Journal of Ankara Medical School

Vol 23, No 1, 2001

Journal of Ankara Medical School

Vol 23, No: 1, 2001

CONTENTS

Journal of Ankara Medical School

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Ankara Üniversitesi Tıp Fakültesi Vakfı - ANKARA

Editorial Office :
A.Ü. Tıp Fakültesi Yayın Komisyonu Başkanlığı Sıhhiye - ANKARA ISSN 1300 - 5464

Design & Preparation: ANTIP A.Ş. 0 (312) 310 63 05 - 362 30 30/7005 Hakan Ellidokuzoğlu
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Journal of Ankara Medical School

Published Quarterly by
ANKARA UNIVERSITY MEDICAL SCHOOL

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EFFECTS OF ACUTE BORIC ACID ON THE RAT TESTICULAR TISSUE*

Pelin ARIBAL KOCATÜRK**

SUMMARY

There are several reports about the effects of boric acid on reproductive system and there are conflincting data about its accumulation in testis.

The purpose of this study, was to determine boron concentration in testis and the histopathological changes after acute exposure to boric acid.

In this study, 30 male, albino Sprague-Dawley rats, 2 months old and weighing approximately 221 g, were administered 1000 mg/kg/day boric acid orally in drinking water for 7 days. As controls 15 male albino Sprague-Dawley rats in the same age and weighing 220 g were used. After 7 days of administration, animals were operated and their testis tissues were removed. There was a significant body weight and testis weights loss in the experimental group at the operation day. Testis boron concentrations were determined spectrophotometrically and were found increased in the experimental group.In histopathological examinations, there were congestion, stasis and also inhibited spermiogenesis.

Conclusively, acute boric acid exposure resulted in accumulation of boron in testis, leading to inhibited spermiogenesis.

Key Words: *Boron, testis, toxicity.*

ÖZET

Sıçan Testis Dokusunda Akut Borik Asit Etkileri

Röprodüktif sistemde borik asitin etkileri konusunda az sayıda yayın mevcuttur, testiste borik asit birikimi konusunda ise çelişkili sonuçlar elde edilmiştir.

Bu çalışmanın amacı, borik aside akut maruziyet sonrasında testiste bor konsantrasyonunu ve ortaya çıkan histopatolojik değişiklikleri belirlemektir.

Bu çalışmada, 2 aylık, yaklaşık 221 g ağırlığında, albino Sprague-Dawley, 30 adet erkek sıçan kullanılmıştır. Sıçanlara 7 gün süre ile 1000 mg/kg/gün borik asid oral olarak içme suyu ile verilmiştir. Kontrol olarak ortalama 220 g ağırlığında aynı yaşta 15 adet erkek albino Sprague-Dawley sıçan kullanılmıştır. Yedi günün sonunda sıçanlar ameliyat edilmiş ve testis dokuları alınmıştır. Deney grubunda, ameliyat gününde, belirgin vücut ağırlığı ve testis ağırlığı kaybı olduğu saptanmıştır. Testis bor konsantrasyonu spektrofotometrik olarak saptanmış ve deney grubunda artmış olduğu görülmüştür. Deney grubunda, histopatolojik çalışmada, konjesyon, staz ve aynı zamanda spermiyogenez inhibisyonu saptanmıştır.

Sonuç olarak, akut borik asit maruziyetinin testiste birikime sebep olarak spermiyogenez inhibisyonuna sebep olduğu sonucuna varılmıştır.

Anahtar Kelimeler: *Bor, testis, toksisite.*

**This manuscript is the summary of a PhD thesis from the Department of Pathophysiology*

This work was supported by The Scientific and Technical Research Council of Turkey (TÜBİTAK) and was presented at the III International Congress of Pathophysiology, Lahti, Finland, 28 June - 3 July, 1998.

***Department of Pathophysiology, Faculty of Medicine, Ankara University*

Received:Jan 09,2001 Accepted:Jan 31,2001

Boron is present in inorganic borates such as borax and boric acid that are used widely in medicine, industry, and commerce (1). Highly concentrated, economically sized deposits of boron minerals, always in the form of compounds with boron bonded to oxygen, are rare and generally found in arid areas with a history of volcanism or hydrothermal activity. Such deposits was discovered in United States and Turkey. As a result, today Turkey is the largest producer of borate and boric acid products in the world (2, 3).

The major uses of boron in our society are in the production of glass and ceramics, detergents, bleaches, fire retardants, disinfectans, alloys, specialty metals, preservatives, pesticides and fertilizers (4, 19). Many people work in the industrial fields of boron compounds, great populations work and live in the areas rich in boron and humans consume several milligrams of boron each day in the foods they eat. As a result, it is not surprising that boron can be found in the tissues and body fluids. In addition there is also environmental contamination of boron in air and surface water sources. Since it is so ubiquitous in its distribution and use, the analysis of trace amounts of boron in biological samples is very important. This investigation was planned to study one of the effects of boron experimentally.

In several animal and human studies it has reported that boron may play a role in cell membrane function, mineral and hormone metabolism, and in enzymatic reactions (5). There are several reports about the effects of boron and boron compounds in rodents, on reproductive, gastrointestinal and central nervous systems (6, 7). Additionally, human infertility, as a result of exposure to boric acid and boron-containing compounds, may be possible. Hence, it was reported that, men exposed to boron-containing tranquilizer had germinal aplasia. Also after an environmental exposure to boron, sperm production was found to be diminished (8, 9).

In experimental studies, many investigators showed that most of the soft tissues appear to contain about the same amount of boron as blood. Bone tends to have a higher level of boron, while fat, muscle, heart, lung, and intestine show lower amuonts of the element but there are conflincting data about its accumulation in testis (9, 10, 11).

The purpose of this study, was to determine boron concentration in testis tissue and its histopathological effects after boric acid exposure for seven days.

MATERIALS AND METHODS

In this study, 30 male, albino Sprague-Dawley rats, 2 months old and weighing approximately 221 g, were administered 1000 mg/kg body weight/day boric acid in drinking water for 7 days. Control group of this study was consisted from healthy 15 male albino Sprague-Dawley rats, in the same age and with average weight of 220 g. After 7 days of treatment, experimental and the control rats were operated and their testis tissues were removed. Testis tissues were weighed and their boron concentrations were determined spectrophotometrically. Analytical method was used for this purpose. The principle of the metod is, in the presence of boron, a solution of asetic acid and tetramethyl urea in concentrated sulfuric acid changes from a bright red to a bluish red or blue, depending on the concentration of boron present (12, 13).

For histopathological examinations, paraffin sections of 6 μm were stained with Hematoxylin-Eosine (HE) and semithin sections of 1 μm were stained with Toluidin blue, azur II and all tissues examined in light microscope and photographed (14, 15).

Statistical analysis of the results are evaluated with t-tests for independent samples and t-tests for paired samples, in the Department of Biostatiscs, Faculty of Medicine, Ankara University.

RESULTS

Body weights of experimental rats were decreased daily by 10 g. Their mean body weight at the end of exposure was 150 g. Mean body and testis weights and also testis boron concentrations

of both the control and experimental groups are shown in Table 1.

Histopathological changes due to acute boric acid exposure are shown on the photographs and detailed information are given below figures. Figures 1-5.

Table 1: Body and testis weights and testis boron concentrations in control and experimental groups at the operation day (mean±standard deviation).

Parameter	Control Group (n=15)	Experimental Group (n=30)	Statistical Analysis
Body weight (g)	222,667±19,791	149,833±20,276	p<0,001
Testis weight (g)	1,180±0,070	1,066±0,180	p<0,01
Testis boron concentration (mg/g tissue)	0,049±0,021	0,281±0,138	p<0,001

Clinical manifestations during acute boric acid exposure are presented in Table 2.

Table 2: Clinical manifestations of boric acid exposure in rats.

Days of treatment	Results
1-2	↑ water intake ↑ food intake Normal physical activity
3-4	↓water intake, because of desoriantation ↓food intake ↑water appetite ↓body weight ↑ physical activity
5-6	↓↓water intake ↓↓food intake ↓water appetite ↓↓body weight ↓ physical activity congestion on tip of the nose yellowish colour change in the nape feather posture change (become hunch- backed)
7	↓↓↓water intake ↓↓↓food intake ↓↓water appetite ↓↓↓body weight ↓↓↓ physical activity ↑congestion on tip of the nose ↑yellowish colour change in the nape feather ↑posture change (become hunch-backed) ataxic movement

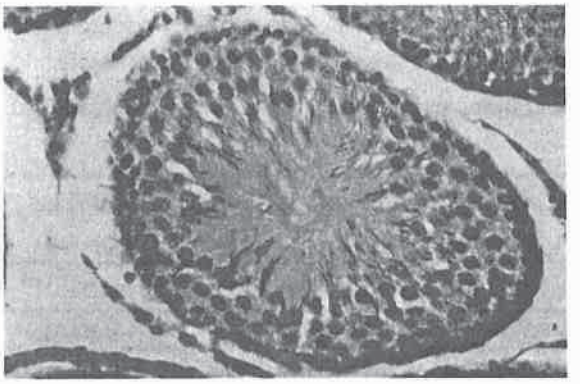

Figure 1: Section of testis from control group, normal seminiferous tubules and germinal epithelium. Hematoxylin-Eosine (HE)x100.

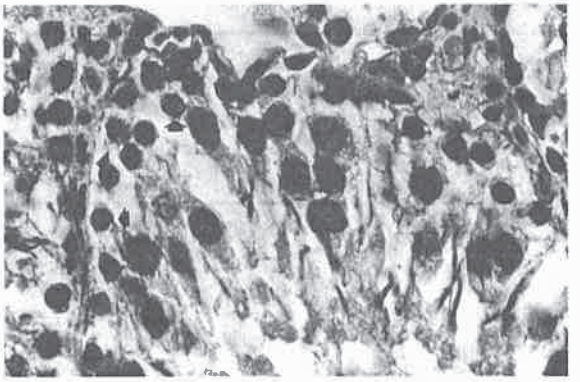

Figure 2: Seminiferous tubule from boric acid treated rat, separation of spermatogonia (←) from the basement membrane (▲). Leydig cell (L). HEx250.

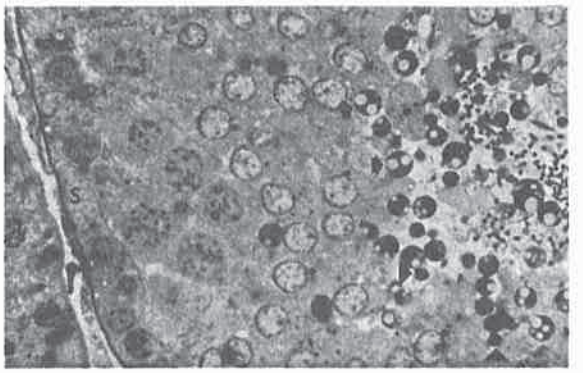

Figure 3: Testis tissue of experimental group, semithin section of seminiferous tubule. Notice decreased metamorphosus, simultaneous vacuolization in spermatid cytoplasm (←) and also unusual mast cell (▲) accumulation . Sertoli cell (S). Toluidin blue,azur IIx250.

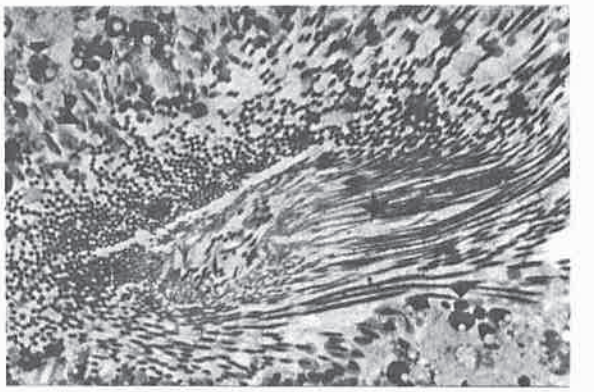

Figure 4: Testis section from experimental group, semithin section of seminiferous tubule. Vacuolization (←), mast cell (▲) accumulation and abundant reticular fiber (★) within the lumen. Toluidin blue,azur IIx250.

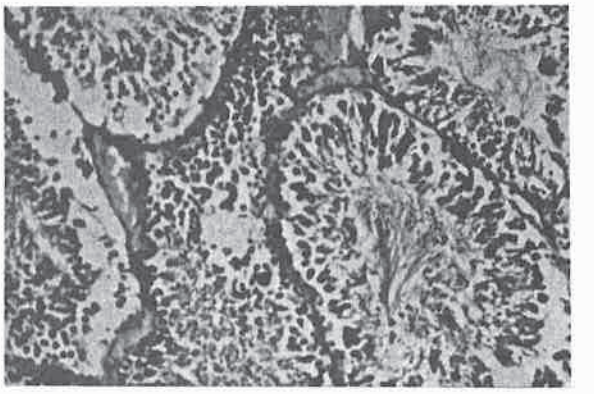

Figure 5: Section of testis from rat treated with boric acid. Marked hyperemia and stasis (←). HEx50.

DISCUSSION

The studies in 1972 established boric acid as toxic agent to male reproductive system, skin, and CNS of the young rat, as well as an inhibitor of growth (16). Fail et all were reported in 1991 that dietary treatment with boron decreased rat body and testicular weight (9). In this study, boron compound, when administered acutely, 1000 mg/kg to rats, tend to cause changes in body weight, posture, adipose tissue, water and food intake and physical activity. Water and food intake showed an increase in the first two days while both of them decreased from the third day of the exposure. It is notable that exposure to boric acid resulted in body weight loss as much

as 10 g/day in this study while the control group showed the expected body weight gain. On the other hand, the loss of fat tissue seen in the experimental rats in this study was thought as another cause of body weight decrease. In a different study, investigators showed that, rat tissue lipids, specifically cholesterol concentrations, were reduced in the liver and in the aorta wall after 14 days administration of boron compounds. In the same study, lipids, particularly cholesterol and triglycerides, were increased in the feces and bile. They considered the reduction in lipids, as a result of boron compounds' inhibition of key enzyme activities in the de novo synthesis of cholesterol (17).

Although water and food intake was increased in the first 2 days of treatment, the marked decrease in body weight of experimental group was suggested as a generalised toxicity of organism. Although there was an increased water appetite, the difficulty to find the place of water because of desoriantation was supported the existance of toxicity affecting the central nervous system. Physical activity appeared to be increased by the third and fourth days of treatment but showed a rapid decrease on the fifth day. Posture change on the sixth day and ataxic movement on the seventh day obligated to do the operation and remove the testis on seventh day of administration. The violet-red colour of the mucosa, yellowish colour change in the nape feather, coarse hair coats, scaly tails and hunched position of treated rats were evaluated as a preletal symptoms of acute boric acid toxicity by several investigators (16). In this study, on the fifth day of treatment, congestion in the nose and mouth mucosa, yellowish colour change in the nape feather were associated with the posture change. These symptoms were reported similar to the signs of normal aging in rats (18).

The results of this study showed that boric acid accumulate significantly in testis tissue after acute administration orally. This accumulation in testis was approximately 6 fold of controls in our study while it was reported as 2 fold by Lee et all in 1978 and approximately 7-11 fold by Ku et all and by Treinen and Chapin (19, 20, 21).

It was determined that there was also a weight loss in testis of experimental group compared to control group. This finding is confirming the literature data (7, 9).

In this study, in histopathological studies, the tissues that embedded in paraffin showed, separation of half part of spermatogonial layer from the basement membrane in experimental group. In testis section of experimental group, the degeneration of spermiogenesis was apparent in many sites, while the spermatogenesis was normal. In the duration of spermiogenesis, the metamorphosis was severly decreased. Specially in semithin sections, the vacualization was present in the cytoplasm of spermatids. In histological study, no mature spermatozoon was detected. Sertoli and Leydig cells were normal, but there were marked accumulation of mast cells and also hyperemia and stasis in testis tissue. These results are confirming the literature data. As a result, boric acid administration for 7 days in rats, caused testicular lesions and inhibition of spermiogenesis. Gavage doses of 1000 mg/kg per day in albino rats or dietary doses of 1.0% in Sprague-Dawley rats caused testicular atrophy after 14 days of gavage (9, 22).

Acute boric acid toxicity may be due to a testicular effect of boron to alter germ cell, Sertoli cell, or Leydig cell function or an induced effect on testicular function via an alteration of the pituitary-hypotalamic axis (19). Additionally, several reports suggest that boron-containing compounds may also interfere in ATP production and other pathways in cellular metabolism. When human spermatozoon were exposed to boron-containing compounds ATP production was diminished and potassium transport was inhibited, this process could disrupt spermatogenesis and alter hormone production (9, 23). In several studies, Sertoli cells possessing a high rate of RNA synthesis in vivo were reported. Boric acid can impair nucleic acid synthesis in rat liver, and might do so in testis. It is postulated that boric acid affects the DNA synthetic activity of both mitotic (spermatogonial) and meiotic (post-spermatogonial) germ cells (24, 25). On the other hand, the result of one study

showed a significant decrease (52%) in FSH-induced intracellular cAMP accumulation only at 10 mM boric acid which is 5- to 10- fold above the highest boron concentrations in vivo studies. This process also could be one of the reason of inhibited spermiogenesis during acute boric acid toxicity (19, 24). Finally, zinc is suggested to be an essential metal in sexual maturation and normal testicular but, testicular toxicants lead to depression in testis zinc concestration. The relation of zinc status and inhibited spermiation is under investigation (24).

CONCLUSION

Acute exposure of boron or its compounds to rats revealed generalized toxic effects with accumulation in testis tissue and histopathological changes leading to spermiogenesis inhibition in acute period.

ACKNOWLEDGEMENT

This work was supported by The Scientific and Technical Research Council of Turkey.

The author is greatfull to Prof. Güzin Özelçi Kavas, M.D., the advisor of this PhD thesis, for all her efforts on this study.

The author acknowledge also; the technical assistance of Bizden Tavil Sabuncuoğlu, MD, from Histology-Embryology Department, the laboratory assistance of Demet Büyükkağnıcı from Pathophysiology Department and finally the statistical computer analyser Nazmiye Kurşun from Department of Biostatistics, Faculty of Medicine, Ankara University.

REFERENCES

1. Culver BD, Shen PT, Taylor TH, Lee-Feldstein A, Anton-Culver H, Strong PL. The relationship of blood- and urine-boron to boron exposure in borax-workers and the usefulness of urine-boron as an exposure marker. Environ Health Perspect 1994; 102 suppl 7: 133-7.
2. Woods WG. An introduction to boron: History, sources, uses, and chemistry. Environ Health Perspect 1994; 102 suppl 7: 5-11.
3. Moseman RF. Chemical disposition of boron in animals and humans. Environ Health Perspect 1994; 102 suppl 7: 113-7.
4. Mastromatteo E, Sullivan F. Summary: International symposium on the health effects of boron and its compounds. Environ Health Perspect 1994; 102 suppl 7: 139-41.
5. Penland JG. Dietary boron, brain function, and cognitive performance. Environ Health Perspect 1994; 102 suppl 7: 65-72.
6. Nielsen FH. Biochemical and Physiologic Consequences of Boron Deprivation in Humans. Environ Health Perspect 1994; 102 suppl 7: 59-63.
7. Chapin RE, Ku WW. The reproductive toxicity of boric acid. Environ Health Perspect 1994; 102 suppl 7: 87-91.
8. Whorton D, Haas J, Trent L. Reproductive effects of inorganic borates on male employees: Birth rate assessment. Environ Health Perspect 1994; 102 suppl 7: 129-32.
9. Fail PA, Geoge JD, Seely JC, Grizzle TB, Heindel JJ. Reproductive toxicity of boric acid in swiss (cd-1) mice: Assessment using the continuous breeding protocol. Fundam Appl Toxicol 1991; 17: 225-39.
10. Heindel JJ, Price CJ, Field EA, Marr MC, Myers CB, Morrissey RE, Schweitz BA. Developmental Toxicity of Boric Acid in Mice and Rats. Fundam Appl Toxicol 1992; 18: 266-77.
11. Ishii Y, Fujizuka N, Takahashi T, Shimizu K, Tuchida A, Yano S, Naruse T, Chishiro T: A fatal case of acute boric acid poisoning. Clin Toxicol 1993; 31: 345-52.
12. Abou-Shakra FR, Havercroft JM, Ward NI. Lithium and boron in biological fluids. Trace Elem Med 1989; 6: 142-6.
13. Agazzi EJ. Extraction-flame photometric determination of boron. Anal Chem 1967; 39: 233-235.
14. Prophet EB, Mills B, Arrington JB, Sobin LH. "Laboratory Methods in Histotechnology", 1992: 25-59.

15. Pease DC. "Histological Tecniques for Electron Microscopy". New York, London: Academic press, 1960.

16. Weir RJ, Fisher RS. Toxicologic studies on borax and boric acid. Toxicol Appl Pharmacol 1972; 23: 351-364.

17. Hall IH, Chen SY, Rajendran KG, Sood A, Spielvogel BF, Shih J. Hypolipidemic, anti-obesity, anti-inflammatory, anti-osteoporotic, and anti-neoplastic properties of amine carboxyboranes. Environ Health Perspect 1994; 102 suppl 7: 133-7.

18. Massie HR. Effect of dietary boron on the aging process. Environ Health Perspect 1994; 102 suppl 7: 45-48.

19. Lee IP, Sherins RJ, Dixon RL. Evidence for induction of germinal aplasia in male rats by environmental exposure to boron. Toxicol Appl Pharmacol 1978; 45: 577-90.

20. Ku WW, Chapin RE, Moseman RF, Brink RE, Pierce KD, Adams KY. Tissue disposition of boron in male fisher rats. Toxicol Appl Pharmacol 1991; 111: 145-51.

21. Treinen KA, Chapin RE. Development of testicular lesions in f344 rats after treatment with boric acid. Toxicol Appl Pharmacol 1991; 107: 325-35.

22. Dieter MP. Toxicity and carcinogenicity studies of boric acid in male and female $B6C3F_1$ mice, Environ Health Perspect 1994; 102 suppl 7: 93-7.

23. Jutte NHPM, Grootegoed JA, Rommerts FFG, Molen HJ. Exogenous lactate is essential for metabolic activities in isolated rat spermatocytes and spermatids. J Reprod Fertil 1981; 62: 399-405.

24. Ku WW, Chapin RE. Mechanism of the testicular toxicity of boric acid in rats: In vivo and in vitro studies. Environ Health Perspect 1994; 102 suppl 7: 99-105.

25. Galdieri M, Monesi V. Ribozomal RNA synthesis in spermatogonia and Sertoli cells of the mouse testis. Exp Cell Res 1973; 80: 120-6.

PREDICTIVE VALUE OF HEART-RATE VARIABILITY FOR THE RECURRENCE OF ATRIAL FIBRILLATION AFTER ELECTRICAL CARDIOVERSION

Ömer Akyürek* ❖ Erdem Diker* ❖ Remzi Karaoğuz* ❖ Muharrem Gürdal* ❖ Derviş Oral*

SUMMARY

Background: *The relation between heart-rate variability (HRV) and occurrence of atrial fibrillation (AF) in paroxysmal AF has been well-studied, but there is not enough evidence as to whether HRV parameters can predict AF relapse after cardioversion of chronic AF.*

Objectives: *In the present study, we compared HRV parameters on the 2nd day of postcardioversion with a healthy control group and investigated their predictive value for AF recurrence.*

Methods: *Forty-one patients with chronic AF (>3 months) who had various cardiovascular disorders as the underlying cause of the arrhythmia were enrolled in the study. Thirty-one patients were successfully cardioverted by external direct current shock, but only 27 patients fulfilled the study's entry criteria. Twenty healthy subjects served as a control group. A 24-hour Holter recording was obtained on the second day of restoration of sinus rhythm, and the following time-domain indexes of HRV were measured: SDNN (standard deviation of mean RR interval, expressed in milliseconds); rMSSD (root mean square of differences of successive RR intervals); SADNN (SD of the averages of RR intervals in all 5-minute segments of the 24-hour recording); and PNN50 (the percentage of adjacent RR intervals that differed by more than 50 ms). Patients were followed-up for six weeks for recurrences of AF.*

Results: *After cardioversion, SDNN and SADNN were found to be significantly lower in the AF group than in the control group (86.4±31.7 ms vs. 142.1±40.2 ms, and 57±17.4 ms vs.124.4±37.7; ms, p<0.001 and p<0.001, respectively). The indexes of vagal modulation of heart rate (rMSS and pNN50) were no different between groups. AF recurrence was observed in 15 patients, all of whom had HRV parameters that were significantly depressed in comparison to those with maintained sinus rhythm, indicating vagal withdrawal. Logistic regression analysis revealed that decreased pNN50 was the only independent predictor of AF relapse (Relative risk=1.5, p=0.02, 95% confidence interval 1.1-2.2). There was also a trend toward shortened SDNN as a predictor of AF recurrences.*

Conclusion: Suppressed HRV is most likely a risk factor for AF recurrences in patients with chronic AF and with structural heart disease as the underlying cause of AF.

Key words: *Atrial fibrillation, recurrence, autonomic tone, heart-rate variability*

ÖZET

Elektriksel Kardioversiyondan Sonra Atrial Fibrilasyonun Tekrarında Kalp Hızı Değişkenliğinin Belirleyiciliği

Amaç: *Paroksismal atrial fibrilasyon (AF)'da aritmi atakları ile kalp hızı değişkenliği (KHD) arasındaki ilişki önceki çalışmalarda oldukça iyi dökümante edilmesine rağmen KHD'nin , sinüs ritmine döndürülmüş kronik AF'de aritmi nüks riskini belirlemedeki rolü henüz çok iyi bilinmemektedir. Çalışmamızda, kardiyoversiyon sonrası 2. günde Holter kaydıyla elde edilen KHD parametrelerini sağlıklı bireyler ile karşılaştırmak ve AF nüksü için belirleyiciliğini bulmak amaçlandı.*

Gereç: *Kronik atrial fibrilasyonu ve altta yatan bir kardiyovasküler hastalığı olan 41 hasta çalışmaya alındı. Eksternal elektriksel kardiyoversion 31 hastada başarılı oldu ancak bunların 27'si çalışma için uygun bulundu. Yirmi sağlıklı birey kontrol grubu olarak seçildi. Yirmidört saatlik Holter, sinüs ritmi sağlandıktan iki gün sonra yapıldı ve KHD'nin şu parametreleri elde edildi: SDNN (RR intervallerinin standard deiviasyonu), SADNN (24 saatlik kayıttaki her 5 dakikalık segmentte bulunan ortalama RR intervallerinin standard deviasyonu), rMSSD (ardışık RR intervallerindeki farklılığın karekökü) ve pNN50 (50 milisaniyeden daha fazla farklılık gösteren ardışık RR intervallerinin oranı). Hastalarda aritmi nüksünü belirlemek için 6 haftalık takip yapıldı.*

Bulgular: *SDNN ve SADNN kariyoversiyon sonrası AF grubunda kontrol grubuna göre anlamlı derecede azalmış bulundu (Sırasıyla, 86.4±31.7 ms'ye karşı 142.1±40.2 ms, ve 57±17.4 ms'ye karşı 124.4±.37.7; ms, p<0.001 ve p<0.001). Kalp hızının vagal modülasyonunu gösteren rMSSD ve pNN50 kontrol grubu ve AF grubu arasında farklı değildi. AF'nin takip süresi boyunca 15 hastada nüks ettiği tespit edildi. AF nüksünün gözlendiği hasta grubunda incelenen tüm HRV parametrelerinin kontrol grubuna göre anlamlı derecede azaldığı gözlendi. Çok değişkenli lojistik regresyon analizi sadece pNN50'deki azalmanın AF nüksü için bağımsız bir belirleyici olduğunu gösterdi (Rölatif risk=1.5, p=0.02, %95 güvenlik aralığı 1.1-2.2). Öte yandan baskılanmış SDNN'nin de aritmi nüksü belirlemede bağımsız bir belirleyici olduğu yönünde istatistiksel bir eğilim saptandı.*

Yorum: *Kronik AF'si ve altta yatan kardiyovasküler bir hastalığı olan hastalarda baskılamış KHD, kardiyoversiyon sonrası AF nüksü riskini artırmaktadır.*

Anahtar kelimeler: *Atrial fibrilasyon, otonomik tonus, kalp hızı değişkenliği*

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Received:Jan 25,2001 Accepted:Feb 13,2001

Atrial fibrillation (AF) is the most common type of arrhythmia, with a prevalence of 0.4-0.5% in the overall population.[1] Its incidence increases with age and with the existence of structural heart disease or hypertension.[2] It is also associated with increased mortality and morbidity.[3] The autonomic nervous system plays an important role in the occurrence of AF. Previous studies have demonstrated that vagal stimulus may induce AF via its effect on the atrial refractory period.[4-6] In fact, the relationship between AF and the autonomic nervous system may be interdependent. A recent study showed that rapid atrial pacing with a duration of 24 hours influenced the autonomic nervous system, suggesting that AF may induce autonomic changes that can facilitate the perpetuation of AF itself.[7] Additionally, Cheng et al showed the adrenergic hypersensitivity of the atrium in prolonged right-atrial pacing models, mimicking high-rate atrial rhythms.[8]

The relation between human AF and the cardiac autonomic tone has not yet been fully clarified. There is evidence of an association between increased sympathetic tone and attacks of AF in paroxysmal AF.[9-10] On the other hand, Kanoupakis et al showed that there was an increased vagal tone after cardioversion of AF and that a higher vagal tone was an independent predictor of AF relapse.[11] There may be a different relationship between the autonomic tone and AF in the diseased heart.

The aim of the present study was to analyze heart-rate variability (HRV) as a quantitative marker of autonomic tone after cardioversion to sinus rhythm in patients with chronic AF and structural heart disease.[12,13] The relation between the autonomic state and recurrence of AF was also investigated.

Methods:

Patients: Patients with chronic AF and structural heart disease were enrolled in the study. AF was considered chronic if it was documented at least twice on 12-lead electrocardiograms without any intervening periods of sinus rhythm. The duration of AF was determined based on medical records. Twenty patients with sinus rhythm and without any structural heart disease or episodes of AF constituted the control group with respect to HRV measurement.

Patients who had valvular heart disease, a valvular prosthesis or who had had myocardial infarction within three weeks or undergone open-heart surgery within three months were excluded from the study. Non-cardiac exclusion criteria were thyroid dysfunction, neurological problems and hepatic or renal failure.

All patients with AF were anticoagulated for at least three weeks before cardioversion with a target INR of 2.5-3.5. Patients received no antiarrhythmic drugs for at least five half-lives before entry in the study. Digoxin was used for ventricular rate control, if appropriate. All patients underwent transthoracic echocardiographic evaluation according to standard methods.[14] Transesophageal echocardiography was performed 24 hours before cardioversion for the interrogation of atrial thrombi. Patients with thrombi were excluded from the study.

Cardioversion: Electrical cardioversion was performed in the postabsorbative state under light anesthesia using midazolam intravenously (0.04 mg/kg). One defibrillator pad with a diameter of 10 cm (S&W, Model 730) was placed in the second intercostal space on the right side parasternally; the other was placed in a left-sided lateral position along the midaxillary line. The cardioversion procedure was initiated with 200 J of stored energy, followed by one application of 300 J and two applications of 360 J until restoration of sinus rhythm or failure to convert.

Holter monitoring: All patients underwent 24-hour Holter monitoring two days after restoration of sinus rhythm. We obtained time-domain measures of HRV on the second day of sinus rhythm in order to overcome potential confounding factors that effect heart rate and HRV, such as anesthetic drugs or defibrillating shocks.[15] Twenty-four hour Holter monitorings of both patient group and control group were obtained in hospital in an attempt to achieve conditions as uniform

as possible. Tape recorded electrocardiograms for each subject were digitally processed and annotated by manual editing with a Holter Analysis System (Oxford Medilog Excel, Oxford Med. Instruments). After QRS configuration classification, the longest and the shortest RR intervals on the RR interval histogram and the largest and smallest RR ratios on the RR ratio histograms were manually confirmed so that QRS complex was not mislabeled as either an artifact or an ectopic beat. Additionally, the QRS filter window excluded the coupling time of all ectopic beats and their compensatory pauses.

Time-domain variables considered in the study were mean RR interval (the mean of all coupling intervals between normal sinus beats, expressed in milliseconds), SDNN (the standard deviation of the mean RR interval, expressed in milliseconds), SADNN (the SD of the averages of RR intervals in all 5-minute segments of the 24-hour recording, rMSSD (the root mean square of differences of successive RR intervals), and PNN50 (the percentage of adjacent RR intervals that differed by more than 50 ms).

Follow-up: After the maintenance of sinus rhythm, no antiarrhythmic medications, digitalis, beta blockers or calcium antagonists were prescribed for patients during the follow-up period. Patients were monitored for AF recurrence on a weekly basis using a 12-lead electrocardiogram. A follow-up period of at least six weeks was planned.

Statistics: Continuous variables were presented as mean ± SD. For each variable, data was tested for normal distribution using a one-sample Kolmogorov-Smirnov test. If the distribution was normal, a student t-test for unpaired variables was performed for comparison between the groups. Categorical variables were compared using a chi-square test if appropriate; if not, Fisher's exact test was used. Forward conditional logistic regression analysis was also performed to determine independent predictors of AF relapse among the HRV parameters and clinical variables studied. The criteria for entry or removal from logistic regression model were 0.05 and 0.10, respectively. The cut-off point of each variable was derived using ROC curves. A p value <0.05 was considered to be statistically significant.

Results:

Forty-one patients were initially recruited for the study. External cardioversion successfully restored sinus rhythm in 31 patients; however, arrhythmia recurred early in two patients, before the acquisition of HRV parameters. In one patient, Holter records could not be interpreted because of artifacts (>20% of all records) and inadequate recording duration (19 hours). Ultimately, 27 patients were enrolled in the study. The baseline clinical features of the groups are presented in (Table 1). There was a trend towards a higher age in the AF group than in the control group. The AF group had greater left atri-

Table 1: Baseline Characteristic of AF and Control Groups

	AF group	Control group	p
Age (years)	66.1±7.9	60.0±11.9	0.06
Sex (M:F)	9:18	8:12	0.8
LVEF (%)	47.9±12.0	60.3±5.4	<0.001
LA diameter (cm)	5.1±0.6	3.8±0.4	<0.001
Underlying heart disease, n(%)		-	-
CAD	12 (44)		
CHF	9 (33)		
Hypertension	6 (23)		

AF: Atrial fibrillation; CAD: Coronary artery disease; CHF: Congestive heart failure; LA: Left atrium; LVEF: Left ventricular ejection fraction

um and lower left ventricular ejection fractions than the control group. In the majority of AF patients, coronary artery disease was the underlying cause of AF. Of the AF patients with coronary artery disease, 10 patients had chronic Q wave myocardial infarction, with a last index event of >6 months before cardioversion.

Group effect on HRV parameters: Comparison between AF group and control group

The mean RR intervals were no different between the control group and AF group two days after cardioversion (Table 2). There were significant differences in time domain parameters between the groups. SDNN, an indicator of overall HRV, and SADNN, which reflects long-term HRV variations, were significantly shorter in AF patients than in controls (Figure 1). On the other hand, pNN50 and rMSSD, which are the indexes of vagal modulation of heart rate, were found to be no different between patients and controls. Although these two parameters were higher in patients than in control subjects, the differences were not statistically significant.

Table 2: Comparison of HRV Parameters Between AF and Control Groups (measured on 2nd day of postcardioversion)

	AF group	Control group	p
ACLS*	845.5±136.9	870.8±127.4	0.5
SDNN (ms)	86.4±31.7	142.1±40.2	<0.001
SADNN (ms)	57.0±17.4	124.4±37.7	<0.001
PNN50 (%)	12.4±16.5	8.5±6.3	0.3
RMSSD (ms)	61.0±51.1	45.1±27.9	0.3

* averaged cycle length of sinus rhythm

Relation between HRV parameters and recurrence of AF:

AF recurred in 15 patients during the follow-up period. Baseline clinical and echocardiographic parameters were found to be similar in patients with AF recurrence and those with maintained sinus rhythm at the end of the follow-up period (Table 3). The duration of AF was slightly higher in patients with relapsed AF compared to patients with maintained sinus rhythm. HRV parameters differed significantly between the groups. Patients who had relapsed AF during follow-up had a significantly depressed HRV in terms of time domain measures. That is, SDNN and SADNN were shortened in patients with recurred AF compared to those who maintained sinus rhythm (71.9±25.5 ms vs 104.6±29.9 ms, and 49±12.2 vs 67±18.1; p=0.005 and p=0.008, respectively). The indexes of the vagal modulation of heart rate (pNN50 and rMSSD) were also significantly lower in relapsed patients than in nonrelapsed subjects (1.9±1.1% vs 23.4±19.3%, and 26.1±12.3 ms and 104.5±47.3, p<0.001 and p<0.001, respectively). Multiple logistic regression analysis revealed that a lowered pNN50 was an independent predictor of AF relapse (Relative risk (RR)=1.5, p=0.02, 95% Confidence Interval (CI) between 1.1-2.2). A cut-off point of pNN50 discriminating the two groups, determined by ROC analysis, was ≤8.5%. Thirteen of 15 patients with a pNN50 value of ≤8.5% had AF relapse, whereas only two of the 12 with a pNN50 value of >8.5% experienced AF recurrence (overall accuracy 85.2%). Additionally, there was a trend toward shortened SDNN as a predictor of AF relapse (RR= 1.1, p=0.07, 95% CI for RR between 1.0-1.2).

Discussion

The present study showed that autonomic tone measured two days after cessation of AF was comparable to that of an age and sex matched control group. However, time domain parameters of HRV, namely SDNN and SADNN were signif-

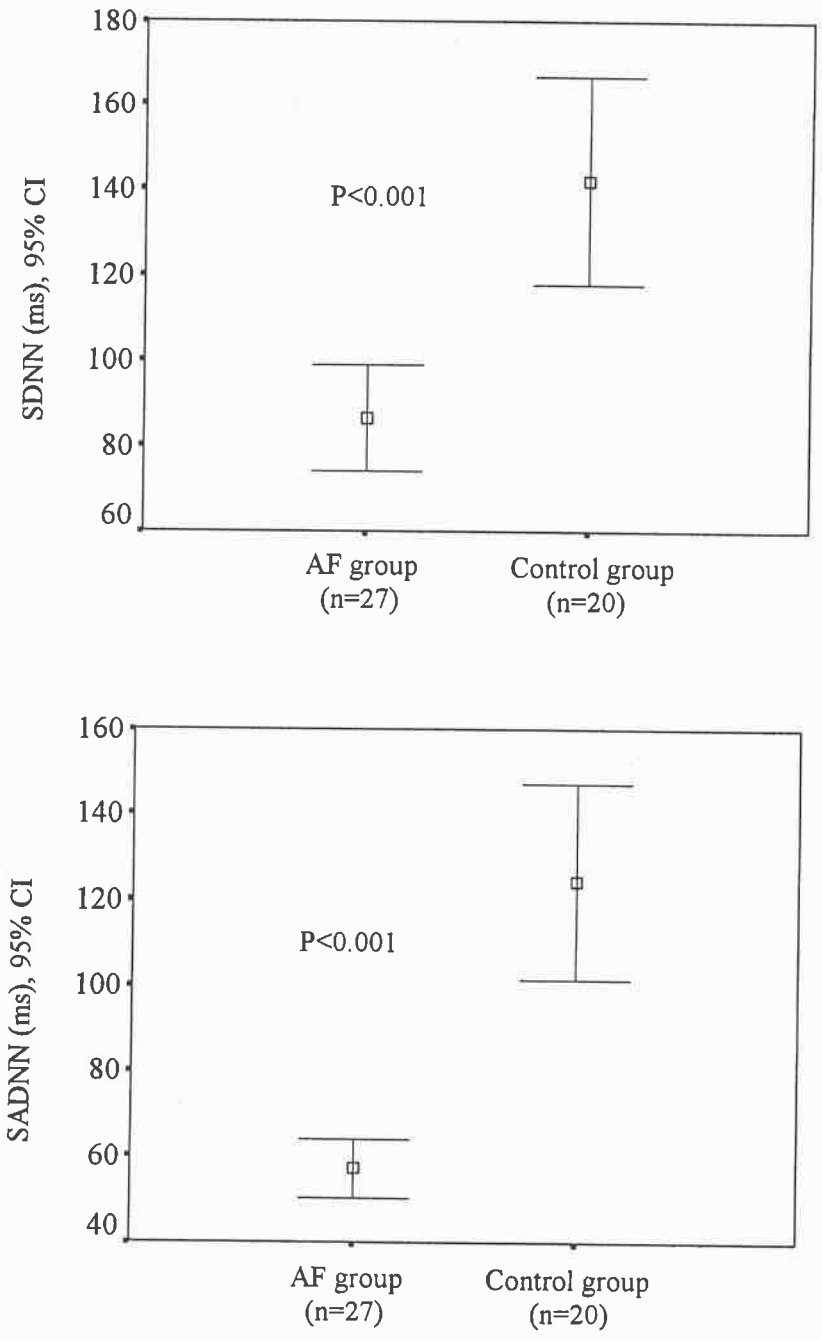

Figure 1: SDNN and SADNN values of the two groups

icantly shortened in AF patients in the intermediate postcardioversion period. Our results also revealed that a depressed vagal tone and HRV variations could be prognostic factors of AF relapse, at least in this particular subset of patients.

The relationship between AF and autonomic tone is complex. Direct vagal stimulation has been shown to decrease the atrial refractory period in a nonuniform manner, increasing the dispersion of refractoriness and thereby creating a more favorable environment for the initiation and maintenance of AF.[5,15] Applications of acetyl-

Table 3: Comparison of Patients with Relapsed AF and Patients with Maintained Sinus Rhythm in Terms of Baseline Clinical Characteristics and HRV Parameters

	Relapsed AF group	Nonrelapsed AF group	p
Age (years)	65.8±5.8	66.5±10.2	0.7
Sex (M:F)	5:10	5:7	0.4
LVEF (%)	49.3±11.9	46.1±12.4	0.5
LA diameter (cm)	5.2±0.7	4.9±0.5	0.3
Underlying heart disease, n			
CAD	6	6	
CHF	5	4	
Hypertension	4	2	
ACLS*(ms)	830.3±121.2	860±159.3	0.6
SDNN (ms)	71.9±25.5	104.6±29.9	0.005
SADNN (ms)	49±12.2	67±18.1	0.008
pNN50 (%)	1.9±1.1	23.4±19.3	<0.001
rMSSD (ms)	26.1±12.3	104.5±47.3	<0.001

* Averaged cycle length of sinus rhythm

choline to the atria or vagal efferent stimulation was reported to be sufficient for the induction of AF.[4,17] Indeed, animal models incapable of sustained AF can be forced to have spontaneous or inducible AF through parasympathetic stimulation.[5,18] On the other hand, AF can itself change the autonomic tone or the sensitivity of atria to autonomic tone possibly, through the alteration of autonomic nerve fibers located in the atria.[7,8,19,20] In the course of the present paper's preparation, Kanaoupakis et al reported an increased vagal tone and suppressed circadian variations during the first 24 hours following cessation of AF, which was detected by HRV parameters.[11] We found that the indexes of vagal modulation of heart rate, namely pNN50 and RMSSD, showed no significant difference from the control group on the second day after reversion to sinus rhythm. This was also consistent with Kanaoupakis et al's results that revealed a comparable vagal tone between controls and patients 48 hours after conversion to sinus rhythm. However, in contrast to their findings, our study showed SDNN and SADNN, which reflect overall and long-term HRV variations, respectively, were still shortened on the second day after cardioversion. The differences in results of the two studies may be related to patient characteristics. All the patients enrolled in the present study had an underlying cause of AF, the majority of which were coronary artery disease and heart failure. These two parameters were previously shown to be markedly depressed in heart failure.[21] It must be noted that mean ejection fraction was <50% in the AF group.

HRV parameters as a predictor of AF recurrence

In the present study, both HRV and vagal tone indexes were significantly depressed in relapsed patients compared to nonrelapsed subjects. Multivariate analysis indicated that a depressed vagal tone, reflected by decreased pNN50, was the independent predictor of AF recurrence. These findings were in complete contrast to Kanaoupakis et al's observations, which stressed a heightened vagal tone as the independent predictor of AF relapse.[11] It is difficult to account for these conflicting results; however, in our opinion, they were the result of patient characteristics. The relation between the autonomic tone and initiation of paroxysmal AF could give an insight into

this discrepancy. In a study of power spectral analysis of heart period variability of preceding sinus rhythm before the initiation of paroxysmal AF, Herweg et al observed a withdrawal of vagal tone before the initiation of AF in patients with daytime AF with various heart diseases, whereas nighttime AF attacks occurred in patients without any cardiac disorders and were accompanied by an increase in vagal tone before the initiation of arrhythmia.[10] Hnatkova and colleagues showed that longer AF episodes were typified by heart-rate acceleration immediately before arrhythmia and stated that an increase in sympathetic tone might be an important factor in the sustenance of periods of paroxysmal AF.[22] The majority of our patients have an underlying cardiovascular cause of AF, suggesting that a depressed vagal tone could be a risk factor for arrhythmia recurrences in such a subset of patients after cessation of chronic AF.

Although the relationship between the parasympathetic tone and the induction of AF is well-studied, the effect of the sympathetic tone on AF is less clear. Coumel suggested increased parasympathetic tone and increased sympathetic tone resulted in different types of AF.[9] Sympathetic stimulation may facilitate AF by decreasing atrial refractoriness in a manner similar to the effect of parasympathetic activity on atrial electrophsiology.[17,23] Barold et al reported a shortening of the right atrial effective refractory period by either α or β adrenergic stimulation by means of phenilephrin and isoproterenol administration during AF.[24] Diseased hearts seem more sensitive to heart-rate acceleration and automaticity.[25] In the present study, a trend toward decreasing sinus cycle length in relapsed subjects versus nonrelapsed patients was noted. Accordingly, our findings can be interpreted in one of two ways. Firstly, a vagal withdrawal and depressed heart-rate variations may enhance the atrial ectopic depolarization or atrial ectopic automaticity in diseased hearts, further increasing the possibility of AF relapse. Secondly, if the parasympathetic withdrawal is associated with sympathetic overdrive (a possibility in our study group, because coronary artery disease and heart failure constitute the majority of underlying heart disease), the electrophysiological milieu of atria become suitable to allow generation of reentry wavelets.

Study limitations: Although depressed heart-rate variations was found to be the independent predictor of AF relapse, certain limitations in this study prevent us from suggesting a clear-cut relation between autonomic tone and AF recurrence. Power spectral analysis might be a more accurate method to evaluate the effect of autonomic tone on heart rate.[9] Since we did not perform this analysis, the net autonomic state of our patients could not be evaluated after cardioversion. Accordingly, we did not have direct evidence of increased sympathetic tone as a risk factor of AF recurrence in diseased hearts. Additionally, since we did not continuously monitor patients by means of a loop recorder, we could determine neither the effect of premature atrial depolarisation on AF recurrence nor heart-rate variations immediately before the initiation of arrhythmia, which could differ from the initial HRV parameters. In our opinion, these issues need to be clarified through further studies in order to explain the relationship between AF relapse and autonomic tone.

Clinical implications: Based on the results of this and previous studies, it can be suggested that the effects of autonomic tone on AF relapse is a complex phenomenon that may vary from patient to patient, depending on the underlying cause of AF. However, a logical approach may be using a tailored therapy for the prophylaxis of AF recurrence, according to HRV parameters after cessation of AF. Based on our results, if patients have an underlying cause of AF such as coronary artery disease or heart failure and depressed HRV parameters, administration of drugs that decrease sympathetic drive or support the vagal tone may more effectively prevent AF relapse than the use of empirical antiarrhythmic drugs after cardioversion. Because the present study did not investigate drug effects, such a treatment strategy should be systematically tested in further studies.

Conclusion: The present study indicates that depressed HRV and decreased vagal tone after cessation of AF are likely predictors for AF recurrence in a particular subset of patients who have an identifiable underlying heart disease as a cause of AF.

REFERENCES

1. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med. 1982; 306:1018-1022.
2. Alpert JS, Petersen P, Godtfredsen J. Atrial fibrillation: natural history, complications and management. Ann Rev Med.1988; 39:41-52.
3. Brand F, Abbott R, Kannel W, Wolf P. Characteristics and prognosis of lone atrial fibrillation. Thirty year follow-up in the Framingham Study. *JAMA* 1985; 254:3449-53.
4. Nahum LH, Hoff HE. Production of auricular fibrillation by application of acetly-beta-methylcholine chloride to localized region of the auricular surface. Am J Physiol 1940; 129:428-436.
5. Zipes DP, Mihalick MJ, Robbins GT. Effects of selective vagal and stellate ganglion stimulation of atrial refractoriness. Cardiovasc Res. 1974;8:647-55.
6. Waxman MB, Wald RW, Cameron D. Interactions between the autonomic nervous system and tachycardias in man. Cardiol Clin. 1983; 1:143-85.
7. Blaauw Y, Tieleman RG, Brouwer J, Van Den Berg, De Kam PJ, De Langen CD, Haaksma J, Grandjean JG, Patberg KW, Van Gelder IC, Crijns HJ. Tachycardia induced electrical remodeling of the atria and the autonomic nervous system in goats. Pacing Clin Electrophysiol. 1999; 22:1656-67.
8. Chang CM Wu TJ, Zhou S, Doshi RN, Lee MH, Ohara T, Fishbein MC, Karagueuzian HS,Chen PS, Chen LS. Nerve Sprouting and Sympathetic Hyperinnervation in a Canine Model of Atrial Fibrillation Produced by Prolonged Right Atrial Pacing. Circulation 2001; 103:22-25.
9. Coumel P. Neural aspects of paroxysmal atrial fibrillation. In: Falk RH, Prodrid PJ, eds. Atrial fibrillation: Mechanisms and Management. New York, NY: Raven Press; 1992:109-25.
10. Herweg B, Dalal P, Nagy B, Schweitzer P. Power spectral analysis of heart period variability of preceding sinus rhythm before initiation of paroxysmal atrial fibrillation. Am J Cardiol. 1998; 82:869-74.
11. Kanoupakis EM, Manios EG, Mavrakis HE, Kaleboubas MD, Parthenakis FI, Vardas PE. Relation of autonomic modulation to recurrence of atrial fibrillation following cardioversion. Am J Cardiol. 2000; 86:954-8.
12. Stein PK, Bosner MS, Kleiger RE, Conger BM. Heart rate variability: a measure of cardiac autonomic tone. Am Heart J. 1994; 127:1376-81.
13. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart Rate Variability. Standards of measurement, physiological interpretation and clinical use. Circulation 1996; 93:1043-1065.
14. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989; 2:358-367.
15. Bode F, Wiegand U, Raasch W, Richardt G, Potratz J. Differential effects of defibrillation on systemic and cardiac sympathetic activity. Heart. 1998; 79:560-7.
16. Alessi R, Nusynowitz M, Abildskov LA. Nonuniform distribution of vagal effect on the atrial refractory period. Am J Physiol 1958; 194:406-410.
17. Burn JH, Vaughhan Williams EM, Walker JM. Effects of acetylcholine in heart-lung prepa-

rations including the production of auricular fibrillation. J Physiol 1955; 128:277-293.

18. Liu L, Nattel SDiffering sympathetic and vagal effects on atrial fibrillation in dogs: role of refractoriness heterogeneity. Am J Physiol. 1997; 273(2 Pt 2):H805-16.
19. Kaseda S, Zipes DP. Supersensitivity to acetylcholine of canine sinus and AV nodes after parasympathetic denervation. Am J Physiol. 1988; 255(3 Pt 2):H534-9.
20. Chiou CW, Eble JN, Zipes DP. Efferent vagal innervation of the canine atria and sinus and atrioventricular nodes. The third fat pad. Circulation. 1997; 95:2573-84.
21. Casolo G, Balli E, Taddei T, Amuhasi J, Gori C. Decreased spontaneous heart rate variability in congestive heart failure. Am J Cardiol. 1989; 64:1162-7.
22. Hnatkova K, Waktare JE, Sopher SM, Murgatroyd FD, Baiyan X, Camm AJ, Malik M. A relationship between fluctuations in heart rate and the duration of subsequent episodes of atrial fibrillation. Pacing Clin Electrophysiol. 1998; 21(1 Pt 2):181-5.
23. Inoue H, Zipes DP. Changes in atrial and ventricular refractoriness and in atrioventricular nodal conduction produced by combinations of vagal and sympathetic stimulation that result in a constant spontaneous sinus cycle length. Circ Res. 1987; 60:942-51.
24. Barold HS, Shander G, Tomassoni G, Simons GR, Wharton JM. Effect of increased parasympathetic and sympathetic tone on internal atrial defibrillation thresholds in humans. Pacing Clin Electrophysiol. 1999; 22(1 Pt 2):238-42.
25. Buxton AE, Waxman HL, Marchlinski FE, Josephson ME. Atrial conduction: effects of extrastimuli with and without atrial dysrhythmias. Am J Cardiol. 1984; 54:755-61.

COMPARISON OF CORONARY ANGIOGRAPHIC AND EXERCISE TESTING PARAMETERS OF SILENT AND SYMPTOMATIC ISCHEMIC PATIENTS WITHOUT PREVIOUS MYOCARDIAL INFARCTION

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SUMMARY

Aim: *The questions whether silent ischemia detected on non-invasive cardiac exercise testing is associated with milder coronary artery disease and whether exercise parameters found in silent ischemia are different from those in symptomatic ischemia have not been answered completely. Therefore, we aimed to compare atherosclerotic risk factors, ejection fractions and angiographic and exercise parameters of patients who had silent ischemia with those of patients who had symptomatic ischemia.*

Methods: *This study included clinically stable 138 patients with positive responses to exercise testing. They underwent coronary angiography. Scores for coronary artery diseases, ejection fractions, exercise testing parameters and risk factors were determined.*

Results: *50 of 80 patients with asymptomatic ST depression (57%) and 42 of 50 patients with symptomatic ST depression (84%) were found to have coronary artery disease ($p<0.05$). There has been no significant difference in risk factors except smoking and heredity between silent ischemia (n=50) and symptomatic ischemia (n=42). The risks of smoking and heredity were higher in patients with silent ischemia ($p<0.05$). Maximum heart rate and double product values were higher ($p<0.01$ and $p<0.05$) respectively) and total exercise duration was longer ($p<0.05$) in patients with silent ischemia. Rate of left anterior descending coronary artery disease was found to be higher in patients with silent ischemia. There was no significant difference in ejection fraction, scores for coronary artery disease, number of diseased vessels between patients with silent ischemia and those with symptomatic ischemia.*

Conclusion: *Exercise-induced ST-segment depression with angina is a better marker for coronary artery disease than exercise-induced ST-segment depression alone. Severity of coronary artery disease in patients with silent ischemia is similar to that in patients with symptomatic ischemia. Better exercise capacity of patients with silent ischemia does not imply milder coronary artery disease.*

Key words: *exercise testing, coronary angiography and silent ischemia.*

ÖZET

Sessiz İskemili ve Semptomatik İskemili Hastaların Karşılaştırılması

Amaç: *Noninvaziv kardiyak egzersiz testlerinde tespit edilen sessiz iskemi daha hafif bir koroner arter hastalığının göstergesi midir ya da egzersiz parametreleri semptomatik iskemili hastalardan farklı mıdır sorusunun cevabı tam olarak bilinmemektedir. Bu nedenle sessiz iskemili ve semptomatik iskemili hastaların aterosklerotik risk faktörlerini, ejeksiyon fraksiyonlarını, anjiografik ve egzersiz parametrelerini karşılaştırmayı amaçladık.*

Yöntem: *Egzersiz testi laboratuarımıza başvuran klinik olarak stabil olan ve egzersiz testine pozitif cevap veren 138 hasta çalışmaya alındı ve hepsine koroner anjiografi yapıldı. Hastaların koroner arter hastalık skorları, ejeksiyon fraksiyonları, egzersiz test parametreleri ve aterosklerotik risk faktörleri analiz edildi.*

Bulgular: *Asemptomatik ST çökmesi olan 80 hastanın 50'sinde (%57), semptomatik ST çökmesi olan 50 hastanın da 42'sinde (%84) anjiografik olarak koroner arter hastalığı tespit edildi ($p<0.01$). Sessiz iskemisi olanlarda sigara ve aile öyküsü daha yüksek oranda tespit edildi ($p<0.05$). Diğer risk faktörleri farklı değildi. Sessiz iskemili hastaların egzersiz testinde ulaştıkları total egzersiz süresi, maksimal kalp hızı ve double product değerleri daha yüksekti (sırasıyla $p<0.05$, $p<0.01$, $p<0.05$). Sol ön inen koroner arter lezyonu sessiz iskemili hastalarda daha yüksek oranda saptanırken ejeksiyon fraksiyonu, koroner arter skoru, hastalıklı damar sayısı, sağ koroner, sol sirkumfleks ve sol ana koroner arter hastalık sıklığı iki gurup arasında anlamlı farklılık göstermiyordu.*

Sonuç: *Tanısal amaçlı yapılan egzersiz testinde, göğüs ağrısı ile birlikte saptanan ST segment çökmesinin tekbaşına ST segment çökmesine göre koroner arter hastalığının daha güçlü bir göstergesi olduğunu düşünmekteyiz. Sessiz iskemili hastaların anjiografi ile tespit edilen koroner arter hastalık ciddiyeti semptomatik iskemili hastalarla oldukça benzerdir ve egzersiz kapasitelerinin daha yüksek olması koroner arter hastalığının daha hafif olduğunu anlamına gelmemektedir.*

Anahtar Kelimeler: *Egzersiz testi, sessiz iskemi, koroner anjiyografi*

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Received:Jan 29,2001 Accepted:Feb 13,2001

Although majority of patients present with chest pain, silent myocardial ischemia can be detected on exercise or in rest (1,2). Framingham study showed that diagnosis of acute myocardial infarction was made in 25% of patients based on ECG recordings performed every two years and half of these patients were found to suffer from silent ischemia (3). Exercise tests are frequently used to diagnose coronary artery disease. Heart rate, blood pressure, chest pain and changes in ST segment detected on exercise testing are considered indications of coronary artery disease. It is thought that patients require further investigations based on variable combinations of the above parameters. Approaches to patients with silent ischemia and to those with symptomatic ischemia detected on the tests are controversial. The concept of silent myocardial ischemia caused us to reevaluate our approach to patients with coronary artery disease, though prognostic value of silent ischemia still remains debatable (4,6). It is not known whether silent ischemia detected on cardiac tests indicates a mild myocardial ischemia and whether its prognosis is different from that of symptomatic ischemia. Although several studies demonstrated that patients with chest pain on exercise had poor prognosis compared to patients with asymptomatic ischemia (7,9), it was not substantiated by recent studies (5,6,10-13). However, most of these recent studies included many patients with previous myocardial infarction. Prognosis of patients without previous myocardial infarction may be different from that of patients with previous myocardial ischemia. Luawaert et al showed that age, number of diseased vessels, ejection fractions and values from exercise stress test were significant indications of prognosis in patients with coronary artery disease without previous myocardial infarction (14). Consistent with the above finding, CASS (Coronary Artery Surgery Study) found that possibility of acute myocardial infarction for patients with silent or asymptomatic ischemia detected on exercise testing was associated with the severity of underlying coronary artery disease and left ventricular dysfunction rather than the symptoms (11). We aimed to compare atherosclerotic risk factors, findings from coronary angiography, ejection fractions and exercise test parameters of patients who had silent ischemia but not previous myocardial infarction with those of patients who had symptomatic ischemia.

PATIENTS AND METHODS

This study included 88 patients with asymptomatic ST segment depression (64 male and 24 female; mean age: 55.5±8.9) and 50 patients with symptomatic ST segment depression (42 male and 8 female: mean age: 56.0±7.8) and was conducted in Department of Cardiology, Selçuk University. Exercise stress test (EST) was performed in all patients in accordance with Bruce protocol using Case 15 Treadmill 50 Hz (Marguatte Electronic Inc.) (15). Drug treatment was discontinued 10 days before the test in patients on digoxine and 3 days before the test in patients on calcium channel blocker, beta blocker and nitrate. Electrocardiography (D_2, V_1 and V_5) was recorded in rest, every three minutes of exercise, in peak exercise and every two minutes of rest and their metabolic equivalence (MET) were determined. Criteria for stopping the test were as follows: ST depression of 2mm or more compared to initial ECG, ST elevation of 1mm or more, decrease of over 10% in systolic blood pressure, no increase in heart rate or bradycardia, blood pressure of more than 250/130 mmHg, development of angina of class 3-4, or development of severe arrhythmia and getting too tired to undergo the test. ST depression (down-sloping, horizontal, up-sloping) and/or elevation of 1mm or more 80msn after J point during the test or in rest compared to initial ECG as well as development of repetitive ventricular tachycardia and/or hypotension with changes in ST segment were accepted as positive criteria for EST. Blood pressure was measured in rest and every two minutes of exercise and rest using a manual manometer. Double product was calculated using the formula, heart rate (rate/sec) X systolic blood pressure (mmHg).

Within 15 days of exercise test, coronary angiography was performed in all patients through femoral artery, using Judkin's method. Left and right vetriculography in oblique planes and right and left coronary angiography were carried out selectively. Ejection fraction of left ventricle in rest was estimated with "area length" method on cineangiography. Coronary angiographies were evaluated by the same clinician blinded to patient groups. Significant coronary artery disease was defined as a narrowing of 50% or more of the diameter of one of the major epicardial coronary arteries or their branches measured visually in two angiographic projections. Coronary arteries were scored on angiography using Friesinger index (16). This index is composed of scores between 0-15. Three main cardiac arteries (left anterior descending coronary artery: LAD, right coronary artery: RCA, left circumflex coronary artery: Cx) were scored separately (between 0-5) based on involvement of segments. Segments of LAD were left main coronary artery, proximal, middle and distal LAD, and first and second diagonal segments. Segments of RCA were proximal, middle, and distal RCA and right posterior descending artery. Cx segments were left main coronary artery, proximal and distal CX and first, second and third optus marginalis. Narrowing of less than 30% in one or all segments of each main artery was scored as 1 point, narrowing of 50-90% 2 points, narrowing of 50-90% in more than one segment of the same artery 3 points, narrowing of 90-100% 4 points and narrowing of 100% in proximal segment without distal flow 5 points. Total score was calculated by adding scores of three main arteries.

Age, sex and body mass index (BMI) of patients were recorded. Smoking, diabetes mellitus, hypertension, hypercholesteremia and family history, which are cardiovascular risk factors, were inquired. BMI was calculated using the following formula: BMI= kg/m^2. Patients with BMI of over $27kg/m^2$ were considered obese. Patients smoking more than 10 cigarettes daily until coronary angiography were regarded as smokers. Patients with history of diabetes, those on antidiabetic drugs or those with fasting hyperglycemia were considered diabetics. Patients with history of hypertension, those on antihypertensive drugs or those with blood pressure of over 140/90 mmHg were considered hypertensive. Patients with total cholesterol level of over 200mg/dl were considered to have hypercholesterolemia. Patients whose first degree male and female relatives had myocardial infarction or died suddenly before the ages of 55 and 65, respectively were considered to have genetic susceptibility.

Patients with previous myocardial infarction, unstable chest pain, cardiomyopathy, congenital, valvular or pericardial heart disease, ejection fraction of less than 40%, hypertrophy of left ventricle on ECG, bundle block or ST depression in rest, coronary artery bypass graft or transluminal coronary angioplasty were not included.

Student's t test was used to compare mean values and standard deviations (±SD) and Chi-square test to compare proportional relationship. $P<0.05$ was considered significant.

RESULTS

Clinical features of patients with ST depression along with chest pain on exercise stress test and those of patients with ST depression alone were shown in (Table 1). There was no significant difference in mean ages of patients, rates of males, hypertension, diabetes, smoking, hypercholesterolemia and obesity and heredity between patient groups. Fifty of 88 patients with asymptomatic ST depression on angiography (57%) were found to have coronary artery disease and assigned into silent ischemia group. Forty two of 50 patients with symptomatic ST depression (84%) were found to have coronary artery disease and assigned into symptomatic ischemia group ($p<0.01$).

Clinical features of patients with silent ischemia and those of patients with symptomatic ischemia were shown in (Table 2). There was no significant difference in mean ages and rate of males between two groups ($p<0.05$). The use of nitrate in the symptomatic ischemia group were found to be higher than those of the silent ischemia group ($p<0.05$). There was no signifi-

Table 1: Clinical features of patients with ST depression along with chest pain on exercise stress test and those of patients with ST depression alone.

	ST segment depression without chest pain	ST segment depression with chest pain	p values
	n	88	50
Age, year (±SD)	55.5 ± 8.9	56 ± 7.8	NS
Male sex (%)	72.7	84.0	NS
Hypertension (%)	46.6	40.0	NS
Diabetes (%)	11.4	8.0	NS
Hypercholesterolemia (%)	36.4	40.0	NS
Smoking (%)	44.3	48.0	NS
Obesity (%)	9.1	10.0	NS
Heredity (%)	38.6	28.0	NS
Angiographic CAD (%)	57	84	p<0.01

(NS: non significant, SD: standard deviation, CAD: coronary artery disease)

Table 2: Clinical features of patients with silent ischemia and those of patients with symptomatic ischemia.

	Silent ischemia (n=55)	Symptomatic ischemia (n=42)	p values
Age, year (±SD)	58.0 ± 8.0	55.0 ± 7.0	NS
Male sex (%)	83.0	90.0	NS
Medication (%)			
Beta-blockers	24	29	NS
Calcium cannel blockers	22	20	NS
Nitrate	21	38	<0.05
ACE inhibitors	30	34	NS
Digital	2	4	NS
Hypertension (%)	45.5	42.9	NS
Diabetes (%)	12.0	9.1	NS
Hypercholesterolemia (%)	38.2	32.9	NS
Smoking (%)	54.5	45.0	p<0.05
Obesity (%)	9.5	7.5	NS
Heredity (%)	41.8	28.6	p<0.05

(NS: non significant, SD: standard deviation, ACE: angiotensin converting enzyme)

cant difference in doses of beta-blocker, calcium channel blocker, angiotensin receptor blocker and digitalis patients took. Although patients with silent ischemia had higher rates of hypertension, diabetes, hypercholesterolemia and obesity, the difference in those rates between patients with

silent ischemia and those with symptomatic ischemia was not significant (p>0.05). Rates of family history of the disease and smoking were significantly higher in patients with silent ischemia (41.8% vs. 28.6%, p<0.05 and 54.5% vs. 45%, p<0.05 respectively).

Findings obtained from exercise testing on patients with silent ischemia and those with symptomatic ischemia were shown in (Table 3). Mean exercise duration was significantly longer in patients with silent ischemia than those with symptomatic ischemia (7.8±2.1min vs. 5.3±2.4min, p<0.05). While patients with silent ischemia reached maximal heart rate was 146.9 ± 17.7 beat/min, maximal heart rate of patients with symptomatic ischemia was 138.8±18.5 beat/min, with a statistical significance (p<0.01). Double product (heart rate X blood pressure) was significantly higher in patients with silent ischemia (p<0.05). There was no significant difference in peak systolic blood pressure, mean ST depression and MET between the groups (p>0.05).

Coronary angiography findings were shown in (Table 4). There was no difference in scores for coronary arteries between patients with silent

Table 3: Findings obtained from exercise testing on patients with silent ischemia and those with symptomatic ischemia.

	Silent ischemia (n=55)	Symptomatic ischemia (n=42)	p values
Mean exercise duration (minute)	7.8 ± 2.1	5.3 ± 2.4	p<0.05
Maximal heart rate (beat/min)	169.0 ± 16.0	135 ± 17.0	p<0.01
Peak systolic blood pressure (mmHg)	187.0 ± 37.0	179.0 ± 28.0	NS
Double product	31566 ± 824	23182 ± 569	p<0.05
MET	2.4 ± 0.7	2.0 ± 0.7	NS
ST segment depression (mm)	2.4 ± 0.6	2.1 ± 0.8	NS

(MET: metabolic equivalent,Double product : heart rate x systolic blood pressure, NS: non significant)

Table 4: Coronary angiographic findings of the patients

	Silent ischemia (n=55)	Symptomatic ischemia (n=42)	p values
Friesinger index	5.9 ± 2.6	6.1 ± 2.8	NS
Single vessel, n(%)	23 (26.0)	19 (38.0)	NS
Two vessels, n(%)	18 (20.5)	14(28.0)	NS
Three vessel, n(%)	14 (16.0)	9 (18.0)	NS
LM, n(%)	3 (3.4)	3 (6.0)	NS
LAD, n(%)	39 (44.3)	32 (64.0)	p<0.05
CX, n(%)	30 (35.1)	20 (40.0)	NS
RCA, n(%)	32 (36.4)	19 (38.0)	NS
LV EF (%)	68.4 ± 10.5	68.6 ± 9.7	NS

(LM: left main coronary artery, LAD: left anterior descending coronary artery, CX: left circumflex coronary artery, RCA: right coronary artery, LV EF: left ventricular ejection fraction, NS: non significant)

ischemia and those with symptomatic ischemia (5.9±2.6 vs. 6.1±2.8, p>0.05). Sixty four percent of patients with symptomatic ischemia were found to have LAD lesion while 44.3% of patients with silent ischemia were so, with statistical significance (p<0.05). Although lesions of RCA, Cx and LM were found to be lower in patients with silent ischemia, the difference between the groups was not significant (p>0.05). There was no significant difference in diseases of one vessel, two vessels and three vessels and ejection fractions, either (p>0.05).

DISCUSSION

History of chest pain and/or chest pain at treadmill test has been accepted as a predictor of prognosis for long years and many physicians took the clinical symptoms of myocardial ischemia into consideration in planning treatment approaches (7,8). Yet, lack of symptoms during attacks of myocardial ischemia does not imply that the disease has a mild course and more favorable prognosis (17). More recent findings have shown that silent myocardial ischemia has prognostic significance as well and prognosis depends on detection of ischemia rather than recognition of clinical symptoms (13). Indeed, ST depression appears to be a more accurate sign of myocardial ischemia and wall motion abnormalities in left ventricle than chest pain (18,19). The fact that three vessel disease and left main coronary artery disease occur more frequently in patients with ST segment depression without chest pain compared to those with solely chest pain supports the above idea (13,20). However, the concurrent presence of chest pain and ST segment depression during exercise was found to be more significant than occurrence of either alone (7,21).

In the present study, coronary artery disease was found at a higher rate in patients having chest pain along with ST segment depression than those with only ST segment depression (57% vs. 84%), yielding a result congruent with those of previous studies (13,18,22,23). Güleç et al have found coronary artery disease at 96% and 79% respectively in patients with symptomatic ST segment depression and those with asymptomatic coronary artery disease (23). Results of the study by Weiner et al were comparable to the above results, with 95% vs. 75% (13).

The data on the prevalence of lesions in coronary arteries is controversial. There are studies (13,18,22) showing that multi or three vessel disease is more prevalent in patients with symptomatic ischemia whilst there are other studies (24,25) indicating that distribution of lesions does not differ between the two groups. Nevertheless, Weiner et al showed a higher rate of silent ischemia in single vessel disease and higher rate of symptomatic ischemia in three vessel disease (21). In the present study, no significant difference was found between patients with symptomatic ischemia and those with asymptomatic ishemia in terms of coronary artery score, prevalence of single, two or three vessel disease and distribution of Cx, RCA and LM lesions. However, LAD coronary artery lesion was found to be frequent in symptomatic patient group compared to asymptomatic group. The different distribution of lesions may be attributed to the variation in patient populations. In previous studies, patient samples, at variable rates, included patients who had myocardial infarct before whereas in our study, only patients who did not have previous myocardial infarction were included in order that confounding factors may be minimized. In a similar study conducted by Detry et al on a patient group consisting of patients without any previous myocardial infarct, no significant difference was found between symptomatic and silent ischemia patients in terms of single, two and three vessel involvement (26). But, they did not inquire about the distribution of lesions in arteries.

In the present study, left ventricle ejection fractions of patients with silent and symptomatic ischemia were found to be quite comparable. However, Bonow et al stated that left ventricle ejection fractions of silent ischemia patients during exercise radionucleid angiography were high compared to those of symptomatic patients (12).

We think that equivalent results obtained can be ascribed to the fact that ejection fractions were measured during rest and that cineangiographic ventriculography method was employed in our study.

Several investigators have stated that exercise capacity of asymptomatic patients were higher than that of symptomatic patients. Maximum heart rate of symptomatic patients during exercise and duration of exercise were found to be significantly high in relation to asymptomatic patients (22,24,27,28) This result was attributed by these investigators to the fact that patients could not maintain the exercise due to angina. In our study as well, mean duration of exercise, maximum heart rate and double product values were significantly higher in silent ischemia group than symptomatic group. However, the findings regarding ST segment changes arising during exercise are contradictory. While there are studies (22,26,29) finding similar degrees of ST depression between asymptomatic and symptomatic ischemia groups, there are studies (12,30) showing that ST depression is less in patients with silent ischemia. In the present study, it was found that ST depression was comparable in two groups. The equivalent results of the aforementioned studies may be related to the differences in patient population. As mentioned by Klein et al, the patient groups examined in these studies comprised quite different patients (31). The patients whose coronary artery diseases were detected by angiography, those with stable clinical presentation, patients who had previous myocardial infarction and the ones developing marked ischemia in exercise tests were included in these studies at varying rates. In addition, the definition of silent ischemia varied across these studies. As to our study group, it comprised patients with similar clinical presentation. Patients were matched for diabetes, hypercholesterolemia and obesity histories, sex and age. Coronary artery disease was established by angiography in all patients and patients with previous myocardial infarction and unstable angina were not included into the study. The low standard deviation values of ST segment also indicate that patients reacted similarly to treadmill test.

It is our conclusion that ST segment depression observed along with chest pain in treadmill test performed for diagnosis is a more reliable indicator of coronary artery disease than ST segment depression by itself. The severity of coronary artery disease diagnosed with angiography in patients with silent ischemia is no less than that in patients with symptomatic ischemia and higher exercise capacity does not necessarily indicate that coronary artery disease is milder in these patients.

REFERENCES

1.Ceachi AC, Dovellini EV, Murchi F, Pucci P, Santoro GM, Fazzini PF. Silent myocardial ischemia during ambulatory electrocardiographic monitoring in patients with effort angina. J Am Coll Cardiol 1983; 1: 934-9.

2.Deanfield JE, Selwyn AP, Chierchia S et al. Myocardial ischemia during daily life in patients with stable angina; its relation to symptoms and heart rate changes. Lancet 1983; 2: 753-8.

3.Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham study. N Engl J Med 1984; 311: 1144-47.

4.Pryor DB, Harrell FE Jr, Lee KL, et al. Prognostic indicators from radionucleid angiography in meically treated patients with coronary artery disease.Am J Cardiol 1984;53: 18-22.

5.Rozanski A, Berman DS. Silent myocardial ischemia. I. Pathophysiology, frequency of occurrence, and approaches toward detection. Am Heart J 1987; 114: 615-26.

6.Rozanski A, Berman DS. Silent myocardial ischemia. II. Prognosis and implications for the clinical assessment of patients with coronary artery disease. Am Heart J 1987; 114: 627-38.

7.Cole JP, Ellestad MH. Significance of chest pain during treadmill exercise: correlation with coronary events. Am J Cardiol 1978; 41: 27-32.

8.Cohn P, Harris PH, Barry WH, Rosati RA, Rosenbaum P, Waternaux C. Prognostic importance of anginal symptoms in angiographically defined coronary artery disease. Am J Cardiol 1981; 47: 233-7.

9.Mark DB, Hlatky MA, Califf RM, et al. Painless exercise ST deviation on the treadmill: long term prognosis. J Am Coll Cardiol 1989; 14: 885-92.

10.Weiner DA, Ryan TJ, McCabe CH, et al. Significance of silent myocardial ischemia during exercise testing in patients with coronary artery disease. Am J Cardiol 1987; 59:725-9.

11. Weiner DA, Ryan TJ, McCabe CH, et al. Risk of developing an acute myocardial infarction or sudden coronary death in patients with exercise induced silent myocardial ischemia. A report from the coronary artery surgery study (CASS) registry. Am J Cardiol 1988; 62: 1155-8.

12.Bonow RO, Bacharach SL, Green MV, LaFreniere RL, Epstein SE. Prognostic implacations of symptomatic versus asymptomatic (silent) myocardial ischemia induced by exercise in midly symptomatic and asymptomatic patients with angiographically documented coronary artery disease. Am J Cardiol 1987; 60: 778-83.

13. Falcon C, de Servi S, Poma E, et al. Clinical significance of exercise induced silent myocardial isshemia in patients with coronary artery disease J Am Coll Cardiol 1987;9:295-9.

14. Luwaert RJ, Melin JA, Brohet CR, et al. Non-invasive data provide independent prognostic information in patients with chest pain without previous myocardial infarction: findings in male patients who have had cardiac catheterization. Eur Heart J 1988; 9: 418-26

15. Bruce RA. Exercise testing of patients with coronary heart disease: principles and normal standards for evaluation. Ann Clin Res 1971;3:323-32.

16. Friesinger GC, Page EE, Ross RS. Prognostic significance of coronary arteriography. Trans Assoc Am Physicians 1970; 83: 78-89

17. Carbajal EV, Deedwania PC. Medical and revascularization therapy for silent ischemia in the elderly. Cardiol Elder 1995; 3: 352-365

18. Miranda CP, Lehmann KG, Lachterman B, Coodley EM, .Froelicher VF. Comparison of silent and symptomatic ischemia during exercise testing in men. Ann Intern Med 1991; 114: 649-56.

19. Hauser AM, Gangadharan V, Ramos RG, Gordon S, Timmis GC. Seguence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: echocardiographic observations during coronary angioplasty. J Am Coll Cardiol 1985; 5: 193-7.

20.Deligönül U, Vandormael MG, Younis LT, Chaitman BR. Prognostic significance of silent myocardial ischemia detected by early treadmill exercise after coronary angioplasty. Am J Cardiol 1989; 64: 1-5.

21. Weiner DA, McCabe C, Hueter DC, Ryan TJ, Hood WB Jr. The predictive value of anginal chest pain as an indicator of coronary artery disease. Am Heart J 1978; 96: 458-62.

22. Kannel WB, Wolf PA, Castelli WP, DeAgustino RB. Fibrinogen and risk of cardiovascular disease. The Framingham Study. JAMA 1987;258:1183-6.

23. Güleç S, Tutar E, Aslan S, Kılıçkap M, Demirbağ F, Çağlar N. Egzersiz testinde sessiz miyokard iskemisi: koroner anjiyografik bulgular ve semptomatik hastalarla karşılaştırılması. MN Kardiyoloji 1996; 3: 191-4.

24.Conti CR. Silent myocardial ischemia: prognostic significance and therapeutic implications. Clin Cardiol 1988; 11: 807-11.

25.Deedwania PC, Nelson J. Pathophysiology of silent myocardial ischemia during daily life. Circulation 1990; 82:1296-1304.

26. Detry JMR, Robert A, Luwaert RJ, Melin JA. Prognostic significance of silent exertional myocardial ischaemia in symptomatic men without previous myocardial infarction. Eur Heart J 1992; 13: 183-187.

27.Narins CR, Zareba W, Moss AJ, Goldstein RE, Hall J. Clinical implications of silent versus symptomatic exercise-induced myocardial ischemia in patients with stable coronary disease. J Am Coll Cardiol 1997; 29: 756-63.

28. Wang XL, Tam C, McCredie RM, Wilcken DE. Determinants of severity of coronary artery disease in Australian men and women. Circulation 1994; 89:1974.

29. Gasperetti CM, Burwell LR, Beller GA. Prevelance of and variables associated with silent myocardial ischemia on exercise thallium-201 stress testing. J Am Coll Cardiol 1990; 16: 115-23.

30.Travin MI, Flores AR, Boucher CA, Newell JB, LaRala PJ. Silent versus symptomatic ischemia during a thallium-201 exercise test. Am J Cardiol 1991; 68: 1600-8.

31.Klein J, Chao SY, Berman DS, Rozanski A. Is "silent" myocardial ischemia really as severe as symptomatic ischemia? The analytical effect of patient selection basics. Circulation 1994; 89:1958-66.

VALVULAR, MYOCARDIAL AND PERICARDIAL INVOLVEMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS

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SUMMARY

Aim: *To examine valvular, myocardial and pericardial involvement in patients with rheumatoid arthritis (RA).*

Methods: *Echocardiography was used to examine 29 RA patients (mean age: 51±11 years) and 29 healthy adults (mean age: 49±11). Wall motion was evaluated subjectively. Pericardial and valvular involvement were evaluated using two-dimensional echocardiography, color Doppler flow mapping and continuous-wave Doppler echocardiography. Disease activity was assessed by erythrocyte sedimentation rate and serum C-reactive protein.*

Results: *Abnormal echocardiographic findings were found in RA patients, consisting of mitral insufficiency (6 patients), aortic insufficiency (6 patients), aortic valve nodules (3 patients) and calcification of mitral annulus (2 patients). None of the controls had abnormal echocardiographic findings. Pericardial effusion was not present in any subject, and wall motion was normal in all subjects. Clinical and laboratory indices of activity were normal in all RA patients.*

Conclusions: *Silent involvement of cardiac valves is a feature of RA, but it is usually clinically insignificant. The pericarditis and myocarditis reported in previous pathological studies also seem to be clinically insignificant.*

Key Words: *Rheumatoid arthritis, Cardiac involvement, Echocardiography*

ÖZET

Romatoid Artritli Hastalarda Kapak, Miyokard ve Perikard Tutulumları

Amaç: *Romatoid artrit (RA) hastalarında kapak, miyokard ve perikard tutulumlarını belirlemek.*

Yöntem: *RA'li 29 hasta (ort. yaş 51 ± 11) ve sağlıklı 29 birey (ort. yaş 49 ± 11) ekokardiyografi ile değerlendirildi. Duvar hareketleri subjektif olarak yorumlandı. Perikardiyal ve miyokardiyal tutulum iki boyutlu ekokardiyografi, renkli Doppler ve continuous-wave Doppler ekokardiyografi ile değerlendirildi. RA'in aktif dönemde olup olmadığı eritrosit sedimentasyon hızı ve serum C-reaktif protein düzeyleri ile belirlendi.*

Sonuçlar: *RA'li hastalarda mitral yetmezliği (6), aort yetmezliği (6), aort kapakta nodül (3) ve mitral anulus kalsifikasyonu (2) saptadık. Kontrol grubundaki bireylerde bu tür anormal ekokardiyografik bulgulara rastlamadık. Olguların hiçbirisinde perikardiyal efüzyon mevcut değildi. Duvar hareketleri tüm olgularda normal bulundu. Klinik ve laboratuvar aktivite kriterleri tüm hastalarda normaldi. Kontrol grubunda mitral anulus kalsifikasyonu ve aort kapakta nodüle rastlanmadı. Aort yetmezliği ve mitral yetmezliği de kontrol grubunda mevcut değildi.*

Sonuç: *RA kalp kapaklarını sessiz olarak tutabilir. Bu tutulum genellikle klinik olarak önemli düzeyde değildir. Daha önceki çalışmalarda bildirilen perikardit ve miyokarditlerin klinik olarak önemli gözükmemektedir.*

Anahtar Kelimeler: *Romatoid artrit, Kardiyak tutulum, Ekokardiyografi*

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Geliş tarihi: 22 Mart 2000 Kabul tarihi: 28 Eylül 2000

Rheumatoid arthritis (RA) is a chronic multisystemic disease that can involve the heart. Myocardial, pericardial and valvular involvement, usually silent, can be observed. Most evidence of cardiac involvement in RA comes from autopsy studies and case reports. Since cardiac involvement is clinically silent in most cases, the incidence of abnormal autopsy findings is higher than that of echocardiographic abnormalities. With advances in echocardiographic techniques developed in recent years, abnormal echocardiographic findings have begun to be reported at about the same rate as in autopsy studies.[1,2]

Pericarditis is the most common type of cardiac involvement in RA, with an incidence of 11-50%. Fibrinous pericarditis, fibrous adhesions and fibrocellular changes are observed most frequently.[3,4] Cardiac tamponade and constrictive pericarditis are rarely observed, with an incidence of less than 1%.[5]

The frequency of valvular involvement in RA is reported to be between 9-13%.[2,8] Autopsy studies report it as between 3-30%.[16] The order of frequency of valvular involvement in RA is similar to that of rheumatic fever: mitral, aortic, tricuspid and pulmonary. Two or more of the cardiac valves can be involved at the same time.[7,10] Lesions similar to rheumatoid nodules can be observed pathologically.

Non-granulomatous inflammation can cause valvular thickening or fibrosis.[7] Nodules on cardiac valves can also be seen; however, they are usually asymptomatic. If the nodules are sufficiently large, clinically significant valvular regurgitation may occur, sometimes resulting in heart failure. Although rare, perforation of the valve due to necrosis of the nodule can also cause significant regurgitation.[11]

Pathological studies have reported the frequency of myocarditis in RA to be approximately 20%. It usually occurs in the form of nonspecific inflammatory reaction, and it rarely causes myocardial dysfunction. Amyloid deposition and myocardial fibrosis are among the other causes of myocardial dysfunction in RA.[6,13]

In a study of 35 patients with RA, Corrao et al observed posterior pericardial effusion, alterations in the aortic root and valvular thickening, which could be typical for rheumatoid involvement.[20] They suggested that these manifestations could be evidence of silent rheumatoid heart disease.

The aim of this study was to look for silent valvular, myocardial and pericardial involvement in RA patients without signs and symptoms of heart disease.

MATERIALS AND METHODS

This study consisted of 20 consecutive patients with RA (50±11 years, age range: 34-75) applying to the outpatient clinic of Physical Medicine and Rehabilitation. The control group consisted of 29 healthy adults of similar ages (49±11 years, age range: 36-71). All subjects underwent complete physical examinations. RA was diagnosed according to 1987 American Rheumatism Association (ARA) criteria.[19] Subjects with hypertension, diabetes mellitus, coronary artery disease or a history of rheumatic fever were excluded from the study. Disease activity was assessed by erythrocyte sedimentation rate and serum levels of C-reactive protein. None of the patients were receiving chloroquine or methotrexate, which have potential cardiotoxic effects.

Echocardiographic examinations were performed using an Agilent Technologies SONOS 5500 system with an S4 transducer. M-mode dimensions were measured as suggested by the American Society of Echocardiography.[14] Valvular involvement was evaluated by color Doppler flow mapping and continuous-wave Doppler echocardiography. The echocardiographer was blinded to the clinical diagnosis throughout the examination. Valvular insufficiency was graded from 1st to 4th degrees subjectively, with 1st degree being the mildest and 4th the most severe.

RESULTS

Erythrocyte sedimentation rates and serum C-reactive protein levels of all subjects were within

normal limits. None of the subjects had clinical or laboratory evidence of active RA, and none showed clinical signs or symptoms of heart failure.

Subjective evaluation of left-ventricular wall motion was normal in both groups. Cardiac chamber dilatation was not present. In other words, there was no clinically observable myocardial dysfunction in any of the subjects.

Valvular involvement was observed in nine RA patients (31%) and none of the controls. Only mitral and aortic valves were involved; tricuspid and pulmonary involvement were not observed. Mitral annular calcification without mitral regurgitation was present in one patient. Regurgitation was observed in eight patients, either mitral (2 patients), aortic (2 patients), or both (4 patients) (Table 1). Continuous-wave Doppler echocardiography did not detect clinically significant valvular stenosis in any of the subjects.

Nodule(s) were observed on the aortic valves of three out of the six patients (50%) with aortic insufficiency. Mitral annular calcification was present in two patients, only one of whom had mitral insufficiency.

Pericardial effusion was not observed in any subject.

DISCUSSION

Pericardial effusion was not observed in any of the patients with RA. Previous studies have reported a rate of pericarditis (with or without effusion) of 11%-50%.[3,4] Our results are not in accordance with the literature; however, we believe that this may be related to the study population. In a previous study in Turkey of 93 patients with RA using clinical and echocardiographic examination, Imeryuz et al found that pericardial disease was present in 5.5% of RA patients and 6.6% of controls. They concluded that pericardial involvement is less severe in a developing nation such as Turkey.[15] The absence of both clinical and echocardiographic evidence for pericardial disease in our study is in accordance with their observations. The absence of pericardial effusion among our patients may also be due to the relatively small number of RA patients.

All of the subjects in our RA group were under sulfasalazine and non-steroidal anti-inflammatory drug therapy. Corrao et al, in their study of 35 RA

Table 1. *Valvular Involvement in Nine Patients with Rheumatoid Arthritis.*

Subjects	Age	Sex	Subjective duration of disease (years)	2-DE findings	Aortic insufficiency (degree)	Mitral insufficiency (degree)
Case 1	52	M	14	NAV	1 - 2	1 - 2
Case 2	51	F	9	-	-	1 - 2
Case 3	38	F	7	-	2 - 3	2
Case 4	62	F	13	-	-	1
Case 5	75	F	30	MAC, NAV	1	1
Case 6	71	F	5	MAC	-	-
Case 7	48	F	10	-	1 - 2	-
Case 8	40	M	7	-	2	1
Case 9	55	F	20	NAV	1	-

2-DE: Two-dimensional echocardiographic, M:male, F: female, NAV: nodule on aortic valve, MAC: mitral annulus calcification.

patients, found no correlation between cardiac abnormalities and inflammatory indices or drug therapy.[20] Therefore, we do not think that anti-inflammatory therapy had an effect on the frequency of pericardial disease in our patients.

The frequency of valvular involvement among our RA patients was 31% (9 patients). Although this rate is higher than what has been reported in most of the previous clinical and echocardiographic studies, it is similar to what has been reported in autopsy studies.[2,8]

We believe that the wide availability of Doppler echocardiography may be responsible for our observation of more frequent valvular abnormalities. The high resolution of the newly developed echocardiography machines may also allow better delineation of small nodules on cardiac valves.

We detected mitral insufficiency in only six patients (20.6%), a frequency similar to that of the aortic insufficiency detected (20.6%). While one of these patients had mitral annular calcification, there was no obvious reason for the mitral insufficiency in the remaining five. Therefore, we attributed the mitral regurgitation in these patients to RA itself. Mitral insufficiency was reported to be more frequent than aortic insufficiency in a previous study.[17] We believe that the nodules on the aortic valves found in three RA patients in our study may be partly responsible for this relatively higher frequency of aortic insufficiency, although the small number of RA patients in our study may also be a factor.

In this study, we also attempted to characterize rheumatoid nodules on the cardiac valves. One 75-year-old female patient with RA had three nodules on two cusps of the aortic valve, which were located close to the aortic annulus and were not interfering with opening of the commissure (Figure 1). On a 55-year-old female patients we observed two nodules on two cusps of the aortic valve, which were also close to the aortic annulus and again were not interfering with the opening of the commissure (Figure 2). In all cases, the nodules on the aortic valves were located on the aortic side of the cusps (Figure 3). Figure 4 shows another eccentrically located nodule on an aortic valve.

When valvular incompetency accompanies the dilatation of aortic annulus, the regurgitant jet is usually located centrally in the left-ventricular outflow tract. We believe that the eccentric nodules on the aortic valves in our patients were responsible for the valvular insufficiency, since

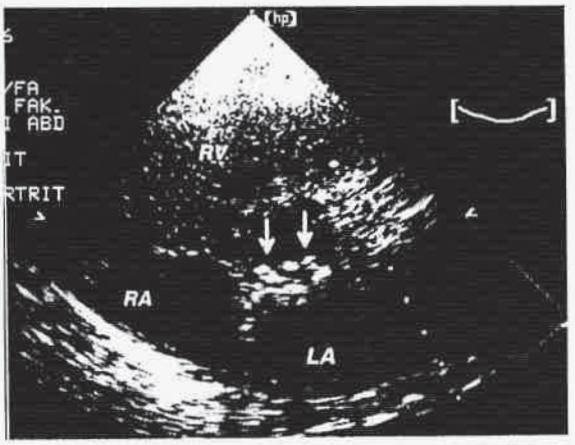

Figure 1: Three nodules on two cusps of the aortic valve (arrows) of a 75-year-old female patient with rheumatoid arthritis (parasternal short axis view). The nodules were on the aortic side of the valve. RV: right ventricle, RA: right atrium, LA: left atrium.

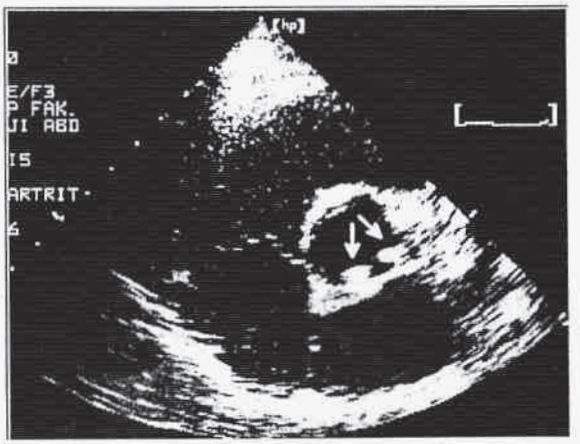

Figure 2: Two nodules (arrows) on different cusps of the aortic valve of a 55-year-old female patient. The nodules are close to the aortic annulus and do not interfere with the opening of the commissures.

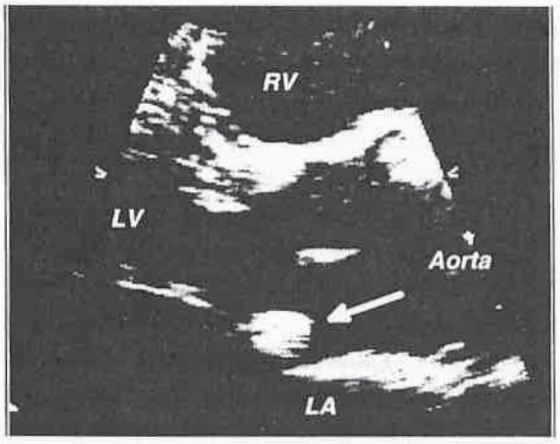

Figure 3: The long-axis view of the aortic valve of the same patient in Figure 2. The nodule is located on the aortic side (arrow) of the valve. RV: right ventricle, LA: left atrium, LV: left ventricle.

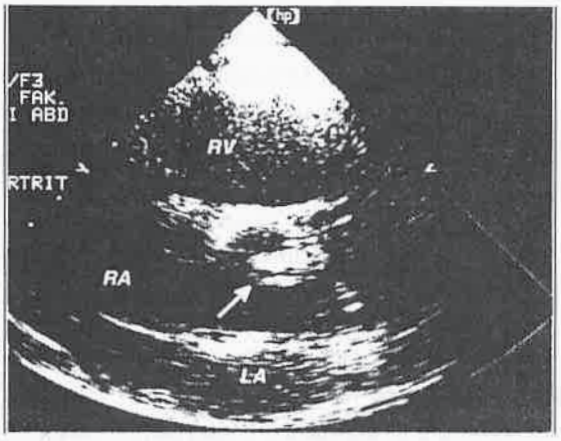

Figure 4: Another eccentric location of an aortic valve nodule in a 52-year-old male patient. RV: right ventricle, RA: right atrium, LA: left atrium.

the regurgitation jets were eccentric in all three cases (Figure 5).

Since it is seen very rarely, the literature contains only case reports of rheumatoid nodule(s) resulting in valvular stenosis.[10,18] Although we observed nodules on the aortic valves of three RA patients, none of them caused significant valvular stenosis.

The frequency of mitral annular calcification

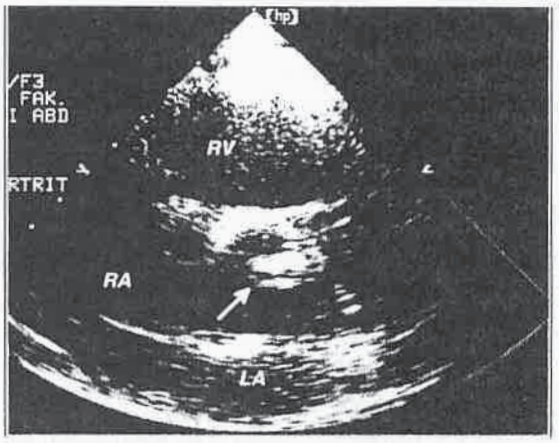

Figure 5: The eccentric (anterior) location of the nodule in Figure 4 caused an eccentric (posteriorly directed) regurgitation jet (small arrow). In a typical case of regurgitation due to aortic annulus dilatation, the regurgitant jet is generally expected to be in the middle of the left-ventricular outflow tract (long arrow).

in our RA group (2 patients, 6.8%) was similar to the results of Mody et al (4.9%).[12] We did not see abnormal left-ventricular wall motion or left-ventricular dilatation in any subject. Pathological studies have revealed a frequency of approximately 20% for myocarditis in RA. Despite this high frequency, myocardial dysfunction in RA due to myocarditis is very rare.[6] Our findings also concur with the previous reports in this regard.

CONCLUSION

Patients with RA have significantly more frequent silent cardiac involvement when compared to healthy subjects. This involvement is usually in the form of mild (1st or 2nd degree) valvular insufficiency and small nodule(s) on aortic valves. Although aortic valvular nodules cause mild degrees of regurgitation, significant stenosis is not observed. Mitral annular calcification may also be seen more frequently in RA. Pericarditis was not observed in our study, which suggests that it is very rare, at least in patients who are in the inactive stage of RA.

REFERENCES

1. Rodevand E, Bathen J, Ostensen M. Rheumatoid arthritis and heart disease. Tidsskr Nor Laegeforen 1999; 119:223-5.
2. Mody G M, Stevens J E, Meyers O L. The heart in rheumatoid arthritis – a clinical and echocardiographic study. Q J Med 1987; 65:921-28.
3. Bacon P A, Gibson D G. Cardiac involvement in rheumatoid arthritis: An echocardiographic study. Ann Rheum Dis 1974; 33:20-24.
4. Hora K S, Ballard D J, Ilstrup D M. Rheumatoid pericarditis: Clinical features and survival. Medicine 1990; 69:81-91.
5. Escalante A, Kaufman R L, Quismorio F P Jr, Beardmore T D. Cardiac compression in rheumatoid pericarditis. Semin Arthritis Rheum 1990; 20:148-63.
6. Badui E, Jimenez J, Saldivar C, Mintz G, Lavalle C, Fraga A. The heart in rheumatoid arthritis: Prospective study of 100 cases. Arch Inst Cardiol Mex 1987; 57:159-67.
7. Asin Ungira J, Pina Salvador J M, Beltran Audera J, Otero Escalante W, Cia Gomez P : Double heart prosthesis in a patient with rheumatoid arthritis. An Med Interna 1989; 6:33-5.
8. Roberts W C, Kehoe J A, Carpenter D F, Golden A. Cardiac valvular lesions in rheumatoid arthritis. Arch Intern Med 1968; 122:141-6.
9. Asin Ungria J, Pina Salvador J M, Beltran Audera J, Otero Ascalante W, Cia Gomez P. Double heart prosthesis in a patient with rheumatoid arthritis. An Med Interna 1989; 6:33-5.
10. Roberts W C, Dangel J C, Bulkley B H. Nonrheumatic valvular cardiac disease. A clinicopathological survey of 27 different conditions causing valvular dysfunction. Cardiovascular Clin 1973; 5:333-46.
11. Leibowitz W B. The heart in rheumatoid arthritis (rheumatoid disease). A clinical and pathological study of 62 cases. Ann Intern Med 1963; 58:102-23.
12. Corrao S, Salli L, Arnone S, et al. Cardiac involvement in rheumatoid arthritis: evidence of silent heart disease. Eur Heart J 1995; 16:253-65.
13. Arnett F C, Edworthy S M, Bloch D A, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31:315-24.
14. Sahn D, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantification in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978; 58:1072-83.
15. Imeryüz N, Yazıcı H, Kocak H, et al. Pericardial and pulmonary involvement in rheumatoid arthritis in Turkey. Clin Rheumatol 1994; 13:239-43.
16. Wislowska M, Sypula S, Kowalik I. Echocardiographic findings and 24-h electrocardiographic Holter monitoring in patients with nodular and non-nodular rheumatoid arthritis. Clin Rheumatol 1998; 17:369-77.
17. Panwar R B, Aggrawal R P, Rajvanshi P, Misra S N. Mitral stenosis and aortic regurgitation in rheumatoid arthritis. J Assoc Physicans India 1991; 39:776-8.
18. Mody G, Stevens J E, Meyers O L. The heart in rheumatoid arthritis. A clinical and echocardiographic study. Q J Med 1987; 247:921-8.

QUANTIFICATION OF RHEUMATIC MITRAL REGURGITATION BY DOPPLER ECHOCARDIOGRAPHY IN CHILDREN: A COMPARISON OF ANGIOGRAPHY AND MULTI-GATED RADIONUCLIDE ANGIOGRAPHY

Semra Atalay ✣ Levent Dilek ✣ H. Ercan Tutar ✣ Halil Gümüş ✣ Metin Kır ✣ Ayten İmamoğlu

SUMMARY

Non-invasive assessment of the severity of mitral regurgitation is important in the management of patients with mitral valvular disease.

The aim of this study was to compare regurgitant fraction measurements obtained using echocardiographic, angiographic and scintigraphic methods in children with chronic rheumatic mitral regurgitation.

Eighteen patients (mean age 12.69±3.47) with isolated chronic mitral regurgitation were evaluated by echocardiography. All patients fulfilled the modified Jones criteria for diagnosis of ARF. Mitral regurgitant volume (RV) was calculated using the Doppler echocardiographic method as the difference between LVIV (Left ventricular inflow volume) and LVOV(Left ventricular outflow volume) determined by the Fisher method. Regurgitant fraction (RF) was calculated as RV/LVIV.

The mean RF measured by Doppler echocardiography was 46.31±14.93%. The mean RF measured by angiography and Multi-gated Radionuclide Angiography (MUGA) methods were 50.05±17.40% and 61.23±16.62%, respectively. Comparisons showed that RF calculated by Doppler echocardiography correlated with RF determined by both cardiac catheterization (r=0.96) and scintigraphy (r=0.80).

In conclusion, this study demonstrates that Doppler echocardiography is capable of quantitatively evaluating these patients with rheumatic mitral regurgitation.

Key Words: *Children,Echocardiography,Mitral regurgitation,Regurgitant fraction*

ÖZET

Çocuklarda Romatizmal Mitral Yetersizliğin Kantitatif Değerlendirilmesi: Anjiyografi İle Karşılaştırılması

Mitral kapak hastalıklarının tedavisinde mitral yetersizliğinin non-invazif değerlendirilmesi önemlidir.

Bu çalışmanın amacı kronik romatizmal mitral yetersizlikli çocuklarda regürgitan fraksiyonu ölçmek ve anjiografik ve sintigrafik metodlarla karşılaştırmaktır.

İzole kronik mitral yetersizliği olan 18 hasta (ortalama yaş:12.69±3.47) ekokardiyografi ile değerlendirildi.Tüm hastalar ARF tanısı için modifiye Jones kriterlerine gore değerlendirildiler.

Mitral regürgitan volüm (RV) Doppler ekokardiyografi ile LVIV ve LVOV farkından Fisher metodu ile hesaplandı. Regürgitan fraksiyon (RF) RV/LVIV formülü ile hesaplandı.

Ortalama RF Doppler ekokardiyografi ile % 46.3±14.93, MUGA metodu ile % 50.05±17.40 ve anjiografik metodla % 61.23±16.2 bulundu. Doppler ekokardiyografi ile hesaplanan RF hem kardiyak kateterizasyon (r= 0.96) hem de sintigrafik metod (r=0.80) ile korele bulundu.

Sonuç olarak,bu çalışma romatizmal mitral yetersizlikli hastaların kantitatif değerlendirilmesinde Doppler ekokardiyografinin yeterli olduğunu göstermiştir.

Anahtar Kelimeler: *Çocuk, Ekokardiyografi, Mitral yetersizliği, Regürgitan fraksiyon*

Rheumatic mitral regurgitation (MR) is a valvular lesion that often leads to excessive ventricular dilatation and dysfunction. It is still common in underdeveloped and developing countries (1-3). An assessment of the severity of MR is important in the evaluation of medical therapy and timing of surgical interventions (1-3).

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Received: Jan 02,2001 Accepted: Feb 08,2001

Classic quantitation of the magnitude of regurgitation has entailed invasive studies and left ventricular cineangiography (4). However, the use of invasive methods is limited in routine serial evaluation of MR. At the present time, a variety of non-invasive techniques, including Doppler echocardiography and radionuclide methods, are available for assessing quantification of MR (5, 6). Although radionuclide angiography has the potential to provide quantitative information, it is limited by its inability to clearly separate overlapping cardiac chambers and its use of ionizing radiation (7). Doppler echocardiography is a non-invasive technique that allows accurate determination of regurgitant fractions in MR (8-10). Studies involving quantitative assessment of MR have usually been done on adult patients (8-10).

This study assessed MR quantitatively and compared the results obtained using Doppler echocardiography, cardiac catheterization and angiography, and MUGA in children and adolescent patients with chronic isolated rheumatic MR.

MATERIAL AND METHODS

Patient Selection:

Eighteen patients with chronic isolated rheumatic MR aged between 7-19 years (mean age: 12.69±3.47 years) were included in the study between November 1994 and May 1996. Acute rheumatic fever was diagnosed according to modified Jones criteria. Patients who had had no activation for the last six years, had no intracardiac shunt or stenosis and/or regurgitation in other valves, who were in sinus rhythm and who had a good quality of image on echocardiography were included in the study. Patients with first-degree MR on color Doppler echocardiography were excluded. Eighteen subjects aged between 7-19 years (mean age: 12.61±3.36 years) with normal cardiovascular findings formed the control group. Patients with MR were separated into three subgroups of second degree, third degree, and fourth degree MR on visual evaluation with two-dimensional color Doppler echocardiography.

Echocardiographic Data:

Echocardiographic examinations were performed using a Toshiba SSH-A equipped with a 3.75 MHz transducer. All M-mode, two-dimensional, pulsed and color Doppler flow data were obtained as part of routine echocardiographic evaluations. Two-dimensional color Doppler images were obtained in apical four-chamber, parasternal short-axis, and parasternal long-axis views for MR analysis. Simultaneous ECG and phonocardiographic records were also obtained during echocardiographic study. All images were recorded on 1.27-cm VHS videotape.

Calculation of Regurgitant Volume (RV) And Regurgitant Fraction (RF) with Echocardiography:

The diameter of the aortic annulus was measured using a parasternal long-axis view just proximal to the points of insertion of the aortic leaflets during early ejection, one or two video frames after maximal systolic leaflet separation. Following initial maximal opening of the anterior leaflet, the diameter of the mitral annulus was measured from the apical four-chamber view as the distance from the lateral inner edge to the medial inner edge of the annulus just below the insertion of the mitral leaflets. Assuming a circular geometry for both valve annuli cross-sectional areas were calculated as pr, where r represents half of the annular diameter.

Left ventricular inflow volume (LVIV) was obtained using Fisher's method as the product of mean diastolic mitral orifice area and mitral inflow time-velocity integral (TVI). In the absence of aortic regurgitation or abnormal flow, mitral regurgitant flow was determined by the difference between LVIV and left ventricular outflow volume (LVOV). Mitral TVI and aortic TVI were obtained from apical four-chamber and suprasternal notch views, respectively. RV was calculated by Doppler echocardiography as the difference between LVIV, as determined by Fisher's method, and LVOV. Doppler-determined RF (RFdopp) was calculated as RV/LVIV.

Cardiac Catheterization and Left Ventriculography:

Cardiac catheterization was performed on all patients. Cardiac output and index were measured

by thermodilution in 16 of 18 patients. Thermodilution stroke volume (SV thermo) was calculated by dividing cardiac output by heart rate.

Left ventriculography was performed in a 30° right anterior-oblique, 60° left anterior-oblique position in order to identify MR in all patients. Left ventricle volumes were calculated using Sandler and Dodge's single-plane area-length method and Kennedy et al.'s regression formula to identify MR quantitatively. Angiographic stroke volume (SV) and RF were calculated using the following formulas:

SVangio = Left ventricle end-diastolic volume (LVEDV) – left ventricle end-systolic volume (LVESV)

RFangio=SVangio – SVthermo/ SVangio x 100

Calculation of RF Using MUGA:

MUGA, with technetium-99 m pyrophosphate for red cell labeling in vivo, was performed in 15 of 18 patients. ECG-synchronized static images were obtained in anteroposterior, left anterior-oblique, and left lateral positions using a General Electric (GE 4000 I) X/RT camera. R-R intervals on ECG were divided equally into 24 parts, and images were obtained on 4,800,000 counts. In the left ventricular area, a deviation in the count between the diastole and systole (left ventricular stroke volume index, LVSVI) was obtained. A count deviation was also obtained in the right ventricular area between the diastole and systole (right ventricular stroke volume index, RVSVI). The RF determined by MUGA (RFmuga) was calculated automatically by the following equation:

RFmuga = RVSVI – LVSVI /RVSVI x 100

STATISTICAL ANALYSIS

Statistical analyses were performed using the Statistical Package for the Social Sciences Program (SPSS). Student's t-test, single-directed variance analysis and related Duncan test; correlation analysis and linear regression analysis were used as statistical methods. $P<0.05$ was accepted as statistically significant.

RESULTS

Of the patients with MR, eight (44.4%) had second degree MR, six (33.3%) had third degree MR and four (22.2%) had fourth degree MR on visual determination using two-dimensional color Doppler echocardiography. There was significant correlation between the visual grading of severity of mitral regurgitation by color Doppler echocardiography and angiography ($p<0.001$). Echocardiographic mitral TVI, aortic TVI, LVIV and LVOV, RV and RF values of MR patients and controls are shown in Table I. Mitral TVI was higher in patients with 4° MR than patients with

Table 1: Doppler Echocardiographic Measurements in Patients with Mitral Regurgitation and Control Subjects

	PATIENTS				CONTROL GROUP
	2° MR (n:8)	3° MR (n:6)	4° MR (n:4)	All patients (n:18)	(n:18)
M-TVI (m)	0.26±0.03	0.25±0.02	0.32±0.04	0.27±0.04	0.24±0.03
Ao-TVI (m)	0.26±0.04	0.24±0.02	0.20±0.01	0.24±0.04	0.28±0.05
LVIV (ml)	108.5±20.0	125.8±19.6	170.3±19.4	128.0±30.8	90.7±12.5
LVOV (ml)	71.9±13.9	64.7±9.3	52.2±1.99	65.1±12.9	87.5±13.7
RVdopp (ml)	36.6±9.5	61.0±15.3	118.1±18.8	62.9±34.8	3.1±5.0
RFdopp (ml)	33.6±4.9	48.0±6.5	69.1±3.2	46.3±14.9	3.6±5.1

M-TVI: mitral time-velocity integral; **Ao-TVI:** aortic time-velocity integral; **LVIV:** left ventricular inflow volume; **LVOV:** left ventricular outflow volume; **RVdopp:** Doppler determined regurgitant volume; **RFdopp:** Doppler determined regurgitant fraction; **MR:** mitral regurgitation

2° and 3° MR and controls (p<0.001). Aortic TVI was lower in patients with 3° and 4° MR than in patients with 2° MR and controls (p<0.01). LVIVs showed an increase with the increase in degree of MR (p<0.01). LVOVs were lower in MR patients than in controls (p<0.001). Mean RFdopp was 46.31±14.93% in patients with MR. RVdopp and RFdopp also increased with an increased degree of MR (p< 0.001).

RVangio and RFangio values are shown in Table II. The mean RFangio was 50.05±17.40 %. An increase in RVangio and RFangio values was observed as the degree of MR increased (p<0.001).

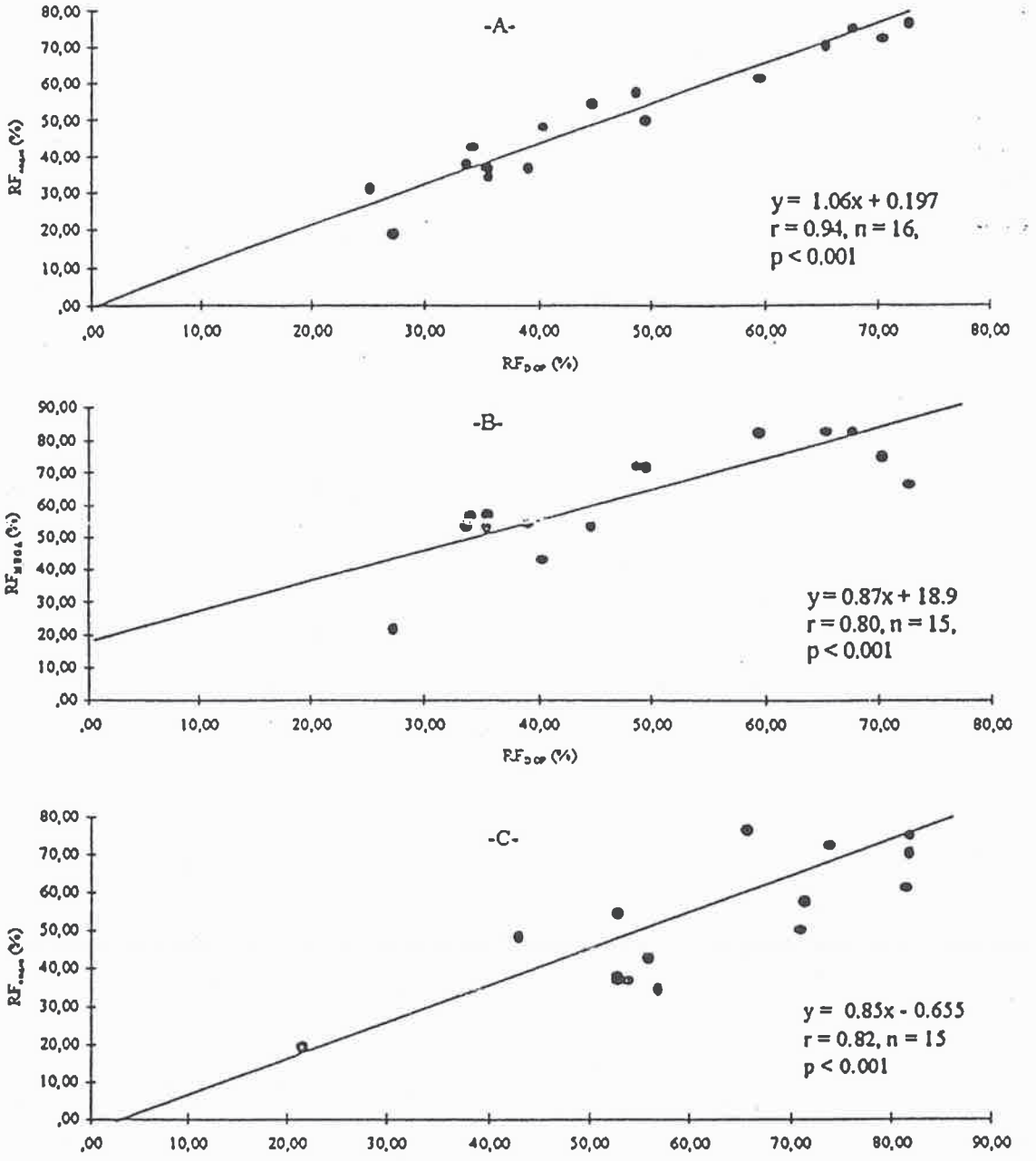

Fig 1: Comparison of the Doppler echocardiography, angiography and multi-gated radionuclide angiography-determined regurgitation fractions (RF) in patients with mitral regurgitation. The best correlation was found between bop and RF_{angio} as shown in Fig. I.A.

Table 2: Echocardiography, Angiography, and Multi-gated Radionuclide Angiography (MUGA) Results of Patients with Mitral Regurgitation

		ECHOCARDIOGRAPHY			ANGIOGRAPHY			MUGA
Patient No	Age(yr) /sex	MR degree	RVdopp (ml)	RFdopp (%)	MR degree	RVangio (ml)	RFangio (%)	RFmuga (%)
1	14/F	2	36.45	33.75	2	27.50	37.60	53.00
2	13/F	2	25.10	27.40	2	13.88	19.00	21.60
3	14/F	2	32.80	25.20	2	28.75	30.90	-
4	15/F	2	34.65	35.60	2	22.51	34.20	57.00
5	13/F	2	57.65	39.10	2	38.69	36.40	54.00
6	7.5/M	2	34.32	34.19	2	26.33	42.44	56.00
7	12/F	2	39.81	38.55	2	-	-	-
8	11/F	2	32.04	35.50	2	26.89	36.60	53.00
9	7/F	3	38.25	40.37	3	30.85	48.00	43.00
10	16/M	3	57.72	45.30	3	-	-	-
11	16/F	3	54.26	48.75	3	52.21	57.40	71.50
12	10/M	3	60.38	44.70	3	61.12	54.10	53.00
13	18/F	3	73.61	49.60	3	61.73	49.95	71.00
14	19/F	3	82.00	59.50	4	58.69	61.00	81.60
15	13/F	4	122.50	70.40	4	100.83	71.99	74.00
16	8/M	4	102.55	65.40	4	84.26	70.04	82.00
17	13/F	4	142.70	72.80	4	96.14	76.20	65.80
18	9/M	4	104.40	67.75	4	76.12	74.90	82.00

MR: mitral regurgitation; **RVdopp:** Doppler determined regurgitant volume; **RFdopp:** Doppler determined regurgitant fraction; **RVangio:** angiographically determined regurgitant volume; **RFangio:** angiographically determined regurgitant fraction.

Calculated RF values using MUGA are presented in Table II (Mean RFmuga: 61.23±16.62%). There was a significant difference in RFmuga between MR 2° and MR 4° patients ($p<0.05$).

RV values calculated by the three different methods were compared with each other. Although RFangio was higher than RFdopp, we found best correlation ($r=0.94$, $p<0.001$) (Fig 1-A). RFmuga was also higher than RFdopp, but a significant correlation was found ($r=0.80$, $p<0.001$) (Fig 1-B). RFangio was lower than RFmuga, but these two methods were also highly correlated ($r=0.82$,$p<0.001$) (Fig 1-C).

There was significant correlation between angiographic grading of the severity of MR and RFdopp ($p<0.001$) (Fig 2). RFdopp values in patients with 2°, 3° and 4° MR were as follows: 20-40 %, 40-60 % and >60%. (Table 3)

DISCUSSION

Although angiography is the most reliable method for determining the degree of MR, its invasivity prevents its use in long-term follow-up of patients (4). Therefore, in recent years, several echocardiographic methods have been developed, and their results have been found to be compatible with those of angiography and MUGA (6-10).

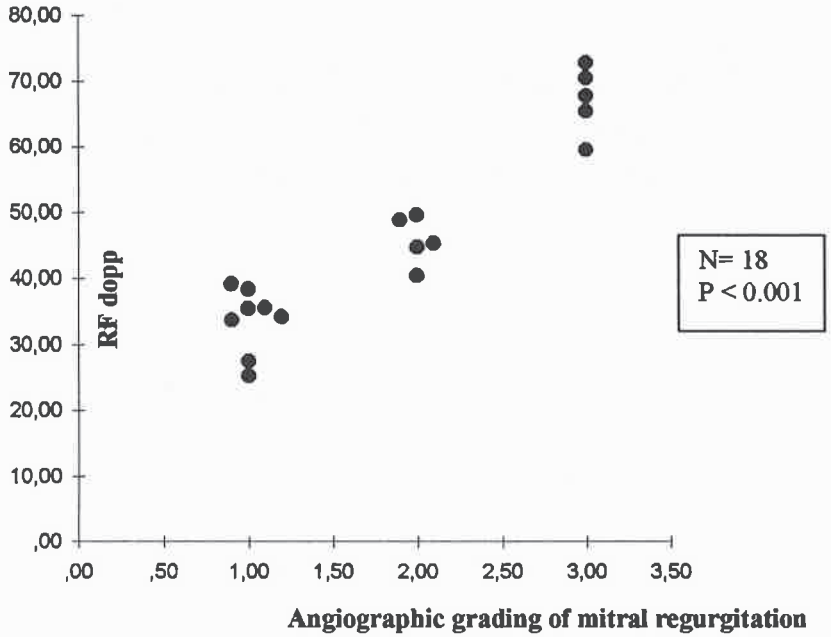

Fig 2. The relationship between angiographic grading of mitral regurgitation severity and Rfdopp

Studies involving quantitative evaluation of valvular insufficiency have usually been performed using adult patients (7-12). The only study of quantitative evaluation of MR in children was done by Tavli et al (13). However, in contrast to our study, they did not use the MUGA method, and their patients were not rheumatic in etiology.

In this study, we found significant correlation between RVdopp and RVangio and between RF values calculated by echocardiography, angiography and MUGA ($p<0.001$). But RVdopp values were higher than RVangio values, and RFdopp values were lower than RFangio values. Results of other studies performed on children and adults concur with our findings of lower RF values in echocardiography when compared to angiography (8,13). These lower values may be due to the multiple measurement and related formula used in Fisher's method and the measurement of LVIV, which is smaller than that of bi-apical Simpson's method (8,13). Although Tribouilloy et al calculated LVIV using the same method, they found increased RF values in echocardiography when compared to angiography in adult patients (14).

Table 3: Relationship Between Angiographic Grading of MR Severity and RFdopp

Patients	Angiographic Grading of MR	RFdopp
8	+ 2	20 RF 40 (25,20- 39,10)
6	+ 3	40 RF 60 (40,37-59,50)
4	+ 4	RF 60 (65,40- 72,80)

RF: regurgitant fraction **MR:** mitral regurgitation

The potential sources of error in Doppler flow calculations have been previously discussed; the most common are those associated with measurements of the aortic or mitral annulus cross sectional area (9,11,14). Sarano et al used two-dimensional Simpson's bi-apical method for calculation and found RFdopp values to be higher than RFangio values (9). We found an increase in RVdopp and RFdopp values in parallel with echocardiographic and angiographic visual MR degrees. RFdopp values in children with 2°, 3° and 4° mitral regurgitation were 20-40%, 40-

60% and >60%, respectively. (Table 3) According to these findings, pulsed Doppler echocardiographic examination is a very useful method for quantitative evaluation of isolated regurgitation in children. In patients without MR, regurgitant fractions of 10-20% have been calculated using color Doppler echocardiography. (8,11,14). We found 3.56±5.15% false positivity of RF values in control subjects, which is similar to that of previous reports.

Although angiography is the most reliable technique for calculating RV and RF, false positive RF values of up to 20% have been reported in normal controls as a results of errors inherent in the methods of measuring left ventricular volumes and forward cardiac output (8,15,16).

Our results showed a significant correlation between RFmuga, RFdopp, and RFangio. However, RFmuga values were higher than those of RFdopp and RFangio. Several studies have reported higher RFmuga values in patients when compared with echocardiographic and angiographic measurements as well as false positive RFmuga values of 1±11% in control subjects (8,17).

In conclusion, we found a significant correlation between RV and RF values calculated by angiography and echocardiography in children. Therefore, we suggest that echocardiography may be used instead of angiography for the quantitative determination of MR degree. MUGA appears to be less sensitive than echocardiography in this respect.

REFERENCES

1. Kennedy JW, Doces JG, Steward DK: Left ventricular function before and following surgical treatment of mitral valve disease. Am Heart J 1979; 97:592-97.
2. Munoz S, Gallardo J, Diaz-Gorrin JR, Medina O: Influence of surgery on the natural history of rheumatic mitral and aortic valve disease. Am J Cardiol 1975; 97:592-95.
3. Rapaport E: Natural history of aortic and mitral valve disease. Am J Cardiol 1975; 35:221-27.
4. Sellers RD, Levy MJ, Amplaltz K, Lillehei CW: Left retrograde cardio-angiography in acquired cardiac disease. Am J Cardiol 1964; 14: 437-47.
5. Marshall RC, Berger HJ, Costin JC, et al: Assessment of cardiac performance with quantitative radionuclide angiography. Circulation 1977; 56:820-29.
6. Zile MR, Gaasch WH, Carroll JD, Levine HJ: Chronic mitral regurgitation: predictive value of preoperative echocardiographic indexes of left ventricular function and wall stress. J Am Coll Cardiol 1984; 3:235-42.
7. Sciagra R, Voth E Tebbe U et al : Evaluation of three methods for quantifying valvular regurgitation using gated equilibrium radionuclide ventriculography. Eur Heart J 1987; 8: 1109-18.
8. Blumlein S, Bouchard A, Schiller NB et al: Quantitation of mitral regurgitation by Doppler echocardiography. Circulation 1986; 74: 306-14.
9. Sarano ME, Tajik AJ, Bailey KR, Seward JB: Color flow imaging compared with quantitative Doppler assessment of severity of mitral regurgitation: Influence of eccentricity of jet and mechanism of regurgitation. J Am Coll Cardiol 1993; 21:1211-19.
10. Spain MG, Smith MD, Grayburn PA et al: Quantitative assessment of mitral regurgitation by Doppler color flow imaging: Angiographic and hemodynamic correlation. J Am Coll Cardiol 1989; 13:585-90.
11. Rokey R Sterling LL, Zoghbi WA et al: Determination of regurgitant fraction by pulsed Doppler two-dimensional echocardiography. J Am Coll Cardiol 1986; 7:1273-78.
12. Royen N, Jaffe CC, Krumholz HM et al: Comparison and reproducibility of visual

echocardiographic and quantitative radionuclide left ventricular ejection fractions. Am J Cardiol 1996; 77: 843-50.

13. Tavlı V, al- Khatib Y, Isabel-Jones J, et al. A comparison of left ventricular volumes and regurgitant fraction by Doppler echocardiography and angiography in children. Acta Paediatrica Jpn 1994; 36: 501-5.
14. Tribouilloy C, Shen WF, Slama MA et al: Non-invasive measurement of the regurgitant fraction by Doppler echocardiography in isolated pure mitral regurgitation. Br Heart J 1991; 66: 290-94.
15. Lopez JF, Hanson S, Orchard RC, Tan L: Quantification of mitral valvular incompetence. Cather Cardiovasc Diagn 1985; 11: 139-52.
16. Sorensen SG, O'Rourke RA, Chandbrimi TK: Noninvasive quantitative of valvular regurgitation by gated equilibrium radionuclide angiography. Circulation 1980; 62:1089-97.
17. Kurokawa S, Takahaski M, Sugiyama T et al: Noninvasive evaluation of the magnitude of aortic and mitral regurgitation by means of Doppler two-dimensional echocardiography. Am Heart J 1990; 120:638-48.

FACIAL ASYMMETRY DUE TO BRANCHIAL ARCH DEFECTS: THREE DIMENSIONAL COMPUTED TOMOGRAPHY FINDINGS

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SUMMARY

Hemifacial microsomia is the most common asymmetrical malformation caused by the underdevelopment of the first and second branchial arches. Syndromes classified as mandibulofacial dysostosis closely resemble the deformities seen in hemifacial microsomia. A well-known member of this group is Treacher-Collins syndrome. In this report, we studied the role of three-dimensional computed tomography in the assessment of these complex craniofacial malformations. Seven patients with facial asymmetry, ranging in age from 11 months to 16 years, were included in the study. Thin sections in the axial plane were obtained, and the axial scan data reformatted into three-dimensional models with bone and soft tissue thresholds. Soft tissue images revealed facial asymmetry, and bone threshold images demonstrated varying degrees of mandibular hypoplasia in all patients. Axial scan data was useful in evaluating the deficiency of muscles of mastication and petrous temporal bones.

In conclusion, three-dimensional images accurately represented the abnormal anatomical structures; bone and soft tissue threshold images allowed precise preoperative assessment.

Key words: *Computed tomography, hemifacial microsomia, mandibulofacial dysostosis, three-dimensional imaging*

ÖZET

Brankial Ark Defektine Bağlı Fasiyal Asimetri: 3 Boyutlu Komputerize Tomografi Bulguları

Hemifasyal mikrozomi en sık gözlenen asimetrik malformasyondur ve birinci ve ikinci brankial arkların gelişimsel bozukluğuna bağlı oluşur. Mandibulofasyal dizostozis olarak sınıflandırılan sendromlardaki deformiteler hemifasyal mikrozomidekilere yakın benzerlik gösterir ve bu grubun en iyi bilinen örneği Treacher-Collins sendromudur. Bu çalışmada kompleks kranyofasyal malformasyonlarda üç boyutlu bilgisayarlı tomografi incelemenin rolü araştırıldı. Yaşları 11 ile 16 arasında değişen fasyal asimetrili 7 olgu çalışmaya dahil edildi. Aksiyal planda ince kesitlerle elde edilen ham görüntülerden kemik ve yumuşak doku eşik değerlerinde üç boyutlu görüntüler oluşturuldu. Olguların tümünde yumuşak doku eşik değerlerindeki görüntüler fasyal asimetriyi gösterebilirken, kemik eşik değerinin seçildiği görüntüler değişik derecelerdeki mandibuler hipoplaziyi net olarak ortaya koydu. Aksiyal ham görüntüler mastikatör kasların yokluğunu ve temporal kemiği değerlendirmede faydalıydı.

Sonuç olarak, üç boyutlu görüntüler anormal anatomik yapıları doğru bir şekilde sunarken, kemik ve yumuşak doku eşik değerlerindeki görüntüler preoperatif kesin değerlendirmeye olanak tanımaktadır.

Anahtar kelimeler: *Bilgisayarlı tomografi, hemifasyal mikrozomi, mandibulofasyal dizostoz, üç boyutlu görüntüleme*

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Received: Jan 30,2001 Accepted: Feb 13,2001

Errors in the development of the numerous branchial arches and pouch elements that contribute to the human head and face can result in various malformations. Following cleft lip and palate, the most common group of facial malformations includes the defects caused by the underdevelopment of the first and second branchial arches, collectively known as the hemifacial microsomia (HFM). The syndromes classified as mandibulofacial dysostosis (MFD) closely resemble the deformities seen in HFM. A well-known member of this group is Treacher-Collins syndrome. The etiological factor in HFM is stapedial artery ischemia, while mutations in the eighth chromosome are responsible for MFD.[1] In HFM, the affected side shows variable underdevelopment of the mandible, temporomandibular joint, muscles of mastication and external and middle ears.[2,3] In Treacher-Collins syndrome, antimongoloid eye-slant, coloboma, craniosynostosis and anomalies of the palate can also be seen.[2] Cephalometric radiography, the conventional imaging technique, is of limited value because of superimposition of normal and abnormal bony structures. Computed tomography (CT) in the axial plane, supplemented by reformation in additional planes, can provide further information; however, these are also two-dimensional images. Three-dimensional CT (3D-CT) is of proven value in the assessment of craniofacial deformities.[3] The advantages of 3D models include an accurate representation of anatomical structures and precise preoperative diagnosis and planning of the operation.[4] In this study, 3D-CT findings in seven cases of HFM and Treacher-Collins syndrome are presented, craniofacial embryological development is reviewed and the role of 3D-CT in the assessment of complex craniofacial deformities is emphasized.

Materials and Methods

In this study, 3D models of seven patients ranging in age from 11 months to 16 years were generated. Six patients had HFM and one had Treacher-Collins syndrome. In order to obtain extensive information and to plan the surgical procedures preoperatively, 3D-CT examination was performed. Contiguous axial 1 mm and 3 mm sections were obtained (100kVp, 100mA), and, on a separate workstation, 3D surface-shaded images with bone and soft tissue thresholds were produced using the software program "Advantage Windows sdC v. 1.2.6 eta. p3".

Results

Soft tissue images demonstrated facial asymmetry in all patients with HFM, one of who also had unilateral preauricular skin tags (Fig 1).

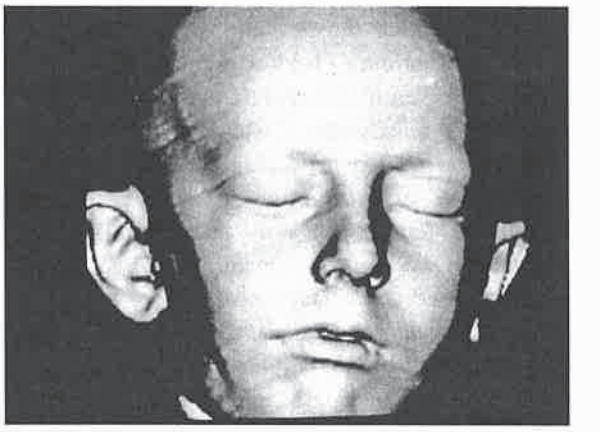

Figure 1: Hemifacial microsomia. Soft tissue threshold 3D image demonstrates mild facial asymmetry and preauricular skin tags on the right side.

Antimongoloid eye-slants and a small, low-set, malformed right auricle were also shown in the patient with Treacher-Collins syndrome (Fig 2).

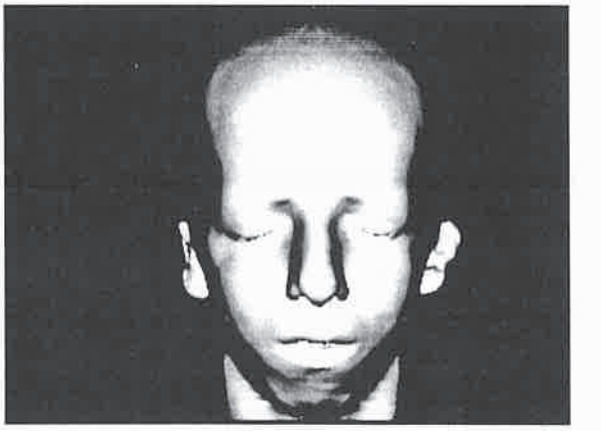

Figure 2: Treacher-Collins syndrome. Soft tissue image shows antimongoloid eye-slant, auricular malformation and micrognathia.

This patient had had a diagnosis of cleft palate after birth. Two patients with HFM also had auricular malformations. Bone threshold images revealed varying degrees of unilateral hypoplasia of the mandible in all patients with HFM (Fig 3)

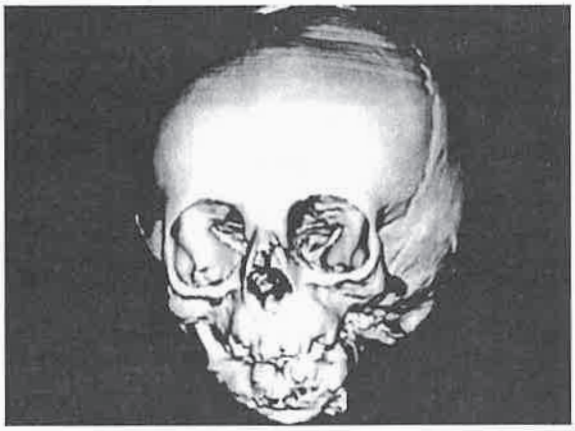

Figure 3: Hemifacial microsomia. Bone threshold 3D image illustrates severe mandibular and maxillary hypoplasia on the left side. Note minimal hypoplasia of the lateral wall of the left orbit.

and bilateral mandibular hypoplasia in the patient with Treacher-Collins syndrome (Fig 4).

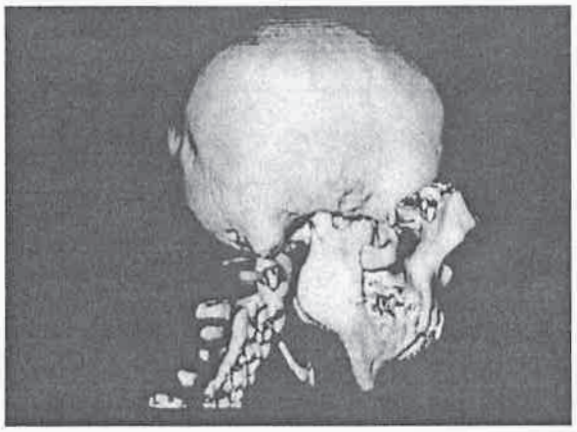

Figure 4: Treacher-Collins syndrome. Bone threshold 3D image (lateral view) shows absent zygomatic arch, micrognathia and minimal maxillary hypoplasia.

Hypoplasia of both mandibular rami and coronoid processes, shallow glenoid fossae and absent sigmoid sulci accounted for various degrees of facial asymmetry. The maxilla was hypoplastic in five patients, and zygomatic arches were hypoplastic in one patient. Zygomatic arches were absent in the patient with Treacher-Collins syndrome (Fig 4). The lateral walls of the orbits were hypoplastic in two patients. Analysis of the axial source images allowed detection of the external auditory canal atresia, hypoplasia of the masticator muscles and the middle ear ossicles in the affected side in four patients with HFM (Figs 5,6).

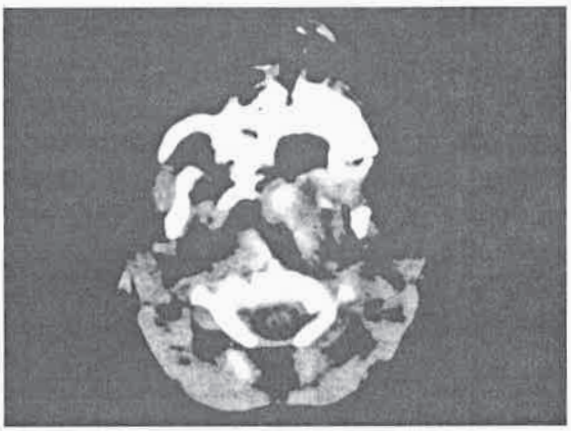

Figure 5: Hemifacial microsomia. Axial source image reveals left-sided hypoplasia of the muscles of mastication on the left side with fatty replacement.

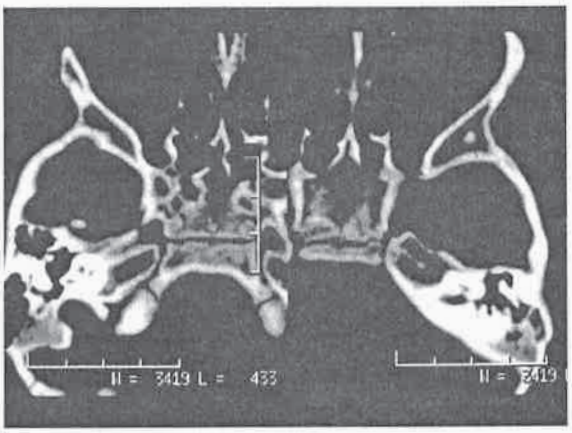

Figure 6: Hemifacial microsomia. Axial image of the petrous bones shows hypoplastic and malformed middle ear ossicles on the right side and normal appearing left middle-ear bones.

The bone and soft tissue abnormalities of the seven patients studied are summarized in the accompanying table.

Discussion

HFM is a unilateral congenital birth defect with involvement of several skeletal, neuromuscular and soft-tissue components of the first and second branchial arches. It may also include ocular, renal, spinal and cardiac involvement.[5] Ischemic necrosis caused by an expanding hematoma arising from the stapedial artery has been implicated as an etiological factor, as the stapedial arterial system provides the initial blood supply to the structures derived from the first and second branchial arches.[1] While unilateral disease predominates, bilateral involvement can be seen in 20-30% of patients. The incidence is one in 5,600 live births, with a slightly more frequent occurrence in male patients and on the right side. HFM is the most widely used name for this defect, whose synonyms include oculovertebral dysplasia (Goldenhar syndrome), which must be considered as a severe form of HFM; craniofacial microsomia; lateral facial dysplasia; and first and second branchial arch syndrome are other terms used. The OMENS (O: orbit, M: mandible, E: ear, N: facial nerve, S: skeletal) classification attempts to include all of the most prominent features of HFM and is the most common classification system currently used. Under this classification system, each entity is graded from 1 to 3, according to the severity of the involvement, and the presence of non-craniofacial involvement is annotated by an asterisk.[1]

MFD syndromes are autosomal dominant disorders that are thought to be the result of muta-

Patient	Syndrome	Age/ Sex	Mandibular hypoplasia	Maxillary hypoplasia	Ears	Petrous Bone	Orbit	Zygoma	Soft Tissue
1	Treacher-Collins Syndrome	14/F	Mild	Minimal	Small, low-set malformed auricle	Normal	Hypoplasia of the lateral wall	Absent zygomatic arches	Antimongoloid eye-slant
2	HFM	1/F	Severe	Severe	Severely malformed auricle with absent pinna	Atresia of EAM Hypoplasia of MEC and ossicles	Hypoplasia of the lateral wall	Normal	Severe facial asymmetry Hypoplasia of the masticator muscles
3	HFM	4/F	Minimal	-	Normal	Normal	Normal	Normal	Minimal facial contour defect
4	HFM	4/M	Mild	Mild	Normal	Normal	Normal	Hypoplastic zygomatic arches	Mild facial asymmetry
5	HFM	16/M	Mild	Minimal	Microtia	Atresia of EAM and MEC and ossicles	Normal	Normal	Mild facial asymmetry and hypoplasia of the masticator muscles
6	HFM	5/M	Minimal	-	Normal auricula with pre-auricular skin tags	Atresia of EAM Hypoplasia of MEC and ossicles	Normal	Normal	Minimal facial asymmetry and hypoplasia of the masticator muscles
7	HFM	12/M	Mild	Mild	Normal	Normal	Normal	Normal	Minimal facial asymmetry and hypoplasia of the masticator muscles

Table. Patient Data

HFM: Hemifacial microsomia

MEC: Middle ear cavity EAM: External auditory meatus

F: Female M: Male

tions in the eighth chromosome. Two genetic disorders involving MFD are Treacher-Collins and Hallerman-Streif syndromes. The former may be an autosomal dominant form and the latter an autosomal recessive form of the same genetic syndrome. Underdevelopment of the lower face and the mandible and associated anomalies of the palate and external ears in MFD result from a deficit of mesenchyme in the first and second branchial arches, which is believed to be due to either defective migration or proliferation of neural crest cells, or excessive cell death.(1)

The degree of mandibular hypoplasia is the most important factor determining the severity of craniofacial deformity. A hypoplastic mandible restricts the growth of the maxilla, zygoma and orbit on the affected side. The hypoplasia of the facial soft tissues and masticator muscles is correlated with the degree of mandibular hypoplasia, whereas underdevelopment of the external and middle ears is unrelated.(3)

Because conventional radiography and axial CT images are of limited value, additional information should be obtained from 3D images in asymmetric malformations. 3D-CT provides a complete qualitative assessment of the abnormal bony and soft-tissue structures. Modern generation scanners with 512x512 matrix image resolution provide virtual reality 3D images in a short time with reduced radiation. Axial images may also be analyzed for anomalies of the facial soft-tissue structures and petrous temporal bone. Three-dimensional images of the anatomic abnormality enable better preoperative orientation, correct planning of the operative technique and comparison of the postoperative status of the patient with the preoperative appearance.(3,4)

REFERENCES

1. Larsen TW. Human Embryology, 1st ed. 1993: 311-340, 352-371.
2. Westesson PL, Katzberg RW. Temporomandibular joints. In: Som PM, Hugh CD Head and Neck Imaging, 3rd ed. 1996: 1352-1361.
3. Whyte AM, Hourian MD, Early MJ et al. Radiological assessment of hemifacial microsomia by 3D-CT. Dentomaxillofac Radiol 1990; 19:119-125.
4. Santler G, Karcher H, Ruda C. Indications and limitations of 3D models in craniomaxillofacial surgery. J Craniomaxillofac Surg 1998; 26:11-16.
5. Vargervik K. Mandibular malformations: growth characteristics and management in hemifacial microsomia and Nager syndrome. ACTA Odontol Scand 1998; 56:331-37.
6. Ono I, Ohura T, Narumi E, et al. Three-dimensional analysis of craniofacial bones using 3D-CT. J Craniomaxillofac Surg 1992; 20:49-60.

TREATMENT OF COMPLETE ACROMIOCLAVICULAR SEPARATION WITH CORACOCLAVICULAR CERCLAGE WIRING

Ali Kemal Us* ✣ Kenan Bayrakcı** ✣ İlksen Gürkan** ✣ Murat Arıkan**

SUMMARY

There is still discussion concerning the surgical methods for treating Type 3 dislocations of the acromioclavicular joints. Since 1993 coracoclavicular cerclage wire fixation with coracoacromial ligament transfer has been performed, with favourable results. In an attempt to define the benefit of the procedure, this was compared with the results of acromioclavicular fixation with Kirschner wire in 7, K-wire and AO tension band combination in 8, and coracoclavicular fixation with Bosworth technique in 13 patients. We recommend cerclage wire stabilisation with coracoacromial ligament repair in treatment of complete acromioclavicular separation because it is easy to apply, complications are low, and there is high potential for rehabilitation postoperatively compared with the other procedures. In this study a brief description of the surgical technique and the comparison of different surgical procedures have been presented.

Key words: *Acromioclavicular joint, seperation, coracoclavicular cerclage, wiring*

ÖZET

Komplet Akromioklavikular Seperasyonların Korakoklavikular Sirkülaj Telleme İle Tamiri

Günümüzde Tip 3 akromioklavikular eklem seperasyonlarının cerrahi tedavisi konusunda halen tartışmalar mevcuttur. 1993 yılından bu yana kliniğimizde, korakoakromial bağ transferi ile birlikte korakoklavikular sirkülaj fiksasyonu başarılı sonuçlarla uygulanmaktadır. Bu cerrahi yöntemin avantajlarını göstermek için sonuçlar; akromioklavikular fiksasyonun kirchner teli ile yapıldığı 7, kirchner teli ve AO tansiyon band kombinasyonunun uygulandığı 8 ve de Bosworth tekniği ile korakoklavikular fiksasayonun yapıldığı 13 vaka ile karşılaştırılmıştır. Biz, tam akromioklavikular seperasyon olan hastalarda: korakoakromial bağ tamiri ile birlikte sirkülaj teli fiksasyonunu teknik olarak öneriyoruz çünkü uygulaması kolay, komplikasyon oranı düşük, ve de diğer cerrahi yöntemlere göre postoperatif dönemde yüksek rehabilitasyon potansiyeli mevcuttur. Bu çalışmada; cerrahi tekniğin kısa bir özeti ve değişik cerrahi tekniklerin kısa bir karşılaştırılması mevcuttur.

Anahtar Kelimeler: *Akromioklaviküler eklem, seperasyon, korakoklaviküler sirkülaj, telleme*

Acromioclavicular (AC) joint dislocations can occur following a direct trauma to the shoulder. The pathomechanism involves force from above, directed not only downwards but also laterally. When the fast movement of the shoulder is suddenly arrested as the clavicle comes in contact with the first rib, decelerating forces will cause the rupture of the ligament if the clavicle is not broken. The AC and coracoclavicular ligament also get injured as much as the severity of the

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Received: Jan 23, 2001 Accepted: Feb 13, 2001

trauma. A complete dislocation, which is a type 3 according to Tossy et al. (15), is associated with complete disruption of the AC joint and coracoclavicular ligaments. The treatment of complete AC separations with ligamentous disruption have been a source of controversy among the orthopaedic surgeons for many years (1,3). Many authors recommended nonoperative management for complete AC separations (2,6,16,18). Today, various combinations of older surgical procedures have been preferred for management of complete AC separations. The surgical alternatives are: Primary AC joint fixation with pins, screws, suture wires, plates, etc., with or without ligament reconstruction; primary coracoclavicular repairs; excision of the distal clavicle with or without coracoclavicular ligament repair or coracoacromial ligament transfer; and dynamic muscle transfers with or without excision of the distal clavicle (12, 17). The problem is that recent studies did not compare the results of different forms of treatment in similar patient groups with comparable injuries. This study compares the results of intraarticular AC and extraarticular coracoclavicular repairs retrospectively in a selected patient group, that we assume to have similar pathologic findings, in order to analyse the results of coracoclavicular cerclage wiring with coracoacromial ligament transfer.

MATERIAL and METHODS

A review of our records between 1987 and 1996 revealed 62 surgical procedures for complete AC separations. This study excluded patients, who received primary resection of the lateral end of the clavicle due to significant injury of the AC joint cartilage or any fracture around it, or unreduced old AC dislocations; and also those with a marked increase (two to three times normal) in the coracoclavicular interspace which indicated severe injury to the surrounding muscles. In the remaining 40 patients with acute complete AC dislocations two different methods have been used: primary AC joint fixation and primary coracoclavicular (CC) ligament fixation. Intraarticular AC repair was performed in 15 patients and extraarticular CC repair in 25. AC joint fixation was made with two Kirschner wires in 7 and with combination of tension band and Kirschner wires in 8. CC fixation techniques included Bosworth technique which was used in 13 patients and CC cerclage wiring in 12 (Figures I, II and III). Coracoacromial ligament was used for reinforcement in 5 of the Boswoth group and

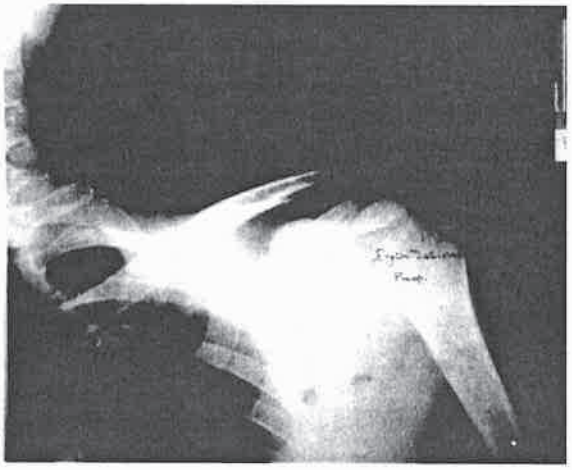

Figure 1: 27 years old man with type III acromioclavicular dislocation. Preoperative antero-posterior x-ray.

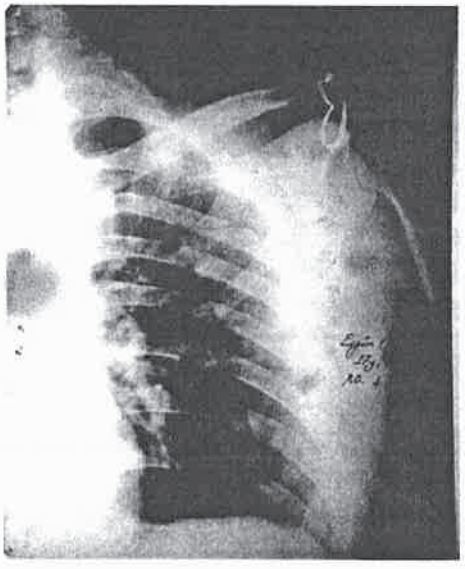

Figure 2: Four weeks later. Coracoclavicular circlage wiring and coracoclavicular ligament reconstruction was done.

in 10 of the CC cerclage-wiring group. In the AC fixation group no attempt was made to recon-

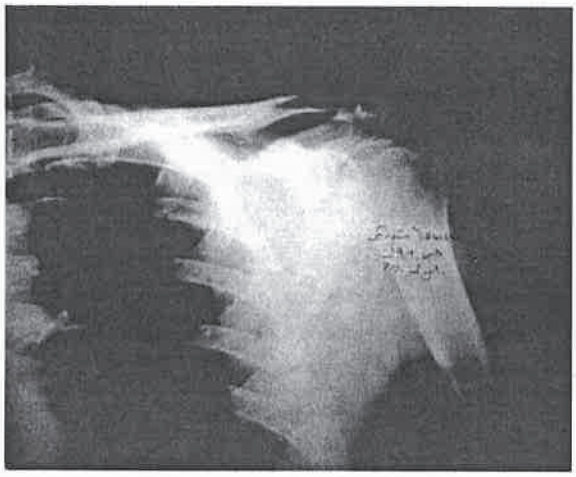

Figure 3: Two years later, after removing K-wires.

struct the AC and/ or CC ligaments.

The follow-up period ranged from 20 months to 9 years (average, 3 years). Patients ranged in age from 17 to 62 years (average, 35 years). There were 27 male and 13 female patients. The causes of injury were: traffic accidents (22 patients), falls directly on the shoulder (10 patients), direct injuries (4 patients), and contact sports injuries (4 patients). In every patient the operation was performed within 2 weeks following the injury.

An acute complete AC dislocation, which was classified as Type III according to Tossy et al, was diagnosed both on clinical and radiological evidence. Complete AC dislocations with the clavicle displaced posteriorly into the trapezius muscle or exaggerated severe vertical separation of the clavicle from the scapula as stated before indicating severe soft tissue injury were excluded. The clinical findings were: a visible, palpable step-off deformity of the AC joint in 28 patients (70%) and tenderness in all (100%), often in association with an abrasion over the injured area. The ligamentous interruption was confirmed in 10 patients by a demonstrative stress roentgenograph. None of the patients had other injuries or pre-existing functional disabilities of the involved extremity, which could interfere with the end results.

Surgical Procedure

The surgical procedure has been described for CC cerclage wire fixation with the transfer of coracoacromial ligament to the acromioclavicular joint. The patient is operated in semi-fowler's position, through an incision in the so called Langer's line over the coracoid and clavicle. The skin incision extends from the posterior edge of the clavicle, a few centimetres medial to the AC joint and then down in Langer's lines to a point just medial to the tip of the coracoid process. The deltoid subperiosteally stripped away minimal from the distal clavicle helps to identify the coracoacromial ligaments, which can then be transferred to the AC joint following its debridement. After a good exposure a loop of cerclage wire is passed under the coracoid process. Then it is passed over the clavicle in the figure of eight. AC joint is debrided and coracoacromial ligament is transferred without detaching its acromial part to the AC joint. The procedure is completed with the insertion of a suction drain.

All patients were immobilised in a Velpeau sling postoperatively for two weeks. As soon as the comfort allowed, pandullary shoulder exercises were initiated. Overhead activities were not allowed until the 6th week postoperatively. After 6-8 weeks cerclage wires, screws and Kirschner wires were removed. Active resistive exercises were only initiated in the CC cerclage-wiring group after 6 to 8 weeks postoperatively. The mean hospital stay was 6 days (ranged from 4 to 10) in all groups.

RESULTS

Assessment of clinical results were made by rating pain (max. 40 points), activities of daily living (max. 30 points), mobility of the shoulder (max. 10 points), and muscle force (max. 10 points). Patients' subjective assessment was also made to evaluate subjective differences in individual clinical symptoms. The criteria for assessment are shown in Table 1. Results were rated as excellent (90-100 points), good (80-90 points), fair (70-79 points), and poor (fewer than 70 points). Pain, the most important factor in patients' evaluation was assigned as 40 points.

Results were rated as excellent or good in 13 patients (%86,6) of AC fixation group and in 24 (%96) of CC fixation group. There were two

Table 1: Clinical Assessment

PAIN (40 pts).....	40 →	None
	35 →	Slight occasional
	30 →	Moderate occasional
	20 →	Severe frequent
	0 →	Severe continuous
ACTIVITIES OF DAILY LIVING (30 pts)...	30 →	Normal
	20 →	Slight reduction
	10 →	Moderate reduction
	0 →	Severe reduction
MOBILITY (10 pts).....	10 →	Mobility ratio ≥ 90%
(Compared to the normal shoulder)	5 →	80% ≤ Mob ratio > 90%
	0 →	Mobility ratio < 80%
MUSCLE FORCE (10 pts).....	10 →	Normal
	5 →	Slight reduction
	0 →	Moderate or severe reduction
PATIENTS SUBJECTIVE ASSESSMENTS. (10 pts)	10 →	Excellent
	5 →	Acceptable
	0 →	Poor

TOTAL SCORE :	90-100 →	EXCELLENT
	80-89 →	GOOD
	60-79 →	FAIR
	< 60 →	POOR

patients with the fair results in the AC fixation group and one in the CC fixation group. Poor results were not recorded in any of our patients. Analysis of the results of all procedures is shown in Table 2.

In the follow-ups radiographs were taken of each patient, to evaluate the reduction of the AC joint and the amount of calcification of the CC joint and to determine the irregularity or ossification around AC joint. Anatomical and radiological results are presented in details in Table 3.

Table 2: Analysis Of Results

	Excellent	Good	Fair	Poor	TOTAL
AC Fixation Technique					
K-Wire Alone	5	1	1	-	7
K-Wire+ Tension band	6	1	1	-	8
CC Fixation Technique					
Bosworth	10	2	1	-	13
CC Cerclage Wiring	10	2	-	-	12

Table 3: Clinical And Radiological Results

	ACROMIOCLAVICULAR		CORACOCLAVICULAR	
	K-Wire alone	K-Wire + Tension wiring	Bosworth	CC Cerclage
CALCIFICATION				
No signs of calcification	3	4	5	8
Slight calcification	3	2	5	3
Severe calcification	1	2	3	1
REDUCTION				
Exact	5	6	6	9
Partial	2	2	5	2
Dislocation	-	-	2	1
DEGENERATIVE CHANGES				
Positive	2	4	3	2
Negative	5	4	10	10

Failure of reduction was observed in 3 patients with the CC fixation. Figures IV and V, illustrates a patient treated with Bosworth technique having a clinically good result in spite of the loss of reduction. Loss of reduction was observed in 4 patients in the AC fixation group (%26,6) and in 10 patients in the CC fixation group (%40). 3 of them were complete dislocations, 2 in Bosworth group and 1 in cerclage wiring group. It has to be emphasised that all losses of reduction were seen in the elderly patients.

Figure 4: 32 years old man. A Bosworth operation was done for type III acromioclavicular dislocation.

Calcification around the CC ligament, from slight to severe degrees was observed in 20 patients. 12 of them (%60) were in the CC fixation group and in 9 of these patients (%75) ligament transfer was performed. Bosworth technique was significantly more complicated with calcification (%66,6). All patients with the CC cerclage wiring and slight to severe degrees of calcifications belong to the coracoacromial ligament transfer group.

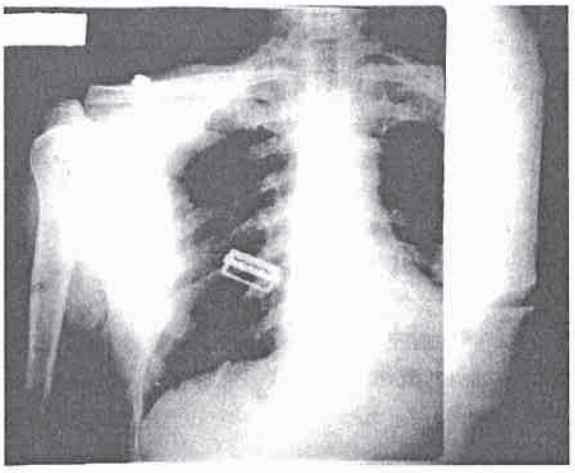

Figure 5: Loss of reduction after 4 months.

4 patients with signs of degenerative changes in the AC fixation group and 2 in the Bosworth group had complaints due to the restriction of the mobility of the shoulder, whereas in the rest of the patients the shoulder mobility was good. There was only one patient who reported having slight pain in her shoulder movements in the CC cerclage-wiring group. Complete freedom from pain was reported in the other 11 patients. 11 patients (%73,3) in the AC fixation group and 10 (%76,9) in the Bosworth group were also recorded painless and having subjectively satisfactory results. 2 patients in the AC fixation group and 1 in the Bosworth group stated that they were not able to perform the same activities of daily living as prior to surgery.

DISCUSSION

The management of complete AC joint dislocations is still controversial, because there are many authors who recommend nonoperative management for complete dislocations (11) and many who prefer surgical stabilisation and reconstruction (7, 8). The importance of surgical treatment and the value of repairing the AC and CC ligaments have been emphasized in many studies (4, 9). But the choice of surgical treatment in complete dislocations should be made by making comparison between the long term results of different types of treatments in similar patient groups. In our opinion, analysis of these similar patient groups should be made by regarding the surgical, anatomical and radiological results.

In their follow-ups patients who underwent CC fixation methods yielded 96% excellent or good results though 40% of these patients experienced some loss of reduction varying from partially subluxation to total luxation. Higher failure rates with coracoclavicular fixation methods have been reported in the literature also (5). The high rate of failure especially in the Bosworth group is decided to be the result of an improper surgical technique and 5 to 8 degrees motion at the AC joint that the rigid fixation by the screw can not resist. All losses of failures were seen in relatively older patients with an average age of 48 years. Considering the overall surgical results in the CC fixation group, we could also say that there was no significant correlation between maintenance of reduction and the final outcome, although recent reports found a much greater incidence of post-traumatic arthritis associated with insufficient results in patients who failed to maintain an anatomic alignment (14).

Treatment of complete AC separation with transfixation of the AC joint seems to increase the frequency of the degenerative changes (8, 14). In the AC fixation group this figured at %40 of the patients whereas this was %23 in Bosworth group and %16,6 in CC cerclage wiring group. A clear tendency towards a more marked limitation in activities of daily living has been reported influencing the surgical result (10). Although there was also a high incidence of degenerative changes in-patients without distal clavicle excision, we believe this should be used for an old, chronic, symptomatic complete AC dislocations and should not be preferred in acute complete dislocations (13, 17).

REFERENCES

1. Copeland S, Kessel L. Disruption of the acromioclavicular joint: Surgical treatment and biological reconstruction. Injury 1980;11:208.
2. Darrow JC, Smith JA, Lockwood RC. A new conservative method for treatment of type III acromioclavicular separations. Orthop Clin North Am 1980;11:727.
3. Fremerey RW, Lobenhoffer P, Bosch U, Freudenberg E, Tscherne H. Surgical treatment of acute, complete acromioclavicular joint dislocation. Indications, technique and results. Unfallchirurg 1996;99:341-5.
4. Fukuda K, Craig EV, Kai-Nan A, et al. Biomechanical study of the ligamentous

system of the acromioclavicular joint. J Bone Joint Surg 1986;68A:434-9.

5. Lancaster S, Horrowitz M, Alonso J. Complete acromioclavicular separations: A comparison of operative methods. Clin Orthop 1987;216:80-

6. Mulier T, Stuyek J, Fabry G. Conservative treatment of acromioclavicular dislocation: Evaluation of functional and radiological results after six years follow-up. Acta Orthop Belg 1993;59:255-62.

7. Neviaser RJ. Injuries of the clavicle and its articulations. Orthop Clin North Am 1987;18: 433-8.

8. Paavolainen P, Björkenheim JM, Paukku P, Slatis P. Surgical treatment of acromioclavicular dislocation: A review of 39 patients. Injury 1983;14:415-20.

9. Post M. Current concepts in the diagnosis and management of acromioclavicular dislocation. Clin Orthop 1985;200:234-47.

10. Rauschning W, Nordesjö LO, Nordgren B, et al: Resection arthroplasty for repair of complete acromioclavicular separations. Arch Orthop Trauma Surg 1980;97:161-4.

11. Rawes ML, Dias JJ. Long term results of conservative treatment for acromioclavicular dislocation. J Bone Joint Surg 1996; 78B: 410-2.

12. Rockwood CA, Williams GR, Young DC. Disorders of the acromioclavicular joint. In: Rockwood CA, Matsen FA, editors. The shoulder. Philadelphia: W.B. Saunders Company, 1998:483-554.

13. Smith MJ, Stewart MJ. Acute acromioclavicular separations. Am J Sports Med 1979;7:62-71.

14. Taft TN, Wilson FC, Oglesby JW. Dislocation of the acromioclavicular joint: An end-result study. J Bone Joint Surg 1987;69A:1045-51.

15. Tossy JD, Mead NC, Simond HM. Acromioclavicular separations: Useful and practical classification for treatment. Clin Orthop 1963;28:111.

16. Van Fleet TA, Bach B. Injuries to the acromioclavicular joint: Diagnosis and management. Orthop Rev 1994;23:123-9.

17. Weaver JK, Dunn HK. Treatment of acromioclavicular injuries, especially complete acromioclavicular separation. J Bone Joint Surg 1972;54A:1187-97.

18. Wojtys EM, Nelson G. Conservative treatment of grade III acromioclavicular dislocations. Clin Orthop 1991;268:112-4.

CORRELATION BETWEEN SERUM AND FOLLICULAR FLUID HORMONE PARAMETERS AND MATURATION OF OOCYTE-CUMULUS-CORONA-COMPLEXES ON THE DAY OF PICK-UP

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SUMMARY

Correlation Between Serum and Follicular Fluid Hormone Parameters and Maturation of Oocyte-Cumulus-Corona-Complexes on the Day of Pick-Up.

The aim of this study was to investigate the relationship between serum and follicular FSH, LH, free testosterone (FT), prolactin (PRL) and b-HCG with oocyte maturation, according to Veeck's classification. Enrolled in the study were 44 infertile patients with tubal-factor or unexplained infertility who were accepted for IVF between January 1997 and November 1998. All patients were given GnRH-a (Decapeptyl-CR, Er-Kim, Istanbul) in a long-term protocol and stimulated either with HMG (Menagon, Erkim, Istanbul) or pure-FSH (Metrodin, Serono, Istanbul). Ovulation was stimulated with 10,000 U HCG (Pregnyl, Organon, Istanbul) when there were at least two follicles larger than 17 mm in diameter. Serum was collected 36 hours after HCG injection on the day of oocyte pick-up. Follicular fluid (FF) and serum hormone levels were classified according to the morphology of Oocyte-Cumulus-Corona-Complexes as mature, immature, intermediate, postmature and empty follicles. Serum PRL levels were significantly high in the mature group (p<0,05). HCG were high in the postmature group (p<0,01) and low in the immature group (p<0,01). FF b-HCG were significantly low in the immature group and correlated with serum HCG. FF FT levels were high in the immature follicles (p<0.05). Serum and FF b-HCG were correlated and found to be low in immature follicles in this small group of patients. b-HCG was observed to be a major determinant in oocyte maturation. Increasing the number of patients in future studies may help in identifying a cut-off value for b-HCG in the grading of oocyte maturation.

Key words: *IVF, hormone, follicular fluid, oocyte maturity, bHCG*

ÖZET

Serum ve Folliküler Sıvı Hormon Parametreleri İle Oosit-Kümülüs-Korona-Komplex Maturasyonunun Pick-Up günü Karşılaştırılması

Amaç: *Serum ve folliküler FSH, LH, free testosterone (ft), prolactin (PRL) ve ßHCG ile Veeck's klasifikasyonuna göre oosit maturasyonu ilişkisini araytırmak.*

Araç-Yöntem: *Ocak 1997 ve Ekim 1998 arasında IVF için tubal faktör ve açıklanmayan infertilite nedenleri ile başvuran 44 infertil hasta çalışmaya dahil edildi. Bütün hastalar uzun protokol GnRH-a (Decapeptyl-CR, Er-Kim, İstanbul) aldı ve HMG (Menagon, Erkim, İstanbul) ile ya da pür-FSH (Metrodin, Serono, İstanbul) ile indüklendi. En az iki follikül 17 mm'den daha büyük çapa ulaşınca ovulasyon 10.000 U HCG (Pregnyl, Organon, İstanbul) ile stimüle edildi. Serum HCG injeksiyonundan 36 saat sonra oosit pick-up günü toplandı. Folliküler sıvı ve serum hormon ölçümleri Oosit-Kümülüs-Korona-Komplex morfolojisine göre matür, intermediate, immatür, postmatür ve boş folliküler olarak gruplandırıldı.*

Bulgular: *Serum PRL düzeyleri matür grupta anlamlı şekilde yüksekti (p<0,05). HCG postmatür grupta yüksekti (p<0,01) ve immatür grupta düşüktü (p<0,01). FF ßHCG immatür grupta anlamlı düşüktü ve serum HCG değeri ile ilişkiliydi. FF ft seviyeleri immatür grupta yüksekti.*

Sonuç: *İmmatür grupta serum ve FF ß-hCG birbirleriyle korele olarak bu küçük hasta grubunda düşük bulunmuştur, ß-hCG oosit maturasyonunda ana belirleyici olarak gözlenmiştir. Hasta sayısı arttırılarak oosit maturasyonu tasnifinde ß-hCG eşik değerinin belirlenebilmesi mümkün olabilir.*

Anahtar kelimeler: *IVF, hormon, folliküler sıvı, oosit maturasyonu, ß-hCG*

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Received: Oct 16, 2000 Accepted: Feb 08, 2001

Folliculogenesis and oocyte maturation are extremely complex processes that are dependent on an integration of cellular and endocrine mechanisms. Follicular fluid (FF) is the fraction of extracellular fluid that accumulates in the antrum of ovarian follicles. As the follicle matures, the volume of follicular fluid as well as the concentrations of steroidal and non-steroidal substances increase, providing a hormonal microenvironment that is influential in the subsequent maturation of the oocyte (1). Since the oocyte-cumulus-corona complex (OCCC) is bathed in follicular fluid throughout its maturation, it is believed that there may be a direct relationship between the biochemical characteristics of follicular fluid and oocyte maturation (2).

Oocyte maturity, as determined by OCCC morphology, is related to successful fertilization in-vitro (IVF). However, OCCC morphology is a subjective parameter that does not always correlate with nuclear oocyte maturity (3). Full maturation of oocytes requires cytoplasmic as well as nuclear changes (4). Follicular steroids may play an important role in both the resumption of meiosis and cytoplasmic maturation (5, 6). Most data on the analysis of follicular fluid indicates a correlation between follicular steroid content and oocyte maturity and, moreover, fertilization capacity (7).

In the current study, we investigated the interrelationship between serum and follicular FSH, LH, free testosterone (FT), prolactin (PRL) and ß-HCG with oocyte maturation, according to Veeck's classification.

MATERIALS AND METHODS

Patients and Protocols: Enrolled in the study were 44 infertile patients with a diagnosis of tubal-factor or unexplained infertility who were accepted for IVF between January 1997 and November 1998.

All of the patients received GnRH-a (Decapeptyl-CR, Er-Kim, Pharmaceuticals, Istanbul, Turkey) in a long-term protocol on day 21 of the cycle preceding IVF and were stimulated either with HMG (Menagon, Erkim, Istanbul.) and/or pure-FSH (Metrodin, Serono, Istanbul). The extent of ovarian suppression and the development of follicles were monitored in all patients using transvaginal ultrasound scans. Ovulation was stimulated with 10,000 U HCG (Pregnyl, Organon, Istanbul, Turkey) when there were at least two follicles >17 mm in diameter. All of the HCG injections were made by a single IVF nurse in order to prevent the improper preparation and administration of the drug, an issue addressed by Asch et al (8). All follicles >16 mm were aspirated using a 17G aspiration needle under endovaginal ultrasound guidance.

Oocytes retrieved from the aspirated follicles were evaluated under stereomicroscope, and their cumulus-coronal cell morphology interpreted as mature, intermediate, immature, postmature or empty. Maturation of oocytes was determined according to the criteria of Veeck et al (9).

Serum was collected 36 hours after HCG injection on the day of oocyte pick-up. Serum and FF samples were immediately centrifuged at 3000xg for 10 minutes and stored at –20 degrees until the day of biochemical assay. FSH, LH and prolactin levels were measured with an Automated Chemiluminescense System, and ft and b-hCG levels were measured by radioimmunoassay.

Statistical analysis: Data was analyzed using SPSS software (version 9.01; SPSS Inc., Chicago, IL) with analysis of variance and x^2 test. Data collected from the patients was analyzed by one of the authors who was blinded to the study. Data is presented as mean±SD. $P<0.05$ was considered as statistically significant.

RESULTS

The number of ampoules injected ($p<0.05$, x^2 test) and the age of patients ($p<0,01$, x^2 test) varied significantly in the immature group. Other groups were comparable in parameters of age, injection days, number of ampoules, number of aspirated oocytes, IVF indications and induction protocols (Table 1).

Serum hormone concentrations were grouped

Table 1: Comparison of Clinical Parameters and Oocyte Maturity

		Mature	Intermediate	Immature	Postmature	Empty	P
Age		32.32±5.16	31.62±4.40	41.76±0.5	31.66±5.68	33.73±6.08	p<0.05*
Day		12.45±1.99	11.60±1.76	13.00±2.24	11.00±1.0	12.26±1.73	NS
No. of Ampoules		39.03±12.811	40.40±17.688	63.00±24.74	31.66±1.52	40.94±12.277	p<0.01**
No. of Oocytes		9.76±6.84	9.52±6.84	9.20±5.22	8.00±1.00	10.89±8.15	NS
Indication	Tubal	48.5%	44%	20%	0%	47.9%	NS
	Unexp.	45.5%	56%	80%	100%	52.6%	NS
Protocol	Long	81.8%	68%	80%	66.7%	84.2%	NS
	Short	18.2%	32%	20%	33%	15.8%	NS
Type	FSH	33%	32%	20%	33%	36.8%	NS
	HMG	63.6%	68%	60%	66.7%	53%	NS

*Immature group was older than the others (X^2 test)

**Number of ampoules injected was greater in immature group (X^2 test)

according to ratings of oocyte maturity and empty follicles (Table 2). Serum PRL levels were significantly high in the mature group (p<0,05, analysis of variance). HCG levels were high in the postmature group (p<0,01, analysis of variance) and low in the immature group (p<0,01, analysis of variance). FSH, LH and FT concentrations did not vary between groups.

Table 2: Comparison of Serum Hormone Parameters and Oocyte Maturity

	FSH (ml U/ml)	LH (ml U/ml)	FT (nmol/ml)	PRL (ng/ml)	bHCG (IU/ml)
Mature	8.43±5.01	0.57±1.04	6.73±11.85	38.60±25.85	83.51±35.84
Intermediate	8.53±4.54	0.50±0.55	2.95±1.46	0.7±11.47	78.55±26.33
Immature	8.88±1.67	0.38±0.10	1.46±0.26	23.74±8.90	27.56±14.49
Postmature	8.10±0.71	0.16±0.16	1.2±0.0	16.5±6.15	144.40±163.8
Empty	9.73±7.01	0.52±0.71	7.67±14.33	29.16±12.93	91.03±33.52
p	NS	NS	NS	p<0.05*	SS**

*Serum PRL was highest in mature group (variance analysis)

**Serum bHCG was highest in postmature (p<0.001) and lowest in immature (p<0.01) groups (variance analysis)

Follicular fluid hormone concentrations were grouped according to oocyte maturity rating. FF bHCG levels were significantly low in the immature group and correlated with serum HCG. FF FT levels were high in the immature follicles (p<0.05) but were not correlated with serum levels. FSH, LH and PRL levels did not differ among the groups (Table 3).

DISCUSSION

Siu et al showed that OCCC correlates significantly and positively with normal fertilization rates and may serve as a useful predictor for pregnancy success in an IVF cycle (10). However, the intrafollicular mechanism involved in the regulation of nuclear and cytoplasmic processes for

Table 3: Comparison of FF Hormone Parameters and Oocyte Maturity

	FSH (mIU/ml)	LH (mIU/ml)	fT (nmol/ml)	PRL (ng/ml)	bHCG (IU/ml)
Mature	5.61±3.77	0.31±0.29	82.39±70.14	33.04±17.52	38.53±24.03
Intermediate	5.82±4.04	0.49±0.66	70.80±57.41	27.40±10.24	35.20±19.13
Immature	6.54±1.77	0.14±0.08	141.24±88.12	23.90±8.30	10.50±7.58
Postmature	4.04±1.33	0.24±0.12	47.55±6.29	16.40±10.61	27.25±0.35
Empty	5.71±3.70	0.26±0.33	70.75±50.16	25.37±10.03	40.80±23.08
p	NS	NS	SS*	NS	SS**

*FF ft was high in immature group ($p<0.05$) (variance analysis)

**FF bHCG was low in immature group ($p<0.05$) (variance analysis)

maturation is not well known. Most data on the analysis of FF indicate a correlation between follicular hormone content and oocyte maturity (7).

In order to mimic the natural midcycle LH surge necessary for final follicular maturation, exogenous HCG is administered. It appears in follicular fluid following injection; however, the relationship of its concentration in follicular fluid to oocyte maturity needs to be clarified. HCG concentration in FF did not differ significantly between stimulated and natural cycles. This may be attributed to the fact that both groups of patients received the same ovulatory-triggering dose of HCG (2).

Blood-borne substances in the follicular fluid, such as HCG concentrations, may reflect the health and maturity of the follicle, its vasculature, and the permeability of the follicular membrane (11). Changes in ovarian blood flow affect the entry of blood-borne HCG into the follicle. Estrogen's affect on ovarian perfusion in GnRH-a cycles might lower the amount of HCG presented to the follicles (12). In this study, FF _-HCG levels were significantly low in the immature group and correlated with serum HCG.

Conflicting data has been reported on concentrations of FF PRL during oocyte maturation in normal and stimulated cycles (13). Laufer et al described close association between a high FF PRL concentration and oocyte maturity in cycles stimulated with a high-dose HMG regimen.

The presence of specific receptors for PRL in human ovaries, animal data, and in-vitro studies suggest that PRL may also directly regulate ovarian function. This study showed that serum PRL levels were significantly high in the mature group. Follicular fluid PRL levels were also high in the mature group but not statically significant.

In this study, FF FT levels were significantly higher in the immature follicles than in all other follicles. It has been suggested that androgens act via conversion to 5_ reductase metobolites, which could then act as inhibitors of aromatization (14). In correlation with previous studies performed on other FF androgens, our study found FF FT levels to be higher in the immature group (15, 16).

Serum and FF bHCG were correlated and found to be low in the immature group. bHCG was observed to be a major determinant in oocyte maturation. Increasing the number of patients may help to determine a cut-off value for bHCG in grading oocyte maturation.

REFERENCES

1. McNatty KP, Moore SD, Makris A, Osathnanondh R, Ryan KJ. The microenvironment of the human antral follicle: interrelationship among the steroid levels in antral fluid, the population of granulosa cells, and the status of the oocyte invivo and invitro. J. Clin. Endocrinol. Metab.1979; 49:851-857.
2. Enien WM, Sahwy SEl, Harris CP, Seif MW, and Elstein M. Human chorionic gonadotropin and steroid concentration in follicular fluid: the relationship to oocyte maturity and fertilization rates in stimulated and natural in-vitro fertilization cycles. Human Reprod 1995; 10:2840-2844.
3. Vanluchene E, Hinting A., Dhont M, De Sutter P, Maele VG, Vandekerckhove D. Follicular fluid steroid levels in relation to oocyte maturity and in vitro fertilization. J. Steroid Biochem Molec Biol, 1991; 38:83-87.
4. Thibault C. Are follicular maturation and oocyte maturation independent processes? J. Reprod Fertil 1977; 51:1-4.
5. Thibault C, Gerard M, Menozo Y. Preovulatory and ovulatory mechanisms in oocyte maturation. J.Reprod Fertil 1975; 45:606-700.
6. Moor RM, Polge C, Willadsen SM. Effect of follicular steroids on the maturation and fertilization of mammalian oocytes. J Embryol Exp Morphol 1980; 56:319-323.
7. De Sutter P, Dhont M, Vanluchene E, Vandekerckhove D. Correlation between follicular fluid steroid analysis of human oocytes that remained unfertilized after in-vitro fertilization. Fertil Steril 1991; 55:958-64.
8. Asch RH, Li HP, Yovich J. Failed oocyte retrieval after lack of human chorionic gonadotrophin administration in assisted reproductive technology. Fertil steril 1992; 58:361-7.
9. Veeck LL, Wortham JWE, Witmyer J, Sandow BA, Acosta AA, Garcia JE, Jones GS. Maturation and fertilization of morphologically immature human oocytes in a program of in vitro fertilization. Fertil Steril 1983; 39:594-600.
10. Siu TNg, Chang TH, Jackson W. Prediction of the rates of fertilization, cleavage, and pregnancy success by cumulus-coronal morphology in an in vitro fertilization program. Fertil Steril 1999; 72:412-17.
11. Carson RS, Salamonsen LA, Findlay JK. Permeability of rat ovarian follicles to LH during development and luteinization. J Reprod Fertil 1986; 76:663-68.
12. Hartshorne MG. Preovulatory follicular fluid: relationship to ovarian stimulation protocol, fertilization, and sperm penetration in vitro. Fertil Steril 1989; 52:998-1004.
13. Piekos MW, Binor Z, Rawlins RG, Radwanska E. Effects of induced hyperprolactinemia on in vitro fertilization cycles. Fertil Steril 1995; 63:371-6.
14. Andersen CY. Characteristics of human follicular fluid associated with successful conception after in vitro fertilization. 1993; 77:1227-34.
15. Lee MS, Ben Rafael Z, Meloni F, Mastroianni Jr L, Flickinger GL. Relationship of human oocyte maturity, fertilization and cleavage to follicular fluid prolactin and steroids. J In Vitro Fert Embryo Trans. 1987; 4:168-172.
16. Lobo RA, DiZerega GS, Marrs RP. Follicular fluid steroid levels in dismature and mature follicles from spontaneous and hyperstimulated cycles in normal and anovulatory women. J Clin Endocr Metab 1985; 60: 81-87.

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 1, 2001 63-68

COLPOSCOPY

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SUMMARY

Cytology and colposcopy are both methods used in the screening of cervical cancer. Cytology is a laboratory method, whereas colposcopy is a clinical method. Both have their relative merits, and a combination of the two may be used to generate screening protocols that might result in more effective and inexpensive screening programs.

Key Words: *Colposcopy.*

ÖZET

Kolposkopi

Kolposkopi, serviks kanserinde tarama metodu olarak kullanılan, sitolojiye ek ikinci bir yöntemdir. Her iki yöntemin de birbirlerine göre üstünlükleri bulunmaktadır. Sitoloji bir laboratuar yöntemidir, kolposkopi ise klinik deneyime dayanmaktadır. Bununla birlikte, sitoloji ve kolposkopi, etkinliği yüksek, maliyeti düşük tarama programlarında kullanılabilecek, birbirini tamamlayan iki farklı tanı yöntemidir.

Anahtar Kelimeler: *Kolposkopi.*

Since its development in 1925, the use of the colposcope has become well established in clinical gynecologic practice for defining and delineating cytologically detected abnormal lesions. An increase in the diagnosis of pre-invasive conditions in conjunction with the decrease in the incidence of invasive cervical cancer has necessitated an increased use of colposcopy in practice.[1]

The colposcope is a binocular microscope that allows for the inspection of the cervix under low magnification (5x-40x). It consists of single or double main objective lenses, binocular tubes (containing a prism system), eyepieces (oculars) with diopter adjustment, a light source and a filter, usually green, to enable the study of blood vessel patterns. Colposcopy is used primarily to identify the source of abnormal cells in a PAP smear and to determine the location of biopsies.[2]

Colposcopy indications are shown in Table 1.

Table 1: Colposcopy Indications[3]

1. Dysplasia or carcinoma in cervicovaginal smear
2. HPV infection in cervicovaginal smear
3. A high-risk woman with a diagnosis of ASCUS or repeated ASCUS in cervicovaginal smear
4. Repeated infection in cervicovaginal smear
5. Cervix with abnormal appearance
6. Exposure of cervix to DES.

The standard steps used in colposcopic examination are shown in Table 2.[4]

Table 2: Colposcopic examination

1. Patient is placed in lithotomy position.
2. Cervix is exposed by speculum examination.
3. Pap smear is repeated, if necessary.
4. Cervix is cleaned with normal saline.
5. 3-5% solution of acetic acid is applied to the cervix and transformational zone. (Repeated

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Received: Nov 17, 2000 Accepted: Jan 25, 2001

if necessary.)

6. Cervix is inspected in a clockwise direction, first without green filter and then with filter.

7. Iodine solution is applied to the cervix.

8. Cervix is inspected again.

9. Sites for biopsy are selected and taken.

10. Hemostasis (Monsel solution or AgNO3).

Use of a 3-5% solution of acetic acid removes excess mucus and cellular debris and provides nuclear swelling (Figures I-2). Vessel structures and color tones can be best understood using a green filter. Iodine stains normal glycogen-containing epithelium dark brown, while other epithelia remain pale.

When evaluating patients with abnormal cytology, it is essential to recognize the area with the most severe epithelial change for sampling. The major characteristics assessed during colposcopy are vascular pattern, intercapillary distance, color tone, surface contour and clarity of demarcation of observable lesions.[2,3] The following terminology is used in the classification of colposcopic findings (Table 3): Aceto-white epithelium: a focal colposcopic pattern of white epithelium seen after application of acetic acid; Leukoplakia (hyperkeratosis): an elevated white, thick, heavy plaque present before acetic acid application; Punctuation: the endings of capillaries, generally resembling red spots, in the aceto-white epithelium; Mosaicism: the appearance of thin blood vessels forming reddish borders; Atypical vessels: irregular vessels resembling commas or spaghetti-like forms.[2]

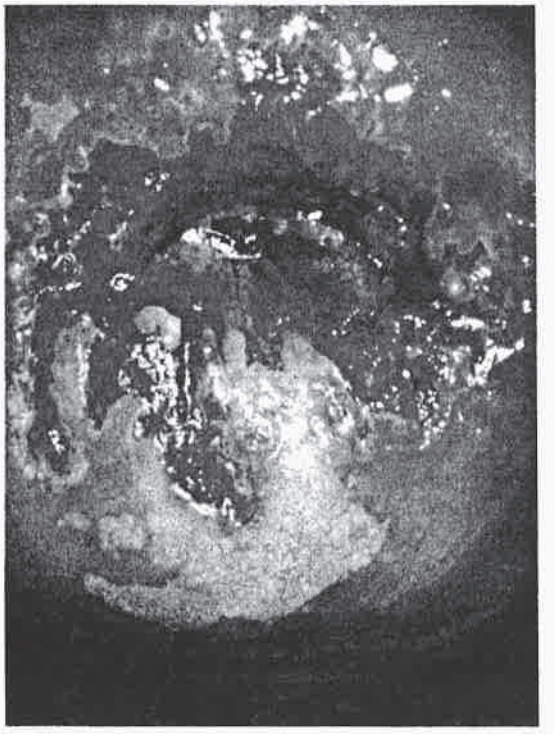

Figure 1: Colposcopic view of external os before the application of acetic acid.

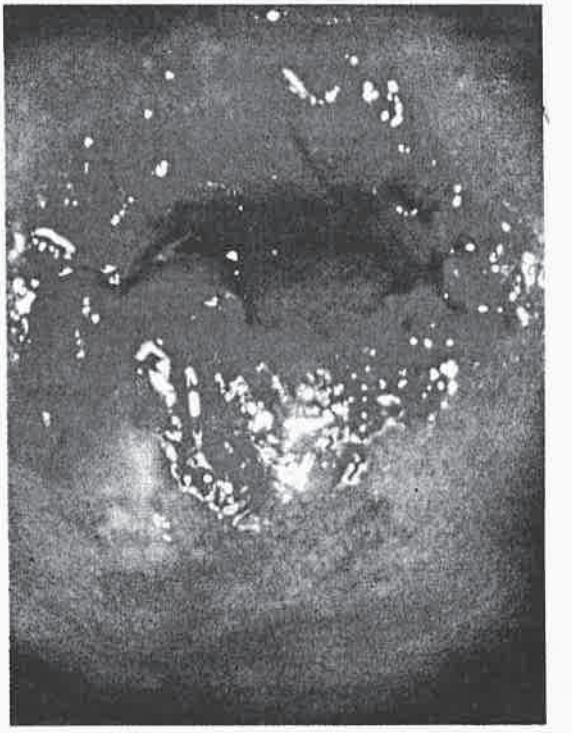

Figure 2: After the application of acetic acid, whitish color and mosaic pattern.

Table 3: Terminology

I. Normal colposcopic findings

A. Original squamous epithelium

B. Columnar epithelium

C. Normal transformation zone

II. Abnormal colposcopic findings

A. Within the transformation zone

1) Aceto-white epithelium

a. Flat

b. Micropapillary or microconvoluted

2) Punctuation

3) Mosaicism

4) Leukoplakia

5) Iodine-negative epithelium

6) Atypical vessels

B. Outside the transformation zone (e.g., ectocervix, vagina)

III. Colposcopically suspect invasive carcinoma

IV. Unsatisfactory colposcopy

A. Squamocolumnar junction not visible

B. Severe inflammation or severe atrophy

C. Cervix not visible

V. Miscellaneous colposcopic findings

Colposcopy and cytology are two methods of cervical cancer screening. Both methods have their relative merits. Cytology is an economical method that does not require a specialist. It is appropriate for screening a population, but it cannot localize a lesion. A well-taken smear should reveal abnormalities in the canal at the same rate as those on the ectocervix. Cytology has its own failure rate, the reasons for which are not always clear. The rate of false negatives is reported to be between 5-30%.

Colposcopy is particularly useful as a secondary screening method to compensate for cytological failures. Because 10-15% of atypical lesions are situated in the canal out of range of the colposcope, colposcopic failure rate is necessarily higher than that of good cytological screening. An additional 5% failure rate is due to misinterpretation of ectocervical changes. It is therefore reasonable to assess colposcopy as 80% accurate in the detection of early cervical carcinoma.[5,6]

Cervical smears assist in determining which patients should undergo colposcopy and therefore decrease the number of colposcopies. Among the low-risk female population, one out of two cases of colposcopically low-grade patterns should be considered indicative of squamous metaplasia. Lukic et al confirmed that colposcopic evaluation is unable to distinguish between immature metaplastic transformation of the epithelium and metaplastic epithelium with initial neoplastic transformation.[7] Teale et al stated that women referred with low-grade cytological abnormalities who have a normal cervix on colposcopy and a negative or borderline repeat smear test may be discharged from the colposcopy clinic.[8]

The value of colposcopy and cytology in screening cervical intraepithelial carcinoma (CIN) was analyzed in a retrospective study that compared cytologic and colposcopic findings with histologic results. Sensitivity and specificity rates of colposcopy were 87% and 15%, respectively, compared to 47% and 77% for cytology. The low sensitivity of cytology suggests that 50% of CIN associated with abnormal colposcopy may be overlooked if cytology alone is used for screening.[9] (Table 4)

Table 4: Value of Cytology and Colposcopy in Cervical Cancer Screening

	Cytology	Colposcopy
False negative rate[5]	5-30%	10-35%
Sensitivity[9]	47%	87%
Specificity[9]	77%	15%

In another study on colposcopy, histologic biopsy results of Grade I atypical transformation zone revealed a 70.6% rate of chronic cervicitis and a 19.6% rate of CIN. Grade I atypical transformation zone with inflammatory smears revealed CIN II-III in only 2.7% of patients. Grade I lesions in association with high-grade SIL

revealed CIN II-III lesions at a rate of 16.6%. These results indicate that Grade I lesions in the presence of inflammatory or low-grade SIL smears can be observed and biopsied only if the changes persist. However, association of high grade SIL with Grade I atypical transformation zone calls for immediate biopsy.[10]

Differences in the sensitivity of colposcopy between premenopausal and postmenopausal women have been described. Suspect cervical lesions are seen in 24% of women <50 years of age, compared with 3% of women >50 years of age. This observation can be explained by the ectocervical location of the squamocolumnar junction in premenopausal women.[11] In women >35 years of age, cervical lesions associated with intraepithelial neoplasm are thinner and thus less colposcopically conspicuous than those in women <35 years of age. Patients >35 years old with aceto-white cervical lesions consistent with trivial changes of doubtful significance should therefore undergo colposcopically directed biopsy independent of their cytologic result.[12]

Baldauf et al reported 95% of loop electrosurgical excision treatment failures could be detected by cytology and colposcopy in the first two postoperative years.[13] These results confirm those of Gardeil et al, who were able to detect 70% of treatment failures at six months and 30% at 24 months following loop electrosurgical excision.[14] Both cytology and colposcopy were able to provide early detection of all treatment failures that occurred after the first two postoperative years, suggesting that follow-up modalities based on cytology might be advisable beyond the second year.

Flannely et al state that follow-up by cytology is essential after treatment for CIN, but colposcopy is optional, although it may increase the detection of persistent disease at six months.[15] Colposcopy may be particularly beneficial for follow-up if the treated lesion was large and if the excision appeared incomplete.[16]

Human papilloma virus infection of the lower genital tract can be present in three states: Latent infection; subclinical infection; and clinically evident exophytic warts. Infection results in different growth patterns, depending on the type of epithelium infected, HPV type and host resistance. HPV infection can involve the lower genital tissues, making it imperative that a complete and extensive colposcopic investigation be undertaken in all HPV patients. HPV-induced changes and their colposcopic characteristics vary. The lesions may appear to be soft, bulky, hard or pedunculated; they may resemble sessile papules; they may be hyperkeratotic or pigmented; and they may be isolated or grouped in clusters.

There are several types of cervical HPV-induced lesions. Flat condyloma is a subclinical cervical HPV lesion that appears as focal or multiple white plaques within and outside the transformation zone. These flat lesions are so similar in appearance to metaplasia and CIN that differentiation is difficult without biopsy. Spiked condylomata are the most frequently encountered form of cervical HPV-induced lesions and are characterized by a surface covered by budding, finger-like projections or spikes.

Persistent presence of high-risk HPV in normal cervical smears is associated with a significantly increased risk of developing abnormal cytology and to a lesser degree with developing an abnormal colposcopic impression.[17]

The aim of colposcopy is the differentiation between benign HPV lesions, intraepithelial neoplasm and invasive cancer. [18] Cervical papillomas are benign tumors originating from squamous epithelium with the contribution of mesenchymal tissue. In one study, the vascular structure of cervical papilloma was shown to become prominent when an oxytocin test was performed during colposcopy.[19] Colposcopy can be used to identify cervico-vaginitis, chronic cervicitis and other inflammatory lesions such as ulcers, cysts and granulomas. Inflammatory patterns after acetic acid application are characterized by diffuse or local red punctuation, white punctuation,

micropapillae and, more rarely, a vesicular pattern. In chronic cervicitis, the columnar epithelium remains red, and contact bleeding occurs very readily after the application of acetic acid.(20)

In conclusion, various combinations of cytology and colposcopy may be used to generate screening protocols that might result in more effective and inexpensive screening programs.

REFERENCES

1. Van Niekerk WA, Dunton CJ, Richart RM, Hilgarth M, Kato H, Kaufman RH et al. Colposcopy, cervicography, speculoscopy and endoscopy. International Academy of Cytology Task Force Summary. Diagnostic Cytology towards the 21st century: An International Expert Conference and Tutorial. Acta Cytol 1998 Jan-Feb; 42 (1): 33-49.
2. Krebs HB. Premalignant lesions of the cervix. In: Textbook of Gynecology. Copeland LJ ed., WB Saunders Com, 2000, 2nd ed, 1241-45.
3. Uslu T. Kolposkopi. In: Jinekolojik Onkoloji. Erten O, Uslu T eds. Dokuz Eylül Yayınları, 1998, 1. baskı, 203-17.
4. Di Saia PJ, Creasman WT. Preinvasive disease of the cervix. In: Clinical Gynecologic Oncology. Di Saia, Creasman eds. Mosby imprint, 5th ed. 1997; pp17-20.
5. Uses of colposcopy. In: Colposcopy-Cervical Pathology. Burghardt E, Öster AG (eds). Thieme Medical Publishers, Inc, 1991, 247.
6. Yüce K. Serviks Kanserinde Tarama ve Erken Tanı; Sitoloji ve Kolposkopi. Obstetrik ve Jinekoloji Sürekli Eğitim Derg 1998;2(1):37-47.
7. Lukic A, Musumeci M, Signore M, Sassi MT, Alo P, Giovagnoli MR, Vetrano G. Critical review of colpo-histological results in cervix pathology. Minerva Ginecol 1999 Oct; 51(10): 365-71.
8. Teale GR, Moffit DD, Mann CH, Luesley DM. Management guidelines for women with normal colposcopy after low grade cervical abnormalities: population study. B M J 2000; 320(7251): 1693-6.
9. Pete I, Toth V, Bosze P. The value of colposcopy in screening cervical carcinoma. Eur J Gynaecol Oncol 1998; 19(2): 120-2.
10. Suneja A, Guleria K, Manishee, Mishra K, Agarwal N: Do all grade I lesions on colposcopy need to be biopsied? Indian J Cancer 1999 Jun-Dec; 36(2-4): 135-40.
11. Cecchini S, Bonardi R, Mazzotta A, Grazzini G, Iossa A, ciatto S. Testing cervicography and cervicoscopy as screening tests for cervival cancer. Tumori 1993;79:22-5.
12. Zahm DM, Nindl I, Greinke C, Hoyer H, Schneider A: Colposcopic appearance of cervical intraepithelial neoplasia is age dependent. Am J Obstet Gynecol 1998; 179: 1298-304.
13. Baldauf JJ, Dreyfus M, Ritter J, Cuenin C, Tissier I, Meyer P. Cytology and colposcopy after loop electrosurgical excision: Implications for follow-up. Obstet Gynecol 1998; 92: 124-30.
14. Gardeil F, Barry-Walsh C, Prendiville W, Clinch J, Turner MJ. Persistent intraepithelial neoplasia after excision for cervical intraepithelial neoplasia grade III. Obstet Gynecol 1997; 89: 419-22.
15. Flannelly G, Longhan H, Jandial L, Mann E, Campbell M, Kitchener H. A study of treatment failures following large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia. Br J Obstet Gynecol 1997; 104: 718-22.
16. Semple D, Saha A, Maresh M. Colposcopy and treatment of cervical intraepithelial neoplasia: are national standards achievable? Br J Obstet Gynecol 1999; 106: 351-5.
17. Hopman EH, Rozendaal L, Voorhorst FJ, Walboomers JM, Kenemans P, Helmerhorst TJ. High risk human papilloma virus in

woman wiyh normal cervical cytology prior to the development of abnormal cytology and colposcopy. B J O G 2000; 107(5): 600-4.

18. Roy M. Colposcopy of genital condyloma. In: Basic and Advanced Colposcopy Part One. Wright C, Lickrish GM, Shier RM (eds). Biochemical Communications, 1995, 2nd ed, Chapter 16.
19. Yardım T, Yüce A, Hamidi Ş, Kılıç T. Serviks Papillomu ve Serviks Prekanseröz Lezyonlarının Ayırıcı Tanısında Kolposkopik Değerlendirme. Jinekoloji ve Obstetrik Derg. 1999;13:26-29.
20. Shier RM. Colposcopic mimics and miscellaneous conditions of the cervix and vagina. In: Basic and Advanced Colposcopy Part One. Wright C, Lickrish GM, Shier RM (eds). Biochemical Communications, 1995, 2nd ed, Chapter 13.

CAUDA EQUINA SYNDROME DUE TO POSTERİOR EPIDURAL MIGRATION OF AN EXTRUDED LUMBAR DISC FRAGMENT

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Altay Bedük* ✣ Şeref Demirkaya**

SUMMARY

Cauda equina syndrom resulting from posterior epidural disc fragment migration is very rare and only two cases have been reported to date. This report represents magnetic resonance imaging of posterior epidural disc fragment migration and clinical evaluation of this rare disease.

Key Words: *Cauda equina syndrome, disc fragment migration, magnetic resonance imaging.*

ÖZET

Kauda Equina Sendromu

Posterior epidural disk fragmanı migrasyonuna bağlı kauda equina sendromu nadir görülmektedir ve günümüze kadar sadece iki vaka bildirilmiştir. Bu makalede posterior epidural disk migrasyonunun manyetik rezonans görüntülenmesi ve klinik evaluasyonu sunulmuştur.

Anahtar Kelimeler: *Kauda equina sendromu, disk fragman migrasyonu, manyetik rezonans görüntüleme.*

Sequestered disc fragments usually stay in the right or left half of the anterior epidural space. Because of posterior longitudinal ligament and its attachments, posterior epidural migration of extruded disc fragments are seen rarely (1,2). Among them there is two cases reported cauda equina syndrom due to posterior epidural migration of an extruded lumbar disc fragment (1,3). Cauda equina syndrom (CES) is generally described as radiating pain in lower extremities, areflexia, sensory and motor disturbances, and bladder and bowel disfunction. With cauda equina lesions, radiating pain is a cardinal feature (4,5). In this case, there was severe radiating pain on any movement of the lower back and we describe a massive posteriorly migrated lumbar disc fragment showed by magnetic resonance imaging (MRI).

CASE REPORT

A 59 years old man was admitted to the neurosurgical unit on June 13, 1998. One year ago his legs were weak for a week and recovered spontaneously, but at that time he didn't apply to a hospital. On his arrival in the neurosurgical unit he was complaining about severe low back pain, and bilateral leg weakness. He couldn't walk without help. The straight leg raising test was limited to 45 degrees in both legs and there was total motor loss in dorsiflexion of the right ankle. Motor strength of the left ankle was 2/5. He had had mild urinary retention for two days. The rectal tone was decreased. Reflexes were decreased at the right knee and absent at the ankle bilaterally. Plantar reflexes were bilateral indifferantiated.

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Received: Dec 20, 1999 Accepted : June 19,2000

Magnetic resonance imaging revealed a posterior epidural lesion at the level of L3- 4 causing

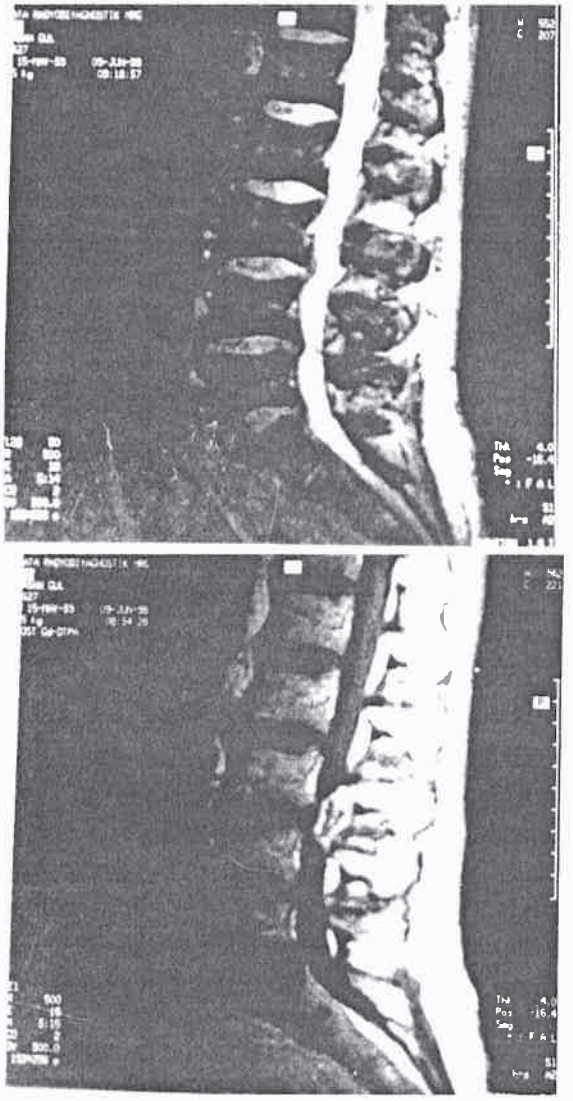

Fig 1: Sagittal T1-weighted magnetic resonance images at L3-L4 before (a) and after (b) contrast enhancement.

cauda equina compression (Fig. 1). The lesion was slightly hiperintense on T1- weighted images and hiperintens on T2 weighted images (Fig. 2), and showed rim enhancement after adminstration of gadolinium (Fig. 1b, 2, 3).

This patient was taken to surgery and L3 hemilaminectomy was performed. The lesion, which is adherent to the dura but not destructed, or invased into other tissues seen in the posterior

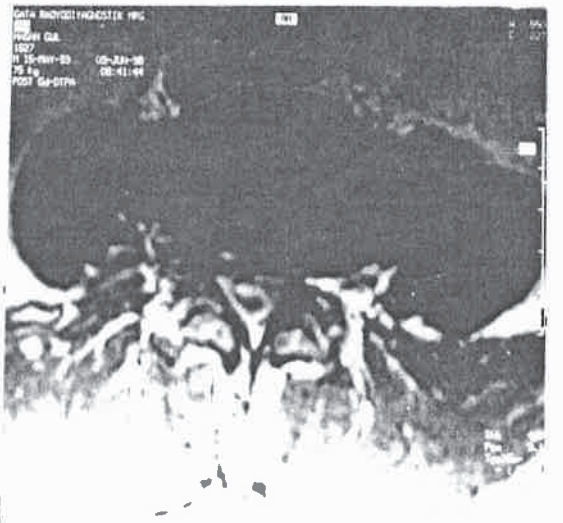

Fig 2: The posterior epidural disc fragment is hiperintense on axial magnetic resonance T1-weighted image with gadolinium enhancement. The disc fragment is posterior and to the right of the thecal sac.

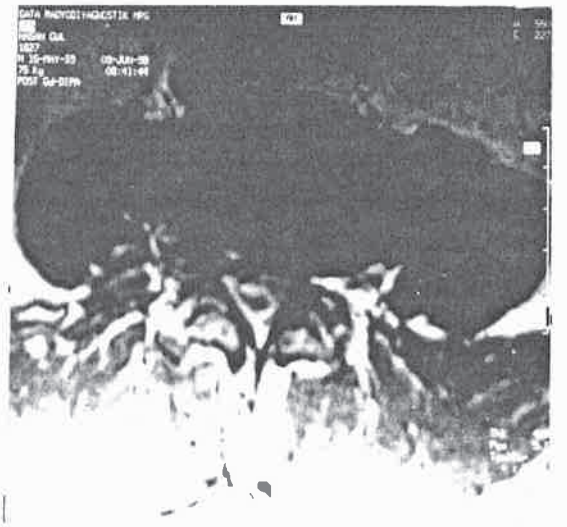

Fig 3: The coronal magnetic resonance T1-weighted image of the posterior epidural disc fragment.

epidural space and removed by using the operating microscope. Then L3 – L4 discectomi was performed. Inspection of the dura showed no dural rent.

The patient's complaining recovered but his right leg weakness continued.

Pathologic examination revealed degenerated disc.

DISCUSSION

This is the third reported case of cauda equina syndrom due to lumber disc herniation with migration to the posterior aspect of the caudal sac (1,3). No posterior epidural disc fragments are described in any published case series of CES secondary to herniated lumbar disc (6,7,8,9,10,11). Lichtor in his case related the posterior migration partly to lumbar fusion (12). Our patient had no trauma or history of an operation related with the specific region. In the anatomy literature there is no consensus on preferred direction of disc fragment migration. Fries et al (13) observed a higher frequency of rostral migration (78 %) while caudal and bidirectional migration was less frequent (40 % and 17 % respectively) .The path of disc fragment migration is determined by the anatomy of the anterior epidural space (2). There is two other septum which is limited posterolateral migration of disc fragment one is sagittal midline septum described by Schellinger (2) the other is the peridural or lateral membrane described by Fick (14) in 1904. But there has been very little new knowledge published about the epidural anatomy and it's variations or irregularities.

MRI (Magnetic Resonance Imaging) has become the modality of choice for the evaluation of disc disease. MRI is also recommended in the evaluation of acute cauda equina compression (15). The differential diagnosis of lumbar disc extrusion and sequestration has been well described but because of it's rare localization, disc fragment migrated to the posterior epidural space should not be considered firstly. The differential diagnosis includes abscess , hematoma and epidural neoplasms such as metastasis , chordoma, lipoma or lymphoma. In our case the lesion was slightly hiperintense on T1 – weighted images and showed rim enhancement after administration of gadolinium. The use of gadolinium can show peripheral enhancement will extend into the disc space itself. The area enhancement most likely represents vascular granulation tissue that occurs in response to tissue injury. Gadolinium is useful in exluding other possible etilogies of an extradural mass such as a neurofibroma, which would enhance uniformly thereby distinguishing it from the peripheral enhancement of this sequestered disc fragment. But because of its localization and, variable signal and enhancement characteristic of epidural neoplasms, in this case, the leading diagnosis before surgery was epidural neoplasm. In this case the precence of an acute CES was an indication of emergency surgical treatment. And MRI is helpful in planning surgical treatment and clearing the preoperative diognastic confusion.

REFERENCES

1. Eugene, A., Bonaroti MD, William C, and Welch MD: Posterior epidural migration of an extruded lumbar disc fragment Causing Cauda Equina syndrome. Spine 23: 378–381, 1998.
2. Schellinger, D., Manz, J.H., Vidic, B., Patronas, J.N., Deveikis, P.J., Muraki, S. A., Abdullah, C.D.: Disc fragment migration. Radiology 175: 831-836, 1990.
3. Sekerci, Z, Ildan F, Yüksel M, Gül B, Kılıç C: Cauda equina compression due to posterior epidural migration of extruded lumbar disc. Neurosurg Rev 15: 311- 313, 1992.
4. Ditunno JFJ, Young W, Donowan WH, Creasey G. American Spinal Injury Association. The international standards booklet for neurological and functional classification of spinal cord injury. Paraplegia 32: 70-80, 1994.
5. Rengachary SS. Examination of the motor and sensory systems and reflexes. In: Wilkins RH, Rengachary SS (eds). Neurosurgery. New York, NY: McGraw-Hill, 1996, pp 156
6. Choudhury, A.R., Taylor J.C.: Cauda equina syndrome in lumbar disease. Acta Orthop Scand 51: 493 – 499, 1980.

7. Dinnig, TAR. , Schaffer H.R.: Discogenic compression of the cauda equina: a surgical emergency. Aust N Z J Surg 63: 927 – 934,1993.
8. Jennet, W.B.: A study of 25 cases of compression of the cauda equina by prolapsed intervertebral discs. J Neurol Neurosurg Psychiatry 19: 109 – 116, 1956.
9. Kostuik, J.P., Harrington I., Alexander D., Rand W., and Ewans D.: Cauda Equina syndrome and lumbar disc herniation. J Bone Joint [Am] 68: 386 – 91, 1986.
10. Shaphiro, S.: Cauda equina Syndrome secondary to lumbar disc herniation Neurosurgery 22: 743 – 747, 1993.
11. Shephard, RH. : Diagnosis and prognosis of cauda equina syndrome produced by protrusion of lumbar disc. Br Med J. 2: 1434 – 1439, 1959.
12. Lichtor, T: Posterior epidural migration of extruded lumbar disc. Surg Neurol 32: 311 – 312, 1989.
13. Fries, J.W., Abodeely, D.A., Vijingco, J.G., Yaeger, V.L., Gaffey, W.R.: Computed tomography of herniated and extruded nucleus pulposus. J Comput Tomogr 6: 874 – 887, 1982.
14. Shapiro, R: The extradural space In: Shapiro, R. (ed): Myelography, Ed 3. Chicago: Year Book Medical 1976, pp 90 – 92.
15. Coscia, M., Leipzig, T., Cooper, D: Acute cauda equina compression. Spine 19: 475 – 478, 1994.

A CASE OF BEHÇET'S DISEASE WITH ANTICARDIOLIPIN ANTIBODY POSITIVITY AND CRYOGLOBULINEMIA

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SUMMARY

Behçet's disease is a multisystem inflammatory disorder. Genetic, viral and immunological disturbances are thought to play a role in the etiopathogenesis. Vascular involvement; which is frequently seen in Behçet's disease; can be seen as aneurysm, arterial and venous occlusions. Researchers have investigated anticardiolipin (ACA) antibody levels in individuals with Behçet's disease and generally it is agreed that ACA antibody positivity has no correlation with vascular involvement of Behçet's disease. We present a patient with Behçet's disease in whom anticardiolipin antibody positivity and cryoglobulinemia was noted. To our knowledge the association of these different entities has not been reported before.

Key words: *Behçet's disease, anticardiolipin antibody, cryoglobulinemia*

ÖZET

Antikardiyolipin Antikoru ve Kriyoglobulinemi İle Birliktelik Gösteren Behçet Hastalığı Olgusu

Behçet hastalığı; genetik, viral, ve immunolojik faktörlerin etyolojide rol oynadığı multisitemik bir hastalıktır. Behçet hastalığında sık karşılaşılan vasküler tutulum anevrizma, arterial ve venöz obstruksiyon şeklinde görülebilir. Antikardiyolipin antikoru (ACA) ve Behçet hastalığı arasındaki ilişkiyi aydınlatmak amacı ile yapılan çalışmalar sonucunda; ACA ve Behçet hastalığında vasküler tutulum arasında bağlantı olmadığı saptanmıştır. Burada antikardiolipin antikor pozitifliği ve kriyoglobulinemi tespit edilen bir Behçet hastası yayınlanmaya uygun bulunmuştur.

Anahtar kelimeler: *Behçet hastalığı, antikardiyolipin antikoru, kriyoglobulinemi*

Behçet's disease is a multisystem inflammatory disorder (1). Although multiple immunologic, infectious, genetic and toxic causes have been proposed, the etiology of the syndrome remains obscure (2). Recurrent vasculitis and vascular thrombosis are key features of Behçet's disease (3). Here we present a patient with Behçet's disease in whom anticardiolipin antibody positivity and cryoglobulinemia was noted. To our knowledge the association of these different entities has not been reported before.

CASE REPORT:

A 33 year old man with Behçet's disease presented with a 2 month history of leg ulcers on his lower legs and cyanosis of his fingers. He had oral aphtae, genital ulcer, papulopustuler eruption, erythema nodosum, thrombophlebitis for 5 years duration and bilateral uveitis for 2 years duration. Physical examination was insignificant. Dermatological examination revealed a minor aphtous ulceration on the lower lip measuring 0.5 x 0.5 cm in diameter and two genital ulcerations on the scrotum measuring 1 x 1 cm and 0.5

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Received: Feb 23, 2000 Accepted: Sept 28, 2000

x 0.5 cm in diameter. Ulcerative lesions around medial and lateral malleolus (Figure 1), acro-

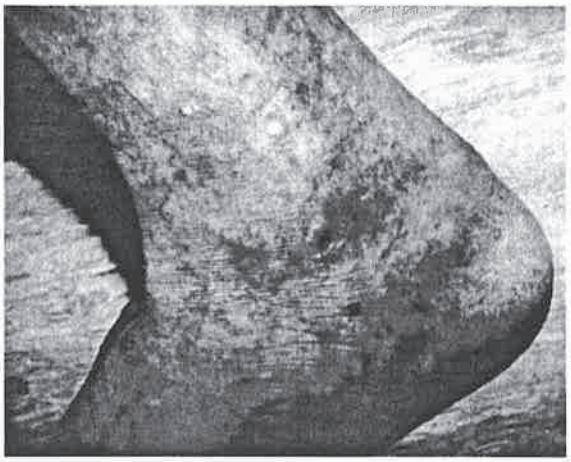

Figure 1: Ulcerative lesion around medial malleolus

cyanosis with ulcer around nail bed (Figure 2) on his legs. There were multiple erythematous tender nodules and livedo reticularis were noted on extensor parts of his legs.

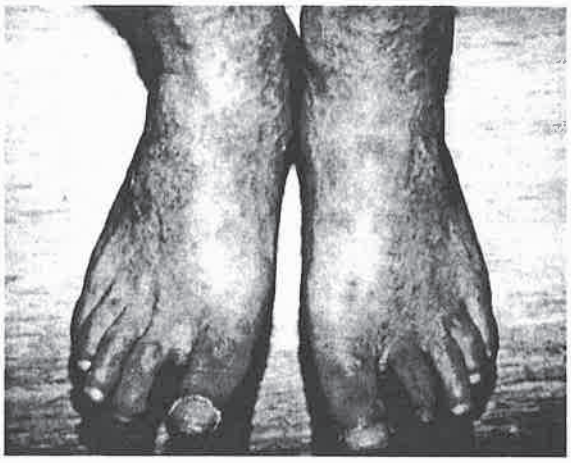

Figure 2: Acrocyanosis with ulcer around nail bed

Laboratory examination revealed normal complete blood count, urine analysis and blood chemistry. Sedimentation rate was 60 mm/hr. ANA was negative, Anti dsDNA was 3.2/ml. Immunological parameters IgG:22.9 g/L, IgA:4 g/L, IgM:2.8 g/L and C3:1.7 g/L, C4:0.29 g/L VDRL, RPR, hepatitis B and hepatitis C antigens were negative. Anticardiolipin antibody IgM, IgG levels were 17 U/ml and 3 U/ml (0-12 U/ml) respectively. Cryoglobulin was positive. Protein C, protein S and antithrombin 3 levels were within normal limits.

Histopathological examination of a biopsy specimen taken from the margin of a leg ulcer showed enlargement of small and medium sized vessels in dermis, fibrin deposits, neutrophil and leucocyte infiltrates, neutrophilic nuclear dust formation around vessels (Figure3). In addition to

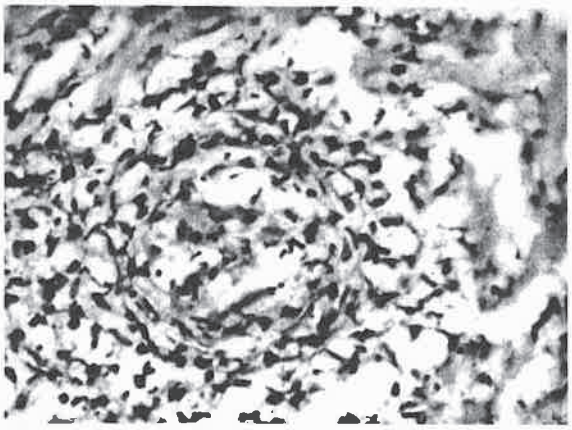

Figure 3: Wall of small dermal vessel is infiltrated by neutrophils and leucocytes

1.5 mg/day colchicium therapy; 60 mg/day prednisolone was initiated. Venous dopler ultrasonography of lower extremities revealed chronic thrombosis in right popliteal and tibialis posterior veins, subacute thrombosis in left vein and thrombosis causing partial obstruction in both femoral veins. The patient was diagnosed as having deep vein thromboses and fraxiparine 0.6cc x 2/ day was initiated. Pentoxyphilline 1200 mg/day and nifediphine 30 mg/day were begun for the treatment of Raynaud's phenomenon.

DISCUSSION:

Behçet's disease is a multisystemic, inflammatory disorder with mucocutaneous, articular, intestinal, urogenital, vascular and neurological involvement (1).

The histopathological findings of the skin lesions revealed a perivascular predominantly round cell infiltrate. The lesions were described

as leucocytoclastic vasculitis; but after many researches there were no signs of vasculitis as described by some authors (4).

Jorizzo et al. found that histopathological assesment of early cutaneous lesions from patients with Behçet's disease reveals findings consistent with either leucocytoclastic vasculitis or Sweet's like vasculitis (5,6).

In 1990 Su et al. studied histopathological changes of erythema nodosum in 30 patients with Behçet's disease. They concluded that no leucocytoclastic vasculitis was seen in their patients. In % 40 of the patients lymphocytic vasculitis was observed (7).

These various research studies indicated that there are contradictory results about the etiology of mucocutaneous lesions seen in Behçet's disease.

The vasculopathy of Behçet's disease is distinctive due to involvement of both arteries and veins of all sizes. It can be seen as aneurysm, arterial and venous occlusions (1,6).

In patients with elevated anticardiolipin antibody levels vascular thrombosis are frequently seen. Because of this there are many studies done to determine the serum levels of ACA and to assess their frequency and clinical relevance in patients with Behçet's disease (2,3). Generally it is agreed that ACA levels are not elevated in Behçet's patients with vascular involvement (2,8,9).

Cryoglobulins are a group of proteins that have the unusual property of reversibly precipitating in cold (10,11). Single-component cryoglobulins may be associated with myeloma, macroglobulinemia and lymphoma; mixed cryoglobulins may be associated with infections, autoimmune diseases, lymphoproliferative diseases (12). The most common cutaneous manifestations of cryoglobulinemia is recurrent purpura, Raynaud's phenomenon, livedo reticularis and distal ulcerations (11). Histologically lesions appear as leucocytoclastic vasculitis in % 50 of cases (10).

In our case recurrent purpura, Raynaud's phenomenon, digital ulcers were present and the skin biopsy revealed leucocytoclastic vasculitis. These findings were consistent with cryoglobulinemia.

Our patient has anticardiolipin antibody positivity, cryoglobulinemia in addition to Behçet's disease. We decided to present this case because to our knowledge the association of these different entities has not been reported before.

REFERENCES

1. Golden BD, Goel A, Mitnick HJ. Behçet-type vasculopathy in a patient without the diagnostic features of Behçet's disease. Arthritis Rheum 1996; 39: 1926-1930.
2. Özdemir Y, Önder F, Yarangümeli A, Küçükkuyumcu C, Kural G. Anticardiolipin antibodies and retinal vascular complications in Behçet's disease. Ophtalmic Surg Laser 1997; 28(8): 653-655.
3. Zouboulis CC, Buttner P, Tebbe B, Orfanos CE, Anticardiolipin antibodies in Adamantiades-Behçet's disease. Br J Dermatol 1993; 128: 281-284.
4. Haim S. The pathogenesis of lesions in Behçet's disease. Dermatologica 1979; 158: 31-37.
5. Jorizzo JL, Solomon AR, Cavallo T. Behçet's syndrome. Arch Pathol Lab Med 1985; 109: 747-751.
6. Scarlett JA, Kistner ML, Yang LC. Behçet's Syndrome. Am J Med 1979; 66: 146-48.
7. Jorizzo JL, Solomon AR, Zanolli MD, Leshin B. Neutrophilic vascular reactions. J Am Acad Dermatol 1988; 19(6): 983-995.
8. Su DWP, Chun S, Lee S, Rogers RS. Histopathological spectrum of erythema nodosum lesions in Behçet's disease. In: O'Duffy JD, Kökmen E ed. Behçet's disease basic and clinical aspects, New York, Marcel Dekker Inc, 1991; 229-240.
9. El-Ramahi KM, Al-Dalaan A, Al-Balaa S, Sheth K, Al-

Kawi MZ, Bohlega S. Antiphospholipid antibodies in Behçet's disease. In: Wechseler B, Godeau P ed. Behçet's disease. Amsterdam, Elsevier Science Publishers 1993; 109-113.

10. Aydıntuğ AO, Tokgöz G, D'Cruz DP, Gürler A, Cervera R, Düzgün N et al. Antibodies to endothelial cells in patients with Behçet's Disease. Clin Immunol Immunopathol 1993; 67: 157-162.
11. Davis MDP, Su D. Cryoglobulinemia: Recent findings in cutaneous and extracutaneous manifestations. Int J Dermatol 1996; 35(4): 240-248.
12. Denman AM. Cryoglobulins and immunopathological manifestations of autoimmune diseases. Clin Exp Immunol 1992; 87: 169-171.
13. Dowd PM. Reactions to cold. In: Champion RH, Burton JL, Burns DA, Breathnach SM ed. Textbook of Dermatology USA, Blackwell Science Ltd. 1998; 971.

EIGHTY TWO-YEAR-OLD MALE WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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SUMMARY

Systemic Lupus Erythematosus (SLE) predominantly affects young women in their twenties. In the elderly, the onset of the disease may be more insidious, and the time interval between onset and diagnosis of the disease may be longer than in younger patients. We present here an 82-year-old male patient diagnosed with SLE.

Key words: *lupus, elderly*

ÖZET

82 Yaşında SLE

Sistemik Lupus Eritematozis (SLE) çoğunlukla 20'li yaşlarda genç kadınlarda görülür. Yaşlılarda hastalığın seyri daha sinsidir ve şikayetlerin başlangıcı ile tanı koyulana kadar geçen süre gençlere göre daha uzun olabilir. Seksen iki yaşında, SLE tanısı koyulan, erkek hastayı takdim ediyoruz.

Anahtar kelimeler: *lupus, yaşlı hasta*

SLE is an autoimmune disease in which tissues and cells are damaged by cellular cytotoxicity and immune complexes. Ninety percent of SLE cases are women, usually of childbearing age. However, children, men and the elderly can also be affected. Prevalence rate of the disease for the United States ranges between 15-50/100,000 (1).

The prevalence of inflammatory disorders of connective tissue in the older age group is quite likely underestimated. The disease may also have a different clinical and serologic course in the elderly than in younger patients (2,3). Age distribution of SLE incidents differ significantly by race, with a younger mean age in black females (35.5 years) compared with caucasian females (41.7 years), and a corresponding earlier peak incidence rate in the 25-34 year age group and the 35-50 year age group, respectively. (4,5). In studies of SLE patients, it was found that onset of the disease was insidious and diagnosis delayed in elderly patients when compared with younger age groups.

CASE REPORT

In September 1998, an 82-year-old male patient who had been undergoing treatment for hypertension for the past four years developed pretibial swelling and, a few weeks later, arthralgias in both knees. At that time he was examined by an orthopedist and told that his symptoms were related to the aging process. A few months later he was admitted to the Department of Infectious Diseases with complaints of severe fatigue, polyarthralgia, an intermittent, prolonged fever, weight loss and exertional dyspnea. Pneumonia was diagnosed, and he was treated with intravenous seftriaxon for two weeks. However, his symptoms did not improve, and his shortness of breath increased. As a result, the family requested a cardiac examination, and the patient was admitted to Ankara University Heart Center Hospital.

In terms of medical history, the patient had been diagnosed with hypertension four years earlier and was being treated with doxasozine (4

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Received: Nov 30, 1999 Accepted: Aug 18, 2000

mg/day). He had smoked one packet of cigarettes a day for 60 years, and he had had no signs of any connective tissue disorder. A physical examination at the heart center revealed a pale physical appearance; blood pressure of 160/80 mmHg; pulse of 80/min and rhythmic; an apical systolic murmur of grade 2/6, which radiated to the axilla and S3; and Grade 2 bilateral pretibial edema. A respiratory examination revealed no respiratory sounds at the base of the right lung. His functional status was assessed as Class 3-4 (New York Heart Association Classification). Laboratory examinations revealed normochrome normocytic anemia with a hemoglobin of 8.3, 8.7 and 9.0 gr/dl, and serial follow-up analysis sometimes showed mild leukopenia at around 3,500/ml. Erythrocyte sedimentation rate (ESR) was 86 mm/hr. He had a urea level of 74 mg/dl, creatine level of 1.4 mg/dl. Urine analysis revealed erythrocyte casts, microscopic hematuria and daily proteinuria of 0.9 gr/day. His serum albumin level was 2.9 gr/dl, and tumor markers were negative, except for a mildly increased CEA. Direct Coomb's test was positive, and the rest of his biochemical parameters were normal. A chest X-ray showed cardiomegaly and pleural effusion in the right hemithorax. An echocardiograph showed a dilated left ventricle with wall motion abnormalities, 2nd degree mitral regurgitation, 1st degree aortic regurgitation and an ejection fraction of 35-40%.

As a result of this clinical presentation, we concentrated mainly on the possibility of heart failure or malignancy and initiated treatment for heart failure. In further thorax CT analysis the patient was noted to have multiple enlarged lymph nodes (the largest one reaching 1.5 cm diameter) and a dilated heart. We examined pleural effusion and found Class 2 cytology and exudative nature. Abdominal ultrasonography was normal. Prior to his admittance to the Heart Center, the patient had had a bone marrow aspiration and biopsy, both of which were normal.

The patient did not respond to heart failure treatment. Immunological markers revealed: polyclonal gammapathy in serum protein electrophoresis (gamma fraction of 29.8%); CRP of 260 mg/lt (normal range: 0-5); romatoid factor-negative; ANA ++++; Anti ds DNA of 14.1 IU/lt (normal range: 0-7). Clinical and laboratory data were presented to the Department of Immunology, and SLE was diagnosed (Table 1) (6).

Table 1: Summary of Criteria for Classification of SLE (6)

1- Malar rash
2- Discoid rash
3- Photosensitivity
4- Oral ulcers
5- Arthritis
6- Serositis
7- Renal disorder
8- Neurological disorder
9- Hematological disorder
10- Immunological disorder (Anti-ds DNA antibody positivity and others)
11- Antinuclear antibody (ANA)

(Patients with four of the 11 criteria are said to have SLE)

Our patient had six of the above lupus criteria: arthritis, serositis (pleural effusion), renal disorder (erythrocyte casts, microscopic hematuria, proteinuria), hematological disorder (mild leukopenia, anemia), ANA positivity (++++), high levels of anti ds-DNA antibody. Although the presence of serositis may be doubtful in that pleural effusion may be related to heart failure (the patient had cardiomegaly and left ventricular dysfunction), the clinical course and the patient's response to steroid therapy (not to positive inotropes and diuretics) led us to believe that his pleural effusion was due to serositis. We initiated prednisolone 1 mg/kg, gradually tapering the dosage. After six weeks, the patient's fatigue, polyarthralgia, dyspnea and intermittent fever all improved, and his functional status improved from Grade 3-4 to Grade 1. His CRP levels and

ESR returned to normal, and his pleural effusion disappeared. Despite blood transfusions his anemia persisted, but we avoided initiating any therapy other than steroids due to his advanced age.

CONCLUSION

SLE is a disease that usually strikes women in their childbearing ages. However, it is possible to diagnose SLE in children, adolescents and the elderly and in the male sex. As an 82-year-old male, the likelihood of SLE in our patient was rare (1.6% incidents in his sex and age group) (7), and, as is usually reported to be the case, his diagnosis was delayed. Despite its rarity, it is prudent to keep in mind the possibility of SLE when diagnosing elderly patients showing elevated ESR levels and diverse symptomatology.

Table 2: Age and sex distribution of SLE patients (7)

Age of onset	No. Females	No. Males	Female/Male ratio
0-9	39	19	2.0:1
10-19	220	39	5.6:1
20-29	369	49	7.5:1
30-39	298	37	8.0:1
40-49	183	35	5.2:1
50-59	98	25	3.9:1
60 and over	58	25	2.3:1
Total	1,265	229	5.5:1

REFERENCES

1. Hahn BH. Systemic Lupus Erythematosus. In: Wilson JD, Braunwald E, Isselbacher KJ, Martin JB, Fauci AS, Kasper DL, Havcer SL eds. Harrison's Principle of Internal Medicine 14th ed. McGraw-Hill 1998: 1874-84.
2. Stevens MB. Connective tissue disease in the elderly. Clin Rheum Dis. 1986; 12: 11-32.
3. Mishra N, Kammer GM. Clinical expression of autoimmune diseases in older adults. Clin Geriatr Med 1998; 14: 515-42.
4. Font J, Pallares L, Cervera R et al. Systemic Lupus Erythematosus in the elderly: clinical and immunological characteristics. Ann Rheum Dis. 1991; 50: 702-05.
5. Gossat DM, Walls RS. Systemic Lupus Erythematosus in later life. Med J Aust. 1982; 1: 297-9.
6. Schur PH. Systemic Lupus Erythematosus. In: Bennett JC, Plum F eds. Cecil Textbook of Medicine. 20th ed. Philadelphia W.B. Saunders 1996: 1475-83
7. Masi AT, Kaslow RA. Sex effects in Systemic Lupus Erythematosus: A clue to pathogenesis. Arthritis Rheum. 1978, 21: 480.

GIANT OSTEOCHONDRAL LOOSE BODY OF THE KNEE JOINT

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SUMMARY

A rare giant loose body in the knee joint and its treatment were reported. Two loose bodies sized 5.5 and 1.5 centimeters were extracted from the knee of a patient who suffered from chronic pain and knee motion restriction. The histopathological evaluation revealed normal bone, hyaline cartilaginous tissue and partly fibrocartilaginous tissue. The appearance of these loose bodies suggested that they separated in small pieces from femoral condyles, were nourished from synovial fluid, and over time adhered to each other in the knee joint.

Key Words: *loose body, knee*

ÖZET

Diz Ekleminde Serbest Dev Osteokondrol Cisim

Diz ekleminde nadir rastlanan dev serbest eklem cismi ve tedavisi bildirildi. Kronik ağrı ve hareket kısıtlılığı şikayetleri olan hastanın dizinden 5,5 cm ve 1,5 cm boyutlarında olan 2 adet serbest eklem cismi çıkartıldı. Histopatolojik çalışma sonucunda normal kemik, hiyalin kıkırdak dokusu ve kısmi fibrokartilaj doku olduğu anlaşıldı. Bu serbest eklem cisimleri femur kondillerinden küçük parçalar şeklinde koptuktan sonra sinovyal sıvı içinde beslenerek ve zamanla kendi kendine birleşerek büyümüşlerdir.

Anahtar kelimeler: *Serbest eklem cismi, diz.*

A loose body in a joint can be attributed to various factors such as osteochondritis dissecans, osteochondral fracture, osteochondroma, synovial chondromatosis or fracture of osteophytes in osteoarthritis (1,2). Loose bodies most commonly appear in the knee joint and are well known in clinical practice (2,3,4).

The case we report here is unusual, as the loose body in the knee was quite large.

CASE REPORT

A 33-year-old amateur soccer player came to us for examination in April 1994. He had pain, swelling, locking and a palpable mass in the right knee. He had an injury to the knee after a fall 13 years ago, and he mentioned a painful swelling. He had been advised to have an operation, but had not agreed to one.

Apart from occasional pain, crepitus and swelling in the knee, he had had no serious trouble until the last two months. Recently, however, he had felt a mobile mass in his right knee.

On physical examination of the right knee, diffuse swelling (effusion), joint-movement restriction, especially flexion loss, mild instability and quadriceps atrophy were found. A lateral roentgenogram showed a fragmented ossified mass situated between the patella, anterior femur and tibia. On the antero-posterior roentgenogram, the larger mass was superimposed between the intercondylar notch and over the lateral tibial condyle, with partial overlap on the lateral femoral condyle. The smaller mass was situated supero-lateral to the patella. Degenerative changes and crater-shaped, articular bone defects were seen on the medial femoral condyle (fig. 1). Routine blood and urine examinations were within normal limits.

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Received:May 9, 2000 Accepted: Aug 15, 2000

Figure 1: Roentgenograms showed a large, fragmented, ossified mass situated between the patella, anterior femur and tibia and a smaller mass situated supero-lateral to the patella.

Diagnostic arthroscopy and removal of the loose body were recommended. During arthroscopic examination of the right knee, an osteochondral loose body of about 1.5x1.5x1 cm was observed in the suprapatellar space. It was mobile and had the typical appearance of a loose body. Another giant osteochondral mass was situated between the anterior cruciate ligament, fat pad and lateral femoral condyle. Its size was 5.5x5x4 cm, and although it was not fixed, it was too large to move about in the knee. The weight-bearing area of the medial femoral condyle had crater lesions and degenerative changes. There were also degenerated medial meniscal tears. Other intra-articular structures were normal arthroscopically. Meniscle tears and irregular chondral flaps on the medial femoral condyle were debrided, and crater lesions were abraded. A lateral parapatellar incision was required to remove the loose bodies.

Gross examination of the loose bodies after removal revealed that the smaller one was a typical ostechondral fragment. The larger one was lobulated and covered hyaline and partly with fibro-cartilaginous tissue (figure 2). These fragments were not strongly adhered to each other, and it was possible to separate them manually

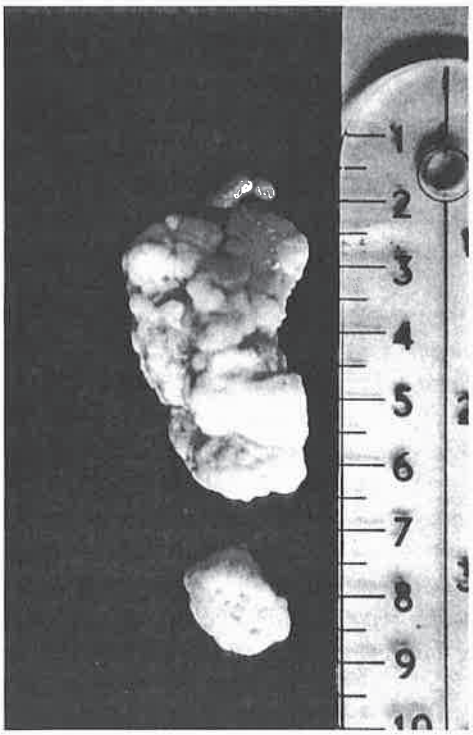

Figure 2: The larger mass, which measured 5.5x5x4 cm, was lobulated and covered hyaline and partly with fibrocartilaginous tissue.

Histological examination revealed normal bone and hyaline cartilaginous tissue and fibrocartilaginous tissue between the small particles. Cellular degenerative findings were discovered in some osseous areas (figure 3).

Figure 3: Histological examination revealed normal bone and hyaline carti-laginous tissue and fibrocartilaginous tissue between small particles. Cellular degenerative findings were found in some osseous areas (HE; x20).

At the sixth month of follow-up, the patient's range of knee motion was 20 degrees greater than at preoperative level, and his pain was lower than at preoperative level. Although range of motion was still good, with less pain four years after the operation, degenerative changes increased considerably.

DISCUSSION

It is possible to observe loose bodies in the knee joint, resulting from various factors. Most of them appear as osteochondritis dissecans, a localized injury or condition affecting the articular surface that causes separation of segments from cartilage and bone (1,2,3,4,5). Weight-bearing surfaces of the medial and lateral femoral condyles are frequently involved (1,3,4). Barrie (6) has pointed out that osteocytes do not survive after detachment but that chondrocytes do, as may the mesenchymal cells of the marrow. Fibrocartilaginous metaplasia of chondrocytes and growth of loose bodies nourished by synovial fluid have been well described for over 100 years (2,6).

Sarmiento and Elkins (7) reported a similar case in a knee joint with a history of an injury followed by swelling 13 years later and surgical removal after another seven years. Das and Mukherjee (8) reported another case similar to ours, in which their had been an injury 15 years earlier. Histologically, it is difficult to determine the origin of an osteochondral loose body. Sarmiento and Elkins were not sure whether the osteochondromatous mass was a chondroma or the result of an osteochondral fracture, but they pointed out that the mass fitted well into the tibial fracture site. Das and Mukherjee reported that a similar mass seemed to originate from the tibial ostechondral fracture.

Our patient had many osteochondral craters of various sizes and serious degeneration on the weight-bearing surface of the medial femoral condyle. The appearance of this giant loose body suggested that it originated from osteochondral fragments separated from the medial femoral condyle, and that these fragments were nourished by synovial fluid and adhered to each other with peripheral fibrocartilaginous tissue. The fact that the surface of the mass was lobulated and easily breakable into harder and smaller fragments supported this thesis.

REFERENCES

1. Schenck RC, Goodnight JM. Current concept review. Osteochondritis dissecans. J bone Joint Surg. 1996; 78(A): 439-56
2. Letson GD, D'Ambrosia RD. Osteochondritis Dissecans. Orthopedics 1987;10:1187-9
3. Aichroth P. Osteochondritis dissecans of the knee. A clinical survey. J Bone Joint Surg. 1971; 53(B): 440-7
4. McGinty JB. Arthroscopic removal of loose bodies. Northup Cline North Am 1982; 13: 313-28
5. Ewing JW, Voto SJ. Arthroscopic surgical management of osteochondritis dissecans of the knee. Arthroscopy 1988; 4: 37-40
6. Barrie HJ. Intra-articular loose bodies regarded as organ cultures *in vivo* . J Path. 1978; 125: 163-8
7. Sarmiento A, Elkins RW. Giant intra-articular ostechondroma of the knee. J Bone Joint Surg. 1975; 57(A): 560-1
8. Das AK, Mukherjee DR. Giant Osteochondral loose body of the knee joint. J Bone Joint Surg. 1978; 60(A):559-60