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# Clinical Determinants of Plasma Metaloproteinase-9 in Systolic Chronic Heart Failure

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## Abstract

Matrix metalloproteinases (MMPs), particularly MMP-9, are estimated to play an important role in the progression of systolic chronic heart failure (CHF); however, the existing data is incomplete and controversial. **Purpose:** The aim of this study was to investigate the changes in plasma MMP-9, associated with CHF and to determine the prognostic value of certain clinical parameters on MMP-9 levels. **Methods:** Plasma MMP-9 was measured in 20 normal elderly controls (NEC) and in 59 patients with CHF. Systolic dysfunction was defined as left ventricular ejection fraction (LVEF) ≤40%. Plasma MMP-9 levels and brain natriuretic peptide (BNP) were measured performing immunoassays. Normally distributed variables were reported with mean and skewed variables with the median. Group comparisons were made with the independent t-test, Mann-Whitney U-test and $\chi^2$-test, where appropriate. Univariate associations of the variables with MMP-9 were investigated using linear regression analyses. Natural logarithmic transformation was used for skewed variables, including MMP-9 and BNP. Multiple linear regression was used to investigate the independent relations to MMP-9. Statistical analyses were conducted on the SPSS version 13.0 (SPSS Inc, Chicago, IL). **Results:** Plasma MMP-9 concentrations (ng/ml) were significantly higher in HF patients (median 1.7, range 0.5-7.3), compared with NEC (median 1.2, range 0.6-2.9) (p=0.01). Circulating BNP and functional class were not significantly correlated with plasma MMP-9. In addition, no significant relationships were observed between MMP-9 and etiology, leucocytes, and creatinkinase (CK). Plasma levels of MMP-9 showed significant correlation with the clinical parameters LVEF, systolic blood pressure (SBP) and atrial fibrillation (AF). Independent predictive effect on MMP-9 levels in multiple regression analysis (F=7.7, p<0.01) were explored for AF, LVEF, SBP and COPD. **Conclusions:** Plasma MMP-9 was observed to increase in subjects with CHF. Expectedly, MMP-9 was independently correlated with the degree of cardiac dysfunction and clinical parameters depending on it, including SBP and AF, and with the presence of COPD. Further studies are warranted on the concrete mechanisms of MMP-9 variations in patients with CHF. IJBM 2011; 1(3):143-149. 

***Key words:*** *metaloproteinase-9, chronic heart failure, atrial fibrillation, systolic blood pressure.*

## Introduction

Over the last decade, considerable evidence was found that identified the role of the myocardial extracellular matrix in maintaining myocardial integrity, cardiac remodeling and mechanical function [1]. These evidences instigated research focused on the family of enzymes recognized as being related to the pathogenesis of left ventricular (LV) dysfunction [2-4]. For instance, the group of matrix metaloproteinases (MMP), a complex group of endopeptidases (zinc-dependent proteases) plays an important role in cardiovascular physiology and pathology, implementing the regulatation of the synthesis and degradation of the myocardial extracellular proteins.

There are, however, limited data on the complex relationship between MMPs, neurohormonal activation and clinical parameters of impaired cardiac function in patients with chronic heart failure (CHF). There is great need for further study on MMP-9 in patients with CHF in the context of the still incompletely clarified mechanisms of MMPs activation and the subsequent plasma profile in CHF patients.

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## Purpose

The aim of this study was to investigate the changes in plasma MMP-9, associated with systolic CHF and to determine the prognostic value of certain clinical parameters of impaired cardiac function on the plasma MMP-9 levels.

## Patient population and study protocol

Plasma MMP-9, was measured in 20 normal elderly controls (NEC) and in 59 patients with systolic CHF, between 48 and 81 years, (mean age 69.3±7.9 years) admitted to the Clinic of Cardiology, Dept. of Internal Medicine, University Hospital Alexandrovska, Medical University of Sofia. A diagnosis of CHF was given in cases where typical symptoms, radiological data for pulmonalry congestion, and/or considerable clinical response to the conducted therapy (ESC 2005) were found. Systolic dysfunction was defined as left ventricular ejection fraction (LVEF) ≤ 40%. Additional exclusion criteria for inclusion in the study included patients with primary pulmonary hypertension, congenital cardiac malformations, patients awaiting cardiac transplantation, having suffered stroke within three months, with any disease of less than a one-year time period of expected survival, known history of alcohol or drug abuse or severe disability due to any cause. Twenty-three (37.1%) patients had ischemic cardiomyopathy identified by cardiac catheterization. The study was approved by the local Ethical Committee at the Medical University of Sofia. Informed consent was obtained from the subjects before they were recruited into the study.

### *Control group*

The control group consisted of healthy subjects, similar in mean age (68.7±7.9 years) to the cases under study. All the subjects were questioned and carefully examined to exclude concomitant pathologic conditions. Only those subjects who were free from any history of the disease and medication were eligible. The total number of controls for analyses and comparisons with the cases under study was 24.

All patients underwent a detailed clinical examination and interview according to the standard protocol, to collect information on biologic and demographic data including age, gender, cardiovascular risk factors and blood pressure (systolic and diastolic). All information on medical history and medication was documented, and anthropometric measurements were performed in a standardized manner. Most part of the interview consisted of questions on clinical characteristics and included queries on the etiology of CHF, comorbidity, NYHA functional class, heart rate and rhythm and clinical signs of CHF.

Instrumental assessment was conducted at admission and included:

- Standard electrocardiogram obtained from 12 leads;
- Radiographic examination assessed for the signs of left chamber enlargement, pleural effusion, pulmonary vascular congestion and cardiothoracic ratio (<0.6 / ≥0.6).
- Echocardiography measured left ventricular ejection fraction (LVEF). LVEF was calculated following standard recommendations based on Simpson's method in the standard two-chamber view position. Left ventricular hypertrophy (LVH) was assessed by calculating the LVH score. The LVH score (mm) is equal to the sum of the thickness of the left ventricular posterior wall and interventricular septum divided by 2.

### *Biochemical tests*

Blood samples were taken at admission from both patients and controls, for biochemical analyses. Blood investigations included information on blood count, serum electrolytes (sodium and potassium), creatinine, enzymes and lipid status.

Plasma MMP-9 and brain natriuretic peptide (BNP) were measured with immunoassays. Blood samples for BNP and MMP-9 were taken at discharge. Plasma BNP was analyzed in the laboratory of Medicobiologic Investigations, Institute of Molecular Biology, Bulgarian Academy of Sciences, through the enzyme related immunosorbent method (ELISA), using the commercially available kit (BNP-32, IBL Hamburg).

Blood samples were collected with Vacutainer (Beckton Dickinson, NJ, USA) in EDTA containing tubes. Samples were centrifuged up to 1 hour after sampling, and plasma and serum were stored at -20° until assayed.

The analyses were done on the ELISA reader of Biolab. Sensitivity of the method was observed to be 4 pg/ml. Intraassay coefficient of variation was assessed as 5%, whereas the interaassay variation was < 14%.

The concentrations of plasma MMP-9 protein were investigated by Ensymeimmunoassay (EIA- ELISA assays) on the ELISA reader Trinitron in the Institute of Biology and Immunology of Reproduction at the Bulgarian Academy of Sciences, Sofia, Bulgaria.

MMP-9 was determined using the MMP-9 kit, IBL Hamburg. The sensitivity of the method of investigation of MMP-9 was found to be 0.05 ng/ml. Intraassay coeficient of variation was assessed as 7.3%, whereas the interassay variation was <10.2%.

### *Statistical analysis*

The data were tabulated in terms of frequencies and percentages for categorical variables, and by mean and standard deviations (SD) for continuous variables. Normally distributed variables were reported with mean and skewed variables with median and interquartile range of values (IQR). Group comparisons were made with the independent t-test, Mann-Whitney U-test and $\chi^2$-test, where appropriate. Univariate associations of the variables with MMP-9 were investigated with linear regression analyses. Natural logarithmic transformation was used for skewed variables, including MMP-9 and BNP. Multiple linear regression was used to investigate the independent relations to MMP-9. Multivariate linear regression models were conducted, including variables with a univariate level of significance of $p<0.010$.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), endsystolic volume (ESV), end-diastolic volume (EDV), end-systolic diameter (ESD), and end-diastolic diameter (EDD) values were entered as continuous independent variables in the linear regression analyses. The rest of the investigated independent variables were entered

in the models as categorical variables.

Statistical analyses were done on the SPSS version 13.0 (SPSS Inc, Chicago, IL).

# Results

***Comparison between the groups***

The detailed characteristics of the CHF patients are listed in Table 1. Biochemical parameters are shown in Table 2.

***Table 1***
*Characteristics of patients with CHF investigated for MMP-9*

| Parameters | Mean (SD) Median (IQR) |
|---|---|
| Age≥ 65 years | 42 (71.2) |
| Women | 25 (42.4) |
| *Comorbidity and risk factors* | |
| Arterial hypertension | 49 (83.1) |
| Diabetes mellitus | 15 (25.4) |
| COPD | 10 (16.9) |
| Smokers | 8 (13.6) |
| Ischaemic etiology | 28 (47.5) |
| Myocardial infarction | 23 (39.0) |
| *Clinical signs* | |
| Chronic atrial fibrillation | 29 (49.2) |
| SBP (mmHg) | 130 (90-180) |
| DBP (mmHg) | 80 (50-100) |
| Pulmonary congestion | 39 (66.1) |
| Peripheral edema | 33 (55.9) |
| NYHA Functional class | |
| II | 15 (25.4) |
| III | 16 (27.1) |
| IV | 15 (25.4) |
| *Instrumental data* | |
| Radiographic data for pulmonary congestion | 35 (59.3) |
| *Echocardiography* | |
| EDV (ml) | 134 (58-456) |
| ESV (ml) | 83 (28-311) |
| LVEF <40% | 25 (42.4) |
| LVH score (mm) | 12 (7-16) |
| $P_{max}$ in *a. pulmonalis* (mmHg) | 47 (30-90) |
| *Therapy at admission* | |
| ACE/ARB | 34 (57.6) |
| β-blockers | 41 (69.5) |

The patients group and control group significantly differed statistically in the values of hemoglobin, total serum cholesterol (TSCH), blood glucose, creatinine and serum sodium levels. Statistically significant differences were also observed for the measured levels of BNP and MMP-9. Median MMP-9 of cases (1.7 range 0.5-7.3) was significantly higher in cases compared with the established median value of the control group (1.2 range 0.6-2.9) (p=0.01) (Table 2).

***Relationship between MMP-9 and clinical parameters in patients with CHF***

The results of the univariate linear regression analyses showed a significant linear relationship between the dependent variable MMP-9 and atrial fibrillation (AF). Values of SBP, LVEF, and LV wall thickness, measured as LVH score were also found to be important univariate determinants of plasma MMP-9 levels (Tables. 3 and 4).

Etiology of CHF was not found to be a significant predictive factor of plasma MMP-9. All of the investigated laboratory variables were not significantly related to the plasma MMP-9. (Table 4).

The relationship between circulating BNP and MMP-9 was not statistically significant although a strong relationship was observed between BNP and LVEF on one side and MMP-9 and LVEF on the other. (Fig. 1, 2, 3).

The independent predictors of plasma MMP-9 were AF, SBP, LVEF and chronic obstructive pulmonary disease (COPD) (Table 5).

# Discussion

The development of an unfavorable LV remodeling is recognized as being of great prognostic importance for patients who survive acute myocardial infarction (AMI). Both the degree of LV remodeling and dilatation strongly correlate with the degree of LV dysfunction and the subsequent probability of development of CHF. The opportunity for inclusion of the MMP-9 in specific and persistent types for HF process of extracellular remodeling is confirmed by the observed significant difference in plasma MMP-9 between the control group and patient group. The results of this study revealed that MMP-9 is closely related both to the LV function and to LV wall thickness. In experimental animal models, the selective MMP inhibition was found to be related to the consequent decrease in the degree of LV wall thinning and dilatation, which corresponds to the established univariate correlation between MMP-9 and LV wall thickness, as noted in this study. As confirmation to that relationship, the data from the Framingham Heart Study has also reported a relationship between MMP-9 and both the LV dimensions, and wall thickness in healthy men, but not in women [5]. The results of this study support to the relationship between MMP-9 and LV wall thickness in patients of both genders, keeping in mind the observed nonsignificant effect of gender on plasma MMP-9.

MMPs were considered to play an important role in the pathogenesis of the tobacco-related diseases in the related discussion on tobacco-dependent mediation of inflammatory cells in lung tissue. Further, it was noted that MMP-9, as well as the MMP-2 increase, in animal studies with modeled emphysema [6]. The results of the relationship between MMP-9 and the investigated risk factors do not confirm the relationship of MMP-9 with smoking, expressed by the lower enzyme levels found in smokers, as established by some investigators. However, an independent prognostic effect of COPD on plasma MMP-9 levels was observed in the multivariate regression analysis after the inclusion of the rest of the significant univariate determinants in the model. Although the non-significant

***Table 2.***
*Comparison between patients with CHF and healthy controls*

| Variables | Patients n=53 | Healthy controls n=24 | p* |
|---|---|---|---|
| BNP (pg/ml) | 650 (401-5974) | 57 (35-118) | <0.05 |
| MMP-9 (ng/ml) | 1.7 (0.5-7.3) | 1.2 (0.6-2.9) | <0.01 |
| TSCH (mmol/l) | 4.6 (0.7) | 5.3 (0.6) | <0.05 |
| Fasting blood glucose (mmol/l) | 6.4 (2.3) | 5.4 (0.8) | <0.05 |
| Hemoglobin (g/l) | 126.5 (19.7) | 144 (19.4) | <0.05 |
| Total bilirubin (μmol/l) | 17.2 (13.5) | 16.2 (9.0) | NS |
| Creatinine (μmol/l) | 126.5 (45.7) | 97.7 (35.4) | <0.05 |
| Sodium (mmol/l) | 140 (3.7) | 144 (3) | <0.05 |
| Leucocytes (*109/l) | 7.8 (2.1) | 7.0 (1.6) | NS |
| CK (U/l) | 93.9 (65.2) | 71.1 (27.8) | NS |

***Notes:*** *The values are presented as mean with SD, median with IQR, depending on the type of data;*
** Mann-Whitney U-test*

***Table 3.***
*Univariate linear-regression analysis*

| Parameters | $R^2$ | F | β | p |
|---|---|---|---|---|
| Age≥ 65 years | 0.00 | 0.02 | 0.02 | NS |
| Women | 0.13 | 0.02 | 0.15 | NS |
| *Comorbidity and risk factors* | | | | |
| Arterial hypertension | 0.01 | 0.28 | -0.11 | NS |
| Diabetes mellitus | 0.06 | 3.61 | 0.13 | 0.06 |
| COPD | 0.06 | 3.58 | -0.36 | 0.06 |
| Smokers | 0.00 | 0.04 | -0.04 | NS |
| Ischaemic etiology | 0.02 | 1.18 | 0.16 | NS |
| Myocardial infarction | 0.02 | 0.59 | 0.12 | NS |
| *Clinical signs* | | | | |
| Chronic atrial fibrillation | 0.07 | 4.35 | -0.30 | **0.042** |
| SBP (mmHg) | 0.07 | 4.18 | 0.007 | **0.046** |
| DBP (mmHg) | 0.01 | 0.37 | 0.004 | NS |
| Pulmonary congestion | 0.01 | 0.30 | 0.08 | NS |
| Peripheral edema | 0.00 | 0.00 | 0.01 | NS |
| NYHA Functional class (II vs. III-IV) | 0.00 | 0.13 | -0.06 | NS |
| *Instrumental data* | | | | |
| Radiographic data for pulmonary congestion | 0.00 | 0.20 | 0.07 | NS |
| *Echocardiography* | | | | |
| EDV (ml) | 0.00 | 0.10 | -0.07 | NS |
| ESV (ml) | 0.08 | 2.15 | -0.33 | NS |
| LVEF <40% | 0.12 | 8.55 | -0.43 | **0.005** |
| LVH score (mm) | 0.09 | 5.21 | 0.09 | **0.027** |
| $P_{max}$ in *a. pulmonalis* (mmHg) | 0.00 | 0.43 | 0.00 | NS |

***Table 3***
*Univariate linear regression analysis for the investigated laboratory factors*

| Parameters | $R^2$ | F | β | p |
|---|---|---|---|---|
| Hemoglobin (g/l) | 0.003 | 0.16 | 0.002 | NS |
| Hematocrit | 0.005 | 0.28 | 0.69 | NS |
| Leucocytes (*$10^9$/l) | 0.020 | 1.04 | 0.04 | NS |
| Creatinine (μmol/l) | 0.028 | 1.49 | -0.20 | NS |
| Sodium (mEq/L) | 0.029 | 1.53 | 0.03 | NS |
| Potassium (mEq/L) | 0.006 | 0.31 | 0.09 | NS |
| CK (U/l) | 0.061 | 2.71 | -0.002 | NS |
| BNP (pg/ml) | 0.016 | 0.81 | -0.10 | NS |

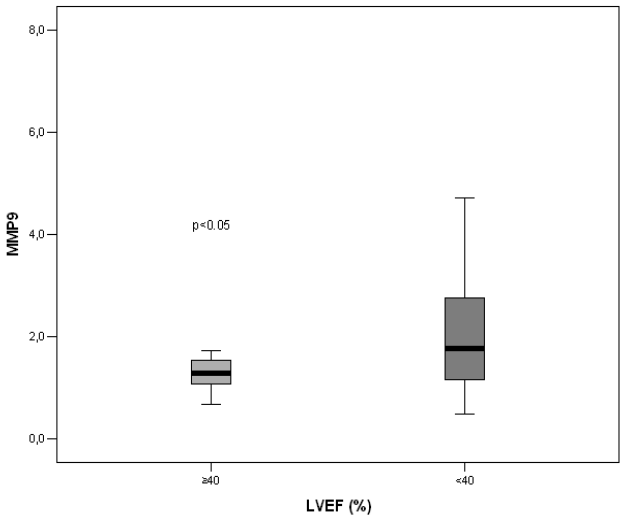


***Fig. 1***
*MMP-9 across the LVEF categories*

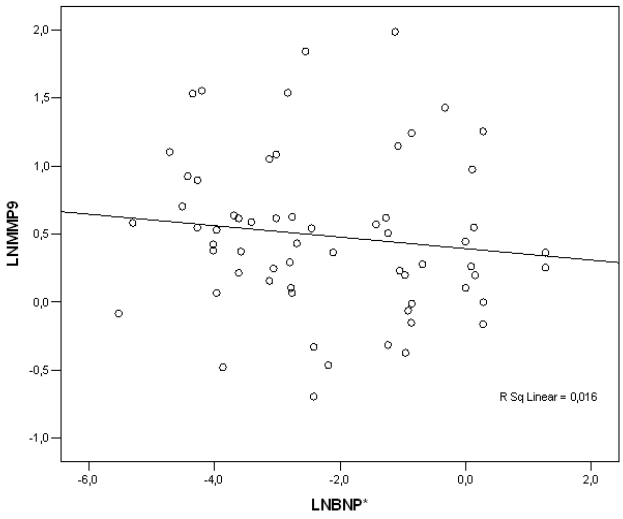


***Fig. 2***
*lnMMP-9 as a function of lnBNP (* — p>0.05)*

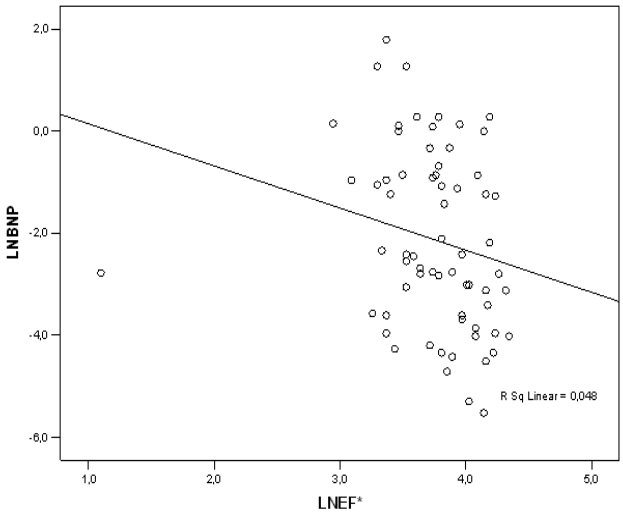


***Fig. 3.***
*lnBNP as a function of lnEF (* — p<0.01)*

***Table 5***
*Multivariate linear regression analysis*

| Parameters | $R^2$ | F | β | p |
|---|---|---|---|---|
| AF | 0.507 | 7.71 | -0.345 | **0.008** |
| SBP (mmHg) | | | 0.011 | **0.001** |
| LVEF (%) | | | -0.43 | **0.002** |
| LVH score (mm) | | | 0.011 | NS |
| DM | | | 0.136 | NS |
| COPD | | | -0.557 | **0.002** |

effect of smoking on MMP-9 was observed, it also became important to underline the considerable frequency of smoking in the COPD group, compared with the proportion of smokers among the COPD-free patient group (30.0%, vs. 10.2%) despite the very low proportion of smokers observed in the group investigated on the whole. The negative correlation observed between COPD and MMP-9 was generally connected with its participation in the pathologic processes related to the concomitant lung tissue inflammation in patients with chronic pulmonary diseases. MMP-9 values are seen to increase in patients with CHF, independently, based on the degree of neurohormonal activation in terms of the observed non-significant relationship between the BNP and the enzyme, a result also supported by other investigators of MMP-9 in patients with CHF. To test that observation and also to exclude problems with the biochemical analyses, the relationship between the BNP and LVEF was investigated and the results showed a strong significant relationship between the two variables, excluding the existing problems with the biochemical analyses. Although a significant relationship was observed between the degree of LV dysfunction and MMP-9, the degree of functional capacity does not predict the peripheral levels of the enzyme. In one of the earliest studies on MMP-9, investigating 51 patients with CHF and 52 healthy controls, Altieri et al., (2003) described the higher activity of the MMP-9 and tissue inhibitor of MMP – 1 (TIMP-1) in the group of patients with CHF and concurring with the results of this study, a nonsignificant relationship between the functional class and plasma MMP-9 [7].

A recent study showed that in patients with different cardiovascular diseases, plasma MMP-9 predicts the risk of fatal coronary disease expressed by a registered increase in MMP-9 after AMI [8]. Quite contrary to our expectations for the existing effect of ischemic etiology on plasma MMP-9 no differences were detected in the enzyme levels across the categories of etiology. In confirmation of the observed nonsignificant predictive effect of the etiology on MMP-9, Spinale et al., (2000) reported that MMP-9 increased in patients with dilated cardiomyopathy independently, based on the etiology of HF [9]. The higher MMP-9 levels observed in patients with CHF are independent of the measured leucocytes count as well as of the CK concentrations, as against the recent reports on such a relationship noted in patients with AMI.

The development of AF is a significant independent predictor of MMP-9. Pathophysiologic changes in arterial hypertension and HF reflect to a greater extent, the presence of more vulnerable thin atrial walls compared with the rest of the myocardium. The extracellular matrix has been established to not only provide support for the myocytes and maintain the structural integrity and

geometry of the heart, but to also interact with the myocytes in activation conduction. Changes in the atrial extracellular matrix components are shown to be associated with the development of sustained AF [10]. The atria are perhaps more sensitive to secretion and mechanical stimuli in the presence of CHF, which could explain the observed independent effect of AF on MMP-9 [11]. As confirmation of our results on the relationship between AF and plasma MMP-9, the results from another study reveal that MMP-9 expression increased in fibrillating atrial tissue, which may have contributed to the atrial structural remodeling and atrial dilatation during AF [12]. Xu et al., for instance, for the first time explored that the alterations of the atrial extracellular matrix components, particularly the collagen subtype (collagen I) distribution and their related MMPs/tissue inhibitor of MMPs, in patients with end-stage heart failure are distinct from those reported earlier in the ventricular myocardium and is correlated to the left atrial dimension, maintenance, and recurrence of AF in end-stage heart failure [13].

The observed independent predictive effect of SBP on plasma MMP-9 includes considerations on clinical stability and the severity of HF, considering the strong and independent relationship between LV function and MMP-9. More specifically, MMP-9 and MMP-2 play an important role in vascular remodeling and are independently related to aortic stiffness in humans [14, 15]. Increased MMP-9 and MMP-2 activity is associated with destruction of the elastic laminae of the arteries and aneurysm formation, whereas functional variants in the promoter region of the MMP-9 gene are associated with systemic arterial stiffness in patients with cardiovascular disease which are specific mechanisms that explain the observed independent predictive effect of SBP [16-18].

In conclusion, the currently existing data on MMP-9 in CHF are incomplete and insufficient. To date there are only five studies done that have investigated MMP-9 in CHF patients. The results from these studies are contoversial for reasons still not fully understood. The explanation for the observed differences among the results of those studies includes variations in the disease stage, etiology, age and gender of the patients investigated. Two of those studies did not reveal any relationship between the MMP-9 and the characteristics of HF patients. The rest of the studies, including the data from this study, support the participation of MMP-9 in the pathologic processes in CHF. Plasma MMP-9 increased in subjects with systolic HF. Expectedly, MMP-9 is independently correlated with the degree of cardiac dysfunction and the clinical parameters depending on it, including AF and SBP as well as the presence of COPD. Further studies are required to further clarify the concrete mechanisms of MMP-9 variations in CHF.

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