

C-type natriuretic peptide: Possible Therapeutic Strategy for Hypertension and Target Organ Damage

Péptido natriurético tipo C: posible estrategia terapéutica para la hipertensión y el daño de órgano blanco

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The study by Caniffi et al. (1) published in this issue of the Journal, represents a step forward in the pre-clinical determination of the use of C-type natriuretic peptide (CNP) as a new therapeutic option for hypertension and target organ damage associated with this condition. Elevated blood pressure levels above normal values (140 mm Hg for systolic blood pressure and 90 mm Hg for diastolic blood pressure) is one of the major causes for the development of cardiovascular diseases which, in turn, constitute the first cause of mortality worldwide.

IMPORTANCE OF TYPE-C NATRIURETIC PEPTIDE

CNP belongs to a family of vasoactive peptides, including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Both ANP and BNP are produced and stored mainly in the endocrine heart, and CNP is produced by the nervous tissue and vascular endothelium. CNP binds type-C natriuretic peptide receptor (NPR-C), which is abundantly expressed in the plasma membrane of endothelial cells. It was initially described as a natriuretic peptide clearance receptor; but, in fact, it is coupled with type 1 and 2 inhibitory G proteins (Gi1 and Gi2). (2) Receptor activation increases phospholipase C-β3 activity and has an inhibitory effect on adenylyl cyclase. These effects reduce cytosolic adenosine 3',5'-cyclic monophosphate (cAMP) and increase inositol trisphosphate and diacylglycerol, (2, 3) inducing increased cytosolic Ca²⁺ which activates endothelial nitric-oxide synthase (eNOS) producing nitric oxide (NO). (3) Nitric oxide is a gas molecule which diffuses into vascular smooth muscle and induces vasodilation. This mechanism was demonstrated *ex vivo* in resistance arteries and in the microcirculation. (3-6) The NO-mediated vasodilator effect of CNP was also demonstrated *in vivo*: after acute administration of CNP in rats, there was a significant reduction in blood pressure, with elevated NO metabolites and increased eNOS activity. (7-9) Therefore, these findings suggest that CNP might play an

important role in blood pressure regulation. (3, 10)

IMPORTANCE OF HYPERTENSION IN THE DEVELOPMENT OF CARDIOVASCULAR DISEASES

Hypertension is defined as systolic blood pressure > 140 mm Hg and diastolic blood pressure > 90 mm Hg. A linear, continuous and positive correlation exists between blood pressure levels and risk of cardiovascular diseases, including stroke, myocardial infarction, angina, myocardial revascularization, heart failure, retinopathy, kidney failure and peripheral vascular disease. Hypertension rarely produces symptoms; therefore, according to the World Health Organization (WHO), hypertension is "a silent and invisible killer".

In 2008, 40% of adults > 25 years worldwide had hypertension. In the most developed countries, the prevalence is lower, about 35% (WHO, 2013), and in the general population in Argentina it was 33.5% between 2008 and 2009. (11)

Hypertension can be prevented through public health campaigns aimed at improving the general knowledge about the complications associated with this condition and how to fight against it by reducing salt intake, increasing physical activity, the quality and access to preventive medicine, and reducing alcohol intake and smoking habits.

Pharmacologic treatment of hypertension has experienced significant progress over the last decades. The drugs more commonly used are renin-angiotensin system inhibitors, diuretics, adrenergic receptors antagonists and calcium channel blockers. Despite these advances, the Argentine RENATA trial showed that 52.8% of hypertensive patients treated did not have adequate blood pressure control. (11) For these reasons, the investigation of the mechanisms involved in the development of hypertension is important to generate new therapeutic strategies for blood pressure control.

The study by Caniffi et al. (1) shows that chronic administration of CNP to spontaneously hypertensive

rats for 14 days produced a significant reduction in systolic blood pressure and increased left ventricular function without reducing the left ventricular hypertrophy seen in these rats. CNP reduced systolic blood pressure by around 15 mm Hg. Interestingly, clinical trials controlled with placebo suggest that reductions of systolic blood pressure between 10 and 12 mm Hg in hypertensive patients reduce the risk of stroke by 40%, but the risk of chronic coronary artery disease by only 14%. (10, 12) On the contrary, recent meta-analyses of several clinical studies suggest that the absolute value of blood pressure reduction is not as important as the type of antihypertensive drug or the combination of drugs used to reduce the risk of developing cardiovascular diseases. (13)

Of note, in the study by Caniffi et al. (1), CNP administration did not affect systolic blood pressure or ventricular function in control rats, suggesting that CNP has no adverse effects on the cardiovascular system under physiological conditions. They also evaluated the effect of chronic administration of CNP on vascular reactivity. CNP decreased phenylephrine-induced vasoconstriction in the aorta of spontaneously hypertensive rats and increased acetylcholine-induced vasodilation. Moreover, the administration of CNP increased eNOS activity in the aorta and left ventricle in both control and spontaneously hypertensive rats, suggesting that the NO pathway participates in the beneficial effects of CNP, as previously described. (7-9)

Li et al. (14) have recently shown that chronic administration of C-ANP4-23, a specific NPR-C agonist, in prehypertensive rats, prevents the development of hypertension in the same model used by Caniffi et al. (1) In line with these authors, when C-ANP4-23 was administered to spontaneously hypertensive rats for 14 days, blood pressure decreased 60 mm Hg accompanied by a reduction in heart rate, with no effect on cardiac hypertrophy, and the vasodilator response to carbachol was restored by 80%. However, in this study C-ANP4-23 reduced the oxidative stress and NO levels.

Of interest, Lorget et al. synthesized BMN 111, a CNP analog, which is resistant to degradation by neutral endopeptidases, and has an extended half-life with the same pharmacologic properties of CNP. (15) The effect of BMN 111 on the cardiovascular system has not been reported yet. As BMN 111 half-life is longer than that of CNP, its clinical applicability would increase, as fewer doses would be necessary to achieve the same clinical benefits. In addition, perhaps it could be administered orally instead of subcutaneously. (15)

In conclusion, *in vitro* and *in vivo* studies suggest that the development of CNP or analogues have great potential as new therapeutic strategies to treat hypertension and prevent target organ damage. This con-

stitutes a public health priority due to the importance of cardiovascular diseases in overall mortality rates.

Conflicts of interest

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REFERENCES

- Caniffi C, Sueiro L, Bouchet G, Romero M, Barrionuevo E, Arranz C, Costa MA. Respuesta cardiovascular a la administración crónica de péptido natriurético tipo C en ratas espontáneamente hipertensas. *Rev Argent Cardiol* 2015;83:107-113.
- Murthy KS, Makhlof GM. Identification of the G protein-activating domain of the natriuretic peptide clearance receptor (NPR-C). *J Biol Chem* 1999;274:17587-92. <http://doi.org/d48sxp>
- Andrade FA, Restini CB, Grandó MD, Ramalho LN, Bendhack LM. Vascular relaxation induced by C-type natriuretic peptide involves the Ca(2+)/NO-synthase/NO pathway. *PLoS One* 2014;9:e95446. <http://doi.org/zsxx>
- Garcha RS, Hughes AD. CNP, but not ANP or BNP, relax human isolated subcutaneous resistance arteries by an action involving cyclic GMP and BKCa channels. *J Renin Angiotensin Aldosterone Syst* 2006;7:87-91. <http://doi.org/dk7jsc>
- Brunner F, Wölkart G. Relaxant effect of C-type natriuretic peptide involves endothelium and nitric oxide-cGMP system in rat coronary microvasculature. *Cardiovasc Res* 2001;51:577-84. <http://doi.org/b74g2b>
- Amin J, Carretero OA, Ito S. Mechanisms of action of atrial natriuretic factor and C-type natriuretic peptide. *Hypertension* 1996;27:684-7. <http://doi.org/zsz>
- Brunner F, Wölkart G. Endothelial NO/cGMP system contributes to natriuretic peptide-mediated coronary and peripheral vasodilation. *Microvasc Res* 2001;61:102-10. <http://doi.org/d4xvf5>
- Costa MA, Elesgaray R, Caniffi C, Fellet A, Arranz C. Role of cardiovascular nitric oxide system in C-type natriuretic peptide effects. *Biochem Biophys Res Commun* 2007;359:180-6. <http://doi.org/b8dq55>
- Caniffi C, Elesgaray R, Gironacci M, Arranz C, Costa MA. C-type natriuretic peptide effects on cardiovascular nitric oxide system in spontaneously hypertensive rats. *Peptides* 2010;31:1309-18. <http://doi.org/b8s8rh>
- Rose RA, Giles WR. Natriuretic peptide C receptor signalling in the heart and vasculature. *J Physiol* 2008;586:353-66. <http://doi.org/dkpxz9>
- Marín MJ, Fábregues G, Rodríguez PD, Díaz M, Páez O, Alfie J y cols. Registro Nacional de Hipertensión Arterial. Conocimiento, tratamiento y control de la hipertensión arterial. *Estudio RENATA. Rev Argent Cardiol* 2012;80:121-9.
- Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13. <http://doi.org/bzsqjj>
- Sever PS, Poulter NR. Blood pressure reduction is not the only determinant of outcome. *Circulation* 2006;113:2754-74. <http://doi.org/cqsks9>
- Li Y, Sarkar O, Brochu ML, Anand-Srivastava MB. Natriuretic peptide receptor-C attenuates hypertension in spontaneously hypertensive rats: Role of nitroxidative stress and Gi proteins. *Hypertension* 2014;63:846-55. <http://doi.org/zs2>
- Lorget F, Kaci N, Peng J, Benoist-Lasselín C, Mugniery E, Oppeneier T, et al. Evaluation of the therapeutic potential of a CNP analog in a Fgfr3 mouse model recapitulating achondroplasia. *Am J Hum Genet* 2012;91:1108-14. <http://doi.org/zs3>

Hypertension and Cardiovascular Risk in Chronic Kidney Disease

La hipertensión arterial y el riesgo cardiovascular en la enfermedad renal crónica

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Over 80% of patients with chronic kidney disease suffer from hypertension. (1) Although this complication is observed in kidney disease patients who still have normal renal function, undoubtedly its prevalence increases significantly as glomerular filtration rate decreases (2). It is not surprising that among the mechanisms postulated for this hypertensive condition, sodium retention by the diseased kidney is the most frequent and important one. This saline expansion leads to a state of generalized vasoconstriction, and the consequent rise in blood pressure is then derived from increased peripheral vascular resistance. The overall mechanism was explained and called by Guyton pressure diuresis. (3) This process aimed at normalizing both extracellular and circulatory volume, involves the sympathetic nervous system (4) the renin-angiotensin system (5) and also the sclerosing stimuli generated by hypertension and several other diseases, such as diabetes, polycystic disease and a great diversity of glomerular diseases. (6) It is important to note that hypertension may induce kidney disease, and vice versa kidney disease may cause hypertension, thus generating a vicious circle where hypertension causes renal injury, and this in turn acts exacerbating hypertension.

Other mechanisms involved include endothelial alterations with deficient nitric oxide synthesis (7) and/or excessive superoxide release. In this regard, the dominant oxidative stress increases the activation of growth factors and fibrosis mediators such as TGF- β and PAI-1. On the other hand, there are other potential reasons for blood pressure elevation. For example, kidney disease patients often show increased central blood pressure (8) and absence of normal nocturnal blood pressure decline (non-dippers) (9). The best explanation for these manifestations is the presence of generalized vascular disease, mainly in the large vessels. If this hypothesis were confirmed, it could clarify the high cardiovascular morbidity and mortality in patients with chronic kidney disease. This is precisely the conclusion pointed out by the interesting study reported in this issue of the Journal by Sarcona and

Diaz. (10) Effectively, the authors, using ambulatory blood pressure monitoring (ABPM), evaluated pulse pressure, the incidence of the “non-dipper” pattern and blood pressure variability in patients with chronic kidney disease. The study is particularly interesting not only because its findings could be strongly related with the high cardiovascular risk present in chronic kidney patients, but also because it might explore the potential mechanisms of hypertension and of kidney disease progression. Indeed, high pulse pressure, as well as the non-dipper pattern and blood pressure variability correlate with greater cardiovascular risk and are also potential markers of vascular stiffness. (11-13). The importance of these concepts stems from the high increase in cardiovascular risk in patients with chronic kidney disease, the restrictions in protection with the current strategies employed and the need to better define the specific risks of this population.

Sarcona and Díaz clearly show an increased pulse pressure, thus adding an important piece to our pathophysiological interpretations of the mechanisms that make chronic kidney disease a dreaded cardiovascular risk factor.

Unfortunately, the authors fail to show significant differences between groups in the other two parameters studied: non-dipper pattern and blood pressure variability. However, and despite the differences in glomerular filtration rate between both groups are small, the inherent variability of the MDRD study abridged formula as glomerular filtration rate estimation might indicate the need to study a greater number of patients. These acknowledged difficulties in the estimation of glomerular filtration rate are the result of the complex pathophysiology of chronic kidney disease, and also of serum creatinine variability according to muscle mass, hydration status, physical activity close to sample collection, antihypertensive drugs used, etc. It is possible that the overall authors' hypothesis can be demonstrated by increasing the number of patients with chronic kidney disease. This possibility is taken into account in the text by the authors. If we accept that elevated pulse pressure is

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an indicator of “central” vascular disease, it is highly probable that there is also great variability, as was undoubtedly considered by the authors. In other words, if there is aortic stiffness, it is very likely that baroreceptor activity is also altered producing exaggerated hemodynamic responses in the presence of moderate or even mild humoral or hemodynamic changes. This might be a purely mechanical effect of aortic wall stiffness, but it could also be the result of an inhibitory effect upon the baroreceptors induced by the “inflammation” that accompanies the atherosclerotic process.

The authors’ hypothesis will certainly generate new research to identify the predictive role of pulse pressure, the non-dipper pattern and blood pressure variability in patients with chronic kidney disease. Indeed, the evaluation of these patients with indisputable and high cardiovascular risk would greatly benefit with the confirmation of these parameters as risk markers.

Conflicts of interest

None declared

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REFERENCES

- Whaley-Connell AT, Sowers JR, Stevens LA, McFarlane SI, Shlipak MG, Norris KC, et al. Kidney Early Evaluation Program Investigators. CKD in the United States: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. *Am J Kidney Dis* 2008;51(4 Suppl 2):S13-S20. <http://doi.org/dhkv4>
- Buckalew VM Jr, Berg RL, Wang SR, Porush JG, Rauch S, Schulman G. Prevalence of hypertension in 1,795 subjects with chronic renal disease: the modification of diet in renal disease study baseline cohort. *Modification of Diet in Renal Disease Study Group. Am J Kidney Dis* 1996;28:811-21. <http://doi.org/dhb26w>
- Guyton AC, Coleman TG, Cowley AV Jr, Scheel KW, Manning RD Jr, Norman RA Jr. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. *Am J Med* 1972;52:584-94. <http://doi.org/cbsf86>
- Neumann J, Ligtenberg G, Klein II, Koomans HA, Blankstijn PJ. Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. *Kidney Int* 2004;65:1568-76. <http://doi.org/cx2zft>
- Long DA, Price KL, Herrera-Acosta J, Johnson RJ. How does angiotensin II cause renal injury? *Hypertension* 2004;43:722-3. <http://doi.org/ddz4cg>
- Bidani AK, Griffin KA. Long-term renal consequences of hypertension for normal and diseased kidneys. *Curr Opin Nephrol Hypertens* 2002;11:73-80. <http://doi.org/d2dz4n>
- Passauer J, Pistrosch F, Büssemaker E, Lässig G, Herbrig K, Gross P. Reduced agonist-induced endothelium-dependent vasodilation in uremia is attributable to an impairment of vascular nitric oxide. *J Am Soc Nephrol* 2005;16:959-65. <http://doi.org/dsfk86>
- London G, Guerin A, Pannier B, Marchais S, Benetos A, Safar M. Increased systolic pressure in chronic uremia. Role of arterial wave reflections. *Hypertension* 1992;20:10-9. <http://doi.org/2fn>
- Portaluppi F, Montanari L, Massari M, Di Chiara V, Capanna M. Loss of nocturnal decline of blood pressure in hypertension due to chronic renal failure. *Am J Hypertens* 1991;4(1Pt 1):20-6.
- Sarcona E, Diaz M. Effect of Renal Disease on Ambulatory Blood Pressure Monitoring. *Rev Argent Cardiol* 2015;83:135-9.
- Safar ME, Plante GE, Mimran A. Arterial stiffness, pulse pressure and the kidney. *Am J Hypertens* Published “on line” 2014; 101093/ajh/hpu 206
- Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Predictors of all-cause mortality in clinical ambulatory monitoring unique aspects of blood pressure during sleep. *Hypertension* 2007;49:1235-41. <http://doi.org/c9p8xc>
- Agarwal R, Andersen MJ. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. *Kidney Int* 2006;69:1175-80. <http://doi.org/c9p8xc>