PROLIDASE LEVEL IS INCREASED IN CORONARY ARTERY DISEASE AND ISCHEMIC MITRAL VALVE INSUFFICIENCY

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Abstract

Background: Serum prolidase levels change decisively in coronary artery disease and valvular disease. The aims of this study are to determine how the serum prolidase level will vary in patients who have undergone coronary bypass surgery due to mitral insufficiency and those without ischemic mitral regurgitation and those with ischemic mitral regurgitation. Methods: A total of 45 patients who were operated with coronary bypass surgery were selected. Group 1 patients were defined as patients who had coronary artery bypass surgery and did not have mitral insufficiency (25 patients), and Group 2 patients were defined as patients who had undergone coronary artery bypass surgery and had mitral insufficiency (20 patients). Before and after coronary artery bypass surgery, blood was taken from the patients and their prolidase levels were measured. Results: In Group 1 patients, pre- and postoperative serum prolidase levels were calculated as 1038.2 and 1289.43 U/L, respectively. In Group 2 patients, pre- and postoperative serum prolidase levels were calculated as 1084.07 and 1337.74 U/L, respectively. There is a significant difference between the serum prolidase (U/L) levels in the blood of group 1 and group 2 patients entering the operation and the blood after CPB ($p<0.05$). Conclusion: Serum prolidase level was found to be high in both patient groups. Pre- and postoperative serum prolidase levels were higher in patients with mitral valve insufficiency. Prolidase level is increased in coronary artery disease and mitral valve insufficiency.

1. INTRODUCTION

Mitral regurgitation (MR) is the second most common disease in heart valve surgery and affects approximately 2% of the population.[1,2] Ischemic mitral regurgitation (IMR) ranks third among the causes of mitral valve surgery and constitutes approximately 10% of mitral valve operation indications.[3] When we look at the causes of MR, it is important to distinguish between primary and secondary disease groups, especially according to the development of the disease. In primary MR, one or more components of the valve apparatus may be affected as a result of mitral valve degeneration, including rheumatic heart disease, fibroelastic insufficiency, or Barlow's disease. Endocarditis is one of the main causes of primary MR, which is especially discussed in the guidelines of the European Society of Cardiology and the European Society of Cardiac and Thoracic Surgery. In secondary MR, the valve apparatus is anatomically intact, and MR disease may develop due to insufficiency, particularly valve closure and valve attachment points. Secondary to MR, ischemic cardiomyopathy due to left ventricular dilatation and dysfunction is observed.[1,4]

IMR develops as a complication of coronary artery disease.[5] IMD is a ventricular disease, not a valvular disease, and it begins to be seen with regional and all-encompassing left ventricular remodeling after AMI.[6,7] Today, morbidity and mortality due to ischemic heart disease (IHD) and its complications are quite high. A significant number of these patients (40%) die due to AMI and its complications.[8]

Ischemic mitral regurgitation is one of the most controversial problems in cardiac surgery practice. In recent years, surgical revascularization and mitral repair attempts have been performed in moderate and severe ischemic mitral regurgitation. Mitral valve repairs in the heart working with retrograde normothermic perfusion can be counted among these interventions. These approaches not only reduce operative mortality, but also affect long-term survival.[9,10]

Papillary muscle dysfunction is prominent in the acutely developing group of these cases, which can also be classified as acute and chronic ischemic mitral regurgitation. Papillary muscle rupture is rarely encountered and its incidence in total acute myocardial infarctions is less than 1%. Rupture can involve the entire muscle, or it can be seen only in one head of the muscle. Rupture of the entire muscle is extremely dangerous and causes severe mitral regurgitation as the movement of half of both leaflets will be impaired. The ruptured papillary muscle should be sutured to the adjacent ventricular free wall. If there is damage only to the tip of the papillary muscle, not the whole, the insufficiency will be less. The ruptured papillary muscle head is repaired by suturing it to the papillary muscle right next to it.

Chronic ischemic mitral regurgitation, on the other hand, develops as a result of papillary muscle elongation secondary to infarction or due to excessive changes in ventricular anatomy that move the papillary muscles away from the mitral annulus. Clinically, leaflet prolapse due to chordae rupture or papillary muscle elongation is seen in some patients. More commonly, restricted mitral leaflet movement caused by left ventricular anatomical changes is observed. Valve repair in ischemic mitral regurgitation depends on the presence of restricted leaflet movement or excessive leaflet movement. In ventricular dilatations that develop as a result of ischemic heart disease, cases of mitral insufficiency are frequently encountered even without papillary muscle damage. In such cases, the papillary muscles displace laterally, causing restricted movement of the leaflets. Pathological examinations show that there is no annular dilatation in these patients and there is no correlation between annulus diameter and regurgitation.[11]

On the other hand, even annuloplasty alone reduces the diameter of the annulus and eliminates the failure by providing leaflet closure. Cases with restricted leaflet movement are only repaired by annuloplasty. In cases where prolapse develops, other surgical repair interventions such as papillary shortening, chordae shortening, leaflet resection are needed in addition to annuloplasty. Cases with restricted leaflet movement seem to have a shorter life expectancy than those with prolapse. In ischemic mitral regurgitation, papillary muscle dysfunction and ventricular deformation cause some problems in mitral valve repairs. As is known, ischemic mitral insufficiency occurs as a result of changes in ventricular anatomy. Since this condition develops after acute myocardial infarction, there is a decrease in left ventricular function. Patients with this condition adversely affect the outcome of cardiac surgery procedures.[12] Therefore, since the results of long-term medical treatment in patients with mitral regurgitation are not at the desired level, some surgeons suggest that valve replacement surgery should be performed to prevent reoperation, assuming that mitral regurgitation may progress.[13,14]

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.[15] They have important roles in physiological and pathological processes such as embryonic development, wound healing, inflammation, carcinogenesis, angiogenesis, cell migration and cell differentiation.[16,17] Proline is commonly found in the central nervous system.[18] It has been reported that proline plays a role as a neuromodulator in synaptic transmission.[19] Serum prolidase (U / L) levels have been evaluated in many diseases and have been found to be high in fibrotic liver disease, metabolic syndrome, hypertension, coronary artery disease (CAD) and valve disease.[20,21]

In this study, we evaluated the prolidase level in patients with and without ischemic mitral insufficiency. In conclusion, wide tissue distribution suggests that changes in prolidase enzyme activity may gain importance in the development and outcome of many diseases.

2. METHODS

In our study; A total of 45 patients (33 men, 12 women) who were taken to cardiopulmonary bypass due to

open heart surgery in the Cardiovascular Surgery department were selected. Group 1 patients were defined as undergoing coronary artery bypass surgery (25 patients), and Group 2 patients as undergoing coronary artery bypass+mitral insufficiency surgery (20 patients). Preoperative (preop) and postoperative (postop) blood samples of these patients were studied. The study was initiated with the approval of the Harran University Ethics Committee. Patients under 18 years of age, chronic kidney and liver failure, patients with low ejection fraction, additional valve disorders, long-term use of angiotensin receptor blockers and aldosterone antagonists, chronic rheumatic disease, aortic aneurysm and collagen tissue disease were excluded from the study. Standard anesthesia protocol, venous and coronary sinus blood were taken. After aortic and venous cannulation after sternotomy in the patients included in the study, operations were completed at 28-32 °C under cardiopulmonary bypass and cross-clamp.

Fresh blood collected in heparinized tubes was 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. On the working day, these bloods were thawed and studied. The unit of measurement used is U / L.

Statistical analysis

Statistical analyzes were performed using the SPSS® Version 16.0 (SPSS Inc. Chicago USA)® computer program. The significance of the difference between the means of the groups was compared with the One-Way ANOVA test. Values less than $p < 0.05$ were considered statistically significant.

3. RESULTS

It was observed that there was an increase between the serum prolidase (U / L) levels in the blood of group 1 patients entering the operation and the serum prolidase (U / L) levels in their blood after extra-corporeal circulation (ECC), and a statistically significant result was obtained here ($p < 0.01$) (Table 1). In Group 1 patients, pre- and postoperative serum prolidase levels were calculated as 1038.2 and 1289.43 U/L, respectively.

Table 1. Serum prolidase (U/L) levels in the blood of Group 1 patients before and after the operation

	Introduction to Operation	After ECC	p
Prolidase, U/L	1038.28 ± 150.09	1289.43 ± 357.34	$p < 0.01$

Considering the serum prolidase (U/L) levels in the blood of the group 2 patients entering the operation, this level caused a significant increase in the serum prolidase (U/L) levels in their blood after ECC and a statistically significant result was obtained ($p < 0.05$) (Table 2). In Group 2 patients, pre- and postoperative serum prolidase levels were calculated as 1084.07 and 1337.74 U/L, respectively. Pre- and postoperative serum prolidase levels were higher in Group 2 patients compared to Group 1 patients.

Table 2. Serum prolidase (U/L) levels in the blood of Group 2 patients before the operation and after ECC

	Introduction to Operation	After ECC	p
Prolidase, U/L	1084.07 ± 260.09	1337.74 ± 397.61	$p < 0.05$

When the serum prolidase (U/L) levels in the blood of the patients in group 1 and group 2 patients are examined, the serum prolidase (U / L) levels in the blood of the group 1 patients will be statistically significant compared to the serum prolidase (U / L) levels of the patients in group 2. no difference was found ($p = 0.463$) (Table 3).

Table 3. Serum prolidase (U/L) levels in the blood entering the operation in Group 1 patients and in the

blood entering the operation in Group 2 patients

	Group 1 Introduction to Operation	Group 2 Introduction to Operation	p
Prolidase, U/L	1038.28 ± 150.09	1084.07 ± 260.09	0,463

When we looked at the serum prolidase (U / L) levels of patients in group 1 and patients in group 2 after ECC, no statistically significant difference was found (p = 0.686) (Table 4).

Table 4 . Serum prolidase (U/L) levels in the blood of Group 1 patients after ECC and in the blood of Group 2 patients after ECC

	Group 1 Post ECC	Group 2 Post ECC	p
Prolidase, U/L	*1289.43 ± 357.34*	*1335.74 ± 397.61*	*0,686*

When the serum prolidase (U / L) levels between the groups were examined, it was observed that there was an increase in serum prolidase (U / L) levels in the blood of both groups after the bypass operation and after ECC (Figure 1).

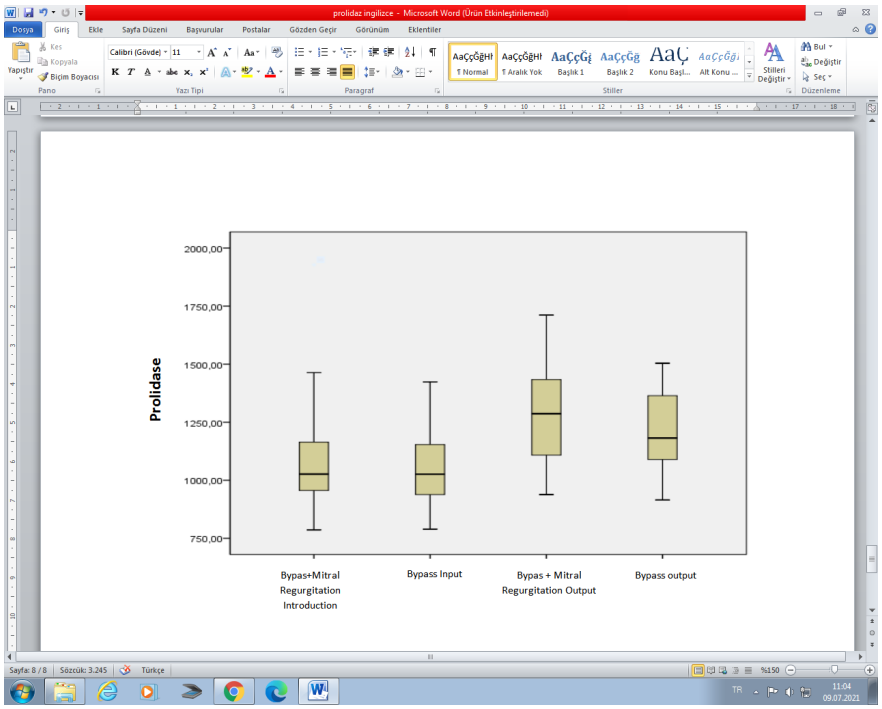

Figure 1. Comparison of Serum Prolidase (U/L) Levels Between Groups

4. DISCUSSION

In a study, it was stated that the serum prolidase (U/L) level increased when patients with CAD were compared with control cases. In the same study, serum prolidase (U/L) levels gave a statistically significant result with Gensin Score. Since coronary atherosclerosis is a complex multifactorial disease, it has been

stated that it may play an important key role in serum prolidase (U/L) level in patients with CAD with the progression of atheroscleratic plaque. [22] These data may show that the changes in serum prolidase (U/L) levels in the Bypass Entry and Bypass outlet blood of the patients in group 1 in our study may be caused by surgical trauma, cross clamp duration, cardiopulmonary bypass technique and extracorporeal circulation and respiratory support.

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.[23]

In a study, it was shown that vascular tissues lose tissue compatibility with advancing age. In the study, it was stated that there was a similar change between serum prolidase (U/L) activity and age. In this study, it was proven that increased prolidase activity is not only associated with aging and female gender, but also with the presence and duration of hypertension. It is requested to draw attention to its importance in the evaluation of prolidase activity in patients with hypertension. To the best of our knowledge, this is the first study to show that hypertension is associated with increased serum prolidase (U/L) activity. As a result of this study, it has been shown that there is a significant increase in serum prolidase (U/L) activity in patients with hypertension.[24]

In a study, they conducted a study on aortic stiffness related to blood and aortic tissue prolidase activity and immunohistochemical expression of prolidase in aortic tissue. Previous studies have shown that serum prolidase (U/L) activity is increased in patients with coronary artery disease (CAD) and hypertension. However, this correlation was thought to be related to prolidase secretion from other organs or drug use. They reported that this study is the first to evaluate the correlation of aortic stiffness with tissue prolidase activity and immunohistochemical expression of prolidase in aortic tissue. They found that plasma prolidase activity was higher in the study group than in the control group, as in previous studies. In addition, patients with pulmonary arterial pressure, diabetes mellitus (DM), dyslipidemia, tobacco use, myocardial infarction and chronic obstructive pulmonary disease (COPD) were reported to be in the majority in the study. Previous studies have shown that aortic stiffness is higher in CAD patients, blood prolidase activity is higher in DM and dyslipidemia patients, and lower in COPD patients.[25]

In the study named serum prolidase (U/L) activity in degenerative and rheumatic heart patients; The patient group who had valve replacement due to rheumatic etiology was compared with a group of patients who had valve replacement due to degenerative etiology and a group of healthy volunteers. They measured prolidase activity in all groups. Their conclusion was that prolidase activity was significantly higher in the control group than in the patient groups. However, there was no statistically significant difference between the patient groups in terms of serum prolidase (U/L) activity. No correlation was found between serum prolidase (U/L) activity and valve disease. In the light of these findings, they concluded that rheumatic and degenerative heart disease is associated with decreased serum prolidase (U/L) activity.[26] In our study; There was an increase in prolidase level in group 2 bypass access and group 1 bypass access blood, but it did not show a significant result. Prolidase level in group 2 bypass outlet and group 1 bypass outlet blood increased, but it did not show a significant result.

In another study, in the evaluation of serum prolidase (U/L) activity in the patient group with coronary artery disease; stated that serum prolidase (U/L) level increased significantly. They stated that serum prolidase (U/L) levels were significant, but prolidase levels decreased in the control groups when compared with coronary artery disease.[27] In our study, there was an increase in the level of prolidase in the blood of group 2 patients, but it did not give statistically significant results in our study.

When we look at the serum prolidase (U/L) levels in the blood of the group 2 patients entering the surgery (1084.07 $\pm$ 260.09 U/L) and exiting the surgery (1337.74 $\pm$ 397.61 U/L), this result gave us a statistically significant difference. ($p < 0.05$). When the serum prolidase (U/L) levels in the blood of the patients in Group 1 at the time of entry to the operation (1038.28 $\pm$ 150.09 U/L) and after the operation (1289.43 $\pm$ 357.34 U/L) were examined, the serum prolidase (U/L) levels increased significantly, making the study

result statistically significant ($p < 0.01$).). There was not much difference in serum prolidase (U/L) levels in the blood entering the surgery of the patients in group 2 and the patients in group 1 in the blood entering the surgery. When the serum prolidase (U/L) levels in the postoperative blood of the study group patients and the postoperative blood of the control group patients were evaluated, the serum prolidase (U/L) level increased in both patient groups compared to the access blood. However, despite the increase in the output blood levels of both groups, this serum prolidase (U/L) level increased at a more serious level in the study group patients who underwent ischemic mitral regurgitation in addition to bypass surgery. We have seen that patients who develop ischemic mitral regurgitation and additionally performing cardiac surgery cause a significant increase in serum prolidase (U/L) levels. The main reason for this increase was that the patient had primarily cardiac surgery and increased prolidase level due to this trauma (Figure 1).

A statistically significant difference was observed between serum prolidase (U/L) levels in group 2 bypass blood and group 2 bypass blood ($p < 0.05$) (Table 1). There is a significant difference between serum prolidase (U/L) levels in group 1 bypass blood and group 1 bypass blood ($p < 0.01$) (Table 2). There was no statistically significant difference between serum prolidase (U/L) levels in group 2 bypass blood and group 1 bypass blood ($P = 0.686$) (Table 3). There was no statistically significant difference between serum prolidase (U/L) levels in group 2 bypass blood and group 1 bypass blood ($P = 0.463$) (Table 4).

In our study, it was observed that the serum prolidase (U/L) level of the patients in group 2 was at a certain level at the entrance to the bypass, while it increased at the exit of the bypass. While the serum prolidase (U/L) level of the patients in Group 1 was at a certain level at the entrance to the bypass, it increased at the exit of the bypass. When we evaluated the serum prolidase (U/L) level of patients in group 2 and patients in group 1, there was no statistically significant difference between the two groups, although there was an increase in serum prolidase (U/L) values in both groups. The prolidase level increased statistically significantly in both groups, but the serum prolidase (U/L) level in the blood of the patients in group 2 was higher than the serum prolidase (U/L) level in the blood of the patients in group 1.

CONCLUSION

As a result of this study, there was no statistically significant difference between the two groups in the evaluation of serum prolidase (U/L) levels in the blood of patients in group 2 and patients in group 1, although the prolidase value increased in both groups. The prolidase level increased statistically significantly in both groups, but the serum prolidase (U/L) level of the patients in group 2 was higher than the serum prolidase (U/L) level of the patients in group 1.

Serum prolidase level was found to be high in both patient groups. Pre- and postoperative serum prolidase levels were higher in patients with mitral valve insufficiency. Prolidase level is increased in coronary artery disease and mitral valve insufficiency.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Harran University Human Research Ethics Committee approved the study. Written informed consent was obtained from participants.

Conflict of interest: The authors declare that there is no conflict of interest.

Disclosure: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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