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# ***Balkan Journal of Health Science***





# Balkan Journal of Health Science

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# Statistical tests for medical waste management

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## Abstract

Every organization has a medical problem with certainty disposal of medical waste harmful to the environment. This paper describes the issues and the possibility of improving safety management systems security risks in the area of medical waste. Risk management is the process of risk identification, risk assessment and take certain steps to reduce the risk to some extent. This paper describes the basic goals and ideas of the risk management process in medical dumps, method of enforcement, and the typical problems that arise in this area. Risk management is the process of risk identification, risk assessment and steps taken to reduce the risk to a certain level. This work provides the basis for the development of an effective risk management program, containing definitions and the practical guidance necessary for assessing and mitigating risk in the system of medical landfills.

**Key words:** statistics, absolute risk reduction, relative risk reduction, medical waste

## Introduction

The reform of the healthcare system in our country is aimed at improving the quality of health services, both in the state, and private sector health care. An important element in improving the quality of health services is adequate disposal of medical waste, which is in accordance with national legislation as well as the basic principles of professional practice of medical waste management, prevention of communicable diseases and health promotion. The objectives of this paper is to initiate the idea of reducing the amount of waste that is generated in the institutions providing health care, especially the separation of waste at the main categories in the place of creation, the proper packaging of the same, marking and disposal, separation of recyclables from waste, recycling, as and the

use of cleaner technologies for sterilization or decontamination of infectious medical waste. Paper proposes statistical tests of risk assessment for the purpose of obtaining good results in the field of environmental protection. The definition of risk phrases: possible variants of action (alternative) and possible (uncertain) achievement, indicating uncertainty. The risk can be discussed only in the context of a specific alternative. [2]

The risk does not mean a safe performing a negative effect on the estimated negative effects whose realization is uncertain.

Risk analysis in this case is very heavy, making it difficult following five factors:

1. uncertainty related to the definition of the problem,
2. difficulties that arise when evaluating the facts,
3. complexity disclosure of relevant values,
4. unpredictable behavior of participants in the process, and
5. inconsistency of the evaluation process.

At the outset it will introduce the basic concepts that are often used in the work. In Table 1 are given concise definitions of the main concepts in the field of risk management taken from the ISO / IEC 14971st Definitions of adverse effect and hazard taken from ISO / IEC Guide 51:1999, definition 3.1 and 3.5.

The term hazard is the basis of most of the methodology for assessing and controlling risks. However, its definition is the cause of many disputes and ambiguities in the process of forming a list of known and foreseeable hazards. Primarily this is due to the fact that almost every situation or event in a device or system can be declared potential cause harmful effects. It should be noted that certain hazard can have one, but several potential causes.

Table 1. Definitions

Term	Definition
Certainty	Absence of unacceptable risk
Risk	The combination of probability and severity of adverse effects
Hazard	Potential cause adverse effects
Adverse consequences	Injury, damage or any danger to the patient, operator, equipment or the environment
Risk Analysis	Identification of as many hazards and their likelihood and severity of harmful effects that cause
Risk Control	The process of reducing the risk of changes to the design, installation of protective measures or giving warnings
Evaluation of risk	Estimated remaining (residual) risk and decision on its admissibility

### 1. Medical waste

There are several definitions of medical waste that are considered acceptable when categorizing and classification medical waste generated in health care facilities. Under medical waste includes all the waste generated in health care facilities (public or private), medical research centers and laboratories. It is a heterogeneous mixture of waste, while 10-25% is hazardous waste risk to human health and the environment. According to the Law on Waste (Draft Law on Waste Management of Bosnia and Herzegovina) waste is defined as any substance or object included in the European Waste Catalogue, which the owner discards or intends or has to reject, in accordance with the law. Waste originating from medical institutions only one part of the medical waste and still be graded in different categories. An important area of work of professionals responsible for handling and disposal of medical waste is a risk assessment, provision of preventive measures to protect employees. This applies primarily to the health sector, consumers of health services, as well as environmental protection. [7]

For good waste management practices is crucial to health workers and associates know exactly what is expected of them in connection with the classification of waste, to be motivated and properly trained for these activities, and that they have adequate

cooperation with the administration of health institutions on such matters. Basically, there are the following two types of medical waste:

- Non-hazardous waste (waste that does not have the characteristics of hazardous waste and is similar to the waste generated in households)
- Hazardous wastes (which in its origin, composition or concentration of hazardous substances may cause danger to the environment and human health, and has one of the least hazardous characteristics defined by special regulations, including the packaging in which the hazardous waste is or has been packed).

The European Commission is still in 1994. The defined comprehensive European Waste Catalogue to introduce common terminology throughout the countries of the European community and enhance the management of waste (Council Directive no. 2000/532/EC). Basically, in the European Waste Catalogue, waste is defined based on the following three criteria [3]:

1. Origin of the waste that is defining the industry or sector from which encourages waste (the first two digits - the health sector - 18).
2. Process where waste is generated (the other two figures - waste generated in the provision of health services in maternity hospitals, the diagnosis, treatment or prevention of disease in humans - 18 01).
3. Type of waste (third pair of digits - non-infectious wastes - wastes whose collection and 03). According to the European Waste Catalogue, each type of waste has its own classification number or code that consists of 6 digits (for example, 18 01 03).

Classification of medical waste according to the European Waste Catalogue [9]:

1. Pathoanatomically waste: a recognizable body parts, placenta...
2. Infectious waste: bandages, swabs, sharps, waste from dialysis Infected blood
3. Municipal waste: regular rubbish, waste from the kitchen,...
4. Hazardous waste: radioactive waste, pharmaceutical agents, chemicals and others.

## 2. International legislation

### 2.1 EU directives

Basically waste management policy in the European Union are set out in the Resolution of the Council of Europe's waste management strategy (97/C76/01) which is based on the Waste Framework Directive (75/442/EEC) and other regulations on waste management in the EU. It was found five basic principles:

- hierarchy of waste management,
- viable disposal facilities,
- best available technology,
- vicinity of waste disposal and
- producer responsibility.

Alongside these are pursued, the following principles: a common definition of waste in all Member States, encouraging cleaner production and use of clean products, promoting the use of economic instruments, regulation of transportation of waste, as well as environmental protection and the internal market. [10]

#### 2.1.1 Basel Convention

Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal (1989) is one of the most internationally accepted legal acts in the field of hazardous waste management. In our country, in force since 1999th year, among other things regulates the transboundary movement and disposal of medical waste (as hazardous waste). The agreement was signed by over 100 countries that have accepted the principle that the only legitimate transport hazardous waste exports from countries that do not have the facilities or qualified personnel for reliable waste disposal, in countries that have facilities and professional staff.

#### 2.1.2 Customizing international legislation

Existing legislation does not cover all aspects of medical waste management and make recommendations for the treatment of specific waste streams, which represents the medical waste. It is essential to its compliance with the European directives and international standards, which includes a clear definition of hazardous medical waste and its various categories, the introduction of integrated management (segregation, collection, storage, handling,

treatment, storage, transport), the system records the principles of legal and financial responsibilities generator waste inspection system that will provide effective law enforcement and criminal provisions.

## 3. The current situation in the country in terms of medical waste management

Medical waste in health care institutions in Bosnia and Herzegovina is created in uneven amounts, depending on the type of facility, number of beds, types of diseases and conditions which are disposed of, and the types of services in health care facilities provide. Disposal of various categories of medical waste in Bosnia and Herzegovina to the 2008th he performed in different ways in different health institutions. The Ministry of Health of Bosnia and Herzegovina's 2007th The specific activity began to introduce a uniform system of medical waste management, and in particular the category of infectious medical waste. Certain categories of medical waste can be a significant threat to the health of employees in health care facilities, and beyond.

In addition to health risks that result from direct contact, medical waste can have irreversible indirect health effects through contamination of waterways and soil during the treatment and final disposal and air pollution through emissions of highly toxic gases when insineracije. It has been proven that there is no method of waste treatment or disposal which completely eliminates the risks of medical waste carries for the population or the environment.

### 3.1 Conditions in the dumps

On dumps in Bosnia and Herzegovina is not done separating medical from other types of waste. The current practice of mixing medical waste with municipal waste in landfills with inadequate system work, can also lead to the rapid spread of infectious diseases, transmission of microorganisms through the air (such as microorganisms become due to air emissions through smoldering waste). The spread of infection through direct contact employees at dumps and other visitors who are not aware of the risks, and collect and landfill waste, as well as by animals and birds (vector) that by landfill roam in search of food, it is also one of the identified routes of infection. Most landfills in Bosnia and Herzegovina are not sanitary landfills,



and on them are still buried waste daily, or further treated. This practice is present in sanitary landfills. Many landfills have arranged access, and they also often leads to the uncontrolled burning of waste.

### ***3.2 Conditions associated with the formation of infectious medical waste***

In hospitals across Bosnia and Herzegovina, there are over 40,000 beds with an approximate number of about 10 million hospital days. The average bed occupancy is 65% per annum. According to the data from the health sector, there is an additional 1700 beds, which are found in military hospitals and private clinics. On the basis of these data, an estimate was made quantities of medical waste generated in health care facilities. According to estimates of the World Health Organization, in hospitals in Bosnia and Herzegovina is produced on average 1.2 kg of medical waste per hospital bed per day. This quantity is proportional to the quantity and average, which is valid for the countries of Eastern Europe. [11]

### ***3.3 Quantities of infectious medical waste***

It is estimated that all health institutions in Bosnia and Herzegovina annually produce about 5 tons. Approximately one ton of waste may be considered hazardous waste. Improper handling of medical waste can be a significant factor in the spread and transmission of infectious diseases. Introducing a system of infectious medical waste management in Bosnia and Herzegovina is of great importance for improving the health of the population of Bosnia and Herzegovina, as well as improving the quality of health services. Activities of the Ministry of Health and Ministry of Environment and Spatial Planning of Bosnia and Herzegovina on the introduction of management systems infectious medical waste, in a unique way at all by administrative districts in the state health institutions and the private sector mode a primarily significantly reducing the amount of creating infectious medical waste.

## **4. Risk Assessment**

Categories of medical waste as defined European waste catalog and defined in this study aimed at defining the basic setup procedures for risk assessment [6]. Risk assessment is a combination

of different decisions and analysis which are obtained using the method of risk assessment in order to achieve security in the work. Risk assessment relating to dangerous activities is the process by which risk is determined based on the probability that there is an accident and the potential risks to human life and health, as well as the environment. The basic elements of risk assessment, the probability and the consequences. Only risk that can be managed is an acceptable risk - the risk that implies that the possible effects on human health and material goods are within acceptable. Under the legislation, both in the domain of health and medicine, environmental protection, there is a need for the development of risk assessment by all entities engaged in waste management. It is necessary also that among the various departments there is constant collaboration of experts involved in waste management. Risk is a combination of threats, assess the severity and probability (the degree to which it is likely) that these threats be realized. Therefore, risk assessment is a process in which:

- Identify hazards;
- Identify and assess threats that are associated with it;
- Assess risks;
- Estimated the importance of risk in the circumstances discussed.

### ***4.1. Basic steps in the risk assessment***

In making those risk assessments are undertaken following five steps:

Step No.1: Identify hazards;

Step No. 2: Determine who / what might be damaged / injured and how;

Step No. 3: Assess the risks and decide whether existing preventive measures, adequate or should take additional measures;

Step No. 4: Record the findings and results of the assessment;

Step No. 5: Check made estimates and revise them if necessary.

### ***4.2 Risk assessment and decide whether the existing precautions are adequate or need to take additional measures***

Quantitative risk assessment can be obtained by determining the probability of unfolding for each hazard, and then multiplying the values obtained

with the measure of the seriousness of the likely consequences. These factors can be expressed quantitatively (numerical values) or qualitative (descriptive), as noted in the following text [4]. ISO 14971:2000 applies to risk management, a group of ISO 9000 specifies the properties that a good development process must meet. Table 2. shows the distribution of risk in accordance with IEC 61508-5, which defines four classes of risk in relation to acceptance:

Table 2. Class of risk with respect to the acceptability of [3]

Class of risk	Interpretation
	Unacceptable
	Undesirable and acceptable only if the reduction is impractical or costs are disproportionately large in relation to the improvement.
	Acceptable if the costs exceed the gains improvements.
	Negligible

The following example is taken from IEC 60601-1-4. It defines six levels of probability of harmful consequences, in order from lowest to highest:

- Extremely amazing
- Amazing
- Rare
- Occasional
- Likely
- Frequent

It also defines four levels of harmful effects:

- catastrophic - more dead or seriously injured
- critical - one or several dead or seriously injured
- limit - possible injury
- negligible - possible minor or no injuries

Table 3. Parameters of the acceptability of risk [3]

The probability of harmful consequences	Weight adverse effects			
	I Disastrous	II Critical	III Limit	IV Negligible
A - Frequent	I-A	II-A	III-A	IV-A
B - Likely	I-B	II-B	III-B	IV-B
C - Occasional	I-C	II-C	III-C	IV-C
D - Rare	I-D	II-D	III-D	IV-D
E - Incredible	I-E	II-E	III-E	IV-E
F - Extremely incredible	I-F	II-F	III-F	

Table 3. shows the simplest way to combine these parameters.

Table 3. contains a graph that helps you make decisions about risk acceptability. White areas in the table are low-risk areas. All risks under him are considered acceptable and does not require taking any measures. Right up there is a high-risk area. All the risks in it objectionable and application protection at the landfill is only possible when it is appropriate measures to eliminate or shift in the central area of ALARP (As Low As Reasonably Possible) risk - the area colored yellow. It is in this area takes most of the decisions regarding the risks. The basic principle is that any risk down to the bottom right corner until it is practicable and while the costs proportionate drawn using one word, reasonable. Also, it is necessary to devote much attention to the fact that the introduction of measures to increase the safety of landfill, it also increases the complexity of which in most cases have a negative impact on the general level of reliability and security. The decision on what is reasonable and what is not, is the key to the whole process. In itself includes cost of implementation measures for risk reduction, the amount of the reduction and the resulting benefits. Often the decision is subjective and therefore recommends that it adopt an interdisciplinary team with multiple perspectives on the same problem. When deciding to be taken and the following guidelines:

- Regulations and instructions of the competent authority
- Discussions and agreements with project partners
- International Standards
- Laws and legal acts.

## 5. Evaluation of risk

After the assessment, each risk in the system must be evaluated in order to establish his eligibility and possible measures for its reduction. Evaluation of the risk out of the strictly technical framework, as it possesses and its legal and ethical aspects. Her goal is to find a balance between the gains that the product offering, pricing and risk, to the satisfaction of users, the development team and other stakeholders. In the context of medical waste in the first place in all safety considerations comes the human factor. Like in previous areas of risk management or evaluation there is no unified methodology. The process further complicated by the fact that the decision to put one at risk, other risks in a new perspective and affects their eligibility, therefore it is necessary to pay attention to the order in which they handle the risks [9]. After the implementation phase of identifying and evaluating risks, access to its reduction for which there is an almost unlimited range of options. The optimal approach is generally already looming in the analysis of the problem, but it is often necessary compromises due to economic, technical and time requirements for its implementation. As a rule, chooses the simplest method, which reduces the risk to an acceptable level. There are a number of statistical tests that can help in making decisions about the selection of interventions to protect medical depot, drawing conclusions about the effects of the various contingency] certain events in situations related to the protection of medical landfills. One of the tests that are commonly encountered is the odds ratio (**Odds Ratio, OR**). The odds ratio is estimated whether the odds of a particular event or outcome the same for both groups of respondents landfills in the overall medical examination dumps a larger region. Explained in more detail, with OR to measure the ratio seems to be an event or result occur, and it seems that this event will follow. IT perspective, it often means that the researcher measures the ratio seems to be to develop a pollution or perform totally pollution due to a failure or virus infection from the dump and it seems that the infection or total pollution will not occur.

### 5.1 The odds ratio: calculation, use and interpretation

The odds ratio (OR) is one of the few statistics that have become increasingly important in IT research and decision-making. Since this test sample size is particularly useful because the researcher offers clear and direct information about which approach to protection has the best prospects for the benefit of the medical depot. Commonly, the data consist of values for each pair of conditions and outcomes and are presented in table format. The most commonly occurring form of tables  $2 \times 2$ , although possibly larger tables. Since it is easy to calculate,

$$OR = (a \times d) / (b \times c)$$

OR can be calculated manually on the spot, if necessary, to determine the odds that a particular event for the medical depot at risk for this event. In addition to assisting informational employees in decisions about care, since it provides simple information that you and the workers at the landfill can understand and thus to participate in decisions about the security that will be based on the prospects of success of applied protection. OR is an indirect measure, which we will explain in detail in the section on the interpretation of the statistical test. [1]

#### Calculating the odds ratio

The calculation of the odds ratio is quite simple. The formula is as follows:

$$\text{The odds ratio} = \frac{XY1/(1 - XY1)}{XY2/(1 - XY2)}$$

where XY1 a chance of doing tested for Group 1 and XY2 a chance of doing tested for Group 2 Another way of presenting the formula is tabular form:

Table 4.

	Standard protection landfill	A new type of sophisticated protection in landfills
Event	a	b
No events	c	d

$$\text{The odds ratio} = (a/b)/(c/d) \text{ or}$$

$$\text{The odds ratio} = (a \times d)/(b \times c)$$



OR is often used to determine the effect size difference between the two treatments (treatment - use of a particular type of care at the landfill). Take for example the protection of landfill infected dangerous virus type 1. Although the rate of infection of the landfill in the range of 25% to 47%, assuming that the test group dumps in the framework of the medical depot one region destruction rate 38% with standard care. However, developed new sophisticated methods of protection against infection and contamination. The question is: what are the odds that the landfill will have an effect on the environment and if the application of new sophisticated methods of protection compared with standard methods applied? OR a way that can be compared if the odds given equal outcomes for two different groups. OR is the ratio of the following two ratios: the ratio of standard care and new sophisticated protection in a group of landfills totally damage the environment and the ratio of standard care and new protection for groups of landfills that have not had the impact on the environment. According to the values in Table 4, is calculated as follows:

Table 5

	Standard protection landfill	A new type of sophisticated protection in landfills
Event	152	17
No events	262	103

$$\begin{aligned} \text{The odds ratio} &= (a/b)/(c/d) = \\ &= (152/17)/(262/103) = 8,94/2,41 = 3,71 \end{aligned}$$

The formula can be expressed as  $(a \times d)/(b \times c)$ , and the result is the same:

$$\begin{aligned} \text{The odds ratio} &= (152 \times 103)/(17 \times 262) = \\ &= (15656/4216) = 3,71. \end{aligned}$$

OR calculation result can be interpreted as follows: in a group of landfills that have been protected by standard methods, totally destroying the environment was 3.71 times higher than in the group of landfills that are protected by the new sophisticated methods. Based on these results, the researcher should conclude and suggest that all the dumps diagnosed with type 1 virus provides a new type of protection (to abandon the standard care).

*And how do you interpret the other results for the OR:* If OR is 1.00, meaning that it is equally likely to dump both groups appear to be very dangerous. OR greater than 1 indicates that it is more likely that the landfill first group (in this case the dump to standard care) play event (*disaster*) than in other groups of landfills. OR less than 1 means that it is less likely that the event will occur in the first group surveyed landfills. However, the OR values less than 1.00 can not be directly interpreted. OR does not work that speaks about the extent to which the less likely that the event will occur in the first group of landfills. It is important to put in the first column group that is expected to have more chances to play the event. Not worth trying to determine how accurately less likely that the first group of the earliest occurrence compared to other groups. If the odds of the first group, in which the event occurred, a small group of other layout, to be replaced of the table so that the second group occurs in the first column, and the first to the second. You will then be able to interpret a statistically significant difference because it will be the team moving to calculate how many more times at the event in the second group than the first [1].

If you replace the columns in the above example, the OR will amount

$$(5/22) / (45/28) = (0.2273 / 1.607) = 0.14$$

As you can see, it does not tell us that in a group of landfill protected new methods were 0.14 times fewer cases of disasters - the devastating effects of landfill on the environment, but at the surveyed landfills protected by standard methods. In fact, this procedure gives a result that can only be interpreted in the following way "seems to be the first group to perform an event smaller than it looks to be at the event to perform other groups." To what extent are the exact odds in the first group smaller than it looks in the other groups is not known. [13]

## 5.2 Relative risk and relative risk reduction

Compared to the ARR, the relative risk - RR implies an entirely different view of risk. He carried the risk of infection from the landfill have protections groups in relation to the risk of landfill group that is not protected. Since this is a test to determine the relative risk, it may not be quite so

clearly and simply explained as a test to determine the absolute risk reduction. However, determining the relative risk gives us a different perspective on the value of care in relation to not use adequate protection. RR is calculated as follows:

$$RR = \text{risk groups with the applied protection} / \text{risk groups with inadequate protection}$$

For example, a 31.6% site to be infected and not applied for protection, and a 16.4% being infected although taken adequate protection. As we know ARR in protected landfill is 15.2. Another way to describe this situation is that the 68.4% of landfills remain uninfested though not protected, while 83.6% of landfills remain non-infested if they were adequately protected:

$$RR = 0,316 / 0,164 = 1.93$$

*This result can be explained by the sedentary:* The risk of infection is unprotected is 1.93 multiplied by the risk of infection in spite of adequate protection.

However, this is not the same as a percentage of risk-reduction provided adequate protection. Statistical test that provides information about reducing risk in relation to the fact that the protection is applied or not, is called **relative risk reduction** – RRR. RRR is calculated by the following formula:

$$RRR = AAR / \text{Baseline Risk}$$

Therefore, the RRR in our example (for the landfill on which the protection is applied):

$$RRR = 15.2\% / 31.6\% = 41.8\%$$

RRR expresses the extent to which protection reduces the risk of danger to the landfill, compared to the natural risk, or the risk of landfills that are not protected at all. It can be interpreted as follows: adequate protection will reduce risk in older landfills to 48.1%, compared to the risk to the same landfill in case the term does not use protection. On the determination of RRR which affects his interpretation seems more complicated than determining the ARR. How to increase the

baseline risk, so does the RRR, but much slower in comparison with the ARR (again, assuming that the risk of protected landfill approximately constant) (Table 6).

*Table 6. The effect of primary risk in a relatively reduced risk*

Baseline Risk	Treated Risk	ARR	RRR
48%	31%	17%	35.4%
55%	31%	24%	43.6%
65%	31%	34%	52.3%
75%	31%	44%	58.7%
85%	31%	54%	63.5%
95%	31%	64%	67.4%

It is clear that the low value of the initial risk, RRR is much higher than ARR, but at higher values of primary risk ARR approaching RRR. Due to the sensitivity of RRR to the baseline risk is important for the researcher to take into account both the statistical test (ARR and RRR) in order to estimate the reduction in risk to which you can apply to get some protection or early application of certain occupational groups landfills. It is also important to remember that every single landfill may or may not benefit from a particular intervention. These statistical tests provide assessment for groups of landfills, and not for each individual landfill. It should be remembered that the concept of “no significant difference” in the majority of statistical tests compared to the difference is 0, and it is generally measured variable means. OR at the situation is different. The term “no significant difference” in the statistical test means a value of 1 Therefore, when CI - Confidence Interval includes the value of 1, the researcher will immediately know that the odds are examined outcomes the same for both (or all) of the group of applied protection standard (and more sophisticated), even if it fails to examine statistical significance. Great importance ratio seems to lie in the fact that it is easy to calculate, very easy to interpret and provides conclusions that can bring IT decisions. Furthermore, sometimes in certain situations helps IT managers that can explain the odds of one outcome, and what else. If you know what their chances of achieving the desired result of protection, executives at medical waste management can more easily decide on the acceptance or rejection of costly care. Many managers want to participate



in making decisions about the safety and protection of resources around the landfill, but in order to effectively participate must obtain information on the likely results in an understandable way. [1]

OR is one of the categories of statistical tests that IT often used to make decisions about safety and protection. Other statistical tests are often carried out in order to make decisions about protecting the landfill include statistical tests of risk assessment such as statistical test absolute risk reduction (absolute risk reduction statistics) and test the relative risk reduction in relative risk reduction statistics). Values OR reveal information about the prospects for a particular outcome in relation to the prospects for the second outcome, and thus this test helps in making IT decisions. In the case of infection with type 1 risk (or odds) total destruction of the environment for the protection of new sophisticated methods of the relative risk due to the applied standard mrtoda protection. Statistical tests are estimates of relative risk (relative risk assessment statistics) are particularly suitable for setting up state of the system and making decisions on the protection of the same, and will talk more about them in one of the following articles.

## 6. Risk and Decision

1. Solving problems is only possible if the problem is defined. This process includes a decision on whether to intervene urgently. You should then define the alternatives and consequences that should not be missed. Before making decisions affecting the choice greatly. The decision to risk a large percentage of uncertainty [12].
2. It is necessary to know the authenticity of the data. Big problem is the treatment of small probability. The most complicated case is one where the probability of the situation, we know that it is very small. There are those cases where the probabilities based on the relative frequency can not assess because it is not available to the data from the past, or has no data - as it comes to a brand new technology. If there is no data, there is the possibility of modeling risk situations, for information extraction. Models can include just about human error.
3. In the analysis of risk situations and making them, should think about the problems of

unstable appraisal principles for decision-making, with which you can easily manipulate. Principles may change in time.

4. People's behavior is extremely contradictory. Sometimes sensitive and rational, while the second time in the same situation the decision irresponsible and irrational. Decision makers in a variety of ways they can have a monopoly over the decisions that are risky.
5. Evaluating the quality of decision-making under conditions of risk must take into account the way the treat unusual, extraordinary situations.

In making the decision (in our case, which give priority to medical landfill) is designed to select the best alternative, that is most acceptable to the decision maker. Choice of an alternative does not mean that it will be so absolutely accept the risk that goes with it. Selecting the best alternative is a very complex problem. Choice of an alternative depends on:

- The possible alternatives,
- As a result,
- The value
- The facts taken into consideration during the decision making,
- From the methods used.

The methodical problem solving allows to evaluate decisions before implementation phase (test), so the risk of errors is known in advance. In this way of solving the problem in the long run, can be calculated with a predetermined probability of error. For decision-makers, however, each proposal suggested by the consultants equally uncertain. In our case, the problem of risk can be broken down into the following parts [15]:

- *Risk Communication* in the request:
- problem source = who says?
- problem message = what he says?
- problem of channels = to say?
- problem accepting = says who?

The problem is related to the source communicator. The essence of the problem is the content of the message you want to say. Channel problem relates to how and in what way are reported. The problem is the acceptance testing of individuals or groups that are the focus of the message.

The most significant characteristics of the sources are: credibility, expertise, competence, credibility, objectivity, acceptability. To make the information become news related to risk, we need the following characteristics:

- Information should be fresh,
- Information should be related to something new, unusual or rare
- Information should clearly indicate who is positive and who is negative character in a given situation [8].

## Conclusion

This multidisciplinary approach ensures the involvement of all stakeholders in the establishment of a unified system of infectious medical waste, based on expert recommendations, legislation and financial resources of Bosnia and Herzegovina. The introduction of a unified system of medical waste management in the health sector in Bosnia and Herzegovina is one of the prerequisites for the regulation of medical waste management in general. Consensus within the working group composed of eminent professionals in the field, it is accepted that the use of the European Waste Catalogue, which defines the basic classification of medical waste, as well as views on segregation or separation, labeling and treatment of various categories of medical waste, for use in health care facilities in Bosnia and Herzegovina. An important area of work of professionals responsible for the handling and disposal of medical waste and the risk assessment and the provision of preventive measures to protect employees primarily in the health sector and health service users, as well as environmental protection.

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- Used standards:
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  2. IEC 61508-3 Functional safety of electrical/electronic/programmable electronic safety-related systems - Part 3: Software requirements
  3. IEC 61508-5 Functional safety of electrical/electronic/programmable electronic safety-related systems - Part 5: Examples of methods for the determination of safety integrity levels
  4. ISO 14971:2000 Medical devices - Application of risk management to medical devices

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# Service quality determinants that affect the service users' commitment to hospitals

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## Abstract

**Objective:** To research perceptions of consumers about service quality that have an effect on their commitment to the hospitals.

**Methodology:** The study was conducted in Turkey in December 2010. A questionnaire was used as the data collection tool. The Cronbach Alpha value and confirmatory factor analysis were used for testing the reliability and validity of the scale. Data were analyzed using descriptive statistical methods, the structural equation model, and the independent samples t test. The results were assessed at a significance level of 0.05.

**Results:** The results indicated that tangibles and the assurance dimensions of quality had an effect on the users' loyalty to hospitals; however, reliability, responsiveness, and empathy did not seem to affect the loyalty. Further, statistically significant differences were found between public and private hospitals in terms of reliability, responsiveness, and empathy. The quality of private hospitals was perceived to be higher than that of public hospitals in all three dimensions.

**Conclusions:** Assurance and reliability were found to be more important than tangibles, responsiveness, and empathy for users of health services. Further, private hospitals appeared better than public hospitals in the dimensions of reliability, responsiveness, and empathy.

**Key words:** Servperf, service quality, hospital, customer loyalty.

## Introduction

Health care is one of the fastest growing sectors in the service sector of Turkey. Its growth has been affected by competitive pressures, as well as emerging treatments and technologies. Thus, service quality has emerged as an important topic for health care providers and marketers. It has been proposed

that service quality could have a significant effect on patient satisfaction. Further, a positive relationship has been found to exist between satisfaction, and purchase intentions and customer loyalty. Service quality might also have practical implications for the physician/patient relationship [1].

Quality has been recognized as a strategic tool for attaining operational efficiency and improved business performance. This is true for both the goods and services sectors. However, the problem with the management of service quality is that quality is not easily identifiable and measurable owing to the inherent characteristics of services that make them different from goods [2]. When purchasing goods, the consumer has several tangible cues for judging quality such as style, hardness, color, label, feel, package, and fit. In contrast, when purchasing services, the consumer has fewer tangible cues such as the service provider's physical facilities, equipment, and personnel [3]. It is generally regarded that service quality is a multi-dimensional construct [4-7]. Further, services are intangible, heterogeneous (service quality can vary by customer, day, or producer), and production is inseparable from consumption. Thus, there is no objective measure for assessing the quality of services. As a result, a measurement of the consumers' perceptions of quality is considered as an appropriate approach for assessing the quality of service. Nevertheless, no quantitative yardstick is available as yet for gauging these perceptions [7].

There are two major measurement scales for the measurement of service quality: SERVQUAL and SERVPERF [4-7]. The main difference between these scales lies in the formulation adopted for their calculation, and more concretely, the utilization of expectations and the type of expectations that should be used [8]. SERVQUAL introduces service quality by comparing the perceptions of the service received with expectations, while SERVPERF maintains only the perceptions of service quality [8].

Parasuraman and colleagues stated that service quality is dependent on the relationship between customer expectations and customer perceptions. They developed SERVQUAL, which contains 22 pairs of items. Half of these items are intended to measure the consumers' expected level of service for a particular industry (expectations). The other 22 matching items are intended to measure consumer perceptions of the present level of service provided by a particular organization (perceptions). Thus, they stated that it is appropriate to calculate service quality by subtracting the expected from the perceived service. In this way, they made an attempt to achieve an overall measure of service quality by averaging the scores of all items [9].

The determinant of service quality is a gap that exists between the perception and the expectation of consumers. The SERVQUAL is differentiated from consumer satisfaction that defines the expectations/ perceptions "gap" as an enduring perception. It consists of five service dimensions. The dimensions are: (1) Tangibles-physical facilities, equipment, and appearance of personnel; (2) Reliability- ability to perform the promised service dependably and accurately, (3) Responsiveness-willingness to help customers and provide prompt service, (4) Assurance- knowledge and courtesy of employees and their ability to inspire trust and confidence, and (5) Empathy- caring, individualized attention the firm provides its customers [7].

SERVQUAL provides hospital administrators with a tool for the measurement of functional quality in their own organizations. Deficient scores on one or more SERVQUAL dimensions will normally signal the existence of a deeper underlying problem in the organization [10]. According to this, SERVQUAL can be used as a diagnostic or prescriptive tool. Periodic measures could be used for identifying problems within specific service processes. The importance of SERVQUAL, particularly as a diagnostic tool, is propelling researchers to refine the measure [11].

Nevertheless, SERVQUAL has been criticized in some studies. It has been suggested in some studies that SERVQUAL has unstable dimensions. Jiang and colleagues used four dimensions of SERVQUAL in their study [12], while Landrum and Prybutok used five dimensions [13]. Cook and Thompson demonstrated that SERVQUAL had

three responsive dimensions [14], rather than the five dimensions originally proposed by Parasuraman and colleagues [7].

It is important to mention Cronin and Taylor among the researchers who criticized the SERVQUAL scale [4]. Their research on the SERVQUAL scale left them unclear about the service satisfaction aspect. Thus, they removed the component of expectation and added performance on the SERVQUAL scale. They termed this new scale as the SERVPERF [2]. According to Cronin and Taylor, their unweighted performance-based SERVPERF scale was a better method for measuring service quality [4]. In their view, performance alone provides better predictive validity than SERVQUAL which is gap-based [4, 15], and numerous studies have presented that performance scores alone exhibit better reliability and validity than difference scores [13, 15-17].

### Methodology

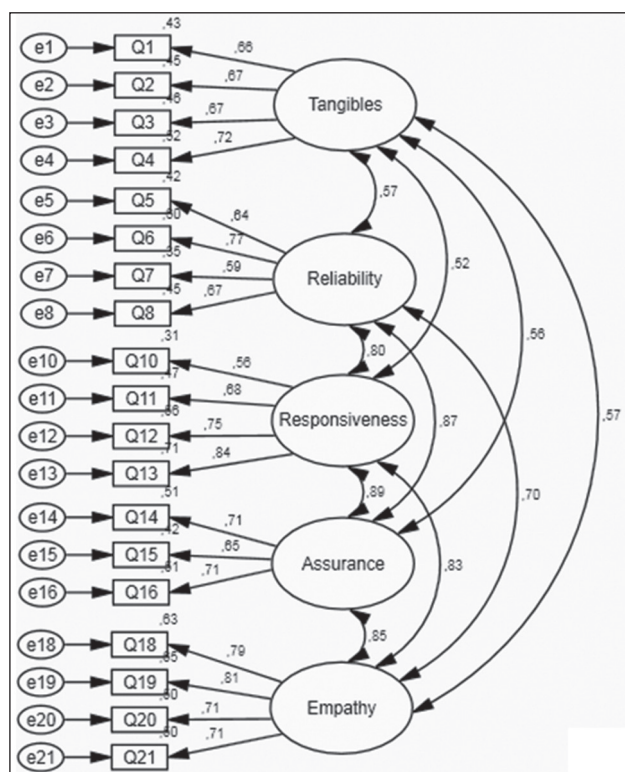
The present study was aimed at revealing the perceptions of consumers about service quality that affected their commitment to the hospital. A questionnaire was used as a tool for data collection in the study that consisted of two parts. The first part of the questionnaire consisted of the SERPERF scale that was developed by Cronin and Taylor [4], and the second part of the questionnaire consisted of the socio-demographical characteristics of participants. The data was collected in the year 2010 from November 15th to December 15th by face-to-face interviews with consumers.

The main mass of the study was comprised of healthcare service consumers who resided within the borders of Sakarya Metropolitan Municipality. The sampling of the study was selected by using the stratified random sampling method of the probability sampling methods. The significance of the sampling was calculated using the following formula  $n = [N * p * q * Z^2] / [(N-1) * t^2 + (p * q * Z^2)]$  [18]. The sampling was found as 384; however, 417 surveys were used in the study.

The alpha value method was used for testing the reliability of the scale. As a result of the analysis conducted, the Cronbach Alpha value of the scale was found as 0.919. These results indicate that the scale is highly reliable. In addition, con-



firmatory factor analysis was used for testing the validity of the scale (The confirmatory factor analysis is aimed at confirming the previously known factor elements.)([19].



CMIN=407.539, DF=139,  $p=0.000$ , CMIN/DF=2.932, RMR=0.095, GFI=0.905, AGFI=0.870, PGFI=0.662, NFI=0.891, RFI=0.866, IFI=0.925, TLI=0.907, CFI=0.925, RMSEA=0.068, AIC=509.539

Figure 1. Confirmatory Factor Analysis for SERVPERF Scale

The SERVPERF scale consisting of 22 items (4 for tangibles, 5 for reliability, 4 for responsiveness, 4 for assurance, and 5 for empathy) was analyzed for confirmatory factor analysis by using AMOS 18. Based on the results of the analysis, three items were removed from the scale as they had distorting effects. These items were: (1) accurate record keeping (in the dimension of assurance), (2) Adequate support from the hospital management so that employees could perform well (in the dimension of assurance), and (3) convenient operating hours (in the dimension of empathy). Subsequent to factor analysis, 19 items were used for measuring the quality of hospital services. As shown in Figure 1, the goodness of fit of scale was within the accepted levels [20]. In addition, very

high covariance relations were observed among the dimensions of tangibles, reliability, responsiveness, assurance, and empathy ( $p < 0.001$ ).

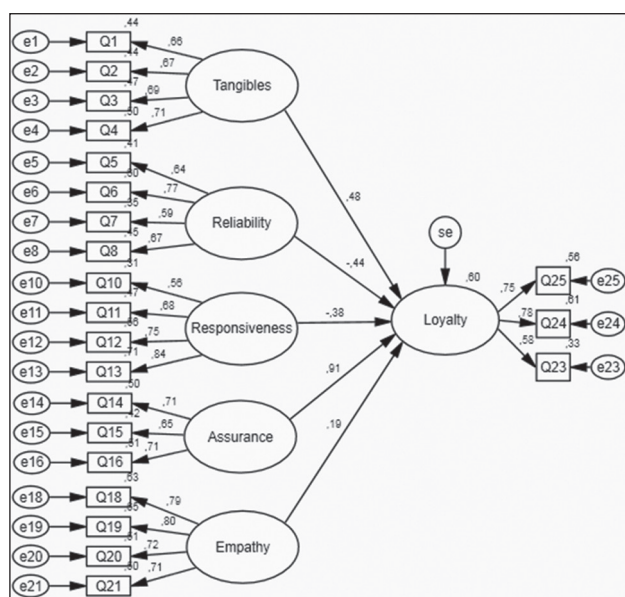
## Results

The descriptive characteristics of the study participants are summarized in Table 1. The sample consisted of public employees (8.2%), private sector employees (7.7%), housewives (27.8%), retirees (7%), artisans (12%), unemployed (7.9%), and students (9.4%). In addition, participants prefer more public hospitals (64.3%) than private hospitals (35.7%) to use of service.

Table 1. Socio-demographic characteristics of participants

Characteristics		n	%
Gender	Male	158	37.9
	Female	259	62.1
Marital status	Single or widowed	163	39.1
	Married	254	60.9
Age	≤25	102	24.5
	26-35	144	34.5
	≥36	171	41.0
Income (Monthly)	≤1000	213	51.1
	1001-2000	150	36.0
	≥2001	54	12.9
Education level	Primary Education	180	43.2
	High School	125	30.0
	Associate degree	56	13.4
	Undergraduate	46	11.0
	postgraduate	10	2.4
Occupation	Public employees	76	18.2
	Private Sector employees	74	17.7
	Housewife	116	27.8
	Retired	29	7.0
	Artisan	50	12.0
	Unemployed	33	7.9
	Student	39	9.4
Hospital Preference	Public	268	64.3
	Private	149	35.7

Prior to testing the structural model or the measurement model, the model was tested by fit measurement indexes to ensure that all causal relationships were sufficient and that the structural model was acceptable. As shown in Figure 2, the goodness of fit of scale was within the accepted levels [20].



CMIN=528.533, DF=191,  $p=0.000$ ,  
 CMIN/DF=2.767, RMR=0.092, GFI=0.894,  
 AGFI=0.860, PGFI=0.675, NFI=0.878,  
 RFI=0.853, IFI=0.919, TLI=0.901, CFI=0.918,  
 RMSEA=0.065, AIC=652.533

Figure 2. Results of structural equation model

It can be seen in Table 2 that customer loyalty was affected by tangibles ( $p < 0.01$ ) and assurance ( $p < 0.05$ ) dimensions of quality. In contrast, the consumer's loyalty was not affected by reliability, responsiveness, and empathy ( $p > 0.05$ ).

It was observed that the loyalty of the users of health services who received services from the hospital was very high to the hospital ( $6.05 \pm 0.928$ ). The dimension of assurance was taken maximal heed by service users ( $6.07 \pm 1.963$ ). This dimension was followed by reliability ( $6.04 \pm 0.922$ ), tangibles ( $5.89 \pm 1.313$ ), responsiveness ( $5.74 \pm 1.075$ ), and empathy ( $5.70 \pm 1.539$ ). According to the analysis on the basis of ownership of the hospitals, there was no statistically significant difference in the dimensions of tangibles and assurance among public and private hospitals ( $p > 0.05$ ). However, there were

statistically significant differences between public and private hospitals in the dimensions of reliability, responsiveness, and empathy ( $p < 0.05$ ). Further, the quality of private hospitals was perceived to be higher than public hospitals in all three dimensions.

## Discussion

In general, it is difficult to objectively measure service quality owing to the service characteristics of intangibility, heterogeneity, and inseparability [21]. Nonetheless, services are inherently relational and perceived relationships are often a central part of loyalty [22]. Thus, in this study, by using one of the generally accepted service quality scales the service quality perceptions of the hospitals were measured and the effect of the perceptions of service quality to loyalty was determined.

Loyalty is in the center of the perception of quality of service users. According to the results of this study, the loyalty of service users to their choice of hospitals was at high levels. This result can be seen as an indicator of the quality performance of hospitals.

On the whole, all dimensions of quality were found to be important to health service users; however, assurance and reliability were considered to be more important than the other dimensions. This result demonstrates for health service users the importance of the fineness, knowledge, confidence, and integrity of health employees (assurance), and the importance of the application skills of health employees that they were promised reliable and punctual service (reliability). Thus, it is recommended that health managers be more sensitive to these issues. In addition, private hospitals were found to be better than public hospitals in the dimensions of reliability, responsiveness, and empathy. As a result, managers of public hospitals must further work to make improvements in these issues.

Table 2. Regression weights

			Estimate	S.E.	C.R.	p
Tangibles	→	Loyalty	0.478	0.092	5.082	0.000
Reliability	→	Loyalty	-0.442	0.269	-1.779	0.075
Responsiveness	→	Loyalty	-0.375	0.151	-1.671	0.095
Assurance	→	Loyalty	0.909	0.403	1.984	0.047
Empathy	→	Loyalty	0.194	0.183	0.937	0.349

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# Expression of low molecular weight proteins in different age groups of the renal failure patients

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## Abstract

Renal failure is a global public health issue with a growing prevalence, poor outcomes, and high cost. High blood pressure, diabetes, poor socioeconomic status and ignorance are one of the major causes of renal failure worldwide. The morbid impact of failure is heightened by its role as a risk factor for cardiovascular diseases.

Study involves 45 confirmed pre-dialysis renal failure (RF) patients (experimental group) and 20 healthy subjects (control group). Serum protein profile of RF patients determined down regulation, up-regulation and expression of many proteins, when compared to the control group. It involved down regulation of serum albumin proteins, up regulation of 24 kDa Trypsinogen protein and appearance of 36 kDa glyceraldehydes 3-phosphate dehydrogenase (GAPDH) and 20 kDa trypsin inhibitor proteins. Statistical analysis by one way ANOVA during the whole study determined a significant change.

**Key words:** Renal failure, protein profile, hypoalbuminemia, proteinemia.

## Introduction

Kidneys play important role to filter the blood and separate the toxic excretions. The performance of kidneys gets affected under diseased condition and if the kidneys fail to function adequately leading to uremia the conditions is referred as renal failure (RF). The increased serum creatinine is referred as biochemical of the RF with an increased glomerular filtration rate (GFR). Globally, RF results in 82,000 deaths [1-4]. RF can be acute, chronic, or acute on chronic differentiated on the basis of serum creatinine trend along with anemia and the kidney size.

Acute renal failure (ARF) is exemplify by a quick progressive loss of function due to damage to the kidneys which leads to retention of nitroge-

nous and non-nitrogenous wastes. The condition if prevails may lead to permanent loss of function otherwise ARF can be reversed. [2-5]. ARF can be pre-renal, intra-renal or post-renal acute renal failure. Pre-renal ARF is caused by decreased blood flow to the kidneys due to hypovolemia, dehydration and fluid loss or excessive use of diuretics, hepato-renal syndrome or nephrotic syndrome. Intra-renal ARF is due to injury to the glomeruli or tubules caused by drugs, heavy metals or viral infection. Post-renal ARF occurs due to obstruction in the urinary tract or at the bladder level due to stones, tumors or anatomic obstruction due to benign prostatic hypertrophy [2,3,6].

An irreversible loss of large numbers of functioning nephrons leads to the chronic renal failure (CRF). The problem persists but remains unnoticeable until 70-75% of the nephrons get damaged. 11% of the adults suffer from the chronic kidney disease [1-3,7].

CRF is naturally a progressive disease, even if the inciting cause is removed due to the fact that as the disease progresses the number of healthy working nephrons decrease and the glomerular filtration rate increases leading to intraglomerular hypertension and hyperfiltration which eventually develops the glomeruli sclerosis with subsequent death, followed by atrophy of the tubules and interstitial fibrosis [2,6,8]. A combination of CRF and ARF leads to the development of acute-on-chronic renal failure (AoCRF). AoCRF may be reversible and in the absence of preliminary history is, difficult to discriminate from chronic renal failure [9,10].

Electrophoresis is a technique for separating molecules in a mixture under the influence of an applied electric field. In SDS-PAGE, the detergent sodium dodecyl sulphate (SDS) is used to denature proteins [11]. The negative charge that the SDS imparts masks the protein's intrinsic charge. SDS-

PAGE therefore separates proteins by gel filtration effect that is according to molecular mass [12-14]. The current study was designed to study the serum protein profile of renal patients of different age groups.

### Materials and methods

Blood samples of pre-treatment pre-dialysis renal failure (RF) patients were collected from National Institute of Kidney Diseases Sheikh Zayad Hospital Lahore while blood samples of control (healthy persons) were collected from Punjab University New Campus Lahore. The study involves the electrophoresis analysis of the protein profile of the renal failure subjects prior to dialysis, a total of 45 confirmed subjects (divided into four age groups) with renal failure and control samples of 19 healthy subjects were studied for comparison.

The subjects were sampled for blood with sterilized disposable syringes (Becton Dickinson, Private Ltd.) and 6 ml of blood was transferred to vacutainers (without any clotting factor) and were left at room temperature for further processing. About one hour after the serum was isolated from clotted blood by centrifugation at 4000 rpm for 10 minutes. The separated serum samples were collected in labeled eppendorfs and were stored at  $-20^{\circ}\text{C}$ , till used for electrophoresis. Polyacrylamide gel was prepared by using method of Laemmli [15]. Low molecular weight proteins were resolved on 12% gel. All the chemicals and low molecular weight markers used in SDS-PAGE were provided by SIGMA® chemicals. The quantification for electrophoretically separated protein fractions was carried out by Image J Gel Documentation System that provided the data based on percentage density of each fraction. The density of bands in a specific well was used to generate the densitometric graph to infer increase or decrease and appearance or disappearance of particular protein fractions as well as new protein fraction in comparison to control (healthy) subjects. Gene Genius Bio-imaging Gel Documentation System was used to determine the mol. wt of the protein fractions. "One-way ANOVA with Dunnett's post test was performed using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego California USA, [www.graphpad.com](http://www.graphpad.com)".

### Results

Serum of control subjects and pre-dialysis renal failure subjects was studied by SDS-PAGE which resolved the serum in protein fractions. Pre-dialysis renal failure patients were divided in four age groups of 1-20 years, 21-40 years, 41-60 years and 61-80+ years. The low molecular weight Sigma® protein marker was used as standard which represented seven protein fractions of 66-14.2 kDa. The gels were analyzed to find out the percentage densities of the protein bands in samples from different patients. For each protein band the molecular weight was determined by Syngene Gene Genius gel documentation system. Percentage densities were determined by performing the densitometric analysis using Image J gel documentation software which gave the peaks and percentage densities of the resolved protein bands. The mean value of percentage density for each band was determined and used to make a graph. Inter-group comparison of specific bands with control or group 1 bands was performed.

Densitometric analysis of control samples revealed seven peaks representing their respective protein fractions while densitometric analysis of RF patients represented more than seven peaks representing their respective molecular weight protein bands (Figure 1). The protein profile of RF patients revealed four protein fractions (of molecular weight 105, 50, 24 and 17 kDa) which coincide with those of control samples. A decrease was observed in the protein bands of molecular weight 105, 50 and 24 kDa of RF patients when compared to their respective control bands. This decrease was statistically significant when analyzed by one-way ANOVA ( $P < 0.00001$ ). A highly significant statistical increase ( $P < 0.0001$ ) was observed by one-way ANOVA in the 17 kDa protein fraction in RF patients when compared to the 17 kDa band of control group (figure 4-E).

In the RF patients statistical analysis for newly appearing protein fractions of high molecular weight 168, 154 and 123 kDa determined a highly significant change ( $P < 0.0001$ ) in the mean values of percentage densities of age groups 21-40 yrs, 41-60 yrs and 61-80+ yrs when analyzed by one-way ANOVA and student's t-test (Figure 2A-2C).

In RF patients One-way ANOVA analysis of the protein fractions of molecular weight 87, 83 and 73 kDa which were absent in control subjects show significant inter-group increase when compared with youngest age group ( $P<0.005$ ; Figure 2E-F, 3A).

An inter-group comparison determined a statistically significant decrease in the protein fractions of molecular weight 66, 57, 54, 40, 36 and 24 kDa while significant increase was observed in the protein bands of molecular weight 24, 20 and 13 kDa when analyzed by one-way ANOVA ( $P<0.05$ ; Figure 3-4).

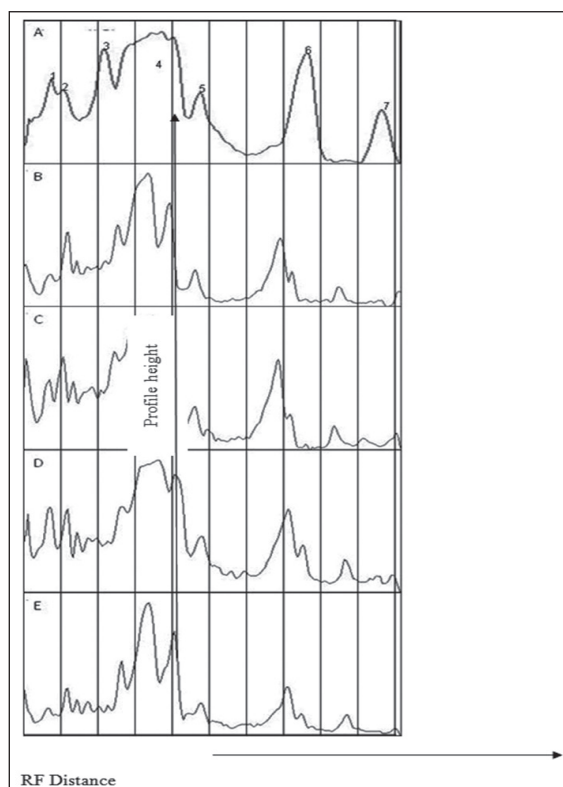


Figure 1. The densitometric analysis of the serum proteins control (A), age group 1-20 yrs (B), 21-40 yrs (C), 41-60 yrs (D), 41-80+ yrs (E). The sera from control subjects have shown 7 peaks. 1-7 representing the densities of proteins of molecular weight 105, 96, 75, 60, 50, 24 and 17kDa, respectively. The subsequent densitometry from the experimental group has shown considerable variations in the protein density with the varied densities corresponding to differences in the conc. of different proteins in the serum.

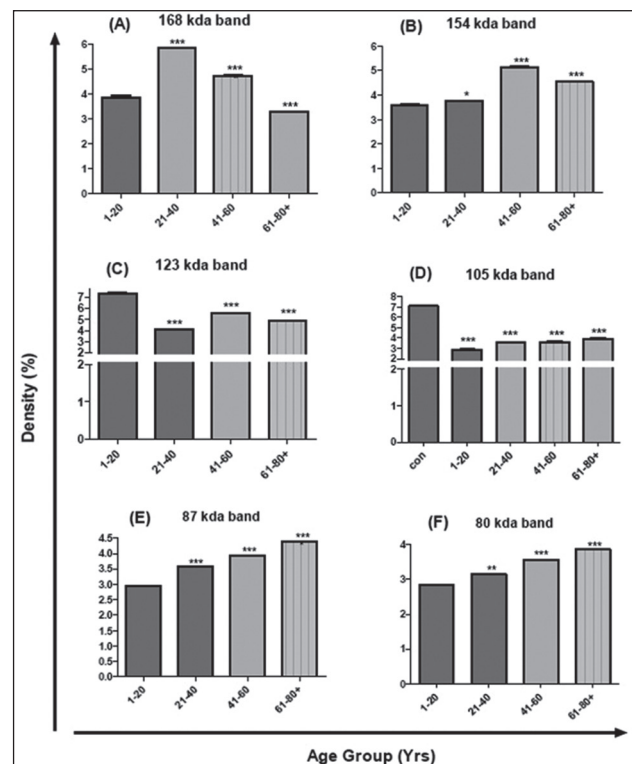


Figure 2. Protein profile of different age groups of renal failure patients. Statistical analysis by one-way ANOVA of percentage densities of protein bands of molecular weight 168 (A), 154 (B), 123 (C), 105 (D), 87 (E) and 80 kDa (F) represent significant intergroup variations. Results represent mean value  $\pm$  S.E.M. (\* $P<0.05$ , \*\* $P<0.01$ , \*\*\* $P<0.001$ ).



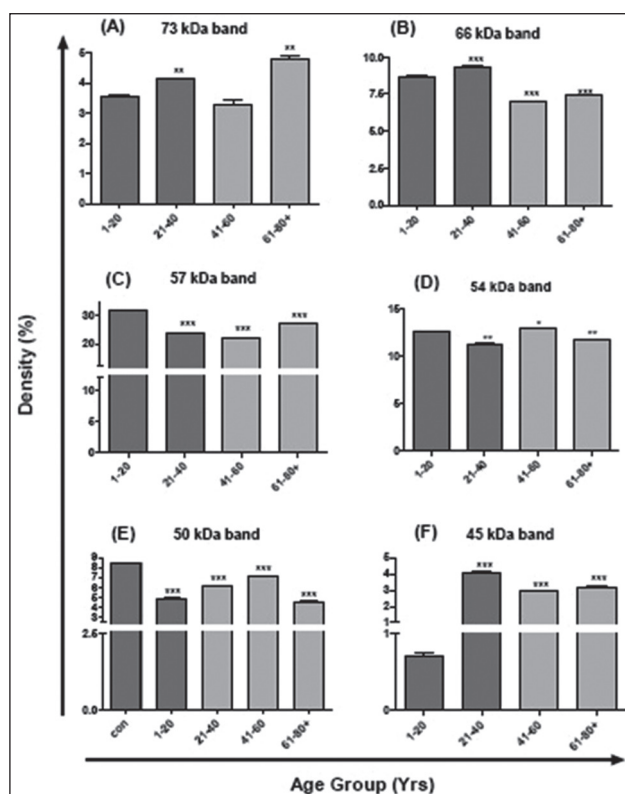


Figure 3. Intergroup comparison of protein profile of renal failure patients. Statistical analysis by one-way Anova of percentage densities of protein bands of molecular weight 73 (A), 66 (B), 57 (C), 54 (D), 50 (E) and 45 kDa (F) represents significant intergroup differences. Results represent mean value  $\pm$  S.E.M. (\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ ).

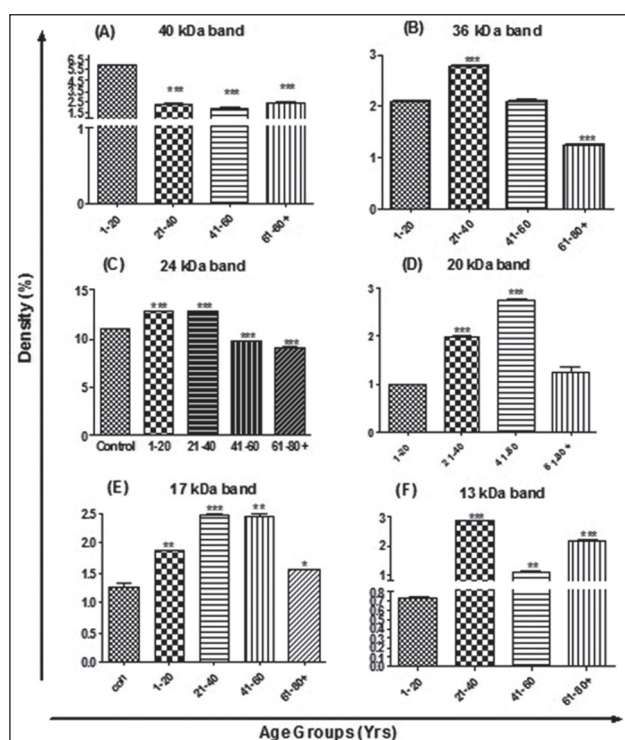


Figure 4. Intergroup comparison of protein profile of renal failure patients. Statistical analysis by one-way Anova of percentage densities of protein bands of molecular weight 40 kDa (A), 36 kDa (B), 24 kDa (C), 20 kDa (D), 17 kDa (E) and 13 kDa (F) represents significant intergroup differences. Results represent mean value  $\pm$  S.E.M. (\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ ).

## Discussion

Limited information is available regarding the serum protein profile in the of pre-dialysis renal failure patients. Present study was carried out on pre-dialysis renal failure patients with main focus on serum protein profile. Renal failure was determined in terms of serum creatinine.

Size fractionation of the proteins under the influence of electric field is a reliable method to study the molecules of different molecular weights separated as per their charge to mass ratio. SDS-PAGE is an excellent single test for investigating proteinuria. It provides much useful information on the underlying renal problem. Yet the literature hardly reports a SDS-PAGE result in the management of renal patients. Serum proteins changes notably under inflammatory or diseased condition [16,17].

The decrease in the percentage densities of several protein fractions (when compared with control or inter-group) indicates the down regulation of the expression of their respective proteins while the significant increase show the up-regulation of their respective proteins. One of the down regulated proteins is the 66kDa albumin protein. Albumin has countless important physiologic effects that are essential for normal health. In the present study, a significant decline was observed in serum albumin levels of RF patients. This hypoalbuminemia has been reported previously in patients and experimental animals with chronic renal failure [18-20]. Hypoalbuminemia in renal failure is possibly due to one of the following reasons or their combined effects. These include inflammation, malnutrition, decreased albumin synthesis and increased degradation of albumin. Hypoalbuminemia is associated with mortality due to cardiovascular events in renal failure patients [21-23]. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is a 36 kDa serum protein found in RF patients. This is a major glycolytic enzyme but

its non-metabolic functions reported by Hara *et al* 2005 include transcriptional activation and apoptosis initiation. In RBC's of CRF patients an increase is observed in the activity of GAPDH along with shortened life span of RBCs in CRF. The apoptotic activity of GAPDH thus may be the culprit behind the abridged life span of RBCs in CRF [24, 25].

Altered concentration of the trypsinogen and trypsin inhibitory proteins were reported in the serum of RF patients. Kidney is the major site for plasma clearance of pancreatic trypsinogen and Trypsin Inhibitor proteins. Elevated levels of serum trypsinogen and Trypsin Inhibitor protein indicate either extrapancreatic secretion of these enzymes or reduced renal elimination [22, 26, 27].

## Conclusions

Taken together these result we can conclude that the renal failure imparts age specific impacts on the serum protein profile. Further the results suggest that detailed transcriptional and translational studies should be carried out for further investigation of pre-dialysis renal failure. For this purpose an animal model can be developed which mimics the physiological and pathological conditions of renal failure. This animal model can be used to study the regulation of the gene expression at transcriptional and translational level.

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# Environmental protection and sustainable development

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## Abstract

One of the basic concepts of economics of natural resources and the environment is the concept of sustainability, or sustainable development. Despite the different interpretations that can be found in the literature, this concept now lies in a central position in the consideration of longevity and prosperity of mankind. Sustainability or sustainable development that occurs as an essential prerequisite, as well as the ultimate goal of efficient organization of numerous human activities on Earth. The notion of sustainability is not new. Its roots can be found in parts of classical economic science in the early attempts to answer the question about the prospects of development of human society.

It is typical for human species to understand the mechanisms that lead to the maintenance of it. Human understanding of the fragility and uncertainty of the environment, usually is a consequence of disasters that reveal the sensitivity of the elements that are considered immutable and eternal. Human distrust of everything that surrounds us and causes daily life, fear of unhealthy food, impure water, impure air, fear of contagion, etching by agents that have wormed their way into the environment, is greater.

Sustainable development strategies attempt to balance the imperatives of economic growth with the limits of planetary resources and capacity to absorb pollution. Modification of the global goals of economic growth will be essential for the maintenance and protection of the environment in the twenty-first century.

**Key words:** Sustainable development, environment, humanity, economic growth, environmental protection.

## Introduction

Contemporary society has been marked as critical for many years, and it seems that even in the

future that out of the crisis is not visible. It is spoken about ecological crisis or environmental crisis, in which the modern society is, or the crisis is in sight.

The idea that industrial systems should break under to a kind of control of the environment was not an integral part of the theory and practice of economic development in the twentieth century. In the twenty-first century, it became clear that the issues of environment and development cannot be separated. That is how the concept of sustainable development appears, which presents the development that satisfies the needs of the present time and allow to future generations to satisfy their own needs. Many researchers are trying to prove that the economic activity of humanity is the major anthropogenic factor of the current environmental disturbances on Earth. From the middle of the nineteenth century, anthropogenic influences on the environment are becoming increasingly important and still dominate.<sup>1</sup>

All countries strive for economic development but economic development politics haven't paid much attention to the environment. In many countries the concept of environment is still new, as the U.S.A established its Agency for Environmental Protection in 1970. Developed countries are concerned that a comprehensive production growth which is expected in developing countries "swallow" profits of efficiency and pollution control, unless the developing countries, which is necessary, to modify their economic goals. These different views don't have to sluceway to a deadlock because there are many opportunities for common environmental improvement, but the proportions of problems are discouraged.

## *Economics of sustainable development and environmental protection*

Environmental protection is not just protection of human life and health, it is also the preservation

of plant vegetation and wild life. The environment is a group of natural and created values whose complex interrelationships make the environment, in fact, space and living conditions. Environmental protection is a set of different actions and measures that prevent environmental degradation in order to maintain biological balance.

In the twenty-first century, it became clear that the issue of environment and development can't be separated, so the concept of sustainable development appeared. The World Commission for Environment and Development considered the issue of the conflict between environment and development. Using of modern technology leads to a general progress of society but that technology must be accompanied by appropriate measures of prevention, in fact, eliminating potentially harmful consequences. Every country, despite the lack of funds, has an interest to realize the public control over the relation between, on the one hand economic activities, and the second hand the environment.<sup>2</sup>

Environmental objectives are the protection of health and life of people, the quality of ecosystems, protection of flora and fauna and cultural heritage created by the man, preserving the balance and economic stability of nature, rational and appropriate use of natural resources.

The implications of the creation of sustainable development are different for developed countries and developing countries. Currently developed countries usually have large fund of capital and extensive infrastructure including thermals, highways, factories and suburban business and housing construction, dams and many other elements that are essential to modern economic production. It is the advantage and disadvantage when it is tried to achieve environmental sustainability. On the one hand, higher economic output and advanced technology make the establishment of environmental protection easier and affordable. On the other hand, developed countries with large existing capital funds, which use resources and create waste and pollution may be faced with technological synchronization, such as dependence on fossil fuels and technologies that are associated with them.

Developing countries have different problems in achieving sustainability, starting from a much lower income levels. Their main social and economic objective is to increase production. Deve-

loping countries also tend to have significant population growth. The combination of rising populations and economic growth creates considerable pressure to increase the use of resources and increase the production of waste and pollution.

Environmental policy is not limited to the control of pollution at the local level, it also has a general global character which is usually quite difficult to control. The global environmental crisis is becoming more and more prominent, which requires application of appropriate tools that operate within the market. Although pollution has become a global world problem, in its resolution primary responsibility is on highly developed industrial countries. Most economists and environmentalists believe that measures of environmental policy should be based on the principles of cost - benefit analysis.<sup>3</sup> Cost - benefit analysis means putting the costs which are caused by a measure on one side, and on the other economic benefits, particularly in increasing income which that measures products. Environmental policy measures except contribution for the protection and preservation of the environment should contribute to increasing income. Economists would like that appropriate measures of environmental policy contain economic rationality within them. Some of them the cost - benefit principle hoists to the level of necessary precondition for the adoption of appropriate measures. However, this calculation of each measure of environmental policy is difficult to implement even in the most developed countries which have developed statistical and methodological infrastructure. Therefore, it is not reasonable to expect that developing countries and countries in transition are able to do something what the developed countries are not able to do. How much developed countries will be credible to assist developing countries and countries in transition, to find the way of development favorable to the environment, will depend on their willingness to take effective measures to reduce their own environmental impacts.

Environmental sustainability is associated with social sustainability. Existing institutions of all types, including corporations, local and national governments and transnational organizations must adopt policies for sustainable development if they do not want to worsen the problems that instigated the development of the concept. Democratic

governance, participation and basic needs are an essential part of a new approach to development.<sup>4</sup>

### ***The rights of future generations to the healthy environment***

The significant growth of regulations in the field of environmental law has led in the past ten years the discussion about the real objectives of environmental policy of the European Union. Neglected environment leads to long-term problems that can undermine the economic goals. It is also clear that the environmental and social issues are associated. The question is whether humanity has a duty to preserve natural resources for future generations and to what extent it should be done?

The opinions of many scientists on this issue are divided. A group of scientists consider reasonable and justified demands to preserve part of the natural resources so that future generations will use their own right to use the limited natural resources. Others believe that this view is wrong, and cite three reasons:

- The first reason, in their opinion, is that the generation that does not exist cannot have any right. They consider it absurd notion that as people who exist only in our imagination, and that's very possible that they will never exist, can be bearers of any rights.
- As another reason they cite that for the future generations should sacrifice the present civilization. As an example it can be specified the use of oil. If we consider that each generation has an equal right to the oil reserves, so we would have to limit supplies of oil for the right of any future man to a small amount of oil.
- The third argument they cite refers to the opinion that we can't claim that someone has a certain right if we do not know that someone wants to use the same right. They assume that the future people may not be genetically the same as we, that they will not have the same desires, needs and requirements as well as the present generation. There is the possibility that future science will find a replacement for some or most of the natural resources and energy sources which we use nowadays.

Although the above arguments with reason attract the attention it seems wrong that the present generations should not worry about the preservation of natural resources, at least for several generations. In the opinion of John Rawls, the principle of justice requires us to surrender the world to our immediate successors not in worse condition than we inherited it from our ancestors.<sup>5</sup> From the ethical point of view it is the right thinking that at least our children and grandchildren have similar life chances and potentials as we have them. Every generation should aim to maximize the beneficial effects and minimize the negative effects of their activities.

An important problem is the fact that the natural resources are now used disproportionately. We can rightly say that environmental pollution is not only the problem of protecting the quality of the environment, but also the question of a healthy society, and the question of value based on today's civilization, which should be devoted by everyone on this planet, especially by highly developed countries. It was proposed many years ago that the emission permits specifying to concentrations of harmful substances and traded on secondary markets, so as to firms that were able to obtain to sell the unused portion to other firms. However, only recently have been created normative terms of trade with carbon credits.

Politics that would be more focused on decentralization, privatization, flexibility, market solutions of the environmental policy of the European Union, the state, and the citizens can only obtain with this. Because of that it is more and more worked on the expansion of international cooperation. The aim is to provide a sustainable development and to preserve the quality of the environment at a level that is necessary for the survival of present and all future generations on the Planet.<sup>6</sup>

Many analysts believe that this is possible only if the scientists and specialists from all world are including in solving accumulated problems. For such activities is necessary to establish especially funds. It was focused on the tenth special session of Global Ministerial Forum under the program of the United Nations for the Environment, which was held in Monaco in February 2008., called Mobilizing Finance for the Climate Action.



### ***Politics for Sustainable Development***

The primary objective of EU politics is to prevent total damage to protected properties in the environment through the application of preventive measures and activities. The precautionary principle was included in Article 174 of the Contract from Rome. This means that even if there is a slightest doubt that there is some risk that the European Union should consider options to prevent the occurrence of adverse effects. The whole planning and decision-making processes that affect the environment, for example, construction of a highway or power plant etc. must consider the impact on the natural habitat, in order to avoid future corrective measures.

However, in the field of environmental protection, individual activity is not always appropriate. The rivers often flow through several countries, animals crossing the border, and the wind carrying many of the harmful substances from one country to another, because of that it's necessary for the engagement of the supranational institutions of the European Union in many cases to react. In addition to regional, there is a global issue, such as the rapid reduction of non-renewable energy, drastic price rises and food shortages, climate change, reducing fish stocks in the seas and oceans, rapidly reducing potable water reserves, biological extinction of whole species, as well as many other problems, which represent the challenges facing humanity as a whole, the results of which are now, in many ways, felt in almost all parts of the world.

The goals of sustainable development can be seen in terms of weak and strong sustainability. In general, advocates of strong sustainability argue that natural systems should remain intact whenever it is possible. They identify critical natural capital such as the sources of water as a resource that should be preserved in all circumstances. According to this view, for example maintaining natural soil fertility is essential even if it is possible to compensate for the degraded soil with additional fertilization. According to the more moderate approach of weak sustainability, a certain degradation or loss of natural capital are acceptable if the loss is compensated by the accumulation of produced capital. Each of these concepts of sustainability and especially the strong version implies that there are limits for economic growth. Economic activity which is largely

based on natural resources, raw materials and fossil fuels can't grow indefinitely. Since the planetary ecosystem has a certain limit, a limit must be applied to the macro scale, the overall level of resource consumption and output selection.

In the limits of the growth prospects, national and global economic systems must follow what is called a logistic curve pattern in which economic activity is approaching a maximum, at least in terms of resource consumption.<sup>7</sup> Some economists observe ecological development as contradictory term. They point out that no system can grow indefinitely. However, some types of economic growth are the essential. There is a large number of people in the world who can't satisfy their basic needs and require more food, better accommodation and other needs. In its report, the National Research Council of the United States calls for the transition to sustainability in the twenty-first century, which means stabilizing population, reducing hunger and poverty, and maintenance of living resources that support life on the planet.

### ***Instruments of environmental protection***

The significant growth of regulations in the field of environmental law has led in the past decade to discussions about the real objectives of environmental politics. These differences are not purely theoretical, as it reflects problems in economic activities and the geographical position of certain countries. -For example, Britain has the advantage that air currents related air pollution away from its territory, while the surrounding seas can receive significant amounts of waste water from many waste contents. The Netherlands and Germany do not have these benefits, so their representatives tend to approach that is based on the potential harm, while other countries prefer to speak of the quality of the environment, which should be achieved. It is consider in advance that some level of contamination must exist as a result of economic and other activities, which should be the ecological price of development. Some economic ecologists have little sensitivity to such theories, such as for its sequel, which says that is into the Environmental Protection rationally invest only until such moment when the marginal benefit and marginal cost of the investment are equalized. Investment that would still increased the marginal cost with marginal benefits collapse would have to

be justified by economic standards. From an economic standpoint it is certainly true, but the problem is that environmental preferences are not established, only in economic textbooks. Values have a strong impact, which is affected by interests, traditions, esthetics and somewhat vague concept of quality of life, and all of them have different importance to different individuals.

Any economic or legal instrument for the protection of the environment has its advantages and disadvantages, making them more or less suitable for the using depending on the specific situation and circumstances that an individual instrument or any combination of instruments should be used. The choice of economic instruments depends on the priority objective to be achieved, for example, if there is a ban on river pollution to a certain level, then its level of contamination is known, and if applicable fines, the level of pollution will be directly dependent on the amount of penalties on one side, and on the other side on the cost of protection. If the level is higher than the penalty amount of the costs of protection, it is expected that economic agents behave rationally and decide to provide adequate level of protection of the environment.<sup>8</sup> In the event that the cost of punishment is lower than the cost of preserving the environment, through the means of protection or expensive materials and procedures, economic agents are likely to determine for paying a fine. On the other side, the penalty will mean revenue for the state budget, which can be used for other purposes, and the environment will be polluted. Specific environmental problems are best solved by a combination of economic and other instruments. Economic instruments applied in isolation will not provide the expected optimum results. Will it be successful in the use of various instruments it will depend on the particular combination of some politics. Economic and legal instruments and other measures for ensure funding and encourage investment in environmentally behavior can be classified into four groups:

- Measures that are market cost-effective directly,
- Measures that are market cost-effective indirectly,
- Measures that are cost-effective in the long run, but for now they can't be valued on the market and

- Measures that will never be market profitable, but they are introduced to the protection of the environment for the state and para government institutions.

Good environmental policies are required to satisfy the condition of PPP, which states that the polluter should bear the cost of implementation and application of environmental standards. Only to the extent that is the case, the polluter has a motive to seek a rational solution. In the moment of introduction environmental regulations, companies must increase the costs of business, and everything what is more expensive is harder to change.

Decline in business activity and lower demand have had a lower impact on employment and less use of other resources. Less employment can be a powerful factor in lowering of environmental standards and for the individual is more important personal employment than cleanliness of the environment, and for the politicians, too.

Nowadays, after decades of promoting environmental politics, it is bad if company do not show environmental awareness, because consumers with an ecological conscience can turn back to their products. Even highly successful large companies which are on the world markets, can come into considerable difficulties if they ignore the environmental standards and cause greater environmental incident.

There are still many areas in which environmental politics could be significantly improved without significantly higher costs. One thing is modest reliance on privatization to solve environmental problems. There, where the property rights can be privatized and where transaction costs are low, it's not necessary for state action and the environment can be achieved through market mechanisms. The rule is that a market solution is more applicable if the problems are more local. For the forms of pollution that pass over the borders of global pollution, state intervention is needed.

## Conclusion

The essence of the concept of sustainable development is an interaction of the environment and mutual complementarity and coherence of development politics and political environment, which

respect the laws of ecological systems. The concept of sustainable development is focused on the conservation of natural ecosystems and the environment, as well as the rational use of natural resources. It can be concluded that the characteristic three basic principles of sustainable development are based on ecological sustainability, socio-cultural sustainability and economic viability.

Sustainable development policy requires from each individuals enough responsibility to recognize that his interests are inextricably linked to the interests of the community. Therefore, the idea of sustainable development and defend the environment depends on the efficient operation of the citizens and modernization of democracy. Sustainable development is defined as development that satisfies present needs without compromising the basis for satisfying the future needs. Needs of the population that is growing must be satisfied, not to increase the demand for resources and creating pollution that exceed the carrying capacity of the ecosystem to support it at all.

For developed countries, this implies a reduction of consumption growth and adoption of technologies that are more favorable for environment. Developing countries, for which consumption growth is necessary, can avoid the production methods that impose a high demand for resources and the impact on the environment.

Ecological problems of modern man are large and must be addressed at the global level. In fact, humanity has to engage all the cognitive resources of our civilization, to begin a global struggle against the consequences which were caused by mankind.

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# Anesthesia for endovascular repair toracic and abdominalis aortic aneurysm (our experience)

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## Abstract

**Introduction:** Endovascular surgery for repair of the aorta is relatively new alternative to the conventional treatment. TEVAR (thoracic endovascular aneurysm repair) and EVAR (endovascular aneurysm repair) procedures are much less invasive procedure. Endovascular aneurysm repair can be done using different anesthetic techniques. In our hospital, anesthetic plan includes radial arterial line in right hand (during TEVAR procedures stent graft can closure left subclavia arteria and monitoring of blood pressure will disappear), CVP line, a large bore venous access (for eventual blood transfusions and the fast administration of fluids) and urin bladder catheterization. We use general anesthesia: introduction are performed with Fentanil, Hypnomidat and after Pavulon patients are intubated. Maintenance of anesthesia are performed with Fentanil, Sevofluran and continuos infusion of Propofol.

**Methods and patients:** All procedures were performed with general anesthesia in hybrid operating room by a team vascular surgerons and interventional radiologist. The whole procedure is finished from 2 to 3 hours. The tasks of anesthesiologist during this procedure are maintain periods of hypotension and bradycardia (IABP are necessary around 60 mmHg) during placement of the stent. Also, is maintain good intra and postoperative hydration to prevent postoperative renal damage caused by the liberal use of contrast to assist placement and deployment of the graft. Anticoagulation should be monitored periodically to maintain the ACT around 250 seconds. At the end of surgery, protamin sulfat is used to reverse the effects of heparin. Transeophageal echocardiogram is used perioperative to guide positioning of the stent.

During a six month period, in The Heart Center KCUS, 15 patients underwent endovascular surgery for repair of the aorta: 8 TEVAR and 7 EVAR procedures.

Patients (7 male and one female) for TEVAR procedures had a men age of 50 years (age range 44-56 years), patients for EVAR (7 male) procedures had a men age of 74,28 years (age range 70-79 years).

**Results:** A total of 15 patients had a successful implantation of the device. None of the patients died within 30 days. Stay in intensive care was averaged one day and hospital stay for all patients were averaged 4 days.

In postoperative period for patients with TEVAR procedures the left subclavian artery was covered in 5 patients: one patient had transient imparment circulation in left hand (coldness, whitening and weakness). Closing of left subclavian artery during and after the TEVAR procedure in patient who had AV fistula for dialysis on left hand did not cause any problem in fistula pattency, and he still has good dialysis. There was one patient with transient signs of subclavian steal syndrome and mild neurological dysfunction in form of headache. For patients with EVAR procedure only one patient had transient neurological dysfunction of right leg which was probably due to mild and transient form of spinal cord ischaemia.

**Conclusion:** The anesthesiologist has to understand this procedure and complications so they can provide adequate anesthesia in its different phases.

**Key words:** Endovascular aneurysm repair, Thoracic aneurysm, Abdominal aneurysm

## Introduction

Endovascular surgery for repair of the aorta is relatively new alternative to the conventional treatment. TEVAR (thoracic endovascular aneurysm repair) and EVAR (endovascular aneurysm repair) procedures are much less invasive procedure. Also, less hemodynamic and metabolic stress, reduced blood loss and early discharge from the hospital are the main advantages than conventi-

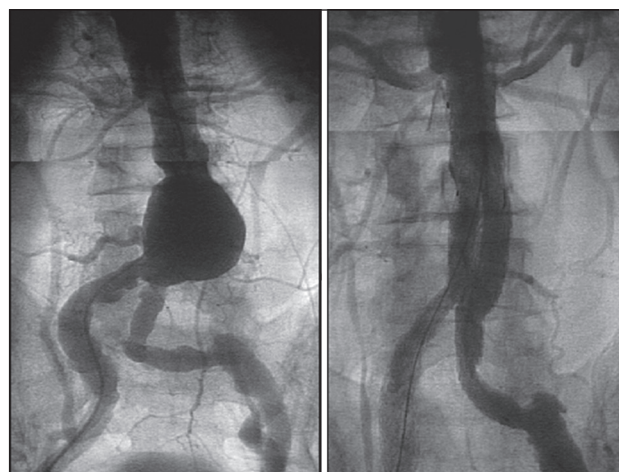
onal vascular reconstruction. This procedure can be performed using general endotracheal anesthesia, local anesthetic infiltrated at the incision site or regional anaesthesia with sedation. Choice of anesthetic technique may be dependent upon a patient's co-existing diseases and skills of surgeon team. In our hospital, anesthetic plan includes radial arterial line in right hand (during TEVAR procedures stent graft can closure left subclavia arteria and monitoring of blood pressure wil disappear), CVP line, a large bore venous access (for eventual blood transfusions and the fast administration of fluids) and urin bladder catheterization. We use general anesthesia: introduction are performed with Fentanyl, Hypnomidat and after Pavulon patients are intubated. Maintance of anesthesia are performed with Fentanyl, Sevofluran and continuos infusion of Propofol.

### Methods and patients

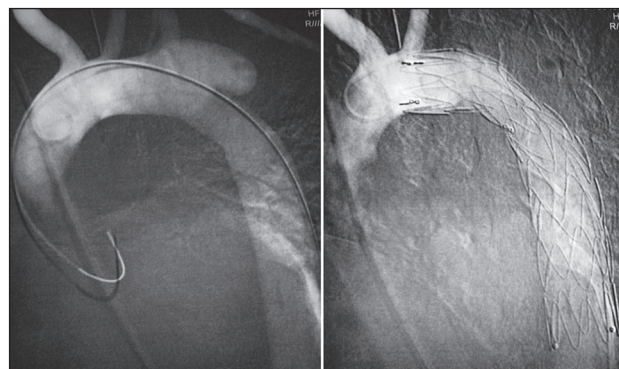
All procedures were performed with general anesthesia in hybrid operating room by a team vascular surgeons and interventional radiologist.

The whole procedure is finished from 2 to 3 hours. The patient is positioned supine and after femoral arteries have been exposed, Heparin is administred (5000IU). Angiography is then performed to confirm the anatomy of aneurism. After positiong of the endoluminal guide, the large endovascular graft delivery sistem is introduced via an arterotomy of the femoral artery and advanced under fluoroscopic guidance to the diseased aortic segment. When the stent graft is deployed within the aorta angiography is then performed again to confirm that there is no leakage of blood into the aneurism sac. The tasks of anesthesiologist during this procedure are maintain periods of hypotension and bradycardia (IABP are necessary around 60 mmHg) during placement of the stent. Also, is maintain good intra and postoperative hydration to prevent postoperative renal damage caused by the liberal use of contrast to assist placement and deployment of the graft. Anticoagulation should be monitored periodically to maintain the ACT around 250 seconds. At the end of surgery, protamin sulfat is used to reverse the effects of heparin. Transesophageal echocardiogram is used perioperative to guide positioning of the stent.

Durin a six month period, in The Heart Center KCUS, 15 patients underwent endovascular surgery for repar of the aorta: 8 TEVAR and 7 EVAR procedures.



a) b)  
Figure 1. 1a/ Angiogram showing an infra renal aortic aneurysm before stent insertion  
1b/ Angiogram showing an infra renal aortic aneurysm after stent insertion



a) b)  
Figure 2. 2a/ Angiogram showing thoracic aortic aneurysm before stent insertion  
2b/ Angiogram showing thoracic aortic aneurysm after stent insertion

### Results

Patients (7 male and one female) for TEVAR procedures had a men age of 50 years (age range 44-56 years), patients (7 male) for EVAR procedures had a men age of 74,28 years (age range 70-79 years). Stay in intensive care was one day and hospital stay for all patients were averaged 4 days. A total of 15 patients had a successful implantation of the device. None of the patients died within 30 days.

In postoperative period for patients with TEVAR procedures the left subclavian artery was covered in 5 patients: one patient had transient impairment circulation in left hand (coldness, whitening and weakness). Closing of left subclavian artery during and after the TEVAR procedure in patient who had AV fistula for dialysis on left hand did not cause any problem in fistula patency, and he still has good dialysis. There was one patient with transient signs of subclavian steal syndrome and mild neurological dysfunction in form of headache. For patients with EVAR procedure only one patient had transient neurological dysfunction of right leg which was probably due to mild and transient form of spinal cord ischaemia.

### Conclusion

Endovascular surgery for repair of the aorta is much less invasive procedure than conventional surgery. This procedure can be performed using general endotracheal anesthesia, local anesthetic infiltrated at the incision site or regional anesthesia with sedation. The anesthesiologist has to understand this procedure and complications so they can provide adequate anesthesia in its different phases.

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# Radiologic findings of non-occupational Asbestos exposure and its relationship to respiratory function disorders: A study in southeast Turkey

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## Abstract

**Background:** There are few studies that compare pulmonary function test (PFT) results with radiological findings in non-occupational asbestos contact cases.

**Objectives:** We aimed to investigate the radiological and spirometric abnormalities caused by asbestos and their relationship to each other in people with non-occupational asbestos exposure.

**Methods:** In this study, PFT results were compared with radiological findings in 112 cases of non-occupational asbestos exposure. The control group of 120 was selected from people who have not been exposed to asbestos dust. All subjects were screened with a chest roentgenogram and spirometry.

**Results:** In the non-occupational asbestos group 30.4% had a restrictive pulmonary function pattern, 16.1% a obstructive type pulmonary function pattern, 24.1% pleural plaques (PP), 14.3% pleural thickening (PT), and 6.2% interstitial fibrosis (IF).

Significant decreases in forced vital capacity (FVC), forced expiratory volume in 1<sup>st</sup> second (FEV1), and mean forced expiratory flow during the middle half of the FVC (FEF 25-75) values were detected in cases of PP, PT, and IF, respectively.

**Conclusions:** Non-occupational asbestos exposure disrupts pulmonary function, and the pulmonary function abnormalities correlate with radiological findings. Obstructive pulmonary function may develop in individuals who have non-occupational exposure to asbestos in the absence of smoking or biomass exposure.

**Key words:** Asbestos, non-occupational exposure, pleural plaques.

## Introduction

Asbestos is a general term for a heterogeneous group of hydrated magnesium silicate minerals that have in common a tendency to separate into fibers (1). These fibers, inhaled and displaced by various means to lung tissue, can cause a spectrum of diseases including cancer and disorders related to inflammation and fibrosis. Nonmalignant asbestos-related disease refers to the following conditions: asbestosis, pleural thickening or asbestos-related pleural fibrosis (plaques or diffuse fibrosis), "benign" (nonmalignant) pleural effusion, and air-flow obstruction (2).

Evaluation of subjects with suspected asbestos-related disease should include spirometry, lung volumes, and the carbon monoxide diffusing capacity. As with other interstitial lung diseases, the classic finding in asbestosis is a restrictive impairment. Mixed restrictive and obstructive impairment is frequently seen; isolated obstructive impairment is unusual. Restrictive impairment may also be observed with pleural disease (2).

Pleural abnormalities associated with asbestos exposure are the result of collagen deposition resulting in subpleural thickening; Pleural abnormalities are divided into pleural plaques (localized pleural thickening), costophrenic angle obliteration and diffuse pleural thickening. Costophrenic angle obliteration should be classified as diffuse pleural thickening. Pleural plaques represent localized pleural thickening, generally of the parietal pleura. Pleural plaques may be seen adjacent to the diaphragm, the chest wall, or at other sites. At times, they are recognized only by their calcification. Diffuse pleural thickening historically has referred to thickening of the visceral pleura. For the purpose of the The International Labour Office (ILO, 2000) Classification, diffuse pleural thick-

ning extending up the lateral chest wall is recorded only in the presence of, and in continuity with, an obliterated costophrenic angle (3).

Recent studies suggest that diffuse pleural thickening is associated with significant pulmonary impairment and that asbestos-induced pleural plaques may cause lung restriction. The presence of pleural plaques can be associated with restrictive impairment and diminished diffusing capacity on pulmonary function testing, even in the absence of radiographic evidence of interstitial fibrosis (4,5). Taking into account the degree of interstitial fibrosis as measured by ILO profusion score (described below), smoking, and duration of asbestos exposure, significant decrements in vital capacity have been observed: a reduction of up 140 ml or more of FVC associated with circumscribed plaques (6). Decrements, when they occur, are probably related to early subclinical parenchymal fibrosis. Plaques are indicators of increased risk for the future development of asbestosis (7). This may reflect greater exposure or retained body burden. An autopsy study has demonstrated more frequent peribronchiolar fibrosis when plaques are present (8). The presence of plaques is therefore an indication to monitor the patient over time for interstitial fibrosis (9). Diffuse pleural thickening may have a significantly greater impact on pulmonary function than circumscribed plaques. A reduction of 270 ml of FVC has been associated with diffuse pleural thickening (6,10). Decrements associated with diffuse pleural thickening reflect pulmonary restriction because of adhesions of the parietal with the visceral pleura. Asbestos exposure has traditionally been considered to cause predominantly restrictive physiologic abnormalities (2). The role of asbestos as a cause of airway obstruction has been controversial. However, asbestos exposure has long been known to be associated with an obstructive physiological abnormality (11-13).

In this study, we aimed to investigate prevalence of radiological and spirometric abnormalities caused by non-occupational asbestos exposure. In addition, we aimed to have the existence of the relationship between obstructive respiratory function disorders and not radiological findings in people with non-occupational asbestos exposure.

## Methods

### *Geographical Area and Subjects*

Turkey is a country where non-occupational asbestos exposure is prevalent, and asbestos deposits are abundant around Diyarbakir; non-occupational asbestos exposure is relatively common in the study area (14). Asbestos deposits have been used for many years by rural inhabitants to make a whitewash or stucco for the walls, floors, and roofs of their houses, and also as a substitute for baby powder in the southeastern region of Turkey (Anatolia). Inhabitants of the region are exposed to asbestos from childhood (15,16). In this region asbestos type was determined to be primarily tremolite (17). Local ethics committee approval was obtained.

### *Study design*

A cross sectional study was conducted in Yukarisehler, a village in Diyarbakir, a city in the southeast of Turkey. The study enrolled 53 male and 59 female subjects older than 30 years of age who were exposed to asbestos. These subjects were not cigarette smokers and were not exposed to another biomass smoke. Similarly they were not exposed to passive smoke. The description of not exposed to passive smoke was decided with the smoking history of subjects. The control group was selected from the villages a population not exposed to asbestos living in neighboring village with similar geographic conditions as Yukarisehler. The control and study group cases were similar in age and sex; a total of 120 control cases were enrolled (57 male and 63 female). Subjects with a history of travel to the village with asbestos exposure were excluded in the control group. Exclusion criteria were age under 18 years, cigarette smoking, biomass exposure, a history of chronic obstructive pulmonary disease, asthma, other obstructive, infectious, interstitial, fibrotic or malignant respiratory disease, atopic diseases, cardiovascular disorders or neuromuscular dysfunction.

### *Questionnaire*

An interviewer administered a questionnaire to the inhabitants of the villages who agreed to participate in the study. The questionnaire included information on demographics, asbestos exposure, respiratory symptoms, as well as present and past

illnesses. All inhabitants were examined and detailed clinical records of their history were obtained by a chest physician.

### ***Radiographic Assessment***

All subjects were screened with a chest roentgenogram, and all clinical and laboratory data were evaluated by two pulmonologists and one radiologist independently. Consensus was defined as the median of the three readings. If there was an inconsistency among the readings for any reason, a second radiologist who had no information about the initial readings evaluated the films. Physicians who were blinded to pulmonary function measurements evaluated for radiographic signs of pleural abnormalities for both exposed and unexposed inhabitants. Radiologic abnormalities were defined as diffuse pleural thickening (PT), pleural plaque (PP), and interstitial fibrosis (IF). No subjects had both PP and PT. Pleural plaques represent localized pleural thickening, generally of the parietal pleura. Pleural plaques may be seen on the diaphragm, on the chest wall, and at other sites. Diffuse pleural thickening was recorded as absent or present along the chest wall.

Asbestos-induced pulmonary parenchymal disease was assessed according to the ILO classification of pneumoconiosis (3). Small opacities were described by profusion, affected zones of the lung, shape (rounded or irregular) and size. The profusion of small opacities refers to the concentration of small opacities in affected zones of the lung. Radiographs read as 0/0 and 0/1 were considered normal; small irregular opacities graded 1/0 or higher than 1/0 were defined as asbestosis.

### ***Spirometry***

A portable spirometer (Gold Pulmonary Analysis Computer, and Pulmograph, Wagner Road, Holland) was used to measure forced vital capacity (FVC), forced expiratory volume in 1<sup>st</sup> second (FEV<sub>1</sub>), FEV<sub>1</sub>/FVC, and mean forced expiratory flow during the middle half of the FVC (FEF<sub>25-75</sub>). Measurements, and the analysis of the spirometric data, were performed according to American Thoracic Society standards (18).

Predicted values for FVC, FEV<sub>1</sub>, FEF<sub>25-75</sub> and the FEV<sub>1</sub>/FVC ratio, based on gender and height, were used to determine respiratory function (18).

Three basic patterns were recognized (19):

- Normal pattern: FEV<sub>1</sub> and FVC above 80% of that predicted  
FEV<sub>1</sub>/FVC ratio above 0.7
- Obstructive pattern: FEV<sub>1</sub> below 80% of that predicted  
FVC normal or reduced – usually to a lesser degree than FEV<sub>1</sub>  
FEV<sub>1</sub>/FVC ratio below 0.7
- Restrictive pattern: FEV<sub>1</sub> normal, or mildly reduced  
FVC below 80% of that predicted  
FEV<sub>1</sub>/FVC ratio normal – above 0.7

### ***Dust Measurement Method***

Previous studies have revealed that there is a significant amount of asbestos in respirable dusts in the village of Yukarisehler and it is known that inhaled asbestos presents a major negative impact on human health (15). In this study, we measured the concentration of inhaled asbestos particles less than 10 µm (PM<sub>10</sub>) that were suspended in the air for a prolonged period of time and therefore presented a dangerous condition for human health in the village of Yukarisehler. The Tecora Isostac Basic device, a Turkak-accredited Environmental Analysis Laboratory of Mechanical Engineers Chamber (Tcr Tecora Srl, Corsico (Milan), Italy), was used in dust measurement. Measurements were taken inside and outside the home, working with the principle of gravimetric dust measurement. Each measurement period was eight hours, and the device operated at a 1 m<sup>3</sup>/hour air suction speed. Dust measurements were used 10% of the houses in the village, including outdoor and indoor.

### ***Statistical Analysis***

Statistical analyses were performed using the statistical package SPSS v10.0 (SPSS Inc., Chicago, IL, USA). For continuous variables, normality was checked. The appropriate nonparametric test was chosen for the variables not normally distributed. Comparisons of continuous variables between the two groups were applied using Student's t test or the Mann-Whitney U test. One-way analysis of variance or Kruskal–Wallis tests were used for



comparing multiple groups. Categorical variables between groups were analyzed using the chi-square test. Results were presented as number, percent, mean  $\pm$  SD (standard deviation), and median (minimum–maximum). A p value less than 0.05 was considered statistically significant.

## Results

The results of dust measurements in Yukarisehler village were mean concentrations of asbestos dust of 1.08 f/cm<sup>3</sup> and 0.45 f/cm<sup>3</sup> for indoors and outdoors respectively. Demographic characteristics of the subjects are provided in Table 1. As seen in Table 1, gender distribution and age range in both the inhabitants who had been exposed to asbestos and those who had not been exposed were similar.

Percentages of predicted FVC, FEV1, FEV1/FVC, and FEF25-75 for subjects with non-occupational asbestos exposure were significantly lower than that of the subjects without non-occupational asbestos exposure ( $p < 0.05$ ). FEV1/FVC values  $< 70\%$  were found in 16.1% and 2.5% in villagers with and without asbestos exposure, respectively; this difference was significant ( $p < 0.0001$ ). FVC values  $< 80\%$  value were found in 30.4% and 3.3% in villagers with and without asbestos exposure, respectively; this difference was also significant ( $p < 0.0001$ ).

There were frequent radiological pleural-parenchymal lesions in the group with asbestos exposure compared to the group without asbestos exposure ( $p < 0.0001$ ). Among the 112 inhabitants exposed to asbestos, 27 cases (24.1%) had PP, 16 cases (14.3%) had PT, and 7 cases (6.2 %) had IF as determined radiologically. The frequency of radiological findings was not significantly different between males and females ( $p > 0.05$ ).

PP with calcifications was the most common asbestos-related radiologic finding (24.1%), and the incidence of PP increased with age (Table 2). Subjects who were at least 60 years old were found to have calcified plaques more frequently than subjects who were under 60 years old ( $p < 0.01$ ). The frequency of PP in subjects over the age of 60 was observed to be 2.7 (1.2 to 5.8) times higher than in subjects under the age of 60. This age-related difference was not significant for PT and IF ( $p > 0.05$ ).

Villagers with asbestos exposure and radiological findings (PP, PT, and IF) had significantly lower FVC, FEV1, FEV1/FVC, and FEF25-75 values than villagers with asbestos exposure but without radiological findings ( $p < 0.05$ ) (Table 3). Predicted FVC values  $< 80\%$  were found in 40.7%, 62.5%, and 71.4% of inhabitants who had PP, PT, and IF, respectively (Table 4). An increased restrictive pattern was found in inhabitants who had

Table 1. Demographic, radiological and spirometric data of the subjects

	Cases with asbestos exposure n (%)	Cases without asbestos exposure n (%)	p
Age (year )	58.2	56.3	$> 0.05$
Gender			
Male	53(47.3)	57(47.5)	$> 0.05$
Female	59(52.7)	63(52.5)	$> 0.05$
Mean asbestos exposure (year)	47.4	0	
Pleural plaque	27(24.1)	0(0)	$< 0.0001$
Pleural thickening	16(14.3)	0(0)	$< 0.0001$
Interstitial fibrosis	7(6.2)	0(0)	$< 0.001$
FVC	84.9 $\pm$ 13.2	91.9 $\pm$ 10.7	$< 0.05$
FEV1	78.5 $\pm$ 16.2	83.3 $\pm$ 12.3	$< 0.05$
FEV1/FVC	73.6 $\pm$ 10.3	79.1 $\pm$ 9.2	$< 0.05$
FEF25-75	69.6 $\pm$ 11.9	76.2 $\pm$ 12.8	$< 0.05$
Obstructive type PFT disorder (FEV1/FVC $< 70$ )	18(16.1)	4(3.3)	$< 0.001$
Restrictive type PFT disorder (FVC $< 80$ )	34(30.4)	3(2.5)	$< 0.001$
Total	112 (100)	120 (100)	

FVC= forced vital capacity, FEV1= forced expiratory volume in 1 s, FEF 25-75= mean forced expiratory flow during the middle half of the forced vital capacity

Table 2. Relationship between radiological findings and age groups of the 112 cases with asbestos exposure

Age (years)	Gender	n	PP n	PP %	PT n	PT %	IF n	IF %
30-40	F	6	0	0	0	0	0	0
	M	8	1	12.5	0	0	0	0
41-50	F	9	1	11.1	2	22.2	0	0
	M	12	2	16.7	0	0	0	0
51-60	F	16	2	12.5	3	18.7	1	6.2
	M	15	3	20.0	3	20.0	1	6.7
61-70	F	19	5	26.3	3	15.8	2	10.5
	M	13	5	38.5	3	23.1	2	15.4
≥70	F	9	5	55.6	1	11.1	1	11.1
	M	5	3	60.0	1	20.0	0	0
Total	F	59	12	20.3	9	15.3	4	6.8
	M	53	15	28.3	7	13.2	3	5.6
	All cases	112	27	24.1	16	14.2	7	6.2

M= Male, F= Female, PP= Pleural plaque, PT= Pleural thickening, IF= Interstitial fibrosis.

Table 3. Relationship between radiological findings and PFT values in cases with and without asbestos exposure

	PP (+) n=27	PT (+) n=16	IF (+) n=7	Asbestos (+) Radiologically lesion (-) n=62	p
FVC	76.3±12.9	73.2±13.3	66.3±14.5	88.3±14.8	<0.05
FEV1	75.9±17.1	70.3±17.8	66.1±15.3	82.4±16.6	<0.05
FEV1/FVC	71.5±15.4	67.8±13.2	65.7±14.7	76.5±15.5	<0.05
FEF 25-75	66.3±16.7	63.3±18.7	60.3±15.6	72.3±17.6	<0.05

PP= Pleural plaque, PT= Pleural thickening, IF= Interstitial fibrosis, FVC= forced vital capacity, FEV1= forced expiratory volume in 1 s, FEF 25-75= mean forced expiratory flow during the middle half of the forced vital capacity.

Table 4. Relationship between radiological findings and disorders of PFT in villagers with and without asbestos exposure

Parameters of spirometry	PP(+) n (%)	PT(+) n (%)	IF(+) n (%)	Asbestos(+) radiologically findings(-) n (%)	p
FVC<80	11 (40.7)	10 (62.5)	5 (71.4)	8 (12.9)	<0.001
FEV1<80	6 (22.2)	6 (37.5)	5 (71.4)	4 (6.7)	<0.001
FEV1/FVC<70	5 (18.5)	4 (25.0)	4 (57.1)	5 (8.0)	<0.001
FEF 25-75<65	5 (18.5)	4 (25.0)	5 (71.4)	7 (11.3)	<0.001

PP= Pleural plaque, PT= Pleural thickening, IF= Interstitial fibrosis, FVC= forced vital capacity, FEV1= forced expiratory volume in 1 s, FEF 25-75= mean forced expiratory flow during the middle half of the forced vital capacity.

radiological findings ( $p<0.001$ ). Predicted FEV1/FVC values  $<70\%$  were found in 18.5%, 25%, and 57.1% of inhabitants who had PP, PT, and IF respectively ( $p<0.001$ ). The obstructive pattern gradually increased from PP to IF ( $p<0.0001$ ). Similarly, the other obstructive parameter, FEF 25-75, gradually increased from PP to IF ( $p<0.001$ ).

## Discussion

It is known that occupational asbestos exposure causes restrictive pulmonary function. However, whether or not asbestos causes airway obstruction remains a controversial issue.<sup>20-23</sup>

Mineral dust, tremolite, and diseases caused by exposure to these substances have been reported

as major health concerns in the southeastern part of Turkey (14,15,24,25).

In a room where the walls have been recently whitewashed or where the floor is regularly swept, the concentration of asbestos can be quite variable, ranging from 0.02 f/cm<sup>3</sup> to 17.9 f/cm<sup>3</sup> (26). Senyigit reported indoor airborne asbestos fiber concentrations ranging from 0.0042 f/cm<sup>3</sup> to 1.24 f/cm<sup>3</sup> in villages using asbestos (17); we found indoor asbestos fiber concentrations of 1.08 f/cm<sup>3</sup> in villages using asbestos.

In one study was found 26.4% IF, 11.2% PT, and 5.9% PP among workers exposed to asbestos (27). In another study conducted in Turkey, asbestosis was found in 5.4% of villagers over the age of 30 with non-occupational asbestos exposure (28). The IF rate was 6.2 % in our study, similar to that of the other study conducted in Turkey (28).

Pleural plaque is the most common manifestation of asbestos exposure, and bilateral scattered calcified PP can be regarded as virtually pathognomonic of asbestos exposure (29,30).

The incidence of PP in the general population not exposed to asbestos ranges from 0.1 to 1.3%. The incidence of PP with non-occupational exposure to asbestos was found to be between 5.2 and 22% in previous studies conducted in Turkey (24,31,32). In our study, the rate of PP was found to be 24.1%, and it increased with age. The percentage of villagers over the age of 60 who had PP was found to be 2.7 times higher than in those under the age of 60, and was found in 57.1% of villagers over the age of 70. These results indicate that incidence of PP increases as exposure time increases.

There is differing data regarding the prevalence of PT in occupational asbestos contact cases. Some studies have found PT in 5-13.5% of asbestos workers (33,34). Similar frequency results of PP and PT were reported by McLoud et al. in 1373 workers exposed to asbestos (33). In our study, PT was found in 14.3% of cases of non-occupational asbestos exposure.

In a study investigating radiologic findings of non-occupational asbestos exposure, investigators detected PP and PT in 10.6% and 3.0% of villagers respectively, and pleural effusion in one patient (35). In another study prevalences of, 14.4%, 0.4%, and 0.4% were found for PP, PT and IF respectively in the villagers.<sup>36</sup> In a recent study in our

region, 288 villagers were scanned with a chest roentgenogram and the relative prevalences were 29.9% (PP), 4.7% (PT), and 0.7% (IF) (25).

In our study, villagers exposed to asbestos had significantly lower FVC, FEV1, FEV1/FVC, and FEF25-75 values compared with villagers without exposure. We also found 30.4% restrictive and 16.1% obstructive type lung function patterns when conducting pulmonary function tests in villagers exposed to asbestos. These results suggest that exposure to asbestos in this study group mainly caused a restrictive type of respiratory dysfunction and less obstruction.

Individuals with PP, PT, and IF were found by chest roentgenogram have lower FVC, FEV1, FEV1/FVC, and FEF 25-75 values than those not exposed to asbestos.

There are various studies regarding different radiological findings of patients with occupational asbestos exposure and the relationship between these findings and the incidence of PFT disorders. In one study significant decreases in FEV1 and FEF25-75 values were found in non-smoker women asbestos workers without radiographic abnormalities.<sup>28</sup> Kauris et al. reported a 5% decrease in FVC and a 6% decrease in FEV1 in 146 cases with PP among 996 asbestos workers (36).

The FVC, FEF25-75, and FEV1/FVC values of workers with PP were found to be significantly lower than workers without PP in a study of cement workers in Croatia. There were 41.9% cases of restriction (2.57 times more than cases without PP) and 7.2% cases of obstruction (similar to cases without PP) in workers with PP (37).

We found respiratory dysfunction in the PP group in whom we observed 40.7% restriction and 18.5% obstruction. Lung function abnormalities were more frequent in the PT group with 62.5% restriction and 25% obstruction.

While PP affects the parietal pleura, PT is both a visceral and a parietal pleura disease. PT is the result of intense fibrosis of the visceral pleura and adjacent interstitium; the parietal pleura also participate in the process and adhere to the visceral pleura. Respiratory function decreases more in cases with PT compared to PP (38,39). The most substantial disruption of pulmonary function tests was observed in subjects who had IF; a significant decrease in all parameters was observed in the presence of IF.



We observed that asbestos exposure frequently causes not only restrictive but also obstructive respiratory disorders. Pulmonary function loss was evident in patients with radiological findings. The correlation between radiological findings and PFT abnormalities are similar to cases with occupational asbestos exposure.

Limitations of this study include the fact that the carbon monoxide diffusion capacity and HRCT scans were not measured due to logistical challenges of study in a relatively remote community.

In conclusion our study showed that non-occupational asbestos exposure is significantly associated with obstructive and restrictive respiratory functions impairment. Obstructive disorder may develop from non-occupational exposure to asbestos in nonsmokers without biomass smoke exposure.

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# Therapy of hirsute

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## Abstract

**The aim of study** is evaluation of therapy of hirsute-excessive hair growth on the body in women. The management of hirsute includes cosmetic treatment and anti-androgen therapy.

**Patients and methods:** In a prospective-retrospective, clinical and descriptive type of study hirsute women age between 20 and 40 years without any acute or chronically diseases were included. The study included 100 female patients with hirsute diagnosed and treated in period for six years.

Detailed medical history taking and physical examination and laboratory's investigations were carried out in all the cases.

**Statistical analysis:** Microsoft Excel was applied to perform statistical analysis.

**Results:** Metformin in therapy used 80% women because it affect on high level of insulin and reduce high level of androgens in circulation. Ant androgens with different cosmetic treatment (waxing, depilation, bleaching, laser, electrolysis) are main ways of therapy.

**Conclusion:** Hirsute at women with menstrual cycle disorders need to be appropriate evaluated and treatment.

**Key words:** Hirsute, PCOS, anti-androgen therapy, cosmetic treatment, metformin.

## Introduction

Hirsute is defined as excessive or unwanted hair growth and often leads to the avoidance of social situations and to symptoms of anxiety and depression. Hirsute is usually the result of an underlying adrenal, ovarian or central endocrine abnormality. Elevated secretion of androgens, increased bioavailability of testosterone and increased sensitivity of hair follicles to androgens all contribute to the condition. The management of hirsute includes cosmetic and medical management (anti-androgen therapy). Laboratory investigation is essential in women with moderate to severe, sudden onset or rapidly progressing hirsute.

## Aim

Aim of study is evaluation of the most common way of therapy for hirsute in way of improving quality of life to women.

## Subjects and methods

In a prospective-retrospective, clinical and descriptive type of study 100 hirsute women age between 20 and 40 years without any acute or chronically diseases were included. The study was conducted at Polyclinic and diagnostic department of Clinic for Endocrinology and Diabetes University Clinical Centre of Sarajevo and included patients with hirsute diagnosed and treated in period between 01.01.2005. to 31.12.2011. Mayor criteria for including female patients in study were: women at age from 20 to 40 with hirsute estimated with *Ferriman-Galweys* score (FG Score); female patients without any acute or chronically disease. Mayor criteria for not including female patients in study were: female patients with age under 20 and older than 40 years with associated acute and chronically diseases.

## Methods

Detailed medical history taking and physical examination. 1) History 2) Physical examination 3) Laboratory's investigations: the levels of serum testosterone, dehydroepiandrosterone sulphate, androstendione, luteinizing hormone, follicle stimulating hormone, LH/ FSH rate, prolactin, thyroid stimulating hormone, cholesterol, triglycerides, basal insulin, glucose, HOMA-IR.

## Statistical analysis

Microsoft Excel was applied to perform statistical analysis.

## Results

Metformin at different daily dose was included in therapy at 80 (80%) patients with hirsute. Thy-



roxin with metformin in therapy was included at 18 (18%) patients in different dose: daily dose of 25 microgram at 11 (11%) patients, daily dose of 50 microgram daily at 5 (5%) patients, daily dose of 100 microgram at 1 (1%) patient and thyroxin in dose of 125 microgram daily at 1 (1%) patient also. Spironolactone in one daily dose of 25 to 100 miligram with metformin was included in therapy at 11 (11%) patients. Dexazon pills in dose of 0,5 miligram in therapy with metformin were included at 9 (9%) patients. Cabergoline in therapy was included at 16 (16%) and bromocriptine at 5 (5%) patients. Oral contraceptive pills (ciproteron-etinilestradiol, drospirinon-etinilestradiol) with metformin were included at 9 (9%) patients. Topical use of 1% Eflornitin creme once daily had 4 (4%) patients.

Daily dose of 750 milligrams metformin divided on three doses daily after the meal had 20 (20%) patients. (Table 1 and Table 2)

*Table 1. Used medicamentation therapy at women with hirsutism*

Type of medicamentation	patients	
	N	%
metformin	80	80
thyroksin	18	18
dexason	9	9
cabergoline	16	16
spironolactone	11	11
oral contraceptive pills	9	9
bromocriptin	5	5
eflornitin creme	4	4

*Table 2. Daily dose of metformin in therapy for women with hirsutism*

Daily dose of metformin	patients	
	N	%
metformin 250 mg	4	4
metformin 425 mg	1	1
metformin 500 mg	20	20
metformin 750 mg	20	20
metformin 850 mg	4	4
metformin 1000 mg	9	9
metformin 1275 mg	4	4
metformin 1500 mg	9	9
metformin 1700 mg	7	7
metformin 2550 mg	2	2
TOTAL	80	80

## Discussion

Aims of therapy for hirsute are remove causes of hormonal misbalance, slowdown or stop excessive hair growth on body and increase self satisfaction of own appearance at hirsute women which affect on quality of life. Ant androgens with different cosmetic treatment (waxing, depilation, bleaching, laser, electrolysis) are main ways of therapy. (1)

Main aim in therapy for hirsute is to obtain central or periphery suppression of androgens by using 4 groups of medicine: inhibitors of androgens production (oral contraceptive pills, gonadotropins releasing analogist and gonodotropins releasing hormones), inhibitors of androgens at periphery (ciproteron acetate, flutamid and spironolactone), enzymes inhibitors (finasterid) and insulin sensitizers (rosiglitazon, metformin). Metformin is safe and efficacy drug in therapy for obese women with hirsutism and with PCOS. The study not shown changes in blood levels of urea, transaminases and creatinine. (2)

For most off patient's monotherapy with oral contraceptive pills composed at least with one ant androgen content is first choice in therapy for hirsute and lead to visible changes after 6 or 9 month of everyday use. (3)

It is over wide spread not improve consider about that progestagen component of oral contraceptive pills can cause hirsute. The truth is that derivatives of 19-nortestosterone which is component of popular oral contraceptive pills very rarely can cause hirsute and acne. (4)

Mio-inozitol as the new way of therapy for hirsute was elaborated in a study in Italy on sample of 46 patients with hirsute. Mio-inozitol belong the vitamins B and in study group minimized excessive hair growth. Laser in cosmetically therapy represent new way of save, fast and efficacy method of destroying excessive hair growth. (6)

Electrolysis as way of removing excessive unwanted body hair has most efficiency but the method is painful, long term and results depend of competition of cosmetician. (7)

Women with hirsutism have predisposition for diabetes mellitus tip 2 because of hyperinsulinism and that women need adequate control with counseling of prevention activity, change of bad life attitude with adequate medicamentation. (8)

## Conclusions

Metformin in therapy used 80% women. PCOS is the most common cause of hirsute at reproductive age women, in background of the same the most common cause is hyperinsulinemia or insulin resistance. Hirsute at women with menstrual cycle disorders need to be appropriate evaluated and treatment.

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# Level of burnout in caregivers working in residential homes and factors affecting burnout

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## Abstract

**Purposes:** This study was carried out to investigate the level of burnout among caregivers working in private and public nursing homes.

**Methodology:** The study was conducted in 7 nursing homes, of which one was public. Ninety-nine caregivers working at these facilities were included in this study. To volunteers who agreed to participate in the study, Maslach Burnout Inventory (MBI) was applied together with a questionnaire. Data were evaluated by using Anova and Student tests for percentages and parametric data; while Mann-Whitney U and Kruskal Wallis tests were used for non-parametric data on the computer.

**Findings:** The mean age of participating caregivers was  $35.56 \pm 7.68$  years. 52.5% were men and 71.7% were elementary school graduates. Emotional burnout subscale scores were high among female caregivers and high school graduates. Dissatisfaction due to workplace environment and entering the profession as an obligation also increased this subscore ( $p < 0.01$ ).

**Conclusion:** Burnout levels were high among caregivers working at public nursing homes, those dissatisfied with physical conditions, those working in elderly health care units and those who considered the profession as obligatory. Levels were also higher among female caregivers.

**Key words:** Caregivers, nurses, burn-out, nursing home.

## Introduction

Rapid population growth, industrialization, urbanization, participation of female gender in the work place, diffusion of nuclear families as well as socio-cultural and economic changes make it difficult to

take care of the elderly at home and thus, more elderly are being placed in nursing homes in our country. (1) Burnout is a psychological reaction triggered by interactions between personal characteristics and stress factors. (2) Burnout syndrome is a well-known psychological reaction among health-care workers. (3,4,5) Triggering factors are personal characteristics such as low sense of coherence (SOC), close patient relations, workload, autonomy, professional development, performance feed-back, work environment and interactions of these and other stress-related strains. (3,6,7,8,9) Burnout usually takes some years to develop, but is less common in older employees with several years of job experience. (3,10,11) Caregivers constitute the biggest group among health care workers providing medical and social care for the elderly in nursing homes. They face problems such as diseases, pain, suffering, death, isolation, incapacitated people in nursing homes. Caregivers who are together with the elderly for most of their time and who are striving hard with all kinds of problems related to elderly such as physical, emotional and social issues are the groups that carry the highest risk for "burnout". (12,13) The burnout concept has first been addressed by Freudenberg in 1974 and later Maslach and Jackson have established the most accepted model of burnout and defined burnout as emotional exhaustion, increase in desensitization and decrease in feelings of personal success. (14,15) This study has been conducted to investigate the levels of burnout among caregivers working at nursing homes by using Maslach Burnout Inventory (MBI).

## Methods

This cross-sectional prospective study was carried out in seven nursing homes, one being pu-



blic and the others being private after obtaining necessary legal permissions and informed consents from respondents. The instrument including the Maslach Burnout Inventory (MBI) and the Questionnaire Form were administered in January and February 2010 to collect data and were completed by 99 members (75%) of the care giving staff. The Questionnaire Form contained various questions on some certain socio-demographical particulars. There were 6 public and 38 private nursing homes in Istanbul at the time. One of the 6 public nursing homes was selected by simple random sampling. The selected public nursing home was one of the largest ones in Istanbul. Sampling was made with the same proportion among private nursing homes and 6 were selected by simple random sampling. 73 of 97 caregivers working at public nursing homes and 26 of 35 caregivers working at six private nursing homes accepted to participate in our study.

Caregivers volunteering to participate were included in the study. "Maslach Burnout Inventory (MBI)" was developed by Maslach and consisted of sublevels as emotional exhaustion, personal success and desensitization. Emotional exhaustion is described as overloading and feelings of being exhausted relevant with the work one does. Desensitization is related to being numbly insensitive for people one gives care to. Personal achievement is defined as overcoming problems and feeling of adequacy. (16) MBI is a self-statement inventory with 22 sentences and 5 choices (0: Never, 1: Very Rare, 2: At times, 3: Mostly, 4: Always). While sublevel points are calculated as above for emotional exhaustion and desensitization, it is quite the opposite for personal success. The points range between 0-36 for emotional burnout, 0-20 for desensitization and 0-32 for personal success. Emotional burnout and desensitization sublevels consist of negative statements while sublevels for personal achievement consist of positive statements. (17) Validity and reliability studies of MBI for Turkish was performed by Ergin. (18)

Data collected therein were evaluated by using SPSS 11.5 software package. Data were analysed by using Anova and Student t test for parametric data and by using Mann-Whitney U and Kruskal Wallis tests for non-parametric data in the computer era.

The study was performed in the province of Istanbul. There were 6 public and 38 private nu-

rsing homes in Istanbul at the time. Caregivers working at nursing homes belonging to minorities, foundations or municipalities were not included in the study. Sampling was done among public and private nursing homes having the largest number of persons in terms of caregivers and the elderly. Despite all of the caregivers working at nursing homes being sampled were included in study, caregivers not accepting to participate in the study and the ones who took off could not be included. Another limitation of the study was the assumption that caregivers included in the study correctly understood the questions in the inventory and gave accurate answers.

### **Ethics**

The participation in the study was voluntary and all participants gave their approval for the study. It was not necessary to obtain the agreement of an ethics committee for the study as this is a survey which was analyzed in an anonymous manner. The study was also approved by the institutions. Before data collection, the purpose of the study was explained and each member of the volunteered care giving staff signed a consent form. The participating institutions were told, prior to the study, that the study results would be published in a medical journal in an anonymous form, to which they gave their consent.

### **Results**

The mean age of participating caregivers was  $35.56 \pm 7.68$  years and 52.5% were men; 71.7% had graduated from primary/elementary schools and 83.8% were married. 73.7% of the caregivers worked at public nursing homes, 64.6% in bedridden services, 75.8% have been working as a nurse for 0-5 years, 37.4% have willingly chosen to be a nurse, 91.1% had affection for the occupation, 54.5% set their hopes on the future of their occupation, 38.4% were not satisfied with the physical conditions of the nursing home they worked, and 48.5% could not participate in social activities sufficiently (Table 1).

Table 1. Some socio-demographic features of caregivers

Variables	Number (n: 99)	% (100)
<b>Institution</b>		
Private Nursing Home	26	26.3
Public Nursing Home	73	73.7
<b>Gender</b>		
Male	47	47.5
Female	52	52.5
<b>Level of Education</b>		
Primary-Elementary	71	71.7
High school	28	28.3
<b>Marital Status</b>		
Married	83	83.8
Single	9	9.1
Widow/Widower or Divorced	7	7.1
<b>Age Group</b>		
Below 30 years	25	25.2
30–39 years	45	45.5
40 years and over	29	29.3
<b>Latest unit</b>		
Bedridden elderly care service	65	64.6
Non-bedridden elderly care service	34	34.3
<b>Working time</b>		
0–5 years	75	75.8
6–10 years	12	12.1
11 years and over	12	12.1
<b>Occupation choice</b>		
Willingly	37	37.4
Random	19	19.2
With advice from relatives	23	23.2
Obligatory	20	20.2
<b>Affection for occupation</b>		
Yes	91	91.9
No	8	8.1
<b>Occupation convenience</b>		
Convenient	77	77.8
Not convenient	22	22.2
<b>Satisfaction from physical conditions</b>		
Not satisfied	38	38.4
Indecisive	22	22.2
Satisfied	39	39.4

In the study, 61.5% of the caregivers working at private nursing homes and 28.8% of those working at public nursing homes stated choosing their occupation willingly. The rates of choo-

sing the occupation willingly were significantly higher among caregivers working at private nursing homes compared to those working at public nursing homes (Chi-square: 8,830;  $p$ : 0,032). 73.1% of caregivers who were working in private nursing homes and 27.4% of caregivers working in public nursing homes stated satisfaction with their physical environment. Satisfaction with the physical conditions of the working place was significantly higher among caregivers working at private nursing homes compared to those working at public nursing homes (Chisquare: 16.875;  $p$ : 0.000).

Of the participants, 87.3% of the caregivers who were elementary school graduates and 53.6% of the caregivers who were high school graduates reported their profession as convenient. The rate of elementary school graduates finding the job convenient was statistically higher than the rate of high school graduates working as caregivers (Chi-square: 13,236;  $p$ : 0.001).

When MBI subpoints of caregivers were evaluated, the average Emotional Burnout (EB) point was  $7.86 \pm 6.99$ , the average Desensitization (D) point was found as  $2.94 \pm 3.45$  and the average Personal Achievement (PA) point was found as  $14.80 \pm 7.80$  making the average total point of the inventory  $25.61 \pm 13.14$  (Table 2).

When MBI average points of caregivers were compared with gender, the average EB subpoint of females was  $9.80 \pm 7.42$ . The average EB subpoint of females was significantly higher when compared to males ( $p < 0.01$ ) (Table 3).

If the average MBI points of caregivers were compared with the level of education of caregivers, the average EB subpoint of high school graduates was  $10.28 \pm 8.01$ . The average EB subpoints of high school graduates were significantly higher than elementary school graduates ( $p < 0.05$ ) (Table 3).

No statistically significant difference was seen when MBI average points of caregivers were compared in terms of marital status, age groups and work time ( $p > 0.05$ ) (Table 3).

If the MBI average points of caregivers were compared according to institutions, the average EB subpoint was  $8.97 \pm 7.56$ , the average D subpoint was  $3.53 \pm 3.68$  and the average PA subpoint was  $16.65 \pm 7.62$  for caregivers working at public

Table 2. The average MBI points of caregivers

MBI Sublevels	Number of Issues	Minimum	Maximum	Average Points X ± SS
Emotional Burnout	9	0.00	29	7.8 6 ± 6.99
Desensitization	5	0.00	13	2.94 ± 3.45
Personal Achievement	8	0.00	32	14.80 ± 7.80
General total		2	50	25.61 ± 13.14

Table 3. The average mbi points of caregivers regarding some of their demographic features

Variables	Emotional	Desensitization	Personal
Gender			
Male (n=47)	5.72 ± 5.85	2.70 ± 3.41	15.76 ± 8.52
Female (n=52)	9.80 ± 7.42	3.15 ± 3.50	13.94 ± 7.07
F/p	F: 4.107 p: 0.003	F: 0.023 p: 0.518	F: 1.507 p: 0.253
Level of Education			
Primary-Elementary (n=71)	6.91 ± 6.36	2.8 3± 3.48	15.07 ± 7.66
High school (n=28)	10.2857 ± 8.01	3.21 ± 3.42	14.14 ± 8.27
F /p	F: 3.070 p: 0.030	F: 0.237 p: 0.621	F: 0.321 p: 0.597
Marital Status			
Married (n=83)	7.63 ± 7.04	2.98 ± 3.52	14.66 ± 8.00
Single (n=9)	8.44 ± 6.26	3.00 ± 2.82	15.88 ± 6.31
Widow-Widower or Divorced (n=7)	9.85 ± 7.94	2.28 ± 3.72	15.14 ± 8.00
K-W /p	K-W: 0.437 p: 0.804	K-W: 0.734 p: 0.693	K-W: 1.365 p: 0.505
Age Group			
Below 30 years (n=20)	10.55 ± 7.67	3.50 ± 3.01	15.75 ± 6.64
30–39 years (n=47)	6.38 ± 5.10	2.55 ± 3.40	13.31 ± 7.16
40 years and above (n=32)	8.37 ± 8.47	3.15 ± 3.79	16.40 ± 9.10
F/p	F= 0,599 p: 0,550	F=0,189 p: 0,828	F=0,706 p: 0,495

F: F value in variation analyses

p: Significance value

K-W: Value in Kruskal-Wallis statistical test

nursing homes. All average subpoints of caregivers working at public nursing homes were significantly higher when compared to those of the caregivers working at private nursing homes ( $p < 0.01$ ) (Table 4).

When the average burnout inventory points of caregivers were compared with emphasis on the service they worked at the nursing homes, the average PA subpoint of caregivers working in bedridden elderly care services was  $16.60 \pm 7.43$ . The average PA subpoint of caregivers working in bedridden elderly care services were significantly higher than those working in non-bedridden elderly care services ( $p < 0.01$ ) (Table 4).

As concerns the average burnout inventory points of caregivers based on their evaluations of physical conditions of nursing homes, the average EB subpoint of caregivers satisfied with the physical conditions were  $5.74 \pm 6.99$ . The average EB subpoint of caregivers satisfied with physical conditions were significantly lower than those who were not satisfied or indecisive ( $p < 0.01$ ) (Table 4).

When the average burnout points of caregivers were compared regarding their affection for the occupation, the average EB subpoint of caregivers who did not love their occupation was  $7.37 \pm 7.70$ . The average EB subpoints of caregivers who did not have affection for their occupation was statisti-



Table 4. Comparison of averages of MBI subpoints of caregivers regarding working conditions and issues related to work

Nursing Home	Emotional	Desensitization	Personal
Private (n=26)	4.76 ± 3.66	1.26 ± 1.88	9.61 ± 5.79
Public (n=73)	8.97 ± 7.56	3.53 ± 3.68	16.65 ± 7.62
F /p	F=12.269 p: 0.008	F=13.685 p: 0.004	F=1.447 p: 0.000
Working Unit			
Bedridden elderly care service (n=64)	8.28 ± 6.89	2.93 ± 3.18	11.41 ± 7.56
Non-bedridden elderly care service (n=34)	7.20 ± 7.30	2.79 ± 3.90	16.60 ± 7.43
F /p	F= 0.214 / P: 0.473	F= 1.140 / P: 0.845	F= 0.021 / P: 0.001
Satisfied with physical conditions?			
Not satisfied (n=38)	9.9737 ± 7.03	3.2632 ± 3.11	16.5789 ± 6.68
Indecisive (n=22)	8.0000 ± 7.74	2.5455 ± 3.67	14.4091 ± 8.06
Satisfied (n=39)	5.7436 ± 6.99	2.8462 ± 3.45	13.3077 ± 7.80
F /p	F= 3.716 / P: 0.028	F= 0.320 / P: 0.727	F= 1.752 / P: 0.179
Affection for occupation?			
Yes (n=91)	7.03 ± 6.32	2.72 ± 3.35	14.63 ± 8.01
No (n=8)	17.37 ± 7.70	5.37 ± 3.88	16.75 ± 4.86
M-U / p	M-U= 3.212 / p: 0.001	M-U= 1.735 / p: 0.083	M-U= 823 / p: 0.411
Occupation choice?			
Willingly	5.89 ± 5.06	2.86 ± 3.30	13.78 ± 8.05
Random	7.00 ± 5.99	2.63 ± 3.83	14.78 ± 8.29
With advice from relatives	6.52 ± 7.41	1.86 ± 2.80	14.78 ± 8.26
Obligatory	13.90 ± 7.58	4.60 ± 3.64	16.75 ± 6.43
F /p	F= 7.593 / p: 0.000	F= 2.438 / p: 0.069	F= 0.617 / p: 0.606

F: F value in variation analyses

p: Significance value

M-U: Value for Mann-Whitney U statistical test

cally higher than those who loved their occupations ( $p < 0.01$ ) (Table 4).

As the average MBI points of caregivers were compared regarding their motivation for choosing their occupations, the average EB subpoint of caregivers who have considered their occupation obligatory was  $13.90 \pm 7.58$ . The average EB subpoints of caregivers who considered their occupation obligatory were statistically higher than those who chose their occupations with other motivations ( $p < 0.01$ ) (Table 4).

## Discussion

Caregivers working at nursing homes in Turkey enter the profession after having undergone a training of 130 hours. In this study, among MBI subpoints of caregivers, the average EB subpoint was found as  $7.86 \pm 6.99$ ; the average D subpoint

was found as  $2.94 \pm 3.45$  and the average PA subpoint was found as  $14.80 \pm 7.80$  making the average total points of inventory  $25.61 \pm 13.14$ . In a study conducted with caregivers working at nursing homes, the average EB and D subpoints were higher, while the average PA subpoints were lower. (19) In another study about burnout in primary care medical staff, the average EB and D subpoints were found to be higher, while the average PA subpoints were lower compared to our study. (20) Meanwhile, the results found in the study was concurrent with another study in the literature which was conducted among the nursing staff working in an elderly nursing home. (21) The high values of EB and D subpoints indicate that the burnout is serious and the high levels of PA indicate that the burnout is mild or moderate. (19) The reason that the burnout level of caregivers in our study were lower than those working at nursing homes or other fiel-

ds might have originated from the fact that 91.1% of our participants enjoyed their occupation and more than half of them had hopes about the future of their occupation. Caregivers in Turkey worked without any formal training until 2008. In 2008, a training related to "Basic Patient and Elderly Care" that lasted 130 hours was made obligatory for all caregivers covering those that were already working and those who were to enter the profession, by the directive 2008/26960. Schools of higher education were founded in 7 universities for training of the caregivers. The low burnout levels found in our study could be related to the improvements obtained through these training efforts.

The average EB subpoints of participating high school graduate caregivers were found to be significantly higher than elementary school graduates ( $p < 0.05$ ). In some studies conducted with caregivers, the average EB subpoints was found lower in high school graduates. (19, 22) In another study, there was not any statistically significant difference between level of education and burnout sublevels. (19) In the study, elementary school graduate caregivers found the occupation more convenient for themselves when compared to high school graduates. The higher average EB subpoints of high school graduate caregivers was due to the fact that they did not find the occupation convenient for themselves and had higher expectations.

In this study, when average MBI points of caregivers were compared with reference to gender, the average EB subpoints of female caregivers were significantly higher than those of males ( $p < 0.01$ ). This might be due to the fact that burnout in females was affected by factors related to job and outside of job, while only factors related to job were in play for males as supported by findings of other studies. (23)

When the average MBI subpoints of caregivers were compared based on the institutions, all subpoints of caregivers working at public nursing homes were significantly higher than those working in private nursing homes ( $p < 0.01$ ). The burnout level of caregivers working at public nursing homes were higher compared to those working at private nursing homes as the caregivers in private nursing homes have chosen their occupation more willingly and as they were satisfied with the physical conditions of the facilities they worked in.

When the average burnout inventory points of caregivers were compared in terms of the services the caregivers worked in, the average PA subpoint of caregivers working in non-bedridden elderly care services were significantly higher than those working in bedridden elderly care services ( $p < 0.01$ ). The high PA subpoints indicated that the burnout level was mild or moderate. (14) The high burnout levels for caregivers working in bedridden elderly care services, might be explained by the high expectations of bedridden elderly, they were more impatient and selfish and they were in a psychological mood that denied senility.

When the average burnout inventory points of caregivers were compared with reference to the physical conditions of the institutions they were working in, the average EB subpoint of those who were satisfied with the physical conditions were significantly lower than those who were not satisfied or were indecisive ( $p < 0.01$ ). Meanwhile, the average EB subpoint of caregivers who had affection for their occupation were significantly lower compared to those who did not love their occupation ( $p < 0.01$ ). In a study conducted on nursing home caregivers, the average EB subpoints of caregivers who were satisfied with their working services were significantly lower than those who were not satisfied. (19) In another study, burnout levels were found lower in those who were satisfied with the general conditions of the occupation. (14)

If we compare the average MBI points of caregivers with reference to the choice of their occupation, the average EB subpoint of caregivers who had obligatorily chosen their occupation were significantly higher than those who had other reasons for choosing the profession ( $p < 0.01$ ). In a study performed with caregivers, the burnout levels of caregivers who had willingly chosen the unit they worked in were found to be lower while emotional burnout and desensitization levels of caregivers who considered the profession obligatory or who were inclined to change their occupation were found to be higher. (13,24) In a study in the literature, it was suggested that the caregivers working at nursing homes should be psychologically and socially supported and that institutional protective and analytic measures should be taken for their burnouts. (25)

## Conclusion

Among caregivers, the burnout levels were higher in those working at public nursing homes, those who were females, who were unsatisfied with the physical conditions of the working unit, who were working in bedridden elderly care services, who considered the profession obligatory and who did not enjoy the occupation. In preventing the burnout in caregivers, it would be effective to improve the physical conditions of the nursing homes, to provide the caregivers with orientations, to provide them compliance and to make arrangements to shift caregivers within the institution between different services. We think that future multi-disciplinary studies related to factors affecting burnout levels in caregivers in wider populations can provide valuable information for preventive actions.

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# Pharmacological agents for postoperative analgesia

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## Abstract

Postoperative pain is unpleasant sensory and emotional experience associated with nociceptive signals after surgical trauma and from inflammatory process that ensues after the injury, influenced by physiological and psychological factors. Pain relief in postoperative period is very important for the recovery, but generally it has been shown to be inadequate.

Besides traditional approach based on administration of opioid and nonopioid analgesics in postoperative which may not attenuate pain in many patients, new perspectives are continuously investigated. On the basis of positive effects in experimental pain models and clinical studies on phantom pain, preemptive analgesia has been advocated. Large randomized controlled studies have been showing controversial results, and beneficial effects of preemptive analgesia has not been confirmed in meta-analyses.

In multimodal approach administration of different analgesics like opioids, nonopioid analgesics and adjuvant analgesics, with different target receptors is aimed to minimize adverse effects of the analgesics and achieve better pain relief and faster mobilization of the patients. Trials with NMDA- receptor antagonists,  $\alpha$ -2 receptor agonists, anticonvulsive drugs, corticosteroids, have shown beneficial effects in terms of prolonged analgesia and minimization of the adverse effects of traditional analgesics.

Recent data suggest that multimodal approach with administration of analgesics before the injury, adequate analgesia intraoperatively and maintaining good analgesia with analgesics and adjuvant analgesics which act centrally and peripherally in postoperative period, might have the best results in terms of good pain relief, better outcome and patients satisfaction.

The aim of this paper is to review the drugs that are used in traditional and new approaches to analgesia in postoperative period.

**Key words:** Postoperative analgesia, opioid analgesics, nonopioid analgesics, adjuvant analgesics.

## Introduction

At the site of surgical injury numerous compounds are released from damaged cells, activated nociceptors and different cells (mast cells, basophils, endothelial cells, keratinocytes and fibroblasts). These factors form „inflammatory soup“ that consist of numerous signaling molecules (neurotransmitters, peptides, eicosanoids and related lipids, neurotrophins, cytokines, chemokines, proteases and protons, potassium ion, ATP). Exposure to all these factors lead to lowering of threshold and increased responsiveness of peripheral nociceptors. This phenomenon, called peripheral sensitization is important for tailoring postoperative pain control. (Figure 1) Central sensitization refers to establishing the state of hyperexcitability of the neurons within the central nervous system after prolonged and repetitive nociceptive inputs from the site of injury, leading to enhanced processing of nociceptive input and in some cases to the stage of chronic pain syndromes.

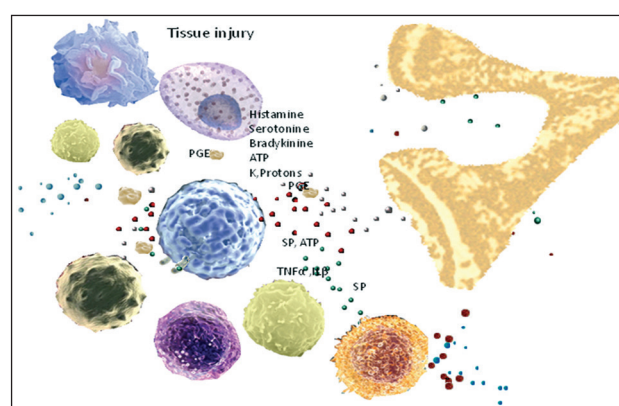


Figure 1. Inflammatory mediators at the site of injury lead to lowering of threshold and increased responsiveness of peripheral nociceptors

Sensory processing in central nervous system is changed and the perception of pain is altered. It is of great importance to prevent development of central sensitization in early postoperative period.

### ***Preemptive analgesia***

Preemptive analgesia is defined as antinociceptive therapy that prevents changes in central processing of afferent nociceptive input in order to diminish the postoperative pain. Many review studies have shown controversial results, partly due to different designs of the trials with different timing of analgesics administration, different protocols of analgesia after surgery, various combinations of analgesics. The results varied from beneficial, partly beneficial in the early postoperative period to no beneficial effects (1, 2, 3).

Results of published experimental trials and data from meta-analyses of clinical trials, provide evidence of efficacy of preemptive analgesia in animal studies, but inconsistent effects in clinical studies.

### ***Multimodal analgesia***

Multimodal or balanced analgesia denotes administration of opioids, nonopioids and adjuvant analgesics which act on different sites from the tissue injury and generation of nociceptive stimuli, along the pathways of transmission and modulation of nociceptive signals to the level of cortical centers of processing of modified signals and final perception of pain. The aim of this concept is achieving

better analgesia with fewer side effects in the light of the development of minimally invasive surgery and fast track surgery which imply faster recovery, early mobilization and shorter hospitalization. For that reason, the proportion of opioids is decreased in regard to other analgesics(4). Many clinical studies have shown the sparing opioid effect associated with administration of nonopioids (COX-inhibitors), local anaesthetics and adjuvant analgesics (alpha-2 agonists, NMDA antagonists, adenosine, anticonvulsive drugs, glucocorticoids, beta blockers and others) (5,6).

## **Analgesics in perioperative period**

### ***Opioids***

During two centuries of the use for attenuation of perioperative pain, besides morphine and morphine derivatives, numerous synthetic drugs that bind to specific opioid receptors have been developed.

After binding at stereospecific opioid receptors in the central nervous system and other tissues opioids mimic the activity of endogenous ligands-endorphins, neuropeptides with potent antialgesic properties. Agonists of mu receptors (morphine, meperidine, fentanyl, sufentanyl, alfentanil, remifentanyl) accounts for supraspinal analgesia, euphoria, and also respiratory depression, pruritus, anorexia, sedation and physical dependency. Opioid agonists-antagonists mainly act on kappa receptors and mediate spinal analgesia, sedation, dyspnea, de-

*Table 1. Opioid analgesics*

<b>Opioid analgesics</b>			
<b>Opiates</b>	<b>Opiate-like synthetic opioids</b>	<b>Endogenous opioids</b>	<b>Opioids agonists/antagonists</b>
Mechanism of action: -binding to stereospecific membrane receptors ( $\mu_1$ , $\mu_2$ , $\kappa$ , $\delta$ , N/OFQ), -Inhibition of release of neurotransmitters Activation of descending inhibitory systems			
Sites of action: CNS (periaqueductal grey, nucleus raphe magnus, magnocellular reticular formation, medulla spinalis, limbic system) - peripheral nervous system - peripheral tissues			
Analgesia: dose-dependent selective attenuation of pain perception (ceiling effect)			
Side effects: Respiratory depression, sedation, nausea, vomiting, GIT dysfunction, urinary retention, itching, tolerance, immune dysfunction			
Indications: acute pain, chronic pain			
Contraindications: decreased respiratory reserve, biliary colic, reduced blood volume, liver failure or insufficiency			



pendence, dysphoria, and respiratory depression. Agonists of delta receptors are probably responsible for psychomimetic actions and dysphoria (7).

Although precious for relieving of strong pain during intraoperative period opioid monotherapy in the postoperative period may elicit many adverse effects (Table1).

In the recent period the focus of clinical investigations and therapeutic approach are on the development of transdermal and transmucosal preparations, which have shown many beneficial effects (8).

### ***Inhibitors of Cyclooxygenase***

Analgesic effects of nonsteroidal antiinflammatory drugs (NSAIDs) are based on inhibition of cyclooxygenase (COX), key enzyme for conversion of arachidonic acid to prostaglandins and other eicosanoids. The use of NSAIDs in early postoperative period is limited due to possible side effects. (Table 2)

While COX-1 constitutive isoform regulates gastric cytoprotection, renal autoregulation of perfusion and platelet aggregation, COX-2 isomer is constitutive in central nervous system, bones, kidney, and inducible in inflammatory conditions (9). Nonsteroidal antiinflammatory drugs (NSAIDs) comprise nonselective inhibitors of COX-1 and selective inhibitors of COX-2, which have 200-300 time stronger inhibition of COX-2 in regard

to COX-1. Besides decreasing the inflammatory response and peripheral sensitization of nociceptive neurons, they can also act at cyclooxygenase in the spinal cord(9). COX-2 selective inhibitors have shown efficacy and safety in different surgical procedures, but in the clinical studies in cardiosurgery numerous complications like higher wound infection, higher incidence of cerebrovascular insults and myocardial infarcts were reported (10,11).

Short time perioperative NSAIDs administration (3-5days) is considered safe and provide better analgesia with better cost-effectiveness ratio for nonselective inhibitors.

Data on the mechanism of action of acetaminophen imply possible inhibition of prostaglandin synthesis and interaction with opioidergic and serotonergic pathways. Weak inhibition of both isoforms of COX lead to fewer gastrointestinal effects in regard to other inhibitors of cyclooxygenase (12).

Development of safe and more effective cyclooxygenase inhibitors could decrease the use of opioids in perioperative period and provide better pain control with minimal side effects. (Table 2)

### ***Local anesthetics***

Local anaesthetics lead to reversible blockade of transmission of electrical potentials acting at sodium channels of peripheral nerves depending on the site of application and of the concentration.

*Table 2. Inhibitors of cyclooxygenase*

<b>Cyclooxygenase inhibitors</b>
<b>salicylates, arylacetic acids, arylpropionic acid derivatives, pyrazolon derivatives, para-aminophenol derivatives, COX-2 inhibitors...</b>
Mechanism of action: - inhibition of cyclooxygenase (COX), and conversion of arachidonic acid to eicosanoids - decrease of inflammatory process
Sites of action: peripheral tissues , CNS and peripheral nerves
Analgesia: decreasing inflammatory process and release of prostaglandins and peripheral sensitization, decreasing prostaglandin generation in CNS
Side effects: <b>NSAIDs</b> - GIT bleeding, hypocoagulability and bleeding, renal tubules dysfunction, allergic reactions and bronchospasm, hypertension <b>COX-2 inhibitors</b> – hypercoagulability, GIT dysfunction <b>Acetaminophen</b> - GIT dysfunction, smetnje, hepatotoxicity , agranulocytosis
Indications: acute and chronic pain
Contraindications: allergy to NSAIDs, age<16, pregnancy, breast feeding, anticoagulant therapy, coagulopathy, active peptic ulcer Attention: asthma, renal dysfunction, liver dysfunction

In clinical practice local anesthetics are used for topical anesthesia, infiltrative anesthesia, peripheral nerve blockade, intravenous regional anesthesia or spinal anesthesia with intrathecal or epidural injection.

Some recent trials have shown that preincisional skin infiltration and application of local anaesthetics in body cavities (intraperitoneal, intraarticular) provide better analgesia postoperatively (13).

Despite the effect of local anesthetics in early postoperative period, pain perception is quite intense after termination of the action, and continuous or intermittent perfusion of the wound or peripheral nerve with local anesthetic are associated with prolongation of duration of analgesia and sparing of opioids. Anesthetics with longer duration of effects that contain liposomes and microspheres have shown to exert longer lasting effects (14). (Table 3)

Table 3. Local anaesthetics

Local anaesthetics	
Amino-esters	Amino-amides
Mechanism of action: reversible blockade of transmission of electrical potentials acting at sodium channels of peripheral nerves depending on the site of application and of the concentration.	
Sites of action: peripheral nervous system, central nervous system peripheral tissues	
Analgesia: blockade of transmission of nociceptive signals from periphery to central nervous system	
Side effects: peripheral nerve injuries, residual motor weakness, arrhythmias, allergy	
Indications: acute pain, chronic pain	
Contraindications: allergy	

### ***$\alpha$ -2 receptor agonists***

Many clinical trials have shown that systemic administration of  $\alpha$ 2-agonists clonidine and dexmedetomidine result in sedative effects and decreased opioid requirements. After premedication and transdermal application of clonidine opioid sparing effect was shown and in other trials analgesia was prolonged when clonidine was administered with peripheral block. Dexmedetomidine can also reduce postoperative pain and opioid consumption. Side effects are mentioned in the Table 4. Many trials with  $\alpha$ -2 receptor agonists confirmed reduction of anxiety, intraoperative analgesic consumption and better analgesia in postoperative period (15).

Table 4.  $\alpha$ -2 receptor agonists

$\alpha_2$ adrenoceptor agonists	
Clonidine	Dexmedetomidine
Mechanism of action: hyperpolarization of excitable neurons	
Sites of action: Supraspinal mechanisms Spinal mechanisms (descending noradrenergic pathways)	
Analgesia: involvement in descending noradrenergic pathways	
Side effects: postoperative sedation, hypotension, bradycardia	
Indications: acute pain, chronic pain	
Contraindications: hypersensitivity, heart block, severe ventricular dysfunction, hypovolemia	

### ***NMDA receptor antagonists***

Key role in the phenomenon of central sensitization, very important for augmentation of acute pain and transformation of acute pain to chronic states, is associated to N-methyl-D-aspartate receptor (NMDA). Dextrometorphan and its metabolite dextrorphan are noncompetitive antagonists of NMDA receptors. Dextrometorphan provide better analgesia in combination with opioids, local anaesthetics and NSAIDs. In some clinical trials if given pre- or intraoperatively, opioid sparing effects and better subjective assessment of pain were evident, while this effect was not shown in other trials (16). Intravenous anaesthetic ketamine shows analgetic effects in subanaesthetic doses, but rather unpleasant psychomimetic effects should be noted (17). Amantadine is NMDA antagonist which has shown positive and negative results in postoperative analgesia. Further larger clinical trials with this group of drugs are needed to clearly define the role of noncompetitive inhibitors of NMDA receptors. (Table 5)

### ***Corticosteroids***

Corticosteroids are powerful antiinflammatory drugs with analgetic, immunomodulatory and antiemetic effects. Besides the inhibition of phospholipase and COX2, many other cellular effects are postulated. They have been in use for neuropathic pain for more than fifty years. In several randomized clinical trials the effect of single dose of glucocorticoids were analysed. Results have shown better analgesia with less incidence of adverse effects of nausea and vomiting (18). (Table 6)

Table 5. NMDA receptor antagonists

N-methyl- d-aspartate receptor antagonists			
Methadon	Dextrometorphan	Ketamine	Amantadine
Mechanism of action: Inhibition of NMDA receptor			
Sites of action: CNS			
Analgesia: inhibition of central sensitization			
Side effects: Side effects: dizziness, drowsiness, GIT upset, hypotension, tachycardia, nistagmus, unpleasant psychomimetic effects			
Indications: acute pain, chronic pain			
Contraindications: simultaneous use of serotonin reuptake inhibitors and monoaminoxidase inhibitors, children with atopic syndrome			

Table 6. Glucocorticoids

Glucocorticoids		
Short acting (Hydrocortisone,Cortisone)	Intermediate acting (Prednisone, Prednisolone, Methylprednisolone, Triamcinolone)	Long acting (Betamethasone Dexamethasone)
Mechanism of action : inhibition of phospholipase and COX2 - Cellular effects		
Sites of action : peripheral tissues and CNS(?)		
Analgesia : attenuation of pain perception		
Side effects (prolonged use): oedema, hypertension, Cushing's syndrome, heart failure, osteoporosis, delayed wound healing, elevated intraocular pressure, hirsutism....		
Indications : chronic pain		
Contraindications : hypertension, diabetes mellitus, peptic ulcer, infection like tuberculosis, ocular herpes simplex and other acute viral infections, renal insufficiency, osteoporosis, thrombosis		

**Anticonvulsive drugs**

Anticonvulsive drugs are efficient in the therapy of neuropathic pain, probably due to membrane stabilization. Gabapentin has been shown as efficacious for the different types of chronic pain(19). Positive results in animal studies for acute postoperative pain, encouraged introduction of gabapentin to clinical trials as one component of multimodal protocol in postoperative period. The results of many randomized trials on the efficacy of single dose of gabapentin given preoperatively and results of many meta-analyses showed positive effects in terms of decreasing of anxiety, better analgesia and antiemetic effects (6). The ratio dose-effect has not been clearly established, and the adverse effects could be serious. It is a promising adjuvant drug for multimodal analgesia and future clinical trials will show the possible role in acute postoperative pain control. (Table 7)

Table 7. Anticonvulsive drugs

Anticonvulsive drugs	
Gabapentin	Pregabalin
Mechanism of action: stabilization of the membrane of neurons	
Sites of action: central nervous system	
Analgesia: stabilization of the membrane of neurons involved in the pain pathways	
Side effects: dizziness, drowsiness, coordination problems, nausea, vomiting, double vision, blurred vision, diarrhea or constipation	
Indications: anticonvulsive drug, chronic pain	
Contraindications: allergy	

**Esmolol**

Beta adrenergic receptors antagonists are used to prevent hemodynamic changes. It has been shown that esmolol, cardioselective beta1 adrenergic receptor antagonist of ultrashort action may have effects similar to those of opioids with possible faster reco-



very of patients in the postoperative period. According to the results of few trials, esmolol could be used as a possible adjuvant drug in some populations of patients in multimodal approach(20). (Table 8)

Table 8.  $\beta$ -adrenergic receptor antagonists

$\beta$ adrenergic receptor antagonists
Esmolol
Mechanism of action: blockade of $\beta_1$ adrenergic receptors
Sites of action: cardioselective
Analgesia: ???
Side effects: hypotension, bradycardia, agitation, dizziness, drowsiness, fatigue, paresthesia, bronchospasm
Indications : supraventricular tachycardia, perioperative tachycardia and hypertension
Contraindications : sinus bradycardia, heart block, shock and heart failure
Attention: pregnancy, nursing mother, children

### Adenosine

Adenosine, endogenous nucleoside, ubiquitous metabolic intermediate compound has important role in many cellular functions including neuro-modulation and neurotransmission. Adenosine A1 and A2 receptors are widely present in central nervous system. The properties of adenosine as a nonopioid analgesic are investigated in many clinical trials which have shown potentiation of sedative and opioid sparing effects in postoperative period(21). It has been proposed that adenosine plays a role in the nociceptive pathways, and clinical research with aim of developing of adenosine receptor agonists that could have clear analgetic action for acute pain therapy are in progress. (Table 9)

Table 9. Nucleosides

Nucleosides
Adenosine
Mechanism of action: binding to A1 and A2 adenosine receptors
Sites of action: CNS
Analgesia: involvement in the pain pathways
Side effects: dyspnea, dizziness, diaphoresis, flushing of face, headache, nausea, hyperventilation
Indications: paroxysmal supraventricular tachycardia
Contraindications: 2 <sup>nd</sup> and 3 <sup>rd</sup> degree heart block, sick sinus syndrome, long QT, severe hypotension, heart failure asthma

### Conclusions

Advancements in the understanding of pain pharmacology and analgesia, molecular biology and development of selective ligands for different classes of receptors involved in the nociceptive pathways and transmission, have shown that pain is extremely complex and dynamic process. Opioid analgesics have important role in the therapy of pain of medium and strong intensity after surgery. But with development of minimally invasive surgery adjuvant analgesic will have greater role. Recent trials have shown that well chosen combinations of opioids, nonopioids and adjuvants could provide optimal postoperative analgesia. Further clinical trials with longer follow up could give data important to evaluate possible better outcomes in administration of multimodal analgesia to patients in clinical and ambulatory settings.

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# Mitral valve prolapse in University of Sarajevo students

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## Abstract

**Introduction:** Mitral valve prolapse (MVP) can occur in a multitude of disorders and, in most instances, it reflects a normal variant rather than a single disease process. Despite years of research, the symptomatology and significance of mitral valve prolapse remain controversial. It was termed the disease of the decade in the 1980s, but now some consider it an interesting finding of dubious importance until mitral regurgitation (MR) manifests. Initial studies that reported associated symptoms of MVP as chest pain, dyspnea, anxiety, and panic were probably flawed by recruitment bias. Studies imply that the incidence of MVP previously was overestimated by inaccurate echocardiography diagnostic criteria and that associated symptoms, other than palpitations, are uncommon. Despite this, patients with MVP are at risk for arrhythmias, endocarditis, stroke, mitral regurgitation (MR), mitral valve replacement (MVR) surgery, and sudden death. Mitral valve prolapse is also associated with migraine (especially migraine with aura), autoimmune disease, and idiopathic sudden sensor-neural hearing loss.

**Objective:** To determine the frequency of mitral valve prolapse in the student population at the University of Sarajevo; To identify the symptoms and physical signs of mitral valve prolapse with students at the University of Sarajevo; To assess the significance of the electrocardiogram and 24h Holter-heart monitoring and ultrasound in the diagnosis of mitral valve prolapse in students at the University of Sarajevo.

**Materials and methods:** The study was conducted as prospective, retrospective, clinical, and descriptive analytical. The sample consisted of the University of Sarajevo students. The sample included students at regular and systematic examinations at the Institute of Public Health of Students at the University of Sarajevo in the period 2005 - 2010.

**Results:** Mitral valve prolapse was recorded in 11 young men, or (28.21%) 44 girls (62.86%), what means total recorded in 55 patients (50.46%).

**Keywords:** mitral valve prolapse, echocardiography, trans esophagus cardiography, electrocardiogram, 24h-Holter monitoring.

## Introduction

Mitral valve prolapse (PMZ) is the displacement of one or both leaflets of mitral valve to the left atrium above the mitral annular plane during systole, with or without mitral regurgitation. It is identified by echocardiography in 3-4% of the total population and is identified in 7 % of autopsies. Mitral valve prolapse is usually benign, but in many cases there are isolated cases of mitral regurgitation (MR), 90% of cases of ruptured chord tendineae, 40% of cases in young patients and 10-15% of endocarditis. Female - male prevalence is 3:1. Age of appearance is 16 years (Plewa et al. 2011). Frequency in the general population varies from 4-12%, 5% for men and 6% for the female population of 2-3% Hayek et al. 2005).

Mitral valve prolapse (MVP) can occur in a multitude of disorders and, in most instances, it reflects a normal variant rather than a single disease process. Despite years of research, the symptomatology and significance of mitral valve prolapse remain controversial. It was termed the disease of the decade in the 1980s, but now some consider it an interesting finding of dubious importance until mitral regurgitation (MR) manifests. Initial studies that reported associated symptoms of MVP as chest pain, dyspnea, anxiety, and panic were probably flawed by recruitment bias. Studies imply that the incidence of MVP previously was overestimated by inaccurate echocardiography diagnostic criteria and that associated symptoms, other than palpitations, are uncommon. Despite this, patients with MVP are at risk for arrhythmias, endocarditis, stroke, mi-



tral regurgitation (MR), mitral valve replacement (MVR) surgery, and sudden death. Mitral valve prolapse is also associated with migraine (especially migraine with aura), autoimmune disease, and idiopathic sudden sensor-neural hearing loss. Mitral valve prolapse (MVP) usually is asymptomatic, non-progressive, and benign.

- Palpitations occur in 40% of MVP cases. This percentage excludes palpitations due to withdrawal syndromes (e.g., alcohol, sedatives), intoxications (e.g., cocaine, amphetamine, phencyclidine), or medication exposures (e.g., caffeine, sympathomimetic, anticholinergic).
- Chest pain and dyspnea previously were considered part of the MVP syndrome, but they are now felt to be no more common in cases of MVP than they are in the general population.
- Although controversial, anxiety and panic disorders may be more common in patients with MVP than the general population.
- Fatigue
- Syncope/presyncope
- Orthostasis

A myxomatous degeneration from collagen dissolution leads to excess mucopolysaccharidose in the middle spongiosa layer of the mitral valve leaflets, resulting in stretching of the leaflets and the chordae tendineae. Mitral valve prolapse (MVP) occurs when the left ventricular (LV) size is small in comparison to an enlarged mitral annulus, leaflets, or chordae tendineae and it can be induced in healthy women with typical body habitus following dehydration that is reversed with rehydration. Mitral valve prolapse resolves during pregnancy and following weight gain in anorexic patients. Studies have shown that abnormalities of elastic fibers found in floppy mitral valves are related to genetic variants in fibrillin, one of the components of the micro fibrils, as well as elastin and collagen I and II. Mitral valve prolapse is associated with a variety of medical conditions involving connective tissues, such as joint hyper mobility disorders, and Ehlers Danlos and Marfan syndromes. Mitral valve prolapse is also associated with autoimmune disorders such as systemic lupus erythematosus and autoimmune thyroid disease; many patients with

mitral valve prolapse have positive auto antibodies including ANA, rheumatoid factor, and anticardiolipin antibody. A constellation of abnormalities (e.g., increased sensitivity to adrenergic stimuli, increased catecholamine, abnormal beta-receptors, increased atrial natriuretic factor, renin-aldosterone deregulation, decreased intravascular volume, magnesium deficiency) has been thought to lead to chest pain, dyspnea, fatigue, dizziness, near-syncope symptoms, and anxiety in a subset of patients with mitral valve prolapse. Cardiac manifestations include supraventricular more so than ventricular arrhythmias, palpitations, mitral regurgitation, bacterial endocarditis, and sudden death. Chest pain may not be more common in patients with mitral valve prolapse than in the general population, and it may be attributed to myofascial syndromes, hyperventilation, coronary spasm, esophageal dysmotility, or gastro esophageal reflux. Mitral valve prolapse can result in cerebrovascular ischemia, which may be related to abnormal platelet activity or coagulation disorders (e.g., anticardiolipin antibody, protein C or S deficiencies). United States MVP is thought to be inherited with increased expression of the gene in female individuals (2:1). The most common form of inheritance is autosomal dominant, but X-linked inheritance has been described. MVP commonly occurs with heritable connective tissue disorders, including Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum. In fact, 90% of patients with Marfan syndrome have MVP due to the increased redundancy of the mitral leaflets and apparatus that occur as a result of myxomatous degeneration. In the 1970s and 1980s, MVP was over diagnosed because of the absence of rigorous echocardiography criteria, with a reported prevalence of 5-15%. Subsequently, Levine et al reported that the 2-dimensional echocardiography characterizations of prolapse, especially on the parasternal long-axis view, are most specific for the diagnosis of MVP. Use of these criteria prevents overdiagnosis. Data from the community-based Framingham study demonstrated that MVP syndrome occurred in only 2.4% of the population. Most patients with MVP are asymptomatic and have a benign prognosis, with survival rates similar to those of the general population. Nonetheless, high-risk patients (i.e., those with moderate-to-severe mitral regurgitation) have increased cardiac morbidity and mortality rates, es-

pecially if reduced left ventricular systolic function is present. MVP occurs more frequently in young women than in men. The most serious consequences of hemodynamically significant mitral regurgitation occur in men older than 50 years. MVP has been observed in all ages. For the following complications, the absolute risk (i.e., annual incidence) and the odds ratios (OR), comparing patients with mitral valve prolapse (MVP) to the general population, are as follows: Sudden cardiac death - 0.06% annual incidence among patients with MVP and severe MR; OR of 50-100 with hemodynamically significant MR and depressed left ventricular function Rupture of chordae tendineae (the most frequent serious complication of MVP) Progressive MR - 0.06% annual incidence of requiring surgery; lifetime risk of surgery is 1.5% for women and 4-6% for men; OR of 30-40; increased risk in males, older than 75 years, elevated body weight, and high blood pressure. Stroke - 0.02% annual incidence versus less than 0.02% in uncomplicated MVP; OR of 4-6 Infective endocarditis - 0.02% annual incidence; OR of 3-8; 1 in 1400 patients per year with MVP and murmur; increased risk in males older than 45 years. Atrial can be persistent in 15% or paroxysmal in 13% when MR is severe enough to require mitral valve replacement (MVR) surgery. These rates are lower than seen with mitral stenosis requiring MVR. Atrial and ventricular arrhythmias are more common in those patients with mitral valve prolapse and moderate-to-severe MR. Individuals with idiopathic sudden sensor-neural hearing loss (ISSNHL) have a higher incidence of MVP, mitral leaflet thickening, and MR, suggesting that MVP

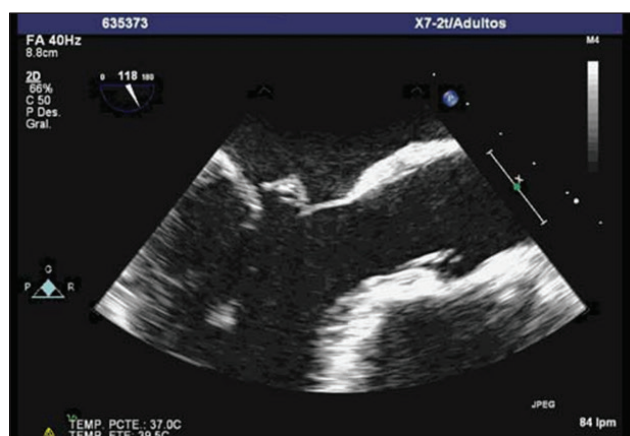


Figure 1. 3D-TEE probe may also be used as a conventional 2D-TEE probe. In this figure we can see a mitral valve prolapse.

## Materials and methods

Sample consisted of the University of Sarajevo students. The sample included students at regular and systematic examinations of the Institute of Public Health of Students at the University of Sarajevo in the period 2007 - 2010. Personal history of young student population between 18-26 years involves assessing the status of the patient through all aspects of life. Questions must not be suggestive. Important life events should be noted to provide the appropriate advice. A very important place occupied by information about previous illnesses, sports and family history. An essential anamnestic data for students is also faculty they attend.

## Research methods

- Personal history data for assessment of cardiac status of the patient and family history of student at the University of Sarajevo;
- Auscultatory data on cardiac rhythm and regularity, intensity and quality of heart sounds, systolic and diastolic sounds, heart noises of students at the University of Sarajevo;
- Electrocardiographic findings in evaluation of mitral valve prolapse with students at the University of Sarajevo;
- 24 h Holter-monitoring in the diagnosis of heart rhythm disorders, mitral valve prolapse with students at the University of Sarajevo.
- Echocardiography and trans esophagus cardiography in diagnosing of mitral valve prolapse of students at the University of Sarajevo.

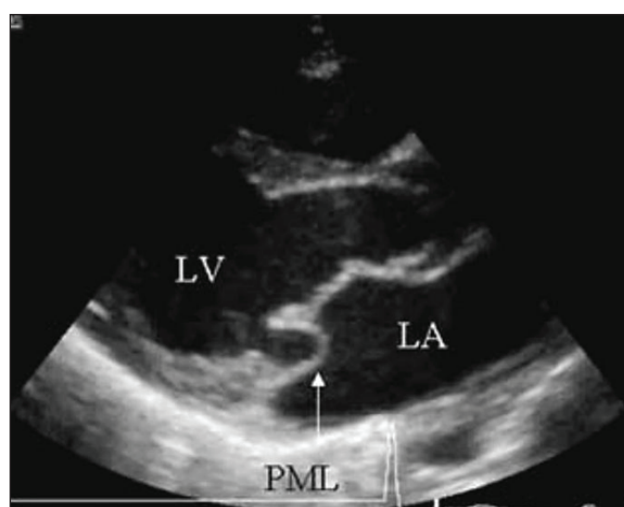


Figure 2. 2D-TTE. In this figure we can see a mitral valve prolapse.

Mitral valve prolapse can be a controversial diagnose performed by 2D echocardiography. Due to the nonlinear relationship between annulus and leaflets, prolapse of the scallops may be seen in one view but not in another by 2D echo. 3D echocardiography is able to provide detailed images of the scallops involved and its relationships with cardiac structures. When mitral leaflets are viewed from the atrial side ("surgical view"), a bulging of the prolapsing leaflets into the left atrium occurs during ventricular systole (Figure 1 & 2), whereas viewing from the LV side one will notice a hollow in that leaflet. Thus, RT-3DE trans-thoracic images allow exact identification and sizing of the prolapsing scallops with an accuracy approaching that of trans-esophageal echocardiography.

## Results

Prolapsus valvulae mitralis (with or without regurgitation) was recorded in female population in 50% of examined patients, with significant difference on level  $p < 0,005$  ( $t=3, t=3,33$  and  $t=3,25$ ). The same was observed in total sample with significant difference on level  $p < 0,005$  ( $t=2,88$ ,  $t=3,15$ ,  $t=3,22$ ,  $t=3,29$  and  $t=3,35$ ) (Table 1-3).

## Discussion

Mitral valve prolapse was documented in 11 young men, or (28.21). Mitral valve prolapse was documented in 44 girls (62.86%). Mitral valve prolapse was documented in total of 55 patients (50.46%). There is a difference in subjective symptoms, clinical picture and electrocardiographic fin-

Table 1. Display of presence of congenital and acquired heart defects in male population of patients

No	Type of disorder	Number of patients	%
1	Prolapsus valvulae mitralis (with or without regurgitation)	11	28,21
2	Insuffitientio valvulae mitralis	3	7,69
3	Regurgitatio valvulae mitralis et tricuspidalis	13	33,33
4	Regurgitatio valvulae aortalis	3	7,69
5	Insuffitientio valvulae aortalis	1	2,56
6	St. post operationem defectus septum ventriculorum	1	2,56
7	St. post operationem stenosis valvulae aortalis	1	2,56
8	Aorta bicuspidia	1	2,56

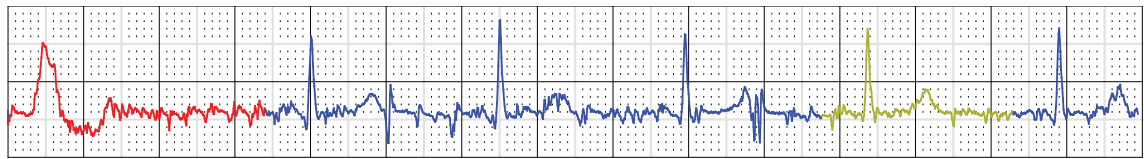
Table 2. Display of presence of congenital and acquired heart defects in female population of patients

No	Type of disorder	Number of patients	%
1	Prolapsus valvulae mitralis (with or without regurgitation)	44	62,86
2	Insuffitientio valvulae mitralis	5	7,14
3	Regurgitatio valvulae mitralis et tricuspidalis	7	10,00
4	Regurgitatio valvulae aortalis	1	1,43
5	Insuffitientio valvulae aortalis	2	2,86
6	St. post operationem defectus septum ventriculorum	1	1,43
7	St. post operationem stenosis valvulae aortalis	0	0,00
8	Aorta bicuspidia	0	0,00

Table 3. Display of presence of congenital and acquired heart defects in all population of patients

No	Type of disorder	Number of patients	%
1	Prolapsus valvulae mitralis (with or without regurgitation)	55	50,46
2	Insuffitientio valvulae mitralis	8	7,34
3	Regurgitatio valvulae mitralis et tricuspidalis	20	18,35
4	Regurgitatio valvulae aortalis	4	3,67
5	Insuffitientio valvulae aortalis	3	2,75
6	St. post operationem defectus septum ventriculorum	2	1,83
7	St. post operationem stenosis valvulae aortalis	1	0,92
8	Aorta bicuspidia	1	0,92

Diagram 1. First display of segment from 24 h Holter-monitoring of heart- report in investigated students with mitral valve prolapse: TABLE of evidenced heart rhythm disorders, ECG details-supraventricular tachycardia and atrial fibrillation.

Heart rates, RR intervals		Average	Max	Min	Max time	Min time
HR [1/min]		64	114	47	22.12.2008 18:53	22.12.2008 15:01
HR equivalent intervals [ms]		937				
RR filtered [ms]		927	1713	360	22.12.2008 14:59	22.12.2008 18:53
RR unfiltered [ms]		925	1770	176	23.12.2008 05:19	22.12.2008 10:20
Tachy / brady / pause		Number of events			Longest event	
					Time	Length
Tachycardia		22			22.12.2008 18:52	1 min 51 s
Bradycardia		40			22.12.2008 14:55	1 min 28 s
Pause ( 2.5 s )		0				
QRS statistics						
	Total	Max/h	Longest		Highest rate	
			Duration	HR [1/min]	Duration	HR [1/min]
Ves						
Isolated	75	26				
Couplet	0	0				
Triplet	0	0				
V-tachycardia	0	0				
Bigeminy	2	1	1 s	129	1 s	156
Trigeminy	0	0				
V.rthym sus.	1					
SVES						
SV-tachycardia	9	2	00:00:08	85	00:00:01	178
Atrial fibrillation	18					
ECG detail 22.12.2008 15:48:09 25 mm/s 10 mm/mV HR=62						
<div><div>A +</div><div></div></div>						
Beats v N N N N S N						
events Atrial fibrillation						

dings in the investigated students. Large number of PMV patients is asymptomatic. Chest discomfort is common complain and pain is mostly atypical regarding its localization. Usually it is not provoked by exertion and it is prolonged in duration. Sometimes there were dizziness and syncope (4.59%) of surveyed students. In the case of progressive mitral regurgitation (22.9%) of students reported the symptoms of heart failure (2.75%). The most important physical finding is mesosystolic click away, which is at least 0.14 sec away from tone.

Finding of telesystolic murmur marks mitral regurgitation. Over time the noise becomes holosystolic, but often with telesystolic stress. Auscultatory finding in MVP, when present, may consist of a click or multiple clicks that move within systole with changes in LV dimensions and / or late systolic murmur or holosystolic MR. The main criteria for PMV confirmation in 1 D echocardiography technique is finding telesystolic or holosystolic displacement mostly often of posterior mitral leaflet to the locks.



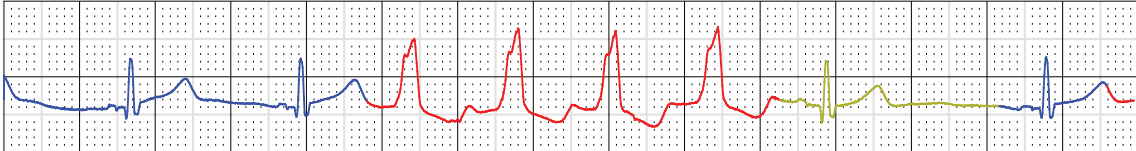
Diagram 2. Second display of segment from 24 h Holter-monitoring of heart-report in investigated students with mitral valve prolapse: TABLE of evidenced heart rhythm disorders, ECG details-ventricular rhythm.

Heart rates, RR intervals		Average	Max	Min	Max time		Min time	
HR [1/min]		73	168	52	10.12.2008 16:45		11.12.2008 02:52	
HR equivalent intervals [ms]		821						
RR filtered [ms]		812	1493	303	11.12.2008 00:38		10.12.2008 08:56	
RR unfiltered [ms]		811	6526	180	10.12.2008 19:41		10.12.2008 15:32	
Tachy / brady / pause		Number of events			Longest event			
					Time		Length	
Tachycardia		436			10.12.2008 16:41		7 min 3 s	
Bradycardia		26			11.12.2008 02:52		9 s	
Pause ( 2.5 s )		1			10.12.2008 08:40		3,3 s	
QRS statistics								
	Total	Max/h	Longest		Highest rate			
			Duration	HR [1/min]	Duration	HR [1/min]		
Ves								
Isolated	61	14						
Couplet	4	2						
Triplet	0	0						
V-tachycardia	0	0						
Bigeminy	1	1	4 s	53	4 s	53		
Trigeminy	0	0						

Heart rates, RR intervals		Average	Max	Min	Max time		Min time	
HR [1/min]		73	168	52	10.12.2008 16:45		11.12.2008 02:52	
HR equivalent intervals [ms]		821						
V.rthym sus.	2							
SVES								
SVES	272	56						
SV-tachycardia	7	3	00:00:10	86	00:00:01	128		
Atrial fibrillation	14							

ECG detail 11.12.2008 05:41:29 25 mm/s 10 mm/mV HR=74

A +



Beats

N      N      V      V      V      V      S      N

events

V run

B +

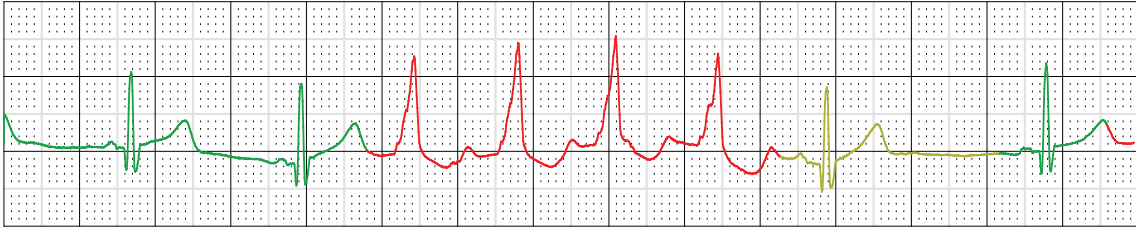
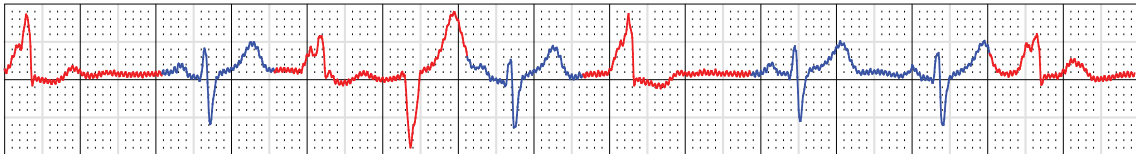
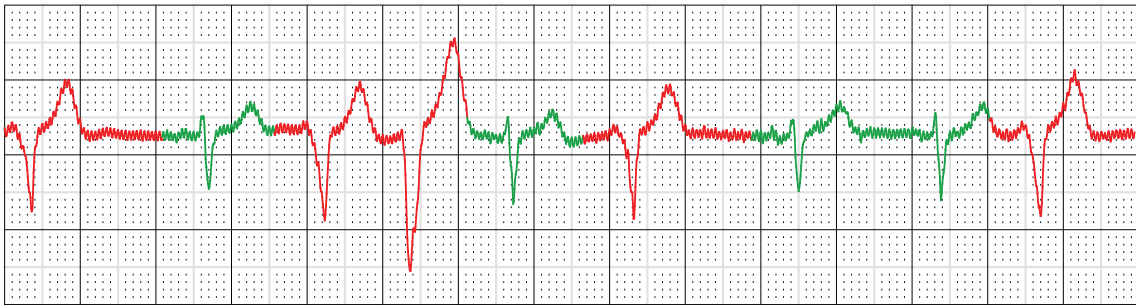
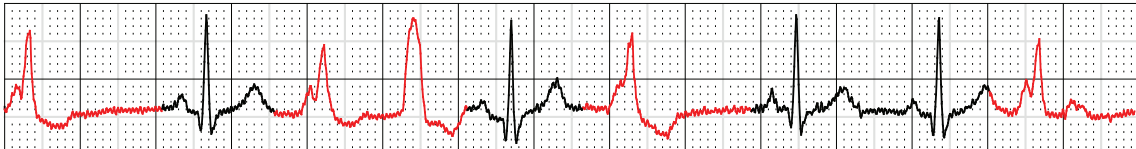


Diagram 3. Third display of segment from 24 h Holter-monitoring of heart- report in investigated students with mitral valve prolapse: TABLE of evidenced heart rhythm disorders, ECG details-bigeminy, couplet, trigeminy.

Heart rates, RR intervals	Average	Max	Min	Max time	Min time	
HR [1/min]	80	139	53	15.5.2008 15:35	16.5.2008 06:04	
HR equivalent intervals [ms]	750					
RR filtered [ms]	778	1493	346	16.5.2008 09:26	15.5.2008 17:02	
RR unfiltered [ms]	741	2166	180	15.5.2008 21:25	15.5.2008 15:32	
Tachy / brady / pause	Number of events			Longest event		
			Time	Length		
Tachycardia	597		15.5.2008 15:30	5 min 17 s		
Bradycardia	3		16.5.2008 06:04	15 s		
Pause ( 2.5 s )	0					
QRS statistics						
	Total	Max/h	Longest		Highest rate	
			Duration	HR [1/min]	Duration	HR [1/min]
Ves						
Isolated	30517	1832				
Couplet	360	96				
Triplet	8	3				
V-tachycardia	0	0				
Bigeminy	640	103	6 min 6 s	78	0 s	180
Trigeminy	2232	175	2 min 55 s	82	2 s	135
V.rthym non s.	26					
V.rthym sus.	12					
RBBB	206					
LBBB	7800					
V.fibrillation	2					
SVES						
SVES	12935	1091				
SV-tachycardia	25	4	00:00:03	98	00:00:02	203
Atrial fibrillation	180					
ECG detail 3.1.2008 14:33:11 25 mm/s 10 mm/mV HR=80						
A + 						
Beats v N v v n v N N V bigeminy V-couplet bigeminy						
B + 						
C + 						

It is accepted that it is necessary that the systolic movement of valve locks to be at least 3 mm away from the line connecting points C and D, and therefore it is called pansystolic PMV. The most important role in the diagnosis of PMZ has echocardiography.

The main criteria for confirmation of PMV in 1 D technique is finding of telesystolic or holosystolic displacement of posterior mitral leaflet to the locks. Application of 2 D techniques has contributed to more secure diagnosis of PMV. One dimensional technique shows sudden motion of the mitral valve toward LA in mesosystola or telesystola. Echocardiography criteria for the classification of PMZ to classical and non-traditional are performed by the (Freed et al.) in Framingham study. Chest skeletal abnormalities, such as straight thoracic spine and pectus excavatum are commonly associated with MVP. Approximately (10 to 15%) of students surveyed showed biphasic and inverted T-waves in the lower lines, then the ST segment changes, various arrhythmias. The most common rhythm disorders are ventricular arrhythmias, sinus tachycardia, supraventricular and ventricular arrhythmias are these are the most common clinical manifestations.

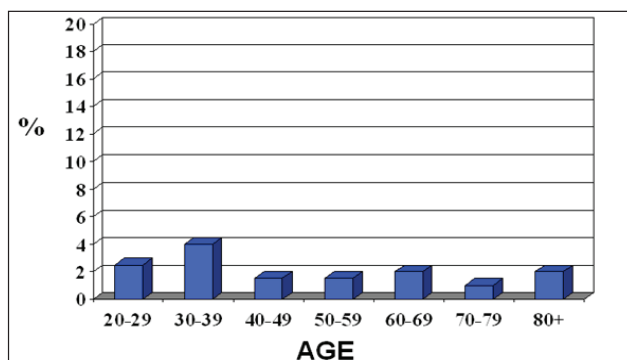
The most common are ventricular premature strokes, with Holter monitoring they were found in (58% - 90%) of investigated students. In all patients, the types of ventricular arrhythmias are not equal. In about half of patients complex ventricular arrhythmias can be found, including salvo, while at other ventricular arrhythmias are rare. Atrial rhythm disturbances are frequently found. With Holter monitoring they were found (35% to 64%) of students. Ranging from simple, single, to complex, including supraventricular paroxysmal tachycardia (48.6%) of investigated students, atrial fibrillation and flutter (31.2%) in investigated students. In these patients often changes in sinus rhythm often happens, including sinus tachycardia, sinus bradycardia, or sinus arrhythmia Tachyarrhythmia extrasystolica ventricularis et supraventricularis was found in (44.00%) of students; Ventricular tachycardia in (7.34%) of students. Mitral valve prolapse (MVP) is the most common condition of the heart valves. Some studies show it affects 6% of all women. MVP is extremely interesting since it is so commonly diagnosed in young women and yet, the incidence decreases markedly in elder women. This drop off in

incidence is not seen in the male population (refer to graph below). The occurrence of MVP in men is consistent in both young and old populations. Previous to the Framingham study, the incidence of MVP was thought to be much higher in women, however, with this new data, it is now believed that MVP affects equal numbers of men and women. This intrigues researchers searching for the cause(s) of mitral valve disease and attempting to explain why the condition manifests itself so differently in men and women. The cause of MVP is usually unknown but occasionally, MVP is associated with other heart conditions (e.g. atrial septal defect, coronary artery disease, diseases of the heart muscle) but most likely, these diseases would have been present with or without MVP. The outcome from MVP differs for men and women too. Recent studies have indicated that, for men, the incidence of mitral prolapse requiring surgical intervention is higher than for women and increases with age. The two graphs below depict the differences in the incidence of mitral valve prolapse in men and women. As the graphs indicate, the incidence remains rather consistent in the male population. Contrastly, occurrence starts off high in females, then sharply declines in older women. Data is derived from the Framingham study.

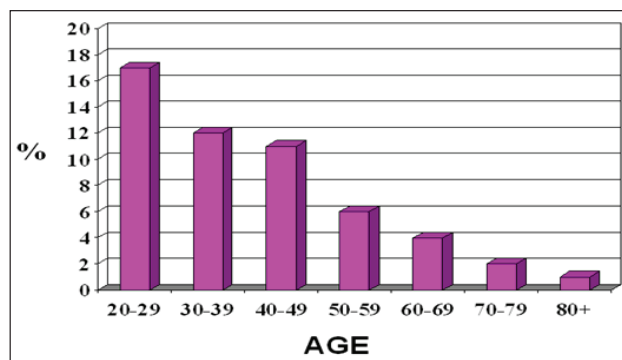
## Conclusion

Mitral valve prolapse was documented in 11 boys (28,21%) associated to following conditions: Athletes' heart 1 (2,56%); Atrial fibrillation 6 (15,38%); Hypertensio art. 3 (7,69%); Insuffitientio valvulae aortalis 1 (2,56%); Insuffitientio valvulae mitralis gr.II 1 (2,56%); Insuffitientio valvulae mitralis gr.III 1 (2,56%); LBBB 1 (2,56%); RBBB 2 (5,13%); St. post syncope 2 (5,13%); St. post febris rheumatica a.a. XXXXV 1 (2,56%); SV tachycardia 10 (25,64%); Tachyarrhyth. extrasystolica supraventricularis 2 (5,13%); Tachyarrhyth. extrasystolica ventric. et supraventricularis 8 (20,51%); Tonsillopharyngitis chr. 1 (2,56%); V. rhythm sus 5 (12,82%); V. tachycardia 2 (5,13%).

Mitral valve prolapse was documented in 44 girls (62,86%) associated to following conditions: Atrial fibrillation 28 (40%); Cardiomiopathia periparthialis susp 1 (1,43%); Focalosis 3 (4,29%); Graviditas HBD XXXVI H gestosis XXXV 1 (1,43%); Hyper-



Graphic 1. Echocardiographical incidence of MVP in males



Graphic 2. Echocardiographical incidence of MVP in females

tensio art. 4 (5,71%); Hyperthyreosis 4 (5,71%); Insuffitientio valvulae aortalis gr I 1 (1,43%); Insuffitientio valvulae mitralis gr.I 3 (4,29%); Insuffitientio valvulae mitralis gr. II 1 (1,43%); LBBB 1 (1,43%); Prolapsus cum regurgitatio valvulae mitralis 25 (35,7%); RBBB 4 (5,71%); Regugitatio valvulae mitralis et tricuspidalis 2 (2,86%); Athletes'Heart Syndrom 1 (1,43%); St. post syncope 3 (4,29%); St. post febris rheumatica a.a. XIV 1 (1,43%); St. post febris rheumatica a.a. XX 1 (1,43%); St. post febris rheumatica a.a. XXII 1 (1,43%); SV. tachycardia 43 (61,4%); Tachyarrhyth. extrasystolica ventric. et supraventricularis 40 (57,1%); Tachycardia 4 (5,71%); Tonsillopharyngitis chr. 8 (11,4%); V. tachycardia 6 (8,57%).

Mitral valve prolapse was documented in 55 patients (50,46%) associated to following conditions: Atrial fibrillation 34 (31,2%); Cardiomyopathia peripartialis susp 1 (0,92%); Focalosis 3 (2,75%); Graviditas HBD XXXVI H gestosis XXXV1(0,92%); hypertensio art. 7 (6,42%); Hyperthyreosis 4 (3,67%); Insuffitientio valvulae aortalis grade I 1 (0,92%); Insuffitientio valvulae aortalis 1 (0,92%); Insuffitientio valvulae mitralis gr.I 3 (2,75%); Insuffitientio valvulae mitralis gr.II 2 (1,83%); Insuffitientio valvulae mitralis gr.III 1 (0,92%); LBBB 2 (1,83%); Prolapsus cum regurgitatio valvulae mit. 25 (22,9%); Prolapsus valvulae mitralis 16 (14,7%); RBBB 6 (5,5%); Regugitatio valvulae mitralis et tricuspidalis 2 (1,83%); Athletes' heart 2 (1,83%); St. post syncope 5 (4,59%); St. post febris rheumatica a.a.XIV 1 (0,92%); St. post febris rheumatica a.a.XX 1 (0,92%); St. post febris rheumatica a.a.XXII 1 (0,92%); St. post febris rheumatica a.a.XXXXV 1 (0,92%); SV. tachycardia 53 (48,6%); Tachyarrhyth. extrasystolica supraventricularis 2 (1,83%); Tachyarrhyth. extrasystolica ventric. et supraventricularis 48 (44,00%); Tachycardia 4 (3,67%); Tonsillopharyngitis chr. 9 (8,26%); V. rhythm sus 25 (22,9%); V. tachycardia 8 (7,34%).

In most situations, the prognosis for patients with mitral valve prolapse is excellent. MR is the most significant risk factor for other complications (e.g., sudden death, stroke, endocarditis, atrial and ventricular arrhythmia). Patients whose echo shows abnormal valve anatomy, men, and those older than 45 years are at an increased risk of developing MR. Cardiovascular mortality is predicted the most by moderate-to-severe MR and ejection fraction less than 50%, and less so by left atrial size greater than 40 mm, flail leaflet, atrial fibrillation.

Patients with a murmur, patients who have echo evidence of nontrivial MR, thickening should inform their dentist and surgeon, although antibiotic prophylaxis prior to dental, respiratory, or infected skin or musculoskeletal tissue procedures would only be indicated if there was a history of infective endocarditis. Patients with palpitations should avoid caffeine, alcohol, stimulants, and smoking. Symptoms of the classic mitral valve prolapse (MVP) syndrome may improve with exercise, meditation, and biofeedback may be involved in the etiology of this sudden hearing loss. Blood pressure control may diminish the risk of progression to mitral regurgitation (MR). Exercise; biofeedback; meditation; and avoidance of smoking, alcohol, caffeine, and stimulants may prevent symptoms.

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# Diagnosis and treatment of traumatic hemothorax

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## Abstract

**Introduction:** Hemothorax marks the presence of blood in the pleural space. Mostly hemothorax occurs as the consequence of the penetrating or blunt trauma of the chest.

**Methods:** For this retrospective, non-interventional study, the data from medical records and operation protocols in Clinical Center Kragujevac are used, in three years period.

**Results:** 86 patients are hospitalized with a diagnosis of the traumatic hemothorax. Traumatic hemothorax caused by the blunt trauma within the observed period had 70 subjects, and penetrating injury had 16 patients. At patients with the blunt trauma of chest, in 31.4% of cases the polytrauma was recorded, and at 68.6% of subjects the chest injury was isolated. Polytrauma was recorded at 31.3% of cases, and an isolated injury of the chest at 68.7%. At hemothorax after the penetrating and blunt trauma there was not reported any statistically significant difference in incidence of unilateral and bilateral hemothorax ( $p=0.186$ ). Statistically significant difference was found in the definitive therapeutic procedure ( $p=0.001$ ). At the blunt trauma, the pleural puncture was done at forty subjects, thoracic drainage at 23 and thoracotomy at 7 patients. At penetrating injury, the pleural puncture was done at 12.5%, thoracic drainage at 50%, and thoracotomy at 37.5% patients.

**Conclusion:** Results show the similarity with other studies, in incidence of hemothorax occurrence as well as in gender-age profile of patients, and the procedure of their treatment, taking in account the observed time period and population in the trial.

**Key words:** Hemothorax, thoracic drainage, thoracotomy.

## Introduction

Hemothorax marks the presence of blood in the pleural space. Mostly occurs as the consequence of the penetrating or blunt trauma of the chest. In rare cases, the hemothorax can be the consequence of an iatrogenic injury. Blood gets in the pleural space after the injury of the chest wall, diaphragm, lungs or mediastinum. Incidence of hemothorax is high at the blunt trauma, even to 37%, and associated with the pneumothorax (hemopneumothorax) up to 58%. Occurrence of the hemothorax is almost comparably frequent without the rib fracture (35%) or associated with the rib fracture (38%). [1, 2]

Hemothorax, after the thoracic trauma, is diagnosed by the presence of the pleural fluids at the radiography of the chest. Development of the traumatic hemothorax can be noticed immediately after injury or the bleeding in the pleural space occurs later, after a few hours or days. Postponed occurrence of hemothorax is also recorded after the blunt and penetrating injury of the chest. [3, 4] Computerized tomography (CT) is a very sensitive method for detection, even small pleural collections of fluid. It is proved method for differentiation of hydrothorax from hemothorax. [5] However, this method is rarely applied at the acute injured patients. Basic aims of the hemothorax therapy are: to evacuate collected blood from the pleural space, to establish the full reexpansion of lungs and to establish the tamponade of the bleeding area by bringing lungs in an immediate contact with parietal pleura. Compensation of the lost blood is parallelly performed with the hemothorax treatment. [6, 7] Treatment of the traumatic hemothorax depends on many parameters including the following: general state of the injured, state of the vital functions, character of the injury, i.e. whether it is the question of isolated thoracic injury or it is

a part of the polytrauma, state of the injured part of the chest (unilateral or bilateral injury) and the occurrence of bony structure fracture, comorbidity of many associated intrathoracic injuries, quantity of lost blood and possible area of bleeding, if the bleeding is recorded immediately after admission or it is detected a few hours or days after the injury, if there is associated pneumothorax with hemothorax etc. [2, 8, 9] Basic precondition for success of thoracic drainage is that the blood in the pleural space is not coagulated. It is applied in most cases not only as the first therapeutic method, but it is definitive therapeutic procedure. By thoracic drainage 85% of patients with the chest injury are treated. At right diagnosed complications for the thoracic drainage, the possibility of occurrence of later complications is decreased [10, 11, 12] Basic aim of the thoracic drainage is to evacuate the pleural content (air and fluid) and to achieve the full expansion of lungs. Urgent thoracotomy was indicated at the hemothorax, complicated by a heart tamponade, injuries of large intrathoracic blood vessels, primary pleural contamination, debridement of devitalized tissue, open thoracic wounds and at the tracheobronchial injuries. Indications for urgent thoracotomy are special after placement of the thoracic chest tube and assessment of the volume of the continued pleural bleeding, i.e. quantity of lost blood in continuity through the thoracic drain. General rules include the rule that urgent thoracotomy is indicated in case of the constant loss at the thoracic chest tube is 200ml per hour, in case that there are no indications to stop the bleeding. It was shown that the pneumonectomy should be avoided in any case, for the mortality after such an operation is almost 100%, i.e. such a resection should be done only if there is no other choice. [13, 14, 15] Frequently the wedge-shaped resection is applied, resection of segments and lobectomy, and it is possible to apply staplers. [16, 17] Thoracotomy is necessary at the traumatic hemothorax at around 20% of the injured. In modern conditions, in cases of the occurrence of hemothorax, the video-assisted thorascopic surgery (VATS), can be applied, but up to recent experiences are still rather modest that it can be accepted that this surgical method belongs to the routine therapeutic methods. [18, 19]

## Aim

Aim of this work is to analyse hemothorax occurrence incidence, a patient's profile, the way of making a diagnosis and surgical treatment of the hemothorax within the Clinic for General and Thoracic Surgery, Clinical Center Kragujevac in the period of three years.

## Materials and methods

This is non-interventional study according to the type of case series. For analysis the data from medical records and operation protocols are used, within the Clinic for General and Thoracic Surgery, Clinical Center Kragujevac, Serbia in the period starting from 01. 01. 2008. to 31. 12. 2010. Patients are divided into two groups for the comparative analysis of all tested parameters, patients with blunt trauma and patients with penetrating trauma as causes for the hemothorax occurrence. Retrospective statistical analysis is done, when the following parameters were processed: division of patients according to the gender, age and place of residence, total number of the injured, as well as the number of injured with the hemothorax, etiological cause of injuries, individually and in both groups separately, relation of an isolated thoracic injury toward the associated injuries of other organs and the chest, referring to the occurrence of hemothorax, total number of unilateral and bilateral hemothoraxes according to the etiological cause of the injury, time period from the moment of injury to the first aid administration and the time period of specialist surgery aid administration, applied diagnostical method for hemothorax determination- especially the radiography of the chest, the first therapeutic procedure at the hemothorax for both groups separately, in relation to the quantity of effusion and the state of the extension of the lung parenchyma, an immediate effect of the first therapeutic procedure, the choice of the definite therapeutic procedure, complications of injuries and their incidence, treatment and final treatment result. For statistical data processing, the objective mathematical and statistical method is used, properly applied to the data variety and type and the statistical test: methods of the descriptive statistics (in Tables, Graphs) and method of non-parametric statistical tests ( $\chi^2$ -test).



## Results

Total number of the injured and treated patients at the Clinic for General and Thoracic Surgery, Clinical Center Kragujevac, Serbia were 1853 patients in total, in the period 01. 01. 2008. - 31. 12. 2010. In the observed period, the injury of chest was diagnosed at 308 patients, being 16.2% from the total number of injuries. General characteristics of the injured, radiographic findings and vital parameters during admission into the hospital are shown in Tables 1 - 4.

Traumatic hemothorax caused by the blunt trauma in the observed period of three years had 70 subjects ( 3.77% from all recorded injuries), but observing only the chest injuries, 22.8% of patients were with this injury. Observing only the chest injuries with present hemothorax, 81.4% of those injuries were caused by the blunt trauma. As mechanisms of the injury caused by the blunt

trauma the following were recorded: fall from the height at 18 patients (25.71% of cases), traffic trauma at 38 patients (54.29%), fight is recorded at 9 subjects (12.86), crush at 5 (7.14%), while trapping was not recorded at any subject. (Graph 1) Within the observed period, the traumatic hemothorax caused by the penetrating injury had 16 patients (0.86% of all injuries). Observing only the chest injuries, 5.14% of these injuries were the penetrating injuries with hemothorax. In the population of the traumatic hemothoraxes (86 subjects), during the observed three years, 18.75% was sustained by the penetrating injury. Most frequent way for the injury was a stab wound during the fight at 8 subjects (50% of all traumatic hemothoraxes caused by the penetrating injury). Penetrating gunshot injuries at two subjects (12.5%), perforating gunshot wounds, as well as the accidental stab wounds at three patients (18.75%), while the iatrogenic stab wound was not recorded

Table 1. General characteristics of subjects with the chest injury

Observed parameters			Average values and incidences (in relation to 308 subjects with chest injury)
Sex		Men	228 (74%)
		Women	80 (26%)
Average age of all subjects (X±SD)			56.66±3.52
Average age (X±SD)		Men	58.2±2.36
		Women	55.12±3.12
Presence of subjects of different sex by observed age groups	15-25 years	Men	30 (9.74%)
		Women	0 (0%)
	26-35 years	Men	40 (12.99%)
		Women	8 (2.6%)
	36-45 years	Men	39 (12.66%)
		Women	13 (7.47%)
	46-55 years	Men	53 (17.21%)
		Women	18 (5.84%)
	56-65 years	Men	39 (12.66%)
		Women	16 (5.19%)
	66-75 years	Men	20 (6.49%)
		Women	13 (4.22%)
	Over 75 years	Men	7 (2.27%)
		Women	2 (0.65%)
Place of residence	City		142 (46.1%)
	Village		166 (53.89%)
Type of thoracic injury	Blunt trauma		238 (77.27%)
	Penetrating trauma		70 (22.73%)



Table 2. General characteristics of subjects with hemothorax during admission to the hospital

Observed parameters		Average values and incidences (in group of 86 subjects with hemothorax)	
Sex	Men	67 (77.9%)	
	Women	19 (22.1%)	
Average age of all subjects (X±SD)		53.38±15.46	
Diagnosis at admission		Polytrauma	27 (31.4%)
		Isolated injury	59 (68.6%)
Type of injury	Blunt injury	Fall from height	18 (20.93%)
		Traffic trauma	38 (44.19%)
		Fight	9 (10.47%)
		Crush	5 (5.81%)
	Penetrating injury	Penetrating gunshot wounds	2 (2.33%)
		Perforating gunshot wounds	3 (3.49%)
		Stab wounds in fight	8 (9.3%)
		Accidental stab wounds	3 (3.49%)

Table 3. X-ray findings-PA radiography at admission

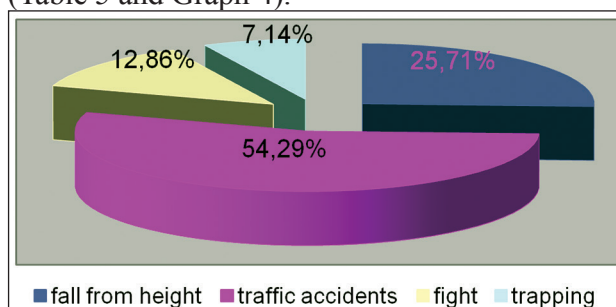
Observed parameters		Average values and incidences (in group of 86 subjects with hemothorax)
Rib fracture	Yes	58 (67.4%)
	No	28 (32.6%)
Localization of rib fracture	Up to V rib	18 (20.9%)
	From VI to XII rib	25 (29.1%)
	Associated	15 (17.4%)
Place of rib fracture	Anterior rib-ends	8 (9.3%)
	Posterior rib-ends	21 (24.4%)
	Lateral rib-ends	29 (33.7%)
Type of rib fracture	One-fold	47 (54.7%)
	Double	11 (12.8%)
X-ray findings at admission	Normal findings	51 (59.3%)
	Pleural effusion	35 (40.7%)

Table 4. Vital signs and laboratory findings of subjects with hemothorax at admission

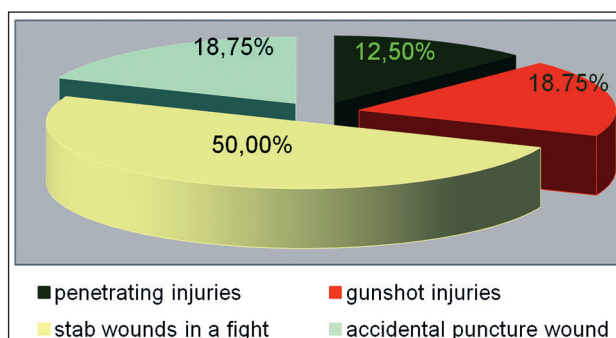
Observed parameters		Average values and incidences (in group of 86 subjects with hemothorax)
State of consciousness at admission	Conscious	78 (90.7%)
	Without conscious	8 (9.3%)
Breathing	Dyspnoea	40 (46.5%)
	Eupnoea	46 (53.5%)
Average value of systolic pressure (X±SD) (mmHg)		116.1±22.13
Average value of diastolic pressure (X±SD) (mmHg)		72.79±13.92
Average value of pulse (X±SD) (1/min)		94±13.99
Average value of saturation (X±SD) (%)		91.9±5.93
Average value of erythrocyte number (X±SD) (x10 <sup>-12</sup> )		3.26±0.63
Average value of haemoglobin (X±SD) (g/l)		109.08±19.32

at any patient. (Graph 2) Observing subjects with the traumatic hemothorax (86 subjects), there is no any statistically significant difference in the presence of patients with polytrauma and isolated chest injury in groups of subjects with hemothorax caused by the blunt or penetrating chest injury ( $\chi^2$ -test;  $p=0.989$ ). At patients with the blunt chest trauma in 31.4% of cases (22 subjects) were recorded the polytrauma, and in 68.6% (48 subjects) the isolated chest injury. Almost identical relation was in the group with the penetrating chest injury where the polytrauma was recorded in 31.3% of cases, and isolated chest injury in 68.7%. (Graph 3). 52 patients were with hemothorax and without lung collapse at admission, and it is 60.47% of recorded hemothoraxes. Observed in relation to the injury type, 48 i.e. 92.31% of patients with hemothorax and without lung collapse at admission had the injury caused by the blunt trauma, while only 4 patients (7.69%) had the penetrating chest injury. Taking into account the whole group of subjects with hemothorax, 55.81% of subjects were with the hemothorax caused by the the blunt injury and without lung collapse at the admission, while 4.65% of patients had the hemothorax caused by the penetrating injury and without lung collapse at the admission. At the hemothorax, after the penetrating and blunt trauma (86 subjects) , there was no any statistically significant difference in the incidence of an unilateral and bilateral hemothorax ( $\chi^2$ -test;  $p=0.186$ ). After the blunt trauma there were 58 unilateral subjects (82.86%) or 67.45% from all hemothoraxes. Bilateral hemothoraxes were 12 (17.14% from all hemothoraxes caused in this way i.e. 13.95%). After the penetrating chest injury, in 93.75% (15 subjects) the unilateral hemothorax is recorded. Bilateral hemothorax is

recorded only in one case (6.75%). In the group of unilateral hemothoraxes there were 17.24% of subjects, who were injured after the fall from the height, and traffic trauma was present in 50% of cases and it was the most frequent cause for this type of injury. In 27.59% of cases the fight was recorded as a cause for the unilateral hemothorax, and in 5.17% of cases, the crush was recorded as a mechanism of injury. Interval between the time passed from the moment of injury to the administering first aid and specialist aid was observed. (Table 5 and Graph 4).



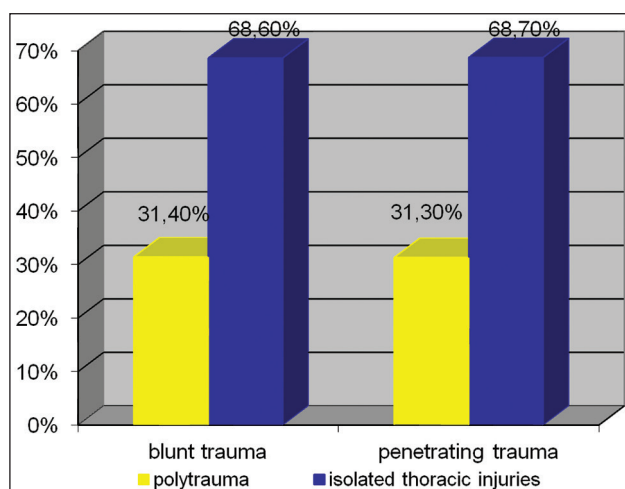
Graph 1. Ways of getting traumatic hemothorax caused by blunt trauma



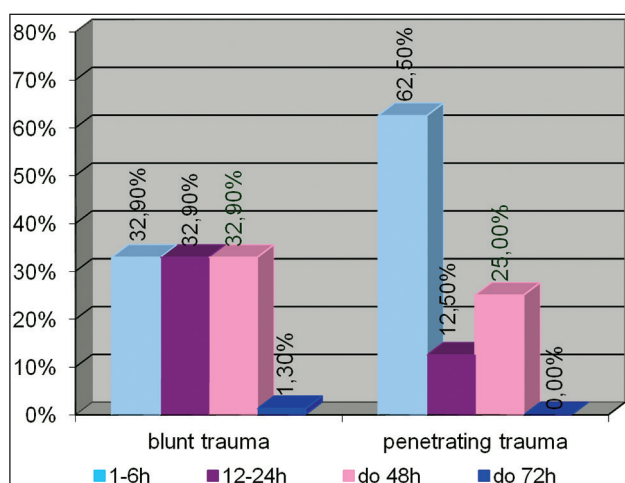
Graph 2. Ways of getting traumatic hemothorax caused by penetrating injury

Table 5. Time of administering of specialist aid at subjects with hemothorax caused by blunt i.e. penetrating chest injury

Time of administering first specialist aid	Hemothorax caused by blunt trauma N° 70(% in relation to all traumatic hemothoraxes)	Hemothorax caused by penetrating trauma N° 16(% in relation to all traumatic hemothoraxes)
1-6 <sup>h</sup>	23 (26.6%)	10 (11.6%)
7-12 <sup>h</sup>	0 (0%)	0 (%)
12-24 <sup>h</sup>	23 (26.6%)	2 (2.3%)
to 48 <sup>h</sup>	23 (26.6%)	4 (4.7%)
to 72 <sup>h</sup>	1 (1.2%)	0 (0%)



Graph 3. Presence of polytrauma and isolated chest injuries at patients with blunt and penetrating chest injury and hemothorax



Graph 4. Time intervals when first specialist aid was administered at subjects with various ways of injury

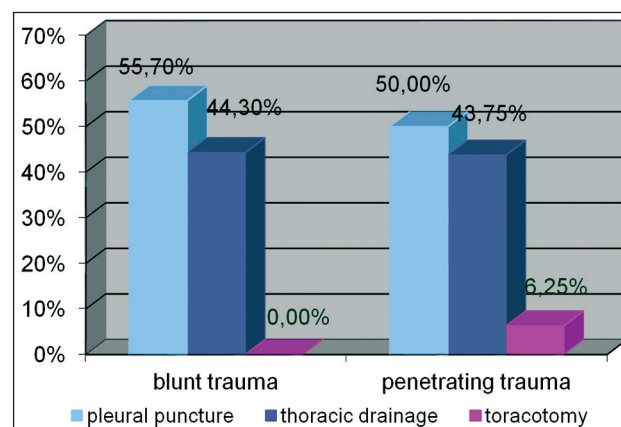
Time of administering first aid and time of specialist surgical aid correspond in the observed group of subjects. Time of administering first aid and specialist surgical aid was observed in relation to the trauma type, but it did not statistically differ ( $\chi^2$ -test;  $p=0.224$ ). Administering first aid was observed in time intervals, starting from 1 - 6<sup>h</sup>, 7 - 12<sup>h</sup>, 12 - 24<sup>h</sup>, to 48<sup>h</sup>, to 72<sup>h</sup> and over 72<sup>h</sup>: At the blunt trauma 23 subjects got the first specialist aid in periods starting from 1 - 6<sup>h</sup>, 12 - 24<sup>h</sup> and to 48<sup>h</sup> after injury, i.e. 32.9%, for all three observed periods in total, 98.7% of subjects with the hemothorax after the blunt trauma. To one of patients (1.3%), the first specialist aid was administered in the period up to 72<sup>h</sup>. At penetrating injuries, more than half of su-

bjects, 10 of them (62.5% from all hemothoraxes caused by the penetrating injury) got the first specialist aid during the first 6 hours. 2 patients (12.5%) got the first specialist aid in the period starting from 12 - 24<sup>h</sup>, and 4 patients (25%) in the period up to 48<sup>h</sup>. During the first examination, the findings at the Roentgen – at the chest statistically differed significantly among subjects with the blunt and penetrating chest injury ( $\chi^2$ -test;  $p=0.049$ ). By analysis of the difference, there is greater presence of subjects with the normal findings in the group with the blunt injury (64.28%) than in the group with the penetrating injury (37.5%). Pathological findings were found in 35.72% of subjects with the blunt and 62.5% of subjects with the penetrating injury. Among subjects with the blunt and penetrating chest injury, the statistically significant difference in incidence of subjects with the different position at the first RTG of the chest ( $\chi^2$ -test;  $p=0.000$ ). In the subject group with the blunt injury, at 52.86%, the first RTG was done in the sitting position, 25.71% was in the lying position, the least x-ray was in standing position. At the penetrating trauma, in 75% of cases the first chest x-ray was done in the lying position, and at 25% in the sitting position. In the Table 6 analyses of therapeutic procedures were shown in 86 subjects, applied as the first method after admission into hospital. Among subjects with the traumatic hemothorax caused by the blunt and penetrating chest injury, there is no any statistically significant difference in the first therapeutic procedure ( $\chi^2$ -test;  $p=0.108$ ). At the hemothorax caused by the blunt trauma, as the first therapeutic procedure in 39 patients, the pleural puncture was done (55.7% from all subjects with the blunt chest injury and hemothorax), in 31 (44.3%) subjects, the thoracic drainage was done. In the group with the penetrating injury, the pleural puncture was done at a half of patients, eight of them in total, the thoracic drainage at seven patients (43.75%) and thoracotomy at one patient (6.25%). (Graph 5) Among subjects with different way of the chest injury, there was no any statistically significant difference in the quantity of evacuated blood during the first therapeutic procedure ( $\chi^2$ -test;  $p=0.797$ ). At subjects with the blunt chest injury and hemothorax in most cases 31 (44.3% of all blunt chest injuries with hemothorax) 300 - 500ml of blood was evacuated, at 27 patients (38.6%) 500 - 1000ml, over 1000ml at eight subjects (11.4%), at four of them (5.7%) from

1000 - 3000 ml. In the group of subjects with the penetrating chest injury and hemothorax at 6 patients (37.5%) from 300 - 500ml of blood was evacuated, at the same number of subject from 500 - 1000ml of blood was evacuated, while the blood quantity of 100 - 300ml and over 1000 ml was evacuated at 2 patients each (12.5%). There was no any statistically significant difference in the occurrence of lung collapse after the first therapeutic procedure between subjects with the blunt and penetrating chest injury ( $\chi^2$ -test;  $p=0.124$ ). Lung collapse was noticed at 6 patients (8.57%) with the blunt chest trauma and at 2 patients (12.5%) with the penetrating chest trauma. Statistically significant difference was found in the definitive therapeutic procedure ( $\chi^2$ -test;  $p=0.001$ ). (Table 7)

At the blunt trauma, the pleural puncture was done at 40 subjects (57.14%), thoracic drainage at 23 (32.86%) and thoracotomy at 7 patients (10%). At the penetrating injury, the pleural puncture was done at 2 (12.5%), thoracic drainage at 8 (50%), and thoracotomy at 6 patients (37.5%). (Graph 6) At subjects with the blunt chest injury, the statistically significant difference was found at the presence of

subjects with and without complications among different therapeutic procedures ( $\chi^2$ -test;  $p=0.002$ ). By analysis of difference, the least presence of complications was noticed at the pleural puncture, only 4 cases (13.78% from those with pleural puncture done in the aim of treatment of hemothorax caused by the blunt trauma), at the thoracic drainage 7 patients (30.44%) had some of the mentioned complications, while at the thoracotomy complications was recorded at 5 subjects (71.44%). (Graph 7)



Graph 5. First therapeutic procedure and trauma type

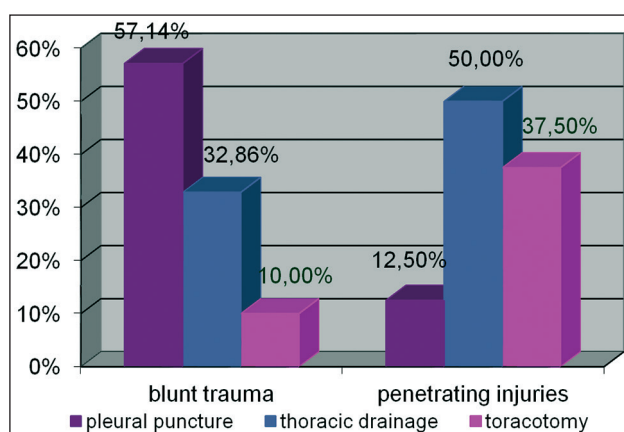
Table 6. Therapeutic procedures, types and quantity of obtained content

Therapeutic procedures			Presence of patients N° 86(% in relation to trauma type)	
			Blunt trauma	Penetrating trauma
First therapeutic procedures	Pleural puncture		39 (55.7)	8 (50)
	Thoracic drainage		31 (44.3)	7 (43.75)
	Thoracotomy		0 (0)	1 (6.25)
Obtained content	Pleural puncture	Coagulate	9 (12.9)	1 (6.3)
		Uncoagulate	30 (42.9)	7 (43.8)
	Thoracic drainage	Coagulate	22 (31.4)	6 (37.5)
		Uncoagulate	9 (12.9)	1 (6.2)
	Thoracotomy	Coagulate	0 (0)	1 (6.2)
		Uncoagulate	0 (0)	0 (0)
Quantity of obtained content	Pleural puncture	100-300ml	4 (5.7)	2 (12.5)
		300-500ml	30 (42.9)	5 (31.3)
		500-1000ml	5 (7.1)	1 (6.3)
		Over 1000ml	0 (0)	0 (0)
	Thoracic drainage	100-300ml	0 (0)	0 (0)
		300-500ml	1 (1.4)	1 (6.3)
		500-1000ml	22 (31.4)	5 (31.3)
		Over 1000ml	8 (11.4)	1 (6.3)
	Thoracotomy	100-300ml	0 (0)	0 (0)
		300-500ml	0 (0)	0 (0)
		500-1000ml	0 (0)	0 (0)
		Over 1000ml	0 (0)	1 (6.3)

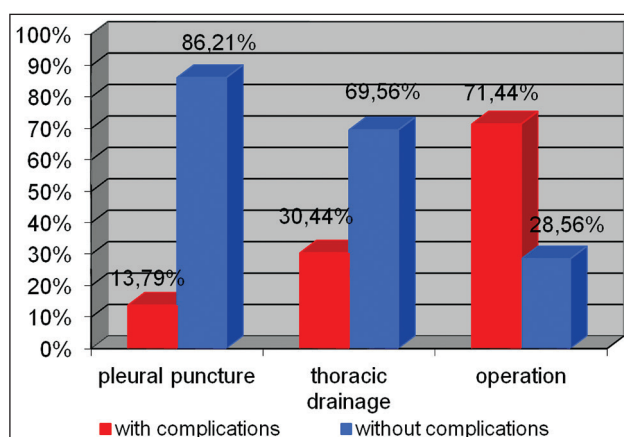


Table 7. Definitive therapeutic choice at hemothorax

Definitive therapeutic choice		Presence of patients N° 86(% in relation to trauma type)	
		Blunt trauma	Penetrating trauma
Conservative treatment	Observation	11 (15.71)	0 (0)
	Pleural puncture	29 (41.43)	2 (12.5)
Thoracic drainage		23 (32.86)	8 (50)
Thoracotomy	Suture of lungs	2 (2.86)	3 (18.75)
	Suture of lungs with resection of chest wall and plastic	1 (1.43)	0 (0)
	Resection of lungs	3 (4.29)	3 (18.75)
	Resection of lungs with partial resection of chest and plastic	1 (1.43)	0 (0)



Graph 6. Definitive therapeutic approach at subjects with hemothorax caused by the blunt and penetrating chest injury



Graph 7. Presence of complications in relation to the type of applied treatment in the group of subjects with the blunt chest trauma and hemothorax

## Discussion

Analysis encompasses 86 patients with the traumatic hemothorax in total. This group of patients was isolated from the group of 308 injured

with the blunt and penetrating chest trauma in total, who had a diagnosis and were treated at the Clinic for General and Thoracic Surgery in Kragujevac, Serbia in the period starting from 01.01.2008. to 31. 12. 2010. Hemothorax marks the presence of blood in the pleural space, in most cases it is the consequence of the penetrating or blunt chest trauma. In rare cases, the hemothorax can be developed as a consequence of the iatrogenic injuries. Blood gets into pleural space after: the injury of chest wall, diaphragm, lungs or mediastinal organs. When it gets into pleural space, the blood quickly coagulates, but it can happen, due to the movement of heart and lungs, that coagulum suffers defibrinization and the content can stay in fluid state. Present blood in the pleural space has a tendency to localize, encapsulate. [20, 21, 22] From 1853 injured, who were admitted, diagnosed and treated within the Clinical Center Kragujevac, Serbia during the analyzed period, 308 patients (16,2%) were with the thoracic trauma. From the group of the injured with the thoracic trauma, the group of 86 patients (27,92%) with the traumatic hemothorax was separated for the analysis and discussion, who did not have the lung collapse at admission. Further analysis of the group was done based on the etiological cause of the chest injury, i.e. in relation to the the blunt and penetrating injury. Observing the demographic data of the injured in the group of 308 patients with the thoracic trauma, the predominance of men is noticed (74% against 26%) in relation to the women, while in the age profile of the injured, it is almost identical (M=58,2 and W=55,12 years). At men the age profile is dominant, at the age of 46 - 55 years (23,25%), at women in the age of 36 - 45 years

(28,75%). However, it is interesting that among the injured men have 13,16% in the age of 15 - 25 years, while such a group at women does not exist. Also it can be noticed that in the age of 66 - 75 years, there were 8,77% men, women twice as many, i.e. 16,25%. Explanation of these data can be found in the structure of profession of the injured, in the whole group was more rural population i.e. 54% urban and 46% rural population, but also in data that the blunt trauma was present in 77,27%, and the penetrating only in 22,73% of the injured. Analysis of 86 patients with the hemothorax shows that the relation of genders among the injured is the same as in the previous group, i.e. M = 77,9% against W = 22,1%, while the age profile for both groups is on the average of 54 years. Separated chest injury is established at 59 (68,6%), but polytrauma followed by the hemothorax at 27 (31,4%) of the injured. Traffic trauma is dominant with 38 injured (44,19%), but the injury as a consequence of the fall from height is significantly present in 18 (20,93%), while among the penetrating injuries, the important role has a stab wound in the fight in 8 injured (9,3%). In the group of 86 injured with the hemothorax, the blunt thoracic trauma is like the etiological factor more present than the penetrating injury (81,4% the blunt trauma and 18,6% penetrating). Most common cause of the injury is the traffic trauma 54,29%, while in the group of the penetrating injury, a stab wound was present at 50% of the observed (8 to 16 injured). Analysis of the group of 308 patients with the thoracic trauma shows that the polytrauma was diagnosed at 34 of the injured (11,04%). As associated injuries with the chest injuries were the head injuries and CNS, limbs injuries and injuries of the intraabdominal organs. Polytrauma associated with the chest injuries is recorded at the blunt trauma, referring mostly to the traffic etiology. At the penetrating injury, in our analysis, wounds with knife stabbing are rarely associated with injuries of other organs. Traumatic hemopneumothorax is relatively frequent findings during analysis of the chest injuries. In our analysis, the hemopneumothorax is established at 60, 38% from 308 patients with the chest injuries. Hemopneumothorax is often caused by the blunt trauma, at 128 of the injured (68,8%) and at the penetrating injury at 58 of the injured (31,8%). Our analysis encompassed

in details the study of the injured with the hemothorax without the lung collapse. At the admission, the hemothorax during the initial examination was found at 52 of the injured (60,47%). In relation to the type of the injury at 48 of the injured patients (92,31%), the cause was the blunt trauma, while the penetrating injury associated with the hemothorax and without the lung collapse was found at only 4 patients (7,69%). Time of administering first aid and specialist surgical aid in the observed group of subjects corresponded to each other. Time of administering first aid i.e. specialist aid observed in relation to the type of trauma did not statistically differ. At the hemothorax caused by the blunt trauma, the aid was administered at 98,7% of patients, in the period up to 48 hours after the injury, i.e. in first 24 hours at 53,2% of the injured. At the penetrating injury the aid was administered at 62,5% of the injured in first 6 hours after the injury. Data referring to the time period passed from the moment of the injury to the diagnosis of the thoracic trauma, in the concrete case of hemothorax were manifold significant. It is the fact index related to the organization of health service, but it has the connection with the quality of diagnostic procedure and prediction related to the final outcome of the treatment. In our analysis, it was shown that the time period from the moment of the injury to the moment of administering aid was satisfactory, due to the fact that part of patients with the hemothorax come to the examination independently, especially those with the blunt chest injuries caused by the fall from the height or in the fight, not rare cause for injuries in our analysis. Diagnosis of the traumatic hemothorax should be taken into account at each patient with the blunt and penetrating chest injury. Physical examination is very important to find out states that directly threaten the patient life. At each injured, regardless of the type of the thoracic injury, the radiographic examination was indicated, being the most important diagnostic method for detection of intrapleural collection of fluid. However, it should not be forgotten that in cases of a massive haemorrhage and hypovolaemia, it is necessary to make a diagnosis and therapy based on the clinical findings (for example, heart tamponade, valve pneumothorax, massive hemothorax etc.). In most cases during the admission of the injured into the

specialized institution, a standard native chest radiography is done in AP or PA position. Then, depending of the consciousness state of the injured, injury character, associated injuries and general state, x-ray is done in the lying position, lateral decubitus and upright position. Difficulties which may occur during the interpretation of the findings on the standard radiography are known, especially when it is done in the lying position. Spilt shadow of the effusion may be discreet and through such a shadow, the ornament of lungs can be noticed, even in cases when there is a significant quantity of fluid. In such cases it is useful to make x-ray in the lateral decubitus, if possible, or in the upright position in lateral, side projection, when the shadow of effusion can be clearly registered as the shadow which closes the costodiaphragmatic sinus. There are difficulties also referring to the detection of smaller quantity of the intrapleural fluid in cases when the associated findings are present, such as the subcutaneous emphysema, contusion of lung parenchyma, massive haematoma in the chest wall, rupture of right diaphragm etc. Standard radiography is not enough sensitive method for detection of the bilateral hemothorax, especially at smaller effusions (in cases when the bleeding is under 200 ml). At least, a surgeon must not forget some facts that the chest radiography does not indicate to functional disorders and it represents only the findings in the moment when x-ray is done. For that reason it is necessary to record the time during each radiography, as well as the position of the patient, and at the same time to complete the findings with functional parameters, for example gas analysis of the arterial blood, haemoglobin values, haematocrit and other. It is desirable that the following x-ray photography is done at the same position of the patient or, if possible, in the upright position. Importance of the repeated x-ray photography, in the time intervals after the first done at the admission is very useful, as shown in our analysis. Also our analysis shows that the hemothorax associated with the rib fracture was diagnosed at 57 subjects (81,43%) with the blunt chest trauma, and the fracture at the penetrating injury was recorded only at one injured. Unilateral fracture at the blunt trauma is diagnosed at 46 injured (65,71%), bilateral fracture at 11 (15,71%). Fracture of the first five ribs had 18 subjects

(25,71%), and the fracture from V - XII ribs was recorded at 24 (34,29%). Associated fractures, of the first and second group of the mentioned ribs had 15 subjects (21,43%). At 49 of the injured (70%) with the blunt trauma, the fracture of the posterior and lateral rib-ends was recorded. Fracture of the sternum is found at 11 patients (15,71%), often associated with the fracture of the anterior rib-ends (8 - 11,43% of the injured). Fractures of other bone structures of the chest are rare, associated fractures of the collar bone, scapula and thoracic vertebrae are recorded at 13 patients. In our analysis the associated injuries of heart or large blood vessels with the sternum fracture were not recorded, but one should always think about it. Choice of treatment for the injured with the traumatic hemothorax is the thoracic drainage. In the past, it was believed that the placement of the thoracic drain had the aim to stop the pleural bleeding by decrease of the pleural pressure. In fact, the assumption was that in cases when the bleeding was caused by the laceration of the pleura, by the decrease of pressure in the pleural space it came to the approaching of two pleurae and the tamponade by which the further bleeding stopped. However, when the bleeding is caused by the lacerated blood vessel, decrease of intrapleural pressure in the pleural space, realized by the thoracic drain, is not sufficient to overcome the transvascular pressure, it means that the bleeding continues. It is believed that in cases of traumatic hemothorax, the placement of thoracic drains of wider volume is indicated (size 36 to 40 FR), for the evacuated blood has a tendency to coagulate. In most cases it is advised to place drains in the mid axillary line through IV or V interrib space, due to the possibility of existence of the diaphragm elevation caused by trauma. Urgent thoracotomy is indicated in cases when there is a doubt about existence of the heart tamponade, the lung injury with significant laceration of the parenchyma and distinct haemorrhage, injuries of the large blood vessels, oesophagus and heart, when there is a primary contamination of the pleural space and foreign body in that space, when the debridement of devitalized tissue is indicated, at the open wounds on the chest wall and in cases of the air loss due to the tracheobronchial injury. It is noticeable that in the choice of the first therapeutic procedure we used: the pleural punctu-

re, thoracic drainage and urgent thoracotomy. It is noticeable that among subjects with the traumatic hemothorax there is no statistically significant difference in the choice of the first therapeutic procedure. At subjects with the hemothorax caused by the blunt trauma at 39 patients (55,7%) the pleural puncture was done, at 31 (44,3%) the thoracic drainage was applied. In the group with the penetrating injury and hemothorax, the pleural puncture and thoracic drainage were done in almost the same percentage of cases. Urgent thoracotomy was done only at one patient in the group with the penetrating injury. Choice of the first therapeutic procedure mostly depends on the general state of the patient, state of the chest wall and degree of damage, i.e. the existing fractures of the bone structure (ribs, their number and character – one-fold, double, posterior, lateral or anterior rib-ends), possibility of presence of associated injuries (especially intraabdominal organs), assessment if there is or there is not the diaphragm rupture, time passed from the record of the effusion, its volume, character and assessment of the injury mechanism etc. As in this study the hemothorax without collapse was researched, the choice of the first therapeutic procedure was aimed at and towards the basic request of the therapeutic procedure not to damage lungs during the intervention, i.e. potentially some of organs of abdominal cavity. In clinical assessment, we started from the fact that at the expended lung and movable chest wall there are conditions that blood, coming into the pleural space, can be defibrinized, i.e. that in time when its evacuation is planned, there won't be any coagulum formed. One of the basic criteria in the choice of the first therapeutic procedure was an assessment of the blood quantity expected during the first evacuation. Our analysis shows that the pleural puncture was applied in most cases in both groups of the injured, when 300 - 500ml of blood was evacuated, while the thoracic drainage was strictly applied at the injured, when the evacuation was from 500 - 1000ml or more than 1000ml. Next part of the analysis is related to differences in a character of the obtained content, i.e. if the blood during the first therapeutic procedure was coagulated or it did not happen. Such an analysis was done for we thought that it was useful for the later assessment of the choice for the definitive therapeutic procedure.

Among subjects, who were subjected to the various first therapeutic procedures, statistically significant difference was found in the obtained content in the group of subjects with the blunt chest trauma. Choice of the definitive therapeutic procedure was related mostly to results realized after the first therapeutic procedure. During making a decision it was important if the desired therapeutic aim was achieved after the first procedure, i.e. if the blood was fully evacuate and the lung stayed expended, and findings on the control x-ray photography provided the right choice. Further collection of blood or the unsuccess of the first procedure was indications for the change of the therapeutic procedure. Among subjects with the blunt trauma and penetrating injury with the hemothorax, statistically significant difference was found in the definitive therapeutic procedure. By analysis, the most frequent definitive therapeutic procedure at the blunt thoracic trauma for solving the hemothorax was the pleural puncture, done at 40 injured (57,14%), then thoracic drainage at 23 patients (32,86%) and thoracotomy at 7 injured (10%). At the hemothorax caused by the penetrating injury, the pleural puncture was definitive therapeutic approach at 2 patients, the thoracic drainage at 8 (50%), and thoracotomy at 6 (37,5%). Indication for the thoracic drainage depended on many parameters, firstly on the fact related to the assessment of the hemothorax size, state of the effused blood and if the fluid was free or it was localized in the pleural space. Choice of the place for drainage at the larger effusions was almost standard, i.e. through V intercostals space in the mid or anterior axillary line. Top of the tube was pointed to the top of the lung. In such cases, the operative thoracostoma with the blunt dissection of the intercostal space was strictly done and digital control of lungs after achieving the pleural space. We used tubes of 28 – 32 Fr and realized fully satisfactory effects in terms of the evacuation of the pleural effusion, blood and achievement of the lung expansion. In case of the unsuccess of the drainage, we performed the thoracotomy, for that was those cases where it was obvious that it would not be possible to evacuate already formed coagulum by the thoracic drainage. We consider that the placement of many thoracic tubes at the hemothorax is not the efficient way of the hemothorax tre-



atment where coagulum was formed. Long lasting retention of tubes in the area where the coagulum was formed, only presents the risk for the occurrence of the pleural infection, and we avoided it by the approach of the thoracotomy and surgical evacuation of the coagulum. We applied the thoracic drainage by the application of the trocar of thoracostoma. Then we placed thoracic tubes of the narrow-bore inner diameter, 20 - 22Fr. Trocar drainage was applied at the patients at whom the minor lung collapse was recorded after the first therapeutic procedure, and those at whom such a drainage could be safely done through II interrib anterior space, i.e. in cases when there was the partial lung collapse with the level of fluid retained after the pleural puncture. In that group were the injured with clearly preserved diaphragm contour, i.e. where we were sure that the rupture did not exist. This type of drainage we applied by directing the top of the tube towards diaphragm, i.e. according to the principle of the tube placement from the highest point in relation to the collection of air and fluid. Tubes, regardless of the applied drainage type, were put on the active suction, using the commercial drainage system or one-bottle system, i.e. system of two-bottles, we had at disposal. We consider that any technique of the thoracic drainage is good if the desired aims are fulfilled. Surgeon, who performs the thoracic drainage, must be completely introduced to the technique of drainage performance, but also with further control of the tube function. We separately analyzed complications caused by the application of the therapeutic procedures in the hemothorax treatment. By statistical analysis we found that the least percentage of complications was recorded after the pleural puncture, only at 4 patients (13,78%), at the thoracic drainage at 7 patients (30,44%), and after the thoracotomy there were 5 operated patients. However, all complications that appeared were solved by simple procedures and they did not have the impact on the stay prolongation of the injured. At the penetrating injuries, statistically significant difference was not noticed referring to the presence of patients with or without complications. In this group, complications were also solved during the patients hospital stay.

## Conclusion

Hemothorax is one of the most frequent complications of the thoracic trauma, regardless of the fact if it was the blunt or penetrating injuries. Fracture of ribs and other injuries of the thoracic wall, associated with the laceration of the parietal pleura, lungs or intrathoracic blood vessels have the occurrence of hemothorax as a consequence. Realized results of treatment of the traumatic hemothorax are excellent, in the terms of bleeding stoppage, as well as in relation to the lung function. By active surgical attitude towards each injured patient with the hemothorax, regardless of the trauma type, it is possible to realize successful assessment of the injury character and to make a choice of the optimal diagnostic and therapeutic procedure.

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# Central nervous system agents to control food intake and energy balance

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## Abstract

The prevalence of obesity is on a rise and is taking on pandemic proportions worldwide despite significant reductions in dietary fat consumption. The increasing incidence of obesity worldwide has renewed interest in the control of food intake and energy homeostasis. The brain–gut axis is central to the mechanism by which the signals energy status to central and peripheral nervous appetite centers. Evidence suggests that most obese individuals have an inappropriate control of their food intake rather than a metabolic defect in energy expenditure. Enhanced knowledge of the complexity of energy balance regulation and the mechanisms that sustain obesity indicate the challenge presented by management of the obesity epidemic. This article reviews that central nervous system agents to control food intake and energy balance.

**Key words:** Obesity, Central Nervous System, Energy Balance, Food Intake, Appetite

## Introduction

The World Health Organization (WHO) estimates that over one billion people worldwide are overweight, and will increase in 30 years [1]. Despite significant reductions in dietary fat consumption, the prevalence of obesity is on a rise and is taking on pandemic proportions. The increasing incidence of obesity worldwide has renewed interest in the control of food intake and energy homeostasis [2]. So, there has been an increase in research about this matter over the past decade, leading to the discovery of many new hormones and neurotransmitters involved in the regulation of food intake [3]. Enhanced knowledge of the energy balance regulation and the mechanisms that sustain obesity indicate the challenge presented by management of the obesity epidemic [2]. This article reviews that central nervous system agents to control food intake and energy balance.

## 1. Central Nervous System (CNS) Mechanism

Appetite regulation is important because it modulates the energy consumption side of the equation. Appetite includes various aspects of eating patterns such as frequency and size of eating episodes, choices of high or low fat foods, energy density of foods consumed, variety of foods accepted, palatability of diet in day-to-day intake. Feeding behavior is controlled by a series of short-term hormonal, psychological and neural signals which act at several central nervous system (CNS) sites but the pathways converge on the hypothalamus, which contains a large number of peptides and other neurotransmitters that influence food intake [4].

### 1.1. Neuroanatomy and Neurophysiology of Regulating Appetite

The hypothalamus, located on the ventral aspect of the brain, is the primary brain site that integrates incoming information from internal and external sources and then propagates and transmits appropriate signals to sustain energy homeostasis [5]. The hypothalamus and dorsal vagal complex are directly involved in the CNS regulation of appetite. The arcuate nucleus (ARC) of the hypothalamus plays an integrative role, receiving both hormonal and neuronal inputs from the periphery [6]. Neurons of the ARC express receptors for gut hormones, and its anatomical proximity to the median eminence, an area lacking a blood–brain barrier, renders the ARC susceptible to influence by circulating factors. Neurons inhibiting or stimulating appetite project to the paraventricular nucleus and other hypothalamic areas important in energy balance [7,8].

## 2. Agents in Central Nervous System

Controlling energy balance demands extensive coordination from the CNS. The CNS regions that control energy homeostasis are accessible to

numerous circulating hormones and other factors including information generated by the sensory experience of eating, and from the periphery indicating the ingestion of food and the utilisation of its component nutrients [2].

**Neuropeptide Y:** Neuropeptide Y (NPY) contains 36 amino acid residues, including a tyrosine at each end. The appetite stimulating effects of NPY and related pancreatic polypeptides (PP) were demonstrated in 1984 [9] and NPY is one of the most potent stimulators of food intake identified to date. It is widely distributed throughout the CNS [10] with high concentrations in the hypothalamic appetite-regulating nuclei, particularly within the ARC where most NPY is derived. NPY injection into the CNS or directly into the PVN or LHA promotes meal initiation and delays the onset of satiety such that the size and duration of the first meal is increased resulting in hyperphagia [11]. The hyperphagic effects of NPY are mediated by specific NPY receptor subtypes. Of the six NPY receptor subtypes identified to date, the Y1 and Y5 receptor subtypes mediate the orexigenic effects of NPY released in the magnocellular PVN (mPVN) [12-14]. This notion that NPY-evoked appetitive drive originates from a subpopulation of Y1 and Y5 coexpressing targets in the mPVN is supported by the evidence that a subpopulation of neurons in the mPVN co-express Y1 and Y5 receptors, Y1 and Y5 receptor antagonists blocked NPY-induced c-fos activation selectively in the mPVN and Y1 and Y5 receptor antagonists individually failed to completely suppress feeding [12-15].

**Melanin Concentrating Hormone (MCH):** Melanin-concentrating hormone (MCH) is an orexigenic cyclic 19 amino acid neuropeptide. It is cleaved from its precursor prepro-MCH (ppMCH) along with several other neuropeptides whose roles are not fully defined [16]. MCH is expressed in a discrete population of neurones in the zona incerta and LHA of the hypothalamus [17] and is often co-expressed with CART [18]. MCH-containing neurones project widely throughout the CNS suggesting an involvement in numerous physiological functions. However, the most widely investigated role for MCH is in the regulation of energy homeostasis. This role was first suggested by the observation of elevated MCH mRNA and peptide levels in the hypothalamus of ob/ob mice

as well as fasted animals. Additionally, repeated central injections to satiated rats produce a rapid and dose-dependent increase in food intake, whilst chronic central infusion of MCH to rodents results in persistent hyperphagia and enhanced body weight and adiposity [19]. Two MCH receptors have been identified. MCH was originally associated with an orphan G-protein-coupled receptor (GPCR) termed SLC-1, although this is now referred to as MCHR1. The structure of MCHR1 is highly conserved across rodents and higher mammals [20] and receptor mRNA and protein levels are widely distributed throughout the brain in a pattern consistent with that of the terminal fields of MCH neurones. High levels have been found in the nucleus accumbens, amygdala, hippocampus and various hypothalamic appetite-regulating nuclei [21]. With this distribution MCHR1 is likely to mediate the orexigenic effects of MCH in conjunction with other feeding-related functions such as taste, reward and olfaction. The second MCH receptor, termed MCHR2, has only a 38% homology with MCHR1. Furthermore, functional MCHR2 has not been identified in rodents, but is present in human and animals [22].

**Orexins/Hypocretins:** The neuropeptides orexin A and orexin B produced in hypothalamic neurons, were initially identified as endogenous ligands for two orphan G-protein-coupled receptors [23]. Orexin A is a 33-amino acid peptide of 3562 Dalton with two sets of intrachain disulfide bonds. It has an N-terminal pyroglutamyl residue and C-terminal amidation [24]. The primary structure of orexin A predicted from the cDNA sequences is completely conserved among several mammalian species. On the other hand, rat orexin B is a 28-amino acid, C-terminally amidated linear peptide of 2937 Da that is 46% identical in sequence to orexin A. The C-terminal half of orexin B is very similar to that of orexin A (73%), whereas the N-terminal half is variable. Orexin B also has a high degree of sequence similarity among species. They were recognized as regulators of feeding behavior because of their exclusive production in the lateral hypothalamic area (LHA1), a region known as the feeding center, and their pharmacological activity [24,25]. There appear to be two orexin receptors, OX1R and OX2R, to which orexin A binds to both with high affinity whereas orexin B binds preferentially



to OX2R [24]. The distribution of the two receptors is also different. Within the hypothalamus OX1R is most highly expressed in the ventromedial nucleus (VMH) and OX2R most highly in the PVN [25]. It has been suggested that orexins induces food intake through regulation of homeostatic pathways. Orexin neurones are stimulated by falls in plasma glucose and by fasting but are promptly inhibited by prandial satiety signals arising from the presence of food in the gut [26]. Such inhibitory signals could include gastric distention and a rise in portal glucose levels both of which are transmitted indirectly to the LHA via the NST as a consequence of vagal signalling [27]. These central responses along with evidence that peripheral orexin neurones located in the enteric nervous system may sense nutritional status in order to modulate GI secretion and motility to prime the digestive tract for the ingestion of food [28] suggests that the orexin system may constitute a mechanism for initiating and terminating feeding episodes possibly to modulate glucose homeostasis. Centrally, orexin neurones sense glucose availability to regulate their own activity and could interact with other neurotransmitters to control feeding including ARC, NPY and POMC neurones [29].

**Agouti-related peptide (AGRP):** AGRP is 132-amino acid peptide that has generated intense interest because of evidence of its role in the regulation of feeding and body weight. AGRP has sequence similarity to the product of the Agouti coat color gene in mice, a paracrine-signaling molecule produced normally in the skin that inhibits the effect of MC-1 receptor [30]. Agouti is constitutively expressed throughout the body of yellow Agouti mice, and this expression gives rise to pleiotropic effects including yellow coat color, obesity insulin resistance, hyperglycemia, and increased body length. Mice homozygous for null mutations of Agouti do not display abnormalities of weight regulation [30]. Humans also have an agouti gene that is normally expressed in adipose tissue [31]. Within the CNS, AGRP is expressed exclusively in the Arc and AGRP mRNA colocalises with NPY mRNA in 95% of NPY positive cells in this nucleus [32]. The one study has shown that like NPY, AGRP is an orexigenic peptide when injected ICV [33] or directly into the PVN or DMH [34]. Uniquely, AGRP acts as an endogenous antagonist at the MC3R and MC4R [35]. The MC4R is constitutively active in the ab-

sence of a ligand and AgRP functions as an inverse agonist, suppressing this constitutive activity [36]. Thus AgRP is orexigenic even in the absence of  $\alpha$ -MSH. Overexpression of AgRP under a ubiquitous promoter leads to obesity [37].

**Galanin and Galanin-Like-Peptide :** Galanin is a neuropeptide which is not a member of any known family of amino-acid neuropeptides, was isolated in 1983 by Tatemoto et al [38]. It is a 29 amino acid C-terminally amidated, highly conserved but unique neuroendocrine peptide originally isolated from intestine. The first 14 aa are fully conserved in almost all species. The first 16 N-terminal amino acids appear to contain galanin-agonist activity on increasing food consumption [39]. This bioactive peptide distributed widely throughout the central and peripheral nervous system and other tissues [38]. As yet, three types of galanin receptors have been identified in these tissues by molecular cloning and characterized pharmacologically in various species [40]. In brain galanin is synthesized in the dorsal raphe nucleus, locus coeruleus (LC), rostral ventrolateral medulla, central nucleus of the amygdala, the paraventricular nucleus (PVN) and the supraoptic nucleus [40]. Besides brain, galanin is also located in the spinal cord and gut. Injection of galanin into the PVN preferentially increases fat intake in comparison to NPY injection into the same area, which induces preferential carbohydrate intake [41]. In addition, a galanin receptor antagonist injected into the PVN reduced spontaneous fat intake [42] suggesting galanin has a physiological role in stimulating fat intake. However this effect appears to be strongly dependent on the test conditions [43,44] and thus a physiological role for galanin in regulating fat intake is yet to be proven.

Galanin-like peptide (GALP), while being structurally similar to galanin, and identical in the first 13 amino acid residues, is encoded by a separate gene, on a different chromosome to galanin [45]. GALP binds to the galanin receptors GalR1, GalR2 and GalR3, with the highest affinity to GalR3 [46]. The distribution of GALP mRNA is much more restricted than that of galanin. GALP expression is restricted largely to the Arc, with a few cells in the DMH [47] and that make close contacts with leutinizing hormone-releasing hormone (LHRH) neurons in basal forebrain. Furt-

hermore, GALP neurons express leptin receptors and respond to leptin treatment by increasing their expression of GALP mRNA. Centrally administered GALP activates LHRH-immunoreactive neurons and increases plasma LH levels [48].

**Opioids:** The opioid system is composed of three families of biologically active peptides, b-endorphin, dynorphin, enkephalins and their receptors, l-opioid receptor, j-opioid receptor, d-opioid receptor, respectively [49]. Since their discovery almost 40 years ago the evidence implicating opioid peptides in the control of food intake has expanded dramatically. The inhibitory effects of opioid antagonists, particularly naloxone, on food intake have been well documented in rodents, with evidence that m, d and k opioid receptors are all involved in the short-term control of feeding [50]. Specifically the endogenous opioid system is implicated in the sensory pleasure derived from food consumption. In animals opioid antagonism seems to selectively reduce the intake of highly palatable foods, characterised by either sweetness or high fat content. Conversely, the consumption of palatable food stimulates hypothalamic b-endorphin release [51]. This has led researchers to conclude that the endogenous opioid system may stimulate food intake through palatability rather than hunger based mechanisms [52].

**Endocannabinoids:** It has long been recognised that food intake increases following the administration of cannabis. Consequently, discovery of cannabinoid receptors and their endogenous ligands in the 1990s led to them being linked with various aspects of feeding behavior [53]. The cannabinoid system consists of two receptors whose subtypes are classified as the central CB1 receptor, which is widely distributed in the CNS and many peripheral tissues, and the 'peripheral' CB2 receptor, which is not significantly expressed in the CNS [54]. It is generally accepted that the influences of cannabinoids on feeding behaviour are mediated by the CB1 receptor. The selective CB1 antagonist, rimonabant, dose-dependently reduces food intake and body weight in rats and blocks overeating produced by the endogenous CB1 ligand anandamide. The endocannabinoids anandamide and 2-arachidonoylglycerol act on CB1 in the brain and many peripheral tissues causing a net anabolic action. This includes increasing food intake, and causing increased lipogenesis

and fat storage in adipose tissue and liver [55]. It also selectively inhibits consumption of palatable food and drink, with decreased intakes of sucrose, alcohol and a sweet diet observed in rats, mice and marmosets, respectively [56]. This indicates that similar to the opioid system, the cannabinoid system may be linked to the hedonic aspect of eating. Furthermore, synergistic actions of rimonabant and the opioid receptor antagonists, naloxone and nalmefene, on food intake have been observed [57].

**Cocaine and amphetamine-regulated transcript (CART):** CART was initially identified as a result of its positive regulation by the psychomotor stimulants cocaine and amphetamine [58]. CART is expressed in the PVN, SON, LH, VMH, DMH and Arc in the hypothalamus [59]. In the PVN CART is colocalised with oxytocin and vasopressin and in the LH is colocalised with MCH. CART colocalises with POMC in the Arc [60] and consistent with the anorectic effect of activation of POMC neurons. Additionally, CART antiserum increases food intake suggesting endogenous CART is anorectic [61]. Current rationale places CART in the role of an endogenous satiety factor which modulates the actions of NPY and leptin. Administration of CART inhibits NPY-induced feeding while central infusion of anti-CART antibodies increases food intake [62]. CART and its receptor present another potential therapeutic target to control feeding and ultimately obesity.

**Melanocortins:** The melanocortin system, comprising of receptors, naturally occurring agonist and inverse agonist, plays a crucial role in the regulation of energy homeostasis and food intake [63]. So, the central importance of the melanocortin system to the regulation of body weight makes it an attractive target as a therapeutic strategy for obesity. This system includes an array of melanocortin peptides that are derived from the common precursor proopiomelanocortin (POMC) and several melanocortin receptors through which they signal their effects [64].  $\alpha$ -Melanocyte stimulating hormone ( $\alpha$ -MSH) is thought to be the most important melanocortin peptide in the control of food intake. The melanocortin-3 and melanocortin-4 receptors (MC3-R and MC4-R) are prominent in hypothalamic nuclei that are concerned with energy homeostasis. Both receptors probably mediate the hypophagic effects of the melanocor-

tins, but recent studies have given MC4-R a central role. Huszar et al reported that MC4-R nullmice are hyperphagic and exhibit an obese phenotype [64]. In human studies, increasing amounts of data provide strong evidence that the MC4-R is involved in mediating the effects of melanocortin peptides on appetite and plays an important role in the development of human obesity. The activity of the melanocortin system is regulated by leptin. Approximately one third of POMC neurones express the leptin receptor and are stimulated by leptin [65]. Leptin administered to ob/ob mice in turn increases the release of  $\alpha$ -MSH into the circulation suggesting a possible feedback loop between the sites of  $\alpha$ -MSH release and the release of leptin from the adipose tissue. However, physiological significance of this putative feedback probably depends upon the underlying state of energy balance, since in the fasting state there is a parallel decrease in plasma leptin and plasma  $\alpha$ -MSH [63,65].

**Serotonin (5-HT):** Serotonin is an important modulator of many developmental, behavioral, and physiological processes such as sleeping, temperature regulation, pain perception, and motor activity [66]. Moreover, 5-HT activation has been associated with the within-meal processes of satiation and the post-meal state of satiety approximately 30 years ago [67]. 5-HT neurones are located in the raphe nuclei of the midbrain particularly to the hypothalamic appetite-regulating nuclei. These neurones express leptin receptors and may partly mediate the effects of leptin on energy homeostasis [68]. Furthermore, activation of the 5-HT system is linked to peripheral signals triggered by fat ingestion. In addition, animals consuming a high carbohydrate diet show increased CNS levels of the 5-HT precursor tryptophan [69]. Increased CNS 5-HT functioning as a consequence of these signals reduces food intake and bodyweight in both rodents and humans; effects that are also demonstrated by serotonergic drugs [70,71]. Over fifteen 5-HT receptor, which research into potential treatments for obesity has centred upon the 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> subtypes, have been identified [72]. Of these, the 5-HT<sub>2C</sub> subtype appears to play a particularly important role in regulating food intake. Knockout mice possessing no functional 5-HT<sub>2C</sub> receptors demonstrate marked hyperphagia and consequently obesity [73]. Furthermore,

5-HT<sub>2C</sub> specific antagonists inhibit the hypophagic actions of sibutramine and other 5-HT enhancing drugs. While most of the focus on 5-HT and weight control has been on drugs against the 5-HT<sub>2C</sub> receptor. The 5-HT<sub>6</sub> receptor is one of the most recent additions to the 5-HT receptor family [74]. It is almost exclusively expressed within the CNS with high levels in cortical and limbic regions [71, 73]. 5-HT<sub>6</sub> selective antagonists have been reported to produce significant reductions in food intake when administered to ob/ob mice, dietary obese mice and rats with these hypophagic effects being accompanied by significant reductions in body weight and insulin levels [75-77]. As reductions in food intake are not accompanied by nausea/malaise, taste aversion or sedation [78] and antagonist administration accelerates and increases post satiety resting in the behavioural satiety sequence [79] these observed effects of 5-HT<sub>6</sub> antagonists on food intake are consistent with enhanced satiety.

**Corticotropin Relasing Factor (CRF):** Corticotropin releasing factor (CRF) is a 41-amino acid mammalian neurohormone that is best known as the major physiological regulator of pituitary ACTH secretion [80]. In addition, it stimulates complimentary stress-related endocrine, autonomic, and behavioral responses [81, 82]. There is considerable evidence indicating that CRF is an endogenous anorectic and thermogenic agent [83]. CRF secretion modulates food intake in the absence of stress by exerting an inhibitory tone on appetite [2]. Injections of CRH centrally decrease food intake, including NPY-induced food intake. CRH also promotes a negative energy balance by stimulating energy expenditure, by increasing thermogenesis via sympathetic pathways. CRH levels are regulated by leptin, suggesting a role for CRH in mediating the effects of leptin. Another member of the CRH family is urocortin, which is more potent at suppressing food intake than CRH. The effects of both urocortin and CRH are mediated by CRHR1 or CRHR2 receptors. However, the weights and basal food intake of both CRHR1 and CRHR2 knockout mice are normal [3].



### 3. Conclusions

Numerous mechanisms regulating energy regulation and the expression of appetite have been identified for the last fifteen years. The regulation of appetite and food intake is a complex process. It involves a coordinated response to many orexigenic and anorexigenic factors in multiple brain regions. Feeding behavior is controlled by a series of short-term hormonal, psychological and neural signals. All these signals act at several CNS sites but the pathways converge on the hypothalamus, which contains a large number of peptides and other neurotransmitters that influence food intake. Gut peptides also constitute a key means by which the periphery signals satiety and hunger to the CNS. It is this integration of the endocrine and the neurological systems which underpins much current thought on the regulation of appetite and increasing food intake concluded to obesity.

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# The effects of story writing learning and painting upon the third grade primary school students creative power

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## Abstract

The main aim of this study is to scrutinize the influx of story writing and painting on the third grade primary school students creative power.

Samplings include all primary school students educating in city of Kerman and 60 students were selected randomly.

this research was experimental kind and research design was of pre-test and post-test kind with control group. The measurement tool was Torrance creative power test in which it measures the following criteria: fluency, flexibility, originality and elaboration

The test is very valid and reliable. The creative power test is performed for 3 groups as a pre-test and afterwards all students experiment group were present in both story-writing and painting classes for four month, every week two section and every section 45 minute.

The final test was performed and results were evaluated by using independent T-Test and ANOVA and descriptive statistical.

Results this research showed that in measuring the mean pre and post tests, the story-writing group had considerable progress in scales, fluency, originality, elaboration and flexibility but the painting group had progress in elaboration scale too.

Results relating to independent T-Test by comparing post test in story-writing and control groups showed that there was significant differences between two groups in originality and elaboration and comparing post tests for painting and control groups showed that there was a significant difference between two groups in flexibility, originality and elaboration scales the result of variance analysis show that story-writing has meaningful effect on flexibility and originality scales and painting has meaningful effect on flexibility, originality and elaboration scales ( $p < 0.01$ ).

**Key words:** learning, story-writing, painting, creativity, primary school.

## Introduction

Torrance, the American researcher believes that we need to motivate our children's creative power since there is no power except creativity in this era despite the existence of many variables e.g. stress in which we can fight the problems. (Salmanian, 2009). One of the important ways to develop children and increase their perception is to encourage them to look at their environments carefully and do not neglect any subject. (Nazari, 2008).

Nowadays the problems are not solvable with yesterday solutions and we should take action to solve the future problems as well.

Today the environmental positions and the vicissitudes are so complex, dynamic and insurable that, the societies can not survive without nourishing creative minds and the rate of developments are so high that, the need to have creative powers is very necessary. Creative powers enjoy four specifications:

- fluency: the ability to gain significant relations between reflection and mind in which is measured in a specific period based on the number of reflections and solutions.
- originality: the ability to ponder in an unusual way consisting of unusual, strange and smart answers.
- Flexibility: the ability to ponder about various solutions for a new problem.
- elaboration: the ability to ponder about details in performing a new task.

McDonough and McDonough (1978) said that the only limited number of colleges and American universities administered creativity education curriculum. Fasko (2001) refers to universities by regret in which they have aimed creativity in recent



decade e.g. Nours central university in Midland and Michigan.

There exists a quiet atmosphere in those universities in which the students sense freedom in discovering their free creativities and it resulted to discover creative experiences, curiosity expansion and creative power as well.

Professor Lipman resulted in his evaluations about the role of reasoning power in humans life that many students lack the above-mentioned power because of the lack of reflection and reasoning during childhood and he designed a new program named the philosophic training of children in the school to improve reflection and reasoning.

Lipman regarded the story writing and various philosophical stories for children in this regard. Various researches have been performed in the case which confirm the program.

Evidence showed that the program is very helpful in more than 50 countries and we must be very diligent in the following three cases:

- 1 we must train the names of known artists and their dexterity to children.
- 2 we must train painting to children without the usage of any traditional tools.
- 3 we must make an image of their creative powers and it is better to design books consisting of paintings, design, mixture of colors and adornment because they create thoughtful minds. (Chilton, 2007).

Harris in 2008 administered two ten days festival working-places and made a general invitation to encourage young writers to create ways to nourish the writing skills. He believed that they are very helpful in nourishing the creativity and those whose mathematics were very good, were considered more creative. Students who were coarse in delivering their thoughts were less creative and they asked tutors to express their ideas exactly and politely. (Chiu, 2008).

In another study the secondary compulsory trainings e.g. intervention and strong programs were delivered to students in which they considered necessary to increase the following skills: reflection, creativity, self-regulatory behaviors and progress and the two approaches were compared.

Results showed that the gained skills are durable (Sanz de Acedo Lizarraga and et al, 2009).

Conroy, Marchand, Webster (2009) performed skillful programs and resulted that the following scales were obtained: writing skills from 55 to 72 percent, interest in writing story-writings from 21 to 34 percent and parents views from 22 to 39 percent. Chakraborty, stone (2008) established communion in writing workshop and instructions and class designs to motivate writing activities. To make students more interested asked them to write about weird refrigerator, cook interesting chocolate, and creation of unstable chocolate. Persons who converted in projection creativity are able to showed idea and self creativity thought in imaged and projected design model.

They also came to the conclusion that those who were skilled in imaginary creative power were also powerful in space one or both e.g. designers, sculptors, painters, directors and very famous tutors. (Ghobadi, 2008).

So the researcher's fundamental question is to find out whether story-writing and painting are effective on student's creativity

### **Method and Material**

Story-writing and painting training are considered two independent variables in which the researcher controls them and the control group of this study is experimental.

The study evaluates the creative power of students and the design of the thesis is pre or pro test with control group.

### ***Samplings and participants***

Samplings include 9-10 year-old female students of the city of Kerman in which 60 students were selected randomly, 40 students belonged to the experimental and 20 ones in control group as well.

### ***Procedures***

Firstly the creativity test was performed in three groups as pre and post tests and the whole students participated in story-writing and painting classes for four months, two sessions in a week and 45 minutes.

### ***Data analysis***

Data analysis was done by using descriptive and deductive approaches pro gathering information. We used distribution index, percentage, mean, variance and standard deviation in descrip-

tive approach and independent t-test and ANOVA in the latter. Statistical measurements were done by spss software as well.

### Measurement tools

#### *Used test of this research*

The test used was Torrance creativity test in A figurative form. The figurative reflection test requires answers which enjoy figurative forms and usage of figurative tests from kindergarten to secondary school levels.

The reason to select the test is considered its validity in the research. The test was used continuously in educational scales. The coefficient of the test was measured 80 and 90 percent based on the results obtained from its instruction manual (Torrance.1999).

### Findings

After collecting some information, data analysis was done by using inferential and descriptive statistics.

The results of above tables show that in all creativity scales, the mean of students' score in post-test is higher that this show story-writing is useful in creativity.

The results of above tables show that in elaboration scale, the mean of students' score in post-test is higher only.

This table show that in painting group students' score even in pre-test are higher than pre-test in story-writing group because previous exercise they have high creativity power in primary.

The results of above tables show that in elaboration scale, the mean of students' score in post-test is higher but in fluency, flexibility and origi-

*Table 1. Descriptive indexes in pre-test and post-test in story-writing group*

Group		mean	meadian	std.dev	skew	range
Fluency	Pre-test	23.00	23.00	5.02	-1.02	16
	post-test	27.95	28.00	0.22	-4.47	1
Flexibility	Pre-test	17.45	18.50	4.29	-0.7	18
	Post-test	22.40	23.00	2.45	-0.39	9.0
Originality	Pre-test	36.25	38.50	1.17	-0.6	46
	post-test	43.00	45.00	7.14	-0.28	25
Elaboration	Pre-test	63.45	60.50	2.20	0.17	75
	post-test	117	112	1.85	1.08	71

*Table 2. Descriptive indexes in pre-test and post-test in painting group*

Groups		mean	meadian	std.devi	skew	range
Fluency	Pre-test	27.20	28	1.88	-3.27	9
	post-test	27.95	28	0.22	-4.47	1
Flexibility	Pre-test	20.95	22	2.56	-0.18	10
	Post-test	21.70	22	1.94	-0.76	8
Originality	Pre-test	43.75	47	7.75	-0.98	30
	post-test	45.80	46	4.40	0.50	19
Elaboration	Pre-test	84.25	89	18.1	-0.84	69
	post-test	121	118	15.3	1.02	61

*Table 3. Descriptive indexes in pre-test and post-test in control group*

Groups		mean	meadian	std.dev	skew	range
Fluency	Pre-test	27.90	28	0.30	-2.88	1
	post-test	28.00	28	0.00	0	0
Flexibility	Pre-test	20.60	20.5	1.23	0.49	4
	Post-test	19.70	20	1.38	0.06	4
Originality	Pre-test	40.60	42	5.11	-1.03	15
	post-test	41.00	42	6.79	-1.15	25
Elaboration	Pre-test	83.60	84	10.2	-0.15	29
	post-test	99.20	102	11.6	-0.37	40

nality scales Mean scores in pre-test are almost similar to post-test. This result show that control group after during 4 month achieved in elaboration scale because theirs ordinary curriculum.

Upper table show that there are significant different between experimental and control groups in post-test of flexibility, originality and elaboration scales.

Upper table show that there are significant different between experimental and control groups in flexibility and elaboration scales. But there are not significant different between experimental and control groups in flexibility and originality scales.

The result of variance analysis show that story-writing has meaningful effect on flexibility and originality scales ( $p < 0.01$ ).

Table 4. T-test for comparison post-test in painting and control groups in creativity scales

		Leven's test for Equality of variance		t-test for equality of means		
Groups		F	sig	t	df	sig
Fluency	E.v.a	4.45	0.041	-1.00	38	0.32
	E.v.n.a			-1.00	19.0	0.33
Flexibili	E.v.a	0.88	0.35	3.74	38	0.00
	E.v.n.a			3.74	34.22	0.00
Orginal	E.v.a	2.00	0.16	2.65	38	0.01
	E.v.n.a			2.65	35.41	0.01
Elaborat	E.v.a	0.75	0.39	5.09	38	0.00
	E.v.n.a			5.09	35.41	0.00

E.v.a: equal variance assumed E.v.n.a: equal variance not assumed

Table 5. T-test for comparison post-test in story-writting and control groups

		Leven's test for Equality of variance		t-test for equality of means		
Groups		F	sig	t	df	sig
Fluency	E.v.a	4.45	0.041	-1.00	38	0.32
	E.v.n.a			-1.00	19.0	0.33
Flexibi	E.v.a	7.84	0.00	4.28	38	0.00
	E.v.n.a			4.28	29.89	0.00
Orginal	E.v.a	0.82	0.37	0.90	38	0.37
	E.v.n.a			2.65	37.90	0.37
Elabor	E.v.a	2.86	0.09	3.64	38	0.00
	E.v.n.a			3.64	31.95	0.00

E.v.a: equal variance assumed E.v.n.a: equal variance not assumed

Table 6. ANOVA for assessment post-test in story-writing and control groups

Groups		sun of squ	df	mean squ	F	sig
Fluency	Bet- gro	0.25	1	0.25	1.0	0.32
	wit-gro	0.95	38	0.25		
	Total	0.97	39			
Flexibility	Bet-gro	72.90	1	72.90	18.34	0.00
	wit-gro	151.0	38	3.97		
	Total	223.9	39			
Originality	Bet-gro	40.0	1	40.00	0.82	0.37
	wit-gro	1846	38	48.57		
	Total	1886	39			
Elaboration	Bet-gro	3204	1	3204	13.29	0.00
	wit-gro	9159	38	241.02		
	Total	12363	39			

Table 7. ANOVA for assessment post-test in painting and control groups

Groups		sun of squ	df	mean squ	F	sig
Fluency	Bet- gro	0.25	1	0.25	1.0	0.32
	wit-gro	0.95	38	0.25		
	Total	0.97	39			
Flexibility	Bet-gro	40.00	1	40.0	14.02	0.00
	wit-gro	108.40	38	2.85		
	Total	148.40	39			
Originality	Bet-gro	230.40	1	230.4	7.03	0.01
	wit-gro	1245.2	38	32.7		
	Total	1475.6	39			
Elaboration	Bet-gro	4846	1	4840.0	25.93	0.00
	wit-gro	7090	38	186.5		
	Total	11930	39			

The result of variance analysis show that painting has meaningful effect on flexibility, originality and elaboration scales ( $p < 0.01$ ).

## Discussion

The main purpose of dynamic and creativity education is creation, the creation of capable fellows to do new tasks and humans who are discoverers and innovators. The problem is more complex in the thousandth century since to deal with complex social and personal problems we need to create people who are the pioneers of technology, suitable culture and science on the strength of their will and wisdom, logic and using of economic products instead of relying on adversity deeds for the future life. By looking to the situation of science development especially in industrial societies and the creation of developed movements e.g. the movements of creative power nourishment and its creation in many countries we consider that the world is going to a rapid change and we should plan to nourish powerful and creative adults since they are the children of the past (Duffy, 2006).

Creativity is a talent that undergirds invention and innovation, making it an important skill in today's society. Although students are often told to "be creative," they many times do not know how and have little practice in this skill. This document presents an analysis of 33 creative products made by adult participants at a state conference for educators working with preK-12 gifted students or their teachers as a model for what teachers can do in their classrooms to allow students to practice creative thinking. During the conference presenta-

tion, Torrance's creative strengths were reviewed with photographic examples, definitions, and suggestions printed on handouts. For the problem-solving game, each participant was given an identical set of recycled/craft materials, and about 30 minutes to create an object or scene fitting with a given theme. This presentation was delivered each of the two days of the conference with a different theme each day: "under water" was the theme the first day and "cool space" was the theme for the products on the second day. Participants each created an object that exhibited creative strengths and followed game-rules using the additional tools of scissors, glue, markers, and thread. Photographs of the final products are shown with their creative strengths identified. Most participants were successful in developing products that showed five creative strengths as required by the game rules. The most common approach to making a creative product that exhibited creative strengths was to tell an original story involving some motion that was detailed, artistically appealing, or humorous, and contained characters with emotional expressions. Because of the success and enthusiasm of participants for the game, the authors recommend it for students, clubs, and recreational activities. (Rule, Zhdanova, Webb, Evans, Judy and et al. 2011). Now with the growth and accessibility of multimedia tools, the practice of storytelling as a counseling tool with children can be expanded through the use of technology. The creation of the digital stories can be therapeutic for both the originator and the viewer (Sawyer, Willis, 2011)

Results this research showed that in measuring the mean pre and post tests, the story-writing gro-



up had considerable progress in scales, fluency, originality, elaboration and flexibility but the painting group had progress in elaboration scale too.

Results relating to independent T-Test by comparing post test in story-writing and control groups showed that there was significant differences between two groups in originality and elaboration and comparing post tests for painting and control groups showed that there was a significant difference between two groups in flexibility, originality and elaboration scales.

The result of variance analysis show that story-writing has meaningful effect on flexibility and originality scales and painting has meaningful effect on flexibility, originality and elaboration scales ( $p < 0.01$ ). The results of this research are the same as the findings of Westman (2008) asked fourth grade primary school children to write about their personal life, and he encouraged their challenges. He discovered that their creative powers have increased and he encouraged 13-year-old students to plan a curriculum without the support of teachers in North Carolina. They read their stories to primary school students and took actions and duties in which it created a powerful perspective to learn eloquent reading and proficiency over writing and creativity (Mak, Coniam, Kwan, 2008).

The stories were the rich sources of creativity, fantasy and wisdom. Students use fantasy and discrete messages to create stories in which induce them to write, read, speak and make relations and communications in a better way. (King, 2007).

Stories, poems and oral tools create self-reflection, competition and attachment in which they must be performed during primary school. (Wellik, Kazemek. 2007). Fantasy story-writings are considered an important tool to creative reflection and reality comprehension as well in the event that American children are not educated in those ones. The writer believes that cooperative story writing should be reinforced in schools. (Wild, 2007). The following cases help to create research skills in which are considered necessary in PH.D courses:

- Purposeful interviews, special communications e.g. informal reflections, friendly communications, discoverable recreations and risk taking and etc. (Whitelock, Faulkner, Miell, 2008).

- Carbonaro, Cutumisu, Duff, Gillis, Onuczko, Siegel, Schaeffer, Schumacher, Szafron, Waugh (2008) discovered that the flow of mind growing in some children who performed computer games were more rapid. A great obstacle of utilizing of the above-said tool is timing and other cases such as: sex, creativity, wisdom capability, timing, time of playing and etc.

The results of the study is analogous to the findings of Resink who is a researcher and innovator in a media laboratory. He created an approach for kindergarten children named “periodic learning” which include computer clubs and PicoCrickets in which they deliver reflective dynamic and digital creativity. (Traylor, 2008).

Mellor (2008) evaluated the usage of computer with music in 13-15-year-old guidance school students and came to two conclusions:

1. the reflections of participants were different in compound approaches.
2. creative reflection in music without any attention to the aim of the participants and their previous experiments by data analysis were confirmed and humans voices are dependent upon their reflections, creativity and nobleness.

Photography is considered an exciting way to secure art and creativity in the realm of social studies. Photography makes students to clear symbols of ancient and historical places and scenes. (Tampson, Williams, 2008).

Lao and Hew (2006) used drama and performed it for 16 weeks and results showed that the experimental group were more creative than control group. Fourth grade students gained better scores but they were weaker than the first grade and there was no significant difference in sex and genders.

Cantor (2006) said that poem writing is very helpful to develop creativity in children.

Loomis, Blumenthal, Rachel (2007) said that artistic subjects such as painting by figures, painting, sculpture, dancing are considered the subjects of pre-school years. They said again that in those years, the only aim is not create a product but pondering and sharing with the reflection of others and being polite with others which increase

creativity. Using colors without reality induce students and help to increase their self-esteem and to analyze their view points and techniques as well. (Lott, 2007). Knowing and recognition of differences in showing dynamics, music and painting depicts creativity. (Bartal, 2003).

Faris in 2002 believed that children who use clay, are more creative in painting their ideas. (Stokes, 2001). another article (Smogorzewska.2012) presents the results of a study comparing the originality, the length, the number of neologisms and the syntactic complexity of fairy tales created with "Storyline" and "Associations Pyramid." Both methods were developed to enhance children's language abilities and their creative thinking. One hundred twenty eight 5-year-old children were asked to tell stories using either the "Storyline" (SL) or the "Associations Pyramid" (AP) method during four routine class activities. Participants worked in 14 groups, five participants per group. The results showed that stories developed with SL and AP methods are comparably original, however more original than stories developed individually. In this report (Zenasni, Lubart,2011) the relationship between the perceived pleasantness of tasks (using divergent thinking and story writing tasks) and creative performance was examined. Overall perceived pleasantness did not differ between tasks. However, results indicate that the perceived pleasantness of the story writing task increased during task completion whereas the perceived pleasantness of divergent thinking tasks remained stable during task performance. The number of generated ideas in a divergent thinking task (fluency) was significantly related to overall perceived pleasantness of the task.

Painting, music, dancing and theater are very effective in humans creative power specially in early years of life. (Nuessel, Van Stewart, Cedeno. 2001).

### Suggestions

In this way it was suggested that education must thought for development of children creativity seriously and recommend to researcher that do same as this research in study different degree that include (high school, university) until if proved this problem education have to sit story-writing and story-telling units in student curriculum.

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## Instructions for the authors

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# Preparing the camera ready paper for Balkan Journal of Health Science

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### Abstract

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**Key words:** Camera ready paper, Journal.

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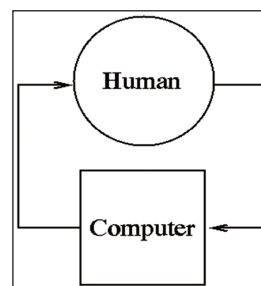


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### Acknowledgements (If any)

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