The Use of High Sensitivity C-Reactive Protein in Cardiovascular Disease Detection

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ABSTRACT - Cardiovascular diseases (CVDs) are responsible for a high mortality rate worldwide. One of the most common causes of CVDs is vascular inflammation associated to atherosclerosis. Inflammatory biomarkers are used to assist the detection of CVDs and monitor their evaluation, prognosis and therapy implementation. C-reactive protein (CRP) is an acute phase protein produced after stimulation by pro-inflammatory cytokines. CRP is a biomarker of the inflammatory reaction and an important mediator of atherosclerosis. Given it actively contributes to the development of the atherosclerotic plaque, instability and subsequent clot formation it is also considered a CVD risk factor. Since 2010, the plasma concentration of hsCRP (high sensitivity CRP) has been used as a biomarker for disease prognosis in patients with intermediate risk for CVDs. It could be useful to establish a high concentration limit of hsCRP that can be used by clinicians for diagnosis of acute myocardial infarction, cardio embolic or ischemic stroke, and hypertrophic cardiomyopathy. The end cost/effectiveness of hsCRP screening is still an area of controversy but it is a priority to make the medical community aware of the positive relation between high hsCRP and CVDs to improve median survival and life quality of the patients.

INTRODUCTION

Cardiovascular diseases (CVDs) are the main cause for death and premature incapacity worldwide (1) and in Portugal (2), despite the considerable reduction of the morbidity and mortality rates observed in the last decades. The high prevalence of CVD risk factors drives a continuous clinical surveillance concerning the prevention, rapid diagnosis, and appropriate treatment (1).

CVDs are inflammatory conditions (3), associated with increased expression of pro-inflammatory mediators (4). Elevated pro-inflammatory mediators following CVD, such as myocardial infarction, are associated to mortality (5). Among several inflammatory biomarkers, such as interleukins (IL) 1 and 6 and tumour necrosis factor-α (TNF- α), C-reactive protein (CRP) emerges as an acute phase protein that is over-expressed in/during CVDs (6). It is produced by several cell types, including hepatocytes and monocytes, in response to CVDs as well as other inflammatory conditions such as arthritis, infection, cancer, and mental diseases (7, 8). Increased levels of high sensitivity CRP (hsCRP) may be used as a tool to facilitate diagnosis, prevention and treatment of CVDs. Thus, hsCRP is considered by several authors, an excellence marker of inflammation (9, 10).

CRP also plays a role in the pathogenesis of atherosclerosis contributing to lesion development, plaque rupture and having a proatherogenic effect. Atherosclerosis is the most frequent cause of CVD besides infections. It contributes to the high mortality rate following a cardiovascular event. Thus, hsCRP should be considered in association with cardiac biomarkers in the early diagnosis and therapeutic monitoring of CVD (11).

ATHEROSCLEROSIS INFLAMMATORY PROCESS AND INFLAMMATORY BIOMARKERS

Atherosclerosis is an inflammatory chronic disease of multifactorial aetiology, slow and progressive, and is considered the most important cause of death and premature incapacity. The formation of the atheroma plaques is essentially caused by the accumulation of lipid, inflammatory cells and fibrotic elements in the blood vessels causing their obstruction. This process is called atherogenesis and it is the number one cause of CVDs (12).

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The atherosclerosis process comprises several stages that start with aggression of the endothelium. Oxygen free-radicals present in the blood and increased by tobacco, diabetes mellitus and genetic mutations, oxidize the circulating Low-Density Lipoprotein (LDL), which passes through the weakened endothelium. This lesion will then promote the recruitment of immune cells like monocytes to the site. These monocytes will penetrate the endothelial membrane and transform in macrophages that will opsonize the modified lipoproteins forming the so-called "foam" cells. These will produce more pro-inflammatory cytokines that will intensify the inflammatory process (13).

Afterwards, smooth muscle cells will move to the site forming a more rigid plaque. At this point two types of atheroma plaques can be differentiated: stable and vulnerable. The stable plaques present a dense fibrotic capsule and a minor lipid and inflammatory content. The vulnerable plaques present a thin fibrotic capsule and a high lipid and inflammatory content. Thus, they present a higher probability of rupture resulting in the content release to the blood flow, creating blood clots (14, 15).

Concerning the main locations of the atheroma plaques, it is important to emphasize that the location and progression of the atherosclerotic plaque depend on the called "Shear stress", meaning the forces of arterial shearing, created by the blood flow over the surface of the endothelium (16) whenever the shearing tension flow exists. A rapid flow reflects high shearing tension, favouring Nitric Oxide (NO) generation, maintaining the integrity of the vessel. Thus a turbulent flow causes endothelium cells dysfunction causing the start and progression of the atheroma. For that reason, regions of bifurcation are very important in the location of the atheroma plaques namely the coronary, carotid and iliac (17, 18).

In the genesis of this atherosclerotic process, the most significant inflammation markers are the cytokines IL-1, IL-6, TNF-α and CRP (19). IL-1 and IL-6 are cytokines produced by the liver and macrophages play an active role in the development of the inflammatory reaction. TNF-α, also a cytokine, interacts with the receptors of the endothelial cells increasing vascular permeability. Adhesion molecules like selectins and cellular adhesion molecules (CAMs), metalloproteinase 3 (MMP- 3) and Reactive Oxygen Species (ROS) can also be used as inflammatory markers of CVDs (20). CRP production is stimulated by IL-6 and both plasma concentrations rise in the inflammatory process (21, 22). Although IL-6 initially promotes the inflammatory reaction, it also contributes to its resolution and tissue repair initiation with both pro and anti-inflammatory effects (23). In contrast, *in vivo* studies indicate that CRP is weakly anti-inflammatory (24) associated to a higher risk of CVD (Figure 1). CRP also acts in the development of the atherosclerotic plaque by activating the complement system *via* C1q. This last one consists of a complex cascade of proteins that integrate the innate immune system participating in opsonisation, leucocyte chemoattraction, lysis and cellular activation. However, CRP activation can be exacerbated causing the complement system to act favouring the inflammatory process (25).

In addition, CRP also plays a role in the destabilization of the fibrotic layer of the atheroma, mainly by stimulating MMP-1 production by macrophages. This MMP-1 and other proteinases will later degrade the atheroma matrix and its collagen coating. The destabilization also occurs due to the decreasing of the fibrinolytic process and the increase in the synthesis of the Plasminogen Activator Inhibitor (PAI-1) also due to CRP (26).

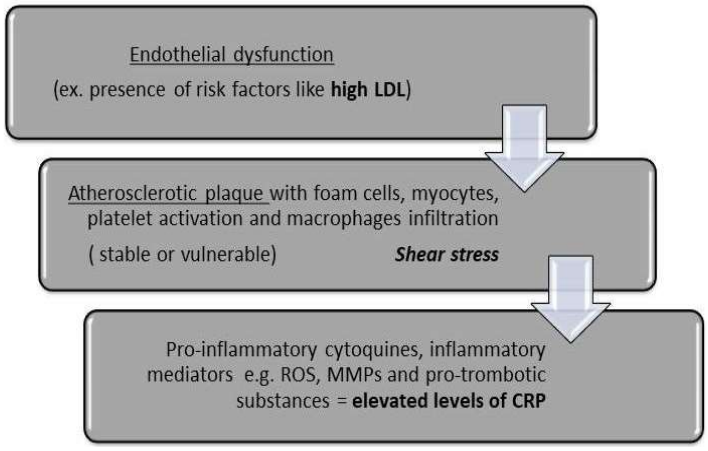

Figure 1. Atherosclerotic process and CRP

The monitoring of known atherosclerotic risk factors can prevent most of CVDs. Major risk factors include age, gender, genetics, cultural habits, diabetes mellitus, smoking, obesity, diet and a sedentary life style (27).

The aging process potentiates the development of cardiovascular complications through accumulation of several pathologies, like hypertension and hypercholesterolemia (28). Arterial hypertension causes the decrease of the resistance of the blood vessels due to the abnormal increase in the arterial pressure. Thus, endothelium damage occurs easily contributing to the inflammatory process (29). Hypercholesterolemia, when associated to the ingestion of a rich diet in saturated fats or associated to a gene mutation in the receptor of LDL, also increases the risk of atherosclerosis and CVD. There is an increase of this lipoprotein in blood which also increases the probability of arterial deposition (30). Men present a higher probability of developing atherosclerosis and CVDs in comparison to women in pre-menopause in the absence of other risk factors. In this period women have an increase hormonal protection due to oestrogen production which benefits the endothelium not only by stimulating NO, an endothelial protector, but also for its antioxidant effects. With the onset of menopause, the risk of CVD induced atherosclerosis increases progressively (31). Also, compared to men, women have more adipocytes thereby increasing the cardiovascular risk in the absence of hormonal protection (32). The genetic heritage also reflects the individual susceptibility to develop a certain disease (33) and to respond differently to a certain pharmacologic treatment (34, 35). Additionally, cultural and socio-economic differences in the access to primary health care may also constitute a risk factor for the atherosclerotic process.

Hyperglycaemia associated with diabetes mellitus causes the production of free oxygen radicals (process that leads to lipid peroxidation and later to the inflammation process) which also causes tissue damage of the endothelium. Insulin treatment stimulates the NO production but as the disadvantage of also stimulating the production of endothelin-1 (ET-1), that as a vasoconstrictor effect (36). Smoking can lead to an increase of free oxygen radicals that are able to LDL oxidation; also toxins, like nicotine and carbon monoxide can cause lesions in the endothelium as well as inflammation (37). A sedentary lifestyle, obesity and diet are associated to fat accumulation in the arterial membranes and the lack of physical exercise can also potentiate the organism atrophy (36).

C-REACTIVE PROTEIN (CRP)

CRP was discovered in 1930 (38) and was named after the C- Polysaccharides *Pneumococos* which caused a reaction in the acute phase of the *Pneumococci's* pneumonia. This protein belongs to the family of pentraxins (pentameric proteins) with 23 KDa. Each subunit has a binding place to phosphatidylcholine and, on the other hand, a binding place for C1q of the complement system (39).

CRP is a protein produced mainly by the liver in response to several inflammatory cytoquines like IL-1 and IL-6, when there is infection or tissue damage. Locally CRP is secreted by endothelial cells, atheroma plaque, muscle cells of the arterial coronary wall and adipocytes (40). Clinically it is an important inflammatory biomarker because its levels are elevated in patients with coronary disease, mainly those with high cholesterol. Since its serum concentration is not affected by diet or circadian variations, its production is not affected by diseases except those of the liver (41, 42).

Concerning the dynamic of CRP, its production starts 4 to 6 hours after a stimulus and doubles each 8 hours, reaching a peak 2 days after the stimulus. It has a semi-life of 19 hours, and it can be days until it returns to basal levels (43). In 1996 (44) showed the prognostic value of increased CRP serum levels in patients with acute myocardial infarction. As mentioned before, CRP serum levels alterations can be measured by hsCRP (45).

HIGH SENSITIVITY CRP CONCENTRATION IN THE DETECTION OF CARDIOVASCULAR DISEASES

Some authors have referred to hsCRP as a non-traditional CVD risk marker due to its action in the atherosclerosis process (46). hsCRP is positively correlated to the risk of cardiovascular events, hence it can be used as a diagnostic tool (Table 1) (45, 47).

A limitation to the use of hsCRP as an inflammatory biomarker is the fact that it is only produced by hepatocytes 4 to 6 hours after stimulus which make CVD quick detection difficult. Another limitation is that CRP takes several days to return to basal levels. Thus, it will not be an accurate biomarker of treatment evolution in the initial phase of recovery after drug treatment (48).

The American Heart Association recommends dismissing hsCRP levels above 10 mg/L as predictors of CVD risk. A different aetiology, like infections, causing high levels of hsCRP should be considered. Also, new measurements of hsCRP should be performed after

2 weeks to validate/confirm the results (49).

As an example of alternative aetiology, post-menopausal women taking oestrogen containing oral hormone replacement therapy can have increased hsCRP levels (50). High hsCRP concentrations may also reflect metabolic disorders, including insulin resistance and adiposity (31, 51).

Since 2003 the American Heart Association has referred the use of hsCRP as a part of a global assessment of cardiovascular risk (52). After some evolution in the concepts the last report in 2010 by the American College of Cardiology Foundation recommends that the assessment of CRP levels is reasonable for patients at intermediate risk (53). Intermediate risk was previously defined as the predicted risk of a cardiovascular event over 10 consecutive years of 10%-20% (54).

Piccardi and colleagues (55) found a clear association between high hsCRP and cardio embolic stroke. Also high hsCRP is associated with a bad prognosis for patients with hypertrophic cardiomyopathy (56) and ischemic stroke (57).

Increased hsCRP is also a reliable predictor of microvascular dysfunction (MVD).MVD is associated with myocardial injury, supporting the central role of inflammation in the pathophysiology of coronary artery disease (58) (Figure 2).

High hsCRP levels were also correlated with recurrent CVD in patients with type 2 diabetes (56), especially those with poor glycaemic control and known cardiovascular disease (59).

Several drugs can modulate hsCRP and are currently used for primary prevention of CVD, like rosuvastatin and aspirin. In 2008 a randomized, double-blind study (Jupiter) in more than 17000 people, belonging to 26 countries, tested the use of therapy with rosuvastatin in the decrease of hsCRP. It reduced the incidence of cardiovascular events (60), encouraging the use of statins as primary prevention in CVD (61).

An alternative to statin therapy is the use of a monoclonal antibody – Canakinumab - that targets Interleukin-1β reducing the inflammation and hsCRP in patients with low and stable LDL. The use of this anti-inflammatory therapy also resulted efficiently in the decrease of the rate of recurrent cardiovascular events (62). This antibody was formerly used in the CANTOS study - Canakinumab Anti-inflammatory thrombosis Outcomes Study (63).

Table 1. Co relation of CVD risk and hsCRP seric concentrations

Risk Classification	hsCRP (mg/L) concentration
Low risk	< 1
Medium Risk	1-3
High Risk	> 3

Adapted from 44.

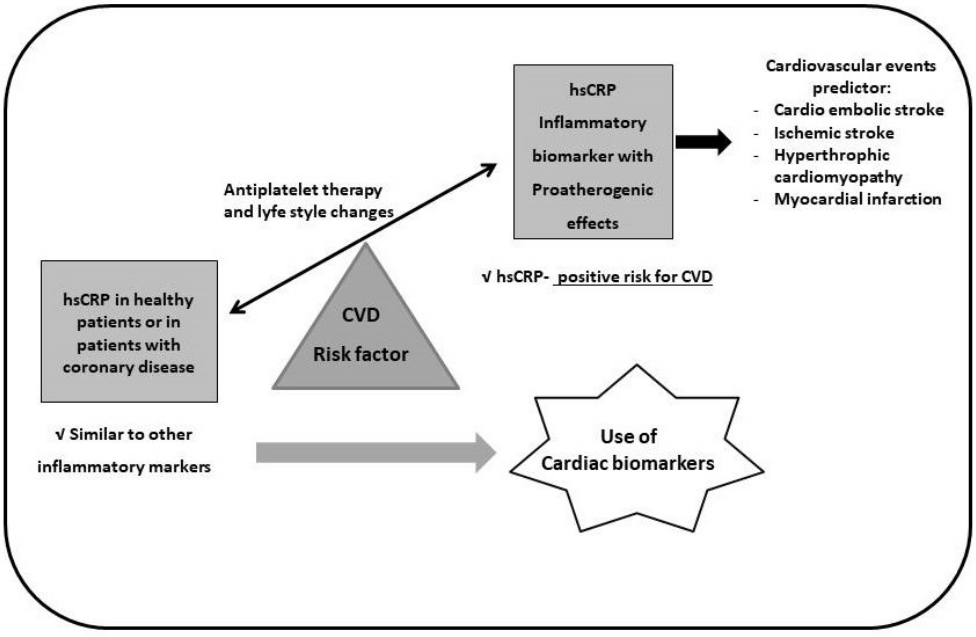

Figure 2. hsCRP and CVD risk

The use of Acetylsalicylic Acid (AAS), more specifically Aspirin GR 100 mg, is also considered a preventive drug for cardiovascular events, reducing the levels of hsCRP (64). Besides pharmacological therapy, it is important to decrease the risk factors/hsCRP concentrations, adopting a healthier life style including low calorie ingestion and low salt diet, physical exercise and smoke cessation (65).

CONCLUSION

The most common CVDs present the same physiopathologic symptoms as atherosclerosis. Although CRP is an acute phase protein produced in the beginning of the inflammatory process, in high concentration it may cause progression and aggravation of the atherosclerosis. Besides acting as an opsonin, it causes the reduction of NO released which is the main key in endothelial dysfunction. It induces monocyte migration across the endothelium and the expression of adhesion molecules like PAI-1 causing more damage to the atheroma plaque. It also increases the uptake of LDL by macrophages. Thus, in the process of inflammatory response CRP is considered both a biomarker and a risk factor for CVDs. As referred before, it slowly returns to basal levels making it a less accurate biomarker in treatment evolution. Thus, there is still a lack of consensus in the use of hsCRP in the clinical practice.

Recently several authors have claimed that very high hsCRP concentrations (>10 mg/L) can be used as a marker to identify patients at risk of cardiovascular events like acute myocardial infarction, stroke, cardio embolic or ischemic, and hypertrophic cardiomyopathy. Furthermore, very high hsCRP levels are studied in patients with type 2 diabetes and poor glycaemic control in connection with CVD.

In addition, high levels of hsCRP can be related to infection or inflammation of a different aetiology pointing to the non-specificity of this biomarker. The concerns that hsCRP measurement is not specific for vascular disease are associated with the studies that show the same high hsCRP levels in patients with other metabolic disorders. hsCRP levels might be useful in the stratification of patients at intermediate risk for a cardiovascular event. Regarding this latest research it could be useful to establish a high concentration limit of hsCRP.

Despite these studies, the cost effectiveness of hsCRP screening is still an area of controversy. For some cardiologists, the primary interventions for patients with high hsCRP are lifestyle alterations together with antiplatelet therapy.

Although there are some limitations to the use of hsCRP, it has recently been found that high levels of hsCRP correlate with a positive risk for CVD development, especially in coronary diseases. In the future this inflammatory biomarker/CVD risk factor may also be useful in the detection of other diseases besides cardiovascular ones caused by atherosclerosis.

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