# Copeptin In Severe Mitral Regurgitation Caused By Degenerative Mitral Disease

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## ABSTRACT

**Introduction:** Copeptin is known to be inreased in cardiac heart failure. The role of copeptin in patients with severe mitral regurgitation has not been assessed in patients with preserved ejection fraction. The objective of this study is to evaluate the role of severe mitral regurgitation caused by degenerative mitral disease in copeptin release.

**Materials and Method:** 39 patients with degenerative mitral regurgitation (DMR group) and 30 control subjects (control group) were included in the study. The clinical and echocardiographic findings were recorded. Blood samples were obtained in 15 minutes before echocardiographic examination for determination of plasma copeptin. Global left ventricular longitudinal and circumferential strains were evaluated by applying 2D speckle tracking imaging.

**Results:** There was no statistical difference among copeptin levels of groups (median values for DMR:10.7 (9.0-17.1); control group:13.2 (10.6-20.7) (p = 0.42). GCSTR and GLSTR were significantly lower in DMR group (-19.2 ± 5.5 vs -23.8 ± 5.3; p = 0.002 and -17.1 ± 4.3 vs -19.9 ± 2.4 p = 0.002 respectively). LAV (83.7 ± 38.8 vs 34.1 ± 7.5 p = 0.0001) , E/e' (9.6 ± 4.0 vs 6.0 ± 1.4 ; p = 0.0001) and E/A (1.79 ± 0.5 vs 0.9 ± 0.24 p = 0.0001) ratios were significantly higher in DMR group.

**Conclusion:** Our study demonstrated that there is no significant change in serum copeptin concentrations in severe mitral regurgitation due to degenerative mitral disease . This can be attached to the filling changes of left atrium, atrial stretch receptors and increased stroke volume.

**Keywords:** Copeptin, mitral regurgitation

# Dejeneratif Mitral Hastalığa Bağlı İleri Mitral Yetersizliğinde Copeptin

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## ÖZET

**Giriş:** Copeptinin kalp yetersizliğinde yükseldiği bilinmektedir. Korunmuş ejeksiyon fraksiyonlu ileri mitral yetersizliği olan hastalarda copeptinin rolü bilinmemektedir. Bu çalışmanın amacı copeptin salınımında dejeneratif mitral hastalığa bağlı ileri mitral yetersizlikliğinin rolünü değerlendirmektir

**Hastalar ve Metod:** Dejeneratif ileri mitral yetersizliği olan 39 hasta (DMR grubu) ve 30 kontrol deneği (kontrol grubu) çalışmaya alındı. Klinik ve ekokardiyografik bulgular kayıt altına alındı. Plasma copeptin düzeyini belirlemek için ekokardiyografik incelemeden 15 dakika önce kan örnekleri alındı. Global sol ventriküler longitudinal ve circumferensiyal değerlendirme 2D specle tracking görüntüleme ile yapıldı.

**Bulgular:** gruplar arasında copeptin düzeyleri açısından anlamlı fark yoktu (median değerleri: DMR: 10.7 (9.0-17.1); kontrol grup:13.2 (10.6-20.7) (p = 0.42)). GCSTR ve GLSTR değerleri DMR grubunda control grubuna göre daha düşüktü (-19.2 ± 5.5 vs -23.8 ± 5.3; p = 0.002 ve -17.1 ± 4.3 vs -19.9 ± 2.4 p = 0.002 sırasıyla). LAV (83.7 ± 38.8 vs 34.1 ± 7.5 p = 0.0001) , E/e' (9.6 ± 4.0 vs 6.0 ± 1.4 ; p = 0.0001) ve E/A (1.79 ± 0.5 vs 0.9 ± 0.24 p = 0.0001) oranları DMR grubunda anlamlı olarak yüksekti.

**Sonuç:** Bizim çalışmamız ; dejeneratif mitral hastalığa bağlı ileri mitral yetersizliğinde kontrol grubuna göre copeptin düzeylerinde anlamlı değişiklik olmadığını göstermiştir. Bu bulgu sol atriyal dolum değişiklikleri, atrial stretch reseptörleri ve artmış stroke volüm ile ilişkilidir.

**Anahtar Kelimeler:** Copeptin, mitral yetersizlik

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***Introduction:***

Neurohormones have been used in the setting of a variety of cardiovascular conditions due to their diagnostic and prognostic values. Vasopressin, an antidiuretic and vasoconstricting hormone, is synthesized in the hypothalamus and excreted by the posterior pituitary gland. Vasopressin has three receptors $V_{1a}$, $V_{1b}$ and $V_2$. Via $V_{1a}$ receptors, vasopressin causes vasoconstriction and cardiac remodeling by increasing afterload, decreasing systemic vascular resistance and increasing cardiac output.[1] $V_2$ receptor is responsible for antidiuretic effect of vasopressin which leads to increased preload and consequently, increased left ventricular (LV) filling.[2,3] Vasopressin also promotes myocardial fibrosis by stimulating cardiac fibroblasts.[4,2,3] Vasopressin level cannot be determined readily because of it is unstable and rapidly cleared feature.[4] Copeptin is a 39-aminoacid-long C terminal segment of the peptide precursor molecule to vasopressin. It is produced with vasopressin and is secreted in equimolar amount. It is more stable and easy to measure.[5] Copeptin has been shown to be increased in cardiovascular diseases, especially in acute coronary syndromes and CHF. Copeptin is also associated with ventricular remodeling due to changes in left ventricular ejection fraction (LVEF) and volumes.[6] It was found to be the strongest predictor of mortality especially in patients NYHA classes 2 and 3.[4,2,1,7] Although vasopressin has beneficial effects in short term in CHF, it may have deleterious effects in the long term owing to vasoconstriction, decrease in cardiac output and contractility.[8] Not only in heart failure and coronary syndromes but copeptin also has been shown increased in patients with mitral and aortic stenosis (AS) in a few study. In a study, copeptin has been found a novel biomarker of degenerative aortic stenosis in patients with preserved LVEF independent of the coexisting coronary artery disease owing to ventricular remodeling and changes in left ventricular volume and LVEF.[3] In another study copeptin was found significantly increased in patients with mitral stenosis (MS) and they also found that after mitral balloon valvuloplasty copeptin levels decreased dramatically.[9] In severe mitral regurgitation (MR) , there is a different physiopathology on atrial filling and cardiac output. The atrial walls has atrial volume receptors that respond to distention rather than pressure which is called atrial stretch receptors.[10] These receptors have substantial effect on vasopressin system. The objective of this study is to evaluate and compare the role of severe MR in release of copeptin in patients with degenerative mitral regurgitation (DMR).

***Methods:***

The study included 39 patients with severe MR who were referred to Kartal Kosuyolu Heart Education and Research Hospital between January 2014 and April 2015 for echocardiographic examination.

30 subjects with no mitral regurgitation and normal LVEF (control group) were taken as control group. The NYHA classes of both groups were II and III. Patients who had DMR (mitral valve prolapse, chordae tendineae rupture) and normal LVEF(>60%), were enrolled in the study prospectively. The patients who had organic MR caused by other reasons including rheumatic or senile degenerative heart valve disease, mitral annular calcification, infective endocarditis and patients with reduced LVEF were excluded from the study. Local Ethics Committee approved this study.

Blood samples were obtained in 15 minutes before echocardiographic examination for determination of plasma copeptin. They were collected using pyrogen-free tubes containing EDTA and centrifuged at 5000 r.p.m. for 10 minutes. Plasma was stored at – 20 ºC until analysis. The plasma samples are analyzed with human copeptin Eliza kit (*SHANGHAI YEHUA Biological technology Co, Ltd, Shanghai China*). Assay range is 0,05 ng/ml-20 ng/ml.

*Echocardiography:*

Standard echocardiographic evaluations were performed using a 1 to 5 MHz X5-1 transducer (*iE33, Philips Healthcare, Inc., Andover, MA*). Patients were examined in the left lateral position. Measurements were averaged over 3 consecutive heart cycles. All standard 2D transthoracic echocardiographic images from parasternal long axis, short axis, apical four, three and two chamber views. Color Doppler and tissue Doppler images were stored in cine loop format triggered to the QRS complex. The left ventricular diastolic and systolic diameters were measured using M-mode or 2-dimensional echocardiography. LVEF was calculated according to Simpson's formula employing a two-dimensional image of the ventricular chamber during systole and diastole in the four- and two-chamber apical views.

Mitral inflow velocities are measured by PW-Doppler where sample volume is placed at the tips of the mitral valve in the left ventricle. E and A wave velocities were recorded. The mitral annular velocities are measured by pulsed wave tissue Doppler imaging (PW-TDI). PW-TDI sample volume is place at the level of the lateral and septal mitral annulus. Septal and lateral E' and A' wave velocities were recorded. E/E' ratio for septal and lateral mitral annulus and E/A ratio were calculated.

The quantification of MR was assessed as recommended.[11] The proximal isovelocity surface area (PISA) is visualized from apical four-chamber view. The radius of the PISA is measured at mid-systole using the first aliasing. Regurgitant volume (RV) and effective orifice area (EROA) are obtained using the standard formula. For DMR, RV > 60 mL/beat or EROA>0,4 $cm^2$ were considered as severe MR.[14] The configuration of mitral leaflets was assessed from the parasternal long axis and apical views. In addition to 2D

transthoracic echocardiographic views, all patients with severe DMR underwent 2D and 3D transesophageal echocardiographic examination which provided precise information on type and extent of anatomical lesions, mechanism of regurgitation, etiology and reparability of the valve. Bicommissural mitral annular diameter was measured by conventional 2D transesophageal echocardiography at 60-75 degrees and anterior-posterior diameter was measured at 120 degree in the parasternal long-axis view. Anterior and posterior leaflet lengths were measured in diastole at 120º.

Tricuspid annular plane systolic excursion in the apical four-chamber view and the tricuspid annulus peak systolic velocity (TAPSV) with TDI were used to evaluate right ventricular function.

Left ventricular circumferential and longitudinal strain parameters [global cicumferential left ventricular strain(GCSTR), global longitudinal left ventricular strain(GLSTR)] was evaluated using 2D speckle-tracking imaging. Global circumferential strain was assessed by applying 2D speckle-tracking imaging to the parasternal short axis views of left ventricle. The longitudinal peak systolic strain was assessed by applying 2D speckle-tracking imaging to the apical four, three and two-chamber views. The interpretation of echocardiograms were blinded to copeptin levels.

***Statistical Analysis***

Data management and analysis were performed using IBM SPSS Statistics 16.0 (*SPSS, Chicago, IL*) software. Data are presented as mean ± standard deviation for continuous variables and as percentages for categorical variables. Normal distribution was analyzed using the Kolmogorov-Smirnov test. Categorical variables were compared using Chi-Square or Fisher's Exact test as appropriate. One-way ANOVA with Tukey post hoc was used to compare continuous variables among groups; when homogenity of variance was not present, the Kruskal-Wallis test was used for nonparametric independent samples. Mann-Whitney test for nonparametric independent samples for inter-group comparisons were performed to confirm significance. Correlations were tested by Pearson or Spearman's correlation tests, as appropriate. A *p* value <0.05 was considered statistically significant.

***Results***

The clinical, echocardiographic and laboratory caharacteristics of patients are shown in ***Table*** 1. Age and gender were not statistically different in all groups (p = 0.96 ; p = 0.36, respectively). Sodium levels (p = 0.42) and also systolic and diastolic blood pressure values (p = 0.54 ; p = 0.06, respectively) were in normal ranges and there was no statistical difference among all groups. Atrial fibrillation was %5,1 in DMR group and none in control group.

Left atrial volumes were statistically different between DMR and control group (p = 0,0001). There was no statistical difference among copeptin levels of two groups (median values are for DMR: 10,7 (9,0-17,1) control: 13,2 (10,6-20,7) ;p = 0.42)

LA ,LVEDD and LVESD were significantly higher in DMR group. Although there was no statistical difference in LVEF (p = 0.22), GCSTR and GLSTR were significantly lower in DMR group (p = 0.002 and p = 0.002 respectively). LAV, E/e' and E/A ratios were significantly higher in DMR group (p = 0.0001 for each value)

***Discussion***

Our study demonstrated that copeptin levels are similar between control and severe DMR group. As known from several studies copeptin levels are increased in several cardiac conditions. But in our patient group we could not find a trend towards an increase in copeptin levels. In our patient group NYHA functional classes were II - III . In a study copeptin was found independently related to mortality in each symptomatic stage of heart failure but NYHA functional classes II and III were the most compelling.[7] Patients with heart failure generally have low osmolality and low sodium levels which cause increased copeptin levels. An inverse relationship between blood pressure and copeptin has also been established.[4] However, In our patients, sodium levels and blood pressure values were in normal ranges. And also, copeptin may not always demonstrate a direct correlation with conventional parameters of cardiac status largely due to its independent features.[2]

In patients with AS increased left ventricular systolic pressure, reduced coronary flow, subendocardial ischemia, decreased stroke volume leads to an elevation of copeptin levels.[6] In patients with MS, decreased preload and stroke volume leads to increase in copeptin levels[9] In patients with MR, there is a different physiopathology unlike patients with AS and MS and effect on copeptin release seen in this present study.

The increased volume of blood that enters the left atrium during ventricular systole is responsible for increased left atrial pressure in severe MR. In long-standing or chronic MR, the left atrium adapts to the larger volume by dilating, which increases its compliance. In DMR group, the regurgitant flow into the left atrium increases left atrial pressure, leading to atrial enlargement and increased compliance. In addition, through the reduced afterload,ventricular overcome the volume overload by increasing the total cardiac output. Increases in preload, wall tension, diastolic volume and stroke volume occur.[12] On the other hand, the atrial walls has atrial volume receptors that respond to distention rather than pressure which is called

atrial type B fibers and as well as atrial stretch receptors.[10] These receptors are considered to respond only to the changes in distention of the atrium which is dependent to changes in filling.[10] Suppression of activities in the neurosecretory cells is produced only by left atrial stretch but not the right. As far as we know, in an experimental study, the distention of left atrium with an indwelling balloon produce increased activity of these receptors and diuresis. Therefore left atrial distention, like 'sudden stretch' of mitral regurgitant volume in severe MR, may lead to activation of these receptors and decrease the release of copeptin. Besides a drop in atrial filling cause a release of copeptin. Some experimental studies showed that there was a better relationship between the level of fiber activity (afferent fibers from receptors affected by atrial distention) and the rate of rise or pulse pressure of the 'v' wave than mean atrial pressure.[10] In DMR group, the presence of an excessive volume load that cause left atrial enlargement and increased left atrial pressure can lead to 'sudden stretch' of left atrium and thus activates this volume receptors and suppress the release of copeptin in the presence of normal cardiac output and left ventricular function. However the release of copeptin is primarily regulated by a change in osmolality and less importantly by input from left atrial volume receptors.[13,14] This may be the reason why our severe DMR group copeptin levels seems lower than control group although it is not statistically significant. But it is suggested that the filling volume of atria which is in a relation to the circulating and thoracic blood volume could be considered together with the information from both stretch and pressure receptors. There are three mechanisms that can explain increased levels of copeptin in heart failure patients: reduced cardiac output, hyponatremia and increased angiotensin II which is a co-stimulator of copeptin.[15]. In our patient group, left ventricle function assessed by global circumferential and longitudinal strain imaging was reduced compared to control group although LVEF was not significantly different between groups. But cardiac outputs were normal and no hyponatremia was determined. Also the markers of left ventricular diastolic function was higher in DMR group there was no correlation between copeptin and diastolic dysfunction markers. Hage et al. found that copeptin was elevated in heart failure patients with preserved ejection fraction but not correlated with markers of diastolic dysfunction.(16)

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***Limitations***

The major limitation of our study is the relatively low number of patients included. Our study included only patients with severe MR. There is no adequate comparable data between severe and mild or moderate MR. Novel biomarkers including NT-pro-BNP, pro-adenomedullin and copeptin may correlate well with each other in certain conditions.[13,14] We used copeptin as a single biomarker but there are some data suggest

that copeptin as a single biomarker approach may oversimplify or overestimate influence of biomarkers in heart failure.[14] And also only patients with chronic severe MR are included in this study.

***Conclusion***

The present study demonstrated that there is no significant change in serum copeptin concentrations in severe mitral regurgitation due to degenerative mitral disease. This can be attached to the filling changes of left atrium, atrial stretch receptors and increased stroke volume. However, further studies are required to investigate the role of MR and copeptin response in patients with preserved LVEF.

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

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| **GROUPS** | **DMR** (n:39) | **control** (n:30) | **P VALUE** |
|---|---|---|---|
| **AGE** | 52,5 ± 15,1 | 52,6 ± 9,3 | 0,96 |
| **GENDER** | 9 (23.1%) | 10 (33.3%) | 0,36 |
| **COPEPTIN (ng/mL)** | 10,7 (9,0-17,1) | 13,2 (10,6-20,7) | 0,42 |
| **UREA (mg/dl)** | 31,0 (25-46) | 31 (26,8-36) | 0,062 |
| **CREATININ (mg/dl)** | 0,86 (0,68-1,0) | 0,8 (0,7-0,9) | 0,42 |
| **SODIUM (mmol/L)** | 139 ± 2 | 139,3 ± 1,6 | 0.42 |
| **SBP (mm Hg)** | 128,8 ± 6,8 | 127,6 ± 9,1 | 0.54 |
| **DBP (mm Hg)** | 80 (75-80) | 80 (75-80) | 0.06 |
| **AF** | 2 (5,1 %) | 0 | 0,0001 |
| **LA** (cm) | 4,18 ± 0,73 | 3,31 ± 0,37 | 0,0001 |
| **LVESD** (cm) | 3,56 ± 0,67 | 2,89 ± 0,40 | 0,0001 |
| **LVEDD** (cm) | 5,80 ± 0,74 | 4,71 ± 0,41 | 0,0001 |
| **LVEF** (%) | 64,5 ± 2,02 | 65,1 ± 1,94 | 0.22 |
| **E** (cm/sn) | 96.2 ±25.5 | 65.1 ± 16.6 | 0,0001 |
| **A** (cm/sn) | 50 (50 – 60) | 70 (60-80) | 0,0001 |
| **Esep (cm/sn)** | 9,3 ± 3,59 | 10,1 ± 3,49 | 0,47 |
| **Elat (cm/sn)** | 11,5 ± 3,95 | 11,0 ± 3,5 | 0,61 |
| **E/e' sep** | 9.2 (7.5 – 13.6) | 6.6 (5.0-9.0) | 0,085 |
| **E/e' lat** | 9,6 ± 4,0 | 6,0 ± 1,4 | 0,0001 |
| **E/A ratio** | 1,79 ± 0,5 | 0,9 ± 0,24 | 0,0001 |
| **LAV** | 83,7 ± 38,8 | 34,1 ± 7,5 | 0,0001 |
| **TAPSE** (mm) | 25 (22-31) | 25 (20,5-28,5) | 0,92 |
| **TAPSV** (cm/sn) | 15,5 (13-18) | 15 (13-17) | 0,71 |
| **EROA** ($cm^2$) | 68,75 ±27,23 | | |
| **PISA** (cm) | 1,31 ± 0,22 | | |
| **RV** (ml) | 95,97 ± 30,6 | | |
| **GCSTR** (%) | -19.2 ± 5.5 | -23.8 ± 5.3 | 0,002 |
| **GLSTR** (%) | -17.1 ± 4.3 | -19.9 ±2.4 | 0,002 |

TABLO I. Baseline characteristics of mean and median values of clinical and echocardiographic parameters

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, AF: Atrial fibrillation, LA: left atrium, LVESD: left ventricular end systolic diameter, LVEDD: left ventricular end diastolic diameter, LVEF: left ventricular ejection fraction, E:mitral inflow e wave, A: mitral inflow a wave, Esep: Septal annular E', Elat: Lateral annular E',E/e'sep: Septal annular E/e', E/e' lat: lateral annular E/e', LAV: left atrial volume, TAPSE: tricuspid annular plane systolic excursion, TAPSV: tricuspid annular peak systolic velosity, EROA: efective regurgitan orifice area, PISA: proximal velosity surface area, RV: regurgitant volume, GCSTR: global cicumferential left ventricular strain, GLSTR: global longitudinal left ventricular strain