Inflammation has been associated with path physiology of hypertension and vascular damage. Resistant hypertensive patients (RHTN) have unfavorable prognosis due to poor blood pressure control and higher prevalence of target organ damage. Endothelial dysfunction and arterial stiffness are involved in such condition. Indeed, we previously showed that RHTN patients have higher arterial stiffness and endothelial dysfunction than controlled hypertensive and normotensive subjects. The relationship between high blood pressure levels and arterial stiffness may be explained, at least in part, by inflammatory pathways. We recently found that hypertensive subjects have higher levels of inflammatory cytokines including TNF-α, IL-10, IL-1β and CRP. Moreover, we showed that IL-1β correlates with arterial stiffness and levels of blood pressure, which are particularly high in patients with resistant hypertension. Increased inflammatory cytokines levels might be related to the development of vascular damage and to the higher cardiovascular risk of resistant hypertensive patients. There is a potential benefit of inflammation inhibition as a future therapy for hypertension. In this context, additional clinical trials are necessary to elucidate the impact of inflammation on resistant hypertension.

Keywords: Resistant hypertension; arterial stiffness; inflammatory cytokines


Copyright: © 2014 The Authors. Licensed under a Creative Commons Attribution 4.0 International License which allows users including authors of articles to copy and redistribute the material in any medium or format, in addition to remix, transform, and build upon the material for any purpose, even commercially, as long as the author and original source are properly cited or credited.

Inflammatory biomarkers is associated with arterial stiffness in resistant hypertension

Resistant hypertension (RHTN) is defined as blood pressure (BP) that remains above goals despite of the concurrent use of 3 antihypertensive agents of different classes, including a diuretic, at optimal dose amounts. Also, patients whose blood pressure are controlled but require 4 or more medications are considered resistant [1]. RHTN patients have unfavorable prognosis attributed to extended time of poor blood pressure (BP) control as well as higher prevalence of target organ damage compared to controlled hypertensive [2-3]. Elevated BP may cause cardiovascular structural and functional alterations leading to organ damage such as left ventricular hypertrophy, arterial...
stiffness and renal dysfunction. On the other hand, such alterations may contribute to uncontrolled BP [4]. Arterial stiffness is a strong and independent predictor of all-cause and cardiovascular mortality in hypertensive patients [5]. It is a risk factor for heart disease that can precede and contribute to hypertension [6]. The relationship between high blood pressure levels and arterial stiffness may be explained, at least in part, by inflammatory pathways [6]. The understanding of the pathophysiology of target organ damage in resistant hypertension may lead to novel therapeutics to prevent its devastating co-morbid conditions.

Arterial stiffness occurs as consequences of structural changes in connective tissue proteins within vascular wall [7]. Pulse wave velocity (PWV) is the “gold standard” method to evaluate arterial stiffness and strong evidences have demonstrated its predictive value for cardiovascular events [8]. Our research group previously demonstrated that RHTN patients have increased PWV and endothelial dysfunction compared to well-controlled hypertensive patients and normotensive subjects [9]. Inflammatory responses contribute in both structural and functional changes in the arterial wall, and have been emerged as a potential determinant of arterial stiffness [6, 10-11]. Indeed, patients with inflammatory diseases such as lupus erythematosus and rheumatoid arthritis have increased arterial stiffness [12-13].

Recent work identified a novel pathway responsible for aortic stiffening in hypertension. They showed that after angiotensin II induced hypertension, remarkable amounts of collagen accumulated in the aortic adventitia compared with control mice. Interestingly, aortic collagen content caused by ang II infusion was attenuated on mice lacking T and B cells (RAG1−/− mice). Angiotensin II infusion did not cause aortic stiffness in RAG1−/−, while increased aortic stiffness was observed in wild type. Adoptive transfer of T-cells to RAG1−/− mice restored the process of aortic stiffening, supporting the role of immune system in vascular damage [14]. The collagen expression in aortic fibroblasts may be mediated by p38 mitogen-activated protein kinases (p38 MAPK), since its inhibition prevented the increase of mRNA collagen in cultured fibroblasts under stretch or cytokine exposition, and inducing aortic stiffness in experimental hypertension [14]. Also, p38 MAPK decreases stretch–induced collagen expression in isolated smooth muscle cells from spontaneously hypertensive rat (SHR) [15]. Indeed, previous data demonstrated that immune system is crucial for the development of hypertension and vascular damage since RAG1−/− or in the absence of interleukin-17a (IL-17a−/− mice) had lower blood pressure, lower collagen deposition in the aorta, lower superoxide production and endothelium-dependent vasodilatation was preserved after angiotensin II infusion [16-18].

Inhibition of inflammatory compounds has become a field of interest on hypertension research. We previously showed that TNF-α inhibition reduced systolic BP and endothelial inflammation in SHR [19]. Endothelial cells incubated with serum of resistant hypertensive subjects had decreased apoptosis after treatment with TNF-α inhibitor (unpublished data). Other authors pointed out that patients with rheumatoid arthritis improved arterial stiffness after administration of TNF-α inhibitor [20]. These data support the role of inflammatory biomarkers on vascular damage.

Cohort studies in healthy volunteers demonstrate that C-reactive protein is related to arterial stiffness [21-24]. The same was observed in never-treated essential hypertension [11]. Evidences showed that lowering inflammation, through hs-CRP levels may decrease vascular events rates [25]. Our study investigated the relationship between inflammatory cytokines and arterial stiffness in RHTN patients. We found that hypertensive subjects (resistant and controlled hypertensive) had higher hs-CRP compared to normotensive subjects. These levels tended to be higher in resistant hypertensive subjects. RHTN subjects also had increased levels of the cytokines IL-10, IL-1β and TNF-α compared to mild to moderate hypertensive and normotensive subjects. Moreover, we showed that IL-1β correlates with arterial stiffness and levels of blood pressure, even after adjust for age and glucose [20]. In accord, we demonstrated that isoprostane levels, an oxidative stress marker, were associated with endothelial dysfunction in these patients [27]. Our data pointed out that inflammation may contribute to pathogenesis of resistant hypertension, in contrast; higher blood pressure may promote inflammatory processes. Interestingly, emerging data suggest pivotal role of IL-1 in pathophysiology of inflammatory diseases such as atherosclerosis, type 2 diabetes, cancer and obesity [26]. This cytokine has been implicated in target organ damage, but its role in pathophysiology of hypertension needs to be clarified.

In summary, we demonstrated that RHTN patients, despite of multiple anti-hypertensive therapy have higher cytokines levels compared with mild to moderate hypertensive and healthy volunteers. In addition, the association between IL-1β levels with arterial stiffness indicates that this cytokine may contribute to increased cardiovascular risk of resistant hypertensive patients. The importance of identifying those at risk for cardiovascular disease in order to prevent new events is emerging. There is a potential benefit of inflammation inhibition as a future therapy for resistant hypertension. In this context, additional clinical trials are necessary to elucidate the impact of inflammation on hypertension.

**Conflicting interests**

The authors have declared that no competing interests exist.
Acknowledgements

This study was supported by the State of São Paulo Research Foundation (FAPESP), SP, Brazil, National Council for Scientific and Technological Development (CNPq) and Coordination for Improvement of Higher Education Personnel (Capes), Brazil.

References


