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CA-125: a promising biomarker in heart failure. Summary of the current knowledge

CA-125 — obiecujący biomarker w niewydolności serca. Podsumowanie bieżącego stanu wiedzy

Maria Sawościan, Małgorzata Lelonek

Department of Noninvasive Cardiology, Chair of Internal Disease and Cardiology, Medical University of Lodz, Łódź, Poland

Abstract

The search for suitable biomarkers for monitoring and treatment of patients with heart failure (HF) is still ongoing. The novel biomarker — carbohydrate antigen 125 (CA-125), used commonly so far in oncology, was proven to be useful in assessing congestion and inflammation in heart failure. Its elevated values are also strongly correlated with impaired right ventricle function. What is more, the increased level of CA-125 correlates positively with HF readmissions and a higher risk of death. Hence, that makes a need to tailor a potential treatment strategy, which was performed in the CHANCE-HF study. Despite the advantages of this biomarker, such as convenient access or significantly low cost of assessments, conducting multicentre and international studies is necessary to implement suitable guidelines.

Key words: heart failure, acute heart failure, echocardiography, biomarkers, clinical practice

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Introduction

The search for new biomarkers in heart failure (HF) that would be useful in patients' monitoring and treatment is still ongoing. Given the fact that HF should be defined as a clinical syndrome, not a single diagnosis [1] and considering its diverse pathophysiology, it is essential to select an appropriate set of biomarkers that can be helpful in the differential diagnosis of HF, risk stratification and modification of treatment [2].

Whereas congestion is one of the biggest challenges in the management of patients with acute heart failure (AHF) [3], the novel biomarker — carbohydrate antigen 125 (CA-125) appears to have great clinical potential that would provide accurate identification of HF patients and monitor their treatment [4]. CA-125 is a commonly used biomarker for monitoring ovarian cancer [5] which is also normally present on the cell surface in different tissues, such as pericardium, endometrium, endocervix, peritoneum, salpinges, lung, pleura or prostate [6]. Since the elevation of CA-125 in non-malignant conditions such as liver cirrhosis or ascites was confirmed [6], the findings which indicate its role in pathophysiological processes in HF appeared as well [7, 8].

This review aims to condense the current state of knowledge about this promising biomarker in prognosis and risk stratification of HF.

Address for correspondence: Maria Sawościan MD, Zakład Kardiologii Nieinwazyjnej, Katedra Chorób Wewnętrznych i Kardiologii, Uniwersytet Medyczny w Łodzi, Żeromskiego 113, 90–549 Łódź, Poland, e-mail: maria.sawoscian@umed.lodz.pl

The role of CA-125 in congestion and inflammation

Congestion is often a reason for a decompensated HF that may require an urgent need for hospitalization [9]. Núñez et al. [10] emphasized the relationship between peripheral oedema, serosal effusion and elevated level of CA-125. The mechanical stress caused by volume overload was found as an association between fluid congestion and increased secretion of CA-125 [6]. Both, mechanical stress and inflammatory stimuli may initiate c-Jun N-terminal kinase pathways which leads to stimulation of CA-125 [11]. On the other hand, Zeillemaker et al. [12] found an association between the secretion of CA-125 and inflammatory cytokines such as interleukin-1 (IL-1), tumour necrosis factor-α (TNF-α) and lipopolysaccharide. Furthermore, Bulska-Będkowska et al. [13] reported additionally that the level of CA-125 correlates positively with the high-sensitivity C-reactive protein and the IL-6. It is also worth noting that congestion and inflammation are interrelated [14] and it also seems that peripheral venous fluid overload leads to increased secretion of inflammatory markers — IL-6 [14]. Although the unknown biological role of CA-125, it was proved that mechanical stress, inflammation or fluid congestion stimulates mesothelial cells to increase the secretion of CA-125 [15]. The mutual interaction between the two components of HF pathophysiology is shown in Figure 1.

CA-125 and echocardiographic parameters

The right ventricle and its function play a significant role in a patient population with left-sided HF, regardless of the ejection fraction of the left ventricle [16]. Hence, CA-125 is firmly correlated with right-sided HF parameters such as tricuspid regurgitation (TR) [16] which is linked with the worse prognosis [17]. Consistently, Kouris et al. [18] reported the correlation of high CA-125 levels with right ventricular systolic pressure as well as a link between CA-125 concentration and severity of AHF and fluid overload. On the contrary, D'Aloia et al. [19] reported the correlation between the CA-125 levels and the echocardiographic parameters regarding right and left heart filling pressures and diastolic anomalies. What is more, significantly higher CA-125 values were found in patients with New York Heart Association class III/IV than in I/II [19]. Subsequently, some findings proved the association between CA-125 serum concentrations and worse prognosis in pulmonary hypertension [20].

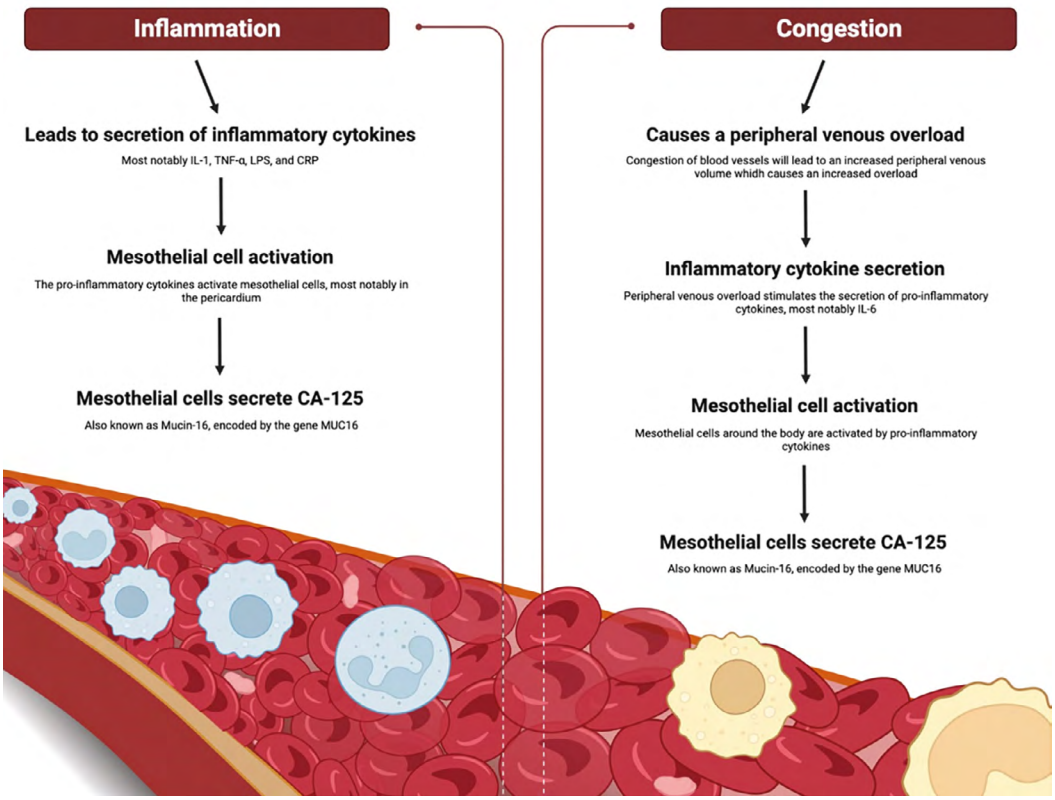

Figure 1. The mutual interaction between inflammation and congestion in heart failure

Table 1. Comparison of selected heart failure biomarkers

Biomarker	Clinical significance	References
CA-125	• congestion assessment • risk stratification	[21], [16], [29]
NT-proBNP	• myocardial injury and remodelling • diagnostic, risk stratification	[22], [23], [30]
hs-CRP	• inflammation • risk stratification, prognosis	[24], [31]
hs-TnT	• myocardial injury • risk stratification	[25], [22], [30]
RDW	• marker of hypoxia • prediction of long-term prognosis	[26]
GDF-15	• inflammation • correlation with CVD events	[27], [22], [30]
Gal-3	• myocardial remodelling • correlation with CVD and all-cause mortality	[28], [22], [30]
IGFBP-7	• metabolic dysfunction • biomarker of prognosis, especially for HFpEF	[27]

CA-125 — carbohydrate antigen 125; Gal-3 — galectin 3; GDF-15 — growth differentiation factor 15; hs-CRP — high sensitivity C-reactive protein; hs-TnT — high sensitivity cardiac troponin; IGFBP-7 — insulin-like growth factor-binding protein; NT-proBNP — N-terminal pro-B-type natriuretic peptide; RDW — red cell distribution width

CA-125 and other heart failure biomarkers

A well-understood role and clinical utility of a particular biomarker allow the selection of the appropriate set of assessments that are necessary for the management of HF patients. Therefore, a comparison of selected biomarkers is presented in Table 1. The purpose of the comparison of those molecules is to indicate their application to clinical practice as well as show their biological role.

CA-125 as a prognostic factor in risk stratification

In the last twenty years, plenty of studies indicate the prognostic value of an elevated CA-125 level in HF. Apart from CHANCE-HF, a randomized clinical trial by Núñez et al. [32], most of the research was an observational study. However, the BIOSTAT-CHF, a multicentre, international, prospective and observational subanalysis regarding worsening HF (n = 2516) is worth mentioning [33]. In multivariable survival analysis, increased CA-125 level was related to a higher risk of mortality and the composite of death/HF rehospitalization ($p < 0.001$ for both results) [33]. What is more, the prognostic role was proved independently of the severity of systemic congestion. The strategy involved managing diuretic treatment based on CA-125 levels (n = 187) vs. standard of care (n = 193) was suggested by the researchers in CHANCE-HF [32]. The CA-125 strategy showed a significant decrease of the primary endpoint, which was assessed as time to first event (66 vs. 84 events; $p = 0.017$) as well as the lessening in the rate of recurrent events in 1-year-follow-up (85 vs. 165 events, IRR: 0.49; 95% CI: 0.28–0.82; $p = 0.008$) [32]. The presentation of selected studies is shown in Table 2. Due to the novel HF treatment more and more patients are treated with sodium-glucose co-transporter 2 inhibitors, which influences the cardiovascular and renal effects [34]. In the retrospective cohort [35] of patients with the diagnosis of HF and diabetes mellitus type 2 that were receiving empagliflozin the decrease of CA-125 level without modifying the N-terminal pro-B-type natriuretic peptide (NT-proBNP) trajectory was observed. Therefore, it confirms a hypothesis that empagliflozin promotes extra-vascular decongestion [35].

CA-125 and its utility in clinical practice

Since CA-125 is not a cardiac-specific biomarker and its elevated values may also appear in other benign and malignant clinical conditions, the results should be carefully interpreted without the HF diagnosis [21]. In order to monitor the patients properly and tailor therapy for them, it is necessary to take into account the long half-life of CA-125 [21]. Since CA-125 provides information about the fluid congestion within the last week, in patients with HF exacerbation it may maintain a stable or even increased level, during the following days after a decongestion [21]. Figure 2 shows different cut-off groups designed by the few last studies that may help define the HF phenotypes according to CA-125 serum level.

Moreover, CA-125 has many advantages that promote it to be commonly performed in clinical practice. First, CA-125 is a well-known biomarker, with years of diagnostic and prognostic use in ovarian cancer. Secondly, the results of CA-125, unlike NT-proBNP are not influenced by age, weight or renal parameters [6]. Finally, the cost of its assessment is significantly lower than the assessment of NT-proBNP [21].

Conclusions

Certainly, CA-125 has proved to be a promising biomarker for the assessment of congestion and inflammation in both acute HF and chronic HF. Common access to CA-125 may lead to widespread implementation of its assessment in clinical practice. However, there still is a need to establish reference ranges, specific to HF. Therefore, it is necessary to conduct multicentre and international studies to provide

Table 2. Summary of the latest studies involving CA-125 risk stratification

Author	Year	Type of study	N	Study population	Proposed CA 125 cut-off	Results
D'Aloia et al. [19]	2003	Observational, prospective	286	Congestive HFrEF	35 U/mL	Patients with CA 125 > 35 U/mL died or were hospitalized due to HF more often at 6-month follow-up
Zhuang et al. [36]	2014	Meta-analysis	4159 (23 studies)	Acute and chronic HF	Not specified	Higher CA-125 levels occurred in patients with a higher risk of short- and long-term mortality
Núñez et al. [32]	2016	Randomized, prospective, multicentre	380	Patients discharged for HF	35 U/mL	CA 125 strategy was found beneficial compared to the SOC in terms of decreasing the risk of 1-year death or AHF readmission
Li et al. [37]	2018	Meta-analysis	8401 (16 studies)	AHF	Not specified	Increased CA-125 values were linked with a higher incidence of HF readmission and risk of death
Soler et al. [16]	2020	Observational, prospective	2961	AHF with TR	Continuous	Higher CA-125 levels were found in patients who had a higher risk of long-term all-cause mortality, especially those with severe TR
Núñez et al. [33]	2020	Observational, prospective, multicentre	2516	Worsening HF	Quartiles, continuous	Patients with a higher risk of 1-year all-cause mortality had increased CA-125 levels, which were positively correlated with clinical indicators of congestion
de la Espriella et al. [35]	2021	Observational, prospective	60	Chronic HF and T2D	35 U/mL	Empagliflozin administration was linked with a decrease in CA-125 values with no modification in NT-proBNP trajectory
Lorenzo et al. [38]	2021	Observational, retrospective	1387	Patients discharged for AHF	35 U/mL	Higher levels of CA-125 in patients with AHF may identify the need for a prolonged hospitalization
Lourenço et al. [29]	2022	Observational, prospective	363	Patients admitted for AHF	35 U/mL, 60 U/mL	Early CA-125 assessment (> 10 days) after an AHF hospitalization may be potentially useful in patient management

AHF — acute heart failure; CA-125 — carbohydrate antigen 125; HF — heart failure; HFrEF — heart failure with reduced ejection fraction; NT-proBNP — N-terminal pro-B-type natriuretic peptide; SOC — standard of care; T2D — type 2 diabetes; TR — tricuspid regurgitation

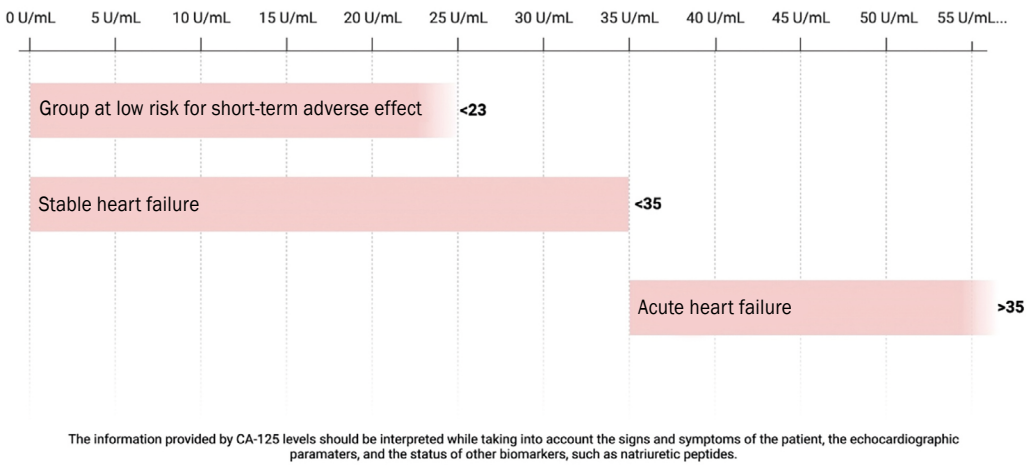

Figure 2. Heart failure cut-off groups according to CA-125 levels

an appropriate strategy regarding diagnosis and treatment monitoring.

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Conflict of interest

None declared.

Streszczenie

Wciąż trwają poszukiwania odpowiednich biomarkerów do monitorowania i leczenia pacjentów z niewydolnością serca (HF). Nowy biomarker — antygen węglowodanowy 125 (CA-125), powszechnie używany do tej pory w onkologii, okazał się przydatny w ocenie zastoju oraz procesów zapalnych w niewydolności serca. Jego podwyższone wartości są ściśle związane z upośledzoną funkcją prawej komory. Co więcej, podwyższone stężenie CA-125 jest związane z ponownymi hospitalizacjami z powodu HF oraz wyższym ryzykiem zgonu. W związku z tym, pojawiła się potrzeba stworzenia potencjalnej strategii leczenia, co zostało wykonane w badaniu CHANCE-HF. Pomimo zalet tego biomarkera, takich jak powszechny dostęp lub znacząco niski koszt oznaczenia, konieczne jest przeprowadzenie wieloośrodkowych i międzynarodowych badań, aby wprowadzić odpowiednie wytyczne.

Słowa kluczowe: niewydolność serca, ostra niewydolność serca, echokardiografia, biomarkery, praktyka kliniczna

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