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Investigation of the Relationship Between Coronary Artery Disease and Mechanical Hemolysis

Koroner Arter Hastalığı ve Mekanik Hemoliz Arasındaki İlişkinin Araştırılması

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ABSTRACT

Background: In coronary artery disease (CAD), atherosclerotic plaques cause varying degrees of coronary stenosis. It is thought that these strictures will lead to hemolysis by causing turbulent flow other than ischemia. The aim of our study is to compare the frequency of mechanical hemolysis and the relationship between CAD intensity and the degree of hemolysis in patients diagnosed with CAD by coronary angiography.

Materials and Methods: Ninety-four consecutive patients who were admitted to cardiology outpatient clinics or emergency department and had coronary angiography were included in the study. Fifty-two patients with significant coronary artery stenosis (>70%) (patient group) and 42 patients without significant stenosis (control group) were compared in terms of demographic, clinical, laboratory and hemolysis parameters, including haptoglobin and schistocyte count.

Results: The patient group was significantly older (62.08±9.33 vs. 56.74±10.36, p=0.010) and had a higher percentage of males (78.8% vs. 50.0%, p=0.005). Use of beta blockers and angiotensin converting enzyme inhibitors were also higher in patient group. When compared by haptoglobin and schistocyte presence there were no difference between groups. On further analysis lower age [odds ratio (OR): 0.930, confidence interval (CI): 95%, p=0.027] in total study group and higher triglyceride levels (OR: 1.022, CI: 95%, p=0.009) in acute coronary syndrome subgroup were associated with schistocyte presence.

Conclusion: Hemolysis parameters were found to be the same in patients with significant CAD when compared to the control group. In addition, especially higher triglyceride levels might be associated with subclinical mechanical hemolysis in acute coronary syndrome patients. Furthermore, the relation of schistocyte presence and higher triglyceride levels in ACS patients could be an indicator of a possible inflammatory state.

Keywords: Coronary artery disease, atherosclerosis, hemolysis, triglyceride, schistocyte, haptoglobin

ÖZ

Amaç: Koroner arter hastalığında (KAH), aterosklerotik plaklar değişen derecelerde koroner darlığa neden olur. Bu darlıkların iskemi dışında türbülanslı akıma neden olarak hemolize yol açacağı düşünülmektedir. Çalışmamızın amacı, koroner anjiyografi ile KAH tanısı konulan hastalarda mekanik hemoliz sıklığını ve KAH şiddeti ile hemoliz derecesi arasındaki ilişkiyi karşılaştırmaktır.

Gereç ve Yöntemler: Kardiyoloji polikliniklerine veya acil servise başvuran ve koroner anjiyografi yapılan ardışık 94 hasta çalışmaya dahil edildi. Önemli koroner arter stenozu (>%70) olan 52 hasta (hasta grubu) ve belirgin darlığı olmayan 42 hasta (kontrol grubu) demografik, klinik, laboratuvar ve haptoglobin ve şistosit sayısı dahil hemoliz parametreleri açısından karşılaştırıldı.

Bulgular: Hasta grubu anlamlı olarak daha yaşlıydı (62,08±9,33'e karşı 56,74±10,36, p=0,010) ve erkek yüzdesi daha yüksekti (%78,8'e karşı %50,0, p=0,005). Beta bloker ve anjiyotensin dönüştürücü enzim inhibitörlerinin kullanımı da hasta grubunda daha yüksekti. Haptoglobin ve şistosit varlığı açısından karşılaştırıldığında gruplar arasında fark yoktu. İleri analizde toplam çalışma grubunda daha düşük yaş [olasılık oranı (OO): 0,930, güven aralığı (GA): %95, p=0,027) ve akut koroner sendrom alt grubunda daha yüksek trigliserit düzeyleri (OO: 1,022, GA: %95, p=0,009) şistosit varlığı ile ilişkili bulundu.

Sonuç: Önemli KAH olan hastalarda hemoliz parametreleri kontrol grubu ile karşılaştırıldığında aynı bulundu. Ayrıca akut koroner sendromlu hastalarda özellikle yüksek trigliserit seviyeleri subklinik mekanik hemoliz ile ilişkili olabilir. Öte yandan akut koroner

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ÖZ

sendrom hastalarında yüksek trigliserit düzeyleri ile şistosit varlığı arasındaki ilişki literatürle uyumlu biçimde enflamatuvar bir durumun habercisi olabilir.

Anahtar Kelimeler: Koroner arter hastalığı, ateroskleroz, hemoliz, trigliserit, şistosit, haptoglobin

Introduction

Coronary artery disease (CAD) is an atherosclerotic disease of inflammatory character that may present with stable, unstable angina or sudden cardiac death (1). It is one of the leading causes of morbidity and mortality worldwide. In the TEKHARF 2010 adult patient follow-up study, the coronary mortality rate was measured as 7.4 per 1.000 in men and 4.1 in women in the general population (2). It is stated that 6 million people in the American society died in 2005 due to causes related to CAD (3). There are several studies on the detection of significant (>50%) stenosis in CAD by acoustic systems. These studies are based on the measurement of the waves created by the post-stenotic turbulent coronary blood flow (4,5).

There are many immunological, infectious, genetic or iatrogenic causes of intravascular hemolytic anemia. In the case of hemolytic anemia, the blood parameters taken into consideration include complete blood count, reticulocyte count, direct and indirect Coombs test, serum lactate dehydrogenase, serum haptoglobin, peripheral blood smear, and bone marrow aspiration and biopsy if necessary (6). Intra-aortic balloon pump implantation (7), cardiopulmonary bypass (8). and mechanical prosthetic heart valves were stated among the causes of mechanical hemolysis. On the other hand, no significant mechanical hemolysis was observed in studies on coronary stents except ticlopidine induced thrombotic thrombocytopenic purpura (9,10,11,12).

In our literature search, no study was found on parameters related to hemolysis in the presence of CAD. We think that CAD may cause significant hemolysis in the presence of turbulent flows in the presence of a significant stenosis. The aim of our study is to compare the angiography data and the degree of stenosis with hemolysis parameters in patients with significant stenosis and to reveal the relationship between them.

Material and Methods

The study protocol received institutional review board approval and all participants provided informed consent in the format required by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Ethics Committee (approval number: 60, date: 11.03.2021).

After obtaining the necessary ethics committee approval, a total of 94 patients who had presented to outpatient cardiology polyclinic with proven ischemia through exercise testing/myocardial perfusion scintigraphy or emergency department with acute coronary syndrome (ACS) were included in the study. Informed consent forms were obtained from all patients. After questioning the patients in terms of age, gender, smoking, diabetes, hypertension, hyperlipidemia, and comorbidities, blood samples which were taken for complete blood count (hemogram), serum haptoglobin, peripheral blood smear for schistocyte count were sent to biochemistry and hematology laboratories. After the coronary angiography of the hospitalized patients, these images were evaluated and the degree of stenoses was recorded. The patients were divided into 2 groups according to whether or not they have significant CAD (at least 1 vessel with ≥70% stenosis). Peripheral blood films were examined from blood drawn on the day of admission for the presence of fragmented red blood cells (schistocytes). The average of five 100X (high power) fields was scored on a 0 to 4 scale as follows: 0 for <1% schistocytes, 1+ for 1-2% schistocytes, 2+ for 2-5% schistocytes, 3+ for 5-10% schistocytes, and 4+ for >10% schistocytes. Inclusion criteria for study participants were being between 18-65 years of age and have the necessary decision-making skills and exclusion criteria were that the patient had a history of hemolytic anemia, had a prosthetic heart valve or coronary stent, had an active bleeding lesion, chronic kidney failure, recent transfusion, active infection, genetic blood diseases and previously detected CAD via angiography. The patient and control groups were compared in terms of demographic and laboratory parameters, haptoglobin and schistocyte presence.

Statistical Analysis

Statistical analysis was performed using SPSS 22 for the Windows Evaluation Version statistical package. The normality distribution was evaluated using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation and median (25-75 percentiles). Categorical variables were summarized as frequencies. Differences between the two groups according to continuous variables were determined by the independent samples t-test or Mann-Whitney U test. Categorical variables were

compared by, chi-square or Fisher's Exact test. After the finding the potential determinants of hemolysis, univariate and multivariate regression analyses were performed to find out which determinants were independently related. A p level of <0.05 was accepted as statistically significant with 95% confidence interval and 5% margin of error.

Results

The patient group (n=52) was significantly older than the control group (n=42) (62.08±9.33 vs. 56.74±10.36, p=0.010) and had more males (78.8% vs. 50.0%, p=0.005). The patient group also had more smokers (9.6% vs. 0%, p=0.039), more beta blocker and angiotensin converting enzyme inhibitor usage and less angiotensin receptor blocker. The demographic and clinical information is shown in Table 1.

In terms of laboratory parameters, the patient group had higher blood urea nitrogen (37.50 vs. 33.50, p=0.015) and creatinine levels (0.90 vs. 0.80, p=0.022). The patient group's C-reactive protein levels were also higher (7.75 vs. 3.25, p=0.001) and HDL levels were lower (38.55±8.83 vs. 43.90±36.00, p=0.018). There was no significant difference between groups in terms of haptoglobin or schistocyte count. Laboratory parameters are shown in Table 1.

Table 1. Demographic, clinical information and laboratory parameters

Variables	Significant stenosis+ (>%70) n=52	Significant stenosis- (<%70) n=42	p
Age, years	62.08±9.33	56.74±10.36	**0.010**
Female sex, n (%)	Female: 11 (21.2%)	Female: 21 (50.0%)	**0.005**
Current smoking, n (%)	5 (9.6%)	0 (0%)	**0.039**
Hypertension, n (%)	36 (69.2%)	29 (69.0%)	0.985
Diabetes mellitus, n (%)	14 (26.9%)	11 (26.2%)	0.936
Cerebrovascular disease, n (%)	2 (3.8%)	1 (2.4%)	0.688
COPD, n (%)	10 (19.2%)	9 (21.4%)	0.792
Beta blocker usage, n (%)	52 (100%)	37 (88.1%)	**0.011**
ACE inhibitor usage, n (%)	33 (63.5%)	16 (38.1%)	**0.014**
ARB usage, n (%)	4 (7.7%)	10 (23.8%)	**0.029**
Diagnosis	CCS: 19 (36.5%) USAP: 2 (3.8%) NSTEMI: 26 (50.0%) STEMI: 5 (9.6%)	CCS: 35 (83.3%) USAP: 3 (7.1%) NSTEMI: 3 (7.1%) STEMI: 0 (0%)	N/A
Hemoglobin, (g/dL)	13.17±1.82	13.05±1.68	0.746
WBC, (count/mm^3)	7.850 (6.525-9.800)	7.550 (6.650-9.325)	0.510
Platelet, (count/mm^3)	232,789±65.72	232,534±61.73	0.475
BUN, (mg/dL)	37.50 (28.25-52.00)	33.50 (25.00-37.50)	**0.015**
Creatinine, (mg/dL)	0.90 (0.70-1.00)	0.80 (0.60-0.90)	**0.022**
Na, (mEq/L)	139.00 (137.00-140.75)	139.00 (137.00-141.00)	0.291
K, (mEq/L)	4.20 (3.90-4.40)	4.30 (3.90-4.50)	0.488
Total cholesterol, (mg/dL)	178.76±38.55	179.28±36.92	0.950
LDL, (mg/dL)	108.20±33.95	104.48±82.50	0.590
HDL, (mg/dL)	38.55±8.83	43.90±36.00	**0.018**
Triglyceride, (mg/dL)	151.00 (142.00-207.00)	126.50 (92.25-200.00)	0.110
CRP, (mg/dL)	7.75 (3.30-19.25)	3.25 (0.88-6.50)	**0.001**

*P<0.05 statistically significant. Continuous variables are reported mean ± standard deviation or median (interquartile range). Categorical variables are reported n (%). Differences between groups are calculated by chi-square test for categorical variables, independent variables student t-test and Mann-Whitney U test for continuous variables.
COPD: Chronic obstructive pulmonary disease, ACE: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, CCS: Chronic coronary syndrome, USAP: Unstable angina pectoris, NSTEMI: Non-ST elevation myocardial infarction, STEMI: ST elevation myocardial infarction, WBC: White blood cell, BUN: Blood urea nitrogen, Na: Sodium, K: Potassium, LDL: Low density lipoprotein, HDL: High-density lipoprotein, CRP: C-reactive protein, significant results are marked bold

After angiographic evaluation and PCI/CABG decision if necessary, SYNTAX scores and the level of maximum stenoses were calculated. The patient group had a median SYNTAX score of 13.75 (7.00-21.38) and median maximum stenosis of 95.00% (90.00-100.00), on the other hand the control group had a median SYNTAX score of 0.00% (0.00-0.00) and median maximum stenosis of 10.00% (0.00-30.00).

On further analysis, the total population was evaluated whether there are other potential factors affecting schistocyte presence. After statistical analyses, lower age (54.39±6.54 vs. 60.95±10.42, p=0.012) was associated with schistocyte presence and higher triglyceride levels also showed a tendency to be significantly associated with schistocyte presence (234.00 vs. 139.00, p=0.011). The factor analyses regarding total population are given in Table 2. When multiple logistic regression analysis was performed, lower age was found to be independently associated with schistocyte presence [odds ratio (OR): 0.930, confidence interval (CI): 95%, p=0.027]. Regression analysis of the complete study group is given in Table 3.

When only ACS patients were analyzed, schistocyte + group (n=7) was showing a tendency to be younger (55.14±5.05 vs. 63.03±10.63, p=0.065) and had significantly higher triglyceride levels (188.00 vs. 132.00, p=0.024). The factors associated with schistocyte presence in ACS patients were shown in Table 4. Univariate and multivariate regression analyses established triglyceride level as an independent predictor of schistocyte presence (OR: 1.022, CI: 95%, p=0.009). Regression analysis is given in Table 5.

Table 2. Factors affecting schistocyte presence-complete study group

Variables	Schistocyte+ (n=18)	Schistocyte- (n=76)	p
Age (years)	54.39±6.54	60.94±10.42	**0.013**
Female sex, n (%)	7 (38.9%)	26 (34.2%)	0.803
Current smoking, n (%)	0 (0.0%)	5 (17%)	0.263
Hypertension, n (%)	11 (61.1%)	54 (71.1%)	0.412
Diabetes mellitus, n (%)	3 (16.7%)	22 (28.9%)	0.289
Cerebrovascular disease, n (%)	1 (5.6%)	2 (2.6%)	0.526
COPD, n (%)	2 (11.1%)	17 (22.4%)	0.285
Beta blocker usage, n (%)	17 (94.4%)	72 (94.7%)	0.960
ACE inhibitor usage, n (%)	7 (38.9%)	42 (55.3%)	0.211
ARB usage, n (%)	4 (22.2%)	10 (13.2%)	0.331
Hemoglobin, (g/dL)	13.38±1.37	13.06±1.83	0.428
WBC, count/mm^3	8.100 (6.850-9.900)	7.750 (6.525-9.550)	0.634
Platelet, count/mm^3	203,000 (174,750-271,500)	235,000 (196,500-264,250)	0.337
BUN, mg/dL	36.50 (29.50-46.25)	35.00 (28.00-43.00)	0.690
Creatinine, mg/dL	0.80 (0.68-1.00)	0.80 (0.70-0.96)	0.782
Na, (mEq/L)	138.50 (136.75-140.00)	139.00 (137.00-141.00)	0.299
K, (mEq/L)	4.30 (3.98-4.43)	4.20 (3.90-4.50)	0.696
Triglyceride (mg/dL)	234.50 (133.50-281.25)	139.00 (97.00-197.00)	**0.011**
Total cholesterol (mg/dL)	193.50±35.28	175.89±38.31	0.094
LDL cholesterol (mg/dL)	113.75±29.21	105.03±33.06	0.332
HDL cholesterol (mg/dL)	41.81±14.40	40.71±9.95	0.712
CRP, (mg/dL)	5.90 (2.00-9.00)	5.00 (1.60-15.00)	0.509
Haptoglobin (mg/dL)	2.40 (1.30-142.00)	2.30 (1.35-143.00)	0.814
SYNTAX score	0.00 (0.00-12.25)	7.00 (0.00-16.00)	0.224

*P<0.05 statistically significant. Continuous variables are reported mean ± standard deviation or median (interquartile range). Differences between groups are calculated by independent variables student t-test and Mann-Whitney U test for continuous variables.
COPD: Chronic obstructive pulmonary disease, ACE: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, WBC: White blood cell, BUN: Blood urea nitrogen, Na: Sodium, K: Potassium, LDL: Low density lipoprotein, HDL: High-density lipoprotein, CRP: C-reactive protein, SYNTAX: Synergy between percutaneous coronary intervention with taxus and cardiac surgery, significant results are marked bold

Table 3. Regression analysis of the potential indicating factors on the presence of schistocytes in total study group

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.932 (0.879-0.987)	**0.016**	0.930(0.873-0.992)	0.027
Triglyceride	1.006 (1.000-1.013)	**0.038**	1.006(0.999-1.012)	0.080

OR: Odds ratio, CI: Confidence interval, significant results are marked bold

Table 4. Factors affecting schistocyte presence in patients with acute coronary syndrome

Variables	Schistocyte+ (n=7)	Schistocyte- (n=32)	p
Age (years)	55.14±5.05	63.03±10.63	0.065
Female sex, n (%)	1 (14.3%)	5 (15.6%)	0.929
Current smoking, n (%)	0 (0.0%)	3 (9.4%)	0.399
Hypertension, n (%)	6 (85.7%)	21 (65.6%)	0.297
Diabetes mellitus, n (%)	1 (14.3%)	7 (21.9%)	0.657
Cerebrovascular disease, n (%)	1 (14.3%)	1 (3.1%)	0.225
COPD, n (%)	0 (0%)	5 (15.6%)	0.263
Beta blocker usage, n (%)	7 (100%)	32 (100%)	N/A
ACE inhibitor usage, n (%)	5 (71.4%)	18 (56.3%)	0.460
ARB usage, n (%)	1 (14.3%)	4 (12.5%)	0.898
Hemoglobin, (g/dL)	13.39±0.97	13.35±1.72	0.962
WBC, count/mm^3	9.800 (8.700-9.900)	7.850 (6.250-9.975)	0.151
Platelet, count/mm^3	175,000 (168,000-260,000)	236,500 (194,250-256,000)	0.186
BUN, mg/dL	39.00 (34.00-49.00)	36.50 (26.50-43.50)	0.761
Creatinine, mg/dL	0.90 (0.70-1.20)	0.90 (0.73-0.98)	0.654
Na, (mEq/L)	137.00 (134.00-139.00)	139.00 (137.25-140.75)	0.089
K, (mEq/L)	4.30 (4.00-4.40)	4.20 (3.83-4.40)	0.707
Triglyceride (mg/dL)	250.00 (193.00-290.00)	132.00 (64.95-181.00)	**0.001**
Total cholesterol (mg/dL)	193.43±43.42	171.00±37.99	0.177
LDL cholesterol (mg/dL)	117.71±33.89	105.97±32.30	0.394
HDL cholesterol (mg/dL)	37.43±8.34	38.84±8.43	0.691
CRP, (mg/dL)	7.40 (3.50-11.00)	11.00 (4.30-39.25)	0.458
Haptoglobin (mg/dL)	2.35 (1.25-52.98)	2.40 (1.59-172.50)	0.717
SYNTAX score	13.00 (6.25-21.38)	12.00 (7.00-27.50)	0.929

*P<0.05 statistically significant. Continuous variables are reported mean ± standard deviation or median (interquartile range). Differences between groups are calculated by independent variables student t-test and Mann-Whitney U test for continuous variables.
COPD: Chronic obstructive pulmonary disease, ACE: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, WBC: White blood cell, BUN: Blood urea nitrogen, Na: Sodium, K: Potassium, LDL: Low density lipoprotein, HDL: High-density lipoprotein, CRP: C-reactive protein, SYNTAX: Synergy between percutaneous coronary intervention with taxus and cardiac surgery, significant results are marked bold.

Table 5. Regression analysis of the potential factors on the presence of schistocytes in acute coronary syndrome patients

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.918 (0.834-1.010)	0.078	-	-
Sodium	0.728 (0.525-1.011)	**0.050**	0.736 (0.508-1.067)	0.105
Triglyceride	1.022 (1.006-1.037)	**0.006**	1.022 (1.005-1.039)	**0.009**

OR: Odds ratio, CI: Confidence interval, significant results are marked bold

Discussion

We found that clinically significant coronary stenosis was not associated with significant mechanical erythrocyte breakdown. This finding persisted when the population was divided and compared according to the diagnosis, cigarette smoking, comorbidities and SYNTAX scores. On the other hand, we found that lower age and higher triglyceride levels were associated with schistocyte presence in the total population and ACS population, respectively.

The effect of lower age on the presence of mechanical hemolysis may be explained by a relatively higher physical activity resulting in muscular compression of erythrocytes. Demirci and Gün (13) suggested that younger individuals that have regular exercise might have a higher rate of mechanical hemolysis because of the breakdown of erythrocytes when they cross minor capillaries with a high speed, the compression resulting from muscle contraction (14) and also in foot soles while walking (15). It is also reported that despite hemolysis is frequent in young, erythropoiesis from bone marrow is more effective than older individuals, protecting these patients from hemolytic anemia. In our study, we also found out that even though hemolysis was more frequent in younger patients, hemoglobin levels were not significantly different, which is explanatory to this phenomenon.

Another finding of this study was the association of higher triglyceride with schistocyte presence in ACS patients. When a literature search is made, one of the rare studies that has a similar finding of high triglyceride in hemolysis was made by Koseoglu et al. (16). The mechanism might be associated with a higher inflammatory or oxidative status resulting in hemolysis. In an older study by Druml et al. (17), it is suggested that increased triglyceride levels which accompany massive hemolysis may be caused by circulatory shock, released cytokines or catecholamine release. On another note, it was shown that in microangiopathic hemolytic anemia, triglyceride levels were also higher (18). Since metabolic stress factors are known to be causing acute triglyceride increase, it may be accompanied with hemolysis.

Our study found that stable CAD was not a causative factor in mechanical hemolysis, unlike mechanical valve prostheses or assist devices. Furthermore, in ACS, triglyceride levels might be an indicator to hemodynamic alteration which ends up with erythrocyte destruction. To our knowledge, this is the first study in literature studying a possible relationship between CAD and its possible relationship with hemolysis.

Study Limitations

Since this was a single center study, the sample size was unfortunately relatively small. These findings therefore should be further evaluated through extensive multicenter researches with bigger sample sizes.

Conclusion

The most important finding of our study is that it highlights hypertriglyceridemia as a possible marker of increased erythrocyte destruction in ACS patients. This matter should be further verified with bigger sample sizes and prospective analyses of patient prognoses.

Ethics

Ethics Committee Approval: The study protocol received institutional review board approval and all participants provided informed consent in the format required by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Ethics Committee (approval number: 60, date: 11.03.2021).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.D., S.M.T., Concept: Ö.D., Design: Ö.D., B.Ö., Data Collection or Processing: Ö.D., B.Ö., M.B.O., S.M.T., Analysis or Interpretation: Ö.D., B.Ö., M.B.O., S.M.T., Literature Search: Ö.D., M.B.O., Writing: Ö.D., B.Ö.

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