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# IRON AND ZINC LEVELS IN BREATH-HOLDING SPELLS

Handan Gençgönül* ✣ Şükrü Cin** ✣ Nejat Akar*** ✣ Gülhis Deda****

*SUMMARY*

*Breath-Holding spells are a dramatic and commonly observed clinical phenomenon in childhood. The underlying pathophysiologic mechanisms in breath-holding spells are result from autonomic nervous system dysregulation. Cerebral anoxia is the ultimate factor responsible for the loss of consciousness observed in the severe forms of breath-holding spells.It's known that, there is relation between breath-holding spells and iron-deficiency anemia, and the spells resolve after oral iron supplemantation.In children with breath-holding spells, even though without anemia, there might be different degrees of iron-deficiency.In early diagnosis of iron- deficiency, sTfR level was very important. At the same time, in children with iron-deficiency ,zinc deficiency also migt be found. That's why, plasma zinc levels should be controlled in those children.*

***Key Words:*** *Breath-Holding Spells, Iron Defiency, sTfR, Zinc Deficiency*

*ÖZET*

***Katılma Nöbetlerinde Demir ve Çinko Düzeyleri***

*Katılma nöbetleri, çocukluk çağında oldukça sık karşılaşılan, dramatik ve korkutucu bir hal alabilen tablolardır. Katılma nöbetlerinde, altta yatan fizyopatolojik mekanizma, otonomik sinir sistemi disregülasyonudur.Ciddi nöbetlerdeki bilinç değişikliklerinden serebral anoksi sorumlu tutulmaktadır.Katılma nöbetleri ile demir eksikliği anemisi arasındaki ilişki ve oral demir tedavisi ile nöbetlerin düzeldiği bilinmektedir.Katılma nöbetli çocuklarda anemi olmasa bile değişik evrelerde demir eksikliği olabilir.Demir eksikliğinin erken tanısında sTfR düzeyleri önemlidir.Demir eksikliği bulunan çocuklarda çinko eksikliği de bulunabileceği için bu çocuklarda çinko düzeyleri de araştırılmalıdır.*

***Anahtar Kelimeler:*** *Katılma Nöbetleri, Demir Eksikliği, sTfR, Çinko Eksikliği.*

Breath-holding spells are a common and frightening phenomenon occuring in healthy children. They occur most commonly within the first 12 months of life and virtually all breath-holders experience their initial spell by the age of 2 years (1,2).

In the prior researches about these spells, pathophysiologic mechanisms are emphazed on autonomic nervous system dysregulation (1-3).

Holowach and Thurston speculated that having an anemia in children who suffered from severe breath-holding spells might have predisposed to loss of consciousness (1,4). They reported that different degrees of the anemia were detected in patients with breath-holding spells (5).

Iron deficiency is still the most frequent cause of anemia in children. A high incidence of iron deficiency anemia has also been reported in Turkey (6).In progressive iron deficiency, a sequence of biochemical and hematologic events occurs. First, the tissue iron stores in bone marrow disappear. In this stage of iron deficiency, only the level of serum transferrin receptor (sTfR) increases. Next, there is a decrease in serum iron and the

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iron-binding capacity of the serum increases.As the deficiency progresses, the red blood cells become smaller than normal and their hemoglobin content decreases (7).

These children might also have both iron and zinc deficiency at the same time. As a structural element of central nervous system proteins, zinc may play a role in syntesis of neurotransmitter and myelin (8).

This study was designed to show relation between iron deficiency stage and breath-holding spells, to determine serum zinc levels in breath-holders and to emphazed the treatment of deficiencies.

## SUBJECTS AND METHODS

In the period from June 1998 to August 1999, all children with breath-holding spells applied to the Pediatrics Department of the Faculty of Medicine Univercity of Ankara were included in the study to analysed serum iron and zinc levels.

Physical examination were performed all children and detail their history about their parents was taken. Relevant information obtained includes age at onset of the symptoms, age at the presentation, frequency of attacks, family history of similar attacks. Blood samples were obtained from all patients for complet blood counter, serum ferritin level, serum iron level, total iron-binding capacity of serum, sTfR level, plasma zinc level and zinc-binding capacity of plasma.

## RESULTS

In our study, 50 patients were evaluated (24 of them was male, 26 of them were female). Family history for similar attacks were detected in 11 children (22%). The clinical findings about patients were shown in Table 1.

When the children were discriminated according to ages at the presentation, 41 cases were under 2 years and 9 cases were between 2 and 6 years.

While anemia was observed in 28 children (56%), 22 children (44%) didn't have an anemia. Different degrees of iron deficiency were found in 22 children who have not anemia.18 of 22 cases who have not anemia had deficiency of iron stores of the bone marrow which was characterised with only increasing sTfR level. 4 of 22 cases who have not anemia had iron deficiency which was detected decreasing transferrin saturation and increasing sTfR level in the serum. As a result, different degrees of iron deficiency was observed in all cases.

Table 2 shows the association between iron deficiency degrees and clinical features.

**Table 1:** Clinical findings of patients.

| | MINIMUM | MAXIMUM | MEDIAN |
|---|---|---|---|
| AGE OF THE PRESENTATION OF SYMPTOMS ( Month ) | 3 | 47 | 16 |
| AGE OF THE ONSET OF SYMPTOMS (Month) | 6 | 48 | 10 |
| PERIOD WITH ATTACKS (Month) | 0.5 | 35 | 6 |
| FREQUENCY OF ATTACKS ( / Month) | 1 | 15 | 5 |

**Table 2** :The association between iron deficiency degrees and clinical features.

| | DEFICIENCY OF IRON STORES OF THE BONE MARROW | IRON DEFICIENCY | IRON DEFICIENCY |
|---|---|---|---|
| AGE AT ONSET OF SYMPTOMS (MONTH) | 13 | 7 | 8 |
| PERIOD WITH SPELL (MONTH) | 1 | 6 | 10 |
| FREQUENCY OF ATTACKS ( / MONTH) | 2 | 5 | 7 |

The correlation between hematological parameters and clinical findings were analysed: If iron deficiency's degree is high, age of the onset of spells is found early, times between attacks is found short and ages of the presentation found late ($p<0.01$).

In this study, zinc deficiency was detected in 12 cases (24%) in addition to different degrees of iron deficiency. Cases with zinc deficiency were shown in Table 3.

There was no statistical difference between children with iron deficiency and children with both iron and zinc deficiency according to the age of the onset of symptoms, period with attacks and frequency of attacks ($p>0.05$).

Subjects allocated to iron deficiency group were given ferrous sulphate solution orally in a dosage of 5 mg/kg per day for 3 months, to both iron and zinc deficiency group were given zinc sulphate solution orally in a dosage of 2 mg/kg per day the first and then ferrous sulphate solution in a dosage as in former group. Patients were followed up monthly until 3 months. At the end of the first month, in children with deficiency of iron stores of the bone marrow, clinical and hematological findings were found as normal. In children with high degrees of iron deficiency, these parameters were found as normal at the end of the third month.

In Table 4, clinical response to iron treatment in children who have only iron decicieny, to iron and zinc treatment in children who have both iron and zinc deficiency.

Evaluating of clinical response of the treatment, there was no difference between the group with iron deficiency and the group with both iron and zinc deficiency.

**Table 3:** Cases with zinc deficiency in 50 children.

| | n | IRON DEFICIENCY | BOTH IRON AND ZINC DEFICIENCY |
|---|---|---|---|
| DEFICIENCY OF IRON STORES OF THE BONE MARROW | 18 | 13 (72.3%) | 5 (27.7%) |
| IRON DEFICIENCY | 4 | 1 (25%) | 3 (75%) |
| IRON DEFICIENCY ANEMIA | 28 | 24 (85.8%) | 4 (14.2%) |

**Table 4 :** Clinical response to iron treatment in children who have only iron decicieny, to iron and zinc treatment in children who have both iron and zinc deficiency .

| | n | DECREASES OF SPELLS | RECOVERY OF SPELLS COMPLETLY |
|---|---|---|---|
| n | | 10 (20%) | 40 (80%) |
| BOTH DEFICIENCY OF IRON STORES OF THE BONE MARROW AND ZINC DEFICIENCY | 18 | 1 (5.5%) | 17 (94.5%) |
| BOTH IRON AND ZINC DEFICIENCY | 4 | 1 (25%) | 3 (75%) |
| BOTH IRON DEFICIENCY ANEMIA AND ZINC DEFICIENCY | 28 | 18 (64.4%) | 10 (35.6%) |

## DISCUSSION

There is a relation between breath-holding spells and anemia, particulary iron deficiency anemia. A number of investigators have demostrated the association of iron deficiency anemia with abnormalities of cognitive, developmental and behavioral problems that may be reversible with early treatment of iron deficiency anemia. Iron deficiency anemia may lead to adverse effects on oxygen uptake in the lungs and reduce avaliable oxygen to the tissues, including central nervous system tissues. Researchers suggested that breath-holding spells may recover with iron therapy (9).

Conventional laboratory indices of iron status include serum iron level, total iron-binding capacity of serum, transferrin saturation and serum ferritin level.But to diagnose of deficiency of iron stores of the bone marrow, these indices are inadequate. Recently, serum concentrations of sTfR have been suggested as a reliable index of iron depletion (10).

In our study, we observed the different degrees of iron deficiency in all patients. Eighteen of the 50 cases had no iron deficiency according to conventional laboratory indices, but, increased sTfR levels were found in these cases. With iron complementation, breath-holding spells were recovered in all patients.

Zinc deficiency may accompany to iron deficiency . At the same time,as a structural element in the central nervous system proteins, zinc may play a role in syntesis of neurotransmitter and myelin (8). There is no data about association between zinc deficieny and breath-holding spells.

In 11 of the 50 patients (22%), we found both iron and zinc deficiency.There was no statistical difference between iron deficiency group and both iron and zinc deficiency group according to the age of the onset of symptoms, period with attacks and frequency of attacks ($p>0.05$).

Consequently, sTfR level must be evaluated to detect of early stage iron deficiency in children with breath-holding spells. Clinical investigations should be increased about association between zinc deficiency and breath-holding spells.

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# THE EFFECTS OF ISOFLURANE AND SEVOFLURANE ON IMMUNE SYSTEM IN MINOR SURGICAL INTERVENTİONS

Nihal Durlu* ✣ Yeşim Batıslam* ✣ Oya Özatamer*


## SUMMARY

*Anaesthesia and surgery have effects on immune system and this impact can further increase the morbidity of procedures. We designed a prospective study in minor surgical patients to elucidate the immunological responses and compare the immunological end-results of inhalation anesthetics sevoflurane and isoflurane with the aim of clarifying most suitable agent providing less immune changes. Forty-four patients without any immunological compromise and undergoing minor surgery were included. After the same induction technique, patients received isoflurane (n: 22) or sevoflurane (n: 22). Laboratory assessment included whole blood count, serum immunoglobulins, complement, lymphocytes, and T-lymphocytes and subgroups. Hematological and most of the immunological measurements were in normal ranges throughout the study and no statistically significant difference was observed between sevoflurane and isoflurane groups. Time related differences observed in each group consisting increases in IgG, B and T lymphocytes and T-helper and decrease in T-suppressor levels with protection of complement levels in isoflurane group. Although the laboratory data showed better immune response for isoflurane, statistical analyses did not support these findings. Even though different aspects of immune system changes have been in the advantage of isoflurane regarding laboratory data, statistical methods did not revealed a meaningful difference in each comparison.*


***Key Words:*** *Immune Response, Isoflurane, Minor Surgery, Sevoflurane,*


## ÖZET

***Minör Cerrahi Girişimlerde İsofloran ve Sevofloranın İmmün Sisteme Etkileri***

*Anestezi ve cerrahinin immün sisteme olan etkileri uzun süredir bilinmektedir ve immün etkileşim girişimlerin morbiditesini arttırabilmektedir. Prospektif çalışmamızda sık kullanılan inhalasyon anestetikleri sevofloran ve izofloranın minör cerrahi uygulanan hastalarda immunolojik etkilerini karşılaştırmayı planladık. İmmünolojik yetmezliği olmayan ve minör cerrahi girişim uygulanan 44 hasta çalışmaya dahil edildi.Aynı indüksiyon tekniği uygulandıktan sonra 22 hastaya izofloran ve 22 hastaya sevofloran uygulandı.Kan örnekleri preoperatif ve postoperatif 1 ve 3. Günlerde olmak üzere 3 kez alındı. Laboratuvar incelemelerde lökosit sayımı, serum immunglobulinler, kompleman, lenfositler, T-lenfosit ve alt grupları bakıldı. İzofloran ve sevofloran grupları arasında hematolojik ve çoğu immünolojik ölçümler normal sınırlar içindeydi ve istatistiksel fark yoktu.*


***Anahtar Kelimeler:*** *İmmün Yanıt, İzofloran, Minor Cerrahi, Sevofloran*

In the present state of knowledge, anaesthesia and surgery depress immune system by direct effects of anesthetic agents and indirect interaction of hormonal and metabolic changes caused by surgical stress. Every component of immunologic profile can be altered during anaesthesia and sur-

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gery (1,2). These changes represent organism's general responses and are dependent on the extent of surgery, anaesthesia and medications (3). It has been clearly proved that anaesthetic agents depress the immune response by compromising phagocytosis, lymphocyte transformation, cytotoxicity, antibody response to antigen and chemotactic functions of immune cells. Moreover, the increased tendency to infections and malignancies with anesthetic inhalation has been linked to the inhibition of lymphocyte transformation, which is the main step in specific immunity to foreign antigens (4,5).

In a group of anaesthesia workers, the immunopathologic consequences of chronic exposure to the inhalation anaesthetics have been downregulation of neutrophiles, leucocytes, B-lymphocytes and natural killer (NK) cells, which are main characteristics of immune system (6). In another study, even minor operations cause immune changes under balanced anaesthesia in children (7). Although the controversial data arising whether the immune effect of surgery has depended on anaesthesia or surgical trauma, it is possible to compare the immune interaction of different anesthetic approaches by evaluating similar patient groups and extend of surgery. A recent study investigating the immune-effects of the first inhalation anesthetic, halothane, revealed that CD4, CD8 cells and B-lymphocytes significantly decreased with repeating doses of halothane (8). Le Cras et al. suggested that spinal anesthesia causes less immunosupression in transurethral resection patients that inferring type of anesthesia has been important factor on surgery (9). Isoflurane and sevoflurane are somewhat new generation inhalation anesthetics that have been extensively utilized in current anesthetic practise. In a recent study, it has been reported that general anesthesia, without surgery, have had transient and minor effects on immune function (10).

In this study, we compared the effects of sevoflurane and isoflurane on immune system in minor surgical patients to clarify the best inhalation modality by means of immune competency.

## Patients and Methods

This prospective randomised study was designed in minor surgical operations in general surgery operating rooms and consisted of 44 (22 female and 22 male) ASA I-II adult patients, who underwent abdominal wall defect repairs (inguinal, femoral and umbilical hernias). Human clinical research committee of the hospital approved the protocol for the study and all patients were informed about the content.

All patients signed a form indicating that they gave their consent taking part in the study. Patient who had been detected not to have immune system related disorders, infections, endocrine pathologies, allergic reactions, and immunologic therapies were included the study groups. Patients who would have surgery due to tumors, endocrine abnormalities, trauma and major surgery were excluded and patients with the prediction of likely blood transfusion were further eliminated from the study in order to obtain more stable comparison of patients' immune profile. Patients fasted after midnight on the operation day and were divided into two groups evenly and both group I and group II included 11 female and 11 male patients with similar demographic data. Intravenous 5% dextrose and 0,9% isotonic balanced solutions (5-7 ml/kg/hour) were started via a peripheral vein preoperatively and continued peroperatively. Both groups were given 2-2,5 $mg \cdot kg^{-1}$ propofol and 0,1 $mg \cdot kg^{-1}$ of vecuronium in induction. Group I had 1.8-2.5% sevoflurane, group II was given 1-1,5% isoflurane and both groups had $N_2O$ in $O_2$ (FIO2 0.33) as inhalation anaesthesia. Heart rate, blood pressure and oxygen saturation were monitored throughout the operations and recorded in every five minutes. No patient needed blood transfusion peroperatively and postoperatively. Ten ml of peripheral venous blood was withdrawn from a no infusion limb in each patient before induction and first and fourth day postoperatively for laboratory assessment of whole blood, serum immunoglobulins, complements and T lymphocytes and subgroups. The postoperative infections were assessed during hospitalization.

Hematological evaluation consisted of, hemoglobin, hematocrit, leukocyte count and le-

ukocyte profile. Immune parameters were assessed by IgG, IgA, IgM, total T lymphocytes and subgroups (T-helper, T-suppressor), and $C_3$ and $C_4$ measurements. Blood samples were divided into two tubes and EDTA containing tubes sent for hematological measurements in automatic hemocytometer (Medonic CA 610 cell analyzer ®Sweden). Lymphocyte subgroups were detected by using flowcytometry (Facsans Model Concert 32 ®Becton Dickinson, USA) in immunology laboratory. Total T and B-lymphocytes were measured by $CD_3$ KD19 (Cen 4/12, Clove K7/467) and T helper/suppressors assessed with $CD_4/CD_8$ monoclonal antibody (Cen 4/HLA-DR, Clove SK7/L243) (Becton Dickinson®). Immunoglobulin levels were measured by the nephelometric technique with the Behring Nephelometer 100 Analyser® in immunology laboratory.

The calculations were given mean ± SD and statistical analyses were performed by two-way variance analysis between groups, student's t test in groups and two-way analysis of variance test inside groups. P value below 0.05 regarded as statistically significant difference.

**Results**

Laboratory results of hematological assessment and most immunologic parameters were in normal ranges and no statistical difference was observed between sevoflurane (group I) and isoflurane (group II). However, time related differences inside each group were recorded ($P < 0,05$). The duration of surgery, patients' demographic data, mean arterial pressure and heart rate at the time of operation were given (Table 1) and these findings did not show statistical difference between groups I and II ($P > 0,05$). No postoperative infections were observed until discharge.

Hemoglobin and hematocrit values showed meaningful decrease in both groups on the first postoperative day. In group I, preoperative hemoglobin and hematocrit values were 13,59±1.32 and 38,26±3.90, respectively, and these values decreased to 11.24±1.03 and 35.48±3.14 on postoperative first day, returning to the preoperative levels on postoperative fourth day. White blood cell count showed stable course throughout the study in both groups ($P < 0,05$). While lymphocyte counts did not change through preoperative day and postoperative fourth day in Group II, it decreased significantly on the postoperative first day from $2.09x10^3/mm^3 \pm 0.90$ to $1.52\ x10^3/mm^3 \pm 0.34$ ($P < 0,05$) in sevoflurane group. This decrease shifted to a significant increase when comparing postoperative day 1 and 4, $1.52\ x10^3/mm^3 \pm 0.34$ and $1.97\ x10^3/mm^3 \pm 0.38$, respectively, in group I. Although immunoglobulin G (IgG) values were founded to be decreased in group I on the postoperative two measurements (day 1 and 4) ($P < 0,05$), this parameter did not change on the first postoperative day and recorded to be increased on the postoperative day 4 in group II ($P < 0,05$). These statistical fluctuations did not occur within IgA and M measurements in all recordings in both groups (Table 2).

Another statistical changes were seen in B and T lymphocyte countings such that B lymphocytes significantly increased in both groups, only on day 4 of the surgery compared to the preoperative day values, whereas T lymphocytes counted to be decreased 1 and 4 days postoperatively in sevoflurane group ($P < 0,001$ on day 1, $P < 0,05$ on day 4) and this decrease was only observed on the fourth day in isoflurane group ($P < 0,0$) (Table 3).

T lymphocyte subgroups measurements were stable and T helper ($CD_4$), T suppressor ($CD_8$) and $CD_4/CD_8$ ratio demonstrated statistically insignificant changes between both groups. (Table 4) Recordings inside the groups were also indifferent ($P > 0,05$), despite some numeric changes postoperative decrease of $CD_8$ in isoflurane postoperatively, first a decrease then an increase of $CD_8$ in sevoflurane groups. Although $CD_4/CD_8$ ratio, decreased in sevoflurane and increased in isoflurane groups, the statistical data were not significantly different in any of statistical analyses ($P > 0,05$ between groups and $P > 0,05$ inside each group).

According to complement measurements, $C_3$ values in both groups were not changed by surgery, on the other hand, $C_4$ significantly decreased and increased on the postoperative 1st and

**Table 1.** Patients demographic data

| | GROUP I | GROUP II |
|---|---|---|
| Age | 38,75± 13,72 | 42,37 ± 10,21 |
| Weight (kg) | 76,81 ± 13,86 | 69,37 ± 11,62 |
| Duration (min) | 89,68 ± 45,73 | 73,43 ± 40,89 |
| MAP (mmHg) | 91,27 ± 6,15 | 88,11 ± 10,21 |
| Heart Rate (/min) | 81,61 ± 9,24 | 82,05 ± 10,72 |

**Table 2.** Immunoglobulin G, A and M levels preoperatively (0), postoperative first (1) and fourth (4) days.

| | GROUP I (g/L) | GROUP II (g/L) |
|---|---|---|
| IgG-0 | 11,10 ± 2,42 | 11,12 ± 3,86 |
| IgG-1 | 10,45 ± 2,21* | 11,50 ± 3,54 |
| IgG-4 | 10,10 ± 2,28* | 14,98 ± 7,18* |
| IgA-0 | 2,44 ± 0,80 | 12,52 ± 0,75 |
| IgA-1 | 2,21 ± 0,65 | 2,31 ± 0,78 |
| IgA-4 | 2,42 ± 1,20 | 2,60 ± 0,86 |
| IgM-0 | 1,45 ± 0,45 | 1,42 ± 0,59 |
| IgM-1 | 1,33 ± 0,49 | 1,27 ± 0,51 |
| IgM-4 | 1,41 ± 0,64 | 1,40 ± 0,59 |

* P <0,05

**Table 3.** B and T lymphocytes throughout the study

| | GROUP I (%) | GROUP II (%) |
|---|---|---|
| B lenf-0 | 10,68 ± 3,96 | 11,12 ± 3,86 |
| B lenf-1 | 10,78 ± 3,91 | 10,50 ± 3,54 |
| B lenf-4 | 13,62 ± 4,47* | 14,98 ± 7,18* |
| T lenf-0 | 73,12 ± 6,21 | 69,93 ± 8,88 |
| T lenf-1 | 70,25 ± 6,68** | 68,56 ± 9,02 |
| T lenf-4 | 72,43 ± 6,10* | 71,50 ± 7,25* |

*P <0,05
** P <0,001

**Table 4.** $CD_4$ and $CD_8$ levels (%) and $CD_4/CD_8$ ratios preoperatively and postoperatively

| | GROUP I | GROUP II |
|---|---|---|
| CD4-0 | 43,00 ± 11,05 | 42,68 ± 7,62 |
| CD4-1 | 41,68 ± 11,34 | 42,37 ± 7,52 |
| CD4-4 | 41,37 ± 9,55 | 46,12 ± 8,46 |
| CD8-0 | 36,75 ± 11,78 | 35,93 ± 9,07 |
| CD8-1 | 35,81 ± 11,32 | 34,50 ± 8,51 |
| CD8-4 | 38,87 ± 12,14 | 33,62 ± 6,92 |
| CD4/CD8-0 | 1,34 ± 0,63 | 1,26 ± 0,43 |
| CD4/CD8-1 | 1,29 ± 0,57 | 1,32 ± 0,45 |
| CD4/CD8-4 | 1,22 ± 0,59 | 1,45 ± 0,50 |

**Table 5.** Complement changes during anaesthesia sessions

| | GROUP I (g/L) | GROUP II (g/L) |
|---|---|---|
| C3c-0 | 1,22 ± 0,39 | 1,09 ± 0,34 |
| C3c-1 | 1,19 ± 0,40 | 1,03 ± 0,33 |
| C3c-4 | 1,21 ± 0,31 | 1,20 ± 0,35 |
| C4-0 | 0,27 ± 0,08 | 0,28 ± 0,10 |
| C4-1 | 0,22 ± 0,08* | 0,28 ± 0,10 |
| C4-4 | 0,29 ± 0,09* | 0,30 ± 0,10 |

*P <0,05

$4^{th}$ day, respectively in sevoflurane group (P < 0,01- P < 0,01) and did not show difference in isoflurane group (P > 0,05) (Table 5)

## Discussion

In recent years, the immune response to anaesthesia has gained attention with sufficient accumulation of knowledge and improvement of techniques in other anesthesiology related areas such as endocrine, neuroendocrine, cardiovascular, respiratory and metabolic aspects. As far as the end results of basic and clinical research have been to provide decreased morbidity and mortality from an anaesthesia session, immunologic effects of anaesthesia has been one of the less investigated areas. Some immunologic changes were reported mainly after major surgical operations, which rendered further morbidity to the procedures (11,12,13,14). Publications, which investigated immune response in anaesthesia, have not agreed on a consensus that "what immunologic changes occur in a particular narrow space of anaesthesia and which side effects may occur due to these changes?" Studies on immunology in anaesthesia have mostly covered major and minor operations with different anaesthesia techniques and different anaesthetic doses. Moreover, surgical trauma, patient related factors such as malignancy, steroid medication, nutrition, age, sex and any neural impulse that could result in immune suppression should be counted to reach more purified conclusion about immunologic effects of anaesthesia (2).

The presented study investigates the role of new generation and two of the most popular in-

halation anaesthetics, sevoflurane and isoflurane on immunologic changes and compares the effects of these two agents on immune system. We attempted to include minor surgical patients without malignancy, medication and immune compromising disorders, with narrow operating area to approach to a more precise description of immune system in anaesthesia.

Despite a decrease of Hb and Hct on the first day of operation in both groups, these values reached to preoperative measurements. This phenomena was linked to the hemodilution due to intravenous liquids and hormonal plasma retention. White blood cell counts did not change in both groups in each measurement, on the other hand, lymphocytes were estimated to be decreased in sevoflurane group on the 1st postoperative day and reached to preoperative ranges on the 4th postoperative day.

Cohnen et al suggested that Ig values depended on the severity of the operation(15) and more desprictional studies revealed that IgG measurements were decreased after open heart surgery (16), while this decrease was not evident in total hip replacement (17). Simultaneous release of immunologic material was found to be responsible from Ig surge from the tissues. Later over-consumption of Ig was likely explanation of postoperative IgG decrease along with hemodilution, protein loss and lack of Ig synthesizing capacity in major operations (1,2,16,17). However, since the half-life of IgG is 20-28 days, IgM is 5 day and IgA is 6 days, lack of Ig synthetic could not interfere with postoperative decreased Ig values. In our study, IgG estimated to be less than preoperative values on the first postoperative day in both groups. Interestingly it increased to above preoperative values in isoflurane and remained decreased in sevoflurane group four days postoperatively. IgA and M measurements did not change throughout the study. Because, immunoglobulins mostly responsible from body defense mechanism to external pathogens and antigens, one could predict more susceptibility to infections in isoflurane group postoperatively. However, close postoperative follow up of the patients in this group did not show any increase in infections when compared to sevoflurane group.

We think that further investigations are necessary to reveal the excess role of anaesthesia on immunoglobulin, with a study design excluding or minimizing surgical trauma.

Complement system is mainly responsible from humoral immunity and inflammation as well as phagocytic response. Moreover complement level, in plasma are controlled by immunoglobulins. Most of the complement system works as an acute phase reactant on complement activity increases in inflammations. In a study 50% decrease of complement activity in trauma patients resulted in various infections and bacteriemia in all patients (18).

Our complement assessments did not indicate immunosuppression, since we observed a decrease in sevoflurane and a stable slope in isoflurane group, in spite of more Ig fluctuations were observed in postoperative Ig measurements in group II (isoflurane).

Similarly, B-lymphocytes reached to above preoperative and postoperative day 1 levels on postoperative day 4 in both groups ($P < 0,01$). Most studies dealing with T and B lymphocyte levels in minor operations reported negligible changes. More surprisingly, suppressor lymphocyte activity, which deteriorates host defense, was found to be increased in sevoflurane group and decreased in isoflurane group postoperatively. Although statistical correlation was insignificant, these results awakened the idea that isoflurane causes less immunosuppression.

Hansbrough et al have pointed that T helper/suppressor ratio fell in minor surgery, indicating depressed cell immunity. However, they did not mention the anaesthetic technique (19). In our study, while T helper/suppressor ratio was decreased in sevoflurane group, this ratio was increased in isoflurane group postoperatively. These changes were not statistically meaningful, however, it is obvious that more decisive conclusion could be reached, with a larger series of minor operations. These findings also added a positive comment to the isoflurane side.

In conclusion, immunologic changes have not been statistically different in isoflurane and sevof-

lurane anaesthesia of minor surgical patients, although there have been some time-related statistically significant changes inside groups. Different aspects of immune system have been found to be changed in the advantage of isoflurane regarding laboratory data. These data revealed increases of IgG, B and T lymphocytes and T helper levels, decrease of T suppressor (yielding an increase of T helper/suppressor ratio) and protection of complement measurements in isoflurane group. Since all measurements were found to be in normal laboratory ranges and no statistical difference could be established between two groups, isoflurane or sevoflurane could not be regarded as the best inhalation agent over the other one for more appropriate immunologic response. Although statistical findings indicate these two inhalation agents have no immunologic superiority against each other, we believe that immunologic research of anaesthetic agents deserves more attention among anaesthetists.

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# NONINVASIVE POSITIVE PRESSURE VENTILATION AFTER CARDIAC SURGERY

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SUMMARY

**Background:** We have reported the results obtained by non-invasive positive pressure ventilation (NIPPV) applied to the patients who had an open heart surgery and suffered from respiratory failure after extubation due to various reasons.

**Materials and Methods:** We applied NIPV support following severe respiratory deterioration in fifteen patients who underwent open heart surgery under cardiopulmonary bypass in our clinic between January 2000 and January 2001. Nine patients (60%) required NIPPV because of acute inflammation of underlying chronic obstructive pulmonary disease (COPD). Remaining six patients (40%) suffered from alveolar hypoventilation despite normal preoperative respiratory function. Despite NIPPV support (avarage 2 to 4 hours), five patients required reentubation due to respiratory failure defined as persistandt hypoxia, hypercapnia and hemodynamic instability. However, respiratory parameters improved significantly in 10 patients and reentubation was avoided.

**Results:** Ten patients who did not require reentubation were supported by NIPPV for avarege of 8±5 hours (range 3-18 hours). One patient (6.66%) died as a result of acute respiratory distress syndrome (ARDS) following aspiration pneumonia during the first week of postoperative period.

**Conclusion:** NIPPV which is less invasive when compared to endotracheal entubation can be life saving. Timely application of NIPPV also prevents possible complications of endotracheal entubation in the patinets who suffered from respiratory failure that did not require immediate entubation after open heart surgery.

**Key Words:** Open Heart Surgery, Respiratory Failure, Non-invasive Ventilation.

ÖZET

*Kardiyak Cerrahi Sonrası Noninvaziv Pozitif Basınçlı Ventilasyon*

**Giriş:** Açık kalp cerrahisi geçiren ve extübasyondan sonra çeşitli nedenlerle solunum sıkıntısı gelişen hastalarda, non-invaziv pozitif basınçlı ventilasyon (NIPPV) uygulaması ile elde ettiğimiz sonuçları bildirdik.

**Materyal ve Metod:** Kliniğimizde ocak-2000 ve ocak-2001 arasında kardiyopulmoner bypass altında açık kalp ameliyatı geçiren ve yoğun bakım takibinde ekstübasyon sonrası solunum fonksiyonları ve parametreleri bozulan 15 hastaya NIPPV desteği uyguladık. Bunlardan 5 tanesinde NIPPV 2-4 saat (ortalama 3±0.5) uygulanmasına rağmen sebat eden hipoksi, hiperkapni ve hemodinaminin bozulması nedeniyle reentübasyon yaptık. Kalan 10 hastada ise NIPPV uygulanması ile hastaların solunum fonksiyonları düzeldi. Bunlarda reentübasyona gerek olmadı.Bir hasta geç dönemde entübe oldu. Hastaların 9'u (%60) preoperatif KOAH'lı olup ekstübasyon sonrası akut alevlenme, 6 (%40) hasta ise preoperatif akciğer fonksiyonları normal olmasına rağmen ekstübasyon sonrası alveolar hipoventilasyon nedeniyle NIPPV'na ihtiyaç duydu.

**Sonuçlar:** Entübasyona gerek kalmayan 10 Hasta ortalama 3-18 saat (ortalama 8±5) arasında NIPPV desteğinde kaldı. 1(%6.66) hasta aspirasyon pnömonisi nedeniyle postoperatif birinci haftada akut respiratuar distress sendromu (ARDS) sonucu eksitus oldu.

**Tartışma:** Açık kalp cerrahisi sonrası acil entübasyonu gerektirmeyen solunum yetmezliği gelişen hasta gruplarında, endotrakeal entübasyona göre daha az invaziv olan NIPPV hayat kurtarıcı olmakta, ve endotrakeal entübasyonun olası komplikasyonlarını önlemektedir.

**Anahtar Kelimeler:** Açık Kalp Cerrahisi, Solunum Yetmezliği, Non-invaziv Ventilasyon

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Although mechanical ventilation using endotracheal entubation is a life saving method in cases with respiratory failure, there has been a search of methods which will lead to sufficient respiration without entubation. With the application of positive pressure at different levels (BEEP UP) to inspiration and expiration using a total face mask or nase mask has reduced the necessity of endotracheal entubation(1). In recent years, non-invasive ventilation has been succesfully used both in acute respiratory failure accompanied by alveolar hypoventilation(2,3). Thus, acute respiratory failure may improve using a less complicated noninvasine method. As a result, hospitalization period of patients is shortened and they are prevented from invasive ventilation complications.

We have shown that NIPPV is an effective method for postoperatively devoleping respiratory failure in patients who have had open heart surgery.

## MATERIALS AND METHODS:

Fifteen patients who had open heart surgery between January 2000-January 2001 and devoleped acute respiratory failure after extubation during intensive care follow-up period were supported by NIPPV.

The avarege age of patients was 55±7 (between 48-62), whereas 9 patients (60%) were of COPD. Eight patients (53.3%) had isolated coranary artery bypass grafting (CABG) operation, one had (6.66%) mitral valve replacement (MVR) and one had (6.66%) (whose preoperative lung functions were normal) CABG+ mitral ring annuloplasty operation. One of the patient with COPD was operated on, left aorta-renal saphenous bypass, due to renal arterial stenosis three months before CABG operation. There was no comorbid factor except for COPD in the other patients.

All the patients were given general anaesthesia and the avarege operation duration was 140±35 minutes. All of them were extubated postoperatively for 12±4 hours on avarege. They were ventilated in the mode of pressure control ventilation during the postoperative period. The patients were extubated in case of $FiO_2$=0.4 and PEEP≤5cm$H_2O$, $PaO_2$>70mmHg and $PaCO_2$<50 mmHg, $SaO_2$<90, $PaO_2$<70mmHg, $PaCO_2$>50 mmHg during the weaning period, perspiration, breathing the spontaneous speed of which is greater (>) than 20 breath/minute, agitation or a decrease in consciousness level, an increase in heart beating more than 20%, a change in blood pressure more than 20%, a decrease in cardiac output greater than 30% or lack of ventricular arhythmias.

The patients were supported by NIPPV ($FiO_2$=0.4) 4±2 hours (on avarege) after extubation due to dispne, takipne, $SaO_2$<90, $PaCO_2$>50 mmHg, $PaO_2$<70mmHg and respiratory asidose.

Five patients (33.3%) couldn't recover from respiratory failure although they were supported by NIPPV for 3±0.5 hours on avarege and they were re-entubated. In the remaining ten patients (66.7%) such a treatment was kept being given for 8±5 hours on avarege when NIPPV worked.

During the respiratory detoriation period of patients, the hemodynamic parameters (cardiac index, central venous pressure, pulmonary arterial pressure and systemic arterial pressure) were at normal levels (Table-1). For all of the patients the following requirements were considered to give them NIPPV support; a) intact bulber function accompanied by coughing reflex, b) minimal secretion, c) hemodynamic stability, d) functional gastrointestinal system, e) spontaneous respiration of the patient, f) cardiac arrhytmias lack of ischemia, g) adaptation of the patient to non-invasive ventilation.

NIPPV was applied through non-invasive ventilation mode of ESPRIT (Resprinocis PIN V-1000 SN VS 3001274) ventilation and a total face mask. Inspiratory positive airtway pressure (IPAP) was between 12-16 cm$H_2O$ on average, where as expiratory airway pressure (EPAP) was 4-7 cm$H_2O$. IPAP and EPAP were optimalized according to the patients tolerance and to keep tidal volume as 8-10 ml/kg.

**Table-1:** Pulmonary gas change parameters in patients with acute respiratory failure and supported:

| Variable | *Baseline* | *NIPPV-15* | *NIPPV-30* | *Post-NIPPV* |
|---|---|---|---|---|
| *$PaO_2$,mm-Hg* | 50±6 | 58±9 | 62±8 | 66±9 |
| *$SaO_2$-Hb,%* | 79±8 | 85±6 | 84±4 | 89±3 |
| *$PaCO_2$,mm-Hg* | 66±10 | 59±10 | 56±8 | 55±6 |
| *PHa* | 7.32±0.05 | 7.41±0.06 | 7.41±0.05 | 7.42±0.04 |
| *$PVO_2$,mm-Hg* | 38±3 | 43±3 | 45±4 | 47±3 |

*$PaO_2$=arterial oxygen tension; $SaO_2$-Hb,%=arterial oxygen saturation; $PaCO_2$= arterial carbon dioxide tension; PHa=arterial pH; $PVO_2$=mixed venous oxygen saturation.*

### Pulmonary Gas Change

Arterial blood gas sampling was obtained through a 18-gauge plastic cannula placed in the radial artery and mixed venous sampling through 7F, three lumen Swan-Ganz catheter (Edwards Swan-Ganz Baxter Healthcare Corp, Irvine, CA), pH, $PaCO_2$ and $PaO_2$ levels were examined in the blood samplings. Pulmonary gas change parameters were recorded (Table-2) just as soon as the patient suffered from respiratory failure, in the fifteenth and thirtieth minutes of NIPPV support and one hour after weaning from NIPPV support.

After 3-18 hours (8±5 on average) the patients were not provided with non-invasive ventilation when $PaO_2$>70 mmHg, $PaCO_2$<50 mmHg, $SaO_2$>90 and when there was tachypnea and consequently their inspiratory and expiratory pressure support was decreased.

**Table-2:** Hemodynamic values in patients given NIPPV treatment due to acute respiratory failure:

| *Hemodinamik değerler* | *Hasta (n=10)* |
|---|---|
| *Cardiac index(L/min/$m^2$)* | 2.2±0.2 |
| *Central venous pressure (mm-Hg)* | 8±2 |
| *Pulmonary capillary wedge pressure (mm-Hg)* | 13±2 |
| *Systemic vascular resistance(dyn/sec/$m^2$)* | 1430±120 |
| *Pulmonary vascular resistance(dyn/sec/$m^2$)* | 130±25 |
| *Heart Rate (beat/min.)* | 90±5 |

**Table-3:** Pulmonary gas change parameters in five patients re-entubated after NIPPV ventilation support:

| *Variable* | *Baseline* | *NIPPV* | *IPPV* |
|---|---|---|---|
| *$PaO_2$,mm-Hg* | 52±5 | 57±6 | 75±7 |
| *$SaO_2$-Hb,%* | 75±7 | 83±5 | 90±3 |
| *$PaCO_2$,mm-Hg* | 67±9 | 60±9 | 48±6 |
| *PHa* | 7.31±0.06 | 7.40±0.06 | 7.43±0.04 |
| *$PVO_2$,mm-Hg* | 38±3 | 42±3 | 50±3 |

*$PaO_2$=arterial oxygen tension; $SaO_2$-Hb,%=arterial oxygen saturation; $PaCO_2$= arterial carbon dioxide tension; PHa=arterial pH; $PVO_2$=mixed venous oxygen saturation.*

## RESULTS

Ten patients tolareted non-invasive positive pressure ventilation well. Treatment of non-invasive ventilation lasted 3-18 hours (8±5 on average). The patients who had difficulty in getting rid of tracheabronchial secretion were aspirated using nasotracheal method. The patients who met the weaning criteria were not given non-invasive ventilation any more.

One out of 10 patients was given pressure support ventilation treatment, providing him with orotracheal entubation due to aspiration and acute respiratory depression. The patient died in the first week of postoperative period due to aspirational pheunomonia, ARDS and multi organ failure.

Sedation was ensured by 1-2 mg midazolam in three patients who had aggitational suffering during non-invasive ventilation treatment. Sternum separation caused by positive pressure ventilation was observed in two patients (20%) and they had sternal revision operations for 7-9 days on average. Anaesthesical agents that had immediate effects were used in sternum revision, those patients were extubated on the operating table and there was no postoperative respiratory diffuculty. NIPPV lenghtened the duration of ICU 2±1.5 days on average. Those patients stayed in ICU for 3±0.5 days on average.

Five patients were re-entubated after 3±0.5 hours on average. Four of those patients were with COPD and one of them suffered from postoperative myocard infarction. Blood gas levels of those patients before and after NIPPV are presented in table-3. Four (80%) of the five patients re-entubated were extubated after 4±2 days on average. These four patients stayed in ICU for 6±2.4 days on average. One patient (20%) could not be extubated for ten days, thus tracheaostomy was applied.

## DISCUSSION

The primary treatment of acute respiratory failure has been mechanical ventilation support using endotracheal entubation for many decades. Endotracheal entubation likely to have complications such as upper respiratory system trauma, barotrauma and nasochomial infection. Non-invasive ventilation applied to specially selected groups of patients have more advantages than invasive ventilation does. However, there may be some problems limiting the treatment such as patient adaptation, atalectasy and facial ulcers cused by mask pressure (4),

The followings are acute respiratoy failure conditions under which non-invasive ventilation can be used; acute respiratory asidose where there is no need for immediate entubation, respiratory distress, co-operation on patient's side, hemodynamic stability, lack of active cardiac arrhytmia or that of ischemia, without active upper gastrointestinal system hemorrage, intact upper respiratory system and without acute facial trauma (5-8).

In many studies, use of NIPPV in patients with respiratory failure caused by various neuromuscular diseases, deformities in thoracic wall, COPD and control anomalies in central respiration has been detected. The diseases for which NIPPV is used during treatment of acute an chronic respiratory failure may be listed as follows; thoracic wall deformities, neuromuscular diseases, central alveolar hypoventilation, bronchiectasy, COPD, tumor fibrosis, pneumonia, ARDS, cardiogenic pulmonary oedema, postoperative complications, cardiac failure, failure in patients with difficulty in termsof weaning from extubation and obstructive sleeping apnea (9-11).

NIPPV prevents artificial respiratory complications, provides flexibility in the beginning and termination of mechanical ventilation, lessens the need for sedation, protects the airway swallowing and speech mechanisms, lessens the need for invasive monitorization and enables us to give patients early mobilization. The disadvantages of NIPPV is that it can not be used in patients with aspiratory risk or excessive secretion, loss of preventive airway reflex and upper airway obstruction and those who require

entubation, it might not be effective in acute respiratory failure with severe hypoxemy, it may lead to distension of stomach, some lesions on the skin, facial ache, sense of drying in the nose, eye irritation (conjunctivity), clostrophobia, sleep disorders and mask leakage (12,13).

NIPPV should not be used in patients who must not be resuscitated or who can not be cooperative, and in cases where secretions can not be removed, and systolic blood pressure is lower than 90 mmHg or where severe asidose, shock, arrhythmias that can not be controlled and obstruction of upper respiratory system is observed (9,14).

NIPPV is an attractive alternative to entubation in acute and chronical study style. If NIPPV fails, then, entubation may be applied. If there is no unsuitable candition to NIPPV in patients, it is perfect choice for the clinician in terms of adaptation of patient with the ventilator (15,16).

It is such an unusual complication that patients who have had open heart surgery may suffer from respiratory failure in ICU after extubation. In many of those patients there are different risk factors such as COPD and excessive weight, most commonly respiration depending on cardiac complications (17-19).

We have succeded in prevention of re-entubation at a rate of 60% in fifteen patients undewent open heart surgery in our clinic and who suffered from respiratory failure by using NIPPV.

We have also shown that NIPPV is an alternative treatment which may be easily applied to patients, where respiratory failure devoleped after open heart surgery and not required immediate entubation and it may elimanete the need of re-entubation in suitable patient groups. NIPPV; decrease the risk of complications of a more invasive method endotracheal entubation.

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# USAGE OF CARNITINE IN BLOOD CARDIOPLEGIA IN CORONARY ARTERY BYPASS GRAFTING

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## SUMMARY

**Background:** This study is performed to compare crystalloid, blood and carnitine blood cardioplegias (CP) in elective coronary artery bypass grafting.

**Methods:** Forty-five patients were randomized to three technique of myocardial protection (15 patients in each): Group I cold crystalloid CP, Group II tepid blood CP, Group III tepid blood CP with 5mM/L of carnitine. Blood samples taken from coronary sinus and arterial blood were collected in preoperative and postoperative period (6, 12, 24, and 48 postoperative hours) for enzyme measurements. Also hemodynamic parameters were measured at same time periods.

**Results:** All the patients involved completed the study. Hemodynamic parameters in all groups were similar. Also neither preoperative nor postoperative myocardial infarction was observed in any group. CK-MB and c Tn-I levels were elevated in all three groups after cross clamping until $6^{th}$ hour and $12^{th}$ hour for LDH all three groups. In all enzyme measurements, especially in cTn-I, decline in enzyme levels started earlier in BCCP group than other two groups.

**Conclusions:** Although there was no significant difference between three groups in hospital mortality and morbidity, blood with carnitine provides better myocardial protection and recovery from ischemia than do crystalloid cardioplegia and blood cardioplegia.


***Key Words:*** *Coronary Artery Bypass Grafting, Cardioplegia, Carnitine, Ischemia-Reperfusion Injury*


## ÖZET

### Koroner Bypassta Karnitinin Kan Kardiyoplejisinde Kullanımı

**Amaç:** Bu çalışma kristaloid, kan ve karnitin kardiyoplejilerinin elektif koroner baypas cerrahisinde miyokard korunması üzerine etkilerini araştırmak üzere planlandı.

**Metod:** 45 hasta her grupta 15er hasta olacak şekilde randomize olarak 3 gruba ayrıldı: Grup I'te kristaloid kardiyoplejisi, Grup II'de kan kardiyoplejisi, Grup III'de de içinde 5mM/L karnitin bulunan kan kardiyoplejijsi kullanıldı. Enzim çalışmaları için koroner sinus ve arteryal hattan preoperatif ve post operatif (6., 12., 24., ve 48. saatlerde) kan örnekleri alındı. Yine aynı zaman dilimlerinde hemodinamik parametreler ölçüldü.

**Sonuç:** Bütün gruplardaki hastalar çalışmayı tamamladı. Hemodinamik parametreler üç grupta benzerdi. Yine hiçbir hastada peri ve postoperatif dönemde miyokard enfarktüsü gözlenmedi. Her üç grupta da CK-MB ve cTn-I seviyeleri krossklempten itibaren 6. saate kadar, LDH'da ise 12. saate kadar yüksek kaldı. Bütün enzimlerde özelliklede cTn-I daki düşme karnitin grubunda diğer gruplardan önce başladı.

**Tartışma:** Her nekadar üç grup arasında hastane morbiditesi ve mortalitesi açısından anlamlı fark yoksa da, karnitin kardiyoplejisi kristaloid ve tek başına kan kardiyoplejisine nazaran daha iyi miyokard koruması sağlamakla beraber reperfüzyon hasarını en aza indirmektedir.


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Despite the modern principles of myocardial protection used in cardiac surgery, functional as well as biochemical signs of ischemia-reperfusion injury can be seen after release of the aortic cross-clamp (1). Reperfusion injury of the myocardium may compromise postoperative cardiac function (1). It can be diagnosed as increased release of SGOT, LDH, CPK, CPK-MB, and Troponin-I and also with ECG changes (2-6).

L-Carnitine is a naturally occurring amino acid that is the requisite carrier of long-chain fatty acids across the mitochondrial membrane where they undergo beta-oxidation (7). Oxidation of long-chain fatty acids is by far most important aerobic source of adenosine triphosphate in the mammalian heart, and adequate myocardial levels of L-Carnitine are essential for normal energy production (8). Multiple clinical and experimental studies have documented that a carnitine deficiency characterized by decreased myocardial carnitine levels can be associated with DM (9,10), infarcted myocardium (11,12), and dilated cardiomyopathy (13,14).

In this study we compared three different cardioplegic solutions used in elective coronary artery bypass grafting (CABG). The effects of these cardioplegics on myocardium were evaluated with measurement of cardiac enzyme levels and hemodynamic parameters.

## MATERIAL AND METHODS:

### *Patient Data*

Forty-five patients underwent CABG, with the same surgical technique and same surgical team were prospectively randomized to receive one of three different strategies of myocardial preservation; Group I (15 patients) received antegrade crystalloid cardioplegia (CCP), Group II (15 patients) received antegrade blood cardioplegia (BCP), and Group III (15 patients) received antegrade blood cardioplegia with carnitine (BCCP). Patients with an ejection fraction less than %30, those undergoing reoperation, or those with concomitant heart valve disease were not included. All randomized patients completed the study. Informed consent was taken from all participating patients, which was approved by the Ethics Committee of Ankara University Faculty of Medicine, Turkey.

### *Operative Technique*

A standard median sternotomy incision was used in all patients and no minimally invasive technique was used. Then left internal mammary artery and saphenous vein were prepared. Canullation for the cardiopulmonary bypass was carried out in the usual fashion; arterial canullation to ascending aorta and venous canullation with a two-stage canulla to right atrial appendage were performed. All the patients cooled to 32 ºC and also topical cooling with ice slush was also applied. A cardioplegia (CP) delivery canulla with separate vent line (DLP Medtronic, Grand Rapids, MI) was inserted into the ascending aorta. Coronary sinus catheter with autoinflating silicone cuff (DLP Medtronic) was positioned by transatrial-closed technique. After cross clamping of the aorta, CP was delivered through the aortic root. As an initial bolus, a 10 to 15mL/kg CP was infused to aortic root with a pressure of 75 mmHg. Additionally a 400ml of CP was given in every 20 minutes during cross clamping period in addition to infusion of a 50-100ml of CP after each vein graft distal anastomosis. If the heart starts to beat also an additional dose of 400ml of CP was given. The re-warming was started during performing the last anastomosis. After completion of all distal anastomosises, the aortic cross-clamp was removed. Proximal anastomosises were performed while partial occluding clamp was applied. In none of the patients retrograde CP was given.

### *Preparation of Cardioplegic Solution*

1) Crystalloid Cardioplegia (CCP):

Plegisol (Abbot CP solution) at 4°C was used, in the following composition 100cc: 643mg sodium Chloride, magnesium Chloride 325,3mg, and potassium chloride 17,6mg (K+ concentration of 16±1 mEq/L).

2) Blood Cardioplegia (BCP):

Blood CP was administered with Dideco D 514 delivery set, which mixes and cools a hyperkalemic crystalloid concentration with oxygenated blood in a 1:3 dilution. To achieve a final potassium concentration similar to that of the crystalloid solution additional potassium was added.

3) Blood and Carnitine Cardioplegia (BCCP):

5mM/L carnitine was added to the BCP. The administration of the cardioplegia was same.

None of the patients in three groups received a terminal "hot shot" of warm cardioplegia.

*Enzyme Measurements*

Samples for LDH, CK-MB, and Troponin-I were taken from coronary sinus during the operation, and from peripheral venous line postoperatively. Blood samples were taken just before cross-clamping, 5 and 10 minutes after cross clamp release, 10 minutes after cardiopulmonary bypass, and postoperatively in $6^{th}$, $12^{th}$, $24^{th}$, and $48^{th}$ hours.

*Techniques for enzyme measurements:*

CK-MB assay:

Photometric determination of the activity of creatine kinase MB–isoenzyme (CK-MB) (N-acetylcysteine-activated) on an immunological basis was used.

Troponin-I assay:

Serum cardiac Troponin-I (cTn-I) concentrations were measured using the Stratus cardiac Troponin-I assay (Dade International Inc. Miami, FL, USA). This is a two-site immunoassay, which uses two monoclonal antibodies that are specific for the cardiac isotype of TnI. Values greater than or equal to 0,6 ng/ml were considered positive.

LDH assay:

LDH concentrations were measured with Olympus AU-600 model autoanalyser.

*Hemodynamic Assessment*

Hemodynamic parameters including heart rate (HR), mean arterial blood pressure (MAP), central venous pressure (CVP), mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), cardiac index (CI) were recorded before CPB, and 1,6,12,24, and 48 hours after CPB. CO was measured in triplicate by using the thermodilution technique.

*Statistical Analysis*

All data were entered on the SPSS statistical analysis program for Windows. The data are presented as mean ± one standard deviation. Significance was assumed if the *p* value was less than 0,05. One way and multiple analysis of variation (ANOVA) F-tests were used to compare the three groups

## RESULTS:

There were no deaths in all groups, and all the patients involved, completed the study. Mean age was 59,4±5, 2 in CCP group, 56,3±6, 2 in BCP group 60,0±5, 5 in BCCP group. Most of the patients in three groups were NYHA Class I or II. There were no significant differences in preoperative data between these three groups (Table 1).

The average bypass time was 111,7±25, 103,9±29 and 107,2±30 minutes in CCP, BCP and BCCP groups whereas cross-clamp times were 44,3±10, 38,4±9 and 41,9±14, with no statistical difference between three in both. There wasn't a significant difference in mean myocardial core temperature immediately proceeding aortic declamping in all groups. LIMA and saphenous vein were used as grafts. LIMA was bypassed to LAD in all patients. Sequential grafts were performed in 8 patients (4 in CCP, 2 in BCP and 2 in BCCP). The number of distal anastomosises was similar in all groups with no significant difference. Operative data is summarized in (Table-2).

Direct comparison of the three groups revealed the enzyme production was significantly greater in CCP.

cTn-I was detectable in three groups before cross clamping. cTn-I levels sharply increased

**Table 1-** Preoperative data of the patients.

| | CCP GROUP (15) | BCP GROUP (15) | BCCP GROUP (15) |
|---|---|---|---|
| Age (years) | 59,4±5,2 | 56,3±6,2 | 60,0±5,5 |
| Sex (no. of men) | 9 | 8 | 10 |
| Body surface area (m2) | 1,87±0,11 | 1,89±0,16 | 1,88±0,13 |
| Ejection fraction | 0,59±0,10 | 0,57±0,9 | 0,58±0,9 |
| Preop cardiovascular intervention | 5 | 4 | 5 |
| Hypertension | 7 | 8 | 6 |
| Diabetes | 2 | 3 | 2 |
| Smoking | 6 | 5 | 6 |
| Family history of CAD | 3 | 3 | 2 |
| NYHA class I | 4 | 5 | 5 |
| NYHA class II | 7 | 7 | 6 |
| NYHA class III | 3 | 2 | 2 |
| NYHA class IV | 1 | 1 | 2 |

**Table 2-** Operative data

| | *CCP GROUP* | *BCP GROUP* | *BCCP GROUP* |
|---|---|---|---|
| Number of anastomosis | 3.1±0.8 | 2,8±1,0 | 3.0±0.9 |
| Cross-clamp time (min) | 67.7±13.1 | 70,1±10,9 | 65.7±11.5 |
| CPB time (min) | 93.9±17.6 | 87,6±16,0 | 85.6±14.3 |
| Temperature of CP (°C) | 5.7±1.3 | 32,7±0,9 | 31.8±0.6 |
| Temperature of myocar. (during cross clamp) (°C) | 12.8±1.7 | 33,4±2,7 | 31.9±3.1 |
| Myocardial Temp after de-clamping (°C) | 36.4±1.0 | 35,8±0,7 | 36.9±0.5 |
| Spontaneous defibrillation | 9 | 7 | 8 |
| Number of conduction disturbances | - | 1 | 2 |

after declamping. No statistical differences were present between three groups until weaning off cardiopulmonary bypass (CPB) ($p>0,05$), but crystalloid group has the highest levels. cTn-I levels peaked after weaning of CPB in BCCP group whereas it was highest 6 hours after the operation in other groups. In all time periods after weaning off CPB we found significant differences between three different cardioplegia groups ($p<0,05$). At the 48$^{th}$ hour only the difference between CCP and BCP was significant (Figure 1).

Like Troponin-I results, no statistical difference was present in CK-MB levels before declamping in three groups ($p>0,05$). After removal of the clamp a sharp increase in all groups was observed. CK-MB levels peaked at the 6$^{th}$ hour and started to decrease in all groups. In all time periods after 6$^{th}$ hour, there were significant differences between three groups ($p<0,05$). Lowest values were recorded in BCCP group whereas CCP group has the highest values. Decrement in cTn-I levels was sharper than it was in other two groups (Figure 2).

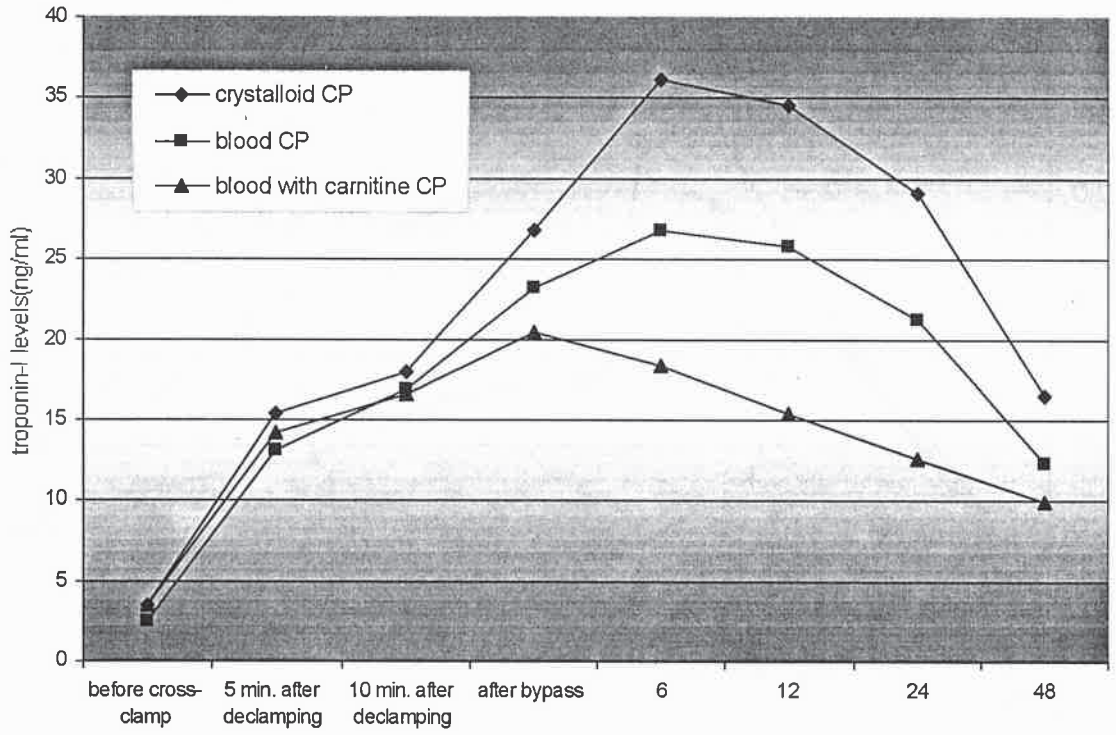


**Figure 1:** Cardiac Troponin-I levels in CCP, BCP and BCCP groups.

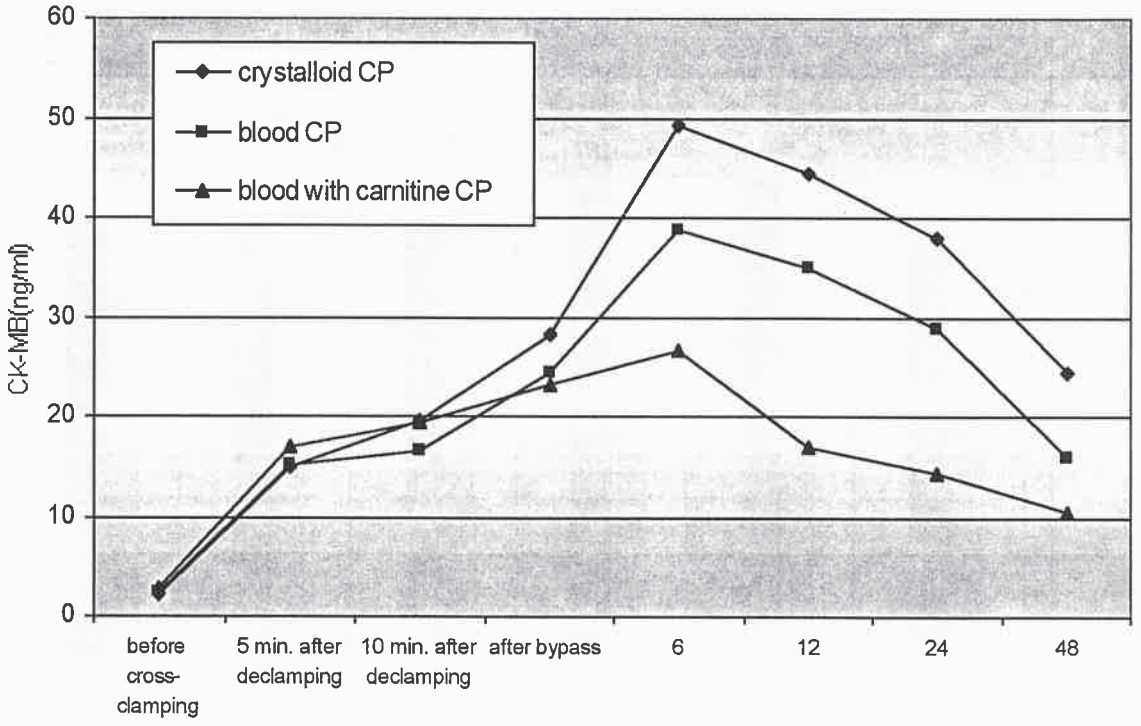


**Figure 2:** CK-MB levels in CCP, BCP and BCCP groups.

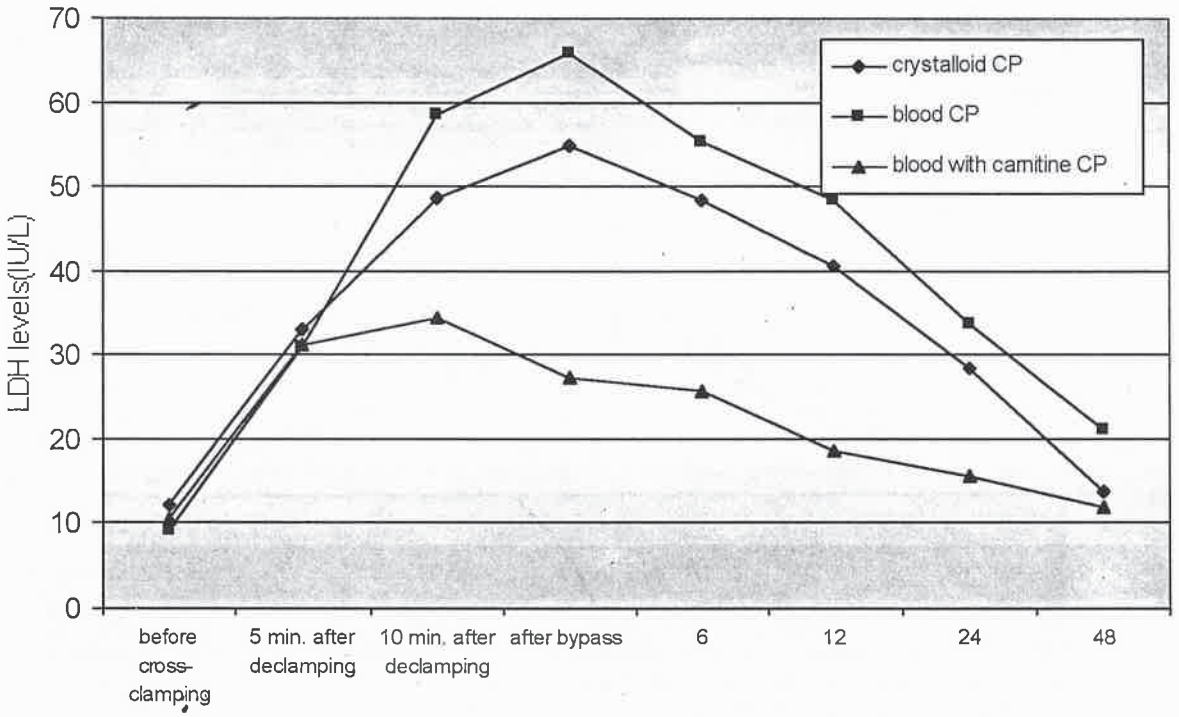


**Figure 3:** LDH levels in CCP, BCP and BCCP groups.

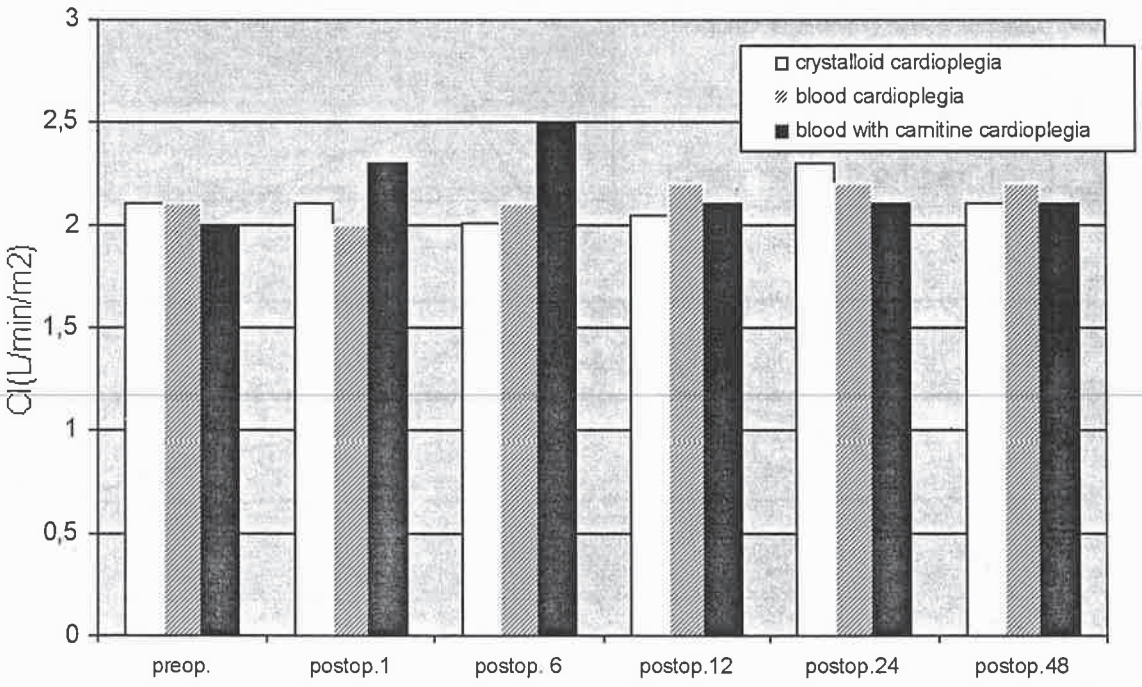


**Figure 4:** Comparison of cardiac index (CI) in CCP, BCP and BCCP groups.

After declamping LDH levels in all groups started to increase and peaked at the $12^{th}$ postoperative hour. In all time periods BCCP group has the lowest values and CCP has the highest. The curve after $12^{th}$ hour was similar of the LDH graphic. A sharp decrease in BCCP group, and more horizontal decrease in other two groups, which were insignificantly different between themselves but the difference between them, and BCCP group were significant ($p<0,05$) (Figure 3).

Hemodynamic measurements were not significantly different between three groups (Figure 4). But especially in the early postoperative period cardiac index (postoperative $6^{th}$ and $12^{th}$ hours) was higher in cTn-I group than other two groups. There were similar results in PVR and SVR measurements.

Neither preoperative nor postoperative myocardial infarction was observed. Also no acquired left bundle branch was observed in either group. 2 patients in CCP, and 1 in BCCP group had an acquired right bundle branch block. Three patients in CCP and BBCP group, and 2 patients in BCP group experienced atrial fibrillation in the early postoperative period (in first 12 hours). All the patients easily recovered with amiodarone treatment except one in CCP group needed cardioversion because of hemodynamic instability. There were no significant differences in arrhythmia incidence between three groups.

## DISCUSSION:

The optimal cardioplegic solutions for myocardial protection and the route of administrating them have been discussed controversially for a long time. Antegrade cold crystalloid cardioplegia is the simplest and first used method of myocardial protection. Crystalloid cardioplegics preserve ventricular function, prevent depletion of high-energy substrates, and maintain ultrastructural integrity (15). Then blood CP was used. The superiorities of blood cardioplegia include a) oxygen delivery, b) the buffering capacity of blood, c) capillary flow distribution where red cells are essential, d) prevention of free radical generation and chain-breaking of their effects, e) maintenance of oncotic pressure and f) restriction of hemodilution (16-18).

Nemoto et al. have successfully demonstrated the effects of carnitine on cardiac functions in experimental isolated adult mammalians hearts (19), but there are few studies like these, done in humans.

CPK-MB, and LDH are released after myocardial injury, but more specific marker of cardiac injury is cTn-I with a wider diagnostic window as compared to CK-MB, and LDH. It has been demonstrated that cTn-I, unlike CK-MB, and LDH, is not influenced by peripheral muscular disease and is usually unchanged after noncardiac operation (20-22).

In this study, cTn-I, CPK-MB, and LDH levels were measured to evaluate the myocardial protection between different groups in selected time intervals. Levels of all these three enzymes elevated after declamping because of ischemia. CK-MB and cTn-I levels were high till $6^{th}$ hour, whereas LDH levels started to decrease after $12^{th}$ hour. This shows that LDH is a less specific cardiac ischemia marker than other two enzymes. Moreover recovery in cTn-I levels was earlier than CK-MB levels.

Codd et al (5) reported that infarct size and CK-MB was significantly greater in patients given crystalloid cardioplegia than in those given blood cardioplegia. There was a similar conclusion in the study of Elwatidy et al (23), which showed tepid blood cardioplegia had superiority in both metabolic and functional recovery. In this study also it is shown that crystalloid cardioplegia had a high incidence of postoperative arrhythmia especially ventricular arrhythmia.

Clinical outcome was favorable in three groups with no hospital deaths or perioperative infarction on electrocardiographic monitoring. These results clearly reflect the adequacy of myocardial protection by all three cardioplegic

solutions in elective myocardial revascularization.

In our study CK-MB and c Tn-I levels were elevated in all three groups after cross clamping until 6th hour and 12th hour in LDH group. In all enzyme measurements, especially in cTn-I, decline in enzyme levels started earlier in BCCP group than other two groups. This shows us that the myocardium protected by BCCP started to recover before other two groups. Probably insignificant increase in cardiac index in the early postoperative period (in the 6th and 12th postoperative hours) was also due to fast recovery with carnitine cardioplegia.

As it is known that carnitine is necessary for the transport of activated long-chain fatty acid esters cross the mitochondrial membrane and stored to be used in Krebs cycle and oxidative phosphorylation. Restoration of normal cardiac metabolism is predicated on maintenance of adequate cellular levels of this substance. Conversion from anaerobic glycolysis to aerobic is one of the earliest reactions after reperfusion. Carnitine given in cardioplegia during ischemia supports substrates to the aerobic glycolysis, which is the main mechanism for ATP production for the cell. Of course increased amount of ATP production will fasten recovery of metabolic functions of the myocyte, which will cause less reperfusion injury.

Also BCP group has significant superiority in recovery to CCP group. This is due to known benefits of BCP. Especially natural buffering capacity of blood which is important in buffering, and blood as an antioxidant that prevents free radical production are the most important factors that cause rapid recovery in BCP than in CCP group.

Although there was no significant statistical difference between three groups in hospital mortality and morbidity, blood with carnitine provides better myocardial protection and recovery from ischemia than do crystalloid cardioplegia and blood cardioplegia.

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# DIABETIC GASTROPARESIS (GASTROPARESIS DIABETICORUM)

Rıfat Emral*

*SUMMARY*

*Complications involving the gastrointestinal tract are common in patients with diabetes mellitus. Diabetic gastroparesis is a common condition. It can be diagnosed in 25% of diabetic patients. However it is generally clinically silent. Typical symptoms are early feeling of satiety, nausea, vomiting, regurgitation, abdominal fullness, epigastric pain and anorexia. It is a cause of "brittle diabetes". Gastroparesis should be considered in patients with irregular glucose control. Management requires rehydration and hospitalization for prolonged vomiting episodes due to diabetic ketoacidosis. An eating style with frequent and small amounts of meals with a low fat content, is suggested. Gastric prokinetic agents such as metochlopromide, cisapride, domperidon and erythromycine can be used. Gastric bezoars should be cleared by endoscopy. In severe gastroparesis where medications are not successful, jejunostomy may be performed for feeding. Surgery has not been proved to be successful.*

***Key Words:*** *Diabetes, Gastroparesis.*

*ÖZET*

***Diyabetik Gastroparezi***

*Diyabetik bireylerde gastrointestinal sistemin tutulmasına bağlı gelişen komplikasyonlar sık görülmektedir. Diyabetik gastroparezi bu durumlardan biridir. Diyabetik hastaların %25'inde saptanabilir. Genellikle klinik olarak sessiz seyreder. Tipik semptomları, erken tokluk hissi, bulantı, kusma, regürjitasyon, karında şişkinlik, epigastrik ağrı ve anoreksidir. Kan şekeri regülasyonunda zorluklar doğurabilir. Düzensiz glukoz kontrolüne sahip hastalarda gastropareziden şüphelenilmelidir. Tedavisinde rehidratasyon ve diyabetik ketoasidoza bağlı uzamış kusma episodlarında hospitalizasyon gereklidir. Sık öğünlü, az besinli, yağ içeriğinin azaltıldığı beslenme biçimi önerilir. Gastrik prokinetik ajanlardan metoklopramid, sisaprid, domperidon ve eritromisin kullanılabilir. Gastrik bezoarların oluşması halinde endoskopiyle temizlenmesi gereklidir. İlaç tedavisinin başarısız olduğu ağır gastroparezide beslenme amaçlı jejunostomi uygulanabilir. Cerrahinin yararı ise kanıtlanmamıştır.*

***Anahtar Kelimeler:*** *Diyabet, Gastroparezi.*

## Diabetic Gastroparesis (Gastroparesis diabeticorum).

Complications involving the gastrointestinal tract are common in patients with diabetes mellitus (1). These symptoms do not correlate with the duration of the disease, metabolic control and other chronic complications other than neuropathy (2). Gastrointestinal disturbances caused by autonomic neuropathy are generally common complications of diabetes leading frequently to morbidity (1). However, gastrointestinal symptoms are generally underdiagnosed and undertreated (3). One of the frequent and important consequences of diabetes is diabetic gastroparesis where stomach is involved. It can be diagnosed in 25% of the patients. It is more common in patients with type 1 diabetes mellitus, in particular if the patient has poor glycemic control, after 10 years of onset. There is no positive correlation between the

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symptoms and the severity of gastroparesis. Although severe diabetic gastroparesis is one of the most problematic gastrointestinal complications of diabetes, it is generally clinically silent (1).

Physiology of gastric emptying is mostly dependent to the function of vagal nerve (4). Basal rhythm of the stomach is initiated by a pacemaker and transmitted to pylor horizontally and circularly. Gastric pacemaker is at the joint part of the fundus and corpus in large curvature. In fasting state the interdigestive motor activity is divided into four phases. Peak activity is observed in phase 3 and in this phase migratory motor complex of the stomach occurs making three contractions in a minute (5). Gastric emptying is controlled by fundus and is dependent upon the volume of the gastric content. As a result of impaired vagal function proximal stomach relaxes less and the emptying of fluids in diabetic patients prolong. The emptying of non-fluid substances are affected by the strong contractions of the antrum. These contractions stains and mines hard substances and transform them into pieces smaller than 1 mm and thus non-fluid substances pass through pylor to duodenum. Phase 3 contractions of interdigestive migratory motor complex are generally not present in diabetic patients. As a result, this causes a loss in the function of digestion and emptying in the antral region and thus gastric retention. Moreover problems may appear about the receptors of gastic relaxation as a result of concomitant present of motility disorders in stomach and duodenum. Pylorospasm may develop as a deterioration and may lead to functional resistance of gastric flow. Disturbed gastric emptying puts patients under the risk for the development of gastric bezoars (6). The real pathophysiology of motility disorders of the stomach is not clear. It is obvious that it can be seen vagal parasympathic functional disturbance. The secretion of motilin, which is the peptide regulating gastrointestinal motility, is under vagal control (7). Motilin stimulates the initiation of third phase of motor activity in migratory motor complex of stomach in patients with gastoparesis. Hyperglycemia, itself, may cause a delay in gastric emptying both in diabetic and healthy individuals (1, 6).

Gastic neuromuscular abnormalities that may occur in diabetic gastropathy are divided into two groups; functional and organic. Gastric dysrythmias known as functional pathology are defined as bradygastry and tachygastry. Gastric dysrythmias resembling normal gastric peristaltic contractions are present in 100% of diabetic patients with eating related symptoms. Loss in vagal tonus and increased sympathic nervous system activity are associated with gastric dysrythmias. Acute hyperglycemia suppresses antral contractions by forming tachygastry (8).

Typical symptoms of diabetic gastroparesis are early feeling of satiety, nausea, vomiting, regurgitation, abdominal fullness, epigastric pain and anorexia (9). The diagnosis of gastroparesis can be made after excluding mechanic or stuctural lesions in patients with symptoms (10). Patients with gastroparesis may vomit foods which they had eaten many hours even many days ago. Episodes of nausea and vomiting may continue for days, months or may appear time to time (11). Even in patients with mild symptoms gastroparesis affects the passage of food into small intestine and thus the relation between glucose absorption and exogenous insulin administration is disturbed. Such alterations result in wide fluctuation in glucose levels, unexpected postprandial hypoglycemia and marked "brittle diabetes". Thus in patients with irregular glucose control gastroparesis should always be suspected. In cases where there is no obstruction, the presence of residual food in stomach after 8-12 hours of fasting is a gold standard for diagnosis (10). Upper gastrointestinal symptoms should not be evaluated as gastroparesis without excluding conditions such as gastric ulcer, duodenal ulcer, gastritis and gastric cancer. Basal diagnostic methods such as upper gastrointestinal endoscopy and direct graphies with barium are helpful for the diagnosis of structural or mucosal abnormalities of gastric system. Gastric emptying can easily be shown with sintigraphic techniques. Such methods requires the administration of fluids and non-fluids which are radionuclide stained.

Technesium-99 labelled solid phase and indium-111 labelled fluid phase sintigraphies can be used. Normally solids should be divided into particles smaller than 2 mm to pass through pyloric syphincter. Solids leave stomach later than fluids. Horowitz et al. have reported a delay in solid food emptying in 58% and 30% of type 1 and type 2 diabetics, respectively (12).

Magnetic resonance imaging and percutaneous electrogastrography are good alternatives for future clinical applications (13). Electrogastrography recording the electrical activity or the stomach by putting electrodes on the surface measures the fasting and postprandial myoelectric activity of the stomach (14, 15). It is not widely used but technically provides detailed information on the pathogenesis of gastrointestinal disturbances. There is a good correlation between gastric emptying and electrogastrography, so abnormalities in the postprandial electrogastrography seem to be able to predict delayed emptying of the stomach. (16). The electrical activity of various parts of stomach are different because each part has its own mechanical activity. The electrical activity of distal stomach is marked and characterized by cyclic depolarization and has a rate of three cycles in a minute. Every cycle begins in the gastric pacemaker at large curvature in gastric body and moves to the distal to pylor with an acceleration of 0.5-4 cm/sec. Gastric neuromuscular function is shown in figure 1.

If the depolarization is larger with the effect of neurotransmitters and hormones action potentials cause gastric contractions. The decrease in the amplitude of depolarization may be related with abnormal rhythm, in other words dysrhythmia such as tachygastry and bradygastry or gastric arrhythmias. Gastric arrhythmias may occur in some of the patients with diabetic gastroparesis. In figure 2, normal gastric myoelectric activity and the effect of hyperglycemia on gastric electrical rhythm are shown in the electrogastrography.

Normally the slow wave depolarization amplitude after meals is very high and is mostly associated with larger contractions. In a study, it was observed that there is normal slow wave cycle in diabetic gastroparesis but the increase in postprandial slow wave length disappears. Gastroduodenal manometry, may be useful to show pylorospasm or the coordination disorder between stomach and duodenum, eventhough patients posses normal gastric emptying but symptomatic. Gastric antral cross-sectional ultrasonography is available for the determination of gastric emptying ratio (15). Neither hemodynamic autonomic function tests nor the glycolysated hemoglobin levels are good indicators of diabetic gastroparesis. On the contrary, in the study of Lacigova et al., among 25 type 1 diabetic patients, cardiovascular and gastrointestinal autonomic neuropathies were

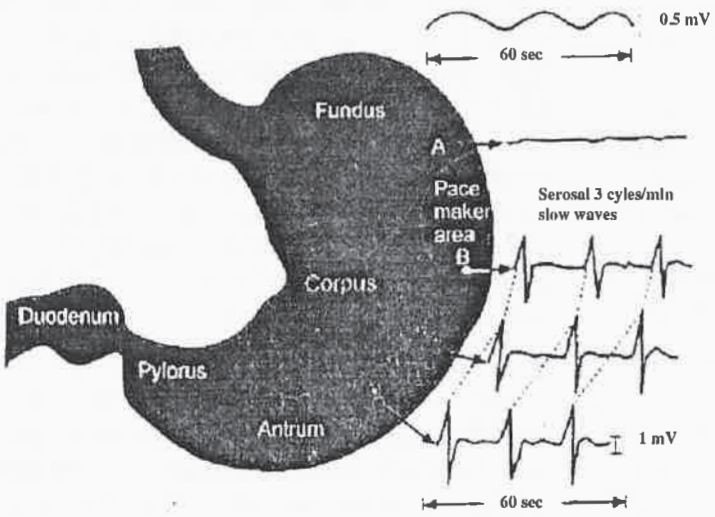


**Figure 1**- Gastric neuromuscular function

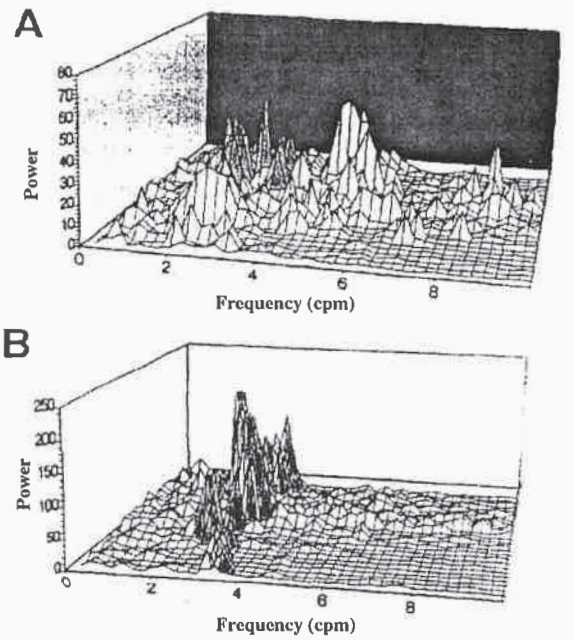


**Figure 2-** Hyperglycemia-induced tachygastria.

**A:** Normal gastric myoelectric activity.

**B:** Effect of hyperglycemia on gastric electrical rhythm in the electrogastrogram tracing.

found to be correlated ($r=0.634$, $p<0.0007$), but no significant correlation was found between gastrointestinal neuropathy and subjective gastrointestinal symptoms (2).

### Treatment of diabetic gastroparesis.

1-Management of underlying pathophysiological cause: In cases of dehydration and prolonged vomiting episodes due to diabetic ketoacidosis, hospitalization is required. In such a case nasogastric tube administration should be performed to the fasting patient. Intravenous fluid should be administered and insulin should be given according to serum glucose and keton levels. In the treatment of diabetic gastroparesis regulation of diabetes should especially be considered. Physiological control of blood glucose levels may improve functional disruption of gastric motility.

2-Regulation of diet: Diet must be arranged for the symptomatic patients. For gastroparesis frequent meals with few food and a low fat content (40 gr/day) is appropriate. Because fatty meals cause prolongation of gastric emptying. To prevent the formation of bezoar a diet with fiber content is suggested in gastroparesis (18).

3-Gastric prokinetic agents: Metoclopramide, cisapride, domperidon and erythromycine may be used.

Metoclopramide is also used as an antiemetic agent. Oral and intravenous forms are available, so it may be used for the severe gastric obstruction due to gastric bezoars. Recommended dose of metoclopramide is 10 mg, 30-60 minutes before meals, four times a day.

Domperidon can not pass blood-brain barier, so side effects due to central nervous system are minimal (19). It improves gastrointestinal motility by increasing antral contractions. Recommended dose is 20-40 mg, 30 minutes before meals, four times a day. Koch et al. showed that administration of domperidon for 6 months improved gastric electrical activity according to electrogastrography results (20). However, in the study of Horowitz et al., acute administration of domperidon caused acceleration in emptying both fluids and solids from stomach, but at the fourth week of treatment, emptying of solids decreased though no such decreament was observed for fluids (21).

Cisapride stimulates gastric emptying. In severe cases, cisapride may be used with the combination of metoclopramide. It is effective even in the long term administration. It may cause ventricular arrhythmias and prolongation of QT in ECG. Patients with frequent hypoglycemia and renal Impairment are also prone to have cardiotoxicity due to cisapride. So cisapride can be dangerous for the highly risky diabetic patients even in monotherapy (22). The drug is now withdrawn from the market due to serious potential side effects.

Erythromycine increases the activity of motilin which is responsible from migratory motor complex activity by binding to motilin receptors and activating them. Erythromycine improves gastric emptying of solids and fluids and

increases antral contractions (23, 24). Recommended oral dose is 250 mg, 30 minutes before meals, three times a day (25, 26). Intravenous erythromycin (3 mg/kg every 8 hours by infusion) is a useful drug for clearance of gastric bezoars.

4-Treatment of associated conditions: Gastric bezoars should be cleaned by endoscopy. Alternatively 1-2 liter fluid is given or 0.5 gr/dl cellulose solution in water for 24 hours on two days is administered, 40 mg metoclopramide is given in 24 hours by infusion for three days. Depressive patients are treated for their condition. Behavioral therapy is also helpful.

5-Jejunostomy for feeding: If drug treatment is not successful or severe gastroparesis remains, feeding jejunostomy may be required. Jejunostomy should be performed to the normal functioning intestine. Both gastrostomy and jejunostomy can be inserted endoscopically. These are palliative procedures for the regulation of hydration and nutrition (27).

6-Surgery: Surgery has not yet been proved to be effective. Gastroenterostomy, vagatomy, pyloroplasty are not successful. In surgical approach for prevention of gastric retention, subtotal or near total gastrectomy and Roux-en-Y gastrojejunostomy are suggested. Patients with diabetic gastroparesis and persistent vomiting can have sufficient efficacy with radical surgical procedure. The 70% of stomach, including antrum and pylor are taken out and Roux-en-Y jejunal loop anastomosis is performed (28). Histopathological findings show that gastromyopathy cause this syndrome.

No effective treatment is available for patients with gastroparesis refractory to standard medical therapy. However, gastric pacing, which is an alternative therapy, seems to be able to improve symptoms of gastroparesis and to accelerate gastric emptying in patients with gastroparesis (29). After placement of the gastric pacemaker, patients rated significantly fewer symptoms and had a modest acceleration of gastric emptying (30).

In symptomatic treatment food can be given at night, freeing patients during the day, and insulin can be adjusted to accommodate the feeding schedule (31). In addition resting the stomach with intravenous alimentation and nasogastric sucking may provide the return of the gastric functions in a few days. Prokinetic agents are frequently used for the treatment of gastroparesis, as well. Unfortunately, in the case of severe gastroparesis, usefulness of oral agents is limited, so they have no advantageous in such cases. Those cases are needed to use intravenous or rectal forms of prokinetic drugs. Tacyhypylaxis to the prokinetic agents results in progressive decrease of the biological effects of the agents. The periodical withdrawal of the drugs provides their effects back and must be performed in unresponsive patients.

Shortly, diabetic gastroparesis consists of one of the most intractible and difficult problem in diabetes mellitus practice. It may cause brittle diabetes and patients must be treated carefully. Because it is silent in general, physicians have to be consider any gastrointestinal symptom in diabetic patients and find out if gastroparesis is an underlying cause or not.

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# COMBİNED INVASIVE AND SURGICAL TREATMENT IN ACUTE INFERIOR MYOCARDIAL INFARCTION COMPLICATED WITH ASCENDING AORTIC DISSECTION

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**Ömer Bayezıt****

*SUMMARY*

*Acute myocardial infarction secondary to aortic dissection may occur due to compression of the coronary arteries by a hemotoma or extension of the dissection into the coronary arterial wall and presents high mortality. A 44-year old man was admitted to the hospital because of sudden severe chest pain. ECG demonstrated acute inferior myocardial infarction, and angiography revealed right coronary occlusion due to ascending aortic dissection. Reperfusion was performed by three stents implanted to the right coronary. After that, a Dacron graft was placed to the ascending aorta. The postoperative course was uneventful and the patient was discharged from hospital on the 9th postoperative day. Acute myocardial infarction secondary to aortic dissection can be succesfully managed by intracoronary stenting until surgical treatment before irreversible complications ensue.*

***Key Words:*** *Myocardial Infarction, Aortic Dissection, Invasive, Surgical Treatment*

*ÖZET*

***Assendan Aort Diseksiyonuyla Komplike Akut İnferior Miyokard İnfarktüsünde Girişimsel ve Cerrahi Tedavi***

*Akut aort diseksiyonuna sekonder gelişen akut miyokart infarktüsü, diseksiyonun koroner arterlere ilerlemesi veya diseksiyona bağlı gelişen hematomun koroner ostiumu kompresyonu sonucu oluşur ve mortalitesi yüksektir.*

*Kırkdört yaşında erkek olgu ani başlayan göğüs ağrısı ile hastaneye başvurdu. EKG de akut inferior miyokard infarktüsü saptandı. Primer girişim yapmak üzere anjiyografi yapıldığında assendan aort diseksiyonu ve diseksiyona sekonder sağ koroner oklüzyonu saptandı. Sağ koronere 3 stent implante edilerek reperfüzyon sağlandı. Sonra assendan aorta dakron greft ile onarıldı. Post operatif dönemde sorunsuz seyreden olgumuz 9'uncu günde taburcu edildi. Aort diseksiyonuna bağlı gelişen akut inferior miyokard infarktüsü ölümcül komplikasyonlar gelişmeden cerrahi tedavi uygulanıncaya kadar intrakoroner stent implantasyonu ile tedavi edilmiştir.*

***Anahtar Kelimeler:*** *Miyokard İnfarktüsü, Aort Diseksiyonu, Girişimsel ve Cerrahi Tedavi*

Ascending aortic dissection (AAD) and acute myocardial infarction (AMI) are major illnesses that require immediate treatment and threathen life. In aortic dissection cases coronary artery occlusion is reported to be 3-15% (1-3). The morbidity and mortality rates of the late surgical operation are high because of expansion in necrotic myocardial area (4-5). This patient, who had inferior AMI secondary to AAD, was operated, and before the operation, coronary stenting was performed in his right coronary artery. Because it is a rare case, we would like to present him.

## Case

A 44 year old male patient came to the emergency service with severe precordial pain. On physical examination, blood pressure was 80/45 mm Hg, pulse was 55 /min. A diastolic murmur was heard in the aortic area. There was an enlargement in the upper mediastinal area on

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chest x-ray. Bradycardia and 5 mm ST elavation in D2-3, aVF were determined in his electrocardiography. In his biochemistry, CPK was 365 IU/L (174 IU/L) and CK-MB was 75 IU/L (25 IU/L). The patient was taken to the coronary angiography laboratory for primary PTCA with a diagnosis of AMI. AAD in aortography and right coronary ostial oclusion in coronary angiography were determined (Figure 1). The other coronary arteries were normal. Reperfusion was provided with implantation of 3 stents (2 x AVE: 3.5x 29 mm and one 3.5x 12mm) into right coronary artery at the 2nd hour of AMI (Figure 2) and after that, he was operated.

### Operational Technique

Cardiopulmonary bypass operation was begun with femoral arterial and bicaval canulation (v.cava inferior and superior). Left ventricle was vented through right superior pulmonary vein. Following total circulatory arrest, patient was cooled down to 18-19°C, and aortotomy was done. It was found that aortic valve was normal, intimal dissection was 2 cm near to coronary ostium but there was retrograde dissection to the right coronary artery ostium. Aortic segment, with intimal dissection, was excluded and a 24 mm Dacron graft was replaced into aortic segment above the coronary ostium. Aorta was supported with Teflon strips interiorly and exteriorly during distal and proximal anastamosis. After distal graft anastamosis, crossclamp was put on graft segment and pump was started and the patient was heated. During the operation, myocardial protection was provided by hot blood glutamate-aspartate and cold crystalloide cardioplegy antegradely and retrogradely. After that, multi dosage cold crystalloide cardioplegy was infused. After the completion of proximal anastamosis, hot blood cardioplegy at 37°C, was infused. When the rectal heat reached to 36°C, hemodynamic stability was obtained and cardiopulmonary bypass was completed succesfully.

During the operation, duration of crossclamping was 60 min. and total perfusion was 127 min. The patient who had no postoperative problem was discharged on the 9th day. It was found that right coronary artery was patent in his postoperative angiography 8 months later. (Figure 3)

### Discussion

Sixtyfive percent of thoracic aortic dissections occur 1-3 cm distal from coronary ostium. AAD could expand to carotid, renal, iliac arteries antegradely and to coronary sinus retrogradely. If aortic dissection affects the coronary sinus, aortic valve prolapse and coronary artery occlusion could occur. Because of anatomic localization, occlusion occurs more in right

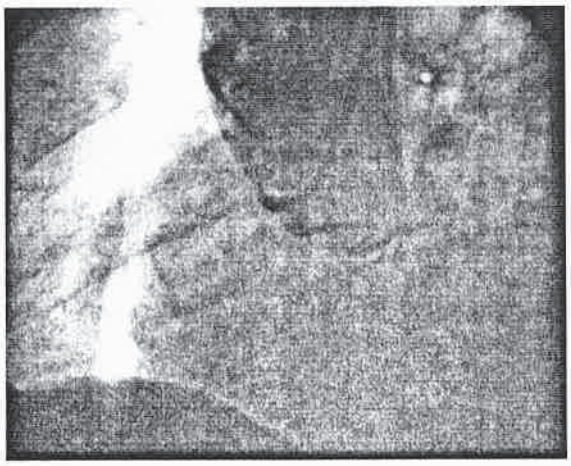

**Figure 1:** Right Coronary Occlusion Secondary to AAD

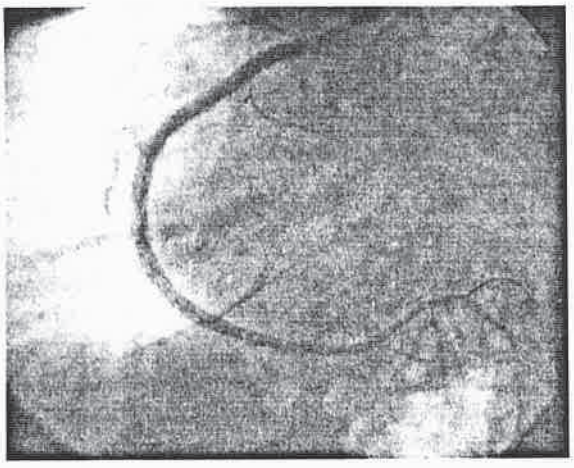

**Figure 2:** Appearance of Right Coronary Artery after Stent Implantation before Surgery

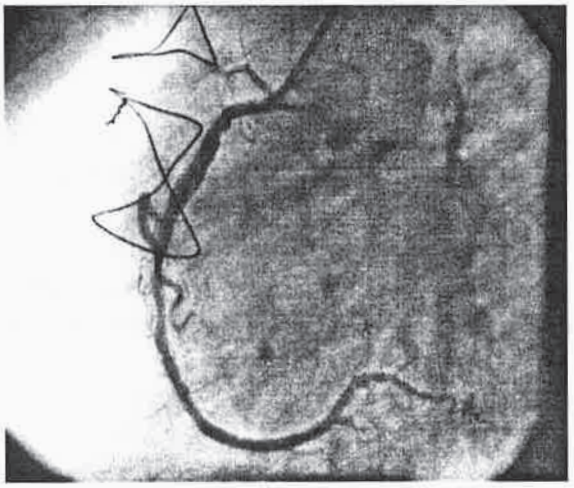

**Figure 3:** Appearance of Right Coronary Artery after 8 Months Following Surgery.

coronary artery (6). Coronary occlusion occurs, when the coronary ostium is interrupted intermittently by the intimal flap, or when a hematoma in the false lumen compresses coronary ostium and dissection expands to the coronary wall (7-8).

AMI with the majority of inferior at the rate 3-10 % accompanies to the cases with AAD. During AMI, occurance of atrioventricular blocks, bradycardia and hypotension in AAD increase surgical mortality (1-3).

In myocardial infarction, secondary to AAD, intra aortic balloon pump for hemodynamic support and thrombolytic treatment are contrindicated. As AAD and AMI show similar symptoms, dissection findings could not be determined completely in some of AMI cases. If thrombolytic treatment is given , aortic rupture could occur and generally the result is death (9-11). Blankenship et al presented that the patients, who have thrombolytic treatment because of AMI, could have cardiac tamponade because of aortic dissection and those patients could die during the operation (9). Kamp et al presented that the mortality rate due to cardiac tamponade is 71% in patients who have myocardial infarction secondary to AAD, if thrombolytic therapy is given (12). For that reason, differential diagnosis between AMI and AAD should be carried out before thrombolytic treatment.

In AMI cases secondary to AAD, infarct area expands because of the delay before surgery. The experimental studies showed that transmural necrosis occurs in 38% at $40^{th}$ min, 57 % at $3^{rd}$ hour, 71 % at $6^{th}$ hour and 85 % at $24^{th}$ hour after coronary arterial occlusion (13). It is showed that when the intervention is carried out within the first 3 hours, more myocardial area could be salvaged (13). Fernandes et al reported a surgical mortality in 5 of 11 AAD cases with right coronary arterial occlusion and the most important point was to perform immediate surgery to prevent infarct expansion (4). Infarct expansion can be prevented by immediate reperfusion. Accordingly, reperfusion was provided with percutaneous stent implantation in the second hour of infarction in our case. Inferior segmentary motion was nearly normal in postoperative echocardiographic examination and there was no Q wave in D2-3, aVF in ECG.

AMI localization is generally inferior in AAD. Conduction system ischaemia is as important as infarct expansion. In inferior AMI, conduction system disturbance could occur beause of ischaemia, which generally improves with reperfusion (14). Improvement of conduction system ischaemia is vital for hemodynamic stability. Cardiogenic shock could occur due to inferior AMI and A-V complete block. In such cases, aortic dissection, right coronary occlusion and aortic valve insufficiency were determined by angiography (15). This case underlines the importance of right coronary flow. Currently, temporary coronary reperfusion could be provided by interventional techniques. Ikari et al has provided permanent reperfusion with stent implantation to right coronary artery in acute inferior myocardial infarction cases secondary to AAD (16). We performed emergency coronary angiography and aortography which showed AAD and right coronary occlusion. Simultenously, we implanted 3 stents into the right coronary artery to provide reperfusion, and then AAD repair was performed. It is reported that stent deformation could occur because of manipulation during the surgery following intracoronary stent implantation (17). In our case, there was no need for CABG as the heart was minimally manipulated

In myocardial infartion cases secondary to AAD, the duration of preoprerative ischemic myocardial damage, long crossclamping time and good myocardial protection contribute to the succes of surgical treatment. It is accepted that following are the most effective protection method; hot blood cardioplegy in induction, multi dose cold blood cardioplegy as a supplement and hot blood cardioplegy in reperfusion(17). In our case, we applied hot blood with glutomate-aspartate in induction, cold crystalloide as a supplement and hot blood with glutomate-aspartate cardioplegy before crossclamping is removed.

In patients with myocardial infarction secondary to AAD, early surgical intervention and proper myocardial protection decrease morbidity and mortality. We belive that in those cases, providing reperfusion with percutaneous coronary intervention has a very important role for surgical success.

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# FALSE-POSITIVE BORRELIA BURGDORFERI SEROLOGY IN ERYTHEMA INDURATUM OF BAZIN

A. Tülin Güleç* ✣ Deniz Seçkin*

*SUMMARY*

*Lyme borreliosis is a multisystem disorder that is diagnosed on the bases of characteristic clinical picture and laboratory confirmation. Although serologic analysis is generally considered the best laboratory method for detecting the disease, false-positive and false-negative results are common with the tests currently in use. We report a case of false-positive Borrelia burgdorferi serology associated with erythema induratum of Bazin.*

***Key Words:*** *Lyme Disease, Erythema Induratum, Serodiagnosis, Borrelia Burgdorferi*

*ÖZET*

***Eritema İnduratum Hastalığında Görülen Yalancı-pozitif Borrelia Burgdorferi Serolojisi***

*Lyme borreliosis, tanısı serolojik bulguların desteklediği karakteristik klinik görünüm ile konan, bir çok sistemi tutan bir hastalıktır. Serolojik inceleme hastalığın tanısını koymada en iyi laboratuar metodu olmasına rağmen, bugün kullanılmakta olan testlerin sonuçlarında yalancı-pozitif ve yalancı-negatif sonuçlar sık görülmektedir. Bu makalede eritema induratum hastalığı ile birlikte görülen yalancı-pozitif Borrelia burgdorferi serolojisi olan bir olgu sunulmaktadır.*

***Anahtar Kelimeler:*** *Lyme Hastalığı, Eritema Induratum, Serolojik Tanı, Borrelia Burgdorferi*

Lyme borreliosis (LB) is a multisystem infection caused by the tick-borne spirochete *Borrelia burgdorferi*(1). Diagnosis of LB is primarily based on history and clinical evidence; however, the characteristic skin lesion, erythema chronicum migrans, may not always develop, and it is possible to confuse the long-term neurological, rheumatological and cardiac manifestations of LB with other diseases(2-4). Serologic testing is the preferred technique for laboratory confirmation of this infection because direct visualization of *B. burgdorferi* in patient specimens is difficult, and cultivation is a low-yielding process(4,5). Currently, the most common serologic tests used in LB diagnosis are indirect immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA)(6,7), enzyme-linked fluorescent immunoassay (ELFA)(8), and Western blotting (WB) (9,10). The test results must be interpreted with caution because false-positive and false-negative results are common with them.

Erythema induratum of Bazin (EIB) is a form of nodular vasculitis associated with *Mycobacterium tuberculosis*(11). Clinically, it is characterized by recurrent, tender nodules subcutaneous usually seen on the legs(12). We describe a patient with EIB whose serology was false-positive for *B. burgdorferi*. An association of tuberculosis with LB has not been reported in the English language literature to date. To our knowledge, this is the first reported case of EIB to feature false-positive *B. burgdorferi* serology.

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## CASE REPORT

In September 1997, a 52-year-old man presented with recurrent, painful, nonulcerative erythematous nodules on the anterior aspect of his right thigh and calf over the last three months (Fig. 1). Two months prior to admission, serum testing with ELFA at another hospital indicated the patient was positive for *B. burgdorferi* ( total Lyme Ig M and Ig G). The lesions seemed to clear after a 2-week course of oral amoxicillin (1g/day) but a relapse was encountered 1 week after completing therapy. We repeated the serology for *B. burgdorferi* by ELFA, and again found a positive result, with an index value of 1.67. ELFA was carried out using an automated VIDAS instrument (bioMerieux Vitek, Inc., Hazelwood, Missouri, USA). The index value is obtained by dividing the relative fluorescent value of the sample by the standart value. An index $\geq$ 1.00 is considered positive. Although there was no history of a tick bite, we pursued further treatment based on the tentative diagnosis of LB. Considering his first antibiotic therapy as inadequate for LB, we prescribed 3 weeks of oral doxycyline (200 mg/day). However, when the patient did not respond to this course of antibiotic therapy, we eliminated LB as a possible diagnosis.

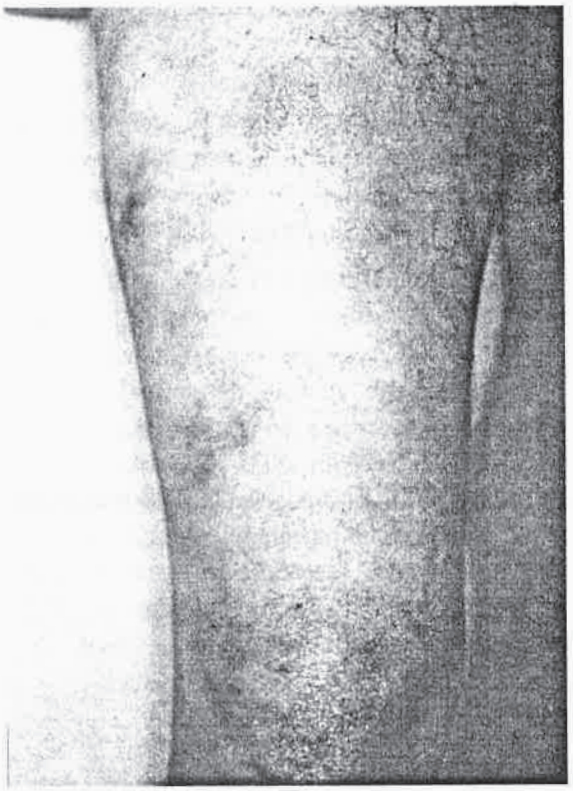

**Figure 1.** Erythematous nodules on the anterior aspect of the patient's right thigh.

Histopathology of an incisional biopsy specimen from one of the lesions on the patient's right thigh revealed granulomatous panniculitis compatible with nodular vasculitis. A positive purified protein derivative test (PPD) (induration area of 15mm x 15mm in 48 hours) and detection of mycobacterial DNA in the lesional skin by polymerase chain reaction (PCR) supported the diagnosis of EIB. The patient was given triple-drug antituberculous chemotherapy (isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 2 g/day) and was free of lesions after the first week of treatment. The pyrazinamide was discontinued after 2 months of therapy, and the patient continued to take isoniazid and rifampicin for another 7 months. One week after completion of therapy, his lesions reappeared. Since this was an indication of potentially insufficient therapy, the same triple-drug regimen was started again; however, the patient's lesions persisted. Thinking this might be due to drug resistance, we added ethambutol (1.5 g/day) and ciprofloxacin (1g/day) in the third month of treatment, and also added prednisolone (1mg/kg/day) 1 month later. After five months of therapy, he was lost to follow up.

## DISCUSSION

Our patient had no history of a tick bite or any of the classic clinical findings for LB. However, his subcutaneous nodules, one of the cutaneous findings in early LB(13), and the positive serology for *B. burgdorferi* supported the tentative diagnosis of LB. Unfortunately, we were unable to complete a two-test protocol, which would have been a more solid basis for diagnosis. We ruled out LB when the patient did not respond to appropriate antibiotic therapy. Histopathological and clinical findings, a positive PPD test and detection of mycobacterial DNA in the lesional skin by PCR led to the final diagnosis of EIB.

Because there are some proteins of *B. burgdorferi* common with the other bacteria(14) the patient's positive serology result for *B. burgdorferi* may reflect immunologic cross-reactivity. Nonetheless, one can not exclude the other causes of false-positivity completely. The English literature contains no reports of immunologic cross-reactivity of *B.burgdorferi* with *M. tuberculosis.*

The diagnosis of LB is based on history, clinical findings and laboratory data. Clinical diagnosis of LB can be challenging. The presence of erythema migrans, a skin lesion unique to this condition, is the best marker during the initial stage of the infection, but it does not always develop or may manifest atypically.2-4 Other cutaneous lesions may also be encountered (13). Later stages of the disease may include severe arthritic, neurologic and cardiac manifestations that can easily be confused with several other disorders(2-4).

Since culturing the organism or visualizing *B. burgdorferi* in specimens from LB patients tends to be difficult, serologic testing is the main diagnostic aid(4,5), ELISA and IFA are the most common serologic techniques used, and both measure the binding of circulating serum antibody to antigen. These tests are not completely sensitive and specific for LB(15). Comparing the two, a number of studies have shown ELISA to be more accurate than IFA(6,7), ELFA is a type of enzyme immunoassay in which the intensity of fluorescence is measured by optical scanner (fluorometer)(8). Western blotting is a technique that is more sensitive and specific than ELISA (9). In WB, spirochete antigens are separated by electrophoresis, and antibodies in the serum to any of these antigens can be characterized. The disadvantages are that this method is time-consuming, nonquantitative and difficult to standardize as the results are observer-dependent. WB is usually favored as the test to confirm ELISA results, and thus improve specificity(9,10). In 1995, Centers for Disease Control and Prevention recommended the use of a two-test protocol for serodiagnosis of LB(16). In this protocol, suspected LB patients are screened with an ELISA test and any positive cases are confirmed with WB. While some reports(10,17) have deemed this approach useful, Goossens and colleagues(18) found that WB did not increase the specificitiy of ELISA testing for LB.

The specificity of serology for detecting *B. Burgdorferi* is limited by a number of issues and circumstances. The main problems are lack of standardization between laboratories, immunologic cross-reactivity, asymptomatic subclinical or previously treated LB(15). Inconsistency between laboratories has produced significant variation in LB test results. Laboratories may use different test methods e.g. ELISA or IFA, different methods of antigen preparation, different cut-off values to define positivity(19) and different techniques in the adsorption step that blocks antibodies that cross-react to other treponemes(20) Borrelia genus shares certain antigens, such as flagellin, with each other and with the treponemes (21), and this explains the false-positive reactions for Borrelia that occasionally occur in other spirochetal infections, such as syphilis, yaws, pinta and relapsing fever(6,7). Hansen and coworkers(14) showed that *B. burgdorferi* has a 60-kilodalton antigen that is common to a wide range of remotely related bacteria. This may explain the false-positive LB serology in our case, and in other bacterial infectious diseases. To our knowledge, *M. tuberculosis* has not been reported to lead to false-positive LB serology. Patients with infectious mononucleosis(20), Rocky Mountain spotted fever(22), mumps meningitis(23), human granulocytic ehrlichiosis (24), and varicella zoster infection(25) have also been reported to have false-positive LB serology. Immunologic cross-reactivity to LB antigen also occurs in systemic lupus erythematosus and rheumatoid arthritis (26), diseases that feature elevated levels of immune complexes. In these diseases, false-positivity may occur due to nonspecific cross-reactive antibodies, or high concentrations of antinuclear antibody, or both(15,27). Once a mature humoral response is mounted in LB, antibodies can be detected for

years, whether or not the patient has received appropriate treatment (6). Therefore, previous infections that have been treated can confound testing and yield false-positive results(15).

We conclude that LB diagnosis should be established primarily on clinical findings. All of the serologic tests currently available for LB must always be interpreted with caution, and in the context of the patient's clinical picture. If accurate laboratory diagnosis of LB is to be achieved in future, advances in laboratory technology and standardization of the methods should be accomplished.

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# SECONDARY AORTOENTERIC FISTULA WITHOUT PERIGRAFT INFECTION FOLLOWING A REOPERATION

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İbrahim Uçar* ✣ İlhan Paşaoğlu*

*SUMMARY*

*Secondary aortoenteric fistula and perigraft infection are rare but devastating complications of prosthetic aortic reconstruction. In addition to difficulties in diagnosing these complications, significant mortality and morbidity despite of advanced treatment modalities are still challenging for surgeons. Revascularization with extra-anatomic bypass prior to total excision of the graft is recommended by most authors especially in the presence of frank graft infection. There are also reports about succesfull local repair or graft replacement in patients with aortoenteric fistula involving the suture line and with minimal infectious elements. We report a 66-year-old man with secondary aortoenteric fistula without perigreft infection which developed 12 days after the second aortobifemoral bypass grafting for graft occlusion. The difficulties in diagnosis and treatment of this compication are discussed. Secondary aortoenteric fistula must always be remembered as a cause of hemoglobin decrease in aorta reconstructions in reoperations and bowel wall must be protected not to come in contact with the prosthetic graft in order to prevent this complication.*

***Key Words:*** *Aortobifemoral Bypass Grafting, Secondary Aortoenteric Fistula*

*ÖZET*

***Reoperasyon Sonrası Perigreft Enfeksiyonu Olmadan Gelişen Sekonder Aortoenterik Fistül***

*Sentetik greft ile yapılan aorta rekontrüksiyonlarının nadir ama önemli komplikasyonları olan sentetik aortoenterik fistül ve perigreft enfeksiyonlar hemen her zaman birlikte görülürler. Tanı konulmasında karşılaşılan güçlüklerin yanı sıra cerrahi olarak üstesinden gelinmesi zor, mortalite ve morbiditesi yüksek komplikasyonlardır. Enfeksiyon lehine bulgular tespit edildiğinde, greft eksizyonundan önce ekstra-anatomik bypass ile revaskülarizasyon önerilmektedir. Enfeksiyonun sınırlı kaldığı ve sadece anastomoz hattını ilgilendiren aortoenterik fistül vakalarında ise, başarılı lokal onarımlar ya da greft replasmanları bildirilmiştir. Greft tıkanıklığı nedeniyle, reoperasyona alınan ve ikinci kez aortobifemoral greft konan 66 yaşında bir erkek hastada, 12 gün sonra perigreft enfeksiyonu olmadan gelişen sekonder aortoenterik fistül bildirilmiş ve tanı ve tedavide karşılaşılan güçlükler tartışılmıştır. Sekonder aortoenterik fistül, aorta rekonstrüksiyonlarından sonra görülen hemoglobin düşüklüğünün nedeni olarak her zaman akılda tutulmalıdır; aortik reoperasyonlarda, bu ağır komplikasyondan kaçınmak için barsak duvarı ile greftin yakın teması önlenmelidir.*

***Anahtar Kelimeler:*** *Aortobifemoral Bypass, Sekonder Aortoenterik Fistül*

Aortoiliac and aortofemoral bypass grafting are widely used operative treatment modalities of aortic reconstruction for both aortic occlusive disease and aneurysms of abdominal aorta. Graft occlusion, pseudoaneurysm formation, aortoenteric fistula and perigraft infection are the late complications of aortic graft surgery. Late graft occusion is by far the most common encountered complication, reported as 10 % in many studies (1). Aortoenteric fistula with or without perigraft infection, on the other hand is a rare but devasting complication with high mortality and morbidity rates. In most series the incidence of aortoenteric fistula is reported as 2 % (2). Mortality rates ranging from 30 to 70 % have been reported in different series with overall operative mortality of 50 % (3,4).

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In 1956, Claytor et al reported the first secondary aortoenteric fistula following the reconstruction of the abdominal aorta with a prosthetic graft (5). Since then, secondary aortoenteric fistula has been a challenging problem of diagnosis and treatment for the surgeons. Mac Kenzie et al described the first succesful repair of a secondary aortoenteric fistula in 1958 (6). In 1974, Szilagi defined aortoenteric fistula and paraprosthetic fistula as two separate entities which had differences in both clinical presentation and management (7). A communication between the suture line and the intestine was termed as an aortoenteric fistula and local contamination of a graft with intestinal erosions was named as paraprosthetic fistula. Aortoenteric fistulae often present with acute onset gastrointestinal bleeding whereas paraprosthetic fistulae which are basically low grade infections, may occasionally progress to frank graft infection and sepsis (8). High mortality of this complication suggests aggressive treatment. These patients are advised to be managed by total graft excision, segmental resection of the intestine, and extra-anatomic bypass (9). Trout has suggested that whenever graft infection was apparent, extra-anatomic revascularization of lower extremities prior to graft excision could lead to more favourable outcome (10). Outcome with graft preservation and in situ replacement have been reported to be poor. High mortality about 70 to 90 % was thought to be unacceptable. Patients died because of persistant sepsis and recurrent aortoenteric fistulae. More recently Thomas and Baird, and Walker and Cooley presented their experience about patients with aortoenteric fistula involving suture line (11,12). Their results are encouraging for more conservative management in selected patients.

## CASE REPORT:

A 66-year-old man had been operated for aortic occlusive disease 11 years ago and underwent aortobifemoral bypass grafting with end-to-side proximal anastomosis. He had also undergone coronary artery bypass grafting 5 years ago. He was suffering from claudication but no further ischemic complaints. Both femoral pulses were diminished and more distal pulses were absent. An aortofemoropopliteal digital subtraction angiography was performed via axillary route. Both limbs of the aortic graft was seen to be occluded. Graft replacement was planned. Occluded graft (Meadox woven double velour – Meadox® Vascular Prosthesis, Boston, USA) was excised leaving proximal aorta-graft end-to-side anastomosis in place and a new prosthetic graft (knitted polyester vascular prosthesis coated with bovine collagen - Cardial Prosthése Dialine® II, Saint-Etienne, FRANCE) was anastomozed to the remnant of the former graft with end-to-end technique. Bilateral femoropopliteal bypass was also performed. The patient had an uneventful early postoperative period but twelve days after the operation, he presented with mild abdominal pain. He had voluntary rigidity but no rebound pain. Blood pressure was 90/60 mmHg and heart rate was 110/min. On laboratory examination, hemoglobin level was 8 mg/dL, hematocrit was 26 %, WBC count was 5 thousand/mm3. Nasogastric tube irrigation was clear and rectal examination did not suggest gastrointestinal bleeding. Plain abdominal x-ray did not show any pathognomonic sign. Hemoglobin level decreased to 7 mg/dL despite of blood transfusion. Abdominal ultrasonography was normal except a few fluid filled bowel loops. Peritoneal cavity was free of fluid. Aortic graft and perigraft area was normal. First upper gastrointestinal tract endoscopy revealed gastritis and focal gastric bleedings and behind pylorus could not be visualized because of hematoma. The amount of gastric bleeding seemed to be far below to explain the decrease in hemoglobin level. The aortic graft was shown to be patent by intra-arterial digital subtraction angiography. No extravasation of radiopaque material could be visualized (fig. 1,2). Conservative therapy was applied. After 6 hours, during the second endoscopy, massive bleeding began (due to peeling of hematoma in pylorus). Finally exploratory laparotomy was performed. A connection between the suture line of the former graft and duodenum was found out when duodenum was incised for any ulcerative formations. There was no evidence of frank

**Figure 1:** Intra-arterial digital subtraction angiogram showing no extravasation in antero-posterior position.

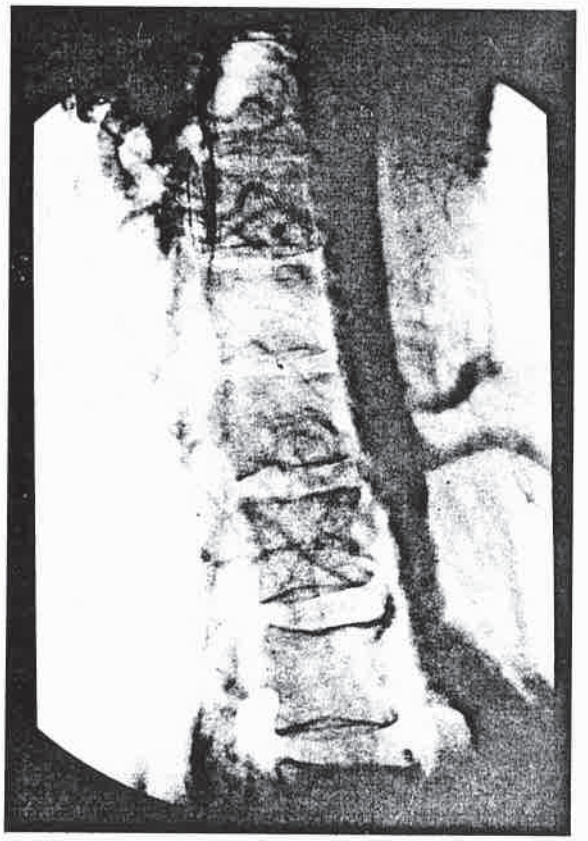

**Figure 2:** Intra-arterial digital subtraction angiogram showing no extravasation in lateral position.

infection around the anastomosis. Duodenal wall erosion was the only finding. Samples for bacterial cultures were obtained. The aorta and the graft was sutured primarily and the duodenum was repaired with tube duodenostomy. The anastomosis was reinforced by an omental wrap. Laparotomy was closed with Bogata bag. Unfortunately disseminated intravascular coagulation developed and the patient died on second postoperative day as a result of cardiac complications.

## DISCUSSION:

Aortoenteric and aortic paraprosthetic fistulae are devastating, late complications in vascular surgery. The interval between initial operation and the onset of symptoms of aortoenteric fistula varies from 2 weeks to 8 years (average 2.8 years) (13). In our case, symptoms of AEF became manifest on postoperative $12^{th}$ day.

Most authors recommend total excision of the graft and revascularization of the lower extremities by extra-anatomic bypass, if there is an evidence of graft infection (8). In our case, the patient did not have clinical and operative evidence of overt graft infection so he was treated by local repair. The patient was under postoperative wide spectrum antibiotic treatment. An infection had to be ruled out and negative cultures of the specimens confirmed this. We considered the probability of AEF when hemoglobin level began to decrease and all the techniques which were recommended for the diagnosis of AEF in the literature were used except CT and gastrointestinal barium contrast study. The presence of periaortic gas or black dots in CT has been proven to be a specific sign of a paraprosthetic-enteric fistula (14) and in the literature CT can help to detect either complication (PGI and AEF) (15). In the present case, CT was not used for evaluating the patient at the very beginning because aortic graft infection and fistula were not suspected to be the first probable complication. Hemodynamic instability of the patient did not permit performing a gastrointestinal barium contrast study. If the correct diagnosis could be defined before the patient deteriorated, operative result

could be successful. Actually, the time passed between the two endoscopies which ultimately led to an explorative laparatomy was only 6 hours.

The etiology of complications following aortic reconstruction with prosthetic grafts, particularly aortoenteric fistulae and paraprosthetic erosions is still controversial. The majority of fistulae and erosions following grafting with synthetic material develop as a communication with the third portion of duodenum. Direct contact between synthetic graft and bowel wall, which predisposes to enteric erosion, can be prevented by the use of techniques such as suturing and wrapping periaortic tissue or aneurysmal wall around the graft and interposing a viable omental pedicle between prosthesis and bowel wall (13). In our case, following the dissection and exploration of the former occluded graft, the graft was incised and thrombotic debris was removed, fibrotic tissue around the anastomosis was peeled out, and the anastomosis was fully exposed. New prosthetic graft was anastomosed end-to-end with the former graft (leaving one cm. rim of the former graft in place). Since it was a reoperation complete closure of the retroperitoneum coluld not be possible. AEF developed between duodenum and suture line of the graft-aorta anastomosis. The aged, hardened graft with sharp edges seemed to erode the duodenal wall because of mechanical friction.

## CONCLUSION:

Secondary aortoenteric fistula is a rare and in many instances mortal complication of prosthetic aortic reconstructions. It can develop at any time during early and late postoperative period. Difficulty in its diagnosis is a well known feature. The most important tool for diagnosis is probably the clinical experience and suspicious attitute of the surgeon. Yet, it is not possible to demonstrate a fistula in every case even if a surgeon keeps it in consideration.

Surgical techniques certainly help to lower the incidence of fistula formation. Retroperitoneal portion of the duodenum is by far the most common site of the fistulae. Complete closure of the retroperitoneum is essential in prevention of such complication. Cases in which total closure can not be possible, are mostly reoperations as in our case. In such conditions omental wrap is useful to keep the aorta and the graft material apart.

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# PELVIC LIPOMATOSIS ASSOCIATED WITH INVASIVE CYSTITIS GLANDULARIS

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*SUMMARY*

*Pelvic lipomatosis is a rare entity with unknown etiology. It often is associated with chronic inflammatory changes or malignancies. We report herein a 56-year-old man with pelvic lipomatosis associated with invasive cystitis glandularis causing severe urinary obstruction with bilateral massive hydroureteronephrosis. The diagnostic procedure and the management of the patient are described.*

***Key Words:*** *Cystitis Glandularis, Pelvic Lipomatosis, Nuclear Magnetic Resonance.*

*ÖZET*

***İnvaziv Sistitis Glandularis ile Birliktelik Gösteren Pelvik Lipomatozis***

*Pelvik lipomatozis etyolojisi bilinmeyen ve nadir görülen bir antitedir. Pelvik lipomatozis sıklıkla kronik inflamatuar değişiklikler veya malinitelerle birliktedir. Bilateral masif hidroüreteronefroz ile birlikte ciddi üriner obstrüksiyona yol açan invaziv sistitis glandülaris ile birlikte pelvil lipomatozisli 56 yaşında bir erkek hastayı sunmaktayız. Hastanın tedavisi ve tanısal prosedür tarif edilmektedir.*

***Anahtar Kelimeler:*** *Sistitis Glandularis, Pelvik Lipomatozis, Nükleer Magnetik Rezonans*

Pelvic lipomatosis is characterized by the proliferation of infiltrating fatty tissue in the bony pelvis. This entity was first described by Engels in 1959 (1). The etiology of pelvic lipomatosis is unclear. Computerized tomography (CT) has been used in diagnosis of pelvic lipomatosis. Nuclear magnetic resonance seems to be supported to diagnosis of pelvic lipomatosis. The incidence of proliferative cystitis in patients with pelvic lipomatosis is high. There also may be an increased risk of upper urinary tract obstruction, urolithiasis and adenocarcinoma of the bladder. We present nuclear magnetic resonance image of patient who has pelvic lipomatosis associated with invasive cystitis glandularis is one of the few cases.

## CASE REPORT

A 56 year-old man presented with hematuria, dysuria, frequency, stranguria and lower abdominal pain with radiation to the bilateral lomber region for 4 months. Physical examination was normal. Urine analysis showed numerous red blood and white blood cells. Urine culture and strain for Mycobacterium tuberculosis were negative. Serum urea, creation and lipid profile were normal. Excretory urography (IVP) revealed bilateral high-grade hydroureteronephrosis with an irregular filling defect in bladder base (Fig. 1). Transrectal ultrasonography confirmed a diffuse irregular and infiltrative mass in the bladder base. Computerized tomography (CT) demonstrated the pre-

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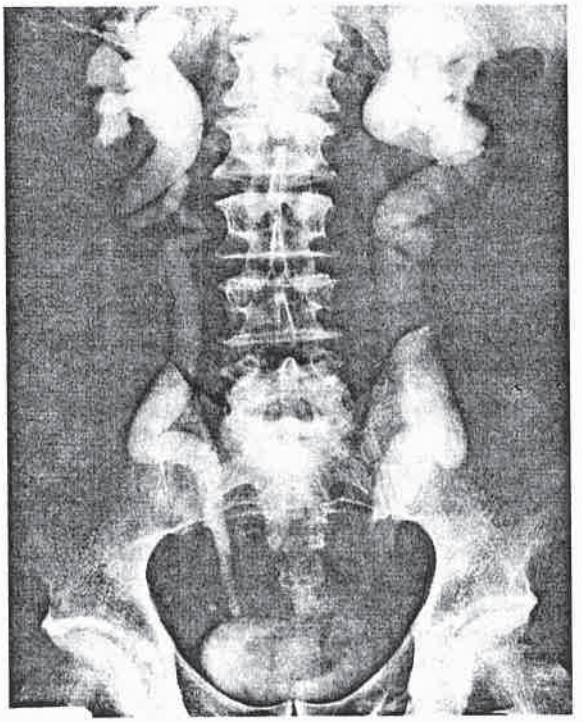

**Figure 1:** Excretory urogram reveals bilateral hydroureteronephrosis and filling defect in bladder base.

sence invasive bladder tumor. Nuclear magnetic resonance (NMR) scan of the pelvis demonstrated invasive bladder tumor with abundant perivesical fatty tissue (Fig. 2). Cystoscopy confirmed significant small bladder capacity and diffuse bullous edema associated with 5x4 cm solid tumor in the bladder base. Multiple biopsies were obtained. Histologic examination of the biopsies revealed a cystitis glandularis with intestinal metaplasia. There was no vesicoureteral reflux (VUR) on voiding cystourethrography (VCUG). Urodynamic evaluation showed hypocompliance and small total bladder capacity (62 cc). We performed bilateral percutaneous nephrostomy for a few weeks. Cystoprostatectomy and ileal conduit urinary diversion were performed. At laparatomy, true pelvis was narrowed by the abundant adipose tissue. Macroscopically, the cystoprostatectomy specimen was covered by excessive fatty tissue. On histologic examination, a 5x4 cm solid tumor was located on the trigone and extended to the

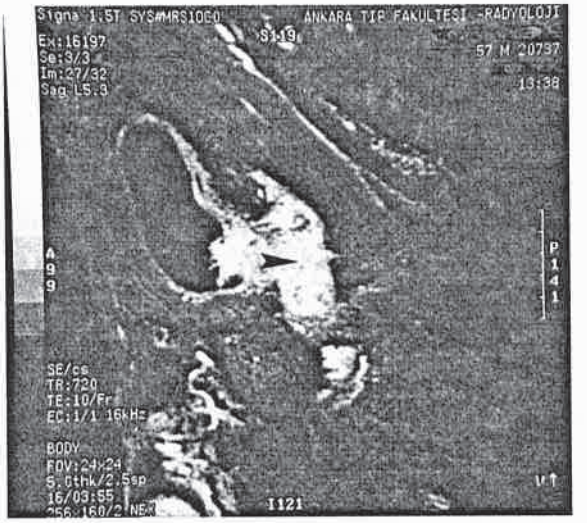


**Figure 2:** Nuclear magnetic resonance imaging in T1 weighted image shows bladder tumor with invasion of the prostate and abundant perivesical fatty tissue (arrow).

perivesical fatty tissue and the prostate was invaded. The tumor demonstrated cystitis glandularis with metaplastic intestinal epithelium (Fig.3). Convalescence was uneventful.

## DISCUSSION

Pelvic lipomatosis is a rare condition by diffuse infiltrating fatty tissue in the true pelvis. In 1959, Engles reported a case with pelvic lipomatosis (1).The pathological entity of pelvic lipoma-

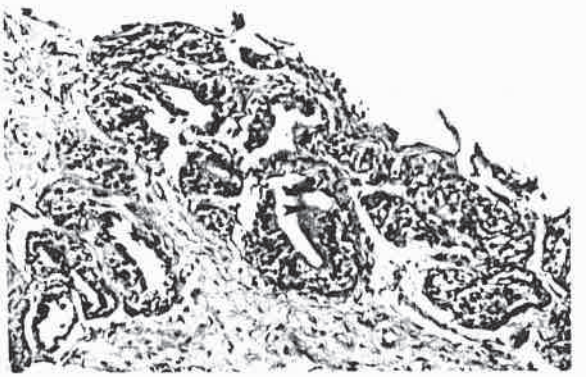

**Figure 3:** Cystoprostatectomy specimen demonstrates Brunner's nest (Right), mucoid and intestinal metaplastic epithelium in central submucosal glands and a Goblet cell (arrow). H&E, X50.

tosis still remains somewhat of enigma as can be witnessed by the variety of clinical presentations, radiological findings and various treatments for the disease. Proliferative cystitis has been observed in most patients with pelvic lipomatosis. The reason for the high incidence of proliferative cystitis in pelvic lipomatosis remains unclear. It is speculated that the associated chronic inflammatory changes in the bladder may be a result of lymphatic obstruction created by the pelvic fat proliferation (2).

Proliferative cystitis may be associated with adenocarcinoma of the bladder. Particularly, an adenomatous proliferation of cystitis glandularis is premalignant. Heyns et al reported a patients with pelvic lipomatosis in whom adenocarcinoma of the bladder developed 6 years after a diagnosis of proliferative cystitis (3).

Computerized tomography (CT) has been used in diagnosis of pelvic lipomatosis. Allen and De Kock evaluated NMR image of a patient with pelvic lipomatosis. They suggested that the diagnosis of pelvic lipomatosis may be supported by a NMR scan of the pelvis (4). NMR image not only allows diagnostic confirmation comparable to that possible with CT but also provides delineation of cephalad displacement of the bladder base, elongation of the bladder neck and posterior urethra, and elevation of the prostate gland. The MR images show characteristic medial and superior displacement of the seminal vesicles and show fatty tissue separating the prostate gland from the rectum.

The present case is one of a few in which the disease has pelvic lipomatosis associated with invasive (perivesical and prostatic invasion) cystitis glandularis. Nuclear magnetic resonance imaging is useful diagnostic tool in pelvic lipomatosis.

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