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*Original Article/Araştırma Makalesi*

# PROLIDASE LEVEL IN CORONARY ARTERY DISEASE AND ISCHEMIC MITRAL VALVE INSUFFICIENCY

## Koroner Arter Hastalığı ve İskemik Mitral Kapak Yetmezliğinde Prolidaz Düzeyi

*Vedat AĞRIÇ[1] Mustafa GÖZ[2] Reşat DİKME[3] Mahmut PADAK[4]*
*Mehmet Salih AYDIN[5] Nazım KANKILIÇ[6] Bişar AMAÇ[7]*
*[1,7]Cardiovascular Surgery Operating Room, Mehmet Akif Inan Training and Research Hospital, Sanliurfa*
*[2]Department of Cardiovascular Surgery, Private Meydan Hospital, Sanliurfa*
*[3,4]Harran University Vocational School of Health Services, Sanliurfa*
*[5,6]Harran University Faculty of Medicine Hospital, Sanliurfa*

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## ABSTRACT

Plasma prolidase levels change as a determining factor for coronary artery disease and heart valve insufficiency. The aim of this study is to compare plasma prolidase levels in two groups with or without mitral regurgitation who underwent coronary artery bypass surgery (CABS). For this purpose, 45 patients who underwent CABS were included in the study; patients without mitral valve insufficiency who underwent CABS (25 patients) Group 1, patients with mitral valve insufficiency who underwent CABS (20 patients) Group 2. Venous blood was taken from all patients before and after CABS and their prolidase levels were measured. Preoperative and postoperative serum prolidase levels in group 1 were 1038.2 and 1289.43 U/L, respectively. In group 2, preoperative and postoperative serum prolidase levels were 1084.07 and 1337.74 U/L, respectively. A significant difference was found between preoperative and postoperative plasma prolidase levels of Group 1 and Group 2 included in the study ($p<0.05$). Plasma prolidase level was high in both groups. However, pre- and postoperative serum prolidase levels were found to be higher in patients with mitral valve insufficiency in Group 2. In conclusion, in this study, it was determined that the plasma prolidase level was higher in patients with mitral valve insufficiency who underwent CABS.

**Keywords:** Cardiopulmonary bypass, Coronary bypass surgery, Ischemic mitral regurgitation, Mitral valve insufficiency, Prolidase.

## ÖZ

Plazma prolidaz seviyeleri, koroner arter hastalığı ve kalp kapağı yetmezliği için belirleyici bir faktör olarak değişir. Bu çalışmanın amacı mitral yetersizliği olan ve olmayan koroner arter baypas cerrahisi (KABC) uygulanan iki grupta plazma prolidaz düzeylerini karşılaştırmaktır. Bu amaçla çalışmaya KABC uygulanan 45 hasta dâhil edildi; mitral kapak yetmezliği olmayan ve KABC uygulanan hastalar (25 hasta) Grup 1, mitral kapak yetmezliği olup KABC uygulanan hastalar (20 hasta) Grup 2 olarak adlandırıldı. Tüm hastalardan KABC öncesi ve sonrası venöz kan alındı ve prolidaz düzeyleri ölçüldü. Grup 1'de preoperatif ve postoperatif serum prolidaz seviyeleri sırasıyla 1038.2 ve 1289.43 U/L olarak hesaplandı. Grup 2'de ise preoperatif ve postoperatif serum prolidaz seviyeleri sırasıyla 1084,07 ve 1337.74 U/L olarak hesaplandı. Çalışmaya alınan Grup 1 ve Grup 2'nin preoperatif ve postoperatif plazma prolidaz düzeyleri arasında anlamlı fark bulundu ($p<0.05$). Plazma prolidaz düzeyi her iki grupta da yüksekti. Ancak Grup 2'de mitral kapak yetmezliği olan hastalarda ameliyat öncesi ve sonrası serum prolidaz düzeyleri daha yüksek bulundu. Sonuç olarak bu çalışmada mitral kapak yetersizliği nedeniyle KABC yapılan hastalarda plazma prolidaz düzeyinin daha yüksek olduğu belirlendi.

**Anahtar kelimeler:** İskemik mitral yetmezlik, Kardiyopulmoner baypas, Koroner baypas cerrahisi, Mitral kapak yetmezliği, Prolidaz.

*Mahmut PADAK✉, mpadak@harran.edu.tr*
*Harran University School of Health Services, Şanlıurfa*



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## INTRODUCTION

Coronary artery disease (CAD) and valvular heart disease (VHD) are responsible for major cardiovascular events (Heart disease and stroke statistics, 2017; Matta et al., 2019). The mitral valve is a dynamic structure with complex interactions with the surrounding anatomical structures. Disruption of any component of the mitral valve or the surrounding anatomy can cause mitral valve regurgitation (MVR) (El Sabbagh et al., 2018). The incidence of MR, the most common valvular heart disease, increases with age (Silbiger et al., 2012). For this reason, it is predicted that the number of patients with MR who require hospitalization or intervention will increase further in the coming years (Andell et al., 2017). Untreated severe MR causes negative results due to excessive volume overload in the left ventricle. MVR is the second most common disease in heart valve surgery and affects approximately 2% of the population (Baumgartner et al., 2017;Lung et al., 2007).

MVR is adversely affected in many cardiovascular disorders, including myocardial infarction. In mitral valve insufficiency, which is caused by various reasons, including CAD, the closure of the valve leaflets is impaired (Pierard et al., 2010). Another important factor in the development of this condition is the change in the geometry of the ventricle. Regardless of its severity, mitral valve regurgitation has been consistently associated with worse left ventricular function, increased risk of heart failure, and higher mortality rates (Sannino et al., 2017).

The balance between extracellular matrix (ECM) synthesis and degradation plays an important role in CAD and MVR (Sultan et al., 2017). In many previous studies, proteolytic enzymes such as matrix metalloproteases (MMPs) have been identified in human coronary atherosclerotic plaques. MMPs mediate vascular remodeling by regulating the degradation of ECM components (Sultan et al., 2017).

Collagen is the main ECM component in atherosclerotic plaques. Although different MMPs initiate the breakdown of collagen, prolidase (peptidase D) plays an important role in the first stage of collagen biosynthesis and the final stage of collagen degradation. Therefore, prolidase is considered to be the main rate-limiting step that regulates collagen turnover (Surazynski et al., 2008).

Prolidase is a cytosolic exopeptidase that cleaves proline or hydroxyproline at the carboxyl terminal position of dipeptides. It is found in various organs such as the brain, heart, uterus and thymus, and in plasma (Cavusoglu et al., 2015). It has important roles in physiological and pathological processes such as embryonic development, wound healing,

inflammation, carcinogenesis, angiogenesis, cell migration and cell differentiation (McRae & Porter, 2012). In support of this idea, prolidase has been shown to be significantly higher in patients with CAD and prolidase activity has been positively associated with severity of CAD (Yildiz et al., 2008). Nevertheless, the impact of prolidase on plaque stability has not been assessed, and it remains unclear whether prolidase levels are predictive of MVR.

Coronary artery bypass graft (CABG) surgery is the most important treatment option in the treatment of severe mitral valve regurgitation (Ferket et al., 2020).

Serum prolidase activity (SPA) levels have been evaluated in many diseases and have been found to be high in fibrotic liver disease, metabolic syndrome, hypertension, CAD and heart valve disease (Horoz et al., 2010; Aktürk et al., 2018).When the studies are examined, the change in plasma prolidase activity during cardiopulmonary bypass (CPB) or extracorporeal circulation (ECC), which allows the surgical treatment of patients with CAD and mitral valve regurgitation, has not been studied sufficiently.

Changes in the enzyme activity of prolidase, which has a wide tissue distribution, are thought to be important in the development and outcome of many diseases. In this study, prolidase level was investigated in patients with CAD with or without ischemic mitral regurgitation.

## MATERIAL AND METHOD

### Ethics Committee Approval And Study Population

Ethics committee approval was obtained from the ethics committee of the Faculty of Medicine of Harran University, dated 16.01.2015 and numbered 01. Patients with or without mitral valve regurgitation who were operated on by CABG were included in the study. In our study; A total of 45 patients who were taken to cardiopulmonary bypass due to open heart surgery in the Cardiovascular Surgery department were selected. Patients with emergency coronary bypass, reoperations, systemic inflammatory disease, chronic autoimmune disease, chronic renal failure, hematological disease were not included in the study.The patients were divided into two groups. Group 1; It was defined as patients (25 patient) who did not have mitral valve insufficiency and underwent CABG operation. Group 2; Patients with mitral valve insufficiency who underwent CABG operation were defined as (20 patient).

### Obtaining Blood Samples From Patients

10 mL venous blood samples were obtained from all patients included in the study before (preop) and after ECC (postop). Venous blood samples taken into heparinized tubes were

centrifuged at 5000 rpm for 10 minutes and their plasmas were separated. The separated plasmas were placed in Eppendorf tubes and kept at -80 degrees. Afterwards, serum prolidase levels were measured by ELISA method. CABG procedures were applied to all patients with standard anesthesia protocol. After sternotomy, aortic and venous cannulations were performed in the patients included in the study, and CPB processes were completed at 28-32 °C.

**Prolidase Assay**

During the study, all plasma samples were brought to room temperature and the plasma was dissolved. Prolidase enzyme levels were studied in the biochemistry laboratory by ELISA method in accordance with the working procedure of the manufacturer. Results were expressed as U/L.

**Statistical Analysis**

Statistical analyses were performed using IBM SPSS for Windows Version 16 (SPSS Inc., Chicago, IL, USA). The normality of the data was defined using the Kolmogorov–Smirnov test. Normally distributed continuous data are shown as mean±standard deviation, whereas non-normally distributed data are shown as median (interquartile range). Normally distributed continuous variables were compared using the independent samples t test, and the Mann–Whitney U test was used if the distribution was skewed. Values less than $p< 0.05$ were considered statistically significant.

## RESULTS

The patients included in the study were 33 man and 12 woman, with a mean age of 59,73 (years), height 158.21 (cm), weight 72.30 (kg) and body surface area 1.72 ($m^2$). Demographic data of 45 patients included in the study are shown in Table 1.

**Table 1.**Demographic Characteristics of the Patients Included in The Study

| **Variable** ± | **Patients (n=45)** |
|---|---|
| Gender (Man/Woman)% | 33/12 (%73.3 / %26.7) |
| Age (years) | 59.73±10.22 |
| Height (cm) | 158.21±23.35 |
| Weight (kg) | 72.30±13.47 |
| (BSA) Body surface area ($m^2$) | 1.72±0.18 |

Plasma prolidase levels before and after ECC in group 1 patients were calculated as 1038.2 and 1289.43 U/L, respectively. An increase in plasma prolidase levels was detected after ECC in group 1 patients. A statistically significant result was obtained between plasma prolidase levels before and after ECC in group 1 patients ($p< 0.01$).

Plasma prolidase levels before and after ECC in group 2 patients were calculated as 1084.07 and 1337.74 U/L, respectively. An increase in plasma prolidase levels was detected after ECC in group 2 patients. A statistically significant result was obtained between plasma prolidase levels before and after ECC in group 2 patients ($p< 0.01$)

Plasma prolidase levels before and after ECC were higher in Group 2 patients than in Group 1 patients (Table 2).

**Table 2.** Serum Prolidase Levels in the Blood Of Group 1 and Group 2 Patients Before and After the ECC

| | Before ECC (Pre op.) | After ECC | p |
|---|---|---|---|
| Group1-Prolidase | 1038.28 ± 150.09 | 1289.43 ± 357.34 | p< 0.001 |
| Group2-Prolidase | 1084.07 ± 260.09 | 1337.74 ± 397.61 | p< 0.005 |

Paired samples t test was used for in-group comparison. Independent samples t test was used for comparison between groups.

When the comparison was made between the groups, no statistically significant difference was found between Group 1 and Group 2 (p=0.463, p=0.686). When plasma prolidase levels were examined between the groups, it was observed that there was an increase in plasma prolidase levels in both groups before and after ECC (Figure 1).

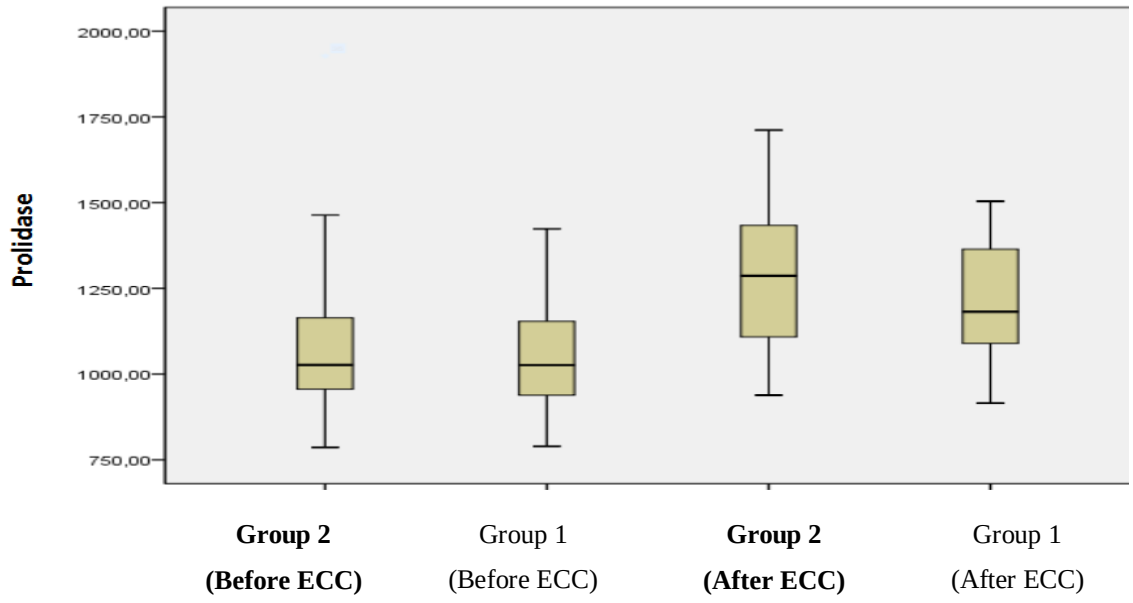


**Figure 1.** Comparison of Plasma Prolidase Levels Between Groups

## DISCUSSION

Although MMPs generally initiate collagen degradation, prolidase mediates the final stage of collagen degradation and the first stage of collagen biosynthesis. Therefore, prolidase is considered to be one of the primary regulators of the collagen cycle (Aciksari et al., 2020). Collagen is the primary ECM component, which accounts for 60% of the total protein content

in atherosclerotic plaques, and possibly, SPA will regulate plaque stability by affecting the collagen cycle in atherosclerotic plaques (Aciksari et al., 2020). With this hypothesis, it has been shown that the SPA is significantly higher in CAD and correlates with the severity of CAD (Gunbatar et al., 2020). Prolidase activity has been detected in plasma, blood cells, and many organs, including the heart. Prolidase activity has been investigated in many diseases and increased SPA has been associated with the presence of cardiovascular diseases (Demirbag et al., 2007). In many studies, it has been determined that inflammatory index levels, especially C-reactive protein, and collagen III expression in various cardiac tissues, increase in patients with mitral valve disease (Rabuş et al.,2010). However, data on the role of SPA in the pathogenesis of heart valve diseases and CAD are not sufficient in the literature.

In a study conducted in patients with CAD (Aktürk et al., 2018; Yıldız et al., 2008) it was stated that the serum prolidase level of the patients increased when compared to the control subjects. In the same study, serum prolidase levels gave statistically significant results with Gensin Score. In atherosclerosis, which is a complex multifactorial disease, serum prolidase level is accepted as an important marker in the progression of atheroscleratic plaque. These data are similar to the results of Group 1 patients in our study. In Group 1 with CAD, plasma prolidase level, which was determined to be high before ECC, increased even more after ECC. Surgical trauma, cross-clamp time, cardiopulmonary bypass technique, extracorporeal circulation and anesthesia process also play an important role in the increase of prolidase level after ECC.

Demirtas et al. (Demirtas et al., 2015) found that SPA is significantly lower in patients receiving anticoagulants and antiplatelet agents than in the control group. Angiotensin convertase inhibitors, such as enalapril, have also been shown to affect prolidase activity by affecting the collagen cycle, such as antiplatelet agents. Patients with acute coronary syndrome undergoing percutaneous transluminal coronary angioplasty have lower levels of prolidase activity due to routine acetylsalicylic acid and anticoagulant treatment (Sultan et al., 2017).

Patients with ischemic mitral regurgitation exhibit different pathology and clinical findings compared to mitral regurgitation due to other etiologies, and also present with a higher risk of mortality, morbidity, and poor prognosis (Gillinov et al., 2010). Rabus et al reported that patients with severe mitral valve stenoz may be associated with the plasma prolidase activity, tissue and plasma oxidative parameters (Rabus et al., 2008).

In our study, the prolidase level was found to be high in both groups. However, the prolidase level was found to be higher in Group 2 patients with MVR. This shows us that prolidase is also elevated in CAD and further increased in mitral valve insufficiency. Prolidase

level, which was high before ECC, gradually increased after ECC. Many processes such as CPB process, extracorporeal foreign material surface, surgical trauma, inflammatory response and anesthesia technique were effective in the increase in prolidase after ECC.

## CONCLUSION

Currently, CVDs are among the most common causes of death worldwide. SPA may play an active role in the physiopathogenesis of many diseases, usually through the collagen cycle and oxidative stress. Several studies have shown that SPA is independently associated with diseases such as CAD and heart valve regurgitation. According to the results of this study, plasma prolidase level was found to be high in Group 1 and Group 2 patients. The plasma prolidase level of the patients in group 2 was higher than the patients in Group 1. After ECC, plasma prolidase level increased in both groups, giving a statistically significant result. No statistically significant difference was found in the comparison of the two groups. Plasma prolidase levels were higher before and after ECC in patients with mitral valve insufficiency. According to the results obtained, it can be said that plasma prolidase level is found to be significantly higher in CAD and mitral valve regurgitation, and prolidase increases during ECC. SPA may be a promising new therapeutic agent in CVDs. Studies on the effect of SPA on CAD prognosis are limited; therefore, more comprehensive studies are needed in the future.

### REFERENCES

Aciksari, G., Demir, B., Uygun, T., Gedikbasi, A., Kutlu, O., ...Atici, A. (2020). Serum prolidase activity in patients with cardiac syndrome X. *North Clin Istanb*, 7(5), 471–477.

Aktürk, E., Aşkın, L., Nacar, H., Taşolar, M. H., Türkmen, S., Çetin, M., …Bozkurt M. (2018) Association of serum prolidase activity in patients with isolated coronary artery ectasia. *Anatol Journal of Cardiol*ogy,19(2),110-116.

Andell, P., Li, X., …Martinsson, A. (2017). Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. *Heart,*103, 1696–1703.

Baumgartner, H., Falk, V., …Bax , J. J. (2017). ESC/EACTS Guidelines for the man Agement of valvular heart disease. *Europen Heart Journal*,38, 2739-2791.

Cavusoglu, E., Marmur, J. D., Hegde, S., Yanamadala, S., Batuman, O. A., …Chopra, V. (2015). Relation of baseline plasma MMP-1 levels to long-term all-cause mortality in patients with known or suspected coronary artery disease referred for coronary angiography. *Atherosclerosis*, 239(1), 268–275.

Demirbag, R., Yildiz, A., Gur, M., Yilmaz, R., Elci, K. & Aksoy, N. (2007). Serum prolidase activity in patients with hypertension and its relation with left ventricular hypertrophy. *Clinical Biochemistry*, 40, 1020-1025.

Demirtas, S., Karahan, O., Yazıcı, S., Guclu, O., Calıskan, A., …Tezcan, O. (2015). Investigation of possible prophylactic, renoprotective, and cardioprotective effects of thromboprophylactic drugs against ischemia-reperfusion injury. *The Kaohsiung Journal of Medical Sciences*,31(3), 115–122.

El Sabbagh, A., Reddy, Y. N. V. & Nishimura, R. A. (2018). Mitral valve regurgitation in the contemporary era ınsights ınto diagnosis, management, and future directions. *JACC: Cardiovascular Imaging*, 11(4), 628-643.

Ferket, B. S., Thourani, V. H., Voisine, P., Hohmann, S. F., Chang, H. L., …Smith, P. K. (2020). Cost-effectiveness of CABG plus mitral-valve repair vs CABG alone for moderate ıschemic mitral regurgitation. *The Journal of thoracic and cardiovascular surgery.*, 159(6), 2230–2240.e15.

Gillinov, A. M., Wierup, P. N., Blackstone, E. H., Bis-hay E. S., Cosgrove, D. M., White, J., Lytle, B. W. &McCarthy, P. M. (2001). Is repair preferable to replacement for ischemic mitral regurgitation? *The Journal of thoracic and cardiovascular surgery,*122, 1125-1141.

Gunbatar, H., Kaplan, H. S. &Yildiz, S. (2020). Is there a correlation between obstructive sleep-apnea syndrome severity and prolidase activity as anoxidative stress marker?.*Niger J Clin Pract*, 23(2), 252–257.

Heart disease and stroke statistics 2017 update. (2017). A report from the American heart association .*Circulation,*135.

Horoz, M., Aslan, M. & Bolukbas, F. F. (2010). Serum prolidase enzyme activity and its relation to histopathological findings in patients with nonalcoholic steatohepatitis. *Journal of Clinical Laboratory Analysis*, 24, 207-211.

Lung, B., Baron, G., …Tornos, P. (2007). Valvular heart disease in the community: A European experience. *Current Problems in Cardiology*, 32, 609-661.

Matta, A. &Moussallem, N. (2019). Coronary artery disease is associated with valvular heart disease, but could it Be a predictive factor. *Indian Heart J.*,71(3), 284-287.

McRae, P. A. & Porter, B. E. (2012). The perineuronal net component of the extracellular matrix in plasticity and epilepsy. *Neurochemistry international*, 61, 963-972.

Pierard, L. A. & Carabello, B. A. (2010). Ischaemic mitral regurgitation: Pathophysiology, outcomes and the conundrum of treatment. *European heart journal*, 31, 2996–3005.

Rabuş, M. B., Demirbağı R., Sezen, Y., Taşar, M., Taşkın, A., Aksoy, N., Kırali, K. &Yakut, C. (2010). Serum prolidase activity in patients with degenerative and rheumatic heart valve diseases, *Turkish Journal of Medical Sciences,*40, 5-3.

Sannino, A., Smith, R. L., Schiattarella, G. G., Trimarco, B., Esposito, G. & Grayburn, P. A. (2017). Survival and cardiovascular outcomes of patients with secondary mitral regurgitation: A systematic review and meta-analysis. *JAMA Cardiology*, 2, 1130–1139.

Silbiger, J. J. (2012). Anatomy, mechanics, and pathophysiology of the mitral annulus. *American heart journal*, 164, 163–76.

Sultan, A., Zheng, Y., Trainor, P. J., Siow, Y., Amraotkar, A. R., Hill, B. G. & DeFilippis, A. P. (2017). Circulating prolidase activity in patients with myocardial ınfarction. *Frontiers in cardiovascular medicine*, Jul 31, 450.

Sultan, A., Zheng, Y., Trainor, P. J., Siow, Y., Amraotkar, A. R., …Hill, B. (2017). Circulating prolidase activity in patients with myocardial infarction. *Frontiers in cardiovascular medicine*, 4, 50.

Surazynski, A., Miltyk, W., Palka, J. & Phang, J. M. (2008). Prolidase-dependent regulation of collagen biosynthesis. *Amino Acids*, 35(4), 731–738.

Yildiz, A., Demirbag, R., Yilmaz, R., Gur, M., Altiparmak, I. H., …Akyol, S. (2008). The association of serum prolidase activity with the presence and severity of coronary artery disease. *Coronary artery disease,*, 19(5), 319-325.