Isfahan Cardiovascular Research Institute

# ARYA Atherosclerosis

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## Original Article(s)



## Review Article(s)



## Case Report(s)



## Letter(s) to Editor



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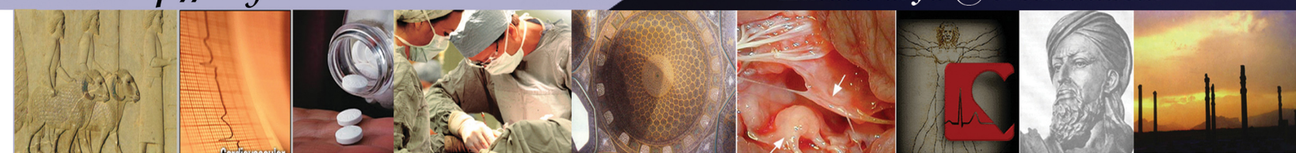

ARYA Atherosclerosis

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# Table of Contents

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# Factors influencing academic autonomy and its dimensions in Isfahan Cardiovascular Medical and Research Center, Iran: A mixed-method study

**Mohammad Reza Shafeie**[1], **Saeid Sharifi**[2]

**Original Article**

## Abstract

**BACKGROUND:** The issue of academic autonomy along with the reduced authority of the government for handling the service-providing section is considered an urgent demand for most of the organizations including hospitals.

**METHODS:** The method of research was a combination of quantitative and qualitative methods from sequential exploratory studies type. In qualitative part, descriptive-phenomenological method using seven-step Colaizzi method and in quantitative part, survey method was used. Statistical population of research of the first part included key experts of the academic autonomy field who were selected purposefully and based on the criterion. With 8 persons, data were saturated. Data collection tool of this part was semi-structured and deep interview. Validation of data was performed by outsider auditors as well as through returning to the interviewees. In quantitative part, a 60-question questionnaire made by the authors was used for data collection which was distributed among officials including hospital managers and key stakeholders of the academic autonomy process in a heart hospital who were 98 persons. Superficial and content validity of the questionnaire was estimated as much as 0.70 for all items. Modeling analysis in inferential level was done through Akaike scale regression.

**RESULTS:** Academic autonomy is in three dimensions: economic, scientific, and organizational and inter-organizational, intra-organizational, and extra-organizational factors contribute to it from which scientific autonomy is more important compared to other factors. Moreover, intra-organizational factors have more contribution to the academic autonomy of these centers.

**CONCLUSION:** The results of this study will be a good guide for academic autonomy of medical centers. In order to achieve academic autonomy, it is more important to pay attention to factors such as autonomy culture capacity, independent signing treaties and international documents, and science-centered society.

**Keywords:** Academic Autonomy; Scientific Autonomy; Economic Autonomy; Organizational Autonomy

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## Introduction

Academic freedom or academic autonomy means that in the core activities or tasks of the university, teaching, and research, decisions are necessarily up to the academic personnel.[1] In Iran, this matter has become a challenge owing to the increasing social collaborations and important and strategic engaging persons, so that most of the universities try to become independent from the decision-maker organizations to reduce their expenses and improve their productivities. Researches mainly consider four dimensions: organizational, financial, staffing, and academic dimensions for academic autonomy. In recent century, European Union (EU) took this definition as the basis of the academic autonomy and evaluates the European universities with these indices.[2]

According to studies performed in developing and developed countries, this presumption that health organizations must be solely administered by the governments has been doubted.[3]

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One of the effective solutions in this regard is to use the model of organizational reforms of the World Bank which includes five components: decision right, market confrontation, owner of the financial debt, response, and social functions.[4] In this model, giving decision-making right to an organization such as a bank improves the management and allocation of the promoted resources and responsibility of these centers since most of the decision makings are transferred from governmental level to the management level.[5]

In 1995, actions are taken for implementation of the autonomy and according to the Article 24 of the Budget Law in 2009, after the evaluation of the university hospitals, ministry of health and medical education is responsible for administration of at least one university hospital with the maximum score with a board of trustees in addition to the available ones.

The purpose of this law was to continuously improve the quality and the performance of the clinical services, increase the productivity, and finally, provide satisfaction of the people of the society. It is estimated that through application of the management strategies for the function of the personnel, operational simplification, operational budgeting, services management, management of the maintenance, implementation of the comprehensive system of the information and health communications as well as the comprehensive system of the hospital management, a novel model can be presented for management.[6]

This new method of hospital management, that is autonomy, is realized through delegation of authority and responsibility as well as confrontation to the market. In fact, this matter results in change in the passive state of hospitals in competitive market.[4]

In 2017, a research was conducted in medical centers of Georgetown University, Washington, United States (US), and results and experiences of eleven countries for giving autonomy to hospitals confirmed the success of the implemented policies. Complete management autonomy and financing for effective handling of the demands is of the necessities of the success in this context.[7] Results suggest that autonomy is accompanied with increased income, increased expenses of personnel, and more investment for infrastructures and equipment.

However, uncertainty of the level of collaboration and more expenses are some of the challenges of the autonomy. Therefore, for the autonomy of the universities, it is necessary that hospitals have an insight over all aspects.[8] From the results of such studies, it can be concluded that complete understanding of the components of the autonomy of the health and academic centers and consensus of the relevant people over it is one of the important issues which must be studied. If managers are provided by such components and model, it will be easier to succeed in responsibility and improvement of the services quality. Hence, the present work is done for the purpose of understanding academic autonomy components to present a model for Shahid Chamran Hospital, Isfahan, Iran. Results will be useful for better decision-making and optimal responsibility for the future health system.

Shahid Chamran Teaching Center is known as a teaching hospital and the most important cardiovascular center in Isfahan and also one of the most advanced heart centers in the south of the country. With its specialized workshops, the hospital has the capacity to achieve academic autonomy as a productive center, while to what extent aspects of autonomy for the university should be considered.

## Materials and Methods

From goal, application, and nature's point of view, this research was a combination of sequential exploratory studies. In the first phase, the qualitative research method was descriptive phenomenology. Statistical population of research included all experts and academics of medical sciences who were familiar with the topic of academic autonomy. Sampling was conducted purposefully and criterion-dependent up to saturation level of eight persons (Table 1).

Semi-structured interview was used for collection of the data. Lincoln and Guba's evaluation method was used for validation.[9]

**Table 1.** Demographic specifications of research sample

| N | Education | Study field | Work experience | Sex |
|---|---|---|---|---|
| 1 | Female | 20 | Medical | Doctor of Medicine |
| 2 | Male | 14 | General medicine | Doctor of Medicine |
| 3 | Male | 15 | Health management services | Doctor of Medicine |
| 4 | Male | 17 | Cardiac anesthesia | Doctor of Medicine |
| 5 | Male | 25 | Healthcare management | Masters |
| 6 | Male | 25 | Pharmacology | Doctor of Medicine |
| 7 | Male | 20 | Healthcare management | Doctor of Medicine |
| 8 | Male | 22 | Healthcare management | Doctor of Medicine |

For this end, authors spent sufficient time and confirmed the process with four academics using two coding and some interviews to ensure the agreement with coders. This improved the validity of the research data.

Furthermore, to ensure the generalizability of the findings, three management experts who did not take part in research were consulted about the findings. In this way, current research was validated. Colaizzi method (1978), also known as seven–step method was used for analysis of data.[10]

In the second phase of the research, descriptive survey method was used.

Statistical population of research included all experts of hospitals and managers in high, middle, and supervisory levels as much as 98 persons. Sample volume was estimated using Cochran's formula as 78 persons. 70 questionnaires were returned yielding 89% response rate. In this section, questionnaire was used for data collection. To determine the validity, Cronbach's alpha was used. Coefficients given in table 2 show the good reliability of the research tool.

**Table 2.** Reliability of the research variables using Cronbach's alpha

| Variables | Cronbach's alpha |
|---|---|
| Scientific autonomy | 0.88 |
| Organizational autonomy | 0.92 |
| Economic autonomy | 0.92 |
| Intra-organizational factors | 0.87 |
| Inter-organizational factors | 0.86 |
| Extra-organizational factors | 0.89 |

## Results

For better answering the research questions about academic autonomy, key owners were interviewed. In this step, written interviews were read several times and their overall content was understood. It was accompanied with listening to the part of recorded information. After implementation of the materials, all of the materials were carefully reviewed and important sentences and terms were extracted. At the end, 118 codes were obtained. This process was separately done by two experts. Then, meanings extracted from the sentences were combined and a common meaning was found. In this step, to ensure the generalizability of the research findings, three management experts in the field of hospitals participated and they were consulted about the statements of the interviewees. Finally, those statements which were stated once were taken out of the analysis cycle and the rest were considered by 61 codes. 61 simplified concepts were organized in the same classes and used for extraction of the essential structure of the phenomenon. Afterwards, 24 components were recognized. Table 3 summarizes the simplified concepts in the same classes.

Going through the data, a comprehensive definition about the phenomenon was classified in a regular and clear structure and the concepts were placed in a more comprehensive description which included all materials and details of the intended phenomenon. Some more general concepts including academic, organizational, inter-organizational, intra-organizational, and extra-organizational autonomy were provided. Table 4 gives a comprehensive description of the subject.

To answer this question, "What is the impact of effective factors on academic independence and its dimensions?", through modeling with Akaike scale, factors contributing to the academic autonomy and their significance level as well as elements of academic autonomy in Isfahan Cardiovascular, Medical, and Research Center are represented in table 5 and figure 1.

As can be seen from the table, inter-organizational, extra-organizational, and intra-organizational factors contributed to the academic autonomy. From these, intra-organizational factors had more contribution to the autonomy. $R^2$ factor was as much as 0.609 and Akaike scale was as much as -109.527, which shows that the model is of good quality and validity. Furthermore, from all dimensions of the academic autonomy, organizational (0.12), financial (0.24), and scientific (0.64) autonomy had the most importance and contribution to the academic autonomy.

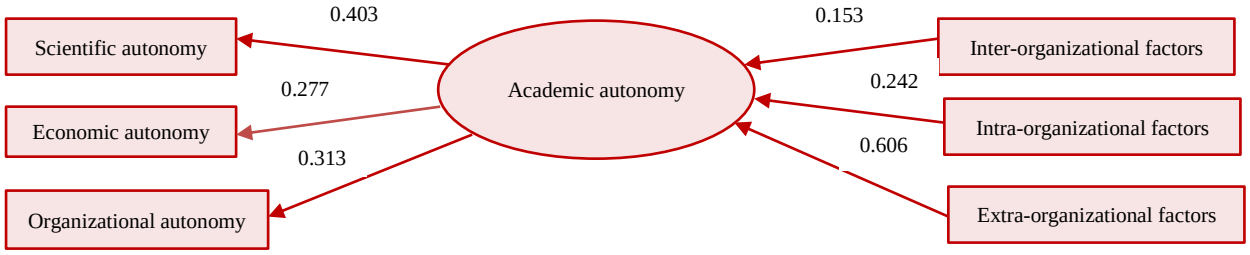


**Figure 1.** Model of cardiovascular academic autonomy and factors contributing to it

**Table 3.** Simplified concepts in the same classes

| Components | Index | Code |
|---|---|---|
| Research authority | Authority of production, distribution, and using research results | 1 |
| | Free determination of external academic relations | 21 |
| Academic authority | Authority of teaching in different languages | 13 |
| | Authority of removing educational programs | 12 |
| | Determination of promotional conditions for faculties | 8 |
| | Determination of curricula and academic content | 11 |
| Academic evaluation | Evaluation and surveying after content production | 50 |
| | Responses to the critics | 51 |
| Administrative authority | Authority of appointing the senior managers | 2 |
| | Determination of the promotional conditions | 52 |
| | Determination of the indices, process of evaluation, and quality assurance (QA) | 14 |
| | Employment authority without the influence of externals | 61 |
| | Determination of jobs and organizational policies | 15 |
| | Creation of appointment workshops and monitoring | 9 |
| Institutionalization authority | Creation of beneficiary legal persons | 5 |
| | Creation of non-profit legal persons | 6 |
| Regulatory authority | Setting internal regulations for university | 4 |
| | Setting time limits for managers | 22 |
| Auditing authority | Considering academic qualities for appointment of officials | 3 |
| | Creation of free choice, evaluation, and monitoring mechanism | 56 |
| Financing authority | Giving authority for definition of tariffs for special services | 23 |
| | Determination of taking money and award from other organizations | 16 |
| Financial management | Determination of salaries and benefits for all personnel | 7 |
| | Setting tuition fees | 19 |
| | Keeping excess money | 18 |
| Budget setting and allocation | Free loaning of the university | 17 |
| | Free selling buildings and assets | 20 |
| Intra-organizational capacities | Authority of relationship with charities | 24 |
| | Tendency of organizations toward collaboration with an independent university | 60 |
| | Independent signing treaties and international documents | 57 |
| Organizational reengineering | Reengineering of organizational structure | 58 |
| | Flexibility of organizational structure | 59 |
| International authority | International collaboration authority | 25 |
| | Authority of accepting and commitment to international conventions | 26 |
| | Authority of attracting immigrant refugees | 27 |
| | Authority in international relations development | 28 |
| Organizational culture | Culture of discipline | 29 |
| | Cultural pluralism | 30 |
| National culture | Science-centered society | 40 |
| | Autonomy culture capacity | 53 |
| Organizational policies and strategies | Capacity of creating long-term scope and plan | 31 |
| | Known internal and external competitors | 34 |
| | Decentralization and localism in management | 36 |
| Management skills | Intellectual autonomy of managers | 33 |
| | Increased responsibility | 32 |
| Response capacity | Response to the social beneficiaries | 35 |
| | Response to the government and market | 37 |
| Politics | Political interactions for university interests | 38 |
| | Creation of political shields | 55 |
| Political capacity | Power and democracy gap in political systems | 43 |
| | Cultural and religious tolerance | 44 |
| | Political views of managers | 45 |
| Political freedom | Political and intellectual opposition | 42 |
| | Political and civil freedoms | 41 |
| Economic capacity | Diversity of income sources | 39 |
| | Capacity of accepting financial documents and bonds | 54 |
| Technological capabilities | Independent control of online communication network | 46 |
| | Utilization of technology without public limitations | 47 |
| Administrative capacities | Transparency in internal relations system | 48 |
| | Supporting system of employees | 49 |

**Table 4.** Combination of results for comprehensive description of the subject

| Dimensions | Component | Code |
|---|---|---|
| Scientific independency | Research authority<br>Educational opportunity<br>Scientific evaluation | 1-21-13-12-8-11-50-51 |
| Institutional independency | Administrative power<br>The power of institutionalization<br>Audit authority<br>Legislative discretion | 2-52-14-15-9-5-6-4-22-3-56 |
| Economical independency | Financing power<br>Financial management<br>The power of allocation and financing | 20-17-18-19-7-16-23 |
| Intra-organizational factors | Inter-organizational capacity<br>National culture | 53-24-60-57-40 |
| Inter-organizational factors | Organizational policies and strategies<br>Management skills<br>Response capacity<br>Organizational culture<br>Technology capabilities<br>Administrative capacities<br>Organizational reengineering | 49-48-58-59-47-46 |
| Extra-organizational factors | Politics<br>Political capacity<br>Political freedom<br>International authority<br>Economic capacity | 41-42-45-44-43-55 |

## Discussion

Results of this research imply to the factors which are considered as the indices of the academic autonomy and as factors underlying such autonomy. The role of these factors in academic autonomy is very important. Findings suggest that three classes, intra-organizational, inter-organizational, and extra-organizational ones contribute to the academic autonomy.

Results of this research are in agreement with that of Karimian et al.,[2] Jafari,[4] London,[8] Hawkins,[11] and Jafari Sirizi et al.[12] London posits that making autonomy is accompanied with increased income, increased salaries, and investment over infrastructures and equipment. Hawkins introduces factors such as management flexibility, increased responsibility about the society and patients, and increased collaboration in the society as the key indices of the hospital autonomy.

On the other hand, Jafari Sirizi et al.[12] emphasize on factors such as decision-making right in strategic management, human resources, and physical resources as well as the ownership of the money. They imply to factors such as strategic management, human resources and physical resources, confrontation with product and logistic market, authority of the money, governance arrangement and responsibility as well as social functions of the hospitals. Moreover, Karimian et al.[2] stress on the scientific freedom, academic autonomy, the effect of foreign policies, lack of financial autonomy and dependence upon public budget, effect of the political relations on the international scientific relations, and effect of the political views of the academic managers on the academic environment. Although it seems that hospitals are relatively independent in this regard, such autonomy is a type of a predetermined movement. Imposing the intention of the political bodies on the organizations is viewed as the authority unless the organizations do not move in contradiction to their interests, while such type of authority has numerous proponents and opponents.

**Table 5.** Details of the cardiovascular academic autonomy model and fitting scale and the model validity (Linear regression)

| Dimensions | Importance | IF | SL | Model validity factor | Akaike scale |
|---|---|---|---|---|---|
| Inter-organizational factors | 0.293 | 0.153 | 0.012 | 0.609 | -109.527 |
| Intra-organizational factors | 0.374 | 0.242 | 0.002 | | |
| Extra-organizational factors | 0.671 | 0.606 | < 0.001 | | |
| Organizational autonomy | 0.120 | 0.313 | < 0.001 | 0.990 | -394.771 |
| Financial autonomy | 0.240 | 0.277 | < 0.001 | | |
| Scientific autonomy | 0.640 | 0.403 | < 0.001 | | |

IF: Impact factor; SL: Significance level

As discussed, reduced interference of government in hospital management results in benefits such as increased productivity, services with more quality, and more options for the patients. Opponents argue that increased privacy leads to unwanted consequences such as reduced value of stocks, reduced productivity, and less quality of the healthcare.

Seemingly, intellectual autonomy of the managers leads to their increased responsibility. Managers who can have a vision independent from the political and party systems have more ability to respond to the social beneficiaries on one hand and try to take actions for responding to the government and the market.

Moreover, to achieve academic autonomy, possibility of the organizational structure reengineering and flexibility of such a structure is a necessity. Inflexible structures make the adaptation of the hospital difficult and in this way, hospital may fail to respond to the environmental changes. In this regard, hospital is able to be independent when transparency of the internal relation systems and supporting system of the personnel is feasible. Concepts such as the organizational fairness, controllability, and opposing corruption become realized through such a system.

## Conclusion

University hospitals of Isfahan, especially specialized hospital of heart, have limited autonomy from different aspects. One aspect is the interference of the organizational bodies through the government and another one is pressures arising from the collaboration of the charities and beneficiaries. Moreover, limitations of the force modulation as well as the pressures of the social environment on the hospital along with the social expectations of the visitors who are not in good mental conditions pose various challenges to the managers of the hospitals.

To increase the awareness of the managers and beneficiaries about the benefits and limitations of the academic autonomy, guidance handbooks are prepared and given to them. To motivate the organizations and bodies to collaborate with the universities, circles must be bet to enforce the treaties independent from the political power of the government. To improve the cultural capacity of the universities, training sessions as well as organizational missions are provided for the managers and employees regarding the autonomy of the hospitals. Signing the international treaties for utilization of the knowledge and experience of the independent hospitals can be useful.

Therefore, it is proposed that the international relations unit of the hospitals take actions for development of such relations.

To improve the authority of interaction with charities, each of the hospitals can provide the network of charities with the possibility of allocating a considerable part of the economic capacities for the hospitals. Media play a pivotal role in development of the awareness in the society. Hence, through TV programs, expectations, knowledge, rights, and social duties of people with respect to the hospitals can be trained so that a science-based society can be realized.

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## Conflict of Interests

Authors have no conflict of interests.

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# Adherence to the algorithmic approach for diagnosis of pulmonary embolism: A teaching hospital experience, Shiraz, Iran

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Original Article

## Abstract

**BACKGROUND:** We evaluated to see if the algorithmic approach of pulmonary embolism (PE) [Wells' score, followed by D-dimer test and computed tomography pulmonary angiography (CTPA)] is appropriately followed in teaching hospitals of Shiraz, Iran.

**METHODS:** From October 2012 to October 2013, we prospectively calculated Wells' score for all patients who underwent CTPA with clinical suspicion to PE; patients with low probability who had not checked the D-dimer or had low level of D-dimer were considered as non-adherent to the guideline and those with high level of D-dimer or high probability of Wells' score were labeled as adherent to the PE guideline. CTPA scans were independently reported by two radiologists.

**RESULTS:** During study period, 364 patients underwent CTPA to rule out PE, of which 125 (34.3%) had Wells' score > 4 (high probable risk) and 239 had Wells' score ≤ 4. Amongst low probable risk patients (Wells' score ≤ 4), only 32 patients had undergone the D-dimer test (23 patients had high level of D-dimer). Based on the algorithmic approach, patients with suspected PE, patients with high probability (125 patients), and patients with low probability with elevated D-dimer level (23 patients) were considered as adherent to the PE guideline; consequently, the total adherence to PE guideline was 148 out of 364 (40.6%).

**CONCLUSION:** We followed the algorithmic approach guideline in about 40.0% of cases; however, we should pay more attention to the algorithmic approach in patients with suspected PE.

**Keywords:** Pulmonary Embolism; Diagnostic Imaging; Tomography; Blood; Spiral Computed Tomography

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## Introduction

Pulmonary embolism (PE), which occurs when a blood clot occludes the main or branches of pulmonary artery, is a life-threating disorder of cardiovascular system.[1-3] Swift diagnosis is vital to start timely and effective therapy, but nonspecific clinical and laboratory findings make the diagnosis difficult, leading to increased mortality rate.[4,5] Angiography has been the gold standard method for diagnosis of PE,[6] but since it is invasive, computed tomography pulmonary angiography (CTPA) scan is being used to make a definite diagnosis.[7]

The approach to suspected cases should be initiated by scoring systems (e.g., Wells); the D-dimer test is the second step in low probability cases and CTPA scan for high probability cases. The Wells' score and Geneva score are developed to

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help physicians for early detection and treatment of PE, according to some important key points in patients' history and physical examination. Many studies have shown that a normal CTPA can safely exclude the diagnosis of PE;[8-11] hence, its usage has increased, especially by physicians in the emergency wards. Due to some complications, such as radiation-induced carcinogenesis, anaphylaxis, and contrast-induced nephropathy (CIN), and also high cost of CTPA, minimizing this method is recommended.[12] We conducted this study to assess the adherence of our physicians to the algorithmic approach in patients suspicious of PE.

## Materials and Methods

From October 2012 to October 2013, we prospectively enrolled all consecutive patients who had been scheduled for CTPA, based on their treating physicians' decision, in two major referral hospitals (Namazi and Faghihi Hospitals with 750 and 363 active beds, respectively), Shiraz, Iran.[13] Patients scheduled for CTPA to find diseases other than PE, e.g., pulmonary artery aneurysm (PAA) or arteriovenous malformation (AVM), were excluded from the study. Then, we recorded all items of Wells' score in a prepared form, such as demographic criteria, arterial blood gases (ABGs), electrocardiography (ECG), D-dimer, echocardiography, and lower extremities color Doppler sonography (CDS) for each patient. Based on standard algorithmic approach to patients with suspected PE, we calculated Wells' score for all participants independent from treating physician's decision who had ordered the CTPA. Patients with low probability who had not checked D-dimer or had low level of D-dimer were considered as none-adherent to the guideline and those with high level of D-dimer or high probability of the Wells' score were labeled as adherent to PE guideline. The following variables and their assigned scores (in brackets) were used to calculate the Wells' score: Clinical symptoms of deep vein thrombosis (DVT) (3.0), no alternative diagnosis (3.0), heart rate (HR) > 100 beats per minute (bpm) (1.5), immobilization or surgery in the previous four weeks (1.5), previous DVT/PE (1.5), hemoptysis (1.0), and malignancy (1.0).[14] In Wells' criteria, values greater than 4 are considered as high probable limit of the suspected PE.[15] CTPA scans were taken by GE Bright Speed 16-slice computed tomography (CT) scanner machine (Milwaukee, WI, USA) and independently reported by two radiologists; in case of disagreement, a third radiologist's opinion was considered.

This study was approved by the local Ethics Committee of Shiraz University of Medical Sciences, Shiraz (IR.SUMS.REC.1390.S5893).

The continuous variables with normal distribution were presented as mean and standard deviation (SD) and non-normal variables as median and interquartile range (IQR). The categorical variables were reported as numbers and percentages. The means of two normally-distributed continuous variables were compared by independent samples t-test. Mann-Whitney U test was used to compare means of two groups of variables not normally distributed. The frequencies of categorical variables were compared using chi-square test. The normality of distribution of continuous variables was tested by one-sample Kolmogorov-Smirnov test (K-S test). The data were analyzed by SPSS software (version 11.5, SPSS Inc., Chicago, IL, USA). A P-value of $< 0.050$ was considered to be statistically significant.

## Results

During the study, 364 patients in the age range of 18-100 years were included. The average age of patients with PE was 56.8 ± 22.0 years and that of patients without PE was 55.2 ± 19.0 years (P = 0.565) (Table 1).

**Table 1.** Age and gender in patients suspicious to pulmonary embolism (PE)

| PE risk factors | Proven PE (n = 85) | Without PE (n = 279) | P |
|---|---|---|---|
| Age (year) (mean ± SD) | 56.8 ± 22.0 | 55.2 ± 19.0 | 0.565* |
| Gender (female) [n (%)] | 33 (38.8) | 144 (51.6) | 0.047** |

* Student's t-test; ** Chi-square test
PE: Pulmonary embolism; SD: Standard deviation

As shown in figure 1, during the study period, 364 patients underwent CTPA for suspected PE, of whom 125 (34.3%) had Wells' score > 4 (high probable risk). Among low probable risk patients (Wells' score < 4), only 32 patients had undergone D-dimer test (23 patients had high level of D-dimer). Considering patients who underwent CTPA, the total adherence to algorithmic approach in patients with suspected PE was 148 (125 high-risk patients plus 23 low-risk patients with positive D-dimer) out of 364 (40.6%).

The level of D-dimer was not measured in 207 out of 239 low-risk patients. The serum level of D-dimer was inappropriately checked in 15 out of 125 patients with Wells' score greater than 4.

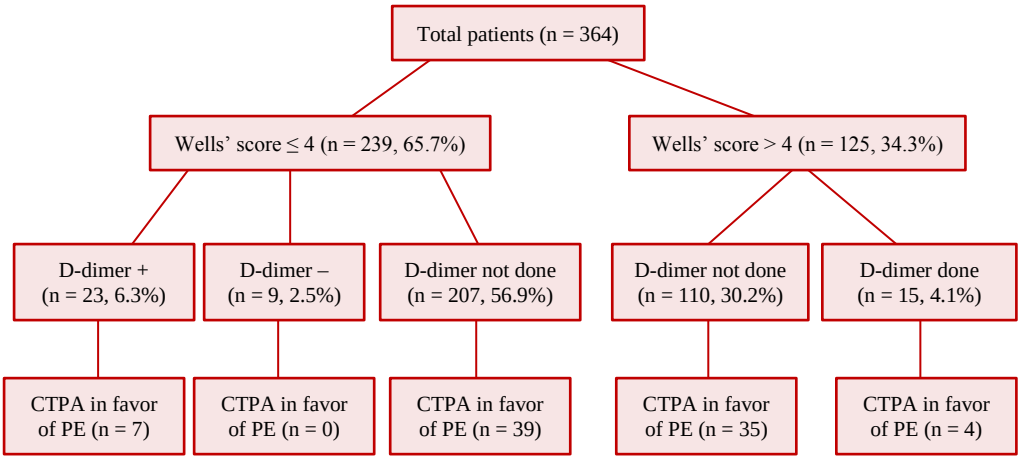


**Figure 1.** The adherence to algorithmic approach to pulmonary embolism (PE) in patients who underwent computed tomography pulmonary angiography (CTPA), Shiraz, Iran, 2012-2013

Table 2 shows that "clinical DVT", "hemoptysis" and "no alternative diagnosis" were significantly higher in the PE group (P < 0.050).

The final report of the CTPA scan was in favor of PE in 85 patients (23.0%).

The D-dimer tests were requested in only 12.9% (32 low-risk patients and 15 high-risk patients) (Table 2), and it was positive in 100% of patients with PE and 55.0% of patients without PE (Table 3, P = 0.009).

The ECGs were requested for 353 patients (Table 2), majority of whom had normal ECG (51.0%). Amongst those who had ECG findings in favor of PE, the most common abnormality was sinus tachycardia.

Table 3 shows the comparison of the results of D-dimer test, ECG, echocardiography, and the Doppler ultrasound of lower extremities in patients suspicious to PE with those without PE in CTPA.

The echocardiography was done for 269 patients. Echocardiographic findings in favor of PE [increased right ventricle (RV) size, decreased RV function, tricuspid regurgitation, McConnell's sign] were seen in 39 patients (14.5%); 16 out of 66 (24.0%) patients with PE and 23 out of 203 (11.0%) patients without PE had these findings (P = 0.015) (Table 3).

Amongst those who underwent CDS of both lower extremities (151 patients), 56 had DVT; 25 (53.2%) with proven PE in CTPA and 31 (29.8%) patients without PE (P = 0.010) (Table 3).

## Discussion

When used appropriately, CTPA has a major role in the diagnostic approach in patients with suspected PE, but the procedure complications such as CIN and radiation-induced carcinogenesis should be considered.

**Table 2.** The frequency of Wells' score items and requested para-clinical data in patients suspicious to pulmonary embolism (PE)

| PE risk factors | Proven PE (n = 85) [n (%)] | Without PE (n = 279) [n (%)] | P* |
|---|---|---|---|
| Previous DVT/PE | 10 (11.7) | 31 (11.1) | 0.846 |
| Surgery | 25 (29.4) | 63 (22.6) | 0.197 |
| Immobilization | 24 (28.2) | 59 (21.1) | 0.185 |
| Clinical DVT | 31 (36.5) | 64 (22.9) | 0.016 |
| No alternative diagnosis | 47 (55.3) | 81 (29.1) | 0.001 |
| Hemoptysis | 12 (14.1) | 16 (5.7) | 0.018 |
| Cancer | 15 (17.6) | 60 (21.5) | 0.540 |
| Tachycardia (HR > 100/min) | 32 (37.6) | 98 (35.1) | 0.699 |
| Requested para-clinical | | | |
| ABG analysis | 69 (81.2) | 231 (82.8) | 0.746 |
| ECG | 80 (94.1) | 273 (97.8) | 0.138 |
| Echocardiography | 66 (77.6) | 203 (72.7) | 0.400 |
| D-dimer | 11 (12.9) | 36 (12.9) | 0.999 |
| CDS | 47 (55.3) | 104 (37.3) | 0.004 |

* Chi-square test

DVT: Deep vein thrombosis; PE: Pulmonary embolism; HR: Heart rate; ABG: Arterial blood gases; ECG: Electrocardiography; CDS: Color Doppler sonography

**Table 3.** The comparison of the results of D-dimer test, electrocardiography (ECG), echocardiography, and the Doppler ultrasound of lower extremities in patients suspicious to pulmonary embolism (PE)

| Requested tests | | Proven PE [n (%)] | Without PE [n (%)] | P* |
|---|---|---|---|---|
| D-dimer (n = 47) | High level | 11/11 (100) | 20/36 (55.5) | 0.009 |
| | Normal | 0 (0) | 16/36 (44.5) | |
| ECG (n = 353) | In favor of PE | 51/80 (63.7) | 123/273 (45.1) | 0.003 |
| | Normal | 29/80 (36.3) | 150/273 (54.9) | |
| Echocardiography (n = 269) | In favor of PE | 16/66 (24.2) | 23/203 (11.3) | 0.015 |
| | Normal | 50/66 (75.8) | 180/203 (88.7) | |
| CDS (n = 151) | In favor of PE | 25/47 (53.2) | 31/104 (29.8) | 0.010 |
| | Normal | 22/47 (46.8) | 73/104 (70.2) | |

* Chi-square test
PE: Pulmonary embolism; ECG: Electrocardiography; CDS: Color Doppler sonography

Considering patients who underwent CTPA in our teaching hospitals, the total adherence to algorithmic approach in patients suspicious of PE was 40.6%. In this study, we evaluated the CT scans of 364 patients suspicious of PE, of which only 23.0% were in favor of PE. Based on previous studies, the prevalence of suspicious cases for PE were 2-3 in every 1000 people,[16,17] which 33.0% of them had PE, while our study showed that 23.0% had PE; hence, it seems that we are overusing CTPA. Our relatively low adherence to PE approach guideline could be partly explained by economic and audit issues in our centers. Quantitative D-dimer is not available at all time and the audit of CTPA requests is not regularly performed. On the other hand, performing CTPA merely takes few hours and that is why our physicians and residents have tendency to use CTPA as an available and theoretically highly accurate option. In the real life situation, the residents and physicians in emergency wards are under tremendous pressure. We must take into account their high stress and anxiety in missing a case with PE. As an administrative solution, adding the prerequisites of the Wells' score value and D-dimer results in the CTPA requests can increase the adherence to the guideline.

Wells' score as a risk stratification questionnaire has an item such as "Is the possibility of other differential diagnoses less than PE?" which is highly dependent on the user experience and clinical judgment; hence, the total score could vary. Nevertheless, if the Wells' score of ≤ 4 is considered as low probable for PE, 65.0% of our patients should be evaluated based on their D-dimer level rather than undergoing CTPA as the first diagnostic approach. However, we underuse D-dimer test as a first modality of diagnosis in patients with low probable PE and it was requested in only 12.0% of the patients.

The PE positive rate for CTPA in our study (23.0%) was higher than Costantino et al. study (10.0%),[18] but less than Perrier et al. study (26.0%).[19] After excluding suboptimal or poor technique CTPA, the negative CTPA studies can be explained with an alternative cause for dyspnea, such as pneumonia, pulmonary edema, pleural effusion, or atelectasis.[11]

The D-dimer assay is very sensitive, but non-specific screening test for venous thromboembolism (VTE) has an important role in diagnostic approach to PE.[20] The proper administration of the D-dimer in patients with low to intermediate risk for PE can reduce 26.0% of CTPA.[21]

Abcarian et al. evaluated the necessity of computed tomography (CT) scan based on quantitative D-dimer results. Out of the 426 patients who had both CT and D-dimer test, 82 patients had less than 0.4 µg/ml of serum D-dimer level and no sign of embolism in their pulmonary CT scan. Thus, it was concluded that if this test was done quantitatively, it would result in high negative predictive value (NPV).[22] Unfortunately, in our center, the D-dimer is not done quantitatively; hence, its predictive value is reduced even in the few occasions when it is requested. Nevertheless, in patients who underwent the test, the D-dimer test results were positive in all patients with PE and in 55.0% of those who did not have PE.

According to the previous studies, the ECG changes are useful, but they have limited sensitivity.[23] We observed the ECG findings in favor of RV strain only in 49.0% of the patients.

Previous studies showed that 25.0% of patients with PE had the echocardiographic findings supporting the dilated RV, and we also found that 24.0% of patients had findings in favor of PE, which is more than patients without PE (P = 0.015). Considering different studies, the sensitivity of the echocardiographic findings of PE is 60%-70%; consequently, its negative results

cannot lead to rejection of PE diagnosis.[24] Thus, as a diagnostic modality, echocardiography in patients with suspected PE with stable hemodynamic state is not recommended.[24] On the other hand, the absence of echocardiographic signs of RV volume overload in high-risk patients with hypotension could reject the PE as a reason of shock.[25] In the present study, the echocardiographic findings of PE were found in 39 out of 269 patients who underwent the procedure; CTPA revealed the evidence of emboli in 16 (24.0%) cases, which can partly be due to lower experience of our cardiology residents as the doer of echocardiography.

As it was shown in the previous studies,[19,26] the analysis of lower extremities CDS detected statistically significant higher rate of DVT in patients with PE. In our study, 25 out of 47 (53.0%) patients with PE who underwent CDS had evidence of DVT.

Limitations: Our study was conducted only in two tertiary hospitals. The echocardiography and CDS were done by different doers, and the D-dimer tests were checked qualitatively.

## Conclusion

Considering the limitations of the study, we concluded that we underused the Wells' score and D-dimer and overused CTPA in our approach to patients with suspected PE. We should pay more attention to the algorithmic approach in patients with suspected PE.

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## Conflict of Interests

Authors have no conflict of interests.

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# The effects of aerobic training, resistance training, combined training, and healthy eating recommendations on lipid profile and body mass index in overweight and obese children and adolescents: A randomized clinical trial

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Original Article

## Abstract

**BACKGROUND:** The aim of this study was to evaluate the effects of 8 weeks of aerobic training, resistance training (RT), combined training, and nutritional recommendations on lipid profile and body mass index (BMI) in obese and overweight children and adolescents.

**METHODS:** This randomized, clinical trial was conducted on 120 children and adolescents (10-19 years of age) with overweight and obesity. Participants were divided into 4 groups, the 3 intervention groups of high-intensity interval training (HIIT), RT, and combined training, and 1 non-exercising control group with healthy eating recommendations. We considered 24 sessions of training during 8 weeks for the intervention groups. The participants' anthropometric indices and lipid profile were assessed before and after the intervention.

**RESULTS:** There were no significant differences between the groups in terms of anthropometric indices and lipid profiles before the intervention. After the intervention, there was a significant difference between the groups in terms of high-density lipoprotein (HDL) level; the control group (37.70 ± 9.45) and the HIIT group (43.65 ± 9.09) displayed the lowest and highest mean, respectively (P = 0.040). Comparison of physical variables and blood lipid profiles before and after the intervention showed a significant difference in waist circumference (P = 0.030), hip circumference (P ≤ 0.001), and HDL level (P = 0.040) in RT, HIIT, combined, and control groups.

**CONCLUSION:** These results demonstrate that the combined training program and HIIT program with nutritional recommendations in overweight and obese children and adolescents were more effective in reducing BMI and hip circumference, respectively.

**Keywords:** High-Intensity Interval Training; Resistance Training; Overweight; Obesity

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## Introduction

Obesity is a metabolic disorder described as the accumulation of adipose tissue and chronic inflammatory reactions. The mechanisms of weight control in children depend on genetics, and environment and growth factors, and any disruption in these parameters can lead to the development of obesity.[1] Today, obesity and overweight are two important health problems and one of the most critical challenges in developed and developing countries due to their increasing prevalence and their association with various comorbidities such as endocrine disorders, cardiovascular disease (CVD),

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the digestive and nervous systems, and mental disorders. Based on scientific findings, the prevalence of obesity and overweight increased by 23.8% in boys and by 22.6% in girls from 1980 to 2013, and its prevalence in Iran in 2011 was 3.22% and 9.27% among tboys and girls, respectively.[2,3] The prevalence of obesity and overweight among high school students in Isfahan, Iran, was 4.3% and 11.5%, respectively.[4,5] Body mass index (BMI), waist circumference, and hip circumference are useful measurable indices for assessing obesity and overweight. In the study by Ahmadi et al., the waist circumference of adolescents living in urban areas was higher in comparison with that of those living in rural areas.[6]

Among the many treatments for overweight and obesity, the implementation of appropriate sports programs and dietary pattern alteration can be the most useful in preventing and controlling overweight and obesity.[1]

However, in many cases, there is a necessity for treatment; dietary changes, medication (such as the use of Omega 3, which can improve endothelial function of the vessels and increase high-density lipoprotein (HDL) especially in obese people), and surgical methods are some of these treatments.[7,8] One of the most important ways for preventing and treating obesity and overweight is optimized physical activity that is implemented in children and adolescents in the form of moderate to severe aerobic exercises 3 days a week for at least 1 hour, and is associated with improvements in individual's health conditions.[9] One of the recommended physical activity programs for controlling overweight and obesity is high-intensity interval training (HIIT) programs, which are a series of physical exercises that include high-intensity short-term courses combined with periods of less intense exercise.[10,11]

Although short-term exercises may interfere with physiological functions, HIIT is associated with significant improvements in the physiological and respiratory state, metabolic reactions, muscle function, and fat mass reduction. Moreover, investigations have shown the practical roles of HIIT in obesity, overweight, and lipid profile control in children and adolescents.[9,11]

Previous researches have shown that HIIT programs are generally beneficial to the body and time-efficient and result in improvements in oxidative capacity and microvascularization of the muscles.[11] Another series of exercises include resistance training (RT) that increases muscle strength by applying tensile force and helps reduce fat tissue.[12] Although it was thought that these exercises might be harmful because of the effect they have on the child's growth, more recent investigations show that if trainers accurately monitor the workouts in children, they can greatly reduce the probability of the injury. Therefore, the use of RT programs to prevent and treat obesity and overweight in children seems to be beneficial.[12,13] Therefore, considering the importance of the mentioned cases and the limited number of studies in this field, the purpose of this study was to evaluate the effects of aerobic, resistance, combined training, and healthy eating recommendations on lipid profile and BMI in overweight and obese children and adolescents.

## Materials and Methods

This randomized, single-blinded, clinical trial was conducted on 120 children and adolescents, with overweight or obesity and 10-19 years of age, referred to the Clinic of the Pediatric Cardiovascular Research Center in the Cardiovascular Research Institute of Isfahan, Iran, in 2017-2018.

The study inclusion criteria included children and adolescents aged 10 to 19 years with overweight (BMI of more than one standard deviation from the specific BMI according to age and sex] and obesity (BMI of more than two standard deviations from the particular BMI according to age and sex based on the World Health Organization (WHO) criteria].[14,15] The exclusion criteria were certain diseases such as thyroid dysfunction, diabetes, or hypertension, history of taking drugs, BMI of less than one standard deviation of BMI according to age and sex, and reluctance to participate in the study.

We selected our participants using simple random sampling method with random allocation software from among eligible cases with overweight and obesity who had a health record at the Clinic of the Pediatric Cardiovascular Research Center.

Finally, 120 participants, using randomized block design, were randomized into 4 groups (30 children and adolescents in each group), 3 intervention groups (including RT, HIIT, and RT + HIIT groups) and 1 control group. Before the beginning of the study, verbal consent was obtained from children and adolescents and written informed consent was received from one of their parents. The ethics committee of Isfahan University of Medical Sciences, Iran, (No. 446755) approved this study. In addition, this study was registered in the Iranian Registry of Clinical Trials (www.irct.ir; IRCT20150428021987N4).

Preliminary data before and after the intervention were obtained by filling out a checklist, measuring anthropometric indices including weight, hip circumference, waist circumference, and BMI,

and receiving blood tests. Before the beginning of the study, anthropometric parameters (weight, height, waist circumference, and hip circumference) were obtained and blood samples were collected from the 4 groups for evaluation of lipid profiles [including triglyceride, cholesterol, HDL, and low-density lipoprotein (LDL)]. The researchers were blinded and allocated to the interventions.

Anthropometric parameters were measured using standard tools before and 8 weeks after the educational intervention. Weight was measured with minimal clothing and without shoes using a Seca scale with an accuracy of 0.1 kg. Height was measured to the nearest 0.5 cm. The waist circumference was measured at the midpoint between the bottom of the rib cage and the top of the iliac crest at the completion of exhalation. The hip circumference was measured in a standing position with a tape measure and on the widest part of the pelvis in a position parallel to the ground.

Blood samples were collected from the 4 groups for evaluation of lipid profiles including at the beginning of and 8 weeks after the study, and sent to a laboratory.

After the data were collected, separate educational intervention (including HIIT as stretch exercises, RT, and combined RT+HIIT program, and healthy eating recommendations) were implemented at different times. The healthy eating recommendations included consumption of vegetables, fruits, whole grains, fat-free or low-fat milk, lean meats, poultry, fish, eggs, beans, and nuts, in addition to lower use of fats, trans fats, cholesterol, salt (sodium), and added sugars. A total of three 60-minute educational sessions of lecture, question and answer, and role-playing were held for the children and adolescents in the intervention groups, and their parents. At the end of the session, participants received educational pamphlets of sports exercises and healthy eating recommendations to continue learning at home. It should be noted that participant in the control group received no training education, but they were provided with healthy eating recommendations in the form of pamphlets.

After the educational sessions, the intervention groups exercised based on a training program designed in the form of 3 separate programs (HIIT as stretch exercises, RT, and combined RT + HIIT program). The training program was conducted for 8 weeks (a total of 24 training sessions). Each exercise session included 10 minutes of warming up (running in place and stretching movements), performing the main phase of the intervention, and then, 10 minutes of cooling down (performing stretching movements). The exercises related to the HIIT group are provided in table 1. For the HIIT group, the total training period was 30 minutes and the rest time was 20 seconds between each item.

**Table 1.** The components of the high-intensity interval training program and its settings

| No. | HIIT program component | Settings |
|---|---|---|
| 1 | X-burpee | 3 minutes |
| 2 | Floor tap squat | 3 minutes |
| 3 | Side to side burpee | 3 minutes |
| 4 | Knee lifting exercise | 3 minutes |
| 5 | Jump squat | 3 minutes |
| 6 | Lunge | 3 minutes |
| 7 | Squat jack | 3 minutes |
| 8 | Controlled burpee | 3 minutes |
| 9 | Scissor squats | 3 minutes |

HIIT: High-intensity interval training

In the RT group, interventions were carried out in 3 sets, each containing 3 items, details of which are given in table 2.

**Table 2.** The components of the resistance training program and its settings

| Set | Exercises | Settings |
|---|---|---|
| Set 1 | Squats | 8-10 times |
| | Push-ups | More than 12 times |
| | Crunches | 30-45 seconds |
| | Glute bridge | More than 12 times |
| Set 1 | Pull-ups | 8-12 times |
| | Bicycle crunches | 30-45 seconds |
| | Shoulder press | 8-12 times |
| Set 1 | Bent-knee bench dip | More than 12 times |
| | Lying back extension | 30-45 seconds |

Between each item, 30 seconds, and between each set, 60 seconds was dedicated to resting. For this group, 30 minutes of training was also considered. In the RT+HIIT group, HIIT and RT exercises were performed at 3-minute intervals (in each session). In total, 30 minutes of training was considered for this group. All intervention groups received instructions on the exercise movements at the Clinic of the Pediatric Cardiovascular Research Center, and subsequently, continued their exercises at home. In order to follow the participants' exercise schedule, we made phone calls every week to obtain this information. As no specific sport intervention had been considered for the control group, the participants in this group merely performed routine activities. Other considerations for this group were similar to the other study groups. At the end of the 8 weeks of educational intervention, to observe ethical considerations, effective methods of weight loss such as dietary advice and exercise training were provided to the control group. Figure 1 presents the flowchart of the study participants.

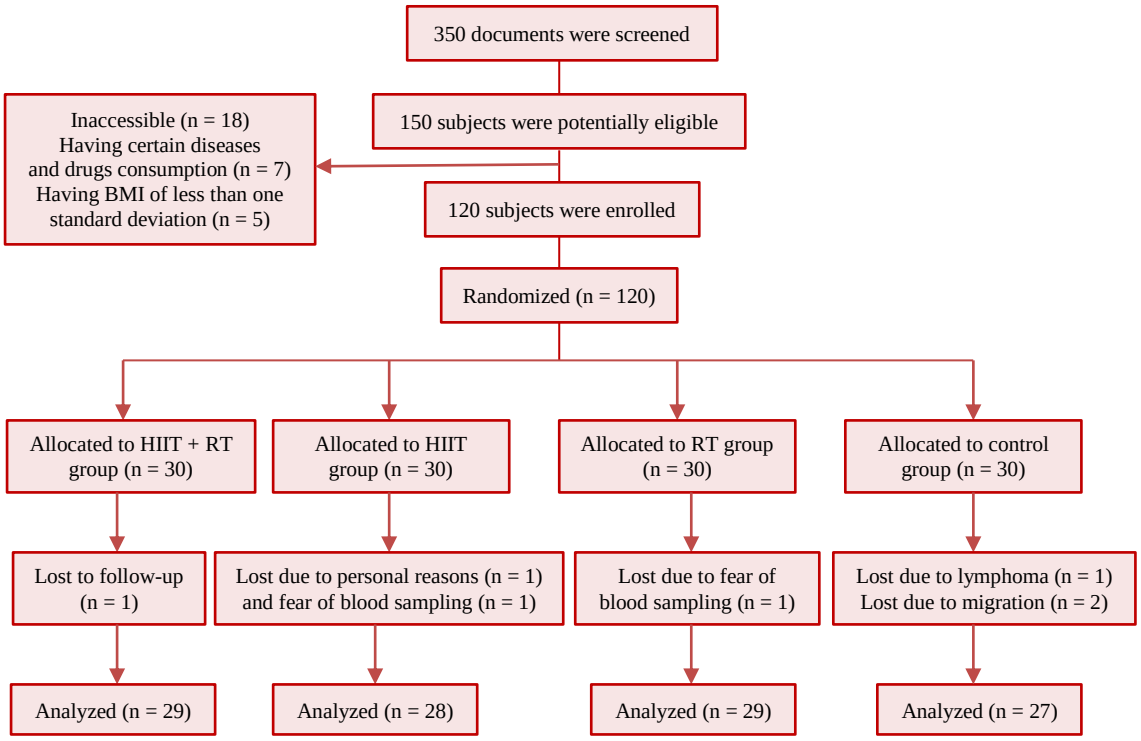


**Figure 1.** Study flowchart

HITT: High-intensity interval training TR: Resistance training

The collected data were imported into SPSS Software (version 23.0.; IBM Corporation, Armonk, NY, USA). Quantitative data were expressed as mean and standard deviation (SD), and qualitative data were expressed as numbers and percentages. To determine the normality assumption of the data, Kolmogorov-Smirnov test (K-S test) was used, and a non-parametric test was used for variables that were not normally distributed. The paired t-test was used for intra-group comparisons before and after the intervention. Analysis of covariance (ANCOVA) was used to compare the measured values after the intervention between groups (with initial effect adjustment). The significance level was defined as P-value < 0.050.

## Results

During the study, from among the 120 participants, 1 subject due to lymphoma, 2 subjects due to migration, and 4 subjects due to unwillingness to participate in the study were excluded. In this study, 113 subjects participated, including 68 (60%) girls and 45 (40%) boys. The mean age of the study subjects was 13.86 ± 2.75 years. The statistical analysis of demographic information showed no significant differences between the groups in terms of age and sex (P > 0.050). Details of the demographic information are provided in table 3.

Comparison of physical variables and blood lipid profiles showed that there were no significant differences between the case and control groups before the intervention. However, after the intervention, there was a significant difference between the groups in terms of the levels of HDL; the lowest mean was observed in the control group (37.70 ± 9.45) and the HIIT group displayed the highest mean (43.65 ± 9.09) (P = 0.040). Tables 4 and 5 show these results.

**Table 3.** Demographic characteristics of the participants

| Variable | HIIT (n = 28) | RT (n = 29) | RT+HIIT (n = 29) | Control (n = 27) | P* |
|---|---|---|---|---|---|
| Sex [n (%)] | | | | | 0.280 |
| Male | 13 (44.8) | 8 (28.6) | 10 (34.5) | 14 (51.9) | |
| Female | 16 (55.2) | 20 (71.4) | 19 (65.5) | 13 (48.1) | |
| Age (year) (Mean ± SD) | 14.55 ± 2.55 | 13.89 ± 2.80 | 14.27 ± 2.77 | 12.70 ± 2.64 | 0.060 |

* Sex difference assessed via chi-square test and age difference assessed via analysis of variance

P < 0.050 was considered significant. HITT: High-intensity interval training; TR: Resistance training

**Table 4.** Comparison of physical variables and lipid profiles (Mean ± SD) before the intervention

| Variable | Before the intervention (Mean ± SD) | | | | P* |
|---|---|---|---|---|---|
| | HIIT (n = 28) | RT (n = 29) | RT+HIIT (n = 29) | Control (n = 27) | |
| Physical variables | | | | | |
| Height (cm) | 163.12 ± 12.16 | 156.30 ± 12.12 | 154.98 ± 14.34 | 154.98 ± 14.34 | 0.050 |
| Weight (kg) | 80.60 ± 20.24 | 71.33 ± 17.88 | 70.66 ± 25.30 | 70.66 ± 25.30 | 0.240 |
| BMI (kg/m$^2$) | 29.97 ± 5.15 | 28.80 ± 4.83 | 29.55 ± 5.60 | 28.48 ± 6.00 | 0.720 |
| WC (cm) | 94.14 ± 13.95 | 88.55 ± 12.03 | 93.68 ± 14.37 | 92.18 ± 14.62 | 0.410 |
| Hip (cm) | 109.36 ± 13.04 | 102.82 ± 12.10 | 100.24 ± 14.40 | 100.24 ± 14.40 | 0.600 |
| Blood variables | | | | | |
| Cholesterol (mg/dl) | 164.17 ± 35.54 | 164.32 ± 33.92 | 164.31 ± 32.23 | 157.60 ± 29.42 | 0.830 |
| TG (mg/dl) | 126.03 ± 59.20 | 123.60 ± 48.11 | 118.68 ± 54.0 | 121.85 ± 43.31 | 0.950 |
| LDL-C (mg/dl) | 88.20 ± 29.96 | 85.46 ± 30.60 | 93.06 ± 30.01 | 87.11 ± 26.70 | 0.770 |
| HDL-C (mg/dl) | 46.44 ± 10.16 | 46.25 ± 9.55 | 44.51 ± 9.93 | 45.25 ± 16.49 | 0.910 |

* One-way ANOVA or Kruskal–Wallis. P < 0.050 was considered significant.

HITT: High-intensity interval training; TR: Resistance training; SD: Standard deviation; BMI: Body mass index; WC: Waist circumference; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

Pre-intervention and post-intervention comparison of physical variables and blood lipid profiles after adjusting for variables showed a significant difference between all groups in terms of waist circumference (P = 0.030), hip circumference (P ≤ 0.001), and levels of HDL (P = 0.040).

Height was increased significantly in all groups. Moreover, body weight had increased during training in the case and control groups, and this increase was significant in the RT group. BMI decreased significantly only in the HIIT+RT group (P = 0.010) after the intervention.

Waist circumference increased during training in all groups except the HIIT group. Hip circumference increased significantly in the RT and control groups, but decreased significantly in the HIIT group (P = 0.030). Waist/hip ratio differed in all groups after the intervention compared to before the intervention, but this difference was not significant.

Serum cholesterol level decreased in the HIIT and RT groups and increased in the control group, but these differences were not significant. Serum triglyceride level decreased only in the HIIT group; this difference was not significant. LDL levels decreased only in the RT group, but this reduction was not statistically significant. HDL levels had not increased after the intervention in all groups, but had significantly decreased in the control group (P = 0.020) (Table 6).

## Discussion

This study showed that the combined RT+HIIT program had a significant effect on the reduction of participants' BMI. However, the post-intervention weight of the groups did not show any significant changes except for the RT group in which weight was significantly increased after the intervention.

Another finding of our study was that waist and hip circumference increased significantly in the RT group. The highest mean hip circumference was seen in the HIIT group, the RT+HIIT group, and the RT group, respectively, which were significantly different compared to the control group. Similarly, the groups were significantly different regarding hip circumference after the training. Although, hip circumference was considerably higher in the RT and control groups, this factor showed a significant decrease in the HIIT group.

**Table 5.** Comparison of physical variables (Mean ± SD) and lipid profiles after the intervention

| Group / Variable | HIIT (n = 28) Mean ± SD | RT (n = 29) Mean ± SD | RT+HIIT (n = 29) Mean ± SD | Control (n = 27) Mean ± SD | P* |
|---|---|---|---|---|---|
| Physical variables | | | | | |
| Height (cm) | 164.40 ± 11.43 | 157.57 ± 11.94 | 161.50 ± 9.20 | 155.81 ± 14.09 | 0.070 |
| Weight (kg) | 80.90 ± 18.66 | 72.70 ± 17.21 | 76.88 ± 19.38 | 71.10 ± 24.81 | 0.180 |
| BMI (kg/m$^2$) | 29.55 ± 5.00 | 28.87 ± 4.65 | 29.05 ± 5.35 | 28.41 ± 5.80 | 0.670 |
| WC (cm) | 93.53 ± 12.91 | 92.32 ± 13.30 | 94.58 ± 13.90 | 93.20 ± 14.55 | 0.890 |
| Hip (cm) | 107.05 ± 11.38 | 105.78 ± 12.06 | 103.46 ± 11.98 | 102.44 ± 14.50 | 0.420 |
| Blood variables | | | | | |
| Cholesterol (mg/dl) | 157.62 ± 23.91 | 157.71 ± 40.30 | 164.51 ± 35.77 | 161.70 ± 43.30 | 0.440 |
| TG (mg/dl) | 118.13 ± 44.43 | 127.92 ± 75.48 | 125.62 ± 61.74 | 137.92 ± 54.70 | 0.330 |
| LDL-C (mg/dl) | 91.65 ± 17.30 | 81.28 ± 20.19 | 96.37 ± 26.36 | 88.77 ± 27.71 | 0.160 |
| HDL-C (mg/dl) | 43.65 ± 9.09# | 43.35 ± 8.85 | 42.55 ± 8.53 | 37.70 ± 9.45# | 0.040 |

* One-way ANOVA or Kruskal-Wallis test; # The difference between the first and forth group was significant.

HITT: High-intensity interval training; TR: Resistance training; SD: Standard deviation; BMI: Body mass index; WC: Waist circumference; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

**Table 6.** Comparison of physical variables and lipid profiles before and after the intervention after adjusting for variables

| Variables | | HIIT (n = 28) | RT (n = 29) | RT+HIIT (n = 29) | Control (n = 27) | P** |
|---|---|---|---|---|---|---|
| | | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | |
| Height (cm) | Pre-intervention | 163.12 ± 12.16 | 156.29 ± 12.12 | 160.05 ± 9.48 | 154.98 ± 14.34 | 0.220 |
| | Post-intervention | 164.39 ± 11.43 | 157.57 ± 11.94 | 161.50 ± 9.20 | 155.81 ± 14.09 | |
| | P* | 0.001 | 0.001 | < 0.001 | < 0.001 | |
| Weight (kg) | Pre-intervention | 80.60 ± 20.24 | 71.34 ± 17.89 | 76.77 ± 20.13 | 70.67 ± 25.31 | 0.370 |
| | Post-intervention | 80.90 ± 18.66 | 72.70 ± 17.21 | 76.88 ± 19.38 | 71.09 ± 24.82 | |
| | P* | 0.617 | 0.010 | 0.807 | 0.251 | |
| BMI (kg/m$^2$) | Pre-intervention | 29.97 ± 5.15 | 28.79 ± 4.83 | 29.54 ± 5.60 | 28.49 ± 6.00 | 0.170 |
| | Post-intervention | 29.56 ± 4.99 | 28.88 ± 4.65 | 29.05 ± 5.35 | 28.41 ± 5.79 | |
| | P* | 0.088 | 0.677 | 0.011 | 0.603 | |
| WC (cm) | Pre-intervention | 94.14 ± 13.94 | 88.55 ± 12.03 | 93.68 ± 14.37 | 92.18 ± 14.62 | 0.030 |
| | Post-intervention | 93.53 ± 12.91¥ | 92.32 ± 13.30¥ | 94.58 ± 13.90 | 93.20 ± 14.55 | |
| | P* | 0.553 | 0.001 | 0.311 | 0.268 | |
| Hip (cm) | Pre-intervention | 109.36 ± 13.08 | 102.82 ± 12.09 | 104.93 ± 11.86 | 100.24 ± 14.40 | < 0.001 |
| | Post-intervention | 107.05 ± 11.38 | 105.78 ± 12.06§ | 103.46 ± 11.98§ | 102.44 ± 14.50 | |
| | P* | 0.034 | 0.004 | 0.261 | < 0.001 | |
| Waist/hip ratio (cm/cm) | Pre-intervention | 0.87 ± 0.08 | 0.86 ± 0.06 | 0.90 ± 0.06 | 0.92 ± 0.05 | 0.220 |
| | Post-intervention | 0.87 ± 0.06 | 0.87 ± 0.06 | 0.91 ± 0.10 | 0.90 ± 0.05 | |
| | P* | 0.992 | 0.282 | 0.161 | 0.222 | |
| Cholesterol (mg/dl) | Pre-intervention | 164.17 ± 35.54 | 164.32 ± 33.93 | 164.31 ± 32.23 | 157.59 ± 29.43 | 0.220 |
| | Post-intervention | 157.62 ± 23.91 | 151.71 ± 40.30 | 164.51 ± 35.77 | 161.70 ± 43.30 | |
| | P* | 0.156 | 0.073 | 0.959 | 0.588 | |
| TG (mg/dl) | Pre-intervention | 126.03 ± 59.21 | 123.60 ± 48.11 | 118.68 ± 54.00 | 121.85 ± 43.32 | 0.350 |
| | Post-intervention | 118.13 ± 44.43 | 127.93 ± 57.48 | 125.62 ± 61.74 | 137.93 ± 54.69 | |
| | P* | 0.358 | 0.672 | 0.411 | 0.191 | |
| LDL-C (mg/dl) | Pre-intervention | 88.21 ± 26.96 | 85.46 ± 30.60 | 93.06 ± 30.01 | 87.11 ± 26.71 | 0.130 |
| | Post-intervention | 91.65 ± 17.29 | 81.28 ± 20.19 | 96.37 ± 26.36 | 88.77 ± 27.70 | |
| | P* | 0.462 | 0.359 | 0.395 | 0.757 | |
| HDL-C (mg/dl) | Pre-intervention | 46.45 ± 10.17 | 46.25 ± 9.55 | 44.51 ± 9.93 | 45.26 ± 16.49 | 0.040 |
| | Post-intervention | 43.56 ± 9.09£ | 43.36 ± 8.85 | 42.55 ± 8.53 | 37.70 ± 9.46£ | |
| | P* | 0.161 | 0.152 | 0.246 | 0.027 | |

* Paired t-test; ** ANOVA test; ¥ The difference between the first and second group was significant; § The difference between the second and third group was significant; £ The difference between the first and forth group was significant.

HITT: High-intensity interval training; TR: Resistance training; SD: Standard deviation; BMI: Body mass index; WC: Waist circumference; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

The evaluation of the lipid profile showed that cholesterol levels in the RT group and HIIT group decreased after the exercise. In the control group, there was also a significant decrease in HDL, and this group had the lowest mean compared to the other groups.

The results of the present study generally show the beneficial role of using the exercise program, especially the combined exercises, in improving the lipid profile status and physical indices; however, some of the parameters did not show much change, and these results are not consistent with some studies.

According to the study conducted by Ramezani and Akbari, after performing the HIIT program, there was no difference between the intervention group and control group in terms of weight, but in the intervention group, BMI showed a significant decrease. This finding is consistent with our study, which may be due to their similar pre-intervention parameters and training programs.[16]

McGuigan et al. showed that while participants developed extensive changes in body composition and fat after the 8 weeks of resistance training, these exercises did not lead to a massive change in BMI.[17] Moreover, the weight of participants at the end of their study had increased somewhat, although it was not statistically significant. BMI-related findings were consistent with that of our research, but outcomes related to weight gain were inconsistent with that of our results, although overall, weight gain was observed after the 8-week program in their subjects. The probable reason for these differences might be that the lean body mass increased and replaced the adipose tissue. Furthermore, the exercises used in their study differed from those in our study in terms of the type of movement, timing, and relaxation interval.[17]

In a study by Racil et al., HIIT was associated with weight loss, BMI improvements, and body fat reduction, and a significant reduction in waist circumference.[18] In another study, they reported an improvement in total cholesterol, triglyceride, and blood glucose levels after HIIT.[19] Although their findings on BMI are consistent with that in the combined group in our study, the significant reduction in weight, some lipid profile parameters, and waist circumference in the HIIT group in their evaluation was not consistent with our study. One of the reasons for these differences between the results of their studies and our investigation may be that their study was only conducted on adolescent girls, while the present study was performed on children and adolescents of both sexes. In addition, they considered 12 weeks of exercises and the duration of the training interval per session was on average more than our study. Moreover, the monitoring of activity in their research was done through the evaluation of oxygen uptake and the direct observation of exercises, while in our study, we monitored our patients using phone call follow-up.

According to the results of the study conducted by Zakavi et al., after performing 12 weeks of combined aerobic and RT, weight, BMI and body fat percentage were significantly improved.[20] However, in our study, post-intervention weight in the combined group was not significantly different, but our results are consistent with the above study regarding BMI. The probable reason for this difference might be their study sample, since they studied male students with a BMI of more than 30; in addition, they considered 12 weeks of training. In their study, lipolysis following a more extended activity was associated with significant weight loss. Furthermore, the exercises in this study and their monitoring were different from our study, which could explain the difference in the results.[20]

Khammassi et al. evaluated the effect of a 12-week HIIT program on the lipid profile of young people and reported improvements in weight, BMI, and waist circumference as a result of the program.[21] Their findings are inconsistent with that of our study because we only found a significant decrease in hip circumference and significant increase in height of the HIIT group. Moreover, in their study, lipid profile parameters did not show significant changes, and these findings are also consistent with the results of the HIIT group in our study. It should be noted that they evaluated young men aged between 18 and 21 years, and had a 12-week training period with a different duration of exercise for each session in different weeks. Furthermore, they monitored their patients through direct observation and oxygen uptake measurement, which helped to improve the accuracy of the measurements and the correctness of the exercises.[21]

Sung et al. reported that an adjusted diet program along with strength training was correlated with improved lipid profiles.[22] In addition, Ouerghi et al. studied 24 subjects aged 21 to 26 years, and reported a decrease in LDL, cholesterol, and triglyceride and an increase in HDL in the HIIT group after 12 weeks of training, and an increase in LDL, cholesterol, and triglyceride, and a decrease in HDL in the control group.[23] It should be noted that

the difference between the results of their investigation and the present study might be due to differences in exercise programs, measurement tools, monitoring methods, sample size, and the ages, racial disparities, and gender of the participants, and the varying degrees of obesity.[23]

Some studies have shown that BMI might not adequately determine the obesity status in children because there is no measurable test to distinguish body fat mass and body lean mass. Various methods such as measuring anthropometric indices, waist-hip ratio, hydrometry, x-ray absorptiometry, and bioimpedance may help determine the structure of the body better, and thus, estimate the body fat tissue more accurately compared BMI.[24,25] Considering that an increase in lean body mass can accompany RT, the lack of reduction in BMI and weight gain in the RT group may be justifiable.[26]

Different sports exercises have been associated with various outcomes on the lipid profile. For example, while in some studies, cholesterol, LDL, triglyceride, and HDL levels improved significantly after conducting HIIT, in some other researches, they did not change significantly.[27] Aerobic exercises, RT, or combinations of these exercises can result in the improvement of HDL status, and subsequently, lead to a reduction in the LDL and triglyceride levels, although more training will be needed to achieve these results.[28] The mechanism of effect of these exercises is not precisely understood yet. However, evidence suggests that the need for energy that increases through exercise may be related to increased activity of the lipoprotein lipase enzyme, and consequently, changes in the levels of lipid parameters in the blood.[28]

Additionally, changes in levels of very-low-density lipoprotein (VLDL) secreted from the liver following exercise and an increase in adiponectin secretions, which accompany fat catabolism and intake of glucose by muscle cells, are some of the factors that are considered as a possible mechanism for adjusting lipid profile and blood glucose following the above exercises in some studies.[19,28]

One of the most important strengths of this study was the attention to exercise at home following a primary education, which can be done with minimal costs and facilities for all overweight and obese children and adolescents in any socioeconomic status. Moreover, at the time of submitting this manuscript, it was the first study to compare the effects of HIIT, RT, and combined HIIT and RT with a control group in children and adolescents.

One of the limitations of the current study was the relatively small sample size, which may complicate the generalization of the results to the whole society. Another limitation was the lack of appropriate monitoring of home-based training interventions, which will limit the assessment of the correctness of the exercises. Our participants were selected from a single research center, and multicenter sampling facilitates the generalization of results to the community. Measuring body fat is better for evaluating the changes in adipose tissue; however, due to the limited equipment in this study, we could not differentiate lean body mass and fat tissue. Considering the above limitations, it is recommended that more extensive studies with larger sample sizes, increased duration of exercise, a diet based on the number of calories per person, and oxygen uptake monitoring to be conducted in the future to obtain more reliable results.

## Conclusion

Our study results demonstrate that the combined training program (RT+HIIT) and HIIT program with nutritional recommendations in overweight and obese children and adolescents significantly reduced BMI and hip circumference, respectively. Further research is required to confirm these findings, as well as the effect of aerobic training, RT, and combined training programs on the reduction of lipid profile and other anthropometric indexes in overweight and obese children and adolescents.

The results of this project can be used to plan for improving overweight and obesity management in children and adolescents, provide suitable training at home and schools, and increase knowledge about controlling obesity and overweight.

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## Conflict of Interests

Authors have no conflict of interests.

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# The effect of calcium in water hardness on digoxin plasma levels in an experimental rat model

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Original Article

## Abstract

**BACKGROUND:** Digoxin is a drug for ventricular rate control in atrial fibrillation (AF). The major challenge in digoxin therapy is to adjust the appropriate concentration range for this drug due to its narrow therapeutic index. Unique physiochemical properties of drinking water affect the pharmacological actions and delivery of drugs to the body whether they are administered orally, topically, or by injection. The aim of this study was to evaluate water hardness effect on digoxin therapy in an experimental rat model.

**METHODS:** 48 rats weighing 200-220 g were randomly assigned to three groups that received drinking water with 50, 400, and 800 mg/l hardness degrees for 28 days. Then each group was assigned into two groups. One received digoxin 0.2 mg/kg a day orally for four days. The other group received normal saline (as control group). Continuous recording of electrocardiogram (ECG) was performed by PowerLab system (AD Instruments Company) before and day 4 of digoxin treatment. Then serum samples were collected and assessed for digoxin, sodium, potassium, calcium, magnesium, blood urea nitrogen (BUN), and creatinine levels.

**RESULTS:** Water hardness in the range of 50-800 mg/l had no effect on serum digoxin levels ($P > 0.050$), but consuming hard drinking water (400 and 800 mg/l) could increase serum calcium levels and then cause mortality (37.5% in both groups), following changes in ECG due to digoxin consumption.

**CONCLUSION:** Consuming hard drinking water probably interferes with digoxin pharmacodynamics in the way of toxicity induction.

**Keywords:** Digoxin; Atrial Fibrillation; Electrocardiogram; Calcium

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## Introduction

Digoxin and other cardiac glycosides (digitals) have been used for years in the treatment of congestive heart failure (CHF) and atrial fibrillation (AF).[1] AF is the most common supraventricular arrhythmia associated with an increased risk of stroke and cardiovascular death.[2] Heart failure (HF) is a common cardiac disorder associated with AF and may contribute to worsening prognosis of patients presenting with both conditions.[3] Digoxin is a purified glycoside extracted from the foxglove plant that increases the force and velocity of myocardial systolic contraction (positive inotropy) and

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decreases conduction velocity through the atrioventricular (AV) node by prolonging its refractory period. The most common dose-dependent adverse effects that happen when digoxin serum levels exceed 2 ng/ml include nausea, vomiting, anorexia, diarrhea, heart block, vision disturbances (yellow/green halo effect), headache, weakness, dizziness, and confusion.[4] Digoxin reversibly binds to the extracellular side of $Na^+/K^+$ -ATPase in cardiac cells and inhibits this enzyme, thereby increases intracellular sodium, which, in turn, inhibits the $Na^+/Ca^{2+}$ exchanger leading to intracellular calcium level increase; and through this mechanism, digoxin exerts its positive inotropic effect.[5] However, digitals are responsible for many cases of iatrogenic morbidity and mortality due to high risk of toxicity; many cardiologists prefer to use digoxin in patients who have both AF and CHF.[6] It is reported that in patients with AF on good anticoagulation control with vitamin K antagonists such as warfarin or acenocumarol, digoxin use was associated with a higher rate of total and cardiovascular mortality.[7] In fact, digoxin like most inotropes, may shorten life and cause life-threatening arrhythmias.[8] Although in a case-control study consisting of 6116 subjects, it was demonstrated that only persons who at least received 1 prescription for digoxin within 7 days before the date of diagnosing acute pancreatitis may have the high relative odds of this outcome.[9] Furthermore, in a recent study, it is demonstrated that digitoxin is a well-tolerated and therapeutic alternative to angiotensin-converting enzyme inhibitors (ACEIs) and beta blockers in patients with HF due to cardiac involvement in myotonic dystrophy type 1 (DM1).[10] There is an increased risk of death from any cause associated with digoxin therapy among women that have HF and depressed left ventricular (LV) systolic function.[11] It is documented that patients with hypercalcaemia should discontinue digoxin therapy and be evaluated for the presence of rhythm disorders while receiving appropriate treatment for hypercalcaemia.[12] Levine et al. found no support for this historical belief of calcium contraindication in patients with digoxin intoxication.[13] However, Gupta et al. believe that several methodological concerns limit the validity of that conclusion.[14]

Our country, Iran, is located in an area with dry climate and as we preliminarily examined, in the most cities in center, east, and south of Iran, the hardness degrees of tap water are in the range of 500 to 600 parts per million (ppm) or even more. Water hardness is a measure of the quantity of divalent ions in water. Calcium and magnesium are the most common sources of water hardness. The hardness of water is reported in milligrams per liter or ppm as calcium carbonate (mg/l $CaCO_3$). It is shown that under similar conditions, the absorbability of the calcium in the drinking water is comparable to the absorbability of calcium in milk. As a result, high-calcium water consumption can make a considerable contribution to total calcium intake. Milk-alkali syndrome is characterized by high blood calcium caused by taking in too much calcium and absorbable alkali that if not be treated may lead to kidney failure or death. Safe and tolerable upper level of calcium intake is set at 2500 mg/day in adults, but this amount is inadequate for pregnant and lactating women. Consuming calcium above this level may produce adverse health effects.[15] On the other side, it is suggested that consumption of high mineral (calcium) drinking water could be beneficial for osteoporosis treatment or in maintaining of bone density.[16] By two different mechanisms, orally-consumed calcium is absorbed from the intestinal lumen: 1) active, transcellular absorption that involves in calcium import into the enterocyte through voltage-insensitive transient receptor potential (TRP) channels, transporting across the cell and exporting into extracellular space via a calcium-ATPase fluid and then blood and 2) passive, paracellular absorption that involves in calcium transport into the blood and it occurs when its dietary level is moderate or high. There are some reports about the effect of water hardness on different aspects of diseases and pharmacologic properties of drugs.

A study in 2003 showed that water hardness reduces bioavailability of enrofloxacin in broilers. Data showed that when water hardness increased, a linear decay of concentration in steady state (Cs) maximum has occurred.[17] In another study, water hardness enhancement under alkaline conditions increased calcium complexation with clofibrate anions; therefore, it increased the removal of clofibric acid by activated carbon filters.[18] In contrast, water hardness decreases caffeine absorption onto activated carbon filters because of caffeine competition between inorganic ions (such as calcium and magnesium).[19] Hair that contains more anionic moieties as a result of chemical treatments such as bleaching and chemical relaxing, has a higher cationic binding capacity and is, thus, more susceptible to water hardness metal uptake than virgin hair.[20]

Dilution of florfenicol, a broad-spectrum antibiotic

as a veterinary medication, in drinking water with different degrees of hardness showed that this drug was stable under a range of water hardness (low to high).[21] Although, in 2015, Wasana et al. found that high prevalence of chronic kidney disease of unknown etiology (CKDU) existed in areas that hardness of drinking water was in the range of 121-180 mg/l $CaCO_3$, aluminium, cadmium, and arsenic concentrations were almost comparable or below World Health Organization (WHO) recommendations. Fluoride concentration in drinking water in the most parts of this area was higher than the WHO recommendations.[22] Conversely, another study in an area in Pakistan reported that hypertension (HTN) was no more common in people taking hard water than those using fresh water.[23]

Obviously, there are conflicting documents about effect of water hardness on biological subjects. In so doing and because of narrow therapeutic index of digoxin, we performed this study to examine if drinking water hardness could influence digoxin plasma levels or induce its toxicity. Furthermore, we determined different electrolytes in serum blood urea nitrogen (BUN) and creatinine as functional renal bio-monitoring indexes.

## Materials and Methods

Digoxin as a white, bitter, odorless powder with molecular weight of 780.95 g/mole, anhydrous $CaCO_3$, disodium ethylenediaminetetraacetic acid (EDTA) dehydrate, sodium salt of 1-(1-hydroxy-2-naphthylazo)-5-nitro-2-naphthol-4-sulfonic acid (No. 203 in the Color Index), 2,2',2"-nitrilotriethanol [also called triethanolamine (TEA)], and 2-methoxyethanol (also called ethylene glycol monomethyl ether) were purchased from Sigma Chemical Company (Tehran, Iran).

*Preparing standard calcium solution (hard water):*[24] To clarify the role of calcium in water hardness in our experiment, hardness was caused only by the presence of calcium; a $CaCO_3$ value of 100 mg/l represents a free calcium concentration of 40 mg/l (dividing $CaCO_3$ value by 2.5). After weighing 1000 g anhydrous $CaCO_3$ powder into a 500-ml dry erlenmeyer flask, we placed a funnel in the flask neck and added a little at a time, drop by drop, hydrochloric acid (HCl) 1N until all $CaCO_3$ was dissolved. Then we added 200 ml distilled water and boiled it for a few minutes to expel carbon dioxide ($CO_2$). After cooling and adding a few drops of methyl red indicator and adjusting to the intermediate orange color by adding 3N ammonium hydroxide ($NH_4OH$) or drop by drop HCl 1N, as required, we transferred it quantitatively and diluted it to 1000 ml with distilled water (1 ml = 1.00 mg $CaCO_3$). Hardness of this sample is 1000 mg/l. However, to determine the distinct hardness, it was measured by chemical titration. After resolving the absolute hardness, we used it as the stock solution and prepared the water hardness of 50, 400, and 800 mg/l by this equilibrium formula:

$C_1 \times V_1 = C_2 \times V_2$; $C_1$: 1000 mg/l; $V_1$: The volume from stock solution needed to prepare solutions with required hardness (50, 400, or 800 mg/l); $C_2$: required hardness (50, 400, or 800 mg/l); $V_2$: Final volume of each solution with required hardness (50, 400, or 800 mg/l)

*Preparing standard EDTA titrant (0.01 M):* 3.723 g of analytical reagent grade disodium EDTA was dissolved in distilled water and diluted to 1000 ml.

### Preparing indicator

*Eriochrome Black T:* We dissolved 0.5 g dye [sodium salt of 1-(1-hydroxy-2-naphthylazo)-5-nitro-2-naphthol-4-sulfonic acid (No. 203 in the Color Index)] in 100 g 2,2',2"-nitrilotriethanol (TEA) or 2-methoxyethanol.

*Titration of sample:* We diluted 25.0 ml sample to about 50 ml with distilled water in a porcelain casserole or other suitable vessel then added 1 buffer solution to give a pH of 10.0 to 10.1. Then we added 2 drops of indicator solution. For titration, we added standard EDTA titrant slowly into the sample, with continuous stirring, until the last reddish tinge disappeared. The last few drops were added at 3- to 5-second intervals. At the end point, the solution normally was blue [hardness (EDTA) as mg $CaCO_3$/l = A × B × 1000/ml sample; A = ml titration for sample and B = mg $CaCO_3$ equivalent to 1.00 ml EDTA titrant].

*Animal experiment:* Male Sprague-Dawley rats (200-220 g) from the Babol University of Medical Sciences Breeding Colony, Babol, Iran, were fed ad libitum for pelleted chow as food but restricted to special water access and housed at 22 ± 2 °C under a 12:12-h light-dark cycle (lights on at 7 AM). Our study complies with the Declaration of Helsinki and all experimental procedures involving animals were approved by the Animal Care Committee of Mashhad University of Medical Sciences, Mashhad, Iran.

Animals (n = 48) were randomly assigned into six treatment groups: 1) Free access to drinking water with hardness of 50 mg/l for 32 days (n = 8), 2) Free access to drinking water with hardness of 400 mg/l for 32 days (n = 8), 3) Free access to drinking water with hardness of 800 mg/l for 32 days (n = 8) (these

three groups were examined to confirm about the effect of water hardness on mortality rate alone), 4) Free access to drinking water with hardness of 50 mg/l for 32 days (n = 8) and 0.2 mg/kg digoxin orally by gavages in the last five days, 5) Free access to drinking water with hardness of 400 mg/l for 32 days (n = 8) and 0.2 mg/kg digoxin orally by gavages in the last five days, and 6) Free access to drinking water with hardness of 800 mg/l for 32 days and 0.2 mg/kg digoxin orally by gavages in the last five days (n = 8). The oral lethal dose, 50% ($LD_{50}$) of digoxin in rat is 28.27 mg/kg.[25]

At the first day of experiment and day 32, 4 hours after the last digoxin administration, rats were anesthetized with ketamine plus xylazine [80 and 8 mg/kg, respectively, intraperitoneal (i.p.)], then continuous recording of electrocardiogram (ECG) was performed by PowerLab (AD Instruments Company) system. At the first day, rats with unmoral ECGs were excluded from the experiment. At the first day of study and after the last ECG recording, blood samples were taken and processed to serum by centrifuging at 3000 revolutions per minute (rpm) for 20 minutes. The serum samples were stored at -20 °C until analysis.

*ECG recording:* Continuous recording of ECG was performed by PowerLab (AD Instruments Company) system. ECG was recorded in lead I by silver/silver chloride (Ag-AgCl) electrode. The output of PowerLab system was inserted in a computer by USB network communication software interface (Chart for Windows Software, Version 7) used to display and save the signal in the computer. For processing the signal, MATLAB software (version 7.6) was used to extract the feature from the ECG. In this paper, QRS complex, ST, and RR interval, T and P waves were extracted from ECG signals by MATLAB. The waves in ECG were obtained in each cardiac cycle by the MATLAB software. Figure 1 shows the comparison of ECGs.

*Electrolytes, BUN, creatinine, and digoxin concentration evaluation:* To evaluate the calcium, magnesium, potassium, and sodium levels, atomic absorption spectrophotometry was used. The BUN and creatinine levels were measured by using High Performance Liquid Chromatography (HPLC) mass spectrometry. Also, the digoxin concentration was measured by enzyme-linked immunosorbent assay (ELISA).

Continuous variables were reported as mean ± standard deviation (SD). In analytical statistics, the normality of quantitative variables was firstly assessed using Kolmogorov-Smirnov test (K-S test). To assess and compare the two groups, Mann-Whitney U test was used. For evaluating the features in 3 levels, analysis of variance (ANOVA) test and Games-Howell test as post-hoc were used. The extracted features from ECG, after and before measurement, were compared using Wilcoxon signed-rank test. A significance level of $P < 0.05$ was considered to be significant. All statistical analyses were performed using SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA).

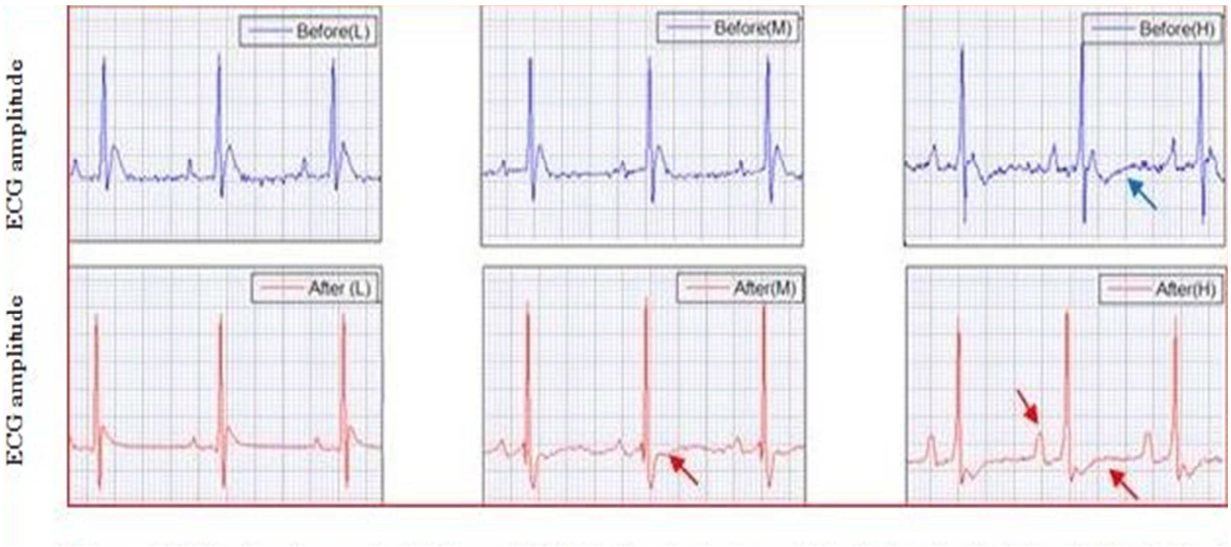


**Figure 1:** Electrocardiogram (ECG) signals recorded before and 4 hours after digoxin treatment (day 4 after first digoxin administration)
L, M, and H represent low, medium, and high hardness degrees of drinking water

## Results

*Effect of water hardness on survival rate:* Values showed 37.5% reduction in survival rate as water hardness increased. From 8 rats that existed in each of 6 groups, in groups with free access to drinking water with hardness degrees of 400 and 800 mg/l for 32 days (n = 8) and 0.2 mg/kg digoxin orally by gavage in the last five days, there were 3 dead ones at the last day of experiment. There was no other mortality in the other groups in the whole study.

*Effect of water hardness on digoxin serum levels:* At the first day of study and after the last ECG recording, blood samples were collected. Analysis of the samples did not show any significant difference in digoxin levels in groups with different degrees of water hardness ($P < 0.050$).

*Effect of water hardness on serum electrolytes, BUN, and creatinine:* As we showed in table 1, free access to drinking water with different hardness did not cause any differences in serum magnesium, sodium, BUN, and creatinine levels. However, calcium levels in both groups with water hardness of medium and hard degrees were significantly increased compared to low water hardness access group ($P < 0.010$ in both comparisons). Moreover, these differences happened with or without digoxin treatment ($P < 0.010$). In all digoxin-treated groups, there were significant differences ($P < 0.001$) in potassium levels before and after digoxin treatments. Water hardness had no influence on these decreases and they happened in all different degrees of water hardness.

*Effect of water hardness on ECG recording:* Evaluation of the extracted features in 3 levels showed differences in ST, T, and QT intervals (ms) and ST and P amplitudes (v) as shown in table 2. ECG recording views are shown in figure 1.

*ST intervals:* ST intervals significantly decreased in medium and high water hardness consuming groups compared to low water hardness consuming group ($4.01 \pm 0.83$, $P < 0.010$ and $4.84 \pm 0.72$, $P < 0.050$, compared to $5.88 \pm 0.64$, respectively). It also happened in digoxin-treated groups ($4.25 \pm 0.65$, $P < 0.050$ and $3.88 \pm 0.35$, $P < 0.010$, compared to $5.36 \pm 0.34$, respectively).

*T intervals:* T intervals significantly increased in high water hardness consuming group compared to low water hardness consuming group ($82.66 \pm 16.32$ compared to $44.25 \pm 15.45$, $P < 0.001$, respectively), but it did not happen in digoxin-treated groups. As the result of digoxin treatment, T intervals significantly decreased in high water hardness access groups ($82.66 \pm 16.32$ compared to $39.25 \pm 6.19$, $P < 0.001$, respectively).

*QT intervals:* QT intervals significantly increased in high water hardness consuming group compared to low water hardness consuming group ($106.32 \pm 10.39$ compared to $65.07 \pm 9.32$, $P < 0.001$, respectively), but it did not happen in digoxin-treated groups. As the result of digoxin treatment, QT interval significantly decreased in medium and high water hardness access groups ($65.90 \pm 6.57$ vs. $49.07 \pm 6.38$, $P < 0.010$ and $106.32 \pm 10.39$ vs. $58.08 \pm 3.87$, $P < 0.001$, respectively).

*ST amplitudes*: ST amplitudes significantly increased in medium and high water hardness consuming group compared to low water hardness consuming group ($0.096 \pm 0.016$, $P < 0.010$ and $0.107 \pm 0.011$, $P < 0.001$ compared to $0.064 \pm 0.008$, respectively). As the result of digoxin treatment, ST amplitudes significantly decreased in high water hardness access group ($0.107 \pm 0.011$ vs. $0.047 \pm 0.028$, $P < 0.001$, respectively).

*P amplitudes*: P amplitudes significantly increased in high water hardness consuming group compared to low water hardness consuming group ($0.083 \pm 0.016$ compared to $0.047 \pm 0.008$, $P < 0.010$, respectively). As the result of digoxin treatment, P amplitudes significantly increased in medium and high water hardness access group ($0.055 \pm 0.011$ vs. $0.085 \pm 0.014$, $P < 0.010$ and $0.083 \pm 0.016$ vs. $0.121 \pm 0.025$, $P < 0.001$, respectively).

## Discussion

According to our findings, consuming water with different degrees of hardness for 32 days did not affect serum digoxin levels as a drug as well as magnesium, sodium, BUN, and creatinine levels. However, calcium levels in both groups with water hardness of medium and high degrees significantly increased compared to low water hardness access group ($P < 0.010$ in both comparisons). Moreover, these differences happened with or without digoxin treatment ($P < 0.010$). Although serum calcium levels increased in both groups with medium and high hardness degrees of consuming water, they were still in the normal range (9-10.5 mg/dl). Analyzing ECGs showed that as hardness degree of consumed water increased, ST intervals significantly decreased and in contrast, T and QT intervals and ST and P amplitudes significantly increased, but these changes did not cause any mortality. On the other side, digoxin treatment caused ST, T, and QT intervals and ST amplitude reduction and P amplitude elevation. In a study, the first important finding after digoxin toxicity in the P-QRS-T complex included wide and tall P wave.[26]

**Table 1.** Serum levels of magnesium, calcium, sodium, potassium, creatinine, and blood urea nitrogen (BUN) before and after experiment in low, medium, and high degrees of drinking water hardness groups

| Digoxin | Water hardness (mg/l) | Magnesium (mg/dl) | | Calcium (mg/dl) | | Potassium (mEq/l) | | Calcium/potassium | | Sodium (mEq/l) | | BUN (mg/dl) | | Creatinine (mg/dl) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day1 | Day32 | Day1 | Day32 | Day1 | Day32 | Day1 | Day32 | Day1 | Day32 | Day1 | Day32 | Day1 | Day32 |
| | | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD |
| + | 50 (low) | 2.66 ±0.27 | 2.32 ±0.31 | 9.55 ±0.39 | 9.52 ±0.48 | 6.22 ±0.95 | 7.05±0.63 | 1.53 ±0.29 | 1.35 ±0.15 | 138.10±1.02 | 136.83±0.84 | 23.84 ±1.56 | 24.33±2.34 | 0.45±0.05 | 0.50±0.04 |
| | 400 (medium) | 2.42 ±0.21 | 2.35 ±0.15 | 9.41 ±0.43 | 10.00±0.30# | 6.81 ±0.39 | 7.12±0.47 | 1.32 ±0.21 | 1.40 ±0.39 | 137.12±1.81 | 136.20±0.84 | 23.10 ±1.01 | 23.00 ±1.73 | 0.50±0.05 | 0.48±0.04 |
| | 800 (high) | 2.61 ±0.20 | 2.76 ±1.32 | 9.53±0.29 | 10.81 ±0.88# | 6.69 ±0.98 | 7.76 ±1.33 | 1.42 ±0.15 | 1.39 ±0.25 | 135.72±0.88 | 137.16 ±2.23 | 22.27 ±2.01 | 23.66±1.50 | 0.50± 0.05 | 0.48 ±0.04 |
| - | 50 (low) | 2.22 ±0.31 | 2.25 ±0.30 | 9.85±0.32 | 8.83 ±0.31 | 6.52 ±1.11 | 5.45±0.67** | 1.51 ±1.94 | 1.62 ±0.29 | 136.52±0.89 | 135.83± 4.26 | 22.34±1.87 | 21.83±1.94 | 0.47±0.04 | 0.50±0.02 |
| | 400 (medium) | 2.31 ±0.12 | 2.49 ±0.17 | 9.51 ±0.41 | 9.60 ±0.26# | 6.44 ±1.02 | 4.55 ±0.33** | 1.48 ±0.25 | 2.10 ±1.94* | 136.32 ±2.78 | 137.25 ±1.71 | 22.92 ±1.43 | 22.25 ±1.50 | 0.50±0.04 | 0.50 ±0.04 |
| | 800 (high) | 2.56 ±0.25 | 2.52 ±0.14 | 9.63 ±0.21 | 9.57 ±0.25# | 6.47 ±0.44 | 4.52 ±0.27** | 1.48 ±0.29 | 2.17 ±0.39* | 138.00 ±2.05 | 139.50 ±1.00 | 24.00 ±2.74 | 22.25 ±1.71 | 0.45±0.05 | 0.50±0.03 |

Data were determined on day 1 and 4 hours after last digoxin administration (day 4 after first digoxin administration).

Data are shown as mean ± standard deviation (SD) (n = 8); * Statistical differences between before and after digoxin administration shown as * $P < 0.050$, ** $P < 0.001$; # Statistical differences compared to low degree of hardness shown as # $P < 0.010$; BUN: Blood urea nitrogen

**Table 2.** The mean and standard deviation (SD) of extracted features from electrocardiogram (ECG) signals

| Water hardness (mg/l) | Effect of water hardness after 32 days | | | Effect of water hardness after 32 days + digoxin 0.2 mg/kg in the last 4 days | | |
|---|---|---|---|---|---|---|
| | 50 (low) | 400 (medium) | 800 (high) | 50 (low) | 400 (medium) | 800 (high) |
| QRS (ms) | 14.940 ± 2.780 | 15.470 ± 1.620 | 18.820 ± 3.880 | 15.540 ± 4.240 | 18.710 ± 4.780 | 14.950 ± 4.120 |
| ST (ms) | 5.880 ± 0.640 | 4.010 ± 0.830$^{\#\#}$ | 4.840 ± 0.720 | 5.360 ± 0.340 | 4.250 ± 0.650$^{\#}$ | 3.880 ± 0.350$^{\#\#}$ |
| ST amplitude (v) | 0.064 ± 0.008 | 0.096 ± 0.016$^{\#\#}$ | 0.107 ± 0.011$^{\#\#\#}$ | 0.058 ± 0.014 | 0.084 ± 0.016$^{\#}$ | 0.047 ± 0.028$^{***}$ |
| RR (ms) | 231.060 ± 27.570 | 219.590 ± 25.160 | 227.180 ± 29.360 | 244.110 ± 18.220 | 257.740 ± 27.940 | 212.770 ± 25.910 |
| T (ms) | 44.250 ± 15.450 | 46.420 ± 9.750 | 82.660 ± 16.320$^{\#\#\#}$ | 33.350 ± 7.070 | 27.110 ± 5.230 | 39.250 ± 6.190$^{***}$ |
| QT (ms) | 65.070 ± 9.320 | 65.900 ± 6.570 | 106.320 ± 10.390$^{\#\#\#}$ | 54.250 ± 4.350 | 49.070 ± 6.380$^{**}$ | 58.080 ± 3.870$^{***}$ |
| P (ms) | 26.510 ± 4.070 | 20.330 ± 6.140 | 30.660 ± 3.740 | 28.330 ± 5.110 | 21.450 ± 5.570 | 22.590 ± 4.160 |
| P amplitude (v) | 0.047 ± 0.008 | 0.055 ± 0.011 | 0.083 ± 0.016$^{\#\#\#}$ | 0.066 ± 0.012 | 0.085 ± 0.014$^{**}$ | 0.121 ± 0.025$^{\#\#\#***}$ |
| PR (ms) | 43.280 ± 11.780 | 44.240 ± 7.470 | 42.440 ± 8.120 | 42.480 ± 10.150 | 45.370 ± 8.710 | 40.710 ± 8.390 |

Extracted features from electrocardiograms (ECGs) are shown as mean ± standard deviation (SD) (n = 8)

$^{*}$ Statistical differences between before and after digoxin administration shown as $^{**}$ P < 0.010, and $^{***}$ P < 0.001; $^{\#}$Statistical differences compared to low degree of hardness shown as $^{\#}$ P < 0.050; $^{\#\#}$ P < 0.010; and $^{\#\#\#}$ P < 0.001

In another clinical study of digoxin-poisoned cases, ECG changes included sinus bradycardia, extrasystole, ST segment depression (a sagging appearance), lowering of the T wave, obvious or apparent shortening of the Q-T duration, first-degree heart block, and finally complete heart block.[27] These findings support our result that in high water hardness consuming group, some degrees of digoxin toxicity have occurred. Digoxin treatment in both medium and high water hardness groups caused 37.5% reduction in survival rate. In all digoxin-treated groups, there were significant differences ($P < 0.001$) in potassium levels before and after digoxin treatments. These changes happened in all different degrees of water hardness. It is reported that along therapeutic serum concentrations of digoxin with automaticity, higher calcium to potassium ratios may exist.[28]

In this study, calcium to potassium ratios after digoxin administration increased significantly in all water hardness degrees ($P < 0.050$). An important part of calcium balance control in the body is parathyroid hormone (PTH) secretion that is stimulated by hypocalcemia and inhibited by hypercalcaemia. PTH works to increase $Ca^{++}$ levels by stimulating bone resorption, decreasing urinary loss of $Ca^{++}$, and indirectly stimulating $Ca^{++}$ absorption in the small intestine by stimulating synthesis of $1,25(OH)_2D$ in the kidney. As a result, consuming high-calcium containing water did not increase blood calcium levels beyond the normal values, but it could cause higher calcium levels (in comparison to low-calcium containing water). These elevations did not cause any mortality by themselves but could induce digoxin toxicity and its consequence, mortality. It is a concern in digoxin therapy when the patient consumes hard drinking water. Altogether, all these documents support this fact that it is not suitable to consume hard water.

## Conclusion

Our data showed that consuming water with high degrees of hardness could induce digoxin toxicity even in therapeutic serum levels. Patients and physicians must be sensitive and alert of this important concern.

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## Conflict of Interests

Authors have no conflict of interests.

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# The commencement of congenital heart diseases registry in Isfahan, Iran: Methodology and design

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Original Article

## Abstract

**BACKGROUND:** Reported prevalence of congenital heart diseases (CHDs) varies widely among studies worldwide. The incidence of CHD, total number of pediatric and adult grown-up congenital heart disease (GUCH), is not determined in Iran. Therefore, we have designed a system to register the information of patients with CHD for the first time in our country.

**METHODS:** CHD registry is a database in which the patients' data are collected by five pediatric cardiologists from three referral hospitals affiliated to Isfahan University of Medical Sciences, Isfahan, Iran, and five outpatient clinics. We enrolled patients with CHD either as new cases who were referred for evaluation of potential CHD or those who were being followed within the outpatient clinics and entered their whole information in a website specifically designed for it. All the information was collected from checklist by those pediatric cardiologists

**RESULTS:** From April 2017 to April 2020, after developing the forms and website, the Quality Control Committee evaluated the first 558 files. 73 files (13%) needed major revisions. Among them, 34 (46%) files were omitted totally and the 39 remaining files were revised and completed. After that revision, we changed our checklist and gathered about 1600 patients accordingly.

**CONCLUSION:** Registry of CHDs not only improves epidemiologic studies but also assists researchers to understand how much a disease management is useful and how to raise the quality of cares and outcomes. Moreover, this provides a better insight for policymakers to understand the extent of health-related problems as well as the issues related to the prevention and management of CHDs all around the world.

**Keywords:** Registries; Congenital; Heart Diseases; Data Collection

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## Introduction

Congenital heart diseases (CHDs) are one of the most common congenital anomalies seen in human. Reported incidence of CHD varies widely among studies worldwide, on average 8 cases per 1000 live births.[1] Nowadays, the number of children born with CHDs is increasing (from 0.4 to 9 cases per 1000 live births).[2,3] Great evolution in cardiovascular diagnostics and surgery methods has enabled the physicians to identify CHDs that are more complex even during the intrauterine periods,

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and to refer those who need emergency therapeutic interventions. In addition, improvements in cardiothoracic surgery have led to a rise in their life expectancy and quality. According to the Civil Status Registration Organization, more than 1500000 babies are born every year in Iran.[4] However, the incidence of CHD is not determined and also the total number of pediatric and adult grown-up congenital heart disease (GUCH) is unclear in our country as well.

Consequently, in order to find the real number of patients with CHDs and also not miss them, we designed a system to register these patients and collect their information for the first time in Iran, according to our knowledge. This will definitely help improve medical knowledge and prevent and treat patients.

## Materials and Methods

CHD registry is a database in which the patients' data from hospitals or outpatient clinics are collected. It is a part of the biggest registry program in Iran - Persian Registry of cardioVascular diseasE (PROVE) - established by Isfahan Cardiovascular Research Center, a World Health Organization (WHO) collaborating center in Isfahan, Iran.[5] We launched the registry program based on the following steps:

*Upgrading the checklist:* The CHD registration program first started in 2015 mainly with limited data but became more advanced by 2017. In the beginning, Ethics Committee affiliated to Isfahan University of Medical Sciences approved our program. We used a population-based protocol to register CHD. The Quality Control Committee, containing epidemiologists, statisticians, specialized physicians, and information technology staff,[5] validated our checklist. It was developed to collect all the information about patients with CHD and categorized the obtained data into six domains: maternal history and birth, medical history, current clinical status, paraclinical data, cardiac diagnosis, and plan and medications which consist of: demographic characteristics and medical history of patient and parents including their job, complete pregnancy history including maternal diseases, used medications, and even address of the location where mother has lived during pregnancy, positive family history of CHDs in parents, other siblings, or close relatives, clinical presentations and diagnostic findings in current visit, and medications and recommendations for management.

All five pediatric cardiologists who are faculty members at Isfahan University of Medical Sciences collected these data from the checklists as principle investigators and importers at three university-affiliated referral hospitals and five outpatient clinics.

*Gathering information from the patient:* In the next stage, referrals were enrolled either as new cases who were referred for evaluation of potential CHD or those who were being followed within the outpatient clinics. All patients or their parents received written informed consent to fill the checklist. The CHDs diagnosis has been principally made by echocardiography although more information was achieved from other diagnostic tests such as angiocardiography and catheterism, computed tomography (CT) and CT angiogram, or cardiovascular magnetic resonance imaging (CMR) in some cases. Then information was classified according to the International Classification of Diseases, 10th Revision (ICD-10) coding system (Q20-26).

*Running website:* Concurrently, a website was designed by Isfahan University of Medical Sciences to connect these five investigators and the data they gathered from every patient. Each investigator enters the information collected from checklists in this site and uses the patient's national code as an identification code. Furthermore, each importer makes an electronic diagnostic file and uploads it on the site. Therefore, other investigators may have online access to both patient's full history and the latest information especially beneficial in emergencies.

This website includes several parts such as patient's condition gathered from checklist, physical exam and the diagnostic tests, demographic, maternal, and birth history, medical history, current clinical and paraclinical data, cardiac diagnosis, and plan and medications. We also provided a part to enter the new information of old patients who have registered in previous visits and already come to follow up. It also allows the investigators to search patients not only by their names or codes but also by entering their ages or congenital heart diagnosis. Furthermore, it can sort the information based on the patient's arrival date and physician or city where the patient was registered.

In order to assimilate our records, we provided a specific dictionary and user manual, consisting of any specific information investigators need to know to complete the files.

The checklist, dictionary, and user manual are available on our website; however, for security reasons, the patient's data are not accessible except for those five principle investigators.

In addition to internal quality control (IQC) of

PROVE, this project was controlled by the team's supervisor evaluated by the committee which is consisted of experienced and trained members who were not one of the PROVE executive members and were unaware of it. They performed an external and continuous control over the entire registry components from the beginning to the end.

## Results

About 1600 patients with CHDs were recruited from April 2017 to April 2020, after developing the forms and website. The Quality Control Committee evaluated the first 558 files. 73 files (13%) needed major revisions. Among them, 34 (46%) files were omitted totally and the 39 remaining files were revised and completed. The information which our staff recorded from our primary checklist was too brief and was not compatible with our system. After the Quality Control Committee's assessment, we changed some parts of our checklist and designed it according to the experts' plan and scientific needs. We categorized the obtained data into six domains: maternal history and birth, medical history, current clinical status, paraclinical data, cardiac diagnosis, and plan and medications. Then all the information was recorded on the system.

After that revision, we changed our questionnaire and gathered about 1600 patients accordingly.

## Discussion

To the best of our knowledge, it is the first registry database established for CHDs in Iran.

In this regard, there is now a lot of research that shows the prevalence of CHD in several parts of the world, extracted from the registry dataset. In one of the largest studies, van der Linde et al. demonstrated that in the course of time, the CHDs prevalence has increased considerably from 0.6 per 1000 live births in 1930 to 9.1 per 1000 live births after 1995. They also found remarkable geographical variances among their patients. The highest prevalence was in Asia and the lowest in Africa.[2] Dolk et al.[6] reported the prevalence of CHDs which were diagnosed from prenatal to infantile periods, and also fetal and perinatal mortality due to CHDs in Europe with the usage of data from European Surveillance of Congenital Anomalies central database.

In China, Qu et al. established a hospital-based CHD registry in Guandong, China, from 2004, to study the epidemiology of CHD including stillbirths and live births and compare the incidence of CHDs in that region to the literatures in 2012. They could find the prevalence of different CHDs' subtypes too.[7] Tankeu et al. have conducted a study to find out the prevalence of CHDs and their different patterns inside African countries but their results have not yet been published.[8]

There are several studies reporting the prevalence of congenital anomalies all around the world through registry programs[9] using a manual which concentrates on population-based and hospital-based surveillance programs[10] and some countries have extracted specific data about congenital heart defects from these available resources. For example, Benavides-Lara et al. could describe the incidence of CHD in Costa Rica and assess their country's registry method.[11] In a large study, Rosa et al. reviewed the association between congenital cardiac and non-cardiac malformations based on congenital anomalies registries.[12]

Registry of diseases is useful for other purposes rather than epidemiologic studies. Nowadays, researchers can achieve more information about the efficacy of treatment by following up patients who registered before. American College of Cardiology (ACC) has published a literature reviewing the safety and efficacy of some specific congenital heart procedures by the use of ACC's IMproving Pediatric and Adult Congenital Treatments (IMPACT) registry.[13] In Sweden, a national registry of CHD has been established since 1990, but Bodell et al. recently evaluated the validity of data used in registry to employ them for medical and research purposes.[14] As well, Pradat conducted a study to determine the association of specific CHDs with extracardiac malformations with the information from the registry.[15] These registry programs are still running in different parts of the world; for example, in the United States of America (USA), Mahle has conducted a cohort as "Congenital Heart Disease Research Registry" in Emory University, Atlanta, since 2014. He not only used the participant's demographic and phenotypic data as well as medical records and assessment data, but also collected their blood samples and preserved them for potential future genetic research.[16]

## Conclusion

Registry of CHDs not only improves epidemiologic studies but also assists researchers to understand how much a disease management is useful and how to raise the quality of cares and outcomes. Moreover, this provides a better insight for policymakers to understand the extent of health-related problems as well as the issues related to the

prevention and managements of CHDs all around the world.

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The study was reviewed by the Ethical Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.086) (Project registration code: 298005).

## Conflict of Interests

Authors have no conflict of interests.

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# The Recommended Food Score and Healthy Nordic Food Index in cardiovascular disease and stroke: A systematic review

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Review Article

## Abstract

**BACKGROUND:** Cardiovascular disease (CVD) includes a group of heart and coronary disorders that can be prevented by promoting the quality of an individual's diet. The Recommended Food Score (RFS) and Healthy Nordic Food Index (HNFI) are suggested for the assessment of diet quality and as indicators of dietary exposures related to disease. The aim of this study was to systematically review the association of the RFS and the HNFI with CVD and stroke.

**METHODS:** Articles were identified by searching PubMed, Google Scholar, and ScienceDirect using relevant keywords for articles published until December 2018. The inclusion criteria were all types of observational studies and English language. Non-English and irrelevant studies were excluded.

**RESULTS:** In total, 14 studies met the inclusion criteria. Of the 7 studies that investigated the association between the RFS and CVD, 6 articles showed a lower risk of CVD in individuals who obtained a higher RFS and lower non-RFS (n-RFS) score. Studies that investigated the relation between RFS and stroke (n = 2) showed that achieving a higher RFS could decrease the risk of stroke. Of the 4 studies that assessed the relationship between HNFI and CVD, 3 showed that adherence to HNFI were related with lower risk of CVD/stroke. However, one study did not show any relationship.

**CONCLUSION:** A higher RFS may result in a decrease in the risk of CVD and stroke. Due to the inconsistency of the findings related to HNFI, more studies are needed to approve the negative relationship between HNFI and CVD.

**Keywords:** Diet; Cardiovascular Diseases; Stroke

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## Introduction

Cardiovascular disease (CVD) is defined as a group of diseases including heart and coronary disorders such as coronary heart disease (CHD), diseases related to brain vessels and/or peripheral vessels, and other conditions.[1] One third of the total mortality rate in the United States is attributed to CVD.[2] Incidence of myocardial infraction (MI) is 5 to 6 times higher in CHD patients. Every year, approximately 32 million people suffer from cerebral and heart vessels disorders and the risk of stroke recurrence is higher in people who have experienced stroke.[3] Stroke is one of the main causes of disability and mortality, so its primary prevention is important.[4]

Despite the undeniable effect of pharmacological treatment on the management of blood pressure and blood lipid, as the main risk factors of CVD, adherence to a healthy lifestyle such as healthy eating habits may be more effective with fewer side effects than that of medication.[5]

Low quality diet is a strong risk factor for all-cause mortality as well as CVD mortality. Moreover, assessment and recording of dietary intake, especially when nutrients data is needed, is difficult and can result in measurement bias.

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In modern epidemiological approach, assessing the overall diet quality is a better indicator of CVD risk than a single nutrient or a food group because foods are not consumed in isolation.[6] In recent decades, some indices such as the Recommended Food Score (RFS) and Healthy Nordic Food Index (HNFI) have been suggested for the assessment of diet quality. RFS separates "good" and "bad" foods to describe a healthy and unhealthy diet.[7] However, the HNFI includes only foods with healthy effects based on the traditional Nordic Diet.[8] These indices are suggested as strong indicators of dietary exposures related to disease.[8]

In the last two decades, the role of healthy eating has been emphasised in the prevention of CVD.[9] Dietary guidelines commonly focus on food patterns more than nutrients.[9] The common factors among these guidelines are promoting the consumption of fruits, vegetables, fish, grains, nuts, and olive oil.[9] The Western dietary pattern has become a common pattern which includes animal products, refined carbohydrates, and low consumption of vegetables and fruits.[9] Healthy dietary patterns try to reverse effect of the Western dietary pattern by increasing the consumption of vegetables and fruits. The purpose of this study was to systematically review the RFS and HNFI indices, which are related to healthy dietary patterns, and their relation with CVD and stroke.

## Materials and Methods

*Data source and search strategies:* Literature search was conducted by searching articles published on PubMed, Google Scholar, and ScienceDirect until December 2018. Moreover, reference lists of the included studies were also searched to find related articles. Terms and words used for the search included "cardiovascular disease", "heart diseases", "heart failure", "myocardial infraction", "coronary heart disease", "stroke", "Recommended Food Score", and "Healthy Nordic Food Score". The Search strategy is explained in detail in figure 1. The literature search was restricted to human studies written in the English language and all kind of observational studies (cross-sectional, cohort, case-control, and longitudinal). The Medical Subject Headings (MeSH) was checked for the selected keywords. Grey literature such as governmental and organizational reports and the reference list of the selected studies were also searched manually for relevant information and articles.

Studies were added to the review if they reported the RFS and HNFI score, but not food or nutrients.

The initial systematic search identified 535 potential articles. Two authors independently screened titles and abstracts based on the eligibility criteria according to the PICOS model (population, intervention, comparators, outcomes, and study design). The population criterion included all age groups and healthy people, intervention (exposure) included adherence to HNFI or RFS, the comparator consisted of the HNFI or RFS scores, the outcome criterion included the risk of CVD or stroke, or CVD or stroke mortality and morbidity, and observational studies (cross-sectional, cohort, longitudinal, etc.) was determined as the study design.

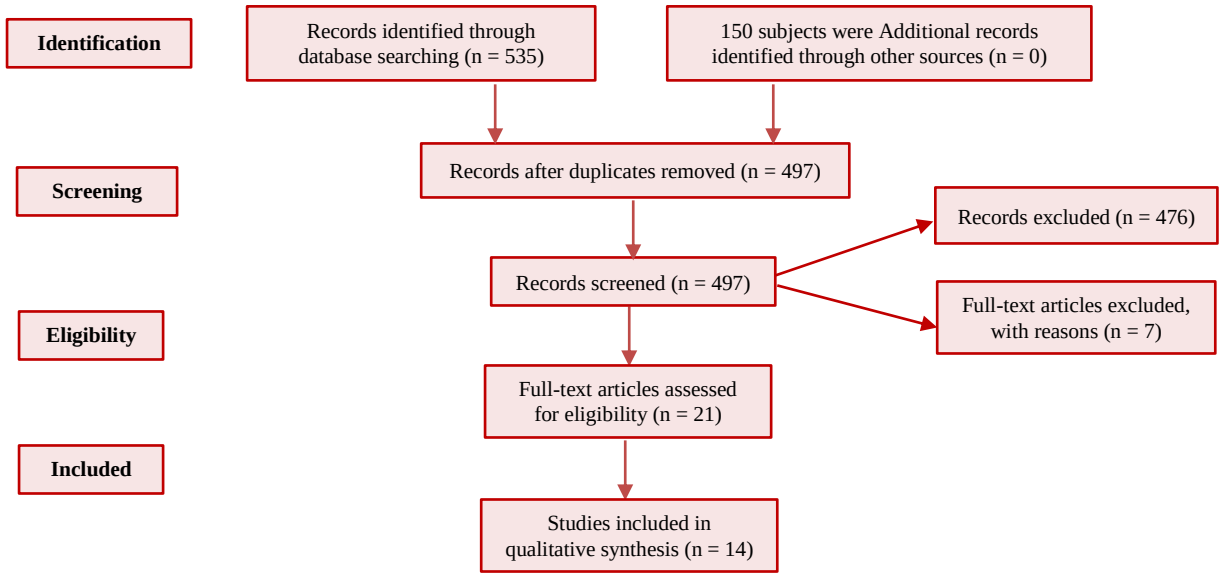


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Next, the full text of potential articles was reviewed by authors based on the inclusion criteria. Furthermore, the study selection process was followed based on the checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10] (Figure 1). The methodology of this systematic review was registered at the International Prospective Register for Systematic Reviews CRD42018095574. Methodology of quality assessment was checked based on PRISMA checklist.[11]

*Data extraction and quality assessment:* For each study, the information extracted included study design, the first author, year of publication, follow-up duration, and location, outcome of the study, study population, age, and dietary assessment tool.

## Results

In total, 14 articles were qualified to be included in the study.[2,4-6,12-21] The main results are presented in tables 1-3.

Of the selected articles, 11 were cohort studies,[4-6,13-15,17-21] 2 were cross-sectional studies,[17,18] and 1 was a cross-national study [a comparative study on cardiovascular health conducted in two different countries: Maine Syracuse Study (Central New York, USA) and ORISCAV-LUX (Luxembourg)].[2] The studies were conducted in Sweden (6 articles),[4,5,14,15,19,21] Denmark (2 articles),[12,13] Brazil (1 article),[17] USA (3 articles),[16,18,20] Luxembourg and New York (1 article),[2] 10 European countries (1 article).[6] A majority of the studies included both genders, except 4 articles that were performed only on women[4,14,15,21] and 2 that were conducted on men.[5,19] The age of the participants ranged from 39[14,15] to 62 years,[18] except in 1 article in which the food habits of 6-14-year-old school aged children was assessed.[17]

Moreover, 9 articles defined RFS,[2,4,5,16-21] and 5 HNFI.[6,12-15] CVD was studied in 11 articles[2,5,6,13-20] among which 2 assessed MI,[5,13] 1 examined ischemic heart disease, arrhythmias, thrombosis, and hypertensive disease,[15] 1 defined cardiovascular health arterial stiffness by pulse wave and pulse pressure,[16] and 3 assessed cardiovascular health by biochemical factors, blood pressure, body fat, and physical activity.[2,17,18] Furthermore, 3 articles assessed CVD mortality,[6,14,19] and 3 investigated the risk of stroke[4,12,21] by cerebral infarctions, hemorrhagic strokes (intracerebral hemorrhages and subarachnoid hemorrhages), unspecified strokes,[4,12,21] total stroke, ischemic stroke, large-artery atherosclerosis, and small-artery occlusion.[12]

Dietary intake was assessed using the Food Frequency Questionnaire (FFQ) in 11 studies[4-6,12-15,17,19-21] and the Nutrition and Health Questionnaire,[2,16,18] which was validated in the EPIC project in 2 studies.[6] In the pan-European cohort study, dietary intake was assessed using a questionnaire that was validated in those countries.[6]

Of the 7 studies that investigated the association between the RFS and CVD, 6 showed a lower risk of CVD in individuals who obtained higher scores in RFS and lower scores in the Non-Recommended Food Score (n-RFS) (Table 1).[2,5,16,18-20] Coelho et al.[17] found no associations between RFS and risk of CVD in students, but after stratifying the participants by age, RFS could predict systolic blood pressure (SBP) and Tetrapolar Percentage of Body Fat only in children (not in adolescents). Moreover, they found an inverse association between RFS and SBP in children after adjusting for family income, gender, biochemical factors, and body fat percentage.[17]

The results of 2 studies that investigated the relationship between RFS and stroke showed that achieving higher RFS could decrease the risk of a stroke in women (Table 2).[4,21]

The other reviewed index was the HNFI as a recently noticed index. The HNFI index and CVD were assessed in 4 studies (Table 3).[6,13-15] Roswall et al.[15] observed no association between HNFI and risk of CVD.[15] In another study, Roswall et al. observed that increment in HNFI score was associated with lower mortality rate of CVD, but the association was no longer present after adjusting for cofounding factors like alcohol, red meat, processed meat, and energy intake.[14] In 2 other studies, it was reported that adherence to HNFI may decrease the risk of CVD.[6,13]

Furthermore, Hansen et al.[12] conducted a cohort study on 28,997 women and 26,341 men in Denmark in 2017. After 13.5 years of follow-up, they found a statistically significant inverse relationship between HNFI and stroke, and higher adherence to this index resulted in a 14% decrease in the risk of stroke after adjustment for confounders (HR = 0.86; 95% CI: 0.76-0.98).

## Discussion

The present review study summarizes the relationship of adherence to RFS and HNFI with CVD and stroke incidence and mortality. This review showed that adherence to healthy food items in the RFS may be related to lower risk of CVD and stroke; furthermore, higher intake of food items in the n-RFS can increase the risk of CVD and stroke. The relation between HNFI and CVD was inconsistent.

**Table 1.** Characteristics of studies (n = 7) examining the relationship between the Recommended Food Score and cardiovascular disease

| Reference | Age (year) | Participants/ gender | Country/ year of publication | Design | Aim of study | Duration of study (year) | Results | OR/HR/ percent change | Dietary assessment method |
|---|---|---|---|---|---|---|---|---|---|
| McCullough et al.[20] | USA 2002 | 38615 men 67271 women | 40-75 | Cohort | Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance | 8-12 | FFQ (130 items) RFS score = 23 | (RR = 0.77; 95%CI: 0.64-0.93) | 23% reduction in risk of CVD |
| Kaluza et al.[19] | Sweden 2009 | 40 837 men | 45-79 | Cohort | Diet quality and mortality: a population-based prospective study of men | 7 | FFQ (96 items) RFS score = 36 n-RFS score = 16 | (RR = 0.71; 95% CI: 0.54–0.93) | Adherence to RFS can decrease mortality due to CVD by 29%. There was no significant association between n-RFS and CVD mortality. |
| Akesson et al.[5] | Sweden 2014 | 20721 men | 45-79 | Cohort | Low-Risk Diet and Lifestyle Habits in the Primary Prevention of MI in Men | 10 | FFQ (96 items) RFS score = 25 n-RFS = 21 scores | (RR = 0.82; 95% CI: 0.69-0.96) | 18% reduction in risk of MI |
| Crichton et al.[16] | Syracuse, New York and surrounding counties 2014 | 201 men 304 women | 18-83 | Cohort | Cardiovascular health and arterial stiffness: The Maine-Syracuse Longitudinal Study | 4-5 | Nutrition and Health Questionnaire RFS score = 23 n-RFS score = 15 | | Individuals who have higher CHS (5-8), have higher mean RFS score (11.6 ± 2.8) and lower mean n-RFS score (2.9 ± 1.6). |
| Crichton et al.[18] | New York 2014 | 399 men 573 women | 18-83 | Cross-sectional | Cardiovascular Health and Cognitive Function: The Maine-Syracuse Longitudinal Study | | Nutrition and Health Questionnaire RFS score = 23 n-RFS score = 15 | | Individuals who have higher CHS (5-8), have a higher mean RFS score (12 ± 2.9) and lower mean n-RFS score (2.8 ± 1.8). |

**Table 1.** Characteristics of studies (n = 7) examining the relationship between the Recommended Food Score and cardiovascular disease (continue)

| Reference | Age (year) | Participants/ gender | Country/ year of publication | Design | Aim of study | Duration of study (year) | Results | OR/HR/ percent change | Dietary assessment method |
|---|---|---|---|---|---|---|---|---|---|
| Crichton et al.[2] | Luxembourg and Central New York, USA 2014 | Luxembourg: 1145 New York: 673 | 30-69 | Cross-national | Cardiovascular health: a cross-national comparison between the Maine Syracuse Study (Central New York, USA) and ORISCAV-LUX (Luxembourg) | Luxembourg: 2 New York: 5 | Luxembourg: semi-quantitative FFQ (134 items) New York: Nutrition and Health Questionnaire RFS score = 18 n-RFS score = 13 | | Individuals with ideal RFS (12-18) and ideal n-RFS (0-2), have higher CHS. |
| Coelho et al.[17] | Brazil 2015 | 738 students | | Cross-sectional | Food habits and risk of cardiovascular disease in school children from Ouro Preto, Minas Gerais | 6-14 | FFQ (120 items) RFS score = 50 | SBP: β= -0.112; 95%CI, -0.462; -0.001. BFP-T: β= -0.131; 95%CI, -0.301; -0.015 | After adjusting for age, RFS predicted SBP and BFP-T. |

OR: odds ratio; HR: Hazard ratio; CI: Confidence interval; FFQ: Food Frequency Questionnaire; RFS: Recommended Food Score; MI: Myocardial infarction; CHS: Cardiovascular health score; SBP: Systolic Blood Pressure; BFP-T: Tetrapolar Percentage of Body Fat

**Table 2.** Characteristics of studies (n = 2) examining the relationship between the Recommended Food Score and stroke

| Reference | Country /year of publication | Participants/ gender | Age (year) | Design | Aim of study | Duration of study (year) | Dietary assessment method | OR/HR/ percent change | Results |
|---|---|---|---|---|---|---|---|---|---|
| Larsson et al.[4] | Sweden 2014 | 31696 women | 49-83 | Cohort | Healthy diet and lifestyle and risk of stroke in a prospective cohort of women | 10.4 | FFQ (96 items) RFS score =25 n-RFS score = 21 | (RR = 0.85;95% CI: 0.76-0.95) | The risk of stroke reduced by 15%. |
| Larsson et al.[21] | Sweden 2014 | 31696 women | 49-83 | Cohort | Overall diet quality and risk of stroke: A prospective cohort study in women | 11 | FFQ (96 items) RFS score =25 n-RFS score = 21 | (RR = 0.80; 95%CI: 0.67-0.95) | After adjusting for confounders, the risk of total stroke in the top quartile of RFS was 20% lower than other quartiles. |

OR: odds ratio; HR: Hazard ratio; CI: Confidence interval; FFQ: Food Frequency Questionnaire; RFS: Recommended Food Score

**Table 3.** Characteristics of studies (n = 4) examining the relationship between the Healthy Nordic Food Index and cardiovascular disease

| Reference | Country/ year of publication | Participants/ gender | Age (year) | Design | Aim of study | Duration of study (year) | Dietary assessment method | OR/HR/ percent change | Results |
|---|---|---|---|---|---|---|---|---|---|
| Roswall et al.[15] | Sweden 2015 | 43310 women | 29-49 | Cohort | No association between adherence to the HNFI and CVD amongst Swedish women: a cohort study | 21 | FFQ | (HR = 1.00; 95% CI: 0.98-1.01) | A 1-point increase in the HNFI score was not associated with incidence of CVD. |
| Roswall et al.[14] | Sweden 2015 | 446961 women | 29-49 | Cohort | Adherence to the healthy Nordic food index and cause-specific mortality among Swedish women | 21.3 | FFQ (80 items) | (MRR = 1.01; 95%CI: 0.92-0.1) | In the fully adjusted models, a 1-point increase in the HNFI score was not associated with incidence of CVD. |
| Lassale et al.[6] | European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom, 2016 | 130370 men 320886 women | 40-60 | Cohort | Diet Quality Scores and Prediction of All-Cause, Cardiovascular and Cancer Mortality in a Pan-European Cohort Study | 8 | Validated country-specific dietary questionnaires | (HR = 0.88; 95%CI: 0.85-0.91) | Adherence to HNFI decrease mortality due to CVD by 12%. |
| Gunge et al.[13] | Denmark 2017 | 57053 men and women | 50-64 | Cohort | Adherence to the HNFI and risk of MI in middle-aged Danes: the diet, cancer, and health cohort study | 4 | FFQ (192 items) | (men: HR = 0.77; 95%CI: 0.62-0.97; woman: HR = 0.55; 95%CI: 0.37-0.82) | Risk of MI significantly decreased in individuals with a score of 5-6 (45% in women and 23% in men). |

OR: odds ratio; HR: Hazard ratio; CI: Confidence interval; FFQ: Food Frequency Questionnaire; HNFI: Healthy Nordic Food Index; CVD: Cardiovascular disease; MRR: Mortality rate ratio; MI: Myocardial infarction

RFS is a kind of healthy diet comprising a combination of consumption of fruit, vegetables, nuts, fish, and low fat dairy, which have beneficial effects on cardiovascular health.[5] The HNFI is a Swedish method[7] developed by Kant et al.;[22] it separates "good" and "bad" food to describe healthy and unhealthy diets based on the foods recommended by dietary guidelines.[22] Michels and Wolk completed the RFS by developing the n-RFS.[7] The items of the RFS and n-RFS, and the method of their calculation are included in table 4.

Studies showed that adherence to RFS could decrease 18% of the risk of MI.[5] In addition, individuals with higher RFS scores and lower n-RFS scores had lower blood pressure, fasting blood glucose, and total cholesterol.[2,16,18]

Almost all studies were carried out among adults. Only 1 study was carried out on children and adolescents, which reported a significant negative relationship between RFS and CVD only in children. This result may be due to the fact that parents and family members have a controlling role in the adherence of children to a healthy diet, but this role was weaker in adolescents because they want to experience more independence ; so, they disobey of their parents rules.[17]

Adherence to RFS can decrease the risk of cerebral infraction, hemorrhagic stroke, and total stroke by 13%, 23%, and 15%-20%, respectively.[4,21] High consumption of foods listed in the n-RFS could increase the risk of cerebral stroke and total stroke by about 22-27 percent.[21]

The risk of stroke is lower in women who have a high quality diet and consume all kinds of healthy foods, because the RFS is compatible with the primarily stroke prevention guidelines. These guidelines include low consumption of salt and saturated fat, high consumption of fruit and vegetables (high density of potassium), low-fat dairy, and fish all of which were included in the RFS.[21]

The HNFI was originally developed by Olsen et al.[8] and includes only healthy food based on the traditional Nordic Diet. The items of the HNFI and its calculation method are provided in table 4. The association of HNFI score with risk of CVD was inconsistent. The average HNFI score in European countries was 2-3.[6,12-15] In 2 studies, it was reported that adherence to HNFI may decrease the risk of MI mortality.[6,13]

**Table 4**. Recommended and non-Recommended Food Score and Healthy Nordic Food Index items and scoring

| Index | | Items | Calculation |
|---|---|---|---|
| RFS | Fruits | apples or pears; oranges; cantaloupe; orange or grapefruit juice; grapefruit, other fruit juices | The RFS score is obtained by calculating the sum of the scores of these 23 items that are consumed at least once a week.* |
| | Vegetables | dried beans; tomatoes; broccoli; spinach; mustard, turnip or collard greens; carrots or mixed vegetables with carrots; green salad; sweet potatoes or yams; other potatoes | |
| | Lean meat or poultry | baked or stewed chicken or turkey; baked or boiled fish | |
| | Whole grains | dark breads like whole wheat, rye, or pumpernickel; cornbread, tortillas, grits; high-fiber cereals, such as bran, granola, or shredded wheat; cooked cereals | |
| | Low fat dairy: | 2% milk and 1% or skim milk | |
| n-RFS | Meat | meat; meat stew; minced meat | The n-RFS score is obtained by calculating the sum of the scores of these 21 items that are consumed at least 1-3 times per month.* |
| | Processed meat | bacon; sausages; blood pudding/sausages; cold cuts; pate | |
| | Visceral meat | liver, kidney | |
| | Fried potatoes | French fries; chips | |
| | High-fat dairy | cheese (high saturated fat); butter; margarine; | |
| | White bread | pancakes, Belgian waffle | |
| | Cookies | | |
| | Ice cream | | |
| | Candy | | |
| | Sugar | | |
| HNFI | fish | | One point was given for each of the food items that were consumed above the sex-specific median intake of the whole study. |
| | cabbages | | |
| | whole grain rye | eaten as rye bread | |
| | whole grain oats | oatmeal | |
| | apples and pears | | |
| | root vegetables | | |

RFS: Recommended Food Score; n-RFS: non-Recommended Food Score; HNFI: Healthy Nordic Food Index

* The numbers of the items in RFS, n-RFS, and the calculation of the score could differ among the studies assessed in this systematic review

However, no association was found between HNFI and CVD (e.g., ischaemic heart disease, arrhythmias, and thrombosis) risk in the study by Roswall et al.[15] This finding can be attributed to the type of FFQ that was used in the study, which did not separate whole-grain and non-whole grain items. Thus, whole grains that have an important role in HNFI score and CVD prevention were disregarded.[6,15,23,24] Furthermore, in the study by Roswall et al., with a 1-point increase in HNFI score no change was observed in CVD mortality that may be due to the low power of the study and use of self-reported cofounders such as BMI.[14]

Components of the HNFI include CVD preventive factors such as ω-3 in fish, β-carotene in root vegetables (carrot), isothiocyanates in cabbage, carotenoid in apple and pears, and fiber in whole grains.[13,23,25] Omega-3 can decrease plasma triglyceride and hepatic very-low-density lipoprotein (VLDL) synthesis as a result of decreasing de novo lipogenesis (DNL) and increasing β-oxidation. Moreover, ω-3 can decrease blood pressure and resting heart rate.[26] Macrophages, which are rich in β-carotene, decrease the cellular cholesterol synthesis and increase the activity of LDL receptors in macrophages. Therefore, dietary consumption of Beta carotene decreases the cholesterol.[27] In addition, carotenoids destroy free radicals, so they can decrease the risk of atherosclerosis.[28] The fiber of the grain group is another preventive factor that decreases LDL and blood pressure.[23]

Down-regulation of messenger ribonucleic acid (mRNA) of the interleukin-18 that is a pre-inflammatory cytokine and has an important role in the incidence of CVD in the elderly is enhanced in individuals with a high HNFI score.[29] Furthermore, SBP, plasma triglyceride, total cholesterol, and VLDL are lower in individuals who earned higher HNFI scores.[30] Most studies showed that despite the fact that a healthy diet is an important determinant of a healthy lifestyle, other factors such as not smoking, higher physical activity, moderate alcohol consumption, and low abdominal adiposity may increase the protective effect of a healthy diet that should be addressed in future studies.[4,5,19,21]

The strengths of the articles reviewed in this study was the cohort design of most studies, their reasonable follow-up period (range: 4-21 years), and their large sample sizes. The reviewed articles had several limitations. First, some studies did not study both genders and the power of some of them was low.[4,5,14,15,21] Second, in some studies, dietary intake information were obtained through self-reporting methods, which may not be as accurate as assessment by trained nutritionists, or they were only measured in one occasion, which may have reduced the precision of the study.[5,12,16,21]

## Conclusion

RFS and HNFI may decrease the risk of CVD and stroke. Due to the inconsistency in the present study results, it is suggested that the relation between HNFI and CVD be further studied. In addition, it is suggested that clinical trials be carried out in order to examine the effect of RFS on CVD control as the potential ecological benefits of the HNFI were discovered in non-experimental studies.

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## Conflict of Interests

Authors have no conflict of interests.

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# What thought to be a cardiac tumor turns out to be a remnant of former surgery

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Case Report

## Abstract

**BACKGROUND:** A textiloma is a rare retained surgical swab with probable serious post-operation complications.

**CASE REPORT:** Here, we reported an asymptomatic patient who had past history of coronary artery bypass grafting (CABG) fourteen months ago and referred to our institute for left atrial mass removal. Echocardiography and chest computed tomography (CT) scan revealed a non-homogenous non-mobile mass and a heterogeneous lesion with low-density as well as high-density areas with spot calcification and gas bubbles at left atrium level, respectively.

**CONCLUSION:** Despite being rare after CABG, textiloma should be considered in the differential diagnosis in case of any suspicious chest mass even in asymptomatic patients.

**Keywords:** Textiloma; Coronary Artery Bypass Grafting; Gossypiboma

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## Introduction

A gossypiboma or a textiloma is a non-absorbable cotton matrix mass which is due to a negligence during the surgery with a granulomatous reaction around it.[1] Although it is a rare condition with the incidence of 1 case per 1000 to 10000 surgeries,[2] it can cause serious complications due to the misdiagnosis. Also, because this phenomenon is considered as a medical error and legal implications, it seems that its incidence is more than that reported in the literature.[3] Textiloma usually occurs in abdominal surgeries, but may also occurs following all other surgeries such as intrathoracic surgeries.[4] We will report an asymptomatic patient with the history of coronary artery bypass grafting (CABG) who referred for cardiac tumor work-ups.

## Case Report

A 65-year-old man was referred to the cardiac surgery department of our hospital, Imam Khomeini Hospital, Tehran, Iran, for left atrial mass removal. He was completely asymptomatic. His past medical history was CABG fourteen months before admission. In fact, the suspicious mass was detected during a follow-up echocardiography. Physical examination showed a regular pulse, heart rate was 72 beats per minute (BPM), blood pressure (BP) was 136/86 mmHg, and body temperature was 36.8 °C. Lung auscultation was normal and clear but a systolic cardiac murmur was heard in the left sternal border. Other physical examinations were normal.

The transthoracic echocardiography (TTE) was repeated in our hospital. The left ventricle size and function were normal [ejection fraction (EF): 55%]. A non-homogenous non-mobile mass at the left atrium level was detected (Figure 1).

The adhesion site of mass could not be defined in TTE. There was no significant stenosis in mitral. TEE was performed; interestingly, no view was detected, maybe because of the mass-like shadow.

The contrast-enhanced computed tomography (CT) scan of the chest, which was with the patient, was reviewed. It showed a heterogeneous lesion with low-density as well as high-density areas.

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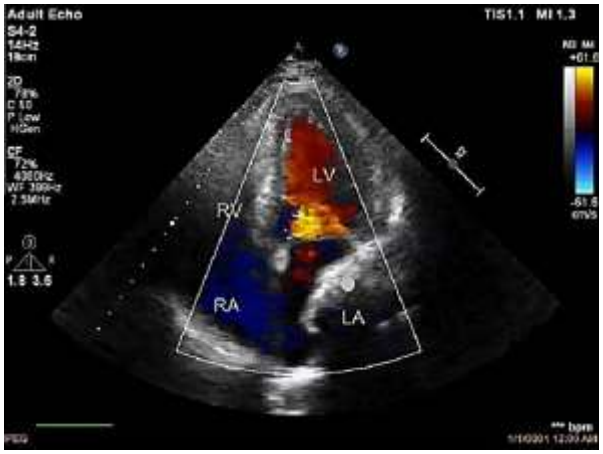


**Figure 1.** Transthoracic echocardiography (TTE) demonstrated a non-homogenous non-mobile mass at left atrium level.

Spot calcification and gas bubbles were also present (Figure 2).

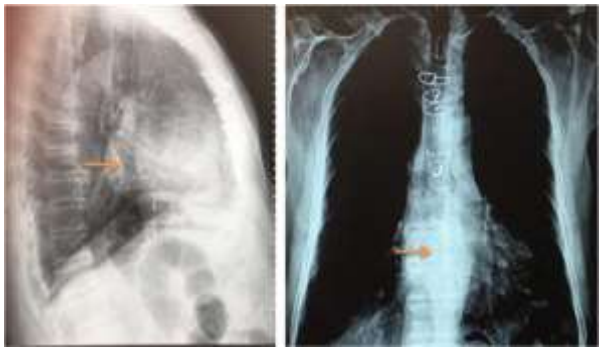

**Figure 2.** Chest X-ray in posteroanterior (PA) and lateral views revealed a mass posterior to the left atrium.

After observing the gas bubbles in mass at CT scan, a chest X-ray [posteroanterior (PA) and lateral] was performed (Figure 3).

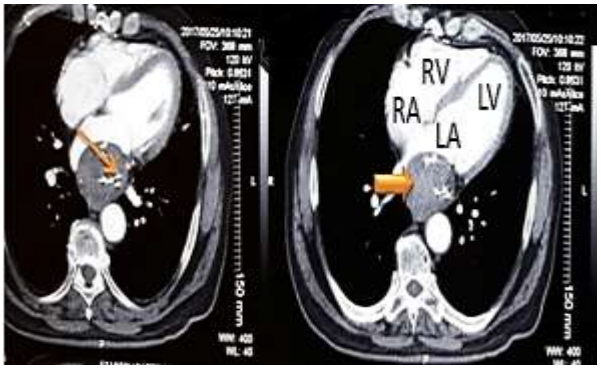


**Figure 3.** Chest computed tomography (CT) scan in axial view demonstrated a heterogeneous mass with spot calcification and gas bubbles.

The retained sponge was seen exactly posterior to the left atrium. Patient underwent operation due to concerns about abscess formation and fistula to adjacent organs. At surgery, the presence of gossypiboma was confirmed in posterior area of left atrium. Histopathological study demonstrated fragments of gauze with a thick fibrous wall calcification and necrosis. The patient's surgery was carried out without any complications, and in the follow-ups, the patient did not mention any problems.

## Discussion

The term textiloma or gossypiboma (also called retained surgical swap, gauzoma, muslinoma, or cottonoid) is used to describe a mass within a patient's body comprising a cotton matrix, which usually refers to a retained surgical sponge or gauze and the surrounding foreign body reaction.[5]

It is a rare condition but associated with serious complications. The most common sites have been reported to be in the abdomen. The sponges can remain silent or induce a series of inflammatory reactions that cause wound infection, abscess, fistula formation, haemoptysis, bilious expectoration, intestinal adhesions or obstruction, aseptic foreign body granuloma, or sepsis.[6] Sponges used during surgical procedures should contain radiopaque markers. Conventional radiology is the most common imaging technique utilized in the postoperative period for the detection of retained sponges. The most characteristic appearance of retained sponge in CT scan is an encapsulated and low-density heterogeneous mass with spongiform appearance with whorls like a gas bubble.[7,8]

Radiographic detection of the sponges on anteroposterior (AP) projections is difficult because of exposure factors and metallic densities such as sternal sutures. Knowledge of the typical location of a lost sponge and use of lateral radiographic projections may aid in early detection of this rare complication.[8]

The best treatment for gossypiboma is surgical exploration in symptomatic patients; there may be a role for conservative approaches in selected asymptomatic patients, particularly if there has been a prolonged retention time.[9] Despite being rare after CABG, textiloma should be considered in the differential diagnosis in case of any suspicious chest mass even in asymptomatic patients. Radiological work-ups especially the chest CT scan is the best way for diagnosis and also assessment of its probable complications.

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## Conflict of Interests

Authors have no conflict of interests.

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# Left ventricular clot: Newly known increased complication of air pollution in dilated cardiomyopathy (DCM)

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**Letter to Editor**

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## Dear Editor

Air pollution is one of the major health problems in the world that impaired cardiovascular function, and is associated with cardiovascular mortality.[1] Numerous studies showed that short-term and long-term exposure to air pollution are associated with cardiovascular mortality.[2] One of the most important pathology findings discussed in this regard is the thrombosis, which increases the cardiovascular mortality.[3] Increased inflammation and oxidative stress as well as hypercoagulation state by air pollution resulting in thrombosis;[4] and many clinical studies have showed that air pollution increased hospitalization and cardiac events as well as subclinical atherosclerosis, and also deep vein thrombosis and pulmonary embolism.[4-7] Till now, based on our knowledge, there is no report of increased left ventricular (LV) and also right atrium (RA) clot rate due to air pollution. Actually in recent months (from September to January), at our heart center in Tehran, Iran, one of the world's metropolitan areas with severe air pollution, we interestingly and unfortunately met a large number of cases with LV apical clot specially in patients with dilated cardiomyopathy (DCM) and also RA clot [with or without pulmonary thromboendarterectomy (PTE)]; with near 30% increase in rate of them. Some of these patients had a history of physical inactivity while surprisingly the rest of them had no risk factor. LV clot occur rarely in patients with DCM and sinus rhythm (13%).[8] While in these days, we saw patients even with mild regional wall motion abnormalities (RWMA) who had large LV clot. In addition, this complication occurred with higher rate in patients with DCM during these days. Noticeable point is that insomuch increase in thrombosis was not seen in the other months when the air was clear. Based on the findings documented in our heart center, we aim to propose a hypothesis that air pollution is also associate with increase LV and also RA clot in mentioned patients. This new finding that we report in this paper could be a new research topic for researchers and future studies in cardiovascular system. We suggest that further clinical study are needed to confirm this hypothesis, and also determine which one of patients are susceptible to these complications of air pollution.

## Conflict of Interests

Authors have no conflict of interests.

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