Cardiovascular Risk Factors from Another Point of View

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ABSTRACT

Cardiovascular diseases remain the main cause of death in western societies. This contributes to the appearance of new diagnostic and treatment methods addressed to reduce the burden of cardiovascular diseases. In the last decades new imaging methods have emerged; furthermore, routine biomarkers were found to be useful in cardiovascular risk stratification. Data reviewed in this article emphasize the multifactorial etiology of cardiovascular disease. The authors describe the role of inflammation in the precipitation and progression of atherosclerosis and atrial fibrillation. Affordable and well-known inflammatory markers can be used alone or in combination with new imaging methods for a better cardiovascular risk stratification. Coronary computed tomographic angiography findings and inflammatory markers are capable to identify patients with high risk of major adverse cardiovascular events or atrial fibrillation. Furthermore, they also have an important role in the choice of treatment strategy and follow-up.

Keywords: cardiovascular diseases, biomarker, risk factor

INTRODUCTION

Europe's population is getting older. Population ageing is the most significant demographic and social trend of the 21st century, affecting every country in the world. The incidence of ischemic heart disease (IHD) and atherosclerosis increases with age, appearing 6–9 years earlier in men than in women. Each year, IHD causes millions of deaths worldwide, and atherosclerotic disease remains the most common cause of death in developed countries.¹ In the last decades, the mortality rate of cardiovascular disease has decreased significantly due to improved diagnosis and treatment methods and primary prevention.² Patients with coronary artery disease can be completely asymptomatic in the early phases, being diagnosed in advanced stages, when the treatment is difficult and the prognosis can be poor. In most cases the symptoms are caused by heart failure and different types of arrhythmias. In elderly patients, the onset of atrial fibrillation can be the first sign of myocardial hypoperfusion.^{3,4} In addition to well-known risk factors, acute or chronic inflammatory states can lead to plaque instability, atherosclerosis progression, and adverse cardiovas-

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cular events.⁵ The most common causes of death in this group of patients are sudden death, acute heart failure, and malignant ventricular arrhythmias, caused by acute coronary syndrome (ACS) and myocardial infarction (MI).⁶ These patients are very vulnerable to the slightest internal or external stimulus. For this reason, patients at high risk of atherosclerosis require regular screening and need to be diagnosed before the acute event. One of the most accurate methods is coronary computed tomography angiography (CCTA), which is capable to assess several aspects of coronary atherosclerosis such as the presence of atherosclerosis, stenosis, markers of potential plaque instability, and atheroma size.⁷

ASSESSMENT OF CORONARY ARTERY DISEASE

In the last decade, the diagnosis of coronary artery disease has become easier, faster, and more accurate. In the past, electrocardiography was the only diagnostic and screening method. The appearance of coronary angiography contributed to the diagnosis of significant coronary stenosis but without providing any information about the structure of the plaques. Nowadays, this method is reserved for acute cases when angioplasty is needed, and it cannot be used widespread for screening and for the assessment of cardiovascular risk. Computed tomography has become an indispensable method in cardiology in the last decade. Numerous large-scale randomized studies have demonstrated that this method has an excellent diagnostic accuracy, in both symptomatic and asymptomatic patients.^{8,9} Several trials, such as HEART (Scottish Computed Tomography of the Heart) and PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), demonstrated that the rate of MI can be significantly reduced using a CCTA-guided treatment strategy.^{10–13} This noninvasive imaging method is able to diagnose patients with coronary atherosclerosis from the early stages and is able to determine long-term cardiovascular risk.

Another important feature of this investigation is that it is able to provide information about the structure of coronary plaques. This technique is capable to determine vulnerable plaque features, such as low-attenuation plaque, positive remodeling, spotty calcification, and napkin-ring sign.^{14–16} In a meta-analysis ($n = 13,977$), Nerlekar *et al.* reported a strong correlation between high-risk plaque features and the incidence of major adverse cardiovascular events (MACE), the presence of two criteria increasing the risk of MACE 9-fold.¹⁷

CARDIOVASCULAR RISK IN PATIENTS WITH CHRONIC INFLAMMATORY DISEASES

Atherosclerosis is the cause and the consequence of inflammation. This systemic disease is associated with a low-grade inflammation of the arterial wall at the level of medium- and large-sized arteries.¹⁸ Galkina *et al.* showed in their review that inflammation has an important role in all phases of atherosclerosis.¹⁹ Several studies demonstrated a positive correlation between chronic inflammatory state and atherosclerosis. We found several clinical trials in the literature dealing with the incidence of cardiovascular disease in patients with chronic inflammatory diseases. Literature data suggest that chronic inflammatory rheumatic diseases (CIRD), such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and seronegative SpA, are associated with significant cardiovascular (CV) morbidity and mortality.²⁰ In a meta-analysis, Aviña-Zubieta *et al.* concluded that CIRD patients have an increased prevalence of CV disease.²¹ The ATHERODENT clinical trial showed a positive correlation between periodontal disease, atherosclerosis, and plaque vulnerability.²² The correlation between atherosclerosis and chronic inflammatory disorders of the gastrointestinal tract is not elucidated.^{23,24} Multiple cohort studies reported a significant correlation between inflammatory bowel disease (IBD) and the incidence of MACE.^{25–27} In a French cohort study ($n = 210,162$), Kirchgesner *et al.* found an increased risk of acute arterial events in patients with IBD. Furthermore, they reported a high risk in young patients. In their group, the risk of MACE increased proportionally with the number, duration, and severity of acute events.²⁸ This finding was also confirmed by an Asian and Danish cohort study, where the authors described a strong correlation between cardiovascular morbidity and mortality in young patients with IBD.^{25,29} Weissman *et al.* concluded in their review that IBD is a risk factor for atherosclerosis and MACE, especially in young and female patients.³⁰

INFLAMMATION AND MAJOR CARDIOVASCULAR EVENTS

Inflammation has also an important role in the precipitation of ACS, as the inflammatory state can lead to plaque disruption. The correlation between inflammation and MACE is complex and not fully understood.³¹ Many types of inflammatory cells are involved in the mechanism of coronary plaque destabilization. Macrophages and neutrophils play an important role in plaque disruption and atherosclerosis progression.³² These cells secrete matrix

metalloproteinase-9 (MMP-9). A disturbance in the ratio of MMP-9 and tissue inhibitors of matrix metalloproteinase (TIMP-1) leads to arterial extracellular matrix breakdown and eventually plaque rupture.³³ Several clinical trials demonstrated that patients with ACS have a significantly higher MMP-9 level.^{34–36} The authors describe other types of MMPs, such as MMP-1 and MMP-2, which are also increased in patients with ACS. Wang *et al.*, in a recent review, concluded that the acquired immune system also contributes to coronary plaque vulnerability.³¹ Helper T cells, especially Th1 cells, are characterized by the production of pro-inflammatory cytokines, such as interferon- γ and tumor necrosis factor- α , which contributes to plaque disruption in ACS.^{37,38} Researchers investigated the correlation between plaque vulnerability and different types of microorganisms but without finding a significant correlation.³⁹ Only a few studies reported that infection with *Chlamydia*, *Mycoplasma pneumoniae* and some viruses may have an additional higher cardiovascular risk.^{40–42}

An acute inflammatory state can lead to ACS without the presence of any coronary artery occlusion. This indirect mechanism of ACS is characterized by the increased oxygen and metabolic needs of the myocardium, and it is called demand ischemia or myocardial infarction (MI) type 2.^{43,44}

THE ROLE OF C-REACTIVE PROTEIN IN CORONARY ARTERY DISEASE

C-reactive protein (CRP) is a widely used inflammatory biomarker, its level being increased in every type of inflammatory disease. It is a valuable marker not only for diagnosis, but also for monitoring. Determination of CRP is easy, inexpensive, and highly available. Recently, the role of CRP in cardiology has been demonstrated. Studies suggest that there is a strong correlation between the level of high-sensitivity (hs)-CRP and MACE.

The role of hs-CRP in primary cardiovascular prevention is not so clear. Several large clinical trials demonstrated that an increased level of hs-CRP is associated with a higher cardiovascular risk. Ridker *et al.*, in several prospective studies, demonstrated that patients with elevated hs-CRP are prone to develop MACE.^{45–49} They described that these patients, without cardiovascular disease, have a three times higher risk for myocardial infarction. They also emphasize that hs-CRP was the best predictor of CV risk among female patients after the onset of menopause. Other authors have also demonstrated this correlation.^{50,51} However, others did not find a significant correlation.^{52–54}

The level of hs-CRP has also an important role in patients with IHD. Studies have shown that hs-CRP is a marker of acute events in patients with IHD. Won-Woo *et al.* assessed the correlation between the level of hs-CRP and CCTA findings. They concluded that the combination of imaging and inflammatory markers contributes to a better CV risk stratification.⁵⁵ Takashi *et al.* found a significant correlation between the level of hs-CRP and the grade of necrosis of culprit lesion, assessed with IVUS.^{56,57} Trans-lesion CRP gradient was calculated by Inoue *et al.*, and they found a higher level distal to the site of coronary plaque. They also reported a higher level in case of unstable plaques.⁵⁸ In the VISTA-16 trial (n = 5,145) the authors reported that elevated hs-CRP levels after an acute cardiovascular episode and subsequent level increases are associated with adverse outcomes.⁵⁹ Several other trials have confirmed this correlation.^{60,61} In 2018, our research group reported that hs-CRP level is in correlation with infarct size in STEMI patients.⁶²

INFLAMMATION AND ATRIAL FIBRILLATION

Inflammation can be either a cause or a consequence of atrial fibrillation (AF). Data from the literature suggest that inflammation has an important role in the structural and electrical remodeling of the atrium. Inflammation causes atrial fibrosis, gap junction modulation, and calcium homeostasis disturbance. These modifications promote ectopic atrial activity and aberrant impulse conduction.⁶³ Studies describe a correlation between systemic inflammation and AF. Patients with IBD, CIRD, psoriasis, SLE or sclerosis are more predisposed to AF.^{64–67} Local inflammatory conditions, such as myocarditis or pericarditis, are also associated with a high risk of AF.⁶⁸

The determination of hs-CRP level can also be useful in patients with AF. There are studies that describe an increased level of this inflammatory marker in case of persistent AF, compared to paroxysmal AF.⁶⁹ Wu *et al.* demonstrated in a meta-analysis that a higher baseline hs-CRP level is associated with a higher risk of AF recurrence after catheter ablation and electrical cardioversion.⁷⁰ An elevated white blood cell (WBC) count is also in correlation with the incidence of AF, as confirmed by several studies such as the Framingham Heart Study.⁷¹ Weymann *et al.*, in their meta-analysis, did not find any correlation between the onset of AF and WBC count. However, they suggest that WBC may have a predictive role in the recurrence of AF. Some authors consider that the determination of the neutrophil/lymphocyte ratio is more accurate.^{72,73}

CONCLUSIONS

In the last decade, due to the increased rate of cardiovascular diseases, further investigations were conducted to identify novel cardiovascular risk factors. Systemic inflammation is directly associated not only with ischemic heart disease, but also with the risk to develop atrial fibrillation. The pathophysiology of atrial fibrillation is multifactorial, inflammation being both a cause and a consequence of this condition. Inflammation can promote ectopic atrial activity and aberrant impulse conduction, and the level of circulating inflammatory markers may predict the risk of recurrence. Inflammatory biomarkers, especially in combination with imaging markers, can be used for a better stratification of cardiovascular risk.

CONFLICT OF INTEREST

Nothing to declare.

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