Current Hypertension Reports (2019) 21:95
https://doi.org/10.1007/s11906-019-1003-2

ANTIHYPERTENSIVE AGENTS: MECHANISMS OF DRUG ACTION (ME ERNST, SECTION EDITOR)

Pro-inflammatory Cytokines and Resistant Hypertension: Potential for Novel Treatments?

Mariana Rodrigues Pioli[1] · Ana Paula de Faria[1]

© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Purpose of Review To gather data from studies evaluating the pro-inflammatory profile of individuals with resistant hypertension (RH), and bring a clinical update of new and potential complementary therapies to treat inflammation in RH.

Recent Findings Increases in pro-inflammatory cytokines are related to elevated blood pressure and target organ damage in RH patients. Clinical and experimental studies have shown that some biological therapies, especially TNF-α inhibitors, regulated pro- and anti-inflammatory cytokines associated with improvements in clinical outcomes, although they are not yet reported in RH.

Summary New emerging therapies to treat inflammation in RH, although promising, are still hypotheses that have not been scientifically confirmed in clinical trials. For this reason, inflammation-target treatments, such as the TNF-α and IL-6 inhibitors, should be encouraged for testing as complementary therapies in RH in order to elucidate their potential benefits.

Keywords Refractory hypertension · Blood pressure · Cytokines · Inflammation · Biological therapies

Introduction

An individual is considered resistant to antihypertensive treatment when they do not achieve optimal blood pressure (BP) levels, despite concomitant use of a calcium channel blocker (CCB), a blocker of the renin-angiotensin system, and a diuretic, at tolerated maximal doses—namely uncontrolled resistant hypertension (RH). Also, the definition includes hypertensive patients who achieve appropriate BP levels, but require ≥ 4 antihypertensive classes, referred to in the literature as controlled RH [1]. True diagnosis of RH includes exclusion of both (i) patients with the white-coat effect and (ii) non-adherence to antihypertensive treatment [1].

The lack of BP control along with coexisting multiple comorbidities, metabolic abnormalities, and target organ damage (TOD) places RH as a high cardiovascular (CV) risk [1]. Due to its complex nature, many pathophysiological mechanisms underly the development and progression of the disease; among them, the inflammatory process has played a critical role in the regulation of BP in RH [2, 3].

Antihypertensive therapies such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and mineralocorticoid receptor (MR) antagonists are widely used in RH. Beyond the reduction in BP levels, decrease in plasma levels of some cytokines has been reported in the literature after the application of drugs from these classes [4, 5]; however, despite these potential benefits, the pro-inflammatory profile of RH remains elevated. Studies have shown that individuals with resistance to antihypertensive therapy have an imbalance in plasma levels of both pro-inflammatory cytokines and adipocytokines, associated with TOD, such as arterial stiffness, CV remodelling, and renal alterations [6, 7••]. However, it has not been well established whether such changes correlate with RH in a causal relationship or simply as a marker for the presence of the condition.

Investigating alternative therapies with biological agents capable of altering the pathways of some cytokines has sparked marked interest in recent years. Agents such as inhibitors of tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 have shown promise in reducing BP in animal models [8•] as well as in humans [9, 10], and thus may represent new

This article is part of the Topical Collection on *Antihypertensive Agents: Mechanisms of Drug Action*

✉ Ana Paula de Faria
ana.cabralfaria@gmail.com; aninha_cfaria@hotmail.com

[1] Department of Pharmacology, FCM 10 Building, School of Medical Sciences - University of Campinas (FCM-UNICAMP), Tessália Vieira de Camargo, 126, Campinas, SP 13083-970, Brazil

Published online: 26 November 2019

pharmacological strategies to treat RH. Therefore, the aim of this review was to gather data from studies evaluating the pro-inflammatory profile of individuals with RH and bring a clinical update of what the new and potential complementary therapies for inflammation are in RH and their possible implications.

Pro-inflammatory Profile of Resistant Hypertension

The pathophysiology of RH is multifactorial and complex and among the many mechanisms involved, the immune system is activated [3, 11]. Hypertension is known to activate the adaptive immune response, which in turn stimulates the production of pro-inflammatory cytokines [12]. Since inflammation is closely related to the pathogenesis of hypertension and other cardiovascular diseases (CVD), the link between angiotensin II (Ang II) and pro-inflammatory cytokines may be important in modulating the hypertensive response. Angiotensin II is an effector peptide of the renin-angiotensin aldosterone system (RAAS), closely related to the pathophysiology of hypertension [13], and because of this biological importance, it has been used to investigate the role of pro-inflammatory cytokines in animal models.

For instance, researchers analyzed BP and plasma levels of IL-17, IL-6, and TNF-α cytokines in wild-type mice compared with IL-17 −/−, IL-6 −/−, and TNF-α −/− mice after chronic Ang II infusion. Wild-type mice showed increased production of these cytokines as well as an Ang II-induced hypertensive response, but these were absent in the knockout mice. [13–15]. Kirabo et al. also explored possible pathways that could lead to hypertension using multiple murine models of hypertension. It was observed that dendritic cells from Ang II–infused mice had increased oxidative stress, accumulated isoketal protein adducts, and released pro-inflammatory cytokines such as IL-6, IL-1β, and IL-23. These cells also produced proliferation and polarization of T cells generating an inflammatory phenotype, by increasing the production of IL-17, IFN-γ, and TNF-α [16]. These experimental results suggest that inflammation plays a pivotal role in the pathogenesis of hypertension, which is substantiated by some clinical studies conducted in different groups of individuals.

Mahdur et al. investigated the plasma levels of IL-17 in diabetic individuals with and without hypertension and observed that the group of hypertensive individuals presented higher levels of this cytokine when compared with the normotensive group (7.1 ± 1.6 pg/mL vs. 2.2 ± 1.4 pg/mL respectively) [15]. The Multi-Ethnic Study of Atherosclerosis (MESA) study has suggested that inflammatory biomarkers, including IL-6, are able to predict the incidence of hypertension in middle-aged or elderly individuals without CVD [17]. In addition, Ridker et al. observed that pro-inflammatory cytokines IL-6 and TNF-α are involved in predicting CVD, regardless of traditional risk factors and hypertension [18, 19].

Based on those clinical and experimental data, a noteworthy question arises: how would the pro-inflammatory profile of RH patients be, given the high CV risk in these patients?

Table 1 represents the main clinical studies reported in the literature that explore cytokines in RH. The most recent study conducted by Chen et al. found that cytokines such as IL-6 and TNF-α are associated with the occurrence of apparent RH in individuals with chronic kidney disease. Interestingly, in this study, no difference was found between the inflammation profile and individuals using ≥ 3 antihypertensive drugs (BP ≥ 140/90 mmHg) and those on therapy with ≥ 4 antihypertensive drugs (BP < 140/90 mmHg), except for fibrinogen and TNF-α, which were slightly higher in uncontrolled patients using ≥ 3 antihypertensives [7••].

Previous clinical studies have shown TNF-α and IL-1β are associated with arterial stiffness in RH patients [20, 21]. Barbaro et al. observed that TNF-α, IL-10, and IL-1β plasma levels are higher in individuals with RH when compared with normotensive individuals. However, no differences in IL-6 levels were found between the groups [20]. Individuals with uncontrolled RH have also been observed to have a deregulation in their adipokine profile consisting of (i) an increase in leptin and resistin plasma levels, and (ii) a decrease in adiponectin [6, 22, 23]. This imbalance was also associated with the presence of metabolic syndrome, [24] TOD [6, 22], and increased BP and aldosterone levels [23] in RH. Adipokines are involved in pathophysiologic mechanisms that regulate inflammation, and therefore play an important role in the pathogenesis of metabolic disorders associated with RH, such as obesity and type II diabetes mellitus [25, 26]. These coexisting co-morbidities further contribute to the activation of the immune system with a consequent increase in pro-inflammatory cytokines [27, 28].

Given the relevance of the inflammatory process in the evaluation, and potentially in the prognosis of RH subjects, researchers have proposed the use of inflammatory scores. This tool was indicated to address, in a single measure, a variety of mechanistically aligned cytokines involved in the pathophysiology of RH [7, 29••]. Such scores may provide a better approach, than when only a single biomarker is analyzed, since they could be more effective in predicting low-grade inflammation and CV risk in high-risk populations, such as RH patients. However, as the authors suggest, to be safe and effective in clinical practice, further studies are necessary to validate this score in larger populations.

These findings suggest that the deregulation in plasma levels of pro-inflammatory cytokines and adipokines contribute to increased CV risk in RH associated with maladaptive consequences (Fig. 1). This leads us to an intriguing idea that drugs able to alter the inflammatory status could have high potential as a complementary therapy in RH.

Table 1 Summary of clinical studies exploring cytokines in resistant hypertension

Author (year)	Population	*n*	Cytokines	Main conclusions
Chen, J. (2019)[7]	ATRH with CKD	3367	IL-1β, IL-6, and TNF-α	Multivariable-adjusted odds ratio (95% CI) of ATRH for the highest tertile vs. the lowest tertile of IL-6 = 1.29 (95% CI, 1.05–1.59) and TNF-α = 1.49 (95% CI, 1.20–1.85).
Barbaro, N.R. (2014)[20]	RH, HT, and NT	72	IL-1β, IL-6, IL-10, and TNF-α	RH has increased IL-1β, IL-10, and TNF-α levels, but not IL-6 when compared with mild-to-moderated HT and NT.
Barbaro, N.R. (2015)[21]	RH and NT	51	TNF-α	TNF-α plasma levels were increased in RH group compared with NT group, associated with arterial stiffness.
de Faria, A.P. (2013)[22]	CRH and UCRH	96	Adiponectin	Adiponectin plasma levels were lower in the UCRH group than in the CRH group.
de Haro-Moraes, C. (2013)[23]	HT, CRH, and UCRH	111	Leptin	Leptin plasma levels were higher in the UCRH group compared with the CRH and HT.
Sabbatini, A.R. (2013)[6]	CRH and UCRH	89	Leptin and adiponectin	Leptin plasma levels were increased, and adiponectin was lower in UCRH group associated with TOD.
Santa Catharina, A. (2019)[24]	HT and RH	236	Leptin and adiponectin	Adiponectin plasma levels were lower and leptin levels were increased in MetS group compared with the subjects without MetS.
de Faria, A.P. (2019)[29]	HT and RH	224	IS (TNF-α, IL-6, IL-8, IL-10, leptin, and adiponectin)	Inflammatory score was higher in the RH group compared with HT group.
Kampmann, U. (2017)[54]	RH	8	IL-1β, IL-6, IL-10, IFN-γ, and TNF-α	IL-1β, IL-6, and TNF-α were detectable in plasma and no changes post renal denervation.
Eikelis, N. (2015)[55]	RH	69	IL-6 and TNF-α	IL-6 and TNF-α concentrations showed no changes post renal denervation.
Eikelis, N. (2017)[56]	RH	57	Leptin, adiponectin, and resistin	Adiponectin concentration was increased after renal denervation but plasma leptin and resistin levels remained unchanged

ATRH apparent treatment-resistant hypertension, *CKD* chronic kidney disease, *IL* interleukin, *TNF-α*, tumor necrosis fator alpha, *CI* confidence interval, *RH* resistant hypertension, *HT* hypertension, *NT* normotensive, *CRH* controlled resistant hypertension, *UCRH* uncontrolled resistant hypertension, *TOD* target organ damage, *Mets* metabolic syndrome, *IS* inflammatory score, *IFN-γ* interferon gamma

Antihypertensive Therapies and their Anti-inflammatory Properties

By definition, RH needs 4 or more classes of antihypertensive drugs, commonly including a CCB, ACEI, or ARB and a diuretic to achieve BP control [1]. Within the commercially available pharmacological range, it has been observed that some classes of antihypertensives are able to change the plasma concentration of pro-inflammatory cytokines, and thus may provide some benefit in this way.

As previously stated, Ang II is involved, not only in mechanisms that elevate BP, but also by promoting vascular remodelling, production of TNF-α in human podocytes, and indirectly stimulating IL-6 via downstream signalling of aldosterone (through activation of MR), which contributes to increase the inflammatory response [5, 30]. Clinical trials have shown that Ang II pathway–altering drugs such as ACEI and ARB are able to reduce plasma levels of pro-inflammatory cytokines. Administration of ramipril—an ACEI—in normotensive individuals with repaired coarctation of the aorta decreased the expression of IL-6 as well soluble CD40 ligand (sCD40L) and soluble vascular cell adhesion molecule 1 (sVCAM-1)—these latter biomarkers also being involved in inflammatory process [31]. In addition, candesartan (when compared with placebo) reduced plasma levels of TNF-α and monocyte chemoattractant protein 1 (MCP-1) in patients with mild-to-moderate hypertension [32]. These results suggest that, regardless of the presence of hypertension, these antihypertensives have antiatherogenic effects, reducing endothelial dysfunction by regulating inflammatory cytokines [31, 32].

Ang II indirectly activates genomic and nongenomic mechanisms that contribute to increased BP by stimulating the glomerular zone of the adrenal cortex gland to produce aldosterone, in turn interacting with its MR. Such effects include increased sodium and water reabsorption, oxidative stress, and vascular inflammation [33]. Antagonism of MR, represented by spironolactone and epleronone, was effective in reducing the expression of several pro-inflammatory cytokines among them TNF-α [34] and IL-6 [5] in humans, in addition to increasing adiponectin levels in obese, diabetic db/db (inactivating mutation in the leptin receptor) mice [35], probably by suppressing the aldosterone pathway.

Despite all the evidence of the anti-inflammatory properties of these antihypertensive classes (Fig. 1)—which are used in routine clinical practice of RH—a deregulation in plasma levels of pro-inflammatory cytokines in RH individuals can still be found, which may contribute to increased CV risk [20]. This justifies the hypothesis of if biological agents with anti-inflammatory effects positively modulate BP levels and associated-clinical features in individuals with RH.

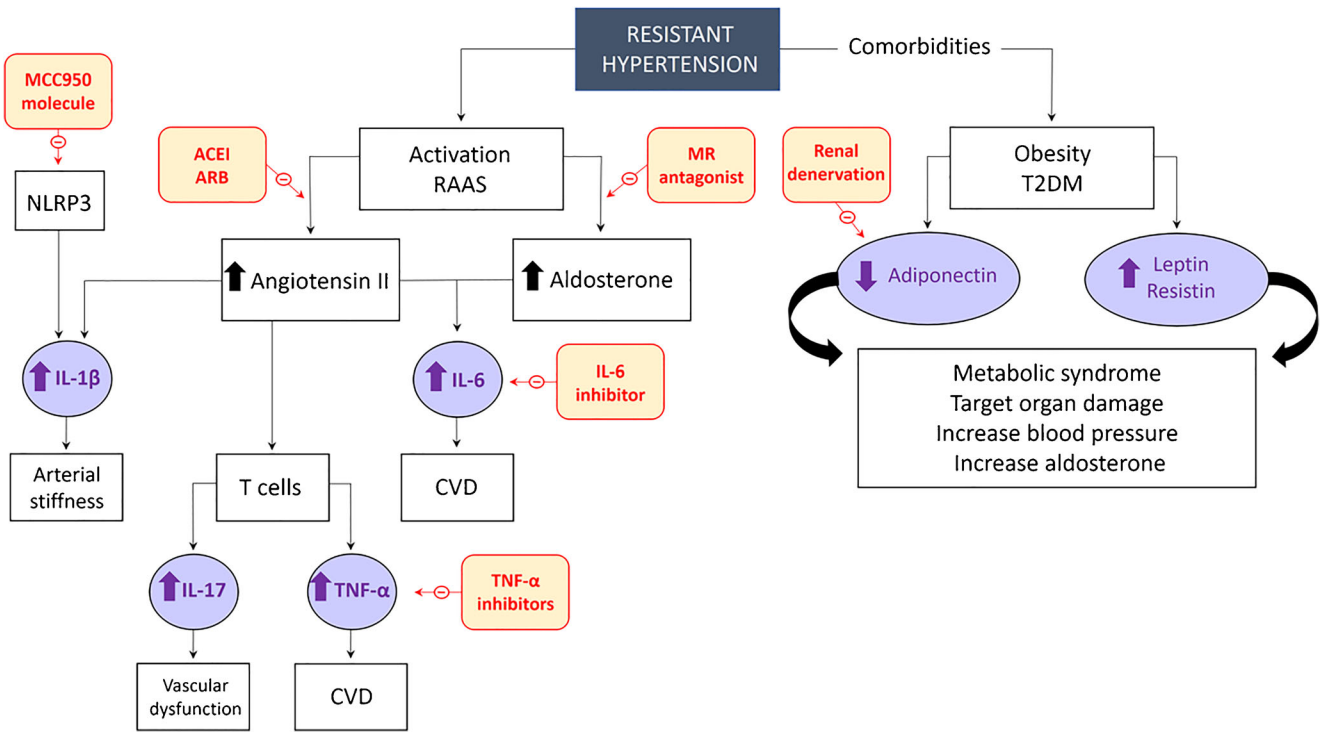

Fig. 1 Summary of the pro-inflammatory profile of resistant hypertension and the therapies to treat inflammation in this condition. This is a representative flowchart relating the pro-inflammatory profile of resistant hypertensive individuals and their possible clinical outcomes, as well as the therapies involved in the improvement of cytokine levels in these individuals. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CVD, cardiovascular disease; IL, interleukin; MR, mineralocorticoid receptor; NLRP3, nucleotide oligomerization domain-like receptor protein-3 inflammasome; RAAS, renin-angiotensin aldosterone system; TNF-α, tumor necrosis factor-alpha; T2DM, type II diabetes mellitus

Clinical Perspectives

TNF-α inhibitors, such as infliximab and etanercept, are commonly used to treat individuals with autoimmune diseases. Currently, they represent the most studied class of biological therapies in hypertension. So far, it is not well established how these agents act to decrease BP in humans, although studies have shown promising results [9, 10, 36, 37].

Experimental studies have shown that TNF-α inhibitors are able to prevent an increase in systolic BP (SBP), mean BP (MBP), and heart rate (HR), as well as improve vascular function in fructose-fed rats [8•, 38].

Etanercept has been able to not only attenuate BP elevation, but also provide renal protection in Dahl salt-sensitive rats on a high-salt diet [39] and in mice with systemic lupus erythematosus [40]. In addition, it regulated IL-6 expression and exerted a positive inotropic effect in a rat model with early heart failure due to hypertension [41]. Chronic inhibition of TNF-α by etanercept in the brain of spontaneously hypertensive rats (SHR) and rats with Ang II-induced hypertension has also shown to (i) slow the progression of hypertension, (ii) restore the balance of pro-inflammatory cytokines, (iii) attenuate oxidative stress, (iv) reduce the sympathetic hyperactivity induced by hypertension and cardiac hypertrophy, and (v) restore the balance between the pro and antihypertensive axes of RAAS [42, 43].

Infliximab was effective in reducing SBP and left ventricular hypertrophy in SHR after 8 weeks of treatment, through the reduction of endothelial inflammation, by recovering both serine/threonine kinase and endothelial nitric oxide synthase [44]. An in vitro study found that human umbilical vein endothelial cells incubated with serum of RH subjects showed increased cell apoptosis and a higher production of reactive oxygen species when compared with cells that were incubated with serum of normotensives. When treated with infliximab, attenuation of apoptosis was observed only in cells incubated with RH serum [21].

Clinical studies involving this class are still scarce and have conflicting results. Infliximab is the most studied so far showing efficacy in reducing SBP and DBP [9, 36], and some parameters of ambulatory BP monitoring in individuals with rheumatoid arthritis (RA) [10]. It is suggested that BP decreases are due to inflammatory suppression and consequently reduction in RA activity that occurs after infliximab therapy [9], resulting in endothelium-dependent microvascular dilation [36] and reduction of sympathetic activity [10]. However, in a retrospective cohort study conducted by Desai et al., no reduced risk of incident hypertension was shown in subjects on any TNF-α inhibitors (adalimumab, certolizumab, etanercept, golimumab, and infliximab) when compared with subjects on non-modifying antirheumatic drug therapies (hydroxychloroquine, sulfasalazine, minocycline, gold compounds, azathioprine, cyclophosphamide, and penicillamine) [37].

Although these studies have associated TNF-α inhibitors with a reduction in BP, there are no reports on the action of these drugs in subsets of a hypertensive population, such as RH. Recently, the study (yet to be published) "Effects of the TNF-alpha Inhibition on Hemodynamic Parameters in Resistant Hypertension" (ClinicalTrials.gov Identifier: NCT02743390) has been conducted by our research group, whose main purpose was to evaluate the change in MBP levels after infliximab infusion, compared with placebo in RH individuals. Such results may provide us with more accurate information which could elaborate more evidence on the potential use of these biological agents in a high-risk group of RH subjects [45••].

Another promising biological agent that possibly modulates the hypertensive pro-inflammatory status is the IL-6 inhibitor, tocilizumab. This drug is a humanized recombinant anti-IL-6R monoclonal antibody used for the treatment of RA and it is responsible for blocking the IL-6-mediated signalling pathway [46]. An experimental study with SHR showed that after administration of tocilizumab, there was a reduction in MBP and HR, but not in SBP. Furthermore, this drug improved vascular function by normalizing the maximum contractile response of the superior mesenteric arteries of fructose-fed rats without changing acetylcholine sensitivity [8]. Since this is the first study of tocilizumab of this kind reported, further studies are warranted, including clinical trials, which may investigate its effects as a complementary therapy for RH.

There is currently on-going research associating the MCC950 molecule with BP reduction [47•, 48•]. This drug is a selective inhibitor of the nucleotide oligomerization domain-like receptor protein-3 (NLRP3) inflammasome, which is associated with IL-1β maturation and secretions in systemic circulation, and activation of the inflammatory process [49, 50]. A pilot study showed that MCC950 was able to reduce BP and improve the pro-inflammatory profile in ASC (−/−) mice, an inflammasome-deficient animal model [47•]. Subsequently, the same group of researchers conducted a further study and observed that this drug has protective effects on renal dysfunction, fibrosis, and inflammation associated with the development of hypertension in the animal model used. Due to its favorable pharmacokinetic and pharmacodynamic properties, the authors suggest that MCC950 is a promising alternative for the treatment of hypertension [48•].

Finally, clinical trials have investigated the efficacy of surgical procedures such as renal denervation performed in individuals with RH as a way to achieve BP control in these patients [51–53]. Some studies have also evaluated whether this therapeutic approach is able to affect the inflammatory profile in RH. Both studies conducted by Kampmann et al. and Eikelis et al. found reductions in BP levels between 3 and 6 months after renal denervation, but none have found changes in pro and anti-inflammatory cytokines after the procedure [54, 55]. However, a subset of obese individuals with RH showed an increase in adiponectin levels and reduction in non-esterified fatty acids after 3 months of renal

denervation, suggesting that BP reduction occurs, in part, through these pathways [56•] (Table 1).

Taken together, all the mentioned procedures and novel emerging therapies discussed above represent potential options in the advancement of treatment of RH (Fig. 1). New treatments that modulate pathophysiological derangements in RH individuals, such as the pro-inflammatory profile, and that may improve their CV risk should be researched in clinical trials to support these preliminary findings.

Conclusions

Despite clinical and experimental preliminary findings in the literature, an improvement in the pro-inflammatory profile associated with BP control and CV risk reduction in RH are still hypotheses that have not been scientifically confirmed in clinical trials. For this reason, treatments able to modulate the immune response, such as the inhibitors of TNF-α and IL-6, are promising and should be encouraged to be tested as complementary therapies to treat RH population. In future, these studies will elucidate any clinical benefits that these inflammation-related therapies may offer to patients with RH.

Acknowledgments Mariana Rodrigues Pioli acknowledges the Coordination for the Improvement of Higher Education Personnel (CAPES), Brazil.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension. 2018;72(5):e53–90. https://doi.org/10.1161/HYP.0000000000000084.
2. Salles GF, Fiszman R, Cardoso CR, Muxfeldt ES. Relation of left ventricular hypertrophy with systemic inflammation and endothelial damage in resistant hypertension. Hypertension. 2007;50(4):723–8. https://doi.org/10.1161/HYPERTENSIONAHA.107.093120.
3. Belen E, Sungur A, Sungur MA, Erdoğan G. increased neutrophil to lymphocyte ratio in patients with resistant hypertension. J Clin Hypertens (Greenwich). 2015;17(7):532–7. https://doi.org/10.1111/jch.12533.
4. Ferrario CM, Strawn WB. Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. Am J Cardiol. 2006;98(1):121–8. https://doi.org/10.1016/j.amjcard.2006.01.059.
5. Luther JM, Gainer JV, Murphey LJ, Yu C, Vaughan DE, Morrow JD, et al. Angiotensin II induces interleukin-6 in humans through a mineralocorticoid receptor-dependent mechanism. Hypertension. 2006;48(6):1050–7. https://doi.org/10.1161/01.HYP.0000248135.97380.76.
6. Sabbatini AR, Faria AP, Barbaro NR, Gordo WM, Modolo RG, Pinho C, et al. Deregulation of adipokines related to target organ damage on resistant hypertension. J Hum Hypertens. 2014;28(6):388–92. https://doi.org/10.1038/jhh.2013.118.
7.•• Chen J, Bundy JD, Hamm LL, Hsu CY, Lash J, Miller ER, et al. Inflammation and apparent treatment-resistant hypertension in patients with chronic kidney disease. Hypertension. 2019;73(4):785–93. https://doi.org/10.1161/HYPERTENSIONAHA.118.12358 **This study indicates that inflammatory biomarkers such as IL-6, TNF-α, and TGF-β are associated with apparent treatment-resistant hypertension**.
8.• Abdelrahman AM, Al Suleimani YM, Ashique M, Manoj P, Ali BH. Effect of infliximab and tocilizumab on fructose-induced hyperinsulinemia and hypertension in rats. Biomed Pharmacother. 2018;105:182–6. https://doi.org/10.1016/j.biopha.2018.05.118 **Infliximab and tocilizumab reduce mean arterial pressure and heart hate, but only infliximab reduces systolic blood pressure**.
9. Klarenbeek NB, van der Kooij SM, Huizinga TJ, Goekoop-Ruiterman YP, Hulsmans HM, van Krugten MV, et al. Blood pressure changes in patients with recent-onset rheumatoid arthritis treated with four different treatment strategies: a post hoc analysis from the BeSt trial. Ann Rheum Dis. 2010;69(7):1342–5. https://doi.org/10.1136/ard.2009.124180.
10. Yoshida S, Takeuchi T, Kotani T, Yamamoto N, Hata K, Nagai K, et al. Infliximab, a TNF-α inhibitor, reduces 24-h ambulatory blood pressure in rheumatoid arthritis patients. J Hum Hypertens. 2014;28(3):165–9. https://doi.org/10.1038/jhh.2013.80.
11. Barbaro NR, Harrison DG. Markers or makers: inflammatory cytokines in treatment-resistant hypertension. Hypertension. 2019;73(4):767–9. https://doi.org/10.1161/HYPERTENSIONAHA.119.12604.
12. Mikolajczyk TP, Guzik TJ. Adaptive immunity in hypertension. Curr Hypertens Rep. 2019;21(9):68. https://doi.org/10.1007/s11906-019-0971-6.
13. Sriramula S, Haque M, Majid DS, Francis J. Involvement of tumor necrosis factor-alpha in angiotensin II-mediated effects on salt appetite, hypertension, and cardiac hypertrophy. Hypertension. 2008;51(5):1345–51. https://doi.org/10.1161/HYPERTENSIONAHA.107.102152.
14. Zhang W, Wang W, Yu H, Zhang Y, Dai Y, Ning C, et al. Interleukin 6 underlies angiotensin II-induced hypertension and chronic renal damage. Hypertension. 2012;59(1):136–44. https://doi.org/10.1161/HYPERTENSIONAHA.111.173328.
15. Madhur MS, Lob HE, McCann LA, Iwakura Y, Blinder Y, Guzik TJ, et al. Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. Hypertension. 2010;55(2):500–7. https://doi.org/10.1161/HYPERTENSIONAHA.109.145094.
16. Kirabo A, Fontana V, de Faria AP, Loperena R, Galindo CL, Wu J, et al. DC isoketal-modified proteins activate T cells and promote hypertension. J Clin Invest. 2014;124(10):4642–56. https://doi.org/10.1172/JCI74084.

17. Lakoski SG, Cushman M, Siscovick DS, Blumenthal RS, Palmas W, Burke G, et al. The relationship between inflammation, obesity and risk for hypertension in the Multi-Ethnic Study of Atherosclerosis (MESA). J Hum Hypertens. 2011;25(2):73–9. https://doi.org/10.1038/jhh.2010.91.
18. Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. Circulation. 2000;101(18):2149–53. https://doi.org/10.1161/01.cir.101.18.2149.
19. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation. 2000;101(15):1767–72. https://doi.org/10.1161/01.cir.101.15.1767.
20. Barbaro NR, Fontana V, Modolo R, De Faria AP, Sabbatini AR, Fonseca FH, et al. Increased arterial stiffness in resistant hypertension is associated with inflammatory biomarkers. Blood Press. 2015;24(1):7–13. https://doi.org/10.3109/08037051.2014.940710.
21. Barbaro NR, de Araújo TM, Tanus-Santos JE, Anhê GF, Fontana V, Moreno H. Vascular damage in resistant hypertension: TNF-Alpha Inhibition Effects on Endothelial Cells. Biomed Res Int. 2015;2015:631594. https://doi.org/10.1155/2015/631594.
22. de Faria AP, Demacq C, Figueiredo VN, Moraes CH, Santos RC, Sabbatini AR, et al. Hypoadiponectinemia and aldosterone excess are associated with lack of blood pressure control in subjects with resistant hypertension. Hypertens Res. 2013;36(12):1067–72. https://doi.org/10.1038/hr.2013.92.
23. de Haro MC, Figueiredo VN, de Faria AP, Barbaro NR, Sabbatini AR, Quinaglia T, et al. High-circulating leptin levels are associated with increased blood pressure in uncontrolled resistant hypertension. J Hum Hypertens. 2013;27(4):225–30. https://doi.org/10.1038/jhh.2012.29.
24. Catharina AS, Modolo R, Ritter AMV, Sabbatini AR, Lopes HF, Moreno Junior H, et al. Metabolic syndrome-related features in controlled and resistant hypertensive subjects. Arq Bras Cardiol. 2018;110(6):514–21. https://doi.org/10.5935/abc.20180076.
25. Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. Front Endocrinol (Lausanne). 2013;4:71. https://doi.org/10.3389/fendo.2013.00071.
26. Knights AJ, Funnell AP, Pearson RC, Crossley M, Bell-Anderson KS. Adipokines and insulin action: a sensitive issue. Adipocyte. 2014;3(2):88–96. https://doi.org/10.4161/adip.27552.
27. Li J, Huang M, Shen X. The association of oxidative stress and pro-inflammatory cytokines in diabetic patients with hyperglycemic crisis. J Diabetes Complicat. 2014;28(5):662–6. https://doi.org/10.1016/j.jdiacomp.2014.06.008.
28. Schmidt FM, Weschenfelder J, Sander C, Minkwitz J, Thormann J, Chittka T, et al. Inflammatory cytokines in general and central obesity and modulating effects of physical activity. PLoS One. 2015;10(3):e0121971. https://doi.org/10.1371/journal.pone.0121971.
29.•• Faria AP, Ritter AMV, Gasparetti CS, Correa NB, Brunelli V, Almeida A, et al. A proposed inflammatory score of circulating cytokines/adipokines associated with resistant hypertension, but dependent on obesity parameters. Arq Bras Cardiol. 2019;112(4):383–9. https://doi.org/10.5935/abc.20190032 **This study suggests an integrated measure of circulating cytokines/adipokines related to resistant hypertension**.
30. Rosa AC, Rattazzi L, Miglio G, Collino M, Fantozzi R. Angiotensin II induces tumor necrosis factor-α expression and release from cultured human podocytes. Inflamm Res. 2012;61(4):311–7. https://doi.org/10.1007/s00011-011-0412-8.
31. Brili S, Tousoulis D, Antoniades C, Vasiliadou C, Karali M, Papageorgiou N, et al. Effects of ramipril on endothelial function and the expression of proinflammatory cytokines and adhesion molecules in young normotensive subjects with successfully repaired coarctation of aorta: a randomized cross-over study. J Am Coll Cardiol. 2008;51(7):742–9. https://doi.org/10.1016/j.jacc.2007.10.036.
32. Koh KK, Ahn JY, Han SH, Kim DS, Jin DK, Kim HS, et al. Pleiotropic effects of angiotensin II receptor blocker in hypertensive patients. J Am Coll Cardiol. 2003;42(5):905–10. https://doi.org/10.1016/s0735-1097(03)00846-5.
33. Briet M, Schiffrin EL. Vascular actions of aldosterone. J Vasc Res. 2013;50(2):89–99. https://doi.org/10.1159/000345243.
34. Bendtzen K, Hansen PR, Rieneck K, Group SAS. Spironolactone inhibits production of proinflammatory cytokines, including tumour necrosis factor-alpha and interferon-gamma, and has potential in the treatment of arthritis. Clin Exp Immunol. 2003;134(1):151–8. https://doi.org/10.1046/j.1365-2249.2003.02249.x.
35. Guo C, Ricchiuti V, Lian BQ, Yao TM, Coutinho P, Romero JR, et al. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. Circulation. 2008;117(17):2253–61. https://doi.org/10.1161/CIRCULATIONAHA.107.748640.
36. Sandoo A, Panoulas VF, Toms TE, Smith JP, Stavropoulos-Kalinoglou A, Metsios GS, et al. Anti-TNFα therapy may lead to blood pressure reductions through improved endothelium-dependent microvascular function in patients with rheumatoid arthritis. J Hum Hypertens. 2011;25(11):699–702. https://doi.org/10.1038/jhh.2011.36.
37. Desai RJ, Solomon DH, Schneeweiss S, Danaei G, Liao KP, Kim SC. Tumor necrosis factor-α inhibitor use and the risk of incident hypertension in patients with rheumatoid arthritis. Epidemiology. 2016;27(3):414–22. https://doi.org/10.1097/EDE.0000000000000446.
38. Tran LT, MacLeod KM, McNeill JH. Chronic etanercept treatment prevents the development of hypertension in fructose-fed rats. Mol Cell Biochem. 2009;330(1-2):219–28. https://doi.org/10.1007/s11010-009-0136-z.
39. Huang B, Cheng Y, Usa K, Liu Y, Baker MA, Mattson DL, et al. Renal tumor necrosis factor α contributes to hypertension in dahl salt-sensitive rats. Sci Rep. 2016;6:21960. https://doi.org/10.1038/srep21960.
40. Venegas-Pont M, Manigrasso MB, Grifoni SC, LaMarca BB, Maric C, Racusen LC, et al. Tumor necrosis factor-alpha antagonist etanercept decreases blood pressure and protects the kidney in a mouse model of systemic lupus erythematosus. Hypertension. 2010;56(4):643–9. https://doi.org/10.1161/HYPERTENSIONAHA.110.157685.
41. Haugen E, Täng MS, Isic A, Andersson B, Fu M. TNFalpha antagonist upregulates interleukin-6 in rats with hypertensive heart failure. Int J Cardiol. 2008;130(1):64–8. https://doi.org/10.1016/j.ijcard.2007.08.047.
42. Sriramula S, Cardinale JP, Francis J. Inhibition of TNF in the brain reverses alterations in RAS components and attenuates angiotensin II-induced hypertension. PLoS One. 2013;8(5):e63847. https://doi.org/10.1371/journal.pone.0063847.
43. Song XA, Jia LL, Cui W, Zhang M, Chen W, Yuan ZY, et al. Inhibition of TNF-α in hypothalamic paraventricular nucleus attenuates hypertension and cardiac hypertrophy by inhibiting neurohormonal excitation in spontaneously hypertensive rats. Toxicol Appl Pharmacol. 2014;281(1):101–8. https://doi.org/10.1016/j.taap.2014.09.004.
44. Filho AG, Kinote A, Pereira DJ, Rennó A, dos Santos RC, Ferreira-Melo SE, et al. Infliximab prevents increased systolic blood pressure and upregulates the AKT/eNOS pathway in the aorta of spontaneously hypertensive rats. Eur J Pharmacol. 2013;700(1-3):201–9. https://doi.org/10.1016/j.ejphar.2012.11.059.
45.•• de Faria AP, Moreno H. Effects of the TNF-alpha inhibiton on hemodynamic parameters in resistant hypertension. 2016. https://

clinicaltrials.gov/ct2/show/NCT02743390. Accessed August, 10 2019. **This study evaluates whether an acute dose of infliximab (controlled by placebo) reduces blood pressure in RH subjects.**

46. Kim GW, Lee NR, Pi RH, Lim YS, Lee YM, Lee JM, et al. IL-6 inhibitors for treatment of rheumatoid arthritis: past, present, and future. Arch Pharm Res. 2015;38(5):575–84. https://doi.org/10.1007/s12272-015-0569-8.
47.• Krishnan SM, Dowling JK, Ling YH, Diep H, Chan CT, Ferens D, et al. Inflammasome activity is essential for one kidney/deoxycorticosterone acetate/salt-induced hypertension in mice. Br J Pharmacol. 2016;173(4):752–65. https://doi.org/10.1111/bph.13230 **This study suggests that the inflammasome/IL-1β pathway is a therapeutic target in hypertension**.
48.• Krishnan SM, Ling YH, Huuskes BM, Ferens DM, Saini N, Chan CT, et al. Pharmacological inhibition of the NLRP3 inflammasome reduces blood pressure, renal damage, and dysfunction in salt-sensitive hypertension. Cardiovasc Res. 2019;115(4):776–87. https://doi.org/10.1093/cvr/cvy252 **This study suggests that inhibition of NLRP3 inflammasome by the MCC950 molecule is an antihypertensive strategy**.
49. Henao-Mejia J, Elinav E, Strowig T, Flavell RA. Inflammasomes: far beyond inflammation. Nat Immunol. 2012;13(4):321–4. https://doi.org/10.1038/ni.2257.
50. Karmakar M, Katsnelson M, Malak HA, Greene NG, Howell SJ, Hise AG, et al. Neutrophil IL-1β processing induced by pneumolysin is mediated by the NLRP3/ASC inflammasome and caspase-1 activation and is dependent on K+ efflux. J Immunol. 2015;194(4):1763–75. https://doi.org/10.4049/jimmunol.1401624.
51. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009;373(9671):1275–81. https://doi.org/10.1016/S0140-6736(09)60566-3.
52. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet. 2010;376(9756):1903–9. https://doi.org/10.1016/S0140-6736(10)62039-9.
53. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393–401. https://doi.org/10.1056/NEJMoa1402670.
54. Kampmann U, Mathiassen ON, Christensen KL, Buus NH, Bjerre M, Vase H, et al. Effects of renal denervation on insulin sensitivity and inflammatory markers in nondiabetic patients with treatment-resistant hypertension. J Diabetes Res. 2017;2017:6915310. https://doi.org/10.1155/2017/6915310.
55. Eikelis N, Hering D, Marusic P, Sari C, Walton A, Phillips S, et al. The effect of renal denervation on endothelial function and inflammatory markers in patients with resistant hypertension. Int J Cardiol. 2015;188:96–8. https://doi.org/10.1016/j.ijcard.2015.04.041.
56.• Eikelis N, Hering D, Marusic P, Duval J, Hammond LJ, Walton AS, et al. The Effect of renal denervation on plasma adipokine profile in patients with treatment resistant hypertension. Front Physiol. 2017;8:369. https://doi.org/10.3389/fphys.2017.00369 **This study was the first to associate renal denervation procedure with adipokines in resistant hypertensive patients**.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.