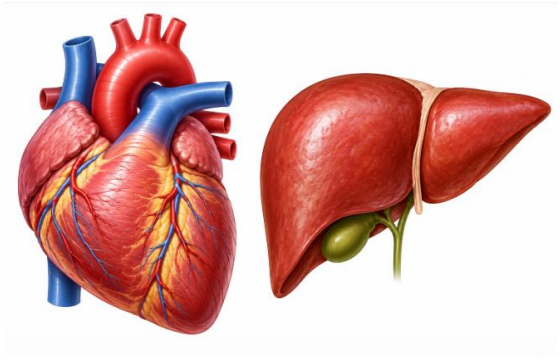

Clinical and Pathogenetic Significance of Neurohumoral Disorders in Patients with Heart Failure and Metabolic Dysfunction-Associated Fatty Liver Disease

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ABSTRACT

Background. The coexistence of heart failure (HF) and metabolic dysfunction-associated steatotic liver disease (MASLD) represents an important clinical problem in modern cardiology and hepatology. The comorbid course of these conditions is determined by complex interactions between metabolic, hemodynamic, inflammatory, and neurohumoral mechanisms. Particular attention is focused on activation of the sympathetic nervous system and the natriuretic peptide system. Therefore, assessment of urinary NT-proBNP and norepinephrine may provide additional information for the comprehensive evaluation of neurohumoral activity in patients with combined cardiometabolic disorders.

Objective. To investigate the characteristics of neurohumoral activation in patients with heart failure associated with metabolic dysfunction-associated steatotic liver disease based on urinary NT-proBNP and norepinephrine levels.

Materials and Methods. The study included patients diagnosed with heart failure and concomitant metabolic dysfunction-associated steatotic liver disease. Urinary concentrations of NT-proBNP and norepinephrine were assessed as markers of neurohumoral activity. The obtained parameters were analyzed in relation to the clinical

severity of heart failure, structural and functional cardiac characteristics, and the severity of metabolic disturbances. The findings were interpreted together with clinical, laboratory, and instrumental data.

Results. Patients with heart failure associated with MASLD demonstrated signs of neurohumoral activation characterized by increased urinary NT-proBNP and norepinephrine levels. Increased NT-proBNP was considered to reflect greater hemodynamic stress and myocardial wall tension, whereas increased urinary norepinephrine indicated enhanced sympathetic nervous system activity. The most pronounced changes were observed in patients with more severe clinical manifestations of heart failure and more substantial metabolic abnormalities.

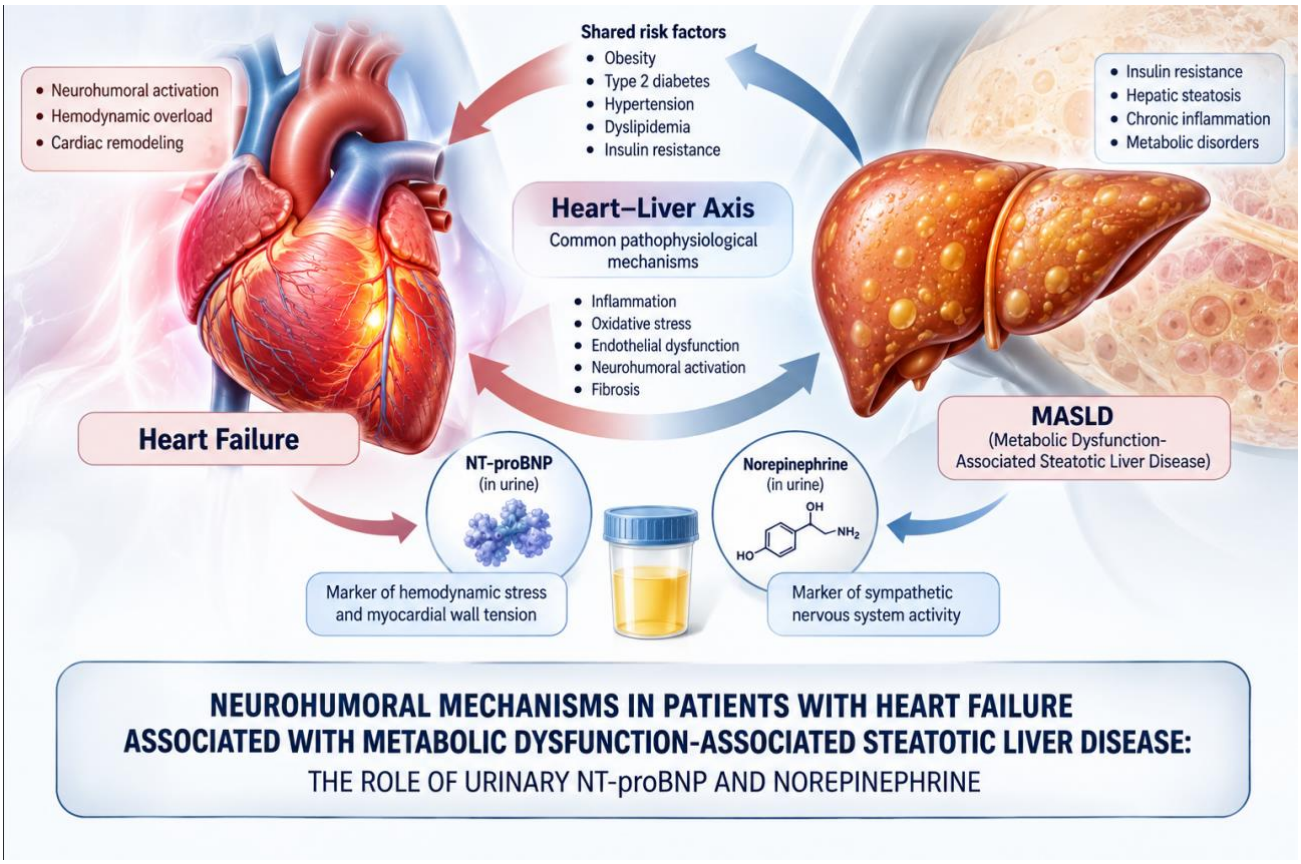
Conclusion. Simultaneous assessment of urinary NT-proBNP and norepinephrine may represent a promising complementary approach for characterizing the neurohumoral profile of patients with heart failure associated with MASLD. Combined interpretation of these biomarkers provides an integrated perspective on the interaction between cardiovascular, neurohumoral, and metabolic systems.

Keywords: heart failure, metabolic dysfunction-associated steatotic liver disease, MASLD, NT-proBNP, urinary norepinephrine, neurohumoral activation, sympathetic nervous system, natriuretic peptides, insulin resistance, cardiometabolic risk.

INTRODUCTION

Heart failure is one of the most common and progressive cardiovascular syndromes and is characterized by the inability of the heart to provide adequate cardiac output and tissue perfusion. The modern understanding of HF pathogenesis extends beyond isolated myocardial injury. Neurohumoral activation, impaired autonomic regulation, chronic inflammation, endothelial dysfunction, metabolic disturbances, and pathological cardiac remodeling all contribute significantly to disease progression.

In recent years, increasing attention has been directed toward metabolic dysfunction-associated steatotic liver disease. MASLD is now regarded as a systemic metabolic disorder closely associated with obesity, insulin resistance, type 2 diabetes mellitus, arterial hypertension, and dyslipidemia. These conditions are also major risk factors for cardiovascular disease.



The pathogenetic relationship between MASLD and heart failure is mediated by several shared mechanisms, including insulin resistance, chronic low-grade inflammation, lipotoxicity, oxidative stress, endothelial dysfunction, and neurohumoral activation. Consequently, the coexistence of hepatic steatosis and heart failure should not be viewed simply as coincidental comorbidity but rather as part of an interconnected cardiometabolic pathological process.

One of the major mechanisms contributing to HF progression is activation of the sympathetic nervous system. A reduction in effective cardiac output leads to increased sympathetic impulses and enhanced release of catecholamines, particularly norepinephrine. Initially, this response is compensatory and helps maintain blood pressure and cardiac output. However, persistent sympathetic activation becomes maladaptive and contributes to tachycardia, vasoconstriction, increased myocardial oxygen demand, arrhythmogenesis, and pathological cardiac remodeling.

Another important component of neurohumoral regulation is the natriuretic peptide system. Increased ventricular wall stress stimulates the synthesis and release of B-type natriuretic peptide (BNP). Its precursor, proBNP, is cleaved into biologically active BNP and the inactive N-terminal fragment, NT-proBNP. Because of its relatively longer half-life, NT-proBNP is widely used as an important biomarker of heart failure.

Thus, NT-proBNP and norepinephrine reflect different but interconnected components of neurohumoral activation. NT-proBNP primarily reflects hemodynamic cardiac stress and myocardial wall tension, whereas norepinephrine provides information about sympathetic nervous system activity.

Particular interest has been given to the assessment of these biomarkers in urine. Previous studies have demonstrated the possibility of measuring urinary NT-proBNP and its association with the severity of heart failure. However, urinary NT-proBNP immunoreactivity may include peptide metabolites or fragments; therefore, laboratory findings should be interpreted according to the analytical characteristics of the assay used.

For this reason, simultaneous assessment of urinary NT-proBNP and norepinephrine in patients with HF associated with MASLD is of both scientific and potential clinical interest.

AIM OF THE STUDY

To investigate neurohumoral activation in patients with heart failure associated with metabolic dysfunction-associated steatotic liver disease by determining urinary NT-proBNP and norepinephrine levels and evaluating their relationship with the clinical severity of heart failure and cardiometabolic abnormalities.

MATERIALS AND METHODS

The study included patients with an established diagnosis of heart failure who simultaneously demonstrated clinical or instrumental signs of metabolic dysfunction-associated steatotic liver disease.

The diagnostic assessment included evaluation of complaints and medical history, physical examination, determination of the functional class of heart failure, laboratory investigations, and instrumental diagnostic procedures.

Two principal biomarkers were analyzed to assess neurohumoral activity:

1. Urinary NT-proBNP — a marker of natriuretic peptide system activity and an indirect indicator of hemodynamic stress on the myocardium.

2. Urinary norepinephrine — a biomarker reflecting activity of the sympathetic component of neurohumoral regulation.

Urine samples were analyzed according to the laboratory protocol and the manufacturer's instructions for the diagnostic system used.

Interpretation of the results took into account the clinical condition of the patients, functional class of heart failure, echocardiographic parameters, presence of obesity, abnormalities of carbohydrate and lipid metabolism, and signs of hepatic involvement.

Echocardiographic assessment included determination of left ventricular ejection fraction, cardiac chamber dimensions, and parameters of diastolic function.

Depending on the distribution of the data, statistical analysis should include calculation of mean or median values. Between-group differences may be assessed

using appropriate parametric or non-parametric statistical tests. Associations between urinary NT-proBNP and norepinephrine levels and clinical or echocardiographic parameters may be evaluated using correlation analysis.

Where sufficient quantitative data are available, ROC analysis may additionally be performed to determine the diagnostic and prognostic value of the studied biomarkers.

RESULTS

The analysis demonstrated alterations in neurohumoral regulation among patients with heart failure associated with metabolic dysfunction-associated steatotic liver disease.

The principal finding was the identification of changes in two biomarkers representing different components of the neurohumoral response: urinary NT-proBNP and norepinephrine.

An increase in urinary NT-proBNP primarily reflects increased hemodynamic stress on the myocardium. As heart failure progresses, ventricular wall tension increases, stimulating the synthesis and release of natriuretic peptides and consequently increasing NT-proBNP production.

Therefore, elevated urinary NT-proBNP in the studied patients may indicate increased cardiac workload and greater severity of heart failure. Previous investigations have also reported that urinary NT-proBNP may increase with worsening HF and may be associated with indicators of cardiac dysfunction.

The second important biomarker was urinary norepinephrine. Its elevation reflects increased sympathetic nervous system activity. In heart failure, reduced effective cardiac output activates baroreflex mechanisms, increases sympathetic neural activity, and enhances catecholamine production.

Chronic sympathetic activation has a dual role. During the initial stages, it helps maintain hemodynamic stability by increasing heart rate and myocardial contractility. However, persistent sympathetic stimulation promotes vasoconstriction, tachycardia, increased myocardial oxygen consumption, and adverse cardiac remodeling.

Thus, increased urinary norepinephrine in patients with HF associated with MASLD may be considered a laboratory indicator of chronic sympathetic activation.

RELATIONSHIP BETWEEN URINARY NT-proBNP AND NOREPINEPHRINE

The simultaneous assessment of these two biomarkers is of particular scientific interest.

NT-proBNP and norepinephrine are not interchangeable biomarkers. Rather, they characterize different components of the underlying pathophysiological process.

NT-proBNP predominantly reflects:

- myocardial wall stretch;
- increased intracardiac pressure;
- hemodynamic stress;
- severity of cardiac dysfunction;
- activation of the natriuretic peptide system.

Norepinephrine predominantly reflects:

- sympathetic nervous system activity;
- intensity of the neurohumoral response;
- impaired autonomic regulation;

- chronic adrenergic stimulation.

Consequently, simultaneous elevation of both biomarkers may indicate a pronounced neurohumoral phenotype of heart failure.

Neurohumoral activation may be observed across different HF phenotypes. Previous clinical studies involving patients with preserved, mid-range, and reduced ejection fractions have demonstrated differences in neurohormonal profiles, with more pronounced neurohumoral activation reported in patients with reduced ejection fraction.

Therefore, combined determination of urinary NT-proBNP and norepinephrine may provide a more comprehensive characterization of the pathological process than assessment of either biomarker alone.

ROLE OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

The presence of MASLD may further increase neurohumoral stress.

Insulin resistance, a characteristic feature of MASLD, is associated with compensatory hyperinsulinemia, impaired lipid metabolism, and increased circulating free fatty acids.

Excessive delivery of fatty acids to the liver promotes hepatic steatosis, lipotoxicity, mitochondrial dysfunction, and oxidative stress.

At the same time, chronic low-grade inflammation develops. Pro-inflammatory cytokines may affect the vascular endothelium and myocardium, aggravating endothelial dysfunction and contributing to adverse cardiac remodeling.

These processes may increase the risk of diastolic dysfunction, arterial hypertension, and heart failure with preserved ejection fraction.

Thus, MASLD may provide a metabolic background that contributes to the progression of heart failure, while HF itself may adversely affect hepatic hemodynamics and metabolic processes.

A bidirectional pathological interaction may therefore be represented as follows:

MASLD → insulin resistance → inflammation → endothelial dysfunction → neurohumoral activation → heart failure → impaired hepatic hemodynamics → progression of hepatic dysfunction.

DISCUSSION

The findings support the concept that heart failure associated with MASLD represents a complex cardiometabolic condition in which neurohumoral activation is one of the major mechanisms contributing to disease progression.

In this context, simultaneous assessment of urinary NT-proBNP and norepinephrine is of particular interest.

An increased NT-proBNP level reflects increased cardiac chamber stress and activation of the natriuretic peptide system. BNP has vasodilatory and natriuretic effects and counteracts RAAS and sympathetic nervous system activity. However, in chronic heart failure, the compensatory capacity of this system may become insufficient.

Norepinephrine, in contrast, is one of the principal mediators of sympathetic activation. Persistent elevation reflects sustained adrenergic stimulation. During progression of HF, sympathetic activation may shift from a compensatory mechanism toward a major contributor to further deterioration of cardiac function.

Importantly, neurohumoral activation is associated with an unfavorable clinical course in heart failure. Previous studies have demonstrated that simultaneous activation of multiple neurohormonal pathways is associated with increased disease severity and adverse outcomes.

In this context, combined elevation of urinary NT-proBNP and norepinephrine may potentially identify patients with a more pronounced neurohumoral imbalance.

However, urinary biomarkers should not automatically be considered direct substitutes for plasma concentrations. In particular, urinary NT-proBNP may contain different immunoreactive peptide fragments, and its analytical characteristics may vary depending on the assay system. Therefore, these biomarkers should preferably be interpreted as components of an integrated clinical and laboratory assessment.

PRACTICAL SIGNIFICANCE

The findings may have potential practical value in the assessment of patients with concomitant heart failure and MASLD.

The use of two biomarkers allows evaluation of two interconnected components of the pathological process:

1. Urinary NT-proBNP — "hemodynamic cardiac stress."

An increased level indicates greater myocardial workload and activation of the natriuretic peptide system.

2. Urinary norepinephrine — "sympathetic regulation."

An increased level indicates enhanced sympathetic nervous system activity.

Therefore, combined assessment of these biomarkers may provide additional information regarding neurohumoral status and potentially contribute to stratification of patients according to the degree of neurohumoral stress.

Of particular interest is the comparison of these biomarkers with left ventricular ejection fraction, functional class of heart failure, body mass index, waist circumference, carbohydrate and lipid metabolism parameters, and the degree of hepatic fibrosis.

CONCLUSION

Heart failure in patients with metabolic dysfunction-associated steatotic liver disease is characterized by complex interactions between metabolic, inflammatory, hemodynamic, and neurohumoral mechanisms. Assessment of **urinary NT-proBNP and norepinephrine** provides information on different components of neurohumoral activation: NT-proBNP predominantly reflects hemodynamic cardiac stress and myocardial wall tension, whereas norepinephrine reflects sympathetic nervous system activity. Simultaneous elevation of these biomarkers may indicate a more pronounced neurohumoral imbalance in patients with HF associated with MASLD. Further studies involving larger patient populations, standardized laboratory methods, correlation analysis, and ROC analysis are required to determine the independent diagnostic and prognostic value of urinary NT-proBNP and norepinephrine. Thus, combined assessment of these biomarkers represents a promising direction for investigating neurohumoral mechanisms in patients with heart failure and MASLD.

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