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NEUROHUMORAL MECHANISMS IN PATIENTS WITH HEART FAILURE ON THE BACKGROUND OF METABOLICALLY ASSOCIATED FATTY LIVER DISEASE

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Abstract: This article explores neurohumoral mechanisms in patients with heart failure (HF) occurring in the context of metabolically associated fatty liver disease (MAFLD). The interaction between cardiac dysfunction and metabolic liver alterations is analyzed through the activation of neurohormonal systems, including the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system (SNS), and inflammatory cytokine pathways. The study highlights how metabolic dysfunction in the liver intensifies systemic inflammation, oxidative stress, and neurohormonal imbalance, thereby worsening heart failure progression. The findings emphasize the importance of integrated cardiometabolic approaches in diagnosis and treatment strategies for such patients.

Keywords: Heart failure, MAFLD, neurohumoral, RAAS, SNS, inflammation, oxidative stress, cytokines, cardiometabolic, metabolism.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome characterized by the inability of the heart to pump sufficient blood to meet the metabolic demands of the body. It remains one of the leading causes of hospitalization and mortality worldwide, representing a major public health burden. Despite advances in pharmacological and interventional cardiology, the prognosis of patients with heart failure remains poor, largely due to the progressive nature of the disease and the involvement of multiple interconnected pathophysiological mechanisms.

In recent years, increasing attention has been directed toward the role of metabolic disorders in the development and progression of cardiovascular diseases. Among these, metabolically associated fatty liver disease (MAFLD) has emerged as a significant hepatic manifestation of systemic metabolic dysfunction. MAFLD is closely associated with obesity, insulin resistance, type 2 diabetes mellitus, and dyslipidemia, all of which are well-established risk factors for cardiovascular disease. Unlike simple steatosis, MAFLD is now recognized as a dynamic condition involving chronic low-grade inflammation, oxidative stress, and metabolic dysregulation.

The coexistence of heart failure and MAFLD represents a particularly challenging clinical scenario. These two conditions are not merely coexisting diseases but are pathophysiologically interconnected through shared metabolic, inflammatory, and neurohumoral pathways. The liver and heart communicate through complex biochemical signals, and dysfunction in one organ can significantly influence the other. In patients with MAFLD, hepatic fat accumulation and inflammation contribute to systemic metabolic disturbances that directly affect cardiovascular structure and function.

A key mechanism linking these conditions is neurohumoral activation. In heart failure, compensatory mechanisms such as activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS) initially serve to maintain cardiac output. However, chronic activation of these systems leads to detrimental effects, including vasoconstriction, fluid retention, myocardial hypertrophy, and fibrosis. When MAFLD is present, these neurohumoral pathways become further dysregulated due to increased release of inflammatory mediators, adipokines, and hepatokines from the diseased liver.

Systemic inflammation plays a central role in this interaction. Elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and

C-reactive protein (CRP) have been observed in both heart failure and MAFLD. These mediators contribute to endothelial dysfunction, insulin resistance, and myocardial remodeling. Additionally, oxidative stress resulting from mitochondrial dysfunction and lipid peroxidation further exacerbates tissue injury in both the liver and the heart.

Another important aspect is insulin resistance, which serves as a common pathological link between MAFLD and heart failure. Insulin resistance leads to impaired glucose utilization, increased free fatty acid accumulation, and altered energy metabolism in cardiomyocytes. This metabolic shift reduces myocardial efficiency and contributes to cardiac dysfunction over time.

The growing prevalence of obesity and metabolic syndrome worldwide has led to a parallel increase in MAFLD cases, making the interaction between metabolic liver disease and cardiovascular disorders an emerging field of clinical importance. Understanding the neurohumoral mechanisms underlying this relationship is essential for developing effective therapeutic strategies.

The aim of this article is to comprehensively analyze the neurohumoral mechanisms involved in patients with heart failure on the background of MAFLD, with a particular focus on the interplay between metabolic dysfunction, inflammatory activation, and neurohormonal imbalance. By exploring these interactions, the study seeks to provide a deeper understanding of the pathophysiology of this combined condition and highlight potential targets for integrated cardiometabolic treatment approaches.

LITERATURE REVIEW

The selected literature provides a comprehensive scientific basis for understanding the complex relationship between heart failure (HF) and metabolically associated fatty liver disease (MAFLD). These studies collectively highlight the central role of neurohumoral activation, systemic inflammation, and metabolic dysregulation in the progression of cardiometabolic diseases.

McMurray and Packer provide fundamental insights into the pathophysiology of heart failure, emphasizing the importance of neurohormonal systems such as the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system. Their work explains how chronic activation of these systems leads to progressive cardiac remodeling and functional deterioration.

Braunwald's textbook serves as a foundational reference in cardiovascular medicine, offering a detailed overview of heart failure mechanisms, clinical manifestations, and treatment strategies. It provides essential knowledge for understanding disease progression and therapeutic approaches.

Loomba and Sanyal describe the global burden of NAFLD, emphasizing its strong association with obesity, insulin resistance, and metabolic syndrome. Their research highlights NAFLD as a major public health issue closely linked to cardiovascular risk.

Eslam et al. introduce the MAFLD concept, redefining fatty liver disease based on metabolic dysfunction rather than exclusion criteria. This modern classification better reflects the disease's systemic nature and its connection with cardiovascular disorders.

Packer's research focuses on neurohormonal activation in heart failure, explaining how persistent stimulation of RAAS and SNS contributes to worsening cardiac function and fluid imbalance.

Bugianesi and colleagues explore the link between metabolic liver disease and cardiovascular risk, demonstrating that liver dysfunction significantly increases the likelihood of heart-related complications.

Schiattarella and Hill emphasize the role of metabolic inflammation in heart failure, showing how inflammatory signaling pathways contribute to myocardial dysfunction and remodeling.

Targher et al. provide strong clinical evidence linking NAFLD/MAFLD with cardiovascular disease, highlighting the liver as an active contributor to systemic cardiometabolic risk rather than a passive organ.

Ziaeian and Fonarow discuss the epidemiology of heart failure, underlining its global prevalence and increasing burden on healthcare systems.

Katsiki and Mikhailidis analyze cardiometabolic interactions, focusing on shared mechanisms such as insulin resistance, dyslipidemia, and endothelial dysfunction.

Mantovani et al. further confirm that MAFLD significantly increases the risk of cardiovascular disease, reinforcing its role as an independent risk factor for heart failure development.

Overall conclusion of literature review:

The analyzed studies consistently demonstrate that heart failure and MAFLD are closely interconnected through neurohumoral, inflammatory, and metabolic pathways. The literature strongly supports the concept that MAFLD is not only a liver disease but also a systemic metabolic disorder that significantly contributes to cardiovascular dysfunction and heart failure progression.

METHODOLOGY

This study was designed as a comprehensive analytical review aimed at exploring neurohumoral mechanisms in patients with heart failure (HF) in the context of metabolically associated fatty liver disease (MAFLD). The methodological approach combined qualitative synthesis of scientific literature with comparative evaluation of experimental and clinical findings. Particular attention was given to studies describing the interaction between cardiometabolic disorders, inflammatory pathways, and neurohormonal activation.

The research process was structured to ensure a systematic and evidence-based analysis of available data. Sources were selected based on their scientific relevance, methodological quality, and contribution to understanding the pathophysiology of heart failure and MAFLD. Emphasis was placed on recent publications in cardiology, hepatology, and internal medicine journals.

Methodological procedures included:

— systematic review of peer-reviewed scientific articles related to heart failure and MAFLD

— analysis of clinical studies describing neurohumoral activation in cardiometabolic disorders

— evaluation of experimental research on RAAS (renin–angiotensin–aldosterone system) dysregulation

— assessment of sympathetic nervous system (SNS) overactivation in heart failure patients

— comparison of inflammatory biomarker levels (TNF-α, IL-6, CRP) in MAFLD and non-MAFLD populations

— analysis of metabolic parameters including insulin resistance, lipid profile, and glucose metabolism

— review of studies focusing on oxidative stress and mitochondrial dysfunction in cardiometabolic disease

— synthesis of data regarding hepatokines, adipokines, and their role in heart–liver interaction

— comparative evaluation of disease progression in isolated heart failure versus HF with MAFLD

— integration of findings into a unified pathophysiological framework

Study design approach:

— qualitative descriptive analysis of existing scientific literature

— comparative interpretation of clinical and experimental results

— thematic categorization of neurohumoral pathways (RAAS, SNS, inflammatory axis)

— identification of common and distinct mechanisms between HF and MAFLD
— logical synthesis of data into cardiometabolic interaction model
Data sources and selection criteria:
— inclusion of recent studies published in indexed medical journals
— preference for research published within the last 10–15 years
— selection of studies involving human subjects and clinically relevant models
— exclusion of incomplete, non-peer-reviewed, or methodologically weak sources
— focus on studies with clear biochemical and clinical outcome measurements
Data analysis method:
— qualitative content analysis of scientific findings
— comparative interpretation of pathophysiological mechanisms
— grouping of results based on neurohumoral pathways
— identification of cause–effect relationships between MAFLD and HF progression
— synthesis of evidence into coherent explanatory framework
Ethical and scientific considerations:
— only publicly available scientific data were used
— no direct patient intervention was performed
— interpretation was based on previously published ethical research
— emphasis was placed on scientific accuracy and objectivity

RESULTS

The analysis of collected scientific data demonstrated that patients with heart failure (HF) in the presence of metabolically associated fatty liver disease (MAFLD) exhibit significantly more pronounced neurohumoral disturbances compared to patients with isolated heart failure. The findings consistently indicate that MAFLD acts as an additional pathological driver that intensifies systemic inflammation, metabolic imbalance, and neurohormonal overactivation.

In clinical and experimental studies, elevated activity of the renin–angiotensin–aldosterone system (RAAS) was one of the most frequently observed features. Increased levels of angiotensin II and aldosterone were associated with enhanced vasoconstriction, sodium and water retention, and progressive myocardial remodeling. These changes contributed to increased cardiac workload and accelerated progression of heart failure symptoms.

Similarly, sympathetic nervous system (SNS) overactivation was significantly more pronounced in patients with combined HF and MAFLD. This was reflected by increased catecholamine levels, elevated heart rate, and heightened peripheral vascular resistance. Chronic SNS stimulation was strongly associated with myocardial hypertrophy, arrhythmogenic risk, and reduced cardiac efficiency.

Inflammatory markers also showed a marked increase in the combined pathology group. Elevated concentrations of TNF-α, IL-6, and C-reactive protein (CRP) indicated a persistent state of low-grade systemic inflammation. This inflammatory environment was found to play a key role in endothelial dysfunction, insulin resistance, and myocardial fibrosis progression.

Metabolic analysis revealed that insulin resistance and dyslipidemia were significantly more severe in patients with MAFLD-associated heart failure. These metabolic disturbances contributed to altered myocardial energy metabolism, increased fatty acid oxidation, and reduced glucose utilization, ultimately leading to decreased cardiac performance.

Oxidative stress markers were also significantly elevated. Increased production of reactive oxygen species (ROS) and mitochondrial dysfunction were identified as important contributors to cellular injury in both hepatic and cardiac tissues. This oxidative imbalance further amplified neurohumoral activation and inflammatory signaling pathways.

Main results obtained from the study:

— RAAS activity was significantly higher in HF patients with MAFLD compared to isolated HF cases

— sympathetic nervous system activation was more pronounced, leading to increased cardiovascular stress

— inflammatory cytokine levels (TNF-α, IL-6, CRP) were consistently elevated in the combined pathology group

— insulin resistance was more severe and closely associated with disease progression

— lipid metabolism disorders contributed to myocardial energy imbalance

— oxidative stress was significantly increased, indicating enhanced cellular damage

— myocardial remodeling and fibrosis progressed faster in patients with combined conditions

— endothelial dysfunction was more evident in MAFLD-associated HF cases

— overall disease severity and symptom burden were higher in the combined group

— neurohumoral imbalance was identified as a central mechanism linking both diseases

DISCUSSION

The findings of this study clearly demonstrate that metabolically associated fatty liver disease significantly worsens the clinical and pathophysiological profile of heart failure through multiple interconnected mechanisms. The interaction between these two conditions is complex and primarily mediated by neurohumoral activation, systemic inflammation, and metabolic dysregulation.

One of the central observations is the excessive activation of the renin–angiotensin–aldosterone system. In normal physiological conditions, RAAS plays a compensatory role in maintaining cardiovascular stability. However, in chronic heart failure, sustained RAAS activation leads to harmful effects such as vasoconstriction, fluid overload, and structural remodeling of the myocardium. The presence of MAFLD further intensifies this system due to increased hepatic release of inflammatory and metabolic mediators, creating a more aggressive neurohumoral environment.

Another critical mechanism is sympathetic nervous system overactivity. Chronic stimulation of the SNS increases cardiac oxygen demand while simultaneously reducing coronary perfusion efficiency. This imbalance accelerates myocardial fatigue and contributes to arrhythmias and progressive cardiac dysfunction. In patients with MAFLD, this process is amplified by systemic metabolic stress and inflammatory signaling originating from hepatic dysfunction.

Inflammation plays a central integrative role in the pathogenesis of both conditions. The liver, when affected by fatty infiltration, becomes a major source of pro-inflammatory cytokines. These cytokines circulate systemically and directly affect vascular endothelium and myocardial tissue. As a result, endothelial dysfunction develops, leading to impaired vascular regulation and reduced tissue perfusion. This inflammatory cascade also contributes to myocardial fibrosis and structural remodeling, which are key determinants of heart failure progression.

Metabolic dysfunction further aggravates these processes. Insulin resistance, a hallmark of MAFLD, disrupts normal myocardial energy utilization. The heart shifts from glucose metabolism to fatty acid oxidation, which is less efficient and increases oxygen consumption. This metabolic shift reduces cardiac efficiency and contributes to energy depletion at the cellular level.

Oxidative stress is another important pathological factor. Excess production of reactive oxygen species leads to mitochondrial damage, lipid peroxidation, and cellular apoptosis. This oxidative damage affects both hepatic and cardiac tissues, reinforcing the bidirectional relationship between MAFLD and heart failure.

Overall, the study confirms that heart failure in the context of MAFLD is not merely a coexistence of two diseases but rather a synergistic pathological condition. Each disorder amplifies the other through shared neurohumoral, inflammatory, and metabolic pathways. This

interaction results in a more severe clinical presentation and faster disease progression compared to isolated heart failure.

From a clinical perspective, these findings highlight the importance of an integrated cardiometabolic approach. Targeting only cardiac symptoms without addressing underlying metabolic liver dysfunction may be insufficient. Therapeutic strategies should therefore focus on simultaneous modulation of neurohumoral activation, reduction of inflammation, and correction of metabolic disturbances.

In conclusion, the results strongly suggest that MAFLD is a significant aggravating factor in heart failure progression, and neurohumoral mechanisms serve as the central link between these two pathological conditions.

CONCLUSION

This study demonstrates that neurohumoral mechanisms play a central and integrative role in the development and progression of heart failure in patients with metabolically associated fatty liver disease (MAFLD). The analysis clearly shows that the coexistence of these two conditions is not accidental but reflects a complex pathophysiological interaction driven by metabolic, inflammatory, and neurohormonal disturbances.

The obtained findings confirm that MAFLD significantly intensifies the activation of key neurohumoral systems, particularly the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS). Persistent activation of these systems leads to vasoconstriction, fluid retention, myocardial overload, and structural remodeling of the heart. As a result, the clinical course of heart failure becomes more severe and progressive.

Another important conclusion is that systemic inflammation acts as a major linking factor between hepatic and cardiac dysfunction. Elevated levels of pro-inflammatory cytokines contribute to endothelial damage, insulin resistance, and myocardial fibrosis. This inflammatory state, originating from fatty liver pathology, further accelerates cardiac deterioration and worsens overall patient prognosis.

Metabolic disturbances, especially insulin resistance and lipid metabolism disorders, also play a crucial role in disease progression. These abnormalities impair myocardial energy utilization, reduce cardiac efficiency, and increase oxidative stress. Consequently, both structural and functional changes in the myocardium become more pronounced in patients with combined pathology.

The study also highlights that oxidative stress and mitochondrial dysfunction are key contributors to cellular damage in both the liver and the heart. These processes reinforce each other and create a continuous cycle of tissue injury, neurohumoral activation, and metabolic imbalance.

Overall, the results of this research confirm that heart failure associated with MAFLD represents a distinct and more severe clinical phenotype compared to isolated heart failure. The interaction between these diseases is mediated through interconnected neurohumoral, inflammatory, and metabolic pathways that mutually aggravate each other.

From a practical clinical perspective, these findings emphasize the necessity of an integrated treatment approach. Effective management should not focus solely on cardiac symptoms but must also address underlying metabolic liver dysfunction and systemic inflammation. Therapeutic strategies aimed at modulating RAAS activity, reducing sympathetic overactivation, and improving metabolic balance may significantly improve patient outcomes.

In conclusion, neurohumoral mechanisms serve as the central link between heart failure and MAFLD, and their dysregulation is a key determinant of disease severity and progression. A better understanding of these mechanisms provides an important basis for developing more effective diagnostic and therapeutic strategies in cardiometabolic medicine.

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