differences in hormones, enzymes, and genetics may justify the magnitude of the observed relationship. As we did not have genetic information about the participants, future studies with genetic testing are warranted. Once a genetic background for uncontrolled HTN is proven, more effective treatment and preventive measures can be developed.

Overall, based on our findings, blood pressure control policies should mainly focus on men and overweight/obese individuals. Since research has shown the increasing trend of overweight and obesity in Iran, a growing number of cases with treatment-resistant HTN are to be expected in the future. Therefore, the Ministry of Health is recommended to emphasize on the design and implementation of weight control policies through either public education or legislations to control fast foods and food products.

Conclusion

Our findings showed that individuals with controlled and uncontrolled HTN had similar knowledge, attitude, and lifestyle, and followed comparable pharmacological treatments. It is, however, of utmost importance to control blood pressure in men and overweight/obese individuals.

Acknowledgments

The baseline survey was supported by grant number

31309304 from the Isfahan Healthy Heart Program. This study was a residency thesis (number 390462) funded by the Research Deputy of the School of Medicine, Isfahan University of Medical Sciences. The authors appreciate the cooperation of Mrs Safoura Yazdekhasti and Nahid Sadeghi.

Conflict of Interests

Authors have no conflict of interests.

References

1. World Health Organization. The World Health Report 2002: Reducing Risks, Promoting Healthy Life. Geneva, Switzerland: World Health Organization; 2002.
2. World Health Organization. Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks. Geneva, Switzerland: World Health Organization; 2009.
3. Talaei M, Sadeghi M, Mohammadifard N, Shokouh P, Oveisgharan S, Sarrafzadegan N.Incident hypertension and its predictors: the Isfahan Cohort Study. J Hypertens 2014; 32(1): 30-8.
4. Lenfant C, Chobanian AV, Jones DW, Roccella EJ. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. Hypertension 2003; 41(6): 1178-9.
5. Wang TJ, Vasan RS. Epidemiology of uncontrolled hypertension in the United States. Circulation 2005; 112(11): 1651-62.
6. Saeed AA, Al-Hamdan NA, Bahnassy AA, Abdalla AM, Abbas MA, Abuzaid LZ. Prevalence, Awareness, Treatment, and Control of Hypertension among Saudi Adult Population: A National Survey. Int J Hypertens 2011; 2011: 174135.
7. Dorobantu M, Darabont RO, Badila E, Ghiorghe S. Prevalence, Awareness, Treatment, and Control of Hypertension in Romania: Results of the SEPHAR Study. Int J Hypertens 2010; 2010: 970694.
8. Cai L, Liu A, Zhang L, Li S, Wang P. Prevalence, awareness, treatment, and control of hypertension among adults in Beijing, China. Clin Exp Hypertens 2012; 34(1): 45-52.
9. Kaur P, Rao SR, Radhakrishnan E, Rajasekar D, Gupte MD. Prevalence, awareness, treatment, control and risk factors for hypertension in a rural population in South India. Int J Public Health 2012; 57(1): 87-94.
10. Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. N Engl J Med 2001; 345(7): 479-86.
11. Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension 2006; 47(3): 345-51.
12. Glynn LG, Murphy AW, Smith SM, Schroeder K, Fahey T. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database Syst Rev 2010; (3): CD005182.
13. Esteghamati A, Meysamie A, Khalilzadeh O, Rashidi A, Haghazali M, Asgari F, et al. Third national Surveillance of Risk Factors of Non-Communicable Diseases (SuRFNCD-2007) in Iran: methods and results on prevalence of diabetes, hypertension, obesity, central obesity, and dyslipidemia. BMC Public Health 2009; 9: 167.
14. Khosravi A, Mehr GK, Kelishadi R, Shirani S, Gharipour M, Tavassoli A, et al. The impact of a 6-year comprehensive community trial on the awareness, treatment and control rates of hypertension in Iran: experiences from the Isfahan healthy heart program. BMC Cardiovasc Disord 2010; 10: 61.
15. Sarraf-Zadegan N, Sadri G, Malek AH, Baghaei M, Mohammadi FN, Shahrokhi S, et al. Isfahan Healthy Heart Programme: a comprehensive integrated community-based programme for cardiovascular disease prevention and control. Design, methods and initial experience. Acta Cardiol 2003; 58(4): 309-20.
16. Sarrafzadegan N, Baghaei A, Sadri G, Kelishadi R, Malekafzali H, Boshtam M, et al. Isfahan healthy heart program: Evaluation of comprehensive, community-based interventions for non-communicable disease prevention. Prevention and Control 2006; 2(2): 73-84.
17. Sarrafzadegan N, Kelishadi R, Esmaillzadeh A, Mohammadifard N, Rabiei K, Roohafza H, et al. Do lifestyle interventions work in developing countries? Findings from the Isfahan Healthy Heart Program in the Islamic Republic of Iran. Bull World Health Organ 2009; 87(1): 39-50.
18. Rabiei K, Kelishadi R, Sarrafzadegan N, Sadri G, Amani A. Short-term results of community-based interventions for improving physical activity: Isfahan Healthy Heart Programme. Arch Med Sci 2010; 6(1): 32-9.
19. Al-Saadi R, Al-Shukaili S, Al-Mahrazi S, Al-Busaidi Z. Prevalence of uncontrolled hypertension in primary care settings in Al seeb wilayat, oman. Sultan Qaboos Univ Med J 2011; 11(3): 349-56.
20. Gee ME, Bienek A, McAlister FA, Robitaille C, Joffres M, Tremblay MS, et al. Factors associated with lack of awareness and uncontrolled high blood pressure among Canadian adults with hypertension. Can J Cardiol 2012; 28(3): 375-82.
21. Keyhani S, Scobie JV, Hebert PL, McLaughlin MA. Gender disparities in blood pressure control and cardiovascular care in a national sample of

ambulatory care visits. Hypertension 2008; 51(4): 1149-55.
22. Ostchega Y, Dillon CF, Hughes JP, Carroll M, Yoon S. Trends in hypertension prevalence, awareness, treatment, and control in older U.S. adults: data from the National Health and Nutrition Examination Survey 1988 to 2004. J Am Geriatr Soc 2007; 55(7): 1056-65.
23. Kayima J, Wanyenze RK, Katamba A, Leontsini E, Nuwaha F. Hypertension awareness, treatment and control in Africa: a systematic review. BMC Cardiovasc Disord 2013; 13: 54.
24. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, et al. Heart disease and stroke statistics-2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007; 115(5): e69-171.
25. Decoste M, Vanobberghen R, Borgermans L, Devroey D. Uncontrolled hypertension among black Africans in the city of Brussels: a case-control study. Eur Rev Med Pharmacol Sci 2013; 17(7): 886-94.
26. Downie DL, Schmid D, Plescia MG, Huston SL, Bostrom S, Yow A, et al. Racial disparities in blood pressure control and treatment differences in a Medicaid population, North Carolina, 2005-2006. Prev Chronic Dis 2011; 8(3): A55.
27. Lloyd-Jones DM, Evans JC, Larson MG, O'Donnell CJ, Roccella EJ, Levy D. Differential control of systolic and diastolic blood pressure: factors associated with lack of blood pressure control in the community. Hypertension 2000; 36(4): 594-9.
28. Kotchen TA. Obesity-related hypertension: epidemiology, pathophysiology, and clinical management. Am J Hypertens 2010; 23(11): 1170-8.

How to cite this article: Arabzadeh S, Sadeghi M, Rabiei K, Sarrafzadegan N, Taheri L, Golshahi J. **Determinants of uncontrolled hypertension in an Iranian population.** ARYA Atheroscler 2014; 10(1): 25-31.

The relation between body iron store and ferritin, and coronary artery disease

Ali Pourmoghaddas[1], Hamid Sanei[2], Mohammad Garakyaraghi[3], Fatemeh Esteki-Ghashghaei[4], Maryam Gharaati[5]

Original Article

Abstract

BACKGROUND: Iron is essential for many physiological processes; whereas, iron overload has been known as a risk factor in progression of atherosclerosis. The aim of this study was to investigate the importance of serum ferritin levels, which are known as an indicator of body iron stored in the incidence of coronary artery disease (CAD).

METHODS: In a case-control study, we evaluated 432 eligible men who underwent coronary angiography at Chamran Cardiology Hospital, Isfahan, Iran. They were separated into two groups of case (with CAD) and control (without CAD). All subjects had given written informed consents. Then, the blood samples were taken after 12-14 hours of fast by a biologist for measuring cardiovascular risk factors and body iron stores, including serum ferritin, serum iron, and total iron binding capacity (TIBC). For statistical analyses, chi-square test, Student's t-test, one-way ANOVA, and the logistic regression were used.

RESULTS: In the present study, 212 participants with CAD in the case group and 220 participants free of CAD in the control group were included in the analysis. At baseline, there were significant differences in serum ferritin ($P < 0.001$) and other cardiovascular risk factors between the two groups. Moreover, when other risk factors of CVD were included in the model, serum ferritin [Odd Ratio (OR) = 1.006, 95% confidence interval of 95% (95% CI) 1.00-1.01, $P = 0.045$] and serum ferritin ≥ 200 (OR = 4.49, 95% CI 1.72-11.70, $P < 0.001$) were associated with CAD.

CONCLUSION: High iron store, as assessed by serum ferritin, was associated with the increased risk of CAD. Furthermore, it was a strong and independent risk factor in the incident of atherosclerosis in the Iranian male population.

Keywords: Iron, Ferritin, Coronary Artery Disease, Coronary Angiography

Date of submission: 4 Oct 2013, ***Date of acceptance:*** 4 Dec 2013

Introduction

Cardiovascular disease (CVD) is the single largest cause of mortality in the world and results from the combination of environmental and genetic factors.[1,2] In this respect, though iron is essential for many physiological processes, iron overload has been known as a risk factor in progression of atherosclerosis.[3,4]

Excessive iron is capable of stimulating the progression of atherosclerotic lesions, to catalyze the production of free radicals, and to promote lipid peroxidation by reducing the levels of antioxidants in plasma; therefore, it can be associated with the progression of atherosclerosis and increase in the risk of ischemic cardiovascular events.[5,6]

Epidemiological studies have provided contradictory results regarding iron stores and subsequent atherosclerosis and coronary artery disease (CAD).[5,7,8] For example, Klipstein-Grobusch et al. observed an independent relationship between serum ferritin levels and carotid atherosclerosis.[8] In addition, another study revealed that iron is an important factor in the process of atherosclerosis.[9] However, Knuiman et al., with a 17-year follow-up study in Australia, evaluated the association between serum ferritin level and coronary heart disease (CHD) and stroke events. The results of their study

1- Associate Professor, Cardiac Rehabilitation Research Center AND Heart Failure Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Associate Professor, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Heart Failure Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- PhD Candidate, Isfahan Neurosciences Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
5- Chamran Heart Center, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Ali Pourmoghaddas, Email: a_pourmoghadas@yahoo.com

did not show any evidence in relation to ferritin level as a risk factor for CVD.[4] Another investigation proposed that excessive body iron stores are not associated with the risk of CHD in women.[10]

To our knowledge, in this respect no comparison was made between patients with CAD, according to the injured vessels, and individuals without CAD. We consequently undertook to further investigate the hypothesis of a link between iron and cardiovascular disease by analyzing the association of serum ferritin levels, as an indicator of body iron stores, with CAD in the Iranian male population, and comparing the differences between patients with CAD, according to the number of injured vessels, and individuals without CAD.

Materials and Methods

In a case-control study, we randomly evaluated 481 men who underwent coronary angiography at the Isfahan referral center for cardiac patients, Chamran Hospital, Iran, from May 2010 until January 2011. In this case-control study, participants were separated into two groups by simple sampling. The case group comprised of 223 patients with CAD if one or more coronary arteries had a stenosis ≥ 50% and the number of significant stenosis vessels were also recorded. The control group comprised of 258 individuals without CAD according to their angiography data and if there was no significant epicardial artery stenosis. The risk of CAD was assessed by the cardiologist through watching selective coronary angiography. Of all of the participants, 432 were considered eligible for participating in the study, 212 in the case group and 220 in the control group. We excluded individuals with a recent history of surgery and acute or chronic inflammatory diseases, such as inflammatory bowel disease (IBD), and rheumatoid arthritis, gastric ulcer, cancer, viral or liver disease, and those who took iron and vitamin supplements. In addition, patients with thalassemia and hemochromatosis were excluded from the study. All subjects completed the questionnaire including medical history and smoking after giving a written informed consent. Mean diastolic and systolic blood pressures were calculated from two independent measurements, each of which was taken with the subject in a supine position after 10 minutes of rest. The blood samples were taken after 12-14 hours of fasting for measuring hematologic indexes, fasting blood sugar, and serum lipids by standard clinical laboratory procedure. Serum lipids, including triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) using enzymatic methods, and low density lipoprotein cholesterol (LDL-C), were calculated according to the Friedewald et al. formula.[11] Serum samples were collected from the case and control subjects simultaneously and frozen at -20ºC until used to determine serum ferritin levels, serum iron, and total iron-binding capacity concentrations (TIBC). Serum ferritin concentration was determined by enzyme-linked immunoassay (Ideal Company). The CVs were 2.8%, 4.0%, and 10.4% for ferritin concentrations of 389, 139, and 27 mg/l, respectively. Serum iron and TIBC were determined by photometry with an eppendorf patient oriented system (EPOS) Chemistry Analyzer. The research protocol was taken under the medical ethics standards and was approved by the Medical Ethics Committee of Isfahan University of Medical Sciences.

Chi-square test and Student's t-test were used to compare case and control groups. For considering the differences in the variables in the patients with the number of involved arteries, one-way ANOVA was employed. The logistic regression was used to estimate the incidence of CAD as dependent variable and serum ferritin as independent variable, adjusted for age, hypertension, diabetes, hyperlipidemia, and smoking. Numerical values were expressed as mean ± standard deviation. P-values less than 0.05 were considered as statistically significant.

Results

In the present study 432 men were evaluated; they were divided into individuals with CAD (n = 212, mean age = 58.76 ± 11.01 years) and individuals without CAD (n = 220, mean age = 52.16 ± 12.72). Chi-square test and Student's t-test were used to compare case and control groups (Table 1). Significant differences were seen in ischemic heart disease, diabetes, hyperlipidemia, hypertension, smoking, and serum ferritin between the two groups. However, significant differences were not observed in other variables. In addition, we compared patients with CAD according to the number of injured arteries. In this section, we employed one-way ANOVA and outcomes showed that these three groups (injury in one vessel, two vessels, and three vessels) did not have any significant differences in serum ferritin, serum iron, and serum total iron binding capacity (TIBC) (Table 2).

Results revealed that CAD was associated with serum ferritin levels when age, diabetes, hypertension, hyperlipidemia, and smoking were included in the model. It showed that the case group that had serum ferritin ≥ 200 had a four-fold higher risk of atherosclerosis than the control group (Table 3).

Table 1. Basic characteristics of subjects in case and control groups

Variable	Case group n = 212	Control group n = 220	P
Hypertension (%)	70 (33.0%)	42 (19.0%)	< 0.001
Diabetes mellitus (%)	57 (26.7%)	25 (11.3%)	< 0.001
Hyperlipidemia (%)	78 (36.7%)	44 (20.0%)	< 0.001
Smoking (%)	145 (66.7%)	37 (16.7%)	< 0.001
Serum ferritin (mg/dl)	206.8 ± 156.3	147.3 ± 132.9	< 0.001
Serum iron (mg/dl)	106.8 ± 46.9	107.6 ± 29.6	> 0.050
Serum TIBC (mg/dl)	310.8 ± 99.6	337.7 ± 56.5	> 0.050
Transferrin saturation (%)	33% ± 22.0	29% ± 21.0	> 0.050

TIBC: Total iron binding capacity

Table 2. Comparison of the patients according to the injured vessels

Variable n = 212	One vessel n = 74	Two vessels n = 39	Three vessels n = 99	P
Serum ferritin (mg/dl)	236.5 ± 173.69	203.66 ± 199.34	187.78 ± 131.54	> 0.05
Serum iron (mg/dl)	118.9 ± 41.11	79.33 ± 46.23	110.07 ± 49.40	> 0.05
Serum TIBC (mg/dl)	341.2 ± 110.89	307.00 ± 130.00	290.78 ± 77.46	> 0.05

TIBC: Total iron binding capacity

Table 3. The association of ferritin and coronary artery disease

Variables	OR (95% CI)	P
Serum ferritin	1.006 (1.00-1.01)	0.045
Serum ferritin ≥ 200 ng/ml	4.49 (1.72-11.70)	0.001

Adjusted for age, hypertension, diabetes, hyperlipidemia, and smoking
OR: Odds ratio, CI: Confidence interval

Discussion

Ferritin is an iron storage protein. Serum ferritin concentrations are directly proportional to intracellular ferritin concentrations; therefore, it is considered to be the best indicator of body iron stores. This case-control study revealed that excess serum ferritin is associated with atherosclerosis in Iranian males with coronary artery disease. In addition, findings showed that the risk of high serum ferritin persisted when other risk factors such as age, hypertension, diabetes, hyperlipidemia, high LDL-C, and smoking were adjusted in the model. Moreover, results indicated that men with CAD and serum ferritin concentration ≥ 200 ng/ml had a four-fold higher risk of atherosclerosis than healthy men. Therefore, elevated serum ferritin level may have an independent adverse effect on the incidence of atherosclerosis in patients with CAD. No significant statistical difference was seen in patients with single vessel, double vessels, and triple vessels disease regarding serum iron, serum ferritin, and serum TIBC. Furthermore, lack of a significant statistical difference in the other parameters such as serum iron, TIBC, and transferrin saturation, which are involved in iron homeostasis, can be attributed to the laboratory errors, the diurnal changes, and the hemolysis of blood samples.[10-12]

Many epidemiological studies have considered the association of iron status and CVD; however, contradictory results have been presented. Haidari et al. concluded that high stored iron concentration, as assessed by serum ferritin, is a strong and independent risk factor for premature CAD in the male Iranian population.[13] Other studies proposed elevated serum ferritin concentrations to be associated with increased risk of CVD and myocardial infarction in elderly population, and that it is the leading cause of death and illness in the world.[8,14] A review article suggested strong epidemiological evidence is available that iron is an important factor in processing of atherosclerosis.[9] Salonen et al. demonstrated that a ferritin concentration ≥ 200 mg/l was associated with a 2.2-fold increase in the risk of acute myocardial infarction in men after adjustment for other risk factors.[15]

Many studies suggested that elevated serum ferritin increased the risk of atherosclerosis in the presence of other risk factors. Ferritin can act as a catalyzer in the production of oxygen free radicals and lipid peroxidation and play a role in the formation of oxidized LDL.[16-18]

Oxidation of LDL causes the accumulation of lipids in endothelial and smooth cells, and prevents macrophages from leaving the arterial wall. Thus,

these effects promote the atherosclerosis lesion.[1,2,9]

On the other hand, there are many investigations that were inconsistent with our findings. Armaganijan and Batlouni suggested that serum ferritin and other organic iron indicators were neither risk factors nor risk markers for coronary atherosclerosis and serum iron levels were higher in the group without atherosclerosis.[19] Auer et al. showed that higher ferritin concentrations and transferrin saturation levels were not associated with an increased extent of coronary atherosclerosis in patients who referred for coronary angiography.[7]

It could be mentioned that these conflicting results may be due to the large variability in estimates of iron stores, which included serum iron, serum ferritin, serum transferrin, and etcetera, the diversity methods in the diagnosis of atherosclerosis, and the variability in the size of demographic samples.[19-21]

The strengths of this study are the large sample size and the exclusion of participants with known diseases and supplementations usage at baseline which reduced potential for some biases. The limitation of this study is that it was conducted in men only and thus the results may not be generalized to women.

In conclusion, high stored iron concentration, as assessed by serum ferritin, was associated with the increased risk of CAD, while the number of injured vessels in these patients did not have any association with the progression of disease. In addition, it should be noted that high stored iron concentration was a strong and independent risk factor in the incident of atherosclerosis in the Iranian male population.

Acknowledgments

We gratefully acknowledge the efforts of Mrs. Safoura Yazdekhasti.

This article is derived from the thesis of an internal medicine resident.

Conflict of Interests

Authors have no conflict of interests.

References

1. Meyers DG. The iron hypothesis:does iron play a role in atherosclerosis? Transfusion 2000; 40(8): 1023-9.
2. Bozzini C, Girelli D, Tinazzi E, Olivieri O, Stranieri C, Bassi A, et al. Biochemical and genetic markers of iron status and the risk of coronary artery disease: an angiography-based study. Clin Chem 2002; 48(4): 622-8.
3. Day SM, Duquaine D, Mundada LV, Menon RG, Khan BV, Rajagopalan S, et al. Chronic iron administration increases vascular oxidative stress and accelerates arterial thrombosis. Circulation 2003; 107(20): 2601-6.
4. Knuiman MW, Divitini ML, Olynyk JK, Cullen DJ, Bartholomew HC. Serum ferritin and cardiovascular disease: a 17-year follow-up study in Busselton, Western Australia. Am J Epidemiol 2003; 158(2): 144-9.
5. Kiechl S, Willeit J, Egger G, Poewe W, Oberhollenzer F. Body iron stores and the risk of carotid atherosclerosis: prospective results from the Bruneck study. Circulation 1997; 96(10): 3300-7.
6. Zheng H, Cable R, Spencer B, Votto N, Katz SD. Iron stores and vascular function in voluntary blood donors. Arterioscler Thromb Vasc Biol 2005; 25(8): 1577-83.
7. Auer J, Rammer M, Berent R, Weber T, Lassnig E, Eber B. Body iron stores and coronary atherosclerosis assessed by coronary angiography. Nutr Metab Cardiovasc Dis 2002; 12(5): 285-90.
8. Klipstein-Grobusch K, Koster JF, Grobbee DE, Lindemans J, Boeing H, Hofman A, et al. Serum ferritin and risk of myocardial infarction in the elderly: the Rotterdam Study. Am J Clin Nutr 1999; 69(6): 1231-6.
9. de Valk B, Marx JJ. Iron, atherosclerosis, and ischemic heart disease. Arch Intern Med 1999; 159(14): 1542-8.
10. Sun Q, Ma J, Rifai N, Franco OH, Rexrode KM, Hu FB. Excessive body iron stores are not associated with risk of coronary heart disease in women. J Nutr 2008; 138(12): 2436-41.
11. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18(6): 499-502.
12. van der AD, Marx JJ, Grobbee DE, Kamphuis MH, Georgiou NA, van Kats-Renaud JH, et al. Non-transferrin-bound iron and risk of coronary heart disease in postmenopausal women. Circulation 2006; 113(16): 1942-9.
13. Haidari M, Javadi E, Sanati A, Hajilooi M, Ghanbili J. Association of increased ferritin with premature coronary stenosis in men. Clin Chem 2001; 47(9): 1666-72.
14. You SA, Wang Q. Ferritin in atherosclerosis. Clin Chim Acta 2005; 357(1): 1-16.
15. Salonen JT, Nyyssonen K, Korpela H, Tuomilehto J, Seppanen R, Salonen R. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. Circulation 1992; 86(3): 803-11.
16. Balla J, Vercellotti GM, Jeney V, Yachie A, Varga

Z, Jacob HS, et al. Heme, heme oxygenase, and ferritin: how the vascular endothelium survives (and dies) in an iron-rich environment. Antioxid Redox Signal 2007; 9(12): 2119-37.
17. Liao X, Lv C, Zhang X, Masuda T, Li M, Zhao G. A novel strategy of natural plant ferritin to protect DNA from oxidative damage during iron oxidation. Free Radic Biol Med 2012; 53(2): 375-82.
18. Kraml P, Potockova J, Koprivova H, Stipek S, Crkovska J, Zima T, et al. Ferritin, oxidative stress and coronary atherosclerosis. Vnitr Lek 2004; 50(3): 197-202.
19. Armaganijan D, Batlouni M. Serum ferritin levels and other indicators of organic iron as risk factors or markers in coronary artery disease. Rev Port Cardiol 2003; 22(2): 185-95.
20. Eftekhari MH, Mozaffari-Khosravi H, Shidfar F, Zamani A. Relation between Body Iron Status and Cardiovascular Risk Factors in Patients with Cardiovascular Disease. Int J Prev Med 2013; 4(8): 911-6.
21. Jankowska EA, Malyszko J, Ardehali H, Koc-Zorawska E, Banasiak W, von HS, et al. Iron status in patients with chronic heart failure. Eur Heart J 2013; 34(11): 827-34.

How to cite this article: 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.

Comparison of cost-effectiveness and postoperative outcome of device closure and open surgery closure techniques for treatment of patent ductus arteriosus

Alireza Ahmadi[1], Mohammadreza Sabri[2], Hamid Bigdelian[3], Bahar Dehghan[4], Mojgan Gharipour[5]

Original Article

Abstract

BACKGROUND: Various devices have been recently employed for percutaneous closure of the patent ductus arteriosus (PDA). Although the high effectiveness of device closure techniques has been clearly determined, a few studies have focused on the cost-effectiveness and also postoperative complications of these procedures in comparison with open surgery. The present study aimed to evaluate the clinical outcome and cost-effectiveness of PDA occlusion by Amplatzer and coil device in comparisong with open surgery.

METHODS: In this cross-sectional study, a randomized sample of 201 patients aged 1 month to 16 years (105 patients with device closure and 96 patients with surgical closure) was selected. The ratio of total pulmonary blood flow to total systemic blood flow, the Qp/Qs ratio, was measured using a pulmonary artery catheter. The cost analysis included direct medical care costs associated with device implantation and open surgery, as well as professional fees. All costs were calculated in Iranian Rials and then converted to US dollars.

RESULTS: There was no statistical difference in mean Qp/Qs ratio before the procedure between the device closure group and the open surgery group (2.1 ± 0.7 versus 1.7 ± 0.6, P = 0.090). The mean measured costs were overall higher in the device closure group than in open closure group (948.87 ± 548.76 US$ versus 743.70 ± 696.91 US$, P < 0.001). This difference remained significant after adjustment for age and gender (Standardized Beta = 0.160, P = 0.031). PDA closure with the Amplatzer ductal occluder (1053.05 ± 525.73 US$) or with Nit-Occlud coils (PFM) (912.73 ± 565.94 US$, P < 0.001) was more expensive than that via open surgery. However, the Cook detachable spring coils device closure (605.65 ± 194.62 US$, P = 0.650) had a non-significant cost difference with open surgery. No event was observed in the device closure group regarding in-hospital mortality or morbidity; however, in another group, 2 in-hospital deaths occurred, two patients experienced pneumonia and seizure, and one suffered electrolyte abnormalities including hyponatremia and hypocalcemia.

CONCLUSION: Although open surgery seems to be less expensive than device closure technique, because of lower mortality and morbidity, the latter group is more preferable.

Keywords: Cost-effectiveness, Outcome, Device Closure, Open Surgery Closure, Patent Ductus Arteriosus

Date of submission: 9 Oct 2013, ***Date of acceptance:*** 4 Dec 2013

Introduction

Within the past decade, various devices have been employed for percutaneous closure of the patent ductus arteriosus (PDA). Coil implantation, especially detectable release coils, are currently utilized particularly in small-diameter ducts.[1] However, in larger ducts, the use of this technique may be accompanied with procedural complexity,

1- Assistant Professor, Isfahan Cardiovascular Research Centre, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Professor, Department of Pediatrics, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
3- Assistant Professor, Division of Cardiovascular Surgery, Department of Surgery, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
4- Fellow of Pediatric Cardiology, Department of Pediatrics, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
5- PhD Candidate, Cardiac Rehabilitation Research Centre, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Alireza Ahmadi, Email: ahmadi_cardio@yahoo.com

such as applying multiple coils.[2] In this regard, the Amplatzer duct occluder has been recently introduced as a device that is more appropriate for larger sized ducts and also has a high rate of success and safety for occlusion of PDA by the percutaneous approach.[3] Furthermore, this procedure results in high occlusion rate and a low rate of procedure-related complications.[4] Some recent studies have shown an occlusion rate higher than 99% during 6 months of device deployment.[5] Even, the majority of occlusions may have occurred within a day of device implantation. Moreover, although open surgical treatment of the PDA is a low-risk procedure, because of the necessity for general anesthesia, occurrence of surgery-related complications, and longer hospital stay, developing a catheter-based technique such as Amplatzer duct occlude and implantation of coils by this technique has gained more interest recently.[6,7] In this regard, although the high effectiveness of this technique has been clearly determined, few studies have focused on the cost-effectiveness and postoperative complications of this procedure in comparison with common applied treatment methods such as open surgery. The present study aimed to evaluate the clinical outcome and cost-effectiveness of PDA occlusion by Amplatzer and coil device in comparison with open surgery.

Materials and Methods

In this cross-sectional study, a randomized sample of 201 patients aged 1 month to 16 years (105 patients with device closure and 96 patients with surgical closure) were selected. The devices implanted for these patients included the Amplatzer ductal occluder (ADO) in 36 patients, Nit-Occlud coils (PFM AG, Köln, Germany) in 63 patients, and Cook detachable spring coils (CDC) in 6 patients. Clinical data, including gender and age, were collected from hospital-recorded files. Before assessment of the procedural results of operation, the ratio of total pulmonary blood flow to total systemic blood flow, the Qp/Qs ratio, was measured. In cardiac catheterization, using pulmonary artery catheter (a Qp/Qs ratio of 1:1) indicates that there is no shunting. A Qp/Qs ratio of > 1:1 indicates that pulmonary flow exceeds systemic flow and defines a net left-to-right shunt. Similarly, a Qp/Qs ratio of < 1:1 indicates a net right-to-left shunt. If the left-to-right shunt equals the right-to-left shunt in magnitude, it is possible to have Qp/Qs of exactly 1:1.[8]

Our cost analysis included direct medical care costs associated with device implantation and open surgery as well as professional fees. All costs were calculated in Iranian Rials and then converted to US dollars ($1 = 12260 Iranian Rials), and updated to 2013 dollars by using the grossdomestic product deflator. Our study endpoint was to evaluate and compare clinical consequences as well as cost-effectiveness of implanted device and open surgery. Results were reported as mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables. The groups were compared using t-test or Mann-Whitney test for continuous variables and the chi-square test or Fisher's exact test if required for categorical variables. The multivariate linear regression analysis was used to assess between-group differences in analyzed direct costs with the presence of the two variables of gender and age. P values of 0.05 or less were considered statistically significant. All statistical analyses were performed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA).

Results

The average age of the study population was 4.37 ± 3.11 years (median 3.9 years) with female to male ratio of 1.9. No significant difference was revealed between the group with device closure and the group with surgical closure in mean age (4.20 ± 3.35 years versus 4.55 ± 2.83 years, P = 0.414) and the prevalence of female patients (66.7% versus 64.6%, P = 0.756). The mean Qp/Qs ratio was not statistically different between the device closure group and the open surgery group (2.1 ± 0.7 versus 1.7 ± 0.6, P = 0.090). The mean measured costs were overall higher in the device closure group than in the open closure group (948.87 ± 548.76 US$ versus 743.70 ± 696.91 US$, P < 0.001). In this context, PDA closure with the ADO (1053.05 ± 525.73 US$) or with PFM (912.73 ± 565.94 US$, P < 0.001) was more expensive than that via open surgery, but PDA closure with Cook coil (605.65 ± 194.62 US$, P = 0.650) had a non-significant cost difference with open surgery. The difference in direct cost between PDA closure by device implantation and open surgery remained significant after adjustment for age and gender (standardized beta = 0.160, t = 2.174, P = 0.031). Regarding postoperative complications, such as in-hospital mortality or morbidity, no events were observed in the device closure group. However, in the other group, 2 in-hospital deaths occurred (mortality rate of 2.1%), 2 patients experienced pneumonia and seizure, and 1 suffered

electrolyte abnormalities, including hyponatremia and hypocalcemia.

Discussion

The ADO and other device-based closure techniques have achieved a definite place in the armamentarium of the interventional cardiologist for the closure of partially large sized PDAs with an occlusion rate higher than 99% within a mid-term following operation.[9] Along with ADO, the PFM, including the detachable release coil, has proven to be an efficacious method for repairing PDA. By developing these nonsurgical closure procedures for treatment of the PDA, the incidence of residual shunt was gradually reduced, the complexity of treatment was considerably decreased, and the unsuitability of surgery for larger PDAs was resolved.[10-12]

The present study reported our recent experience on the use of different devise closure techniques for minimizing limitations of open surgery with regard to postoperative complications and its cost-effectiveness. Our observation could not support higher cost-effectiveness of these device-based techniques compared with open surgery; however, postoperative adverse events, including early mortality and morbidity, have been shown to be notably lower following employment of the former techniques. Thus, applying device-based closure techniques may be preferable in comparison with open surgeries. The main reason for occurrence of early complications after open surgery may be thoracotomy, and therefore trans-catheter methods were evolved to avoid thoracotomy.[13] The rare, but serious, complication of trans-catheter closure of the PDA is device embolization, which is relatively common early in the experience with coils. Followed by this complication, flow disturbance in the proximal left pulmonary artery or descending aorta from a protruding device, hemolysis from high-velocity residual shunting, femoral artery or vein thrombosis related to vascular access, and infection may be consequences of using these devices, none of which were reported in our observation.[13] Beside device-based techniques, despite greater pain and morbidity, open surgery is a safe and effective procedure; however, due to development of device closing techniques, surgical ligation or division of the PDA remains the treatment of choice for the rare very large ductus. As shown in our survey, despite no reported complications related to the device closure group, the open surgical ligation method was accompanied with 2.1% and 3.1% early mortality and morbidity rates, respectively. Mavroudis et al. reported the surgical procedural success rate to be 100% with a morbidity rate of 4.4% and mortality rate of 0% in a single-institution cohort over a 46-year period.[13] Similar morbidity and mortality rates have been seen in other patient cohorts, and a general estimate of the surgical mortality rate is < 0.5%.[13-16]

Reviewing the literature has shown that the closure rates of surgical ligation has been estimated to be 94% to 100% comparable with device-based methods, but with up to 2.0% mortality rate.[17-19] In our experience, the main surgery-related complications included pneumonia, pneumothorax, seizure, and some electrolyte abnormalities, including hyponatremia and hypocalcemia. According to previous reports, the major complications of open surgery are bleeding, pneumothorax, infection, and, rarely, ligation of the left pulmonary artery or aorta. Recently, due to the development of transaxillary muscle-sparing thoracotomy and the technique of video-assisted thoracoscopic ligation of the PDA, morbidity rate has been reduced, hospital stay has shortened, and cost-effectiveness of surgery has increased.[20,21]

In conclusion, although open surgery seems to be less expensive than the device closure technique, because of its lower mortality and morbidity rate, the latter technique is more preferable.

Conflict of Interests

Authors have no conflict of interests.

References

1. Sreeram N, Yap SC. Detachable coils. In: Rao PS, Kern MJ, Editors. Catheter Based Devices: For the Treatment of Non-Coronary Cardiovascular Disease in Adults and Children. Philadelphia, PA: Lippincott Williams & Wilkins; 2003. p. 187-92.
2. Masura J, Walsh KP, Thanopoulous B, Chan C, Bass J, Goussous Y, et al. Catheter closure of moderate-to large-sized patent ductus arteriosus using the new Amplatzer duct occluder: immediate and short-term results. J Am Coll Cardiol 1998; 31(4): 878-82.
3. Faella HJ, Hijazi ZM. Closure of the patent ductus arteriosus with the amplatzer PDA device: immediate results of the international clinical trial. Catheter Cardiovasc Interv 2000; 51(1): 50-4.
4. Bilkis AA, Alwi M, Hasri S, Haifa AL, Geetha K, Rehman MA, et al. The Amplatzer duct occluder: experience in 209 patients. J Am Coll Cardiol 2001; 37(1): 258-61.

5. Pass RH, Hijazi Z, Hsu DT, Lewis V, Hellenbrand WE. Multicenter USA Amplatzer patent ductus arteriosus occlusion device trial: initial and one-year results. J Am Coll Cardiol 2004; 44(3): 513-9.
6. Butera G, De RG, Chessa M, Piazza L, Delogu A, Frigiola A, et al. Transcatheter closure of persistent ductus arteriosus with the Amplatzer duct occluder in very young symptomatic children. Heart 2004; 90(12): 1467-70.
7. Duke C, Chan KC. Aortic obstruction caused by device occlusion of patent arterial duct. Heart 1999; 82(1): 109-11.
8. Sommer RJ, Hijazi ZM, Rhodes JF. Pathophysiology of congenital heart disease in the adult: part I: Shunt lesions. Circulation 2008; 117(8): 1090-9.
9. Boehm W, Emmel M, Sreeram N. The Amplatzer duct occluder for PDA closure: indications, technique of implantation and clinical outcome. Images Paediatr Cardiol 2007; 9(2): 16-26.
10. Rashkind WJ, Mullins CE, Hellenbrand WE, Tait MA. Nonsurgical closure of patent ductus arteriosus: clinical application of the Rashkind PDA Occluder System. Circulation 1987; 75(3): 583-92.
11. Hosking MC, Benson LN, Musewe N, Dyck JD, Freedom RM. Transcatheter occlusion of the persistently patent ductus arteriosus. Forty-month follow-up and prevalence of residual shunting. Circulation 1991; 84(6): 2313-7.
12. Latson LA, Hofschire PJ, Kugler JD, Cheatham JP, Gumbiner CH, Danford DA. Transcatheter closure of patent ductus arteriosus in pediatric patients. J Pediatr 1989; 115(4): 549-53.
13. Mavroudis C, Backer CL, Gevitz M. Forty-six years of patient ductus arteriosus division at Children's Memorial Hospital of Chicago. Standards for comparison. Ann Surg 1994; 220(3): 402-9.
14. John S, Muralidharan S, Jairaj PS, Mani GK, Babuthaman Krishnaswamy S, et al. The adult ductus: review of surgical experience with 131 patients. J Thorac Cardiovasc Surg 1981; 82(2): 314-9.
15. Fisher RG, Moodie DS, Sterba R, Gill CC. Patent ductus arteriosus in adults-long-term follow-up: nonsurgical versus surgical treatment. J Am Coll Cardiol 1986; 8(2): 280-4.
16. Schneider DJ, Moore JW. Patent ductus arteriosus. Circulation 2006; 114(17): 1873-82.
17. Ghani SA, Hashim R. Surgical management of patent ductus arteriosus. A review of 413 cases. J R Coll Surg Edinb 1989; 34(1): 33-6.
18. Galal O, Nehgme R, al-Fadley F, de MM, Abbag FI, al-Oufi SH, et al. The role of surgical ligation of patent ductus arteriosus in the era of the Rashkind device. Ann Thorac Surg 1997; 63(2): 434-7.
19. Cetta F, Deleon SY, Roughneen PT, Graham LC, Lichtenberg RC, Bell TJ, et al. Cost-effectiveness of transaxillary muscle-sparing same-day operative closure of patent ductus arteriosus. Am J Cardiol 1997; 79(9): 1281-2.
20. Hawkins JA, Minich LL, Tani LY, Sturtevant JE, Orsmond GS, McGough EC. Cost and efficacy of surgical ligation versus transcatheter coil occlusion of patent ductus arteriosus. J Thorac Cardiovasc Surg 1996; 112(6): 1634-8.
21. Laborde F, Folliguet TA, Etienne PY, Carbognani D, Batisse A, Petrie J. Video-thoracoscopic surgical interruption of patent ductus arteriosus. Routine experience in 332 pediatric cases. Eur J Cardiothorac Surg 1997; 11(6): 1052-5.

How to cite this article: Ahmadi A, Sabri M, Bigdelian H, Dehghan B, Gharipour M. **Comparison of cost-effectiveness and postoperative outcome of device closure and open surgery closure techniques for treatment of patent ductus arteriosus.** ARYA Atheroscler 2014; 10(1): 37-40.

Does percutaneous nephrolithotomy cause elevated cardiac troponins?

Hassan Shemirani[1], Reza Khanjani[2], Mehrdad Mohammadi-Sichani[3], Sarah Mozafarpour[4], Majid Rabbani[5], Javad Shahabi[6]

Original Article

Abstract

BACKGROUND: Percutaneous nephrolithotomy is the treatment of choice in large and staghorn renal stones, and myocardial infarction is one the possible complications during and after the surgery. We investigated if renal and skeletal muscle injury, caused by percutaneous nephrolithotomy, can cause elevation in cardiac troponins (cTn).

METHODS: This study was conducted on otherwise healthy patients with renal stone undergoing percutaneous nephrolithotomy. A baseline 12-lead electrocardiogram, echocardiography, and cTn assessment confirmed no cardiac pathology in any patients. Cardiac troponins T (cTnT) and I (cTnI), and also creatine kinase (CK) were assessed before and after surgery.

RESULTS: A total of 55 patients (69.1% males, mean age: 40.5 ± 13.8 year) were included. Serum creatinine level ranged from 0.7 to 1.3 mg/dl (mean = 1.03 ± 0.17). The level of CK was significantly increased by 469.5 ± 201.4 U/l ($P < 0.001$), and no positive cTnT or cTnI was observed after surgery.

CONCLUSION: The results of the present study showed that renal cell injury, caused by percutaneous nephrolithotomy, is not associated with elevated cardiac troponins. These findings show that increasing troponins in patients undergoing percutaneous nephrolithotomy indicate a cardiovascular pathology.

Keywords: Percutaneous Nephrolithotomy, Coronary Artery Disease, Acute Coronary Syndrome, Cardiac Markers, Troponin

Date of submission: 28 Oct 2012, ***Date of acceptance:*** 6 May 2013

Introduction

Percutaneous nephrolithotomy (PCNL) is the treatment of choice for renal staghorn stones.[1]

Postoperative myocardial insult is a common surgical morbidity and mortality. Up to 40% of all coronary artery disease patients undergoing major non-cardiac operations develop post-surgical silent myocardial ischemia (MI), and between 2–4% experience myocardial damage or cardiac death.[2,3] Cardiovascular disease in patients scheduled for PCNL is common (23%).[4] Accordingly, it is expected that patients encounter cardiac symptoms after surgery. We had a similar case in our clinic; PCNL was performed on a 62-year old diabetic man in our department, and 3 hours after the surgery the patient developed dyspnea. Electrocardiography and symptoms were unremarkable, but a three-fold increase in troponin was observed. We doubted whether renal and skeletal muscle trauma caused by PCNL could have increased serum troponin. The aim of this study was to investigate the diagnostic accuracy of cardiac troponin in patients undergoing PCNL.

Previously, diagnosis of acute MI relied upon the combination of symptoms, electrocardiographic (ECG) abnormalities, and elevations in serum

1- Associate Professor, Hypertension Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Department of Internal Medicine AND Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Assistant Professor, Department of Urology AND Urology and Kidney Transplantation Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
4- Medical Student Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
5- Hypertension Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
6- Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Mehrdad Mohammadi-Sichani, Email: m_mohammadi@med.mui.ac.ir

cardiac enzymes. Since symptoms and ECG abnormalities may be nonspecific or absent after surgery, diagnosis of MI has been increasingly dependent on the evaluation of cardiac enzymes.[1] End stage renal disease (ESRD), old age, diabetes mellitus (DM), and some non-cardiac surgeries can complicate the clinical presentation of acute coronary syndrome (ACS).[2,3] A large number of these patients have significant coronary artery diseases despite being asymptomatic or manifesting with atypical symptoms. Thus, the accurate interpretation of serum concentrations of cardiac enzymes is extremely important in these patients.[1,3,5]

When available, cardiac troponins (cTn), including troponin T (cTnT) and troponin I (cTnI), are the markers of choice for early evaluation of patients suspicious for ACS. The skeletal muscle and cardiac isoforms of troponin T and troponin I are distinct and skeletal muscle isoforms are not detected by the currently used monoclonal antibody-based assays.[1] Although cTnI and cTnT are specific markers for myocardial damage and MI, there are some other conditions, including renal failure and chronic kidney disease, accompanied with elevation of these enzymes in the absence of detectable myocardial damage or MI.[6] Several studies reported sporadic or persistently increased level of cardiac troponins (> 0.1 ng/ml) among 20% to 53% of patients with ESRD, with cTnT being more frequently elevated in patients on dialysis than cTnI.[3]

The underlying mechanisms of the elevated cTn in ESRD patients are not clear and studies have controversial results. Previous studies have proposed that increased cTnT in asymptomatic patients with ESRD indicates a subclinical myocardial necrosis/injury caused by ischemia due to coronary artery disease (CAD), cardiac hypertrophy, and fluctuations in blood volume.[1,2] Abnormalities of troponin catabolism and clearance caused by renal failure or dialysis are also suggested to have a role in increased levels of troponins in ESRD patients.[3,7] Some studies suggested that cardiac enzymes in serum of ESRD patients without evidence of ischemic heart disease are originated from the skeletal muscle and not from the heart.[8,9] Other studies also found elevated expression of cTnT in examined biopsy specimens from the skeletal muscle of dialysis patients, likely associated with uremic-induced skeletal myopathy.[10,11] PCNL is a unique surgery with known parenchyma damage. Extensive search of literature did not reveal any related articles.

It seems that the effect of renal surgeries and specifically PCNL on cardiac troponins has not been previously studied.

We carried out this study in order to investigate whether renal injury, induced by PCNL, can cause elevation in cardiac troponins.

Materials and Methods

Patients and settings

This study was conducted on 55 consecutive patients with renal stone referring to Alzahra University Hospital for PCNL between February 2011 and February 2012. All patients were interviewed and examined by a cardiologist for symptoms, signs, and history of cardiovascular disease. A 12-lead ECG and echocardiography were done before the operation and patients with any abnormalities were not included in the study. Those with history, risk factors (DM, hypertension, hyperlipidemia, and smoking), or symptoms of any cardiovascular diseases and those with renal dysfunction (serum Cr > 1.5) were not included. The study was approved by the Ethical Committee of Isfahan University of Medical Sciences and an informed consent was obtained from each patient.

Percutaneous nephrolithotomy

The surgical procedure is summarized as follows: After general anesthesia, a 5 or 6 Fr ureteral catheter was inserted and fixed to a Foley catheter. The patient was then turned to a prone position with special care for the pressure points. The desired calyx was punctured under fluoroscopic guidance and a guide wire was inserted. Tract dilation was performed by Amplatz dilators in a one-shot manner. After Amplatz sheath insertion, nephroscopy was performed and stones were fragmented by a pneumatic lithotripter (Litho Crack, Sp. Swiss-Germany) and removed. Normal saline (0.9% NaCl) was used for continuous irrigation. In the case of residual stones more than 2 cm in diameter that could not be accessed by the first tract, a second access was established.

Residual stones less than 2 cm in diameter were scheduled for shock wave lithotripsy (SWL). Foley and ureteral catheter were removed 24 hours after the operation. Nephrostomy tube was clamped 48 hours after operation and was removed after 24 hours if no leak, pain, or fever was present. Demographic, perioperative data such as age, sex, stone burden, laterality, co-morbid diseases, stone opacity, operation time, number and site of accesses, and complications during and after surgery were recorded by the surgeon. Patients with

excessive bleeding or hypotension during the operation were excluded from the study. Patients were kept hydrated during the operation and postoperative pain was controlled by narcotics. No non-steroidal anti-inflammatory drugs were used. Ceftriaxone was prescribed before the operation and continued until discharge.

Assessments

The serum levels of cTnT and cTnI were assessed before and 6 hours after surgery in automated immunoanalysis system (VIDAS® Troponin I Ultra, BioMérieux SA, Marcy l'Etoile, France). This system uses the enzyme-linked fluorescence assay (ELFA) principle, combining the enzyme linked immunosorbent assay (ELISA) method with a final fluorescent reading. CK was also assessed as a marker of renal injury before and 6 hours after lithotripsy using automated analyzer (Greiner Diagnostic GmbH, Bahlingen, Germany).

Statistical analysis

Data were analyzed using SPSS for Windows (version 16.0; SPSS Inc., Chicago, IL, USA). Categorical data were reported as frequencies and percentages. Continuous data were reported as mean and standard deviation (SD). Comparison of quantitative data before and after lithotripsy was done using the paired t-test. A P value of less than 0.05 was considered as significant.

Results

A total of 55 patients (69.1% males, mean a ge = 40.5 ± 13.8 years) were studied. The mean operating time and mean hospital stay were 116 ± 24 minutes and 3.93 ± 1.47 days, respectively. Moreover, 7 patients (12.7%) required second access tract. Auxiliary procedures were performed in 5 patients (9%). In addition, 50 patients were completely stone free leading to a stone-free rate of 90%. Complication occurred in 17 (31%) patients; fever in 13 (23.6%) patients, transfusion in 3 (5.4%) patients, and delayed hematuria in 1 (1.8%) patient.

Serum creatinine level ranged from 0.7 to 1.3 mg/dl (mean = 1.03 ± 0.17). Data regarding cTnT, cTnI, and CK are presented in table 1. The level of CK was significantly increased by 469.5 ± 201.4 U/L after surgery (P < 0.001). No positive cTnT or cTnI was observed after PCNL.

Discussion

This observational study demonstrates that none of the patients undergoing PCNL developed elevated cardiac enzymes after the operation. It confirms that renal and skeletal muscle injury induced by percutaneous nephrolithotomy, which was documented by elevation in CK level, is not associated with elevation in cTnT or cTnI.

Troponin is a cardio-specific enzyme, now universally used as the standard marker for detection of cardiac ischemia. It rises 4 to 6 hours after the myocardial injury and remains elevated for up to 10 days.[12] It is also well-accepted as a marker of non-ischemic cardiac muscle injury such as myocardial trauma. However, it is falsely elevated in medical conditions, other than acute coronary syndrome, which occasionally makes the clinical use of this biomarker challenging.[13]

The value of troponin in patients with conditions such as dialysis or renal transplant has already been studied.[3,14-16]. However, there is no report so far on the clinical application of cardiac enzymes in patient undergoing PCNL.

Data regarding the serum levels of cardiac troponins in patients undergoing other urological procedures, such as renal transplant and extracorporeal shock wave lithotripsy (ESWL), exist. Bozbas et al. showed that cardiac troponin I should be the biomarker of choice in renal transplant patients as it remains unchanged during the procedure.[17] In a survey by Greenstein et al. on 32 patients undergoing SWL for kidney stones, the results provide confirmatory evidence of previous researches. No myocardial damage was detected and troponin is advised as a suitable tool in the evaluation of patients complaining of chest pain after SWL.[18] In another report, lithotripsy induced arrhythmias were shown not to be associated with myocardial damages and the serum troponin levels did not increase.[19]

Table 1. Cardiac troponins and creatine kinase before and after the lithotripsy

	Before	After	P*
CK, U/l	112.2 ± 47.0	581.7 ± 235.1	< 0.001
cTnT > 0.1 µg/l	0	0	-
cTnI > 0.1 µg/l	0	0	-

Data are presented as mean ± standard deviation

* P value

CK: Creatine kinase; cTnT: Cardiac troponins T; cTnI: Cardiac troponins I

Shroff et al. retrospectively studied 376 consecutive renal and renal/pancreas transplant recipients for a period of one year. They investigated cardiac events during the hospital stay and within 1 year after renal transplantation. Interestingly enough, all patients with a cardiac event during their hospital stay had abnormal cTnI in the immediate postoperative period.[14]

Thus, negative cTnI immediately following transplantation had a high negative predictive value in distinguishing patients likely to develop in-hospital postoperative MI. They also found that the occurrence of at least one abnormal postoperative cTnI level immediately following renal transplantation was associated with increased rates of coronary revascularization at 1 year.[14]

Hypotensive episode is proved to be associated with increased infarction rates in patients undergoing surgeries. Therefore, in patients with perioperative bleeding risk factors, cardiac events should be monitored more closely. Although severe bleeding leading hypovolemic shock is reported to have an occurrence rate of less than 3% of patients; however, troponin measurement might have a more diagnostic value in patients with hemorrhage risk factors undergoing PCNL.[20,21]

PCNL is accepted as a relatively safe procedure for removal of kidney stones.[22] Mohta et al. monitored hemodynamic, electrolyte, and metabolic changes before, during, and after the irrigation in PCNL patients. They found no significant alterations in the aforementioned variables such as heart rate, systolic and diastolic blood pressure, arterial blood gases, and electrolytes.[23] Likewise, we found PCNL to be a safe procedure with regard to alterations in cardiac muscle injury-related markers. Shen et al. showed that PCNL induces less inflammatory systemic response than open surgery. They examined the immunological markers of tissue damage, such as CRP and IL-6, and found that the tissue damage markers in PCNL group were significantly less than the open surgery group.[22] On the other hand, in our study, the troponin levels have been measured both before and after the surgery in order to better monitor the level changes. However, patients with medical conditions such as renal impairment, diabetes, and hypertension have not been included in the study; therefore, the role of cardiac enzymes in patients with these medical conditions undergoing PCNL should be examined by future studies. In order to define the value and cost-effectiveness of routine post-PCNL measurement of cardiac troponins, trials with large sample sizes are required to identify the incidence of cardiac events in these patients.

Another point of our study was that we only monitored the troponin level once after the urologic procedures, we did not examine the long term cardiac events in the patients; hence, prospective evaluations with longer follow up period are needed to define the accuracy of cardiac enzymes in PCNL patients in diagnosis of late cardiac events.

Conclusion

The results of the present study showed that renal cell injury, modeled by percutaneous nephrolithotomy, is not associated with elevated cardiac troponins. Thus, in postoperative chest discomfort, troponins could be a valuable marker of myocardial infarction. An elevated post PCNL cardiac enzyme is highly sensitive for a cardiac event and requires prompt attention.

Acknowledgments

This study was supported as a thesis for obtaining specialty in cardiology by Isfahan University of Medical Sciences. Authors are thankful to Dr. Ali Gholamrezaei (Poursina Hakim Research Institution) for helping us in data analyses and preparing this report.

Conflict of Interests

Authors have no conflict of interests.

References

1. Alpert JS, Thygesen K, Jaffe A, White HD. The universal definition of myocardial infarction: a consensus document: ischaemic heart disease. Heart 2008; 94(10): 1335-41.
2. Wang AY, Lai KN. Use of cardiac biomarkers in end-stage renal disease. J Am Soc Nephrol 2008; 19(9): 1643-52.
3. Roberts MA, Hedley AJ, Ierino FL. Understanding cardiac biomarkers in end-stage kidney disease: Frequently asked questions and the promise of clinical application. Nephrology (Carlton) 2011; 16(3): 251-60.
4. de la Rosette J, Assimos D, Desai M, Gutierrez J, Lingeman J, Scarpa R, et al. The Clinical Research Office of the Endourological Society Percutaneous Nephrolithotomy Global Study: indications, complications, and outcomes in 5803 patients. J Endourol 2011; 25(1): 11-7.
5. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, et al. Characteristics and short-term prognosis of perioperative myocardial

infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med 2011; 154(8): 523-8.
6. Agewall S, Giannitsis E, Jernberg T, Katus H. Troponin elevation in coronary vs. non-coronary disease. Eur Heart J 2011; 32(4): 404-11.
7. Diris JH, Hackeng CM, Kooman JP, Pinto YM, Hermens WT, van Dieijen-Visser MP. Impaired renal clearance explains elevated troponin T fragments in hemodialysis patients. Circulation 2004; 109(1): 23-5.
8. Nakai K, Nakai K, Nagane Y, Obara W, Sato M, Ohi K, et al. Serum levels of cardiac troponin I and other marker proteins in patients with chronic renal failure. Clin Exp Nephrol 2004; 8(1): 43-7.
9. Sutidze M, Sulakvelidze M, Kochiashvili D, Labadze D, Rukhadze I. Creatine kinase mb, cardiac troponin T and cardiac troponin I as the markers of rhabdomyolysis in chronic hemodialysis patients. Georgian Med News 2006; (132): 68-71.
10. McLaurin MD, Apple FS, Voss EM, Herzog CA, Sharkey SW. Cardiac troponin I, cardiac troponin T, and creatine kinase MB in dialysis patients without ischemic heart disease: evidence of cardiac troponin T expression in skeletal muscle. Clin Chem 1997; 43(6 Pt 1): 976-82.
11. Freda BJ, Tang WH, Van LF, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. J Am Coll Cardiol 2002; 40(12): 2065-71.
12. Zimmerman J, Fromm R, Meyer D, Boudreaux A, Wun CC, Smalling R, et al. Diagnostic marker cooperative study for the diagnosis of myocardial infarction. Circulation 1999; 99(13): 1671-7.
13. Kelley WE, Januzzi JL, Christenson RH. Increases of cardiac troponin in conditions other than acute coronary syndrome and heart failure. Clin Chem 2009; 55(12): 2098-112.
14. Shroff GR, Akkina SK, Miedema MD, Madlon-Kay R, Herzog CA, Kasiske BL. Troponin I levels and postoperative myocardial infarction following renal transplantation. Am J Nephrol 2012; 35(2): 175-80.
15. Iliou MC, Fumeron C, Benoit MO, Tuppin P, Courvoisier CL, Calonge VM, et al. Factors associated with increased serum levels of cardiac troponins T and I in chronic haemodialysis patients: Chronic Haemodialysis And New Cardiac Markers Evaluation (CHANCE) study. Nephrol Dial Transplant 2001; 16(7): 1452-8.
16. Roberts MA, MacMillan N, Hare DL, Ratnaike S, Sikaris K, Fraenkel MB, et al. Cardiac troponin levels in asymptomatic patients on the renal transplant waiting list. Nephrology (Carlton) 2006; 11(5): 471-6.
17. Bozbas H, Yildirir A, Muderrisoglu H. Cardiac enzymes, renal failure and renal transplantation. Clin Med Res 2006; 4(1): 79-84.
18. Greenstein A, Sofer M, Lidawi G, Matzkin H. Does shock wave lithotripsy of renal stones cause cardiac muscle injury? A troponin I-based study. Urology 2003; 61(5): 902-5.
19. Eaton MP, Erturk EN. Serum troponin levels are not increased in patients with ventricular arrhythmias during shock wave lithotripsy. J Urol 2003; 170(6 Pt 1): 2195-7.
20. Gallucci M, Fortunato P, Schettini M, Vincenzoni A. Management of hemorrhage after percutaneous renal surgery. J Endourol 1998; 12(6): 509-12.
21. Osman M, Wendt-Nordahl G, Heger K, Michel MS, Alken P, Knoll T. Percutaneous nephrolithotomy with ultrasonography-guided renal access: experience from over 300 cases. BJU Int 2005; 96(6): 875-8.
22. Shen P, Wei W, Yang X, Zeng H, Li X, Yang J, et al. The influence of percutaneous nephrolithotomy on human systemic stress response, SIRS and renal function. Urol Res 2010; 38(5): 403-8.
23. Mohta M, Bhagchandani T, Tyagi A, Pendse M, Sethi AK. Haemodynamic, electrolyte and metabolic changes during percutaneous nephrolithotomy. Int Urol Nephrol 2008; 40(2): 477-82.

How to cite this article: Shemirani H, Khanjani R, Mohammadi-Sichani M, Mozafarpour S, Rabbani M, Shahabi J. **Does percutaneous nephrolithotomy cause elevated cardiac troponins?** ARYA Atheroscler 2014; 10(1): 41-5.

Seasonal pattern in admissions and mortality from acute myocardial infarction in elderly patients in Isfahan, Iran

Abdollah Mohammadian-Hafshejani[1], Nizal Sarrafzadegan[2], Shidokht Hosseini[3], Hamid Reza Baradaran[4], Hamidreza Roohafza[5], Masoumeh Sadeghi[6], Mohsen Asadi-Lari[7]

Original Article

Abstract

BACKGROUND: Seasonal variation in admissions and mortality due to acute myocardial infarction has been observed in different countries. Since there are scarce reports about this variation in Iran, this study was carried out to determine the existence of seasonal rhythms in hospital admissions for acute myocardial infarction, and in mortality due to acute myocardial infarction (AMI) in elderly patients in Isfahan city.

METHODS: This prospective hospital-based study included a total of 3990 consecutive patients with acute myocardial infarction admitted to 13 hospitals from January 2002 to December 2007. Seasonal variations were analyzed with the Kaplan-Meier table, log rank test, and Cox regression model.

RESULTS: There was a statistically significant relationship between the occurrence of heart disease based on season and type of acute myocardial infarction anatomical ($P < 0.001$). The relationship between the occurrence of death and season and type of AMI according to International Classification of Diseases code 10 (ICD) was also observed and it was statistically significant ($P = 0.026$). Hazard ratio for death from acute myocardial infarction were 0.96 [Confidence interval of 95% (95% CI) = 0.78-1.18], 0.9 (95%CI = 0.73-1.11), and 1.04 (95%CI = 0.85-1.26) during spring, summer, and winter, respectively.

CONCLUSION: There is seasonal variation in hospital admission and mortality due to AMI; however, after adjusting in the model only gender and age were significant predictor factors.

Keywords: Acute Myocardial Infarction, Season, Admission in Hospital, Mortality, Isfahan

Date of submission: 11 Mar 2013, ***Date of acceptance:*** 21 Dec 2013

Introduction

Cardiovascular disease (CVD) is the most common cause of death in Iran.[1] There has been an increasing trend in proportional mortality rate since 1981. In 1995, 47.3% of all deaths were due to CVD. According to the first national burden of disease study for the year 2003, the third highest disability-adjusted life years (DALYs) in all ages and both sexes (16% of total burden) attributed to this disease which included one billion years of life lost (YLL) due to premature mortality and 500 thousand years lived with disability (YLD).[2]

During recent years, admission rate for myocardial infarction (MI) has risen. According to the World Health Organization (WHO) Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project, 28-day case-fatality rates ranged from 37% to 81% for men (average, 48% to

1- Deputy of Health, Isfahan University of Medical Sciences, Isfahan AND PhD Candidates, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
2- Professor, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Researcher, Hypertension Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Associate Professor, Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
5- Assistant Professor, Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
6- Associate Professor, Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
7- Associate Professor, Department of Epidemiology, School of Health AND Oncopathology Research Center, Iran University of Medical Sciences, Tehran, Iran
Correspondence to: Mohsen Asadi-Lari, Email: asadilari@tums.ac.ir

49%), and from 31% to 91% for women (average, 54%).[3] Studies in the UK showed similar results.[4,5] The figure is very diverse in Iran; from 16% to 65.5%.[4,5] In a study recently performed in Iran (Isfahan), 28-day case-fatality rate was 9.1%.[6]

However, seasonal variation in admissions and mortality due to acute myocardial infarction has been observed in different countries.[7-10] Therefore, most studies suggest that the highest occurrence of acute myocardial infarction, or admission to hospital and mortality has occurred during the winter[9-11] and the lowest during the summer.[10,11] However, one study concluded that the highest occurrence rate of disease is in spring.[12] Previous studies have reached diverse conclusions regarding the association of weather and weather change with the threat of having or dying from an acute myocardial infarction (AMI). Although AMI is the most serious coronary disease all around the world, background of its beginning and mortality are not wholly understood, particularly in Iran. The aim of this paper is to explain seasonal admissions to hospitals and AMI mortality pattern in elderly patients in Isfahan, Iran.

Materials and Methods

This study is a prospective hospital-based study that was implemented to appraise seasonal patterns of hospital admissions and mortality from AMI. The study population consisted of patients who had suffered their first AMI at the age of 65 or over during 2002-2007 in 13 private and academic hospitals in the city of Isfahan. In this study we used convenience sampling. However, given that all patients with acute myocardial infarction admitted to the hospital were included in the study, and given the fact that data were collected from 13 hospitals in Isfahan city, it can be inferred that the study population was a good representative of the population. The research team consisted of a cardiologist, a number of nurses trained in receiving and recording patient information, and biostatisticians and epidemiologists. Patients with AMI were diagnosed by cardiologists at hospitals based on the International Classification of Diseases code (ICD10). Basic information related to patients was collected by trained nurses, who used special forms to interview patients or obtained information from their hospital records, and then the data was collected in the Isfahan Cardiovascular Research Center (ICRC).

Patients were investigated after admission to hospitals, and patients with AMI related to different event locations were assigned a specific code according to ICD10, these codes were I21.0, I21.1, I21.2, I21.3 I21.4, and I21.9, considering categorized acute myocardial infarction.

Monica and the World Health Organization protocol defined AMI as a 28-day repeated attack, not considered as separate attacks but in fact related to the first AMI; however, following the first night of the 27th day after the attack it is considered as a new attack. Patients who died during the first 28 days are considered as death due to first AMI. The first 28-day follow-up, considered incidence symptoms, abnormal electrocardiogram (EKG), or abnormal enzymes at first day of onset.[13]

After collecting basic information about patients, their survival or death during the 28 days after the AMI were evaluated. A 28-day follow-up was performed for each patient, their survival rate and death was also evaluated based on each case. The follow-up was started from hospital for the hospitalized patients. For discharged patients, follow-up was first executed by telephone, but when their survival rates were not determined after 3 telephone calls we went to the patients' homes. When previous efforts in terms of getting information about survival rate failed, using the organization's registration information and Rizwan Garden, we tried to find out if the patient had died; we found the cause of death, and exact date and location of the burial.

This study included only patients who were living in Isfahan with first AMI. If a patient died during the 28 days after the first attack due to accident, suicide, homicide, chronic obstructive pulmonary disease, cancer, liver cirrhosis, rheumatic heart disease, vascular disease, or atherosclerosis without mention of any cardiovascular disease they were excluded from the study. In addition, if the exact date of the occurrence or death from the disease was not specified, the patient was excluded from the study; because the 28-day duration after the attack could not be calculated in these cases.[13] This study was performed on patients aged 65 and over, because according to other studies on the occurrence of heart disease by season the greatest difference was visible in older patients.[3,11,12]

Statistical analysis

In this study, to compare average age between the two genders we used Student's independent t-test, and for comparison of the mean age at the time of the occurrence of disease and death according to different seasons ANOVA test was used. Furthermore, for the evaluation of the relationship between seasons and the occurrence of and mortality due to AMI according to the ICD10

(International Classification of Disease) chi-square test was used. In addition, in order to assess survival according to season the Kaplan-Meier analysis, and to compare survival rate the logrank test were used. To calculate the hazard ratio of death during the 28 days of onset acute myocardial infarction Cox regression was used, and the category with the lowest mortality rate was considered as reference group. SPSS for Windows (version 15; SPSS Inc., Chicago, IL, USA) was used for data analysis. All values of $P < 0.05$ were considered significant.

Results

Overall, 4497 patients with acute myocardial infarction were admitted to the hospitals of Isfahan during the study period. Among these, 241 patients (152 men and 89 women) were excluded because their acute myocardial infarction type was not determined according to the International Classification of Diseases ICD10. An additional 180 patients (108 men and 72 women) were excluded because outcome was unknown. Finally, 86 patients were eliminated because of missing information on baseline clinical and demographical variables. Therefore, 3990 patients, 2469 (61.9%) men and 1521 (38.1%) women, remained in the study (Table 1).

In this study, the average age of patients at the time of disease occurrence (3990 patients) was 73.39 ± 6.10, in men (2469 patients) it was 72.98 ± 5.88 and in women (1521 patients) 74 ± 6.38; this difference was statically significant ($P < 0.001$). The average age of patients who died during the 28 days after the onset (724 deaths) was 75.29 ± 6.6, in men (386 patients) it was 74.58 ± 6.32 and in women (338 patients) 76.11 ± 6.82; this difference was not significant ($P = 0.446$). The average occurrence age of the disease at the time of admission to hospitals and mortality of disease during the first 28 days after the onset was compared based on season; their difference was no significant ($P = 0.670$, and $P = 0.853$, respectively) (Figure 1). The difference between average follow-up time for all patients and the death group according to season was not significant ($P = 0.478$, and $P = 0.801$, respectively (Figure 1).

Table 1. Demographic and clinical data of hospitalized myocardial infarction patients

Variables		Alive	Death	Total
Sex	Male	2083	386	2469
	Female	1183	338	1521
Age	74-65	2054	336	2390
	84-75	1104	326	1430
	85 years and older	108	62	170
EKG	Abnormal	2606	565	3171
	Possible changes	41	7	48
	Ischemic changes	522	83	605
	Normal	10	1	11
	Arrhythmia	58	37	95
	Lost	29	31	60
Cardiac enzymes	Normal	268	44	312
	Atypical	409	65	474
	Typical	2523	495	3018
	Miss	66	120	186
Type of acute myocardial infarction, according to ICD10	Acute subendocardial myocardial infarction	388	15	403
	Acute transmural myocardial infarction of other sites	107	8	115
	Acute transmural myocardial infarction of inferior wall	946	138	1084
	Acute transmural myocardial infarction of anterior wall	1105	194	1299
	Acute myocardial infarction, unspecified	679	345	1024
	Acute transmural myocardial infarction of unspecified site	41	24	65
Hospital	Private hospitals	237	65	302
	Public-education hospitals	3029	659	3688
Occurrence season	Spring	875	199	1074
	Summer	749	162	911
	Autumn	793	157	950
	Winter	849	206	1055
Streptokinase	The group receiving Streptokinase	1517	302	1819
	Group not receiving Streptokinase	1749	422	2171

EKG: Electrocardiogram; ICD10: International Classification of Diseases code 10

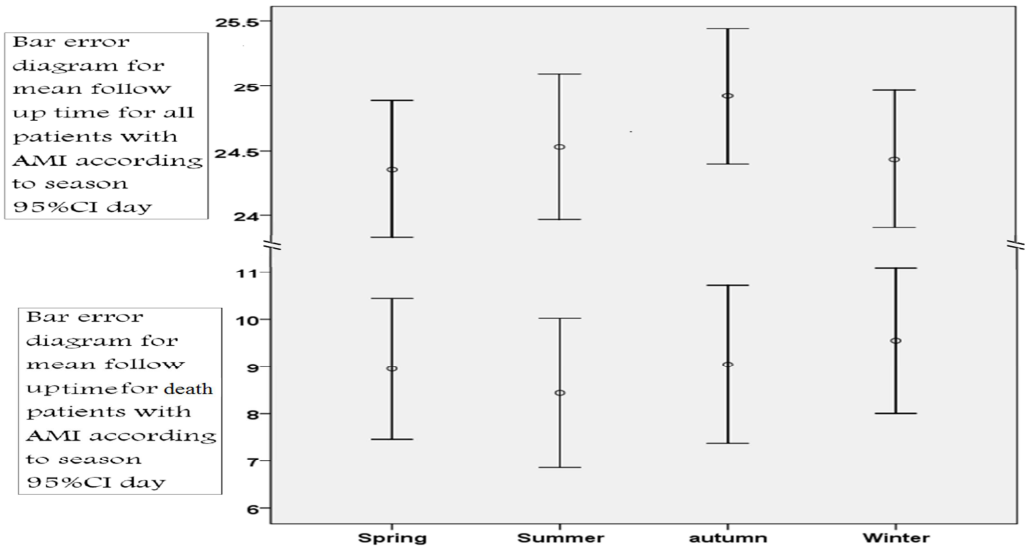


Figure 1. Bar error diagram for mean follow up time for death and all patients with AMI according to season
AMI: Acute myocardial infarction; CI: Confidence interval

In the Evaluation of patients admitted to the hospital, the lowest hospital admission for AMI was seen during the summer season and highest during the spring. They increased 17.8%, 15.8%, and 4.2% during the spring, winter, and autumn, respectively, more than the summer. Assessment of the occurrence of death according to season showed that the lowest mortality rates occurred during the autumn, the highest percentage was in winter; 30.5% in winter, 26% in spring, and 5.1% in summer increased compared with autumn. The highest survival rate was observed in patients who were suffering in autumn and the lowest survival was observed in patients who were suffering during the winter. However, significant differences in survival were not observed in different seasons (P = 0.358) (Figure 2 and Table 2).

A statistically significant relationship was observed between admission in hospital on the basis of season and type of AMI according to ICD10 (P < 0.001), and between the occurrence of death based on season and type of AMI according to ICD10 (P = 0.026) (Table 2).

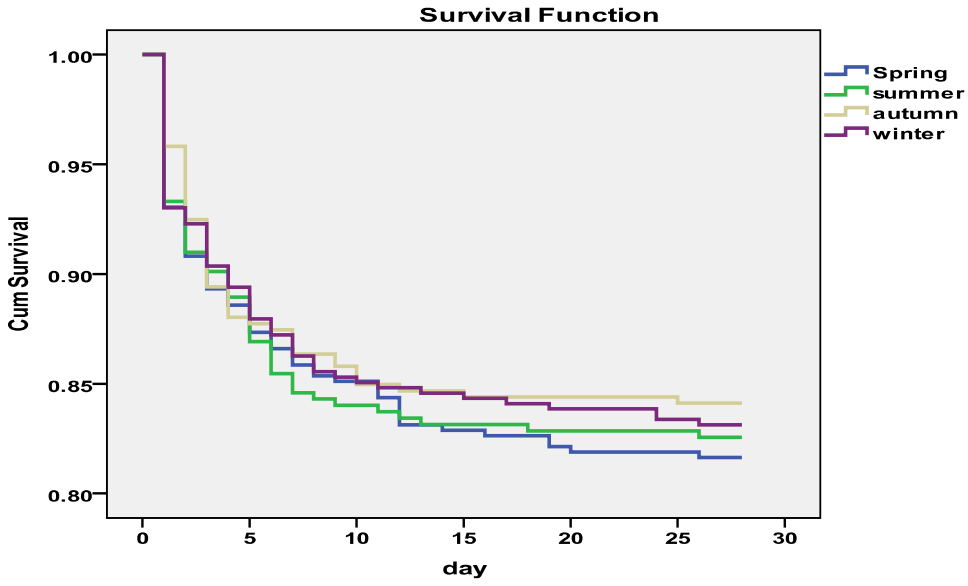


Figure 2. 28 day survival in patients with acute myocardial infarction according to season

Assessment of the hazard ratio of mortality resulting from acute myocardial infarction showed that the lowest mortality was in the autumn; to calculate the hazard ratio, this season was considered as a basis and the multiple regression Cox model was used. We observed that the hazard ratio for death from acute myocardial infarction were 0.96 CI95% 0.78-1.18 during spring, 0.9 CI95% 0.73-1.11 during summer, and 1.04 CI95% 0.85-1.26 during winter; however, for females it was 1.38 CI95% 1.19-1.6, and in the 70-74 years age group was 1.29 CI95% 1.04-1.6, in 75-79 years group 1.77 CI95% 1.43-2.2, in 80-84 years group 2.2 CI95% 1.73-2.8, and for 85 years and higher it was 3.08 CI95% 2.28-4.16 (Table 3).

Table 2. Survival, hospital admission, and death of acute myocardial infarction according to season

	Total	Spring	Summer	Autumn	Winter	P
Overall patients	3990	1074	911	950	1055	
Number of deaths	724	199	162	157	206	
Patients surviving	3266	875	749	793	849	0.358
Survival rate	81.9%	81.5 %	82.2%	83.5%	80.5%	
Survival time (mean ± SD)	24.57 ± 0.136	24.42 ± 0.268	24.53 ± 0.288	24.92 ± 0.266	24.45 ± 0.270	
Type of MI						
Acute transmural myocardial infarction of anterior wall	1299	369 (28.4%)	306 (23.6%)	280 (21.6%)	344 (26.5%)	
Acute transmural myocardial infarction of inferior wall	1084	285 (26.3%)	260 (24.0%)	258 (23.8%)	281 (25.9%)	
Acute transmural myocardial infarction of other sites	115	27 (23.5%)	27 (23.5%)	28 (23.8%)	33 (28.7%)	0.001
Acute transmural myocardial infarction of unspecified sites	65	18 (27.7%)	5 (7.7%)	6 (9.2%)	36 (55.4%)	
Acute subendocardial myocardial infarction	403	96 (23.8%)	91 (22.6%)	117 (29%)	99 (24.6%)	
Acute myocardial infarction, unspecified	1024	279 (27.2%)	222 (21.7%)	261 (25.5%)	262 (25.6%)	
Death during the 28 days						
Acute transmural myocardial infarction of anterior wall	197	55 (27.9%)	45 (22.8%)	42 (21.3%)	55 (27.9%)	
Acute transmural myocardial infarction of inferior wall	138	30 (21.7%)	30 (21.7%)	27 (19.6%)	51 (37.0%)	
Acute transmural myocardial infarction of other sites	8	1 (12.5%)	0	5 (62.5%)	2 (25.0%)	0.026
Acute transmural myocardial infarction of unspecified sites	24	6 (25.0%)	4 (16.7%)	3 (12.5%)	11 (45.8%)	
Acute subendocardial myocardial infarction	14	4 (28.6%)	6 (42.9%)	0	4 (28.6%)	
Acute myocardial infarction, unspecified	344	102 (29.7%)	80 (23.3%)	80 (23.3%)	82 (23.8%)	

MI: Myocardial infarction

Table 3. Hazard ratio of death from acute myocardial infarction according to age, sex, and season of occurrence

Variable	HR	95% CI for HR	P
Autumn	R	-	-
Spring	0.96	(0.78-1.18)	0.713
Summer	0.90	(0.73-1.11)	0.326
Winter	1.04	(0.85-1.26)	0.677
Male	R	-	-
Female	1.38	(1.19-1.60)	< 0.001
65-69	R	-	-
70-74	1.29	(1.04-1.60)	0.019
75-79	1.77	(1.43-2.20)	< 0.001
80-84	2.20	(1.73-2.80)	< 0.001
85 and higher	3.08	(2.28-4.16)	< 0.001

HR: Hazard ratio; CI: Confidence interval

Discussion

In this study, we observed that the highest rate of hospital admission occurred in spring and the second highest in winter, and the lowest was in summer. The lowest mortality rate was during autumn, the highest percentage was in winter. The difference between the occurrence of the disease, hospital admissions, and deaths in relevance with the seasons has been reported in different parts of the world.[7-10] However, in Iran a study on this topic has not been administered with a large sample size. In this study, we surveyed 3990 patients with acute myocardial infarction during 2002-2007 in private and public-education hospitals in the Isfahan city. They were included and categorized in accordance with the International Classification of Diseases ICD10. Identification of particular patterns at the time of the beginning of AMI has scientific value, because such patterns mean that there are triggers peripheral to the atherosclerotic plaque.

Age is a factor that has a large impact on mortality from heart attack; older people are at greater risk of mortality from acute myocardial infarction. In a study conducted in Japan by Isao Kubota et al., it was observed that the average age for patients who died 28 days after the occurrence of AMI was 76.1 ± 9.4 and for patients that survived was 67.6 ± 11.8, and this difference was statistically significant.[14] Moreover, in a study performed by Macintyre et al. on patients who had their first acute myocardial infarction and survived by hospital admission, the average age was compared with the cohort of patients who died before reaching hospital. The results maintained that dead patients were 7 years older than the surviving patients.[15] Based on these studies, it can be concluded that if the average age of patients admitted to hospital differs according to season, there if higher probability of death in the season in which the average age is higher, parallel mortality is higher and vice versa. Consequence probability differences in mortality between seasons are a result of differences in average age of patients based on season. to asses this assumption, the average age of patients was compared with season. There were no statistically significant differences between the average age of patients in the episode and death from the disease. In fact, the average age of patients at the time of occurrence of disease and death during the first 28 days of AMI on the basis of season was similar. Gender is one of the important factors that influence mortality from AMI; women are at a greater risk for mortality from this disease. In a study conducted by Herman et al., 28-day survival rates in men and women were compared with each other; the survival rate was 83.9% in men and 76.9% in women. This difference observed between the two sexes was statistically significant and women had a weaker prognosis than men.[16] Of course, the lower survival and higher mortality rates in women than men were observed in a number of other studies.[17-26] However, perhaps the difference in mortality between seasons is due to the difference in percentage of female patients in each season. For examination of this theory we identified the percentage of occurrence of AMI between seasons for each sex. We observed that this percentage for females is between 26.5%-27.7%, and in fact the almost constant percentage of patients belonged to women. On the basis of this result we can express that the seasonal variation in the mortality from the disease has not been influenced by gender.

In this study, we observed that the highest rate of hospital admission occurred in the spring and the second highest rate occurred in winter, and the

lowest in summer. Of course, in a number of studies the major event occurred in spring. In a study conducted by Kriszbacher et al. on 81,956 patients between 2000 and 2004, the highest incidence of disease was observed in spring and lowest in summer.[8] The results of our study are in accordance with this study and other studies conducted in different regions of the world.[8,27] However, in a number of studies, the highest rate of hospital admission or the occurrence of disease was considered to be during winter.[9,12] In many studies the lowest rate of hospital admission occurred during summer.[12,27,28]

The minimum and maximum rate of hospital admission for AMI, respectively, was in summer and spring. They increased 17.8%, 15.8%, and 4.2% during spring, winter, and autumn, respectively, in comparison to summer. However, in a study conducted by Stewart et al. it was observed that in winter hospital admissions, compared with average, increased about 15% to 18%. In fact, hospital admissions increased in winter compared with other seasons.[11]

The highest rate of mortality during the first 28 days in patients with AMI was in winter and spring, and the lowest in autumn. In a study conducted by Rumana et al., the highest mortality rate of AMI in the first 28 days after the occurrence of AMI was in winter and the second highest in spring.[9]

In the present study, the magnitude of seasonal variation was fairly modest. However, the reason for seasonal variation of AMI in ICRC is not clear. There are no administrative procedures (e.g., submission of reporting forms to meet a specific deadline at definite times of the year) that would create a misleading seasonal variation. We do not believe that a simulate, such as ICRC coordinator of summer or Nowruz holiday was effective on the observed seasonal pattern, because the examination was based on the date of AMI onset rather than on the dates that the case report forms were submitted to ICRC. We think that the most logical reason is that the seasonal variation in AMI cases of ICRC may, in fact, reveal an increased prevalence of AMI onset at certain times of the year.

Some studies found a statistically significant relationship between low temperature and mortality from acute myocardial infarction.[29] A study conduct by Larcan et al. in France compared the meteorological parameters of the day when the infarct occurred with that of the day preceding its occurrence. This study concluded that the occurrence of myocardium infarct was paralleled to a climatic tendency conforming to cold, bad, or deteriorating weather.[30] Peters et al., in a study, concluded that raised concentrations of fine particles in the air may transiently elevate the risk of MIs within a few hours and 1 day after exposure.[31] Vasconcelos et al., in a study conducted in portugal, observed the negative outcome of cold weather conditions on acute myocardial infarctions; for every degree decrease in PET in winter, there was an increase of up to 2.2% (95% CI = 0.9%; 3.3%) in day by day hospital admission.[32] In the study by Sarna et al. atmospheric pressure was found to be the meteorological variable with the highest correlation with the occurrence of myocardial infarction. Rapid decrease in atmospheric pressure was also related with increased incidence of acute myocardial infarction.[28] In a study by Foster et al., a significant relationship was found between influenza and acute myocardial infarction, whereas this correlation was not seen in stroke.[33]

Furthermore, Ulmer et al. found that cholesterol, blood pressure, and body mass index vary according to season and were also significantly higher during winter in comparison to other seasons, and this finding was observed in all age groups and both sexes.[34] However, different explanations exist for the observed variation in hospital admission and mortality from AMI in different parts of the world. Ornato et al., in their study concluding from other studies in this scope, explicated that numerous ideas have been offered to make clear an increased prevalence of AMI or its complications in the winter and cold season.[29] Weather or a quick conversion in the climate can increase arterial blood pressure, blood viscosity, arterial spasm, plasma fibrinogen and factor VII, and serum cholesterol levels (by 2% to 3%), platelet, and red blood cell counts. Exposure to cold weather has also important hemodynamic effects, including an increase in systemic vascular resistance, myocardial oxygen intake, and body metabolic rate. Contemporary infections, particularly those involving the respiratory band, during the winter months have also been claimed as a trigger for mortality due to acute cardiovascular. Other mechanisms that have been proposed to describe the increase in cardiovascular events during cold weather include seasonal variation in bodily activity, food, weight, and worry and stress during the holiday season and seasonal variety in the secretion of physiologically active substances similar to those that trigger seasonal depression. The other

possibility is that the seasonal pattern could be payable to a summer decline in events relative to other times of the year.[29]

This article was extracted from a research project with the title "Evaluation of 28-day survival and predictors of survival in patients with acute myocardial infarction in Isfahan" that was done with the cooperation and support of the Isfahan Cardiovascular Research Center with the approved code of 84130 in 2011.

Limitations

In this study, other groups of patients were not included in the study, such as MI cases that were managed at home or in health cores. This figure might be very small, because MI event is considered as an emergency in the health care system in Iran and all hospitals must admit such patients irrespective of their insurance status. In the Danish MONICA population this amount was measured to be less than 1% of the entire MI cases in a year. Another problem that can be expressed in this study is that patients who died before reaching the hospital or patients who failed to receive medical care due to their lack of access to information were not considered.

Conclusion

The results presented indicate that there is a classical seasonal pattern with increased admissions during spring and winter, and the lowest rate in summer. The highest mortality rate was observed in winter and the lowest in autumn, although these differences were not significant**.** There are seasonal variations in hospital admission and mortality due to AMI; however, after adjusting the model only gender and age were significant predictor factors.

This paper was extracted from the MSc theses of Abdolah Mohammadian Hafshejane in Epidemiology from Tehran Medical University that was conducted in the Isfahan Cardiovascular Research Center (ICRC) of the Isfahan Medical University.

Conflict of Interests

Authors have no conflict of interests.

References

1. Talaei M, Sarrafzadegan N, Sadeghi M, Oveisgharan S, Marshall T, Thomas GN, et al. Incidence of cardiovascular diseases in an Iranian population: the Isfahan Cohort Study. Arch Iran Med 2013; 16(3):138-44.
2. 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.
3. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation 1994; 90(1): 583-612.
4. Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, Neil HA. Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. The Oxford Myocardial Infarction Incidence Study Group. Heart 1998; 80(1): 40-4.
5. Norris RM. Fatality outside hospital from acute coronary events in three British health districts, 1994-5. United Kingdom Heart Attack Study Collaborative Group. BMJ 1998; 316(7137): 1065-70.
6. Mohammadian Hafshejani A, Baradaran attar Moghaddam HR, Sarrafzadegan N, Allah Bakhsi Hafshejani F, Hosseini Sh, AsadiLari M. Evaluation of short-term survival of patients with acute myocardial infarction and the differences between the sexes in Isfahan and Najaf Abad between1999-2008. Razi j Med Sci 2012; 19(95): 25-34. [In Persian].
7. Loughnan ME, Nicholls N, Tapper NJ. Demographic, seasonal, and spatial differences in acute myocardial infarction admissions to hospital in Melbourne Australia. Int J Health Geogr 2008; 7: 42.
8. Kriszbacher I, Bodis J, Csoboth I, Boncz I. The occurrence of acute myocardial infarction in relation to weather conditions. Int J Cardiol 2009; 135(1): 136-8.
9. Rumana N, Kita Y, Turin TC, Murakami Y, Sugihara H, Morita Y, et al. Seasonal pattern of incidence and case fatality of acute myocardial infarction in a Japanese population (from the Takashima AMI Registry, 1988 to 2003). Am J Cardiol 2008; 102(10): 1307-11.
10. Dilaveris P, Synetos A, Giannopoulos G, Gialafos E, Pantazis A, Stefanadis C. CLimate Impacts on Myocardial infarction deaths in the Athens TErritory: the CLIMATE study. Heart 2006; 92(12): 1747-51.
11. Stewart S, McIntyre K, Capewell S, McMurray JJ. Heart failure in a cold climate. Seasonal variation in heart failure-related morbidity and mortality. J Am Coll Cardiol 2002; 39(5): 760-6.
12. Gonzalez HE, Cabades OA, Cebrian DJ, López Merino V, Sanjuan MR, Echanove Errazti I, et al. Seasonal variations in admissions for acute myocardial infarction. The PRIMVAC study. Rev Esp Cardiol 2004; 57(1): 12-9.
13. WHO MONICA Project. MONICA Manual, revised edition. Geneva, Switzerland:

Cardiovascular Diseases Unit, WHO; 1990.
14. Kubota I, Ito H, Yokoyama K, Yasumura S, Tomoike H. Early mortality after acute myocardial infarction: observational study in Yamagata, 1993-1995. Jpn Circ J 1998; 62(6): 414-8.
15. MacIntyre K, Stewart S, Capewell S, Chalmers JW, Pell JP, Boyd J, et al. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. J Am Coll Cardiol 2001; 38(3): 729-35.
16. Herman B, Greiser E, Pohlabeln H. A sex difference in short-term survival after initial acute myocardial infarction. The MONICA-Bremen Acute Myocardial Infarction Register, 1985-1990. Eur Heart J 1997; 18(6): 963-70.
17. Karlson BW, Herlitz J, Hartford M. Prognosis in myocardial infarction in relation to gender. Am Heart J 1994; 128(3): 477-83.
18. Rouleau JL, Talajic M, Sussex B, Potvin L, Warnica W, Davies RF, et al. Myocardial infarction patients in the 1990s--their risk factors, stratification and survival in Canada: the Canadian Assessment of Myocardial Infarction (CAMI) Study. J Am Coll Cardiol 1996; 27(5): 1119-27.
19. Kober L, Torp-Pedersen C, Ottesen M, Rasmussen S, Lessing M, Skagen K. Influence of gender on short- and long-term mortality after acute myocardial infarction. TRACE study group. Am J Cardiol 1996; 77(12): 1052-6.
20. Bueno H, Vidan MT, Almazan A, Lopez-Sendon JL, Delcan JL. Influence of sex on the short-term outcome of elderly patients with a first acute myocardial infarction. Circulation 1995; 92(5): 1133-40.
21. Marrugat J, Sala J, Masia R, Pavesi M, Sanz G, Valle V, et al. Mortality differences between men and women following first myocardial infarction. RESCATE Investigators. Recursos Empleados en el Sindrome Coronario Agudo y Tiempo de Espera. JAMA 1998; 280(16): 1405-9.
22. Vaccarino V, Horwitz RI, Meehan TP, Petrillo MK, Radford MJ, Krumholz HM. Sex differences in mortality after myocardial infarction: evidence for a sex-age interaction. Arch Intern Med 1998; 158(18): 2054-62.
23. Gottlieb S, Harpaz D, Shotan A, Boyko V, Leor J, Cohen M, et al. Sex differences in management and outcome after acute myocardial infarction in the 1990s: A prospective observational community-based study. Israeli Thrombolytic Survey Group. Circulation 2000; 102(20): 2484-90.
24. Goldberg RJ, Gorak EJ, Yarzebski J, Hosmer DW, Dalen P, Gore JM, et al. A communitywide perspective of sex differences and temporal trends in the incidence and survival rates after acute myocardial infarction and out-of-hospital deaths caused by coronary heart disease. Circulation 1993; 87(6): 1947-53.
25. Krumholz HM, Douglas PS, Lauer MS, Pasternak RC. Selection of patients for coronary angiography and coronary revascularization early after myocardial infarction: is there evidence for a gender bias? Ann Intern Med 1992; 116(10): 785-90.
26. Kudenchuk PJ, Maynard C, Martin JS, Wirkus M, Weaver WD. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women (the Myocardial Infarction Triage and Intervention Registry). Am J Cardiol 1996; 78(1): 9-14.
27. Kriszbacher I, Czopf L, Bódis J. The effects of seasonal variations and weather conditions on the occurrence of heart attacks in Hungary between 2000-2004. Orv Hetil 2007: 148(16): 731-6.
28. Sarna S, Romo M, Siltanen P. Myocardial infarction and weather. Ann Clin Res 1977; 9(4): 222-32.
29. Ornato JP, Peberdy MA, Chandra NC, Bush DE. Seasonal pattern of acute myocardial infarction in the National Registry of Myocardial Infarction. J Am Coll Cardiol 1996; 28(7): 1684-8.
30. Larcan A, Gilgenkrantz JM, Stoltz JF, Lambert H, Laprevote-Heully MC, Evrard D, et al. Climatologic parameters and myocardial infarction. Ann Cardiol Angeiol (Paris) 1983; 32(2): 83-92.
31. Peters A, Dockery DW, Muller JE, Mittleman MA. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 2001; 103(23): 2810-5.
32. Vasconcelos J, Freire E, Almendra R, Silva GL, Santana P. The impact of winter cold weather on acute myocardial infarctions in Portugal. Environ Pollut 2013; 183: 14-8.
33. Foster ED, Cavanaugh JE, Haynes WG, Yang M, Gerke AK, Tang F, et al. Acute myocardial infarctions, strokes and influenza: seasonal and pandemic effects. Epidemiol Infect 2013; 141(4): 735-44.
34. Ulmer H, Kelleher C, Diem G, Concin H, Ruttmann E. Estimation of seasonal variations in risk factor profiles and mortality from coronary heart disease. Wien Klin Wochenschr 2004; 116(19-20): 662-8.

How to cite this article: Mohammadian-Hafshejani A, Sarrafzadegan N, Hosseini Sh, Baradaran HR, Roohafza H, Sadeghi M, et al. **Seasonal pattern in admissions and mortality from acute myocardial infarction in elderly patients in Isfahan, Iran.** ARYA Atheroscler 2014; 10(1): 46-54.

Safety of herbal medicine in treatment of weight loss

Jamshid Najafian[(1)], Morteza Abdar-Esfahani[(2)], Morteza Arab-Momeni[(3)], Afshan Akhavan-Tabib[(4)]

Case Report

Abstract

BACKGROUND: Obesity is a common health problem in both developed and developing countries. There are many unconventional therapies, including herbal medicine, to treat this condition. Some people believe that herbal medicines are safe. This case and review is about adverse complication of treating obesity with some herbal medicine.

CASE REPORT: A 19 year old male with sever obesity (120 kg) used green tea (15 cups of green tea per day) and an intensive dietary regimen to lose weight. He lost 30 kg after 2 months. At that time, one day after usual exercise he suddenly lost consciousness due to left ventricular fibrillation.

CONCLUSION: Use of herbal medicine for weight reduction is not always safe. Moreover, for some herbal medicine the risk is sufficient to shift the risk–benefit balance against the use that medicine.

Keywords: Herbal Medicine, Sudden Death, Complication, Obesity

Date of submission: 7 Sep 2013, ***Date of acceptance:*** 20 Nov 2013

Introduction

Obesity remains a global health problem.[1] When conventional medicine fails to treat conditions such as obesity, many people seek unconventional therapies, including herbal medicine, thinking they have no adverse events. This article is a case report about use of green tea and severe dietary restriction to treat obesity that leads to ventricular fibrillation and cardiac arrest.

Case Report

The case reported in this essay is an aborted sudden cardiac death due to intensive dietary regimen and green tea. A 19 year old male was admitted to Alzahra Hospital of Isfahan University of Medical Sciences in an unconscious state. He had been rejected in an employment exam because of sever obesity 3 months earlier (weight = 120 kg). At that time he had begun an intense dietary regimen.

The dietary regimen consisted of 15 cups of green tea and 10 spoons of rice daily. After 2 months his weight was reduced to 90 kg and he was employed in the police force. His training course began, 14 days later, 1 hour after daily exercise he suddenly lost consciousness and his pulse was not palpable. Cardiopulmonary resuscitation was begun and he was transferred to the nearest hospital, where ventricular fibrillation was detected by electrocardiography and his heart was defibrillated, the rhythm changed to sinus rhythm and the patient was stabilized. Then, 5 hours later, he had an attack of tonic-clonic seizure which was controlled by midazolam. The patient was transferred to intensive care unit (ICU) of Alzahra Hospital, and cardiology and neurological consultations were done.

In primary evaluation brain computed tomography (CT) scan was normal and no space-occupying lesion was detected. In echocardiography, ejection fraction (EF) was 25%, global hypokinesia was seen in electrocardiogram (ECG), and the QT interval was

1- Assistant Professor, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Associate Professor, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Resident, Hypertension Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Researcher Assistant, Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Afshan Akhavan-Tabib, Email: afshan.akhavantabib@gmail.com

prolonged with no ST and T changes.

Blood chemistry revealed the fallowing data: creatinine = 1.4; sodium = 143; potassium = 3.4; calcium = 8.8; magnesium = 1.1; white blood cell = 10100; hemoglobin = 12; platelets = 240000; aspartate aminotransferase (AST) = 251; alanine aminotransferase (ALT) = 203; lactic dehydrogenase (LDH) = 840; and troponin I = 0.1.

Infusion of magnesium sulfate was begun (8g/day) and continued for the fallowing 5 days.

In the first 5 days, he had episodes of tonic colonic seizures that were controlled by diazepam, levotyrosetam, and levodopa. On the 5th day serum magnesium level reached 2.1 mg/dl; therefore, magnesium infusion was replaced by oral magnesium 800 mg/day. At this time the patient was stabilized, serum electrolyte were corrected, and the seizures were controlled, but the patient was still unconscious [Glasgow Coma Scale (GCS) = 7]. On the 7th day echocardiography was repeated. EF was 55% with no wall motion abnormality. After 2 weeks the patient's GCS had not changed; therefore, cerebrolysin infusion 50 cc/day was initiated and continued until the 15th day, when the patient's level of consciousness was increased. On the 4th week the patient was in a vegetation state.

Discussion

In MEDLINE database search we could find only one case report about severe dietary regimen and weight reduction that leads to sudden cardiac death, this case was a 16-year-old girl who had sudden cardiorespiratory arrest at school. She had attempted weight loss using a low-carbohydrate/high-protein, calorie-restricted dietary regimen.[2]

In our patient, sever dietary regimen was simultaneous with the use of a large amount of green tea, a herbal remedy that is relatively safe for weight loss and also for the heart.[3,4]

In this case, two mechanisms could be proposed as the cause of long QT interval and ventricular fibrillation. First, severe diet caused magnesium deficiency that induced prolonged QT interval and increased the risk of ventricular arrhythmia. Second, the green tea that was used by this patient may have been mixed with other herbal substances that contained synephrine; this adrenergic component of drug increases sympathetic stimulation, which together with magnesium deficiency could have caused ventricular arrhythmia.

It must be considered that the patient had used a large amount of green tea that may have caused significant sympathetic stimulation enough to induce cardiac arrhythmia.

Green tea

Green tea is brewed from the unfermented dried leaves of the plant camellia sinensis.[5] Like other natural products, the leaves of this plant contain an array of phytochemicals that vary in concentration by the harvest season, age of the plant, climate, environmental conditions, and processing conditions.[5-7]

Early mechanistic work suggested that green tea may increase energy expenditure. The relationship between green tea and caffeine or other substances, and thermogenesis is, at present, unclear.[3,7] Other possible anti-obesity mechanisms include increased fat oxidation, decreased appetite, and disrupted nutrient absorption.[8,9]

Green tea may be an innovative therapeutic candidate to prevent the occurrence, maintenance, and recurrence of atrial fibrillation. On the other hand, inhibition of inflammation, modulation of oxidative stress, targeting tissue fibrosis, and favorable effects on cardiac function and arrhythmias are mechanisms of green tea.[4,8]

Borchardt and Huber provided evidence that green tea inhibits catechol O-methyltransferase (COMT), the enzyme that degrades norepinephrine (NE), thus prolonging the action of sympathetically-released NE in the synaptic cleft.[9] It must be considered that consumption of a large amount of green tea may have a significant effect on sympathetic activity.[10] There is no report about the adverse effect of green tea on cardiac function and rhythm. Several reports have been published in the medical literature describing patients presenting with marked liver toxicity in the form of acute hepatitis attributable to the consumption of supplements containing green tea extracts. The reported toxicity of green tea extract, although sporadic, was deemed important enough that both French and Spanish authorities had the green tea extract Exolise removed from their markets in 2003.[11-18]

Synephrine

Synephrine is 'the active component' of plants and dietary supplements used in weight loss. Synephrine acts on several adrenergic and serotonergic receptors and its activity on trace-amine-associated receptors has long been discussed.[19,20] Adverse cardiac events, including hypertension, tachyarrhythmia, variant angina, cardiac arrest, QT prolongation, ventricular fibrillation, myocardial infarction, and sudden death,

have been the most common adverse effects associated with synephrine intake.[21,22]

Hydroxycut

Hydroxycut is a multicomponent herbal, dietary weight loss supplement devoid of sympathomimetic amines. There is a case report of an obese 63-year-old Caucasian female with a 2-day history of symptomatic paroxysmal atrial fibrillation (AF) with rapid ventricular response following a 2-week course of therapy with hydroxycut. Epigallocatechin (EGCG), a principal ingredient in the hydroxycut preparation is the suspected causative component. Given the serious risks associated with AF, patients at risk of developing AF should avoid dietary supplements containing EGCG until more information on the adverse effects of EGCG is known.[22]

Ephedra plus caffeine

Multicomponent dietary supplement containing ephedra and caffeine (DSEC) was widely used for weight loss and energy enhancement. There are reports of intractable ventricular fibrillation caused by this drug.[23] The Food and Drug Administration (FDA) banned the sale of DSEC in 2004, because of side effects such as cardiotoxicity.[15] The direct cardiotoxicity of ephedra, synergistic effect of caffeine and ephedra, and hypokalemia may cause refractory ventricular arrhythmia.[11,23]

Ephedra sinica

Based on 50 randomized and non-randomized trials, the most rigorous safety assessment to date concludes that herbal ephedra and ephedrine-containing food supplements are associated with an increased risk of heart palpitation, and psychiatric, autonomic, and gastrointestinal adverse events.[24]

For herbal ephedra and ephedrine-containing food supplements an increased risk of psychiatric, autonomic or gastrointestinal adverse events and heart palpitations has been reported.[11-18]

Paullinia cupana

Guarana is prepared from the seeds of Paullinia cupana and is indigenous to the Amazon basin.[25] Guarana contains relatively large amounts of caffeine and is reported to increase the speed of gastric emptying. A number of adverse events are reported with use of guarana, such as irritability, heart palpitations, anxiety, and other central nervous system events.[26]

Pausinystalia yohimbe

Yohimbe (Pausinystalia yohimbe) is a tall evergreen tree, which is native to Central Africa. Yohimbine, an alpha-2 receptor antagonist, is the main active constituent of the ground bark of Pausinystalia yohimbe. The adverse events reported with the use of yohimbine are well documented and include hypertension, anxiety, and agitation.[27] For an herbal preparation of yohimbe, one case report of severe acute headache and hypertension is reported.[27]

Conclusion

Severe and rapid weight loss is not safe and herbal drugs that are used for weight loss may directly or indirectly induce dangerous and fatal conditions for overweight patients. Some articles reported risks that were sufficient to shift the risk-benefit balance against the use of most of the reviewed herbal weight-loss supplements.

Conflict of Interests

Authors have no conflict of interests.

References

1. Popkin BM. Recent dynamics suggest selected countries catching up to US obesity. Am J Clin Nutr 2010; 91(1): 284S-8S.
2. Stevens A, Robinson DP, Turpin J, Groshong T, Tobias JD. Sudden cardiac death of an adolescent during dieting. South Med J 2002; 95(9): 1047-9.
3. Westerterp-Plantenga MS, Lejeune MP, Kovacs EM. Body weight loss and weight maintenance in relation to habitual caffeine intake and green tea supplementation. Obes Res 2005; 13(7): 1195-204.
4. Zeng X, Li Q, Zhang M, Wang W, Tan X. Green tea may be benefit to the therapy of atrial fibrillation. J Cell Biochem 2011; 112(7): 1709-12.
5. Liu JP, Zhang M, Wang WY, Grimsgaard S. Chinese herbal medicines for type 2 diabetes mellitus. Cochrane Database Syst Rev 2004; (3): CD003642.
6. Westerterp-Plantenga MS. Green tea catechins, caffeine and body-weight regulation. Physiol Behav 2010; 100(1): 42-6.
7. Rains TM, Agarwal S, Maki KC. Antiobesity effects of green tea catechins: a mechanistic review. J Nutr Biochem 2011; 22(1): 1-7.
8. Hill JO, Wyatt HR, Reed GW, Peters JC. Obesity and the environment: where do we go from here? Science 2003; 299(5608): 853-5.
9. Borchardt RT, Huber JA. Catechol O-methyltransferase. 5. Structure-activity relationships for inhibition by flavonoids. J Med Chem 1975; 18(1): 120-2.
10. Brown WJ, Williams L, Ford JH, Ball K, Dobson AJ. Identifying the energy gap: magnitude and determinants of 5-year weight gain in midage women. Obes Res 2005; 13(8): 1431-41.
11. Peyrin-Biroulet L, Petitpain N, Kalt P, Ancel D, Petit-Laurent F, Trechot P, et al. Probable hepatoxicity from epigallocatecol gallate used for

phytotherapy. Gastroenterol Clin Biol 2004; 28(4): 404-6.
12. Abu el Wafa Y, Benavente FA, Talavera FA, Perez Ramos MA, Ramos-Clemente JI. Acute hepatitis induced by Camellia sinensis (green tea). An Med Interna 2005; 22(6): 298.
13. Duenas SC, Fabregas PS, Durandez R. Hepatotoxicity due to Camelia sinensis. Med Clin (Barc) 2004; 122(17): 677-8.
14. Garcia-Moran S, Saez-Royuela F, Gento E, Lopez MA, Arias L. Acute hepatitis associated with Camellia thea and Orthosiphon stamineus ingestion. Gastroenterol Hepatol 2004; 27(9): 559-60.
15. Pedros C, Cereza G, Garcia N, Laporte JR. Liver toxicity of Camellia sinensis dried etanolic extract]. Med Clin (Barc) 2003; 121(15): 598-9.
16. Bonkovsky HL. Hepatotoxicity associated with supplements containing Chinese green tea (Camellia sinensis). Ann Intern Med 2006; 144(1): 68-71.
17. Molinari M, Watt KD, Kruszyna T, Nelson R, Walsh M, Huang WY, et al. Acute liver failure induced by green tea extracts: case report and review of the literature. Liver Transpl 2006; 12(12): 1892-5.
18. Shekelle PG, Hardy ML, Morton SC, Maglione M, Mojica WA, Suttorp MJ, et al. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. JAMA 2003; 289(12): 1537-45.
19. Surawicz B, Waller BF. The enigma of sudden cardiac death related to dieting. Can J Cardiol 1995; 11(3): 228-31.
20. Rossato LG, Costa VM, Limberger RP, Bastos ML, Remiao F. Synephrine: from trace concentrations to massive consumption in weight-loss. Food Chem Toxicol 2011; 49(1): 8-16.
21. Karth A, Holoshitz N, Kavinsky CJ, Trohman R, McBride BF. A case report of atrial fibrillation potentially induced by hydroxycut: a multicomponent dietary weight loss supplement devoid of sympathomimetic amines. J Pharm Pract 2010; 23(3): 245-9.
22. Takeuchi S, Homma M, Inoue J, Kato H, Murata K, Ogasawara T. Case of intractable ventricula fibrillation by a multicomponent dietary supplement containing ephedra and caffeine overdose. Chudoku Kenkyu 2007; 20(3): 269-71.
23. Vial T, Bernard G, Lewden B, Dumortier J, Descotes J. Acute hepatitis due to Exolise, a Camellia sinensis-derived drug. Gastroenterol Clin Biol 2003; 27(12): 1166-7.
24. Capasso F, Gaginella TS, Grandolini G, Izzo AA. Phytotherapy: A Quick Reference to Herbal Medicine. Berlin, Germany: Springer; 2003.
25. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med 2000; 343(25): 1833-8.
26. Ernst E, Pittler MH. Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomized clinical trials. J Urol 1998; 159(2): 433-6.
27. de Smet PA, Smeets OS. Potential risks of health food products containing yohimbe extracts. BMJ 1994; 309(6959): 958.

How to cite this article: Najafian J, Abdar-Esfahani M, Arab-Momeni M, Akhavan-Tabib A. **Safety of herbal medicine for weight loss.** ARYA Atheroscler 2014; 10(1): 55-8.

Atrioventricular block as the initial presentation of calcified bicuspid aortic valve

Reza Karbasi-Afshar[(1)], Nematollah Jonaidi-Jafari[(2)], Amin Saburi[(3)], Arezoo Khosravi[(4)]

Case Report

Abstract

BACKGROUND: Bicuspid aortic valve (BAV) is one of the most common and important congenital heart disorders in adults. If a patient with congenital disorders is not diagnosed early, the patient's disease may progress to a severe condition and thus diagnosis of the main disorder will be rendered difficult.

CASE REPORT: A 34 year-old male patient referred to a referral medical care unit for cardiac electrophysiological study with cardiac shock due to complete heart block 3 months ago and he underwent Dual-Chamber permanent pacemaker (PPM) implantation. Thick and calcified bicuspid AV with invasion to interventricular septum, moderate to severe valve insufficiency (AI), severe aortic valve stenosis (AS), and dilated ascending aorta were observed at his echocardiography. Aortic valve replacement (AVR), aneurysm of ascending aorta, root replacement with tube graft (Bentall Procedure), and also a 3 chambers intracardiac defibrillator (ICD) were used. After 2 weeks of operation, he was discharged and at the first post-hospitalization visit (1 week later), his cardiovascular condition was acceptable.

CONCLUSION: Thick calcified aortic root is a less studied and potential contributing risk factor for AV block after AVR. Therefore, in candidates of aortic valve replacement, considering conductive disorders, especially in patients with calcified valve, is mandatory. Irreversible AV block requiring PPM implantation is a rare condition following AVR.

Keywords: Atrioventricular Block, Bicuspid Aortic Valve, Calcified Valve

Date of submission: 30 Dec 2012, ***Date of acceptance:*** 22 May 2013

Introduction

Bicuspid aortic valve (BAV) is one of the most common and important congenital heart disorders in adults.[1] BAV can occur along with other co-morbid heart abnormalities which are secondary to BAV and make its diagnosis easier due to further cardiac assessment.[2] Aortic valve stenosis (AS), aortic valve insufficiency (AI), aortic valve calcification, and aneurysm of aorta (AA) can complicate BAV and can induce patients symptomatic especially with aging. Moreover, they can raise the mortality rate of BAV and also BAV repairing process.[1,3,4] BAV as a congenital disorder is diagnosed at childhood, but it is rarely reported at old age. Moreover, with ageing aortic root or ascending aorta disorders may complicate BAV.[5] Therefore, when a patient with congenital disorders is not diagnosed early, the patient's disease may progress to a severe condition, making it difficult to diagnose the main disorder. We would like to report an adult case of calcified BAV presented initially with atrioventricular (AV) block.

Case Report

This case was a 34 year-old male patient referred to our medical care center (Baqiyatallah Hospital, a referral medical care unit for cardiac electrophysiological study) with cardiac shock due to complete heart block [Echocardiography (ECG) findings: pace rhythm (Figure 1)]. He had a history of AV block (ventricular rate: 30, atrial rate: 60) 3 months prior to referral and he had undergone dual-Chamber permanent pacemaker (PPM) implantation. At echocardiography, which is

1- Department of Cardiovascular Diseases, School of Medicine AND Atherosclerosis Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
2- Health Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
3- Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
4- Assistant Professor, Department of Cardiovascular Diseases, School of Medicine AND Atherosclerosis Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
Correspondence to: Arezoo Khosravi, Email: md.researcher@yahoo.com

shown in figure 2, he had severe left ventricular enlargement, less than 30% ejection fraction, normal right ventricular size with mild dysfunction, mild to moderate mitral valve regurgitation (2+), thick and calcified bicuspid AV with invasion to interventricular septum (with area of 1.4*1 cm), moderate to severe AI, severe AS, and dilated ascending aorta (aneurysm = 5 mm).

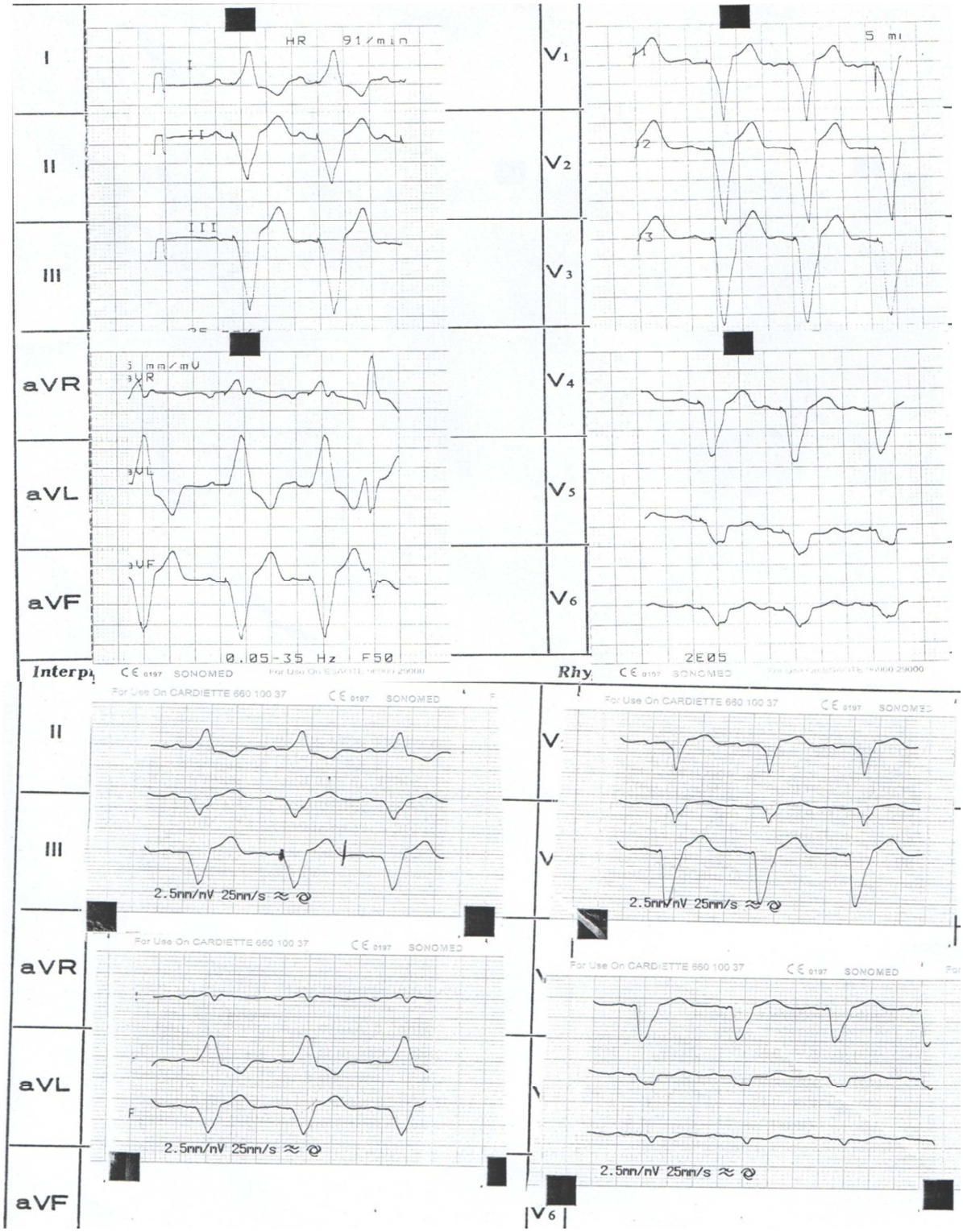


Figure 1. Electrocardiography study at admission (pace rhythm)

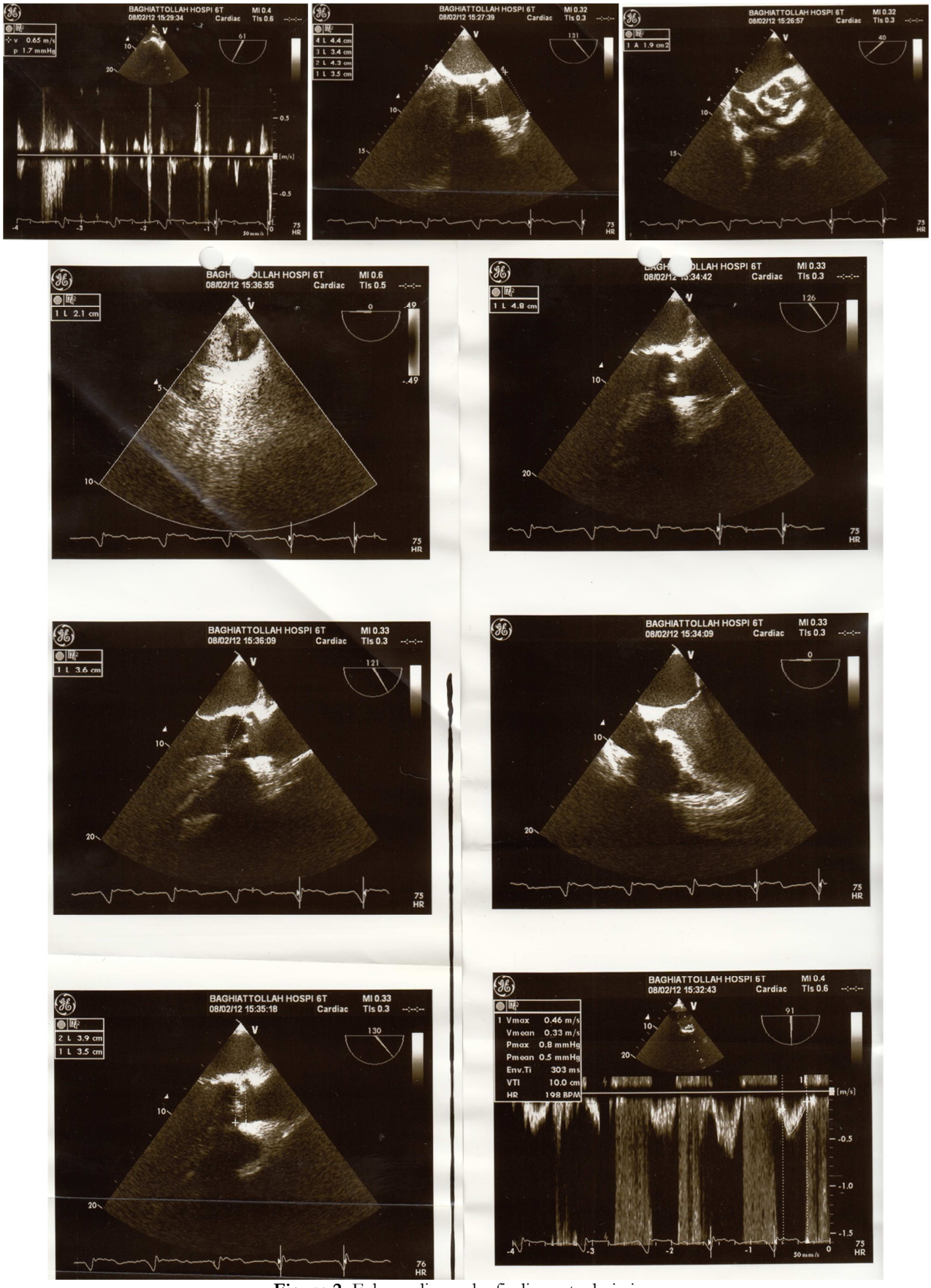


Figure 2. Echocardiography findings at admission

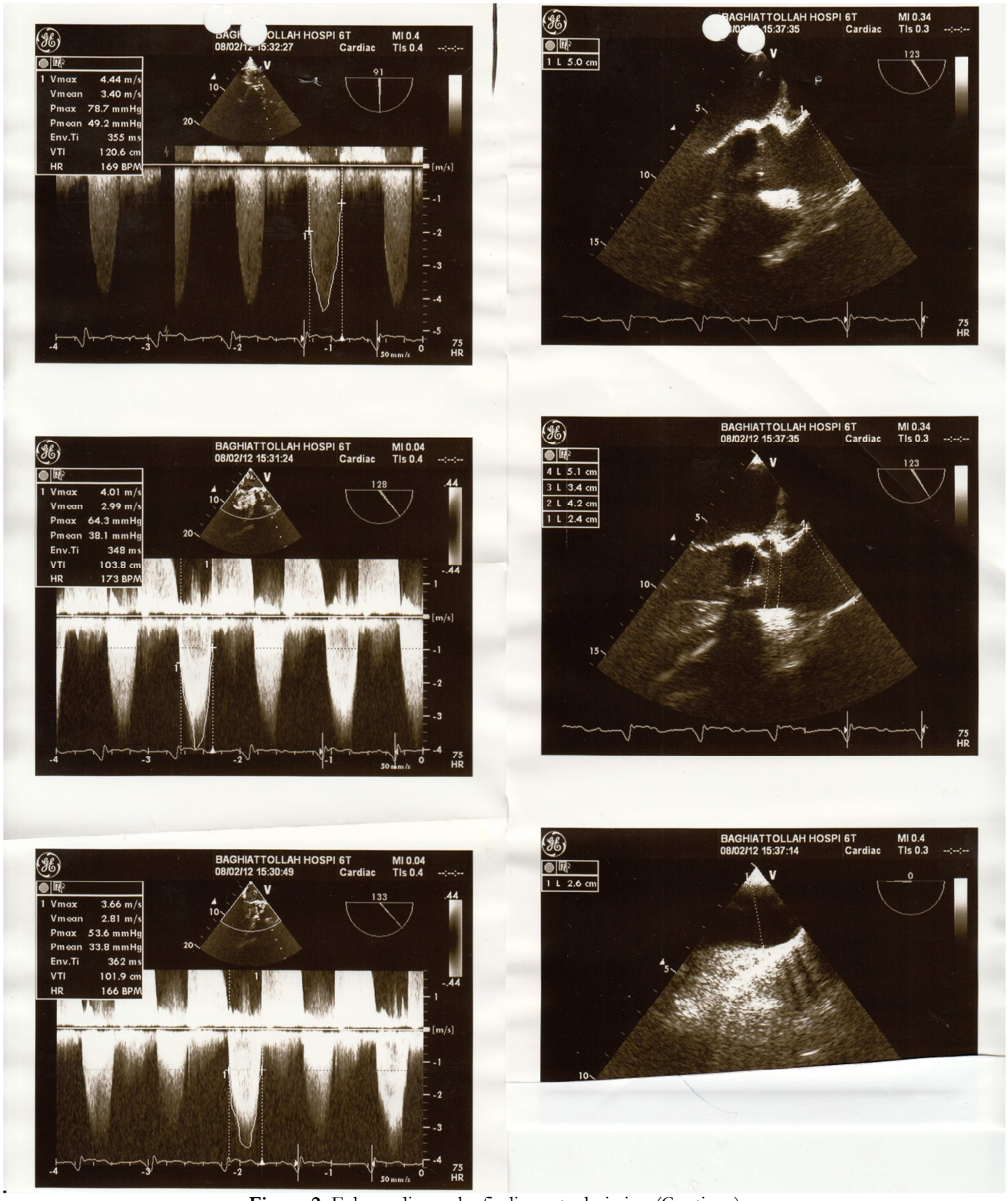


Figure 2. Echocardiography findings at admission (Continue)

The aortic valve properties in echocardiography included aortic valve velocity-time integral (AV VTI) = 120 cm, left ventricular outflow tract velocity-time integral (LVOT VTI) = 11 cm, aortic valve pressure gradient (AVPG) = 78 mmHg, aortic valve mean gradient (AVMG) = 50 mmHg, Anulus = 2.6 cm, valsalva sinus = 4.2 cm, and ascending aorta = 5.0 cm. After admitting the

patient to intensive care unit and stabilizing his general medical condition, the patient was referred to a cardiac surgeon for aortic valve replacement (AVR), replacement of ascending aorta, and root aneurysm with tube graft (Bentall procedure) which is a standard procedure in such cases.[6] Furthermore, a 3 chambers intra-cardiac defibrillator (ICD) was used for him. After 2 weeks of operation, he was discharged and at the first post-hospitalization visit (one week later), his cardiovascular condition was acceptable; there was no considerable dysfunction in implanted valve and pacemaker.

Discussion

There are many reports about the rare presentation of congenital aortic valve abnormalities. In 1978, Edwards et al. report 11 (9%) cases of BAV among 119 cases of fatal dissecting aneurysm of the aorta.[7] They concluded that: "Compared to an estimated incidence of bicuspid aortic valve of about 1 to 2% in the population, the high incidence among subjects with dissecting aneurysm suggests a causative relationship between BAV and aortic dissecting aneurysm."[7] Moreover, they stated that the most common background among patients with fatal dissecting aneurysm of the aorta and BAV is hypertension (73%), but our case neither hypertension nor dissection of aorta.[7] In one of the oldest reports (1953), Gore found a 24% incidence of BAV among 38 cases of dissecting aneurysm of the aorta.[8] Regarding previous reports, it seems that BAV is an associated congenital abnormality among patients with dissecting or aneurismal lesion of the aorta. Suzuki et al. reported a 52-year-old man with aortic valve stenosis and calcification complicated with complete AV block.[9] They concluded that the cause of complete AV block was a considerable progressive calcification involving the conduction system. In addition, they recommended that "the generator implantation be performed in the several days after the operation because of destruction of the pacemaker function by counter shock for arrhythmia in the early post-operative period".[9] The function of the pacemaker in our cases was followed after surgery and it was rearranged before discharge.

Some congenital disorders such as Marfan's syndrome can be associated with these two cardiac disorders (BAV and aneurismal lesion of the aorta), but it is not permanently constant such our reported case.[7] On the other hand, the higher incidence of AV block as a conductive abnormality is associated with aortic valvular stenosis and regurgitation.[10] In these cases with BAV, infectious endocarditis is more frequent than a normal valve, but in our case there is no evidence for endocarditis.[11] Thick calcified aortic root is a less studied and is a potential contributing risk factor for AV block after AVR.[10] Therefore, in candidates of aortic valve replacement considering conductive disorders, especially in patients with calcified valve, is mandatory. Irreversible AV block requiring PPM implantation is a rare condition following AVR, but in some cases, such as our reported case, AV block can be an initial presentation of disorders of the aortic valve.[12] Moreover, due to aortic root abnormalities, such as dissection and aneurysm, which was frequently reported in these cases, more accurate diagnostic methods such as computed tomography (CT) angiography is suggested before further interventions.[13]

Acknowledgments

We would like to thank Dr Hamidreza Taghipour and the personnel of the medical records ward of Baqiyatallah Hospital for their kind cooperation.

Conflict of Interests

Authors have no conflict of interests.

References

1. Tzemos N, Therrien J, Yip J, Thanassoulis G, Tremblay S, Jamorski MT, et al. Outcomes in adults with bicuspid aortic valves. JAMA 2008; 300(11): 1317-25.
2. Zeppilli P, Bianco M, Bria S, Palmieri V. Bicuspid aortic valve: an innocent finding or a potentially life-threatening anomaly whose complications may be elicited by sports activity? J Cardiovasc Med (Hagerstown) 2006; 7(4): 282-7.
3. Glancy DL, Devarapalli SK, Wang WL, Wilklow FE, Rochon BJ, Helmcke FR, et al. Ecg of the month. Unusual electrocardiogram 42 years after operation for supravalvular aortic stenosis and 6 years after aortic valve replacement. Sinus rhythm with first degree atrioventricular block. J La State Med Soc 2008; 160(2): 64-7.
4. Morita Y, Mizuno J, Yoshimura T, Morita S. Efficacy of amiodarone on refractory ventricular fibrillation resistant to lidocaine and cardioversion during weaning from cardiopulmonary bypass in aortic valve replacement for severe aortic stenosis with left ventricular hypertrophy. J Anesth 2010; 24(5): 761-4.
5. Oliver JM, Alonso-Gonzalez R, Gonzalez AE, Gallego P, Sanchez-Recalde A, Cuesta E, et al. Risk of aortic root or ascending aorta complications in patients with bicuspid aortic valve with and without coarctation of the aorta. Am J Cardiol 2009; 104(7): 1001-6.

6. Ghavidel AA, Tabatabaei MB, Yousefnia MA, Omrani GR, Givtaj N, Raesi K. Mortality and morbidity after aortic root replacement: 10-year experience. Asian Cardiovasc Thorac Ann 2006; 14(6): 462-6.
7. Edwards WD, Leaf DS, Edwards JE. Dissecting aortic aneurysm associated with congenital bicuspid aortic valve. Circulation 1978; 57(5): 1022-5.
8. Gore I. Dissecting aneurysms of the aorta in persons under forty years of age. AMA Arch Pathol 1953; 55(1): 1-13.
9. Suzuki Y, Sakai A, Kubo E, Nie M, Oosawa M. A case report of aortic valve stenosis combined with complete A-V block during chronic hemodialysis. Kyobu Geka 1993; 46(6): 528-31.
10. Schurr UP, Berli J, Berdajs D, Hausler A, Dzemali O, Emmert M, et al. Incidence and risk factors for pacemaker implantation following aortic valve replacement. Interact Cardiovasc Thorac Surg 2010; 11(5): 556-60.
11. Park MY, Jeon HK, Shim BJ, Kim HN, Lee HY, Kang JH, et al. Complete Atrioventricular Block due to Infective Endocarditis of Bicuspid Aortic Valve. J Cardiovasc Ultrasound 2011; 19(3): 140-3.
12. Limongelli G, Ducceschi V, D'Andrea A, Renzulli A, Sarubbi B, De FM, et al. Risk factors for pacemaker implantation following aortic valve replacement: a single centre experience. Heart 2003; 89(8): 901-4.
13. Mehrpooya M, Salehi M, Eskandari R, Shajirat Z, Golabchi A, Mazoochi M. Diagnostic dilemma: Saccular aneurysm or pseudoaneurysm of the ascending aorta with dissection above level of leaflets. ARYA Atheroscler 2012; 8(3): 167-9.

How to cite this article: Karbasi-Afshar R, Jonaidi-Jafari N, Saburi A, Khosravi A. **Atrioventricular block as the initial presentation of calcified bicuspid aortic valve.** ARYA Atheroscler 2014; 10(1): 59-64.

The concept of Maslow's pyramid for cardiovascular health and its impact on "change cycle"

Mohaddeseh Behjati[(1)]

Short Communication

Abstract

Since the leading cause of morbidity and mortality is cardiovascular diseases, every individual should think regularly about possessing and maintaining cardiovascular health. In reality, this self-processing is delayed until the occurrence of complications related to cardiovascular inefficiency manifested as chest pain and/or dyspnea. However, people should be trained to think about their cardiovascular health issues as a vital need from early childhood. This goal is achievable by understanding it as a "true human derive" and its consecutive "behaviors". Most people are unaware of their real needs, and even if they know all of their cardiovascular needs, this knowledge is not projected in their behaviors. In the present paper, I try to outline the Herzberg two-factor hypothesis and Maslow's hierarchy of needs.

Keywords: Maslow's Pyramid, Change Cycle, Cardiovascular Health

Date of submission: 9 May 2013, ***Date of acceptance:*** 11 Jul 2013

Introduction

"Do not only add years to life but also life to years".[1] For this goal, since the most common cause of morbidity and mortality are cardiovascular diseases, each person should think regularly about possessing and maintaining cardiovascular health.[2] This self-processing should not be delayed until the occurrence of complications related to cardiovascular inefficiency such as chest pain. But how can people be trained to think about cardiovascular health issues from early childhood as one vital need? The answer is embedded in understanding it as a "true human derive" and its consecutive "behaviors". Based on Sigmund Freud's belief, people are most often unaware of their real needs. Even if people know all of their cardiovascular needs, they differ in their behaviors in this regard.

In fact, each behavior is a hierarchy of activities. In each social system, ability and incents are fundamental keys in the determination of appropriate functioning communication. In this way, actions, interactions, and incents are tightly inter-related. By the strengthening or weakening of one factor, other factors will be terribly affected. Stronger incents mean tighter interactions. This chain moves toward accomplishment of a balanced state through a spiraling process. In this case, cardiovascular system is a highly social one through the presence of delicate interactions between bone-marrow stem cells, endothelial progenitor cells, endothelial cells, platelets, immune cells, fibroblasts, and other cells. By the dysfunction of one, the basis is prepared for loss of cardiovascular safety and health. The goal of the present essay is to link Maslow's pyramid for cardiovascular health with its impacts on the "change cycle".

Discussion

According to the motivators-hygiene hypothesis or the two-factor hypothesis by Fredrick Herzberg (1959s), the correct function of a system depends on two factors, hygiene factors and motivators.[3,4] The hygiene factors are related to principal key features which are not directly involved in efficiency, but only prevent complications related to reduced functional capacity by facilitating correct functioning. These factors describe environmental variables.[5] Unsatisfying hygiene factors may lead to reduced functional capacity, but by recovery of suitable conditions the production power will be refreshed. In the cardiovascular system, these factors can be interpreted as the present milieu, on which cardiovascular cells are embarked. In normal

1- Isfahan Cardiovascular Research Center AND Heart Failure Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Mohaddeseh Behjati, Email: behjati@med.mui.ac.ir

milieu, the cardiovascular system works in its optimal efficiency and, vice versa, a healthy cardiovascular system is involved in the maintenance of a healthy milieu. Diseased vessels impose a great threat on the health of the whole cardiovascular system through creation of an unhealthy milieu, which describes the impact of "peer pressure" both in cardiovascular system health and disease states. Motivators ensure better functioning. In this case, presence of motivators at the appropriate stage of life will guarantee "the sense of" having a healthy cardiovascular system. People differ with respect to their motives, the backbone of behaviors. Motives are the reason for the initiation and maintenance of behavioral traits and determine the total direction of behaviors. In healthy persons with affected relatives, these motivators act strongly, but with the passing of time these factors may fade gradually if they feel safe. This is because people usually act according to their perceptions, not reality. Thus, motivators need regular reinforcement. In diseased persons, motivators are stronger because the drive is stronger. Learnt behaviors become persistent if the success rate of mitigating chest pain or other complications of an unhealthy cardiovascular system is higher than failure rate; because patients gain positive attitudes and motives. However, motivators may gradually fade if the patient feels unsuccessful in the recovery of health after enough attempts. Often, a brief or single episode of failure will not result in loss of the motivated state. The force of satisfied or hinted motives will decrease over time and more essential derives replace them. Therefore, a person with a healthy cardiovascular system or even a person with full recovery after a cardiovascular event seeks to reply to their dominant needs. By contrast, persons with an unhealthy cardiovascular system try to eliminate the involved situation, but their attempts may be unsuccessful. In order to overcome the tension induced by failure, this patient will search for a new way through trial and error. In this case, the patient may develop coping behaviors. On the other hand, the patient may replace their aims to satisfy their needs. Further failure may lead to cognitive dissonance, which means disproportional feelings. This increases tension, and by ongoing failure the patient reaches a state of frustration. The following states, as defense mechanisms, might be rationalization, fixation, and resignation.

Therefore, for regular monitoring of cardiovascular health, everybody should regularly assess his/her own cardiovascular hygiene factors and motivators. Herzberg's cosmopolitan hypothesis is completely expandable to cardiovascular universe, but ignorance of cardiovascular health by most healthy cases is un-interpretable by this theory. The difference between behaviors of healthy and diseased cases is "priority of needs" which is interpretable by Maslow's pyramid of needs. Maslow refers to needs and motivations but Herzberg discusses aims and stimulators which satisfy these needs. Hierarchically, deficiency or D-needs (physiologic, safety, belonging/love/social, and esteem) and self-actualization needs form a pyramid in staged levels.[6] For patients with an impaired cardiovascular health state, the first level of the cardiovascular pyramid is economic issues. Patients should be able to pay for pills and physician-advised interventions, surgery, and rehabilitation sessions. Patients, especially elder ones, with intractable symptoms, like very low threshold angina or cases with end-stage heart failure, are in an emotionally delicate state. Indeed, chronicity of disease can be very tiresome for family and friends. Thus, family and social support will be the second level of the pyramid. Availability of automated defibrillators at public places is a kind of social support. Patients with cardiovascular disease, especially cases affected at early stages of life as complex congenital heart diseases, peripartum cardiomyopathy, dilated cardiomyopathy, and etcetera, may find difficulties in meeting the need for belonging and love. Esteem refers to the way patients see themselves. Depression is a great threat for patients, especially if the diseased state has caused great limitations in their life activities. Finally, a patient with a severely damaged cardiovascular health state and with decreased quality of life (such as cases who experience chest pain with small activities or device dependent heart failure patients), will not experience the self-actualization state. However, this stage could be interpreted as seeking optimal self-care, self-management, and adherence. This stage is achievable after meeting D-needs. In a healthy person, with or without risk factors, this pyramid differs which is depicted in figure 1. In this case, availability of a healthy diet and sufficient rest and recovery are the first level. Then, the evaluation of the cardiovascular health state of the safe case is necessary. If risk factors such as smoking, unhealthy diet, over weight and obesity, stressful life style, physical inactivity, strong family history, metabolic problems, lipid disorders, and other risk factors are

found, the next level is the modification of risk factors and therapeutic life style changes. This will progress to cardiovascular enhancement through appropriate cardiovascular exercise. Based on the overload principal, this cardiovascular training should be strong enough (not very weak, but not very strong) to exert strengthening pressure on the cardiovascular system.[7] Finally, these hierarchies of cardiovascular needs constitute the first level of Maslow's hierarchy of needs (physiologic or biologic needs). This means the presence of a pyramid inside a bigger pyramid. However, it should be noted that some persons may decide to sacrifice one level for another level. The cardiovascular health pyramid may be sacrificed in order to climb the pyramid to esteem or self-actualization levels of Maslow's hierarchy of needs. Indeed, people in various geographic locations differ regarding their belonging to levels. In developed countries, most people are at the top of the pyramid, but in under-developed countries people are usually in the stage of finding a healthy diet for the cardiovascular system. Developing countries pass the stage between these extremities of the pyramid.

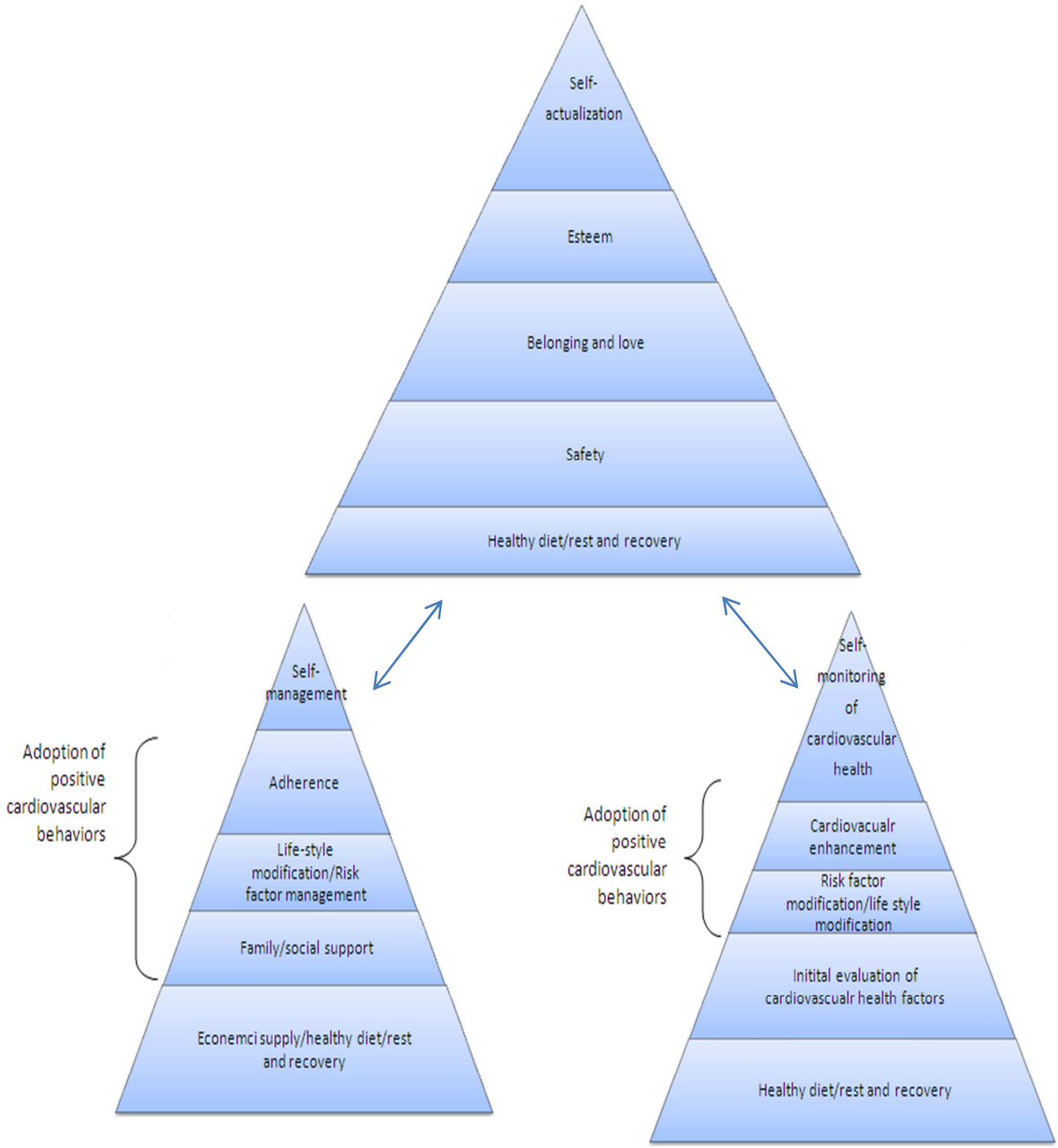


Figure 1. Maslow's pyramid and "change cycle" for cardiovascular health in healthy person with or without risk factors

In this need-oriented approach, stronger needs determine behaviors, but the person may feel cyclic variations in needs. As long as behaviors are enforced, they find a strong typical pattern and are hard to change. Thus, ignorance of cardiovascular health and its requirements becomes a permanently set behavior for most people. Promotion of cardiovascular health is not a phenomenon related to one specific stage of life. Since cardiovascular diseases most often affect elderly people, behavioral changes in this population are only possible in suitable conditions and after a prolonged time, which is not cost-benefit. Behavioral training should be started at early stages of life. Earlier and striking inputs produce bigger feedback loops with more prominent behaviors. In this regard, expectancy and availability are two factors which affect need power. Expectancy is based on the person's experiences in the past or present. A healthy person with strong family history for cardiovascular diseases has strong expectancy for infliction by cardiovascular diseases. This expectancy imposes upon his/her behaviors vastly. Stronger expectancy is parallel with stronger motives. This is true for cases with other diseases which affect the cardiovascular system such as diabetes mellitus, hyperlipidemia, hyperhomocysteinemia, and etcetera. However, this environmental factor always affects expectancy. For a patient with orthopedic problems or restricted physical activities, the routine walking advice is not applicable, and in other terms it would be "unavailable". Other examples are economic problems with inability to afford the costs for cardiovascular pills and/or percutaneous cardiovascular or surgical interventions. Thus, behavioral activities can be divided into goal-oriented activities and goal activities. Their difference is regarding to their different impact on needs. The former lasts longer, but it should be noted that in cardiovascular system health some goals are unachievable. Physicians should make it clear to patients that in some instances, such as patients with impaired left ventricular function, achievement of complete recovery is impossible.

Diseased patients first feel the need to change. Cardiologists play an important role in the change process. Physicians should be familiar with the "change cycle". By self-insight, changes made by the participative "change cycle" last longer at the expense of the long time labored for them. Changes made by coerced "change cycles" are developed rapidly, but last shorter. Thus, for effective prevention, group-based changes are preferred. It is true that all fellow-sufferers want to be in the same boat. In behavioral approach, unfreezed traits are controlled by outputs. Newly developed behaviors should be enforced for fixation and refreezing to prevent extinction. For vascular enrichment, cardiologists should be involved in the behavioral enforcement cycle. Reinforcement strengthens discriminated operant behaviors in order to increase their resistance to disruption and extinction.[8] The most permanent behaviors are made by initial continuous enforcement followed by intermittent enforcement. Life style modification behaviors need strong enforcement, since extinction rate is high especially in environments with counter attitudes. Continuous enforcement is parallel with the rapid rate of induction and rapid fading, but intermittent enforcement is associated with both slower induction and extinction rate due to internalization. For risk factor modification, such as smoking cessation, stress management, and ongoing physical activities, physicians should be involved in preventive measures in the way that patients apply internalization as an adaptive response. In families with great attention to cardiovascular health promotion, due to great knowledge or due to an affected case, family members may adopt identification adaptive response. In these families, children adopt healthy behaviors earlier in life which means stronger commitment to these behaviors.

Therefore, for training a society for the adoption of healthy cardiovascular behaviors and a successful "change cycle", physicians should pay great attention to needs, motives, and behaviors.

Conflict of Interests

Authors have no conflict of interests.

References

1. Do not only add years to life, but also add life to years–as well as to people with disabilities [Online]. [cited 2003]; Available from: URL: http://www.eu-seniorunion.info/en/activities/projects/Leipzig-Life2years_disabled-enw.pdf/
2. Ohira T, Iso H. Cardiovascular disease epidemiology in Asia: an overview. Circ J 2013; 77(7): 1646-52.
3. Sharp TP. Job satisfaction among psychiatric registered nurses in New England. J Psychiatr Ment Health Nurs 2008; 15(5): 374-8.
4. Sachau DA. Resurrecting the Motivation-Hygiene Theory: Herzberg and the Positive Psychology Movement. Human Resource Development Review

2007; 6(4): 377-93.
5. Antunes AV, Sant Anna LR. Satisfaction and motivation in nursing. Rev Bras Enferm 1996; 49(3): 425-34.
6. Sumrow A. Motivation: a new look at an age-old topic. Radiol Manage 2003; 25(5): 44-7.
7. Quinn E. The Principle of Overload - Definition [Online]. [cited 2007 Nov 29]; Available from: URL: http://sportsmedicine.about.com/od/glossary/g/Overload_def.htm/
8. Nevin JA. Resistance to extinction and behavioral momentum. Behav Processes 2012; 90(1): 89-97.

How to cite this article: Behjati M. **The concept of Maslow's pyramid for cardiovascular health and its impact on "change cycle".** ARYA Atheroscler 2014; 10(1): 65-9.