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IM - REVIEW

Novel biomarkers to assess the risk for acute coronary syndrome: beyond troponins

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Abstract

Current diagnostic biomarkers for ACS are mainly represented by troponin I and troponin T. Dosing of these two molecules often leads to false positive results, since their plasma levels can increase in several different systemic settings. Therefore, identification of new markers able to detect patients with acute coronary syndromes is an emerging priority. On this view, many studies have been performed on different microRNAs, mitochondrial peptides, inflammatory cytokines and adhesion molecules with very promising results. Besides their introduction in screening programs, further studies are now needed in the acute setting, beyond or in association with troponin levels. This will help to better discriminate the real occurrence of an ACS in many patients accessing the emergency department for chest pain.

Keywords Acute coronary syndrome · Biomarkers · MicroRNAs · Mitochondrial peptides · Cytokines · Adhesion molecules

Introduction

To date, cardiovascular diseases represent the leading cause of death worldwide and, according to the World Health Organization, ischemic heart disease (IHD) and stroke rank among the top. Despite several attempts to realize reliable prediction models, we still cannot rely on efficient tools to estimate patient's risk of developing acute coronary syndromes (ACS) for all individuals [1].

While current diagnostic biomarkers for ACS are mainly represented by troponin I (TnI) and troponin T (TnT). Dosing of these two molecules often leads to false positive results, since their plasma levels can increase in several different settings, such as heart failure, chronic kidney disease and sepsis and many other conditions [2, 3]. Moreover, blood levels of cardiac troponins only rise after myocardial cell death, a process that usually takes place after 2–4 h from the ischemic event, and they remain detectable in the peripheral blood for days [4]. Therefore, identification of new strategies to early detect patients with ACS is an emerging priority as it may allow to start an immediate treatment thus reducing mortality [1]; in this regard, a large number of studies have been conducted to identify a set of new biomarkers useful for an early assessment of ACS. In this review, we provide an update of the most recent literature about those novel biomarkers, with a special focus on microRNAs (Mir), mitochondrial peptides, inflammatory cytokines and adhesion molecules.

MicroRNAs

According to our research, miR-146a, miR-26a, miR-499 and miR-34 were the most studied (Table 1).

As for miR-146a, we found three studies that observed how it is involved in the development of coronary heart disease (CAD). A study on murine models demonstrated that miR-146a is involved in MI development by targeting two important toll-like receptors, thus inducing an inflammatory state that drives to atherosclerotic plaque formation [5]. Raitoharju et al. showed that miR-146a is significantly upregulated in coronary atherosclerotic plaques when compared with normal internal thoracic arteries [6], while Xue et al. studied patients with acute myocardial infarction (AMI) compared with healthy controls, observing how miR-146a represents an optimal diagnostic biomarker for this condition [7].

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Table 1 Brief summary of all studies performed on each microRNA in relation to IHD

MicroRNA	References	Subjects	Results
miR-15	Hullinger et al. [17]	Animal models (mice and pigs)	Knocking the expression of miR-15 is cardioprotective after IHD
miR-214	Aurora et al. [16]	Murine models	miR-214 is cardioprotective after CAD
miR-34	Bernardo et al. [11]	Murine models	Silencing miR-34 is cardioprotective after MI
	Boon et al. [12]	Murine models	miR-34 and its target PNUTS are cardioprotective after MI
miR-3113-5p	Chen et al. [15]	Murine models	miR-3113-5p is a stable marker for early diagnosis of cardiac I/R injury
miR-499	Wang et al. [44]	Murine models	miR-499 is cardioprotective against H2O2-induced injury after MI
	Zang et al. [10]	216 CAD patients and 90 controls	miR-499 downregulation protects endothelial cells from inflammatory damage during CAD
miR-146a	Raitoharju et al. [6]	12 Atherosclerotic plaques and 6 internal thoracic arteries	miR-146a is significantly up-regulated in human atherosclerotic plaques
	Wang et al. [5]	Murine models	miR-146a is involved in MI development by targeting 2 toll-like receptors
	Xue et al. [7]	31 AMI patients and 27 controls	miR-146a is a potential diagnostic biomarker for CAD
miR-26a	Xue et al. [7]	31 AMI patients and 27 controls	miR-26a is an accurate diagnostic biomarker for AMI
	Chiang et al. [8]	Murine models	miR-26a expression is reduced in the infarct zone of the heart
miR-133b	Kumar et al. [13]	78 Patients with CAD	miR-133b expresses a negative correlation with CAD risk and is early detectable
miR-21	Kumar et al. [13]	78 Patients with CAD	miR-21 expresses a positive correlation with CAD risk and is early detectable
miR-145-3p	Gigante et al. [14]	100 patients with acute CV events and 100 controls	miR-145-3p correlates with a high risk of acute CV disease
miR-720	Gigante et al. [14]	100 Patients with acute CV events and 100 controls	miR-720 correlates with a low risk of acute CV disease
lcnRNA-Coromarker	Yang et al. [18]	CAD patients and controls	Coromarker is a stable, sensitive and specific biomarker for CAD
lncRNA-Lipcar	Li et al. [19]	46 STEMI and 40 controls	Lipcar expresses a positive correlation with troponins and a negative correlation with LVEF

The same study also pointed out how miR-26a is a good biomarker in the early detection of AMI [7], even though, more recently, Chiang et al. observed that its expression is reduced in the infarct area of the heart in murine models [8]. The role of MiR-499 role in CAD is currently equivocal; while Wang et al. showed that it protects from H_2O_2-induced heart injury following MI in mice [9], Zhang et al. observed that its downregulation protects endothelial cells from inflammatory damage during CAD in a large cohort of patients and controls [10]. This is why its role in ACS warrants further investigation. MiR-34 family seems to be involved mostly in chronic heart diseases [11], despite results from studies in murine models suggest that targeting this particular miR and its substrate PNUTS might confer a cardio-protective effect after MI [12].

Studies on patients affected by CAD and in healthy controls showed that miR-133b and miR-720 express a negative correlation with the risk of CAD, while miR-21 and miR-145-3p correlate with a higher risk of acute cardiovascular events. Moreover, miR-133b and miR-21 seem to be early detectable in course of CAD [13, 14].

Similarly, Chen et al. demonstrated that miR-3113-5p represents a stable marker for an early diagnosis of cardiac injury following an acute cardiovascular event in mice [15].

Evidences about the cardioprotective role of miR-214 after CAD have been shown by Aurora et al. in murine models [16], while Hullinger et al. suggested that knocking out the expression of miR-15 may guarantee the same effect [17].

Finally, long non-coding RNAs (lcnRNAs) were shown to be good biomarkers for IHD, as observed by Yang et al.; in particular, they identified Coromarker as a stable, sensitive, and specific biomarker for CAD [18]. Similarly, Li et al. observed how Lipcar expresses a positive correlation with

Tns and a negative correlation with left ventricular ejection fraction after MI [19].

Mitochondrial peptides

MOTS-c, SHLPs and Humanin are the most analyzed mitochondrial peptides that have been investigated as potential biomarkers for CAD (Table 2).

MOTS-c mainly produces metabolic effects: it prevents insulin resistance by enhancing glucose uptake and utilization, but also stimulates fatty acids oxidation and inhibits oxidative respiration [20]. However, MOTS-c has also been shown to protect against coronary endothelial dysfunction by reducing the release of inflammatory cytokines and adhesion molecules [21].

As for SHLPs (small humanin-like peptides), they are encoded by the same mDNA region of humanin, but seem to provide different biological effects. Several types of SHLPs have been found in different tissues, but only a very limited number of studies are available about these molecules [22].

Humanin has been thought to be beneficial in attenuating stress caused by ischemia/reperfusion injury [23], and there are evidences that treatment with humanin reduces both infarct size and loss of cardiac function following an ischemic damage [24]. Initially believed to guarantee a neuroprotective effect, Humanin also acts as a protector of vascular system from disease processes and toxic damage [25, 26]. In a study involving 40 patients undergoing coronary angiography whose endothelial function was tested, Widmer et al. demonstrated that preserved human coronary endothelial function is uniquely associated with higher systemic humanin levels [27].

Concerning ACS, several studies demonstrated that MDPs have a protective role in myocardial ischemia–reperfusion injury, probably by activating the AMPK-endothelial NO synthase-mediated signaling and regulating apoptotic factors. Indeed, administration of humanin to mice after a MI determined an improvement in left ventricular function and a decrease in the infarct area [24]. In particular, ischemic-reperfusion injury is mainly mediated by oxidative stress and Humanin has shown to alleviate mitochondrial damage induced by ROS [28].

Cytokines

Among all, interleukin (IL)-17 family seems to be the most involved in the inflammatory processes associated with CAD, despite other cytokines have been investigated as well (Table 3).

IL-17A was shown to be increased in plasma of patients with MI or unstable angina in a study focused on patients suffering from ACS and in controls [29]; at the same time, IL-17A levels increase in the infarct area of the heart after a MI and after left coronary artery ligation and reperfusion on murine models [30]. In these experiments, anti-IL-17A immunoglobulins and IL-17A knockout markedly ameliorate ischemia/reperfusion injury [31].

Analyzing coronary arteries from patients with atherosclerosis and healthy individuals, Xu et al. observed that IL-17E is significantly higher in coronary arteries and plasma of patients suffering from CAD compared to controls, and that the increase levels were proportional to the severity of the disease [32].

From the analysis of a large cohort of subjects with CAD and healthy controls, Tajfard et al. obtained results showing how IL-6 and MCP-1 can be considered predictors of high mortality in CAD patients [33] (Table 3).

In a randomized, double-blind trial, Ridker and his team demonstrated that reducing the inflammatory process through the anti-IL-1β canakinumab leads to a significantly lower rate of recurrence of cardiovascular events, thus identifying IL-1β as a major responsible for CAD [34] (Table 3).

Interleukin-1 receptor antagonist (IL-1RA) has also been fully investigated in the last years. IL-1RA is an endogenous inhibitor of IL-1β and acts as a counter-regulator of IL-1β activity. While dosage of IL-1β is very difficult to be obtained, due to its extremely low plasma

Table 2 Brief summary of the results of all studies performed on each mitochondrial peptide in relation to IHD

Mitochondrial peptide	References	Subjects	Results
MOTS-c	Qin et al. [21]	40 Patients with recurrent angina	MOTS-c protects against coronary endothelial dysfunction
SHLPs	Not enough studies to be assessed		
Humanin	Muzumdar et al. [24]	Murine models	Humanin reduces infarct size and loss of cardiac function after ischemic injury
	Widmer et al. [27]	40 Patients undergoing coronary angiography	High serum humanin level correlates with preserved endothelial function
	Thummasorn et al. [28]	Murine models	Humanin protects against I/R injury-induced mitochondrial dysfunction

Table 3 Brief summary of all the studies performed on each inflammatory peptide in relation to IHD

Cytokine	References	Subjects	Results
IL-17A	Liang et al. [29]	10 Pts with ACS, 11 with stable angina and 12 controls	IL-17A is increased in plasma of patients with MI or unstable angina
	Avalos et al. [30]	Murine models	IL-17A levels are increased in the infarct area of the heart
	Liao et al. [31]	Murine models	IL-17A is elevated after left coronary artery ligation and reperfusion; anti-IL-17A immunoglobulins or IL-17A knockout markedly ameliorate ischemia/reperfusion injury
IL-17E	Xu et al. [32]	6 Normal and 10 atherosclerotic human coronary arteries	IL-17E is elevated in coronary arteries and plasma of patients (proportionally to the disease severity)
IL-6 and MCP-1	Tajfard et al. [33]	342 CAD patients and 120 controls	IL-6 and MCP-1 may predict high mortality in CAD patients
IL-1β	Ridker et al. [34]	Randomized double-blind trial with canakinumab on 10,061 with prior MI	Reducing inflammation with anti-IL1β canakinumab significantly lowers recurrence rate of cardiovascular events

levels, the level of circulating IL-1RA can be easily and reliably quantified. Consequently, IL-1RA may serve as a surrogate parameter for high IL-1β activity (Schofer et al. [35]). Promising results came from phase III studies on IL-1 blockade in patients with MI, thus identifying this biomarker as a therapeutic target (Leo et al. [36]). Zi-Heng et al. have demonstrated that IL-1 blockade treatment decrease cardiovascular risk in a recent meta-analysis. In fact, they analyzed eight randomized controlled trials including 15,647 participants and measured the effect of IL-1 blockade on different parameters. Results showed that IL-1 blockade reduce the risk of MACE (RR 0.88, 95% CI 0.82–0.94), unstable angina (RR 0.80, 95% CI 0.66–0.98) and heart failure (RR 0.44, 95% CI 0.22–0.87) [37]. Similar results were obtained by Herder et al., who reported the occurrence of a positive association between IL-1RA levels and cardiovascular diseases [38]. Schofer et al. conducted a study aimed at assessing the prognostic impact of IL-1RA in patients with CAD. By studying 1337 patients, they demonstrated that patients with IL-1RA levels in the highest tertile showed a higher prevalence of ACS, were more commonly treated with PCI and had a lower ventricular ejection fraction, and higher C reactive protein levels. Moreover, a significant association was found between IL-1RA levels and all cause of mortality (adjusted HR 1.45; 95% CI 1.16–1.82) and cardiovascular mortality (adjusted HR 1.93, 95% CI 1.33–2.80) [35]. A study performed by Hiort et al. demonstrated that high levels of eight biomarkers, including IL-1RA increased probability of non-obstructive coronary arteries 3 months after occurrence of MI [39]. Concerning mechanisms by which IL-1RA protect myocardial ischemia, Quian et al. have recently demonstrated that it may downregulate inositol trisphosphate three receptors, attenuating Ca^{++} overload and the consequent systolic and diastolic dysfunction and inhibit of apoptosis in injured cardiomyocytes thus reducing myocardial infarct size in vivo [40].

Adhesion molecules

Lately, some studies demonstrated that ICAM-1 and VCAM-1 take part in the inflammatory process that leads to the development of atherosclerotic plaque.

As for ICAM-1, its gene rs5498 has been studied in correlation with CAD, but controversial results have been obtained, since some authors identified this molecule as a risk factor [41], while others as a protective factor [42]. A meta-analysis by Yin et al. however, showed that ICAM-1 gene K469E is associated with an increased risk of acute cardiovascular events [37]. Finally, a recent study on human coronary arteries obtained from patients with different grades of atherosclerosis and/or sudden cardiac death demonstrated that the expression of ICAM-1 and 0X40L is positively correlated with the stability of the atherosclerotic plaque and sudden coronary death [43] (Table 4).

VCAM-1 expression on endothelial cells and formation of microparticles at the site of coronary plaque positively correlate with the extent of vascular inflammation in patients with MI, as provided by a study from Radeche et al. [44]. Furthermore, serum VCAM-1 seems to be associated with the extent of coronary lesions and it may represent an alternative to improve the cardiovascular risk classification in patients without CAD [45] (Table 4).

Table 4 Brief summary of all the studies performed on each adhesion molecule in relation to IHD

Adhesion molecule	Authors	Subjects	Results
ICAM-1	Hulok et al. [41]	45 Patients with CAD and 18 patients without CAD	ICAM-1 gene rs5498 is a risk factor for CAD
	Liu et al. [42]	Meta-analysis	ICAM-1 gene rs5498 is a protective factor for CAD
	Yin et al. [43]	Meta-analysis	ICAM-1 gene K469E is associated with increased risk of CAD
	Wang et al. [44]	118 Human coronary arteries with different degrees of atherosclerosis and/or sudden coronary death and 28 controls	The expression of OX40L and ICAM-1 positively correlates with the stability of the atherosclerotic plaque and sudden coronary death
VCAM-1	Radecke et al. [45]	47 Patients with CAD and 25 with MI	Increased VCAM-1 expression on endothelial cells and formation of microparticles at the site of coronary plaque positively correlates with the extent of vascular inflammation in patients with MI
	Dos Santos et al. [46]	74 Patients with CAD and 25 with MI	Serum VCAM-1 may be associated with the extent of coronary lesions and it may represent an alternative to improve the cardiovascular risk classification in patients without CAD

Discussion

Despite its high prevalence, diagnosis of IHD still represents a real problem worldwide; current tests are not able to identify all patients affected by this condition, thus explaining such a high mortality [3]. This is why looking for novel biomarkers may be a wise strategy for an early detection of patients at a high risk of ACS development.

MiRs are small, non-coding RNAs that regulate gene expression at a post-transcriptional level: they bind to specific, complementary mRNAs in order to modulate the translational process leading to protein synthesis. Therefore, miRs play a fundamental role in developmental timing, cell death, cell proliferation, hematopoiesis, and patterning of the nervous system [41]. Recently, different miRs have been shown to take part in the development of several cardiovascular conditions, including of IHD and MI, leading to the conclusion that their dosage in the peripheral blood offers the opportunity to monitor the biological status of the cardiovascular system [42–45]. In a recent review, De Rosa et al. described that some cardiac-specific and muscle-specific miRs might represent useful biomarkers for patients with ACS, since they show a good correlation with Tns. They also proposed miRs as an alternative diagnostic tool to high-sensitivity Tns (hsTns), considering their earlier detectability in the peripheral blood. Some studies, in fact, showed a very early myocardial release of some miRs within 30 min from symptom onset, with consequent significant elevation of miRs at a time where hsTn was still negative [46]. Furthermore, some research teams have reported that miRs can also be used as a marker of progression and prognosis of the disease [47, 48].

In our review, we identified a large number of miRs potentially involved in atherosclerosis and CAD; some of these may have a cardioprotective role, while others seem to correlate with a major heart injury during or after an acute cardiovascular event. Moreover, miRs are apparently easy and early detectable in the peripheral blood of patients with a CAD, and some of them express a direct correlation with the severity of the disease. Therefore, detection of specific clusters of miRs could represent in the future a useful tool to assess the risk of developing an acute cardiovascular event. Nevertheless, larger studies are needed to better understand the correlation between these molecule levels and IHD risk, and to identify only miRs really associated with the occurrence of acute cardiovascular events.

Mitochondrial-derived peptides (MDPs) are a new class of small peptides encoded by mitochondrial DNA that play a cytoprotective role and take part in a number of cellular processes such as cell survival, metabolism, response to stressors, and inflammation [22, 24]. Due to their numerous metabolic effects, some authors pointed out how MDPs are so important actors in the pathogenesis of atherosclerosis, thus considering them as optimal potential biomarkers for those conditions. From our research analysis, MOTS-c and humanin are the most studied so far, and both of them seem to act in protecting heart tissue from the damage occurring during and after a MI.

Currently, there is a common agreement upon the inflammatory process as a crucial phenomenon in atherosclerotic plaque formation and rupture, then causing ACS. Therefore, many inflammatory mediators have been investigated as potential biomarkers for IHD and possible target for novel therapies [34, 49–51, 54]. Our results show

that IL-17 family better correlate with the development of CAD, since both IL-17A and IL-17E plasma levels are increased in such patients. IL-17, indeed, is produced by Th-17 lymphocytes, whose role in atherosclerosis is already well known [52–54]; nevertheless, a specific correlation with acute cardiovascular events may only be hypothesized and further investigation is needed in order to confirm this hypothesis. The same association has been found for IL-6 and IL-1β as well; the latter also represents a potential therapeutic target to reduce the rate of future cardiac ischemic attacks. Very promising results have also been reported for IL-1RA, which may discriminate cardiovascular risk and represent a potential therapeutic target in patients with ACS.

ICAM-1 and VCAM-1 are adhesion molecules involved in the leukocyte recruitment process during inflammation, which allow leukocytes to firmly adhere to the endothelium before their transmigration across blood vessels. Thus, it is reasonable to suppose that they might have a role in perpetuating the inflammatory process that leads to atherosclerosis and MI.

Despite the role of ICAM-1 is still controversial, it positively correlates with the stability of the atherosclerotic plaque and sudden coronary death. As for VCAM-1, instead, studies agree that its expression positively correlate with the extent of coronary plaques, thus suggesting a potential but concrete employment of VCAM-1 for risk assessment of CAD.

In conclusion, we currently need to exert a more precise assessment of CV risk and to identify biomarkers more precise that Ths for a fast and safe rule out of patients presenting in ED with chest pain. There are now several potential novel biomarkers able to early detect patients at a high risk to develop ACS, beyond Tns [4]. Besides their introduction in screening programs, further studies are now needed to test their predictive value in the acute setting, beyond or in association with Tn levels. This will help to better identify patients with ACS accessing the emergency department.

Compliance with ethical standards

Conflict of interest No conflict of interest.

Statement of human and animal rights Not applicable.

Informed consent Not applicable.

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