Review paper

Circulating biomarkers in the setting of stress test-induced myocardial ischemia – a review of potential candidates for introduction into clinical practice

Krążące we krwi biomarkery niedokrwienia mięśnia sercowego indukowane w testach obciążeniowych – przegląd potencjalnych kandydatów do wprowadzenia do praktyki klinicznej

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Słowa kluczowe: niedokrwienie mięśnia sercowego, test obciążeniowy, biomarkery sercowe.

Abstract

The essential goal in the diagnostic approach to chronic coronary syndromes is to identify patients with significant stenoses in the coronary arteries who could benefit from invasive treatment while avoiding exposure to unnecessary interventional treatments or diagnostic procedures for patients who are unlikely to have significant stenoses in their coronary arteries. Early myocardial ischemia leads to a dynamic molecular response in the affected myocardium. A promising minimally invasive strategy is to access changes of concentrations of certain biomarkers circulating in blood during stress test-induced myocardial ischemia. This novel approach may change the landscape of non-invasive assessment of cardiac ischemia. However, there is a need for careful selection of possible candidates to be evaluated in future clinical trials. Several biomarkers have been proposed as potentially useful in this context and they are discussed in this review paper.

Streszczenie

Podstawowym celem w diagnostyce przewlekłych zespołów wieńcowych jest identyfikacja pacjentów z istotnymi zwężeniami w tętnicach wieńcowych, którzy mogliby odnieść korzyść z leczenia inwazyjnego, unikając jednocześnie narażenia na niepotrzebne inwazyjne procedury diagnostyczne lub lecznicze pacjentów, którzy prawdopodobnie nie mają istotnych zwężeń w tętnicach wieńcowych. Niedokrwienie mięśnia sercowego już na wczesnym etapie prowadzi do dynamicznej odpowiedzi na poziomie molekularnym. Obiecującą minimalnie inwazyjną strategią jest ocena zmian stężeń pewnych biomarkerów krążących we krwi podczas niedokrwienia mięśnia sercowego wywołanego testem wysiłkowym. To nowatorskie podejście może zmienić strategie nieinwazyjnej oceny niedokrwienia serca. Potrzebna jest staranna selekcja potencjalnych kandydatów do oceny w badaniach klinicznych. Co najmniej kilka biomarkerów zaproponowano jako potencjalnie użyteczne w tym zakresie i omówiono w niniejszym artykule przeglądowym.

Introduction

Coronary artery disease (CAD) is a pathological process of plaque formation in the epicardial arteries that may lead to their narrowing and closure. The dynamic nature of CAD is associated with a variety of clinical manifestations accounting for 45% of all deaths in Europe annually [1]. In order to reduce such high mortality, along with preventive measures, it is important to achieve early detection of patients with symptoms due to worsening of CAD. Therefore, newer techniques or modification of already known procedures are being tested to improve the diagnostic and prognostic potential.

Stress test-induced ischemia and biomarker testing

The various diagnostic modalities have different optimal performance ranges for the detection of anatomically and functionally significant CAD. Due to its availability, echocardiography is often the first line imaging procedure in patients with suspected cardiovascular disease. Stress echocardiography (SE) by provoking regional ischemia through exercise or pharmacological agents (predominantly dobutamine) can detect the presence and extent of coronary artery disease. According to the current guidelines, SE is recommended as an initial test for the diagnosis of CAD

in symptomatic patients for whom coronary stenosis cannot be ruled out by clinical evaluation alone [2, 3]. A meta-analysis of 30 randomized controlled trials also revealed that for patients with low-risk acute coronary syndrome, an initial diagnostic strategy of stress echocardiography is associated with fewer referrals for invasive coronary angiography and revascularization procedures than non-invasive anatomical testing, without an apparent impact on the future risk of myocardial infarction [4]. Furthermore, another study showed that SE might be useful in identifying microvascular disease (MVD), particularly if no other imaging options are available. When small vessel disease is possible, the infusion of a vasodilator or contrast echocardiography is the preferred modality [5]. However, there are some limitations; since SE relies on the qualitative assessment of wall motion, it may be difficult to make an accurate interpretation. Depending on the publication, the sensitivity and specificity of SE range from 33% to 96% and 38% to 97%, respectively [6, 7]. As much depends on the healthcare professional performing the examination, educating, training and monitoring of competence are of the utmost importance to maintain the quality of the test. Some researchers suggest that the validity of SE may be increased by the simultaneous determination of biomarkers released into the circulation in response to the stress. Siriwardena *et al.* documented the release of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hsTnT) during dobutamine SE in patients with CAD and in healthy volunteers [8]. The study detected a relationship between the absolute change in the hsTnT concentration and the cumulative dobutamine dose in the CAD patients [8]. Another study confirmed that higher resting levels of high-sensitivity troponin are correlated with stress-induced myocardial ischemia in patients with CAD [9]. The above studies confirm that elevated cardiac troponin and positive dobutamine SE are powerful predictors for future cardiac events. Nevertheless, it should be noted that episodes of ischemia not leading to cardiomyocyte necrosis may occur without troponin elevation, even when associated with instability in the atherosclerotic plaque with a risk of coronary occlusion. Therefore, troponins do not have sufficient independent prognostic value to advise systematic measurements in patients with stable CAD [10, 11]. It is supposed that the risk for CAD occurrence and progression is mediated by metabolic disturbances. Finding biomarkers with the ability to identify this initial phase of ACS should give promising results [12]. The perfect biomarker is one that could reliably reflect the short-lived ischemia which occurs with stress testing and whose standard concentration is associated with the level of risk of negative outcomes. It is clear that the simplicity of sampling and the cost of testing also play a role in real-world clinical practice.

Early myocardial ischemia leads to a dynamic response in both affected and non-affected myocardium. There are various possible interactions between inflammation and hypoxia leading to the development of atherosclerosis. Cardiac tissue markers investigated in humans and *in vivo* models can be broadly categorized into five groups by physiologic and pathophysiologic function: adaptive, e.g. hypoxia-inducible factor 1α (HIF-1α), B-cell lymphoma 2 (BCL-2), vascular endothelial growth factor (VEGF), heat shock protein (HSP)-70 and HSP-27, B-type natriuretic peptide (BNP); cell death, e.g. membrane attack complex (MAC), caspase-3 (CASP3); structural, e.g. heart-type fatty acid binding protein (H-FABP), troponins, creatine phosphokinase-MB (CK-MB), myosin, actin; inflammatory, e.g. interleukin (IL)-1β, IL-6, fibrinogen, C-reactive protein (CRP); and pleiotropic, e.g. nerve growth factor (NGF), cellular communication network factor (CCN1), microRNA [11].

Heat shock proteins (HSPs)

The heat shock proteins are often the first line of defense against the tendency of protein or polypeptide denaturation and misfolding associated with stress [13]. As their name suggests, hyperthermia is one of the main and best-known triggers of HSP expression, but they can also be overexpressed in many other situations, such as hemodynamic stress caused by heart diseases, physical exercise and administration of some substances [14]. The HSPs work as a cellular defense mechanism as the oxidative stress induces an increase in the expression of one or several HSPs acting protectively by repairing [15]. The HSP group, among other members, includes HSP-27 and HSP-70, which are typically expressed in cardiovascular cells including endothelial cells and cardiomyocytes [16]. It was confirmed that during atherosclerosis, HSP-27 is down-regulated in the most severe plaques or the plaque core [17]. Meanwhile in patients with cardiovascular disease overexpression of HSP-27 suppresses reactive oxygen species (ROS) and atherosclerosis progression through inhibiting mitochondria apoptosis pathway [18]. Abaspour *et al.* found that patients with stenosis of more than one coronary artery had a higher HSP-27 level [13]. The above findings suggest that the molecule may be a good biomarker of CAD correlating with the severity of disease. As for other molecules from the HSP group, Zongshi *et al.* documented a positive correlation of HSP-70 with progression of heart failure (HF) and its level was elevated even in those patients with no significant abnormalities in other studies but who may progress silently toward future HF [19]. Another study by Runda *et al.* revealed that reduction of HSP-70 levels during 1 week after myocardial infarction (MI) was negatively correlated with an improvement of left ventricle ejection fraction (LVEF) after 1 year of follow-up [20]. These findings suggest that a decreased level of HSP-70 in the acute phase of MI may be associated with a lower risk of developing (HF) 1 year after the in-

cident. However, it is worth noting that not all HSP molecules play a protective role. Lately, HSP-60 has been reported to trigger innate and adaptive immune responses which result in initiation of the earlier, but reversible inflammatory stage of atherosclerosis [21]. Veres *et al.* investigated a relationship between familiar risk for heart disease and HSP-60 level. The study showed a higher family risk of CAD among children with elevated antibodies to human HSP-60 [22]. While our full understanding of the roles of these major HSPs in heart disease is incomplete, there is a clear potential for therapeutic modulation of their expression in clinical practice. Changing HSPs' expression or avoiding the use of practices that could jeopardize their function and benefits is a potential future point of treatment.

Hypoxia-inducible factor 1α (HIF-1α)

Besides HSPs, another adaptive marker is HIF-1α, which is a master regulator of oxygen homeostasis consisting of HIF-1α and HIF-1β subunits. It is overexpressed in the lungs of COPD patients and it is known to facilitate bacterial infections in this group of patients. Hypoxia-inducible factor 1α is in no way cardiac tissue-specific, but myocardial hypoperfusion caused by coronary artery stenosis induces local hypoxia and increases HIF-1α production [23]. A study by Li *et al*. showed that in patients with high coronary artery calcification (CAC) scores, the HIF-1α level was also significantly higher [23]. The multivariate logistic regression model carried out in the study showed HIF-1α to be an independent risk factor for the presence of CAC [23]. Furthermore, not only protein level matters but also its stability. Various studies suggest that the enhanced stability of HIF-1a during hypoxia promotes beneficial effects in terms of the outcome of myocardial infarction [24]. The increasing level of HIF-1α is one of the earliest adaptive changes during ischemia [25]. In the case of hypoxia the HIF-1α molecule enhances angiogenic growth factor production and triggers vascular remodeling, which consequently leads to increased flow in collateral vessels. In elderly patients or those with chronic diseases, this response of HIF-1α is impaired [26]. Despite previous promising studies, there has been a recent disagreement on whether HIF-1α may be a new cardiac hypoxia marker in ACSs [27].

Heart-type fatty acid binding protein (H-FABP)

Heart-type fatty acid binding protein seems to be a promising marker for the early evaluation of suspected acute coronary syndrome. During myocardial ischemia, H-FABP is released into the plasma from the cardiomyocyte cell membrane. Its quick release kinetics has been compared with changes in troponin cumulation. The levels of H-FABP may be detected in the blood already 90 min after an ischemic event, which makes it the earliest available plasma marker of cardiac injury [12, 28]. Okamoto *et al.* reported that H-FABP is more sensitive than myoglobin and creatinine kinase isoenzyme MB for the diagnosis of acute MI in the early phase [29]. Moreover, patients with a clinical diagnosis of unstable angina also often show an elevated concentration of the H-FABP [30]. There are some publications emphasizing the prognostic role of H-FABP as its increased plasma concentration was shown to be an early and independent predictor of future cardiovascular events [12, 31, 32]. A Taiwanese multicenter registry study showed that a higher H-FABP level was an independent predictor for CV events, particularly for cardio- and cerebrovascular death and acute heart failure-related hospitalizations in patients with stable CAD [33]. Although H-FABP is more specific to cardiac tissue than most other biomarkers discussed in this paper, it has been noted that H-FABP lacks absolute cardiac specificity, so considering it as a CAD marker may lead to false-positive assignments. Therefore, it seems advisable to combine H-FABP testing with another, more specific biomarker or another test for CAD, such as stress echocardiography. This was confirmed in a recent study by Akinci *et al*. where serum H-FABP levels increased significantly at 1 h in the presence of ischemia induced by dobutamine stress echocardiography in patients with stable clinical coronary syndromes [34]. As the authors pointed out, adding H-FABP measurements to pharmacologic stress tests may improve their diagnostic accuracy.

Myostatin (MSTN)/growth differentiation factor-8 (GDF8)

Myostatin, also known as growth differentiation factor-8 (GDF8), is a protein produced and released by myocytes which acts as a muscle growth and differentiation inhibitor. A study by Castillero *et al.* showed that cardiac MSTN activation occurs rapidly after cardiac ischemia [35]. Moreover, some studies proved the correlation of higher MSTN levels with the extent of myocardial scarring as defined by SPECT imaging among patients with HF [36]. This confirms the observation that cardiomyocytes express more MSTN after cyclic mechanical stretch and pathological loading. Another way to activate stress pathways in the heart is to simulate exercise or stress through the use of sympathomimetic amines. In a study by Bish *et al*., administration of a phenylephrine in a mouse model revealed MSTN activation after 60 min, and this effect was sustained through 18 h [37]. Some results suggest that MSTN levels could reflect the extent of myocardial damage during AMI [38]. The same study showed that among patients with the highest MSTN levels the risk of developing in-hospital VT/VF was higher.

Studies on the role of MSTN levels in patients with stable CAD are lacking. However, the role of GDF8 in regulating tissue glucose uptake has been well documented, and it was found that in patients with insulin resistance, MSTN inactivation is a potential target for the prevention of risk factors associated with the development of ischemic cardiovascular diseases [38, 39]. Notably, myostatin levels are typically decreased in physically active individuals and may be altered in patients with different pathologies of skeletal muscles, including muscular dystrophies.

Hexokinase-2 (HK2)

Hexokinases (HK) are multifunctional proteins that orchestrate metabolic, antioxidant and direct anti-cell death effects. The predominant HK isoform in the adult heart, HK2, dynamically shuttles between the mitochondria and cytoplasm, protecting the heart from ischemia and reperfusion injury [40]. Most of the hexokinase studies published to date are based on animal models. Research by Wu *et al*. showed that the reduction in HK2 levels causes altered remodeling of the heart after MI by increasing cell death and fibrosis and reducing angiogenesis [41]. In another study the role of HK2 in coronary endothelial dysfunction in type 2 diabetic (T2D) mice was examined. It was found that overexpression of HK2 restored endothelial function in diabetes and reduced reactive oxygen species (ROS) production [42]. The authors suggest that these findings may be useful in the treatment of patients with microvascular disease.

Contemporary and future roles of biomarkers in CAD

Biomarkers improve prediction of long-term mortality in CAD patients when compared to established risk prediction algorithms and might allow more accurate classification of patients with stable CAD, enabling physicians to choose more personalized treatment regimens for their patients [43, 44]. Incorporation of cardiac troponins, NT-proBNP, copeptin, and IL-6 improved risk prediction in CAD patients even after adjustment for classical risk factors [45]. Biomarkers of endothelial dysfunction and inflammation are promising targets for preventive or therapeutic strategies aimed at protecting the endothelium or reversing endothelial damage in CAD and related complications [46]. There are numerous studies aimed at establishing diagnostic and prognostic models based on biomarkers and metabolites in CAD patients (ClinicalTrials.gov IDs: NCT05138731, NCT03855436, NCT03146208, NCT04144725). Although the assessment of circulating biomarkers in stable conditions is encouraging, even more promising would be the assessment of changes in biomarker concentration after stress-induced ischemia, for example by incorporating blood sample collections in stress imaging protocols. This is especially important when assessing cardiac ischemia as most biomarkers discussed in this paper are not cardiac-specific and their baseline concentration may be confounded by other conditions such as autoimmune or neoplastic disorders or chronic obstructive pulmonary disease [47–50].

Summary

Only some of the biomarkers well known so far have been discussed in detail in this paper. While our understanding of these biomarkers in heart disease is incomplete, there is a clear potential role for the diagnostic and therapeutic modulation of it in the practical clinical context. However, there is marked heterogeneity in the prognostic impact of biomarkers between studies, reflecting differences in sampling times and the population at risk. Some of these proteins have a very short plasma half-life time, so the negative results may be explained by inadequate sampling. In addition, the concentration of biomarkers may depend on the patient's sex, age, renal function, diet or medications taken. These limitations require precise determination of standards for testing individual biomarkers. Moreover, some researchers have pointed out that the study design in which all patients undergo coronary angiography followed by a long-term follow-up can provide more precise information about the clinical applicability of biomarkers determined during stress tests preceding coronary angiography. We hope that our publication will encourage researchers to investigate the usefulness of biomarkers in patients with suspected coronary artery disease.

Conflict of interest

The authors declare no conflict of interest.

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