Role of Insulin Resistance in Vascular Inflammation

Nicolás Federico Renna, Jésica Magalí Ramirez,
Rodrigo Damián Garcia and
Roberto Miguel Miatello

Additional information is available at the end of the chapter

Abstract

Cardiovascular diseases (CVDs) such as ischemic heart disease (IHD), stroke, and peripheral artery disease (PAS) are the leading causes of mortality and morbidity around the world; about 30% of global deaths and 10% of global disease burden a year are due to CVDs. In this chapter, we will analyze the classic concepts of vascular remodeling, to later expand the concepts and physiopathological mechanisms of vascular inflammation. The role of immunomodulation from IL-6R alpha and the JAK/STAT3 intracellular cascade, will be proposed as an activator of vascular remodeling mechanisms. In addition, the role of new drugs such as LCZ696 and immunomodulators involved in the local inflammatory response will also be analyzed. The concept of remodeling and vascular inflammation, which a decade ago was only important at the level of basic research, step-by-step has proven crucial in the appearance of atherosclerosis, called subclinical atherosclerosis. Even though much progress has been made in the treatment and discovery of pathophysiological mechanisms, it has not been possible to reduce of cardiovascular risk, this is perhaps, it the decade in which we can advance in this.

Keywords: vascular remodeling, vascular inflammation, LCZ696, insulin resistance, IL-6R alpha

1. Introduction

Cardiovascular diseases (CVDs) such as ischemic heart disease (IHD), stroke, and peripheral artery disease (PAS) are the leading causes of mortality and morbidity around the world; about 30% of global deaths and 10% of global disease burden a year are due to CVDs [1, 2]. In the past three decades, these diseases have been increasing in underdeveloped and developing

countries. Although deaths from CVDs have declined in some developed countries with better healthcare interventions and systems and primary prevention, population growth and aging will drive up global CVDs in the coming decades [1, 2].

Vascular diseases, including atherosclerosis, media calcification, macrovascular expression of diabetes vascular disease, and microangiopathy, are very prevalent in these patients and are primary causes of death and disability in these individuals (see **Figure 1**) [3].

The nexus between microangiopathy and macroangiopathy is not yet fully explained, but it is much more important than a simple time line, although it could be said that microangiopathic pathology precedes macroangiopathy in 5–10 years in the natural history of the disease. Atherosclerosis occurs earlier in patients with diabetes, frequently with greater severity and a more diffuse distribution. Diabetes and metabolic syndrome are associated with vascular function abnormalities and ensuing morphological changes associated with vascular remodeling and atherosclerosis [4, 5].

One way to study vascular disease in diabetes mellitus is through experimental models in animals. One of them consists of feeding with carbohydrate-enriched diets to normal rats for induced metabolic syndrome [6, 7]. Fructose-fed rats (FFR) have been used to assess the pathophysiological mechanisms involved in the development of this syndrome [8]. This model has proven to be very interesting, since it allows the study of vascular changes, associated with metabolic syndrome, without the effects produced by hypercholesterolemia.
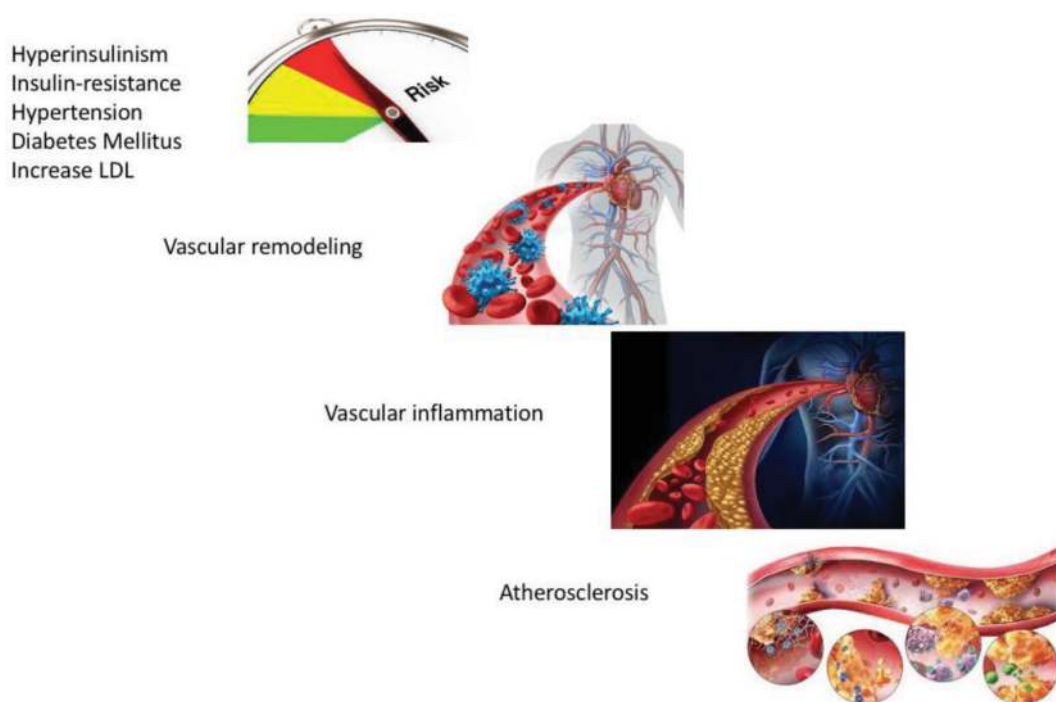

Figure 1. The evolution of vascular disease, with atherosclerosis being the final stage and vascular remodeling of the vascular disease manifested as vascular insufficiency.

2. Physiopathological changes

2.1. Role of insulin

Recent studies have suggested that insulin and Ang II share a cross talk at multiple levels (**Figure 2**). Insulin signaling is initiated by binding to its receptor. The insulin receptor is a heterotetrameric tyrosine kinase that after binding insulin undergoes a rapid tyrosine auto-phosphorylation that activates the receptor kinase and allows transient interaction with IRS-1. Interaction of tyrosine-phosphorylated IRS-1 with PI3K results in PI3K activation and Akt phosphorylation, which stimulates translocation of Glut-4 to the sarcolemma to facilitate glucose uptake and NO production in the endothelium to induce vasorelaxation [9].

Ang II has been shown to inhibit the insulin-PI3K signaling pathway in both vascular and skeletal muscle cells. Ang II inhibits downstream signaling, including Akt phosphorylation, Glut-4 translocation to the sarcolemma, and NO production in the endothelium [9].

In the vasculature, insulin stimulates two major signaling transduction cascades: PI3K and MAPK. Insulin stimulation of NO production through activation of the PI3K pathway leads to vasodilation and increased blood flow and subsequent augmentation of glucose disposal in skeletal muscle. Insulin also stimulates the MAPK pathway, which mediates cellular growth and migration as well as production of prothrombotic and profibrotic factors [10].
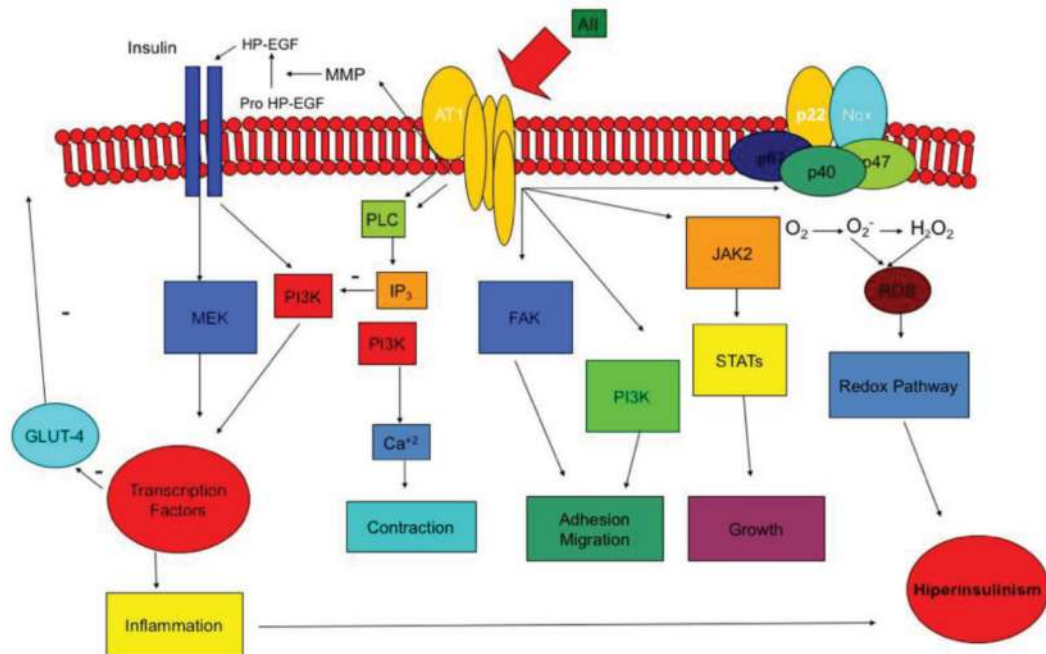

Figure 2. Insulin-Ang II relationship. Insulin signaling is initiated by binding to its receptor. The insulin receptor is a heterotetrameric tyrosine kinase that after binding insulin undergoes a rapid tyrosine autophosphorylation that activates the receptor kinase and allows transient interaction with IRS-1. Interaction of tyrosine-phosphorylated IRS-1 with PI3K results in PI3K activation and Akt phosphorylation, which stimulates translocation of Glut-4 to the sarcolemma to facilitate glucose uptake and NO production in the endothelium to induce vasorelaxation.

Fasting plasma insulin levels in a normal insulin-sensitive individual are usually in the low-picomolar range (50–150 pM). At this range, insulin constitutively stimulates the PI3K pathway, which participates in the regulation of the metabolic effects of insulin and maintenance of vascular tone [11].

In insulin-resistant states, such as obesity and diabetes, fasting insulin levels may reach the nanomolar range and are often associated with activation of RAAS. In addition, insulin stimulation of the PI3K pathway is selectively impaired.

2.2. Vascular changes

The spectrum of clinical and morphological changes that can be displayed has changed over time. One of the classifications we find is that proposed by author Gibbons [12]. These changes are shown predominantly in the relationship of light/medium vessel by changing the ratio of wall thickness by an increase in muscle mass or reorganization of the cellular and noncellular components. These changes increase vascular reactivity, which promotes increased peripheral resistance in diseases such as hypertension. Another form of vascular remodeling involves primarily changes in the dimensions of the light. In this example, the restructuring of the active components of cellular and noncellular vascular wall results in significant changes in the dimensions of the vascular lumen, with relatively small changes in wall thickness. The clinical examples of this type include remodeling associated with vascular dilation of blood flow which is consistently high, for example, an arteriovenous fistula or loss in cellularity and proteolysis of extracellular matrix, resulting in the formation of an aneurysm. By contrast, a mass reduction vascular caliber results from a long-term reduction in blood flow. In fact, rarefaction of the microcirculation is another form of vascular remodeling. The architecture of the vascular wall is also markedly changed in response to vascular injury. Neointima is formed as part of a repair response to injury involving thrombosis, migration, and proliferation of vascular cells, production of the matrix, and infiltration of inflammatory cells.

The term "remodeling" is limited to situations in which there is a change in the lumen of a vessel relaxed, measured under a standard intravascular pressure, and where changes in the characteristics of the wall material (i.e., the wall stiffness) do not consider the change in the vascular lumen [13].

Chronic changes in hemodynamic forces produce structural alterations in the vascular wall, as stated above. Furthermore, hemodynamic changes are not the only production mechanisms of vascular remodeling [14], and the role of the inflammatory response and changes in matrix components have been suggested as mediators in this process of vascular adaptation [15].

To complete the above concept, the vascular wall remodeling is the result of changes in cellular and noncellular components, depending on the disease process causing the changes. Changes in growth and migration of VSMC, endothelial dysfunction, the inflammatory process, synthesis, or degradation of extracellular matrix components may be present in this process.

2.3. Vascular remodeling and inflammation

The traditional view of atherosclerosis as a lipid storage disease crumbles in front of the large and growing evidence that inflammation contributes to the center at all stages of the

disease, from initial injury until the final stage of thrombotic complications that compromise the bloodstream. Researchers now appreciate that the mere narrowing of the arterial lumen does not necessarily presage myocardial infarction and that simply treating narrowed blood vessels does not prolong life. Although invasive procedures such as angioplasty and coronary bypass will remain necessary in some cases, we now understand that medical treatment and lifestyle modification (diet and physical activity) produce benefits that may result from reductions in the processes inflammatory [16].

2.4. Initiation of atherosclerosis

It has been shown that atherosclerosis is not only a disease of lipid deposition but also a complex interaction between resident cells, inflammatory cells, and extracellular matrix, associated with a characteristic phenotypic change of macrophages to foam cells.

A key part of this interaction between the endothelium and the leukocytes is the vascular cell adhesion molecule-1 (VCAM-1). VCAM-1 binds to monocytes and T lymphocytes; these leukocytes are found in early atherosclerotic plaques. The most important stimuli for the membrane docking of this molecule are the nuclear factor kB (NF-kB) as well as the interleukin-1β (IL-1β) and the tumor necrosis factor (TNF-α) [10].

Cell adhesion molecules (CAM) are essential in the mediation of adhesion and transendothelial migration of leukocytes. In several murine models, the absence of CAM reduces atherogenesis [17]. We have demonstrated the presence of VCAM-1 in the endothelium in an experimental model of metabolic syndrome, in which the expression of this protein is familiar with the AT1 receptor (AT1R) and the local inflammatory process. High levels of ICAM-1 are predictive of cardiac events and are also independent cardiovascular risk factors [18]. This relationship was examined by Pradhan et al. [19], who showed that men with and without prior ischemic heart disease, accelerated atherogenesis, are associated with elevated levels of ICAM-1.

VCAM-1 is expressed in endothelial cells at sites predisposed to plaque formation [20]. By contrast, ICAM-1 is expressed throughout the plate; VCAM-1 is detected only in areas of rupture. In addition, VCAM-1 levels have a consistent association with atherosclerosis; high levels of VCAM-1 in the transcardiac gradient correlate with endothelial dysfunction and the progression of coronary atherosclerosis [21].

3. Pharmacology on vascular remodeling

3.1. New drugs

LCZ696 is the first of a new class of drugs that simultaneously block angiotensin 1 receptor blocker (ARB) and neprilysin or neutral endopeptidase protein (NEP); hence, they are referred to with the acronym ARNI [22].

This complex system results in multiple effects on the cardiovascular system. In the first instance, according to different experiments, LCZ696 can increase the half-life of BNP through the initiation of NEP, managing to increase natriuresis and vasodilation through activation

of the NPRA receptor. On the other hand, the blockade of AT1R can decrease fibrosis, induce vasodilation, reduce the retention of sodium and water, lower blood pressure, and other effects [23].

The most important clinical study that demonstrated the reduction of cardiovascular morbidity and mortality in patients with heart failure was the PARADIGM-HF study, which showed a clear benefit in patients who were in the branch receiving LCZ696. However, studies in experimental animals and pathophysiological analyses are scarce. Thus, the precise mechanism by which LCZ696 reduces cardiovascular mortality remains unclear. Some authors have proposed different hypotheses: (1) a sustained increase in natriuretic peptides by inhibition of NEP, (2) a direct hemodynamic effect that reduces stress on the left ventricular wall, (3) a reduction in arrhythmias and by a reduction in fibrosis or myocardial hypertrophy, and (4) an improvement of regional myocardial perfusion [4].

Previously, drug-intervention studies in this model have shown that some antihypertensive treatments, with candesartan, telmisartan, and losartan, not only lower blood pressure but also cause an improvement in redox balance and regression of structural changes in resistance arteries, although not a regeneration of the endothelium. In other words, reversing adverse effects associated with hypertension does not improve the normal structure and function of endothelial cells [8, 9].

Within the inflammatory cascades activated in this experimental model, we found that the determinant of the previously evidenced changes is that of the IL-6 receptor. Two different forms of IL-6 cell receptors have been described: an 80 kDa ligand-binding chain, known as IL-6R (IL-6Ra, CD126), and a 130 kDa signal transduction chain, gp130 (IL-6Rb, CD130). Gp130 is present in many places and situations; in contrast, IL-6R shows a more limited expression pattern [24].

In a recent publication of our group, it can be concluded that LCZ696 can reverse the changes associated with vascular remodeling, even more important than just blocking AT1R. The proposed pathway to demonstrate this finding was through the inhibition of the intracellular cascade of STAT3/JAK in intimate relation with IL-6R alpha, thus demonstrating an intrinsic anti-inflammatory effect. In addition, from the inhibition of STAT3, LCZ696 managed to significantly increase the amount of EPC at the vascular level, thus mediating endothelial repair [25].

The physiopathological mechanisms proposed in our work are summarized in **Figure 3**. The dual blocking of NEP/AT1R by LCZ696 could reduce the expression and phosphorylation of STAT3 through JAK, either by blocking AT1R, reducing oxidative stress, or controlling systolic blood pressure.

The reduction of STAT3 produced a decrease in the inflammatory transcription factors in the nucleus and a release of hsCRP in the blood circulation, which produces an increasing docking of the alpha subunit of IL-6R toward the membrane. Through this pathway, vascular remodeling and LVH were reduced because part of the growth factors and migration of muscle cells depend on the activation of the inflammatory cascade.
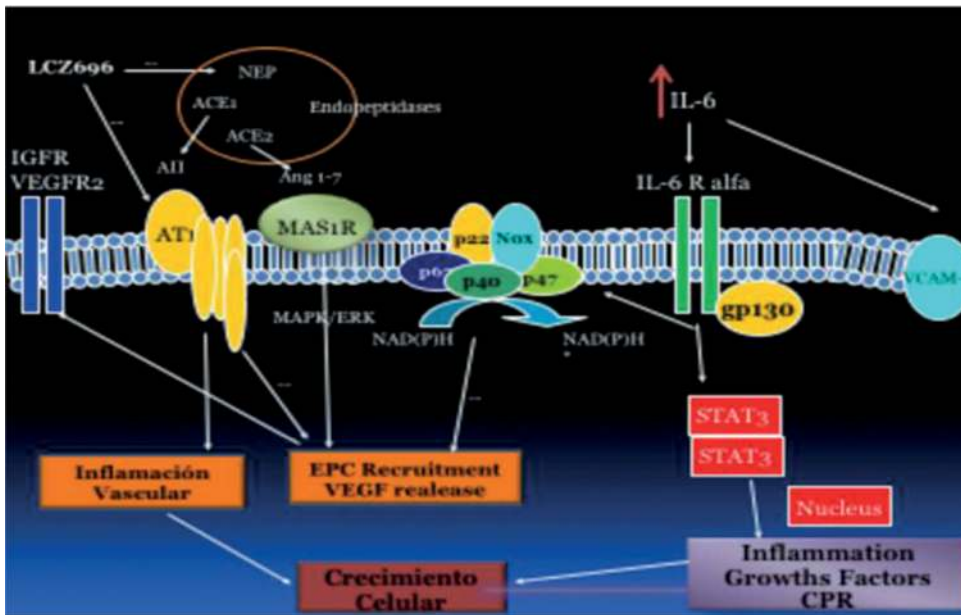
Figure 3. The phytopathological mechanisms proposed in our work are summarized in this image. The dual blocking of NEP/AT1R by LCZ696 could reduce the expression and phosphorylation of STAT3 through JAK, either by blocking AT1R, reducing oxidative stress, or controlling systolic blood pressure. The reduction of STAT3 produced a decrease in the inflammatory transcription factors in the nucleus and a release of hsCRP in the blood circulation, which produces an increasing docking of the alpha subunit of IL-6R toward the membrane. On the other hand, NEP and ACE2 probably induce the conversion of angiotensin II in different intermediate metabolites, such as angiotensin 1-7 (Ang 1-7), which produces antagonistic effects to angiotensin II by MAS1R. The intracellular cascade of MAS1R, by MAPK/ERK, produces a fundamental effect, namely, the production of VEGF and its two receptors: VEGFR1 and 2. From this mechanism, the endothelium could be repaired and/or replaced, favoring the maturation of circulating EPCs on resident EPCs at the endothelial level. MAS1R could be counter-regulated by IL-1ß.

On the other hand, NEP and ACE2 probably induce the conversion of angiotensin II in different intermediate metabolites, such as angiotensin 1-7 (Ang 1-7), which produces antagonistic effects to angiotensin II by MAS1R. The intracellular cascade of MAS1R, by MAPK/ERK, produces a fundamental effect, namely, the production of VEGF and its two receptors, VEGFR1 and VEGFR2. From this mechanism, the endothelium could be repaired and/or replaced, favoring the maturation of circulating EPCs on resident EPCs at the endothelial level. MAS1R could be counter-regulated by IL-1ß [26–28].

In conclusion, we postulate that LCZ696, by MAS1R activation, is not only able to improve endothelial function but also able to repair the endothelium, and this probably allows for improved functionality of the entire cardiovascular system. In addition, LCZ696 could reduce the expression of hsCRP through reduction in the expression of STAT3, a sign also demonstrated in different clinical studies such as JUPITER and CANTOS, which have allowed a great reduction in morbidity and mortality, revolutionizing modern cardiology. The anti-inflammatory and angio-repairing effect of LCZ696 is probably reflected in an improvement in the survival of patients who receive a treatment regimen with this drug in studies such as PARADIGM-HF [29–31].

3.2. Gliptin on vascular inflammation

Renna et al. suggest that incretin system dysfunction, as happens in patients with diabetes mellitus or metabolic syndrome, allows activation of inflammatory response in different levels. The consequence is the creation of a vascular microenvironment that is conducive to the creation, perpetuation, progression, and destabilization of vascular injury, with either a simple eutrophic mechanism of vascular remodeling or the generation of an atherosclerotic lesion [32].

Several mechanisms may underlie these results: (1) increase the circulating levels of GLP-1 [33]. The cardiovascular actions of GLP-1 may occur either directly through the GLP-1 receptor or through a GLP-1 receptor-independent effect of the degradation product of GLP-1 [38]; (2) DPP-IV also degrades GIP and potentially cytokines and certain chemokines (including stromal-derived factor 1-α). Thus, other substrates of DPP-IV may be responsible for the improvement in endothelial function. Alternatively, DDP-IV inhibition might improve endothelial function by influencing insulin and glucose levels. Insulin causes vasodilation by increasing endothelial production of NO [34].

The improvement in endothelial function and oxidative stress could result in a decrease in activation of the inflammatory process.

Other authors have suggested that the DDP-IV inhibitors may have anti-inflammatory effects, such as reduced activation of TNF-alpha during macrophage activation [33, 35].

4. Conclusion

There is sufficient evidence to show that insulin resistance and hyperinsulinism produce significant changes at the vascular level [7, 25, 32, 36, 37]. The proposed mechanisms are (1) the IGF-1 receptor, (2) through the coactivation between IG-1 and AT1R, (3) by activating nuclear transcription factors such as NF-KB or AP-1, (4) by dimerization of IL-6R, and (5) from the activation of oxidative cascades such as NADP (H) oxidase, peroxynitrites, or superoxide dismutase (SOD). However, the effects of hyperglycemia are more erratic: moderate hyperglycemia is sufficient to induce adverse structural changes in the mesenteric vasculature, but more severe hyperglycemia is essential to cause endothelial dysfunction.

It is more interesting that the blocking of these pathways has significant effects on the activation/deactivation of vascular remodeling, independent of the correction or not, of hyperinsulinism or insulin resistance. This shows that intracellular cascades, in most of these mechanisms, have no feedback from insulin or glucose receptors.

On the other hand, it is likely that the vascular remodeling associated with insulin resistance, due to the stimulation of growth factors, from the pathways, is due to changes in vascular hemodynamics or to the increase in peripheral resistances, as in the case of arterial hypertension.

The new drugs, which modify the inflammatory modulating response, such as tocilizumab (anti-IL-6R alpha) and canakinumab (anti-IL-1b), will be drugs that could further modify the cardiovascular risk of these patients in the future, since it could modify the vascular inflammatory

microenvironment, preventing vascular modeling and the subsequent formation of atheromatous plaques. Another pharmacological group that has gained importance in recent years is LCZ696, which, as several clinical studies have shown, modifies the cardiovascular morbidity and mortality of one of the most frequent pathologies of clinical practice, heart failure. However, new studies show that it is capable of producing effects in vascular repair, increasing the CPE at the vascular level, and avoiding vascular remodeling, even in experimental models with insulin resistance.

The concept of remodeling and vascular inflammation, which a decade ago was only important at the level of basic research, step-by-step has proven crucial in the appearance of atherosclerosis, called subclinical atherosclerosis. Much progress has been made in the treatment and discovery of pathophysiological mechanisms, rest improve the studies of deterrence, and its correlation with the reduction of cardiovascular risk; this is, perhaps, the decade in which we can advance in this.

Conflict of interest

The authors have no "conflict of interest" to declare.

Author details

Nicolás Federico Renna[1,2]*, Jésica Magalí Ramirez[3], Rodrigo Damián Garcia[1,2] and Roberto Miguel Miatello[1,2]

*Address all correspondence to: nicolasfede@gmail.com

1 Department of Pathology, School of Medicine, National University of Cuyo, Argentina

2 National Council of Scientific and Technical Research (IMBECU-CONICET), Argentina

3 Department of Cardiology, Spanish Hospital of Mendoza, Argentina

References

[1] Shanthi M, Pekka P, Bo N. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva: World Health Organization; 2011

[2] Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics-2017 update: A report from the American Heart Association. Circulation. 2017;**135**:e146-e603

[3] Kaplan N. The deadly quartet hyperbody obesity, glucose intolerance, hypertriglyceridemia, and hypertension. Archives of Internal Medicine. 1989;**149**:1514-1520

[4] Reaven G, Laws A. Insulin resistance, compensatory hyperinsulinemia and coronary heart disease. Diabetologia. 1994;**37**:948-952

[5]   de Champlain J, Wu R, Girouard H, Karas M, El Midaoui A, Laplante MA, Wu L. Oxidative stress in hypertension. Clinical and Experimental Hypertension. 2004;**26**:593-601

[6]   Hwang I, Ho H, Hoffman B, Reaven G. Fructose-induced insulin resistance and hypertension in rats. Hypertension. 1987;**10**:512-516

[7]   Miatello R, Risler N, Castro C, Gonzalez S, Rüttler M, Cruzado M. Aortic smooth muscle cell proliferation and endothelial nitric oxide synthase activity in fructose-fed rats. American Journal of Hypertension. 2001;**14**:1135-1141

[8]   Bell R, Ryan E, Finegood D. Consequences of high dietary fructose in the islet-transplanted rat with suboptimal beta-cell mass. The American Journal of Physiology. 1996;**270**: E292-E298

[9]   Andreozzi F, Laratta E, Sciacqua A, Perticone F, Sesti G. Angiotensin II impairs the insulin signaling pathway promoting production of nitric oxide by inducing phosphorylation of insulin receptor substrate-1 on Ser(312) and Ser(616) in human umbilical vein endothelial cells. Circulation Research. 2004;**94**:1211-1218

[10] Nigro J, Osman N, Dart AM, Little PJ. Insulin resistance and atherosclerosis. Endocrine Reviews. 2006;**27**:242-225

[11] Zhou MS, Schulman IH, Zeng Q. Link between the renin–angiotensin system and insulin resistance: Implications for cardiovascular disease. Vascular Medicine. Oct 2012;**17**(5): 330-341

[12] Gibbons GH, Dzau VJ. The emerging concept of vascular Remodeling. The New England Journal of Medicine. 1994;**330**(20):1431-1438

[13] Norrelund H, Christensen KL, Samani NJ, Kimber P, Mulvany MJ, Korsgaard N. Early narrowed afferent arteriole is a contributor to the development of hypertension. Hypertension. 1994;**24**:301-308

[14] Hacking WJ, VanBavel E, Spaan JA. Shear stress is not sufficient to control growth of vascular networks: A model study. American Journal of Physiology. Heart and Circulatory Physiology. 1996;**270**(1):H364-H375

[15] Pasterkamp G, Galis ZS, de Kleijn DPV. Expansive arterial remodeling: Location, location, location. Arteriosclerosis, Thrombosis, and Vascular Biology. 2004;**24**(4):650-657

[16] Libby P. Inflammation and cardiovascular disease mechanisms. The American Journal of Clinical Nutrition. 2006;**83**(2):456S-4460S

[17] Miller MA et al. Cellular adhesion molecules and blood pressure: Interaction with sex in a multi-ethnic population. Journal of Hypertension. 2004;**22**(4):705-711

[18] Ridker P, Hennekens C, Roitman-Johnson B. Plasma concentrations of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. Lancet. 1998;**351**:88-92

[19] Pradhan AD, Rifai N, Ridker PM. Soluble intercellular adhesion molecule-1, soluble vascular adhesion molecule-1, and the development of symptomatic peripheral arterial disease in men. Circulation. 2002;**106**(7):820-825

[20] Cook-Mills JM. VCAM-1 signals during lymphocyte migration: Role of reactive oxygen species. Molecular Immunology. 2002;**39**(9):499-508

[21] Ridker PM, Buring JE, Rifai N. Soluble P-selectin and the risk of future cardiovascular events. Circulation. 2001;**103**(4):491-495

[22] Braunwald E. The path to an angiotensin receptor antagonist-Neprilysin inhibitor in the treatment of heart failure. Journal of the American College of Cardiology. 2015;**65**(10): 1029-1041

[23] Desai AS, McMurray JJ, Packer M, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. European Heart Journal. 2015;**36**:1990-1997

[24] Kishimoto T. IL-6: From its discovery to clinical applications. International Immunology. 2010;**22**:347-352

[25] Garcia R, Ramirez J, Peral de Bruno M, Miatello R, Renna NF. Dual ARB/NEP Inhibition with LCZ696 improved endothelial regeneration in an experimental model of metabolic syndrome. Journal of Hypertensio. 2018 (in press)

[26] Hoffmann BR, Stodola TJ, Wagner JR, Didier DN, Exner EC, Lombard JH, Greene AS. Mechanisms of Mas1 receptor-mediated Signaling in the vascular endothelium. Arteriosclerosis, Thrombosis, and Vascular Biology. 2017;**37**:433-445

[27] Fraga-Silva RA, Da Silva DG, Montecucco F, Mach F, Stergiopulos N, da Silva RF, Santos RA. The angiotensin-converting enzyme 2/angiotensin-(1-7)/mas receptor axis: A potential target for treating thrombotic diseases. Thrombosis and Haemostasis. 2012;**108**:1089-1096

[28] Ridker PM. Closing the loop on inflammation and atherothrombosis: why perform the CIRT and CANTOS trials? Transactions of the American Clinical and Climatological Association. 2013;**124**:174-190

[29] Vidt DG, Ridker PM, Monyak JT, Schreiber MJ, Cressman MD. Longitudinal assessment of estimated glomerular filtration rate in apparently healthy adults: A post hoc analysis from the JUPITER study (justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin). Clinical Therapeutics. Jun 2011;**33**(6):717-725

[30] Ridker P, Everett B, Thuren T, MacFadyen J, Chang W, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker S, et al, CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. New England Journal of Medicine. Sep 21, 2017; **377**:1119-1131

[31] Simpson J, Jhund PS, Silva Cardoso J, Martinez F, Mosterd A, Ramires F, Rizkala AR, Senni M, Squire I, Gong J, Lefkowitz MP, Shi VC, Desai AS, Rouleau JL, Swedberg K, Zile MR, McMurray JJV, Packer M, Solomon SD, PARADIGM-HF Investigators and Committees. Comparing LCZ696 with enalapril according to baseline risk using the MAGGIC and EMPHASIS-HF risk scores: An analysis of mortality and morbidity in PARADIGM-HF. Journal of the American College of Cardiology. Nov 10, 2015; **66**(19):2059-2071

[32] Renna NF, Diez E, Miatelo RM. Effects of dipeptidyl-peptidase 4 inhibitor about vascular inflammation in a metabolic syndrome model. PLoS One. Sep 3, 2014;**9**(9):e106563

[33] Kahlberg N, Qin CX, Anthonisz J, Jap E, Ng HH, Jelinic M, Parry LJ, Kemp-Harper BK, Ritchie RH, Leo CH. Adverse vascular remodeling is more sensitive than endothelial dysfunction to hyperglycemia in diabetic rat mesenteric arteries. Pharmacological Research. Sep 2016;**111**:325-335

[34] Shah Z, Kampfrath T, Deiuliis JA, Zhong J, Pineda C, et al. Long-term dipeptidyl-peptidase 4 inhibition reduces atherosclerosis and inflammation via effects on monocyte recruitment and chemotaxis. Circulation. 2011;**124**:2338-2349

[35] Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. Endocrine Reviews. 2012;**33**:187-215

[36] Renna NF, Lembo C, Diez E, Miatello RM. Role of renin-angiotensin system and oxidative stress on vascular inflammation in insulin resistance model. International Journal of Hypertension. 2013;**2013**:420979

[37] Renna NF. Oxidative stress, vascular remodeling, and vascular inflammation in hypertension. International Journal of Hypertension. 2013;**2013**:710136

[38] Nauck M, Meier J, Cavender M, Abd El Aziz M, Drucker D. Cardiovascular Actions and Clinical Outcomes With Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors. Circulation. 2017;**136**:849-870. DOI: 10.1161/CIRCULATIONAHA.117.028136