

Inflammation and hypertension: the search for a link

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Introduction

The last decade has shown an increase in the relevance of inflammation and its mediators in vascular biology; thus, the role of inflammation during atherogenesis is now a matter of intense investigation [1,2]. Basic science studies proved that elements belonging to both innate and adaptive immunity can be involved in the formation, progression and complication of atherosclerosis [2]. Plasma levels of circulating inflammatory molecules, such as C-reactive protein (CRP) and interleukin-6 (IL-6), have been shown to be predictive of future cardiovascular disease (CVD), and drugs which modify their levels can reduce the risk of myocardial infarction and stroke [3]. It has been known for years that hypertension represents an important risk factor for CVD and its treatment is mandatory to prevent future adverse events. To date, however, very little data are available concerning a potential link between inflammation and hypertension. Inflammation and hypertension may share some pathophysiological mechanisms, and this raises the question of whether the treatment of one of the two conditions could have some impact on the other.

Epidemiological evidence

The idea that hypertension and inflammation are somehow linked emerges from the recent cross-sectional and prospective studies showing that circulating inflammatory molecules are increased in hypertensive patients, and their levels predict the onset of hypertension. Some cross-sectional studies showed

that, compared to normotensives, the plasma levels of inflammatory markers, such as CRP; cytokines, such as tumor necrosis factor- α (TNF- α) and IL-6; chemokines, such as Monocyte Chemoattractant Protein (MCP-1); and adhesion molecules, such as P-selectin and sICAM-1, are increased in patients with essential hypertension and no evidence of CVD [4–6]. The same association has been recently observed in patients with pre-hypertension, defined as systolic blood pressure (SBP) between 120 and 139 mmHg and diastolic blood pressure (DBP) between 80–89 mmHg. In fact, these subjects exhibit higher plasma levels of CRP, TNF- α , amyloid-A, homocysteine and white blood cell counts compared to controls [7]. Some authors showed that hypertensive patients also have increased plasma-soluble CD40L level and elevated CD40/CD40L expression on platelets [8]. In an attempt to determine whether this low-grade chronic inflammatory condition could be predictive for the development of hypertension or is a consequence of increased blood pressure, some prospective studies have been conducted. Engstrom *et al.* [9] observed that, among 1796 healthy men without hypertension, those with high plasma levels of fibrinogen, α 1-antitrypsin, aptoglobin, ceruloplasmin and orosomucoid were at higher risk of becoming hypertensive. In particular, the risk of future hypertension was higher among subjects with a concomitant increase of more than three proteins, underlining the importance of the level of inflammation, more than the effect attributable to a single molecule. More recently, Sesso *et al.* [10] showed that, in a cohort of 20,525 females of the Women's Health Study, the levels of high-sensitive CRP (hs-CRP) predicted the development of hypertension, during a follow-up of 7.8 years. This association was independent of the baseline levels of SBP and DBP and was also observed among those with very low initial blood pressure. This data has been recently confirmed by Niskanen *et al.* [11] showing that, during a follow-up of 11 years, middle-aged men with hs-CRP levels >3.0 mg/l are at increased risk of developing hypertension as compared to those with hs-CRP <1.0 mg/l. Interestingly, these authors also observed that the association between the low-grade inflammatory condition and the risk of becoming hypertensive, remained statistically significant even after adjustment for features of the metabolic syndrome. In the last

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few years, different epidemiological studies showed the presence of a co-clustering of inflammation and hypertension in patients at high CVD risk. This was especially the case for patients with metabolic syndrome where hypertension, atherogenic dyslipidemia, insulin resistance and obesity are frequently accompanied by an increase in circulating levels of inflammatory markers (mainly CRP). However, the nature of the link between hypertension and inflammation in this group of patients is still not clearly defined [12]. Even if we cannot exclude that they represent two independent phenomena, some basic science evidence suggests a pathophysiological connection between hypertension and inflammation.

Potential pathophysiological connection

According to the traditional view, hypertension acts as a major determinant of endothelial dysfunction and vascular damage, promoting inflammatory activation of endothelial cells, recruitment of inflammatory cells in the arterial wall and activation of vascular resident elements. In agreement with this theory, it has been shown that an inflammatory response can develop in the arteries of animal models of hypertension. This phenomenon is characterized by the expression of cytokines (IL-6, IL-1, TNF- α), chemokines (MCP-1), adhesion molecules (ICAM-1, VCAM-1), and has been linked to NF- κ B system activation [13–15]. Mechanisms leading to this inflammatory response are not clarified and can include both mechanical stress of the arterial wall and pro-inflammatory effects of humoral factors, such as Angiotensin II (AngII). Accumulating evidence from basic science researches and clinical studies showed that AngII, besides regulating the vascular tone, may exert some pro-inflammatory effects on the arterial wall. AngII, in fact, induces NF- κ B activation triggering the production of inflammatory cytokines, promotes the activation of NADPH oxidase followed by the release of reactive oxygen species (such as superoxide anion) and impairs endothelium-dependent vasodilatation by reducing nitric oxide (NO) generation [16]. The treatment of animal models of hypertension with Angiotensin-II Receptor Blockers (ARBs) reverses most of the detrimental effects of AngII on endothelial function and reduces the level of inflammatory activation in the vessels [13,16]. These basic science results were recently confirmed by clinical studies showing that treatment with ARBs can reduce the circulating levels of some inflammatory mediators, such as IL-6, TNF- α , MCP-1 and CRP [17,18].

Mechanical stress and humoral factors are also considered important stimuli for the activation of cellular elements resident in the media or adventitia layers of the arterial wall. In this context, a major role is played by vascular smooth muscle cells (VSMC) which display remarkable plasticity in terms of differentiation, proliferation and motility. We and others observed that specific immature type of VSMC

populations exist in the arterial wall, and they play a fundamental role in the progression of vascular remodelling in hypertension [19]. The VSMC could undergo a phenotypic dedifferentiation process leading to the acquisition of a 'synthetic' (or undifferentiated) phenotypic profile followed by migration towards the intima layer and the production of new collagen matrix. Endothelial dysfunction, inflammatory cells recruitment and the neointima formation are now considered initial steps for atherogenesis development and may help to define the pathophysiological connection between hypertension and atherosclerosis development. The amplification of the inflammatory response in the artery could increase the plasma levels of the circulating inflammatory molecules, and could partly explain the low-grade inflammatory status observed in hypertensive subjects.

The recent epidemiological observation, that a systemic low inflammatory status precedes the onset of essential hypertension, poses new questions about the genesis of the link between inflammation and high blood pressure. Can inflammation promote hypertension? The evidence now available does not clarify whether or not the inflammation *per se* can induce structural and functional modification in the arterial wall and promote the development of hypertension. However, several lines of research on this topic are emerging, and different theories are now under investigation. First, it could be hypothesized that, independently from their source, some circulating molecules could be involved in altering the mechanisms of vascular tone regulation. For example, some data suggest that CRP itself can promote detrimental effects on the vascular wall, inducing endothelial dysfunction and reducing NO bioavailability [20]. Moreover, CRP could interact with lipoproteins, promote inflammatory activation of monocytes, VSMC and endothelial cells, and trigger the onset of thrombotic complications. For this reason, the potential involvement of CRP in atherogenesis has been lately investigated. However, data now available on this topic are conflicting and non-definitive [21]. Cytokines and chemokines might also play an active role in modulating proliferation, migration and synthetic behaviour of VSMC, observed during atherosclerosis and restenosis [22]. As mentioned above, the pathological remodelling of the vascular wall is often characterized by the presence of VSMC with an immature phenotype. We recently observed that arterioles obtained from hypertensive patients showed an increased presence of VSMC with an immature phenotype compared with those obtained from normotensive subjects [23]. Further studies are needed to clarify whether, besides modulating VSMC phenotype during atherogenesis, the inflammatory mediators can have some impact in controlling the morphological and functional behaviour of VSMC in the resistance arterioles.

As observed during atherogenesis, the inflammatory molecules may contribute to the structural changes of the arterial wall. The rise in SBP, the fall in DBP and

the resulting increase in pulse pressure are considered a manifestation of the presence of central arterial stiffening. Structural changes in stiffened arteries include fracturing of the elastin, collagen proliferation and calcium deposition. The traditional view interprets reduced elasticity of the arteries as a consequence of hypertension. However, some recent studies underline the possibility that arterial stiffening may precede the development of hypertension [24]. Interestingly, pulse wave velocity (PWV), a measure of large vessels distension, has been recently associated with the circulating levels of some inflammatory molecules (such as CRP, IL-6 and TNF- α) [25–27] suggesting that inflammation may contribute to arterial stiffness. The latter also characterized some clinical conditions such as diabetes and end stage renal disease (ESRD) and has been shown to be predictive of the future CVD [28]. Vascular calcification is a major determinant of arterial stiffening, especially among patients with ESRD, and it has been related to the increased cardiovascular mortality observed in this group of subjects [29]. Emerging evidence suggests that calcium deposition cannot be considered just a passive phenomenon [30]. Osteogenic cells have been observed *in vivo* inside atherosclerotic lesions [31] and *in vitro* experiments showed that VSMC can acquire an osteogenic phenotype and deposit calcium [30]. This transition of VSMC towards an osteoblast/chondrogenic phenotype can be induced by inorganic phosphate [32], uremic factors and inflammatory mediators (such as TNF- α and IL-6) [33]. It seems likely that all these factors can synergistically contribute to the promotion of calcium deposition in the arteries, leading to arterial stiffness and worsening of blood pressure levels; this may also favour the onset of future CVD events.

Vascular and tubulointerstitial structural changes occurring in the kidneys have been related to the pathogenesis of essential hypertension [34]. Evidence obtained from animal models of spontaneously developed hypertension (such as SHR) showed that an inflammatory infiltration by macrophages and lymphocytes occurs in the kidney. This renal tubulointerstitial inflammation is observed at a young age in the animals and seems to precede the onset of hypertension [35]. Recent studies in this animal model of hypertension showed that the recruitment of immune cells in the kidney can be prevented by blocking NF- κ B activation. This phenomenon is accompanied by a complete abrogation of hypertension development in spontaneously hypertensive rats (SHR) [36]. Even if the factors inducing the inflammatory response in the kidney are not defined, it could be assumed that the infiltration of immune cells and the oxidative stress in the renal interstitium can play a pathogenic role in the future development of hypertension. However, we do not actually know if this phenomenon has some relevance in humans. If so, it could be hypothesized that the low grade inflammatory status preceding hypertension development could mirror a silent inflammatory damage occurring in the kidney.

Conclusions

It appears that the search for the link between hypertension and inflammation represents a new, stimulating field of research. Data now available from basic science studies show a complex mosaic of interplay between systemic inflammation, vascular cells activation, and structural changes in the arteries. Inflammation and hypertension may interact with each other in a bidirectional manner, determining the pathological modifications of vascular biology that represent the soil for atherosclerosis development and future CVD complications. However, some recent epidemiological studies showed that the presence of a chronic low grade inflammatory status can anticipate the future development of hypertension. This novel observation suggests that the increase in plasma levels of inflammatory mediators observed among hypertensive patients cannot be solely attributed to the vascular damage induced by high blood pressure. New lines of research are now investigating the possibility of a direct pathogenic effect of inflammatory mediators in altering mechanisms of vascular tone regulation leading to the onset of high blood pressure. In the near future we expect that the studies conducted in this direction will clarify the pathophysiological mechanisms linking hypertension and inflammation.

Conflict of interest statement. None declared.

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