The search for hidden truths behind established concepts and dogma is often a never-ending, uphill climb, and the history of science and medicine is full of examples of this. “To raise new questions, new possibilities, to regard old questions from a new angle, requires creative imagination and marks real advances in science” (Albert Einstein). The story of the renin-angiotensin system (RAS), hypertension, and kidney disease began nearly 2 centuries ago, with report of a clinical-pathophysiological study of albuminuria in patients followed by Goldblatt’s induction of hypertension in experimental dogs in the 1930s. It took 7 more decades of basic, translational, and clinical research to discover the pressor effect of renal extracts (ascribed to renin) in 1898 and another 10 decades of imaginative work by many to culminate in the discovery of angiotensin II (Ang-II), the primary effector peptide of the RAS, and its receptors (AT1R and AT2R) in 2000. Since then, expansion of the RAS to the renin-angiotensin-aldosterone (RAAS) system and discovery of several bioactive peptides produced through Ang-II degradation has contributed to the increasing complexity of the RAS (Figure), and the search continues.

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Since the 1990s, therapy based on inhibition of the effects of Ang-II with angiotensin-converting enzyme (ACE) inhibitors and AT1R blockers has dominated the experimental and clinical research arenas. Cumulative evidence has indicated that the RAS, through Ang-II generated primarily by the ACE, plays a critical role in the regulation of blood pressure, fluid and electrolyte balance, cardiovascular and renal homeostasis, and pathophysiology of hypertension and cardiovascular and renal disease. Ang-II was implicated in cardiovascular and renal disease nearly 2 centuries ago, with report of a clinical-pathophysiological study of albuminuria in patients followed by Goldblatt’s induction of hypertension in experimental dogs in the 1930s. It took 7 more decades of basic, translational, and clinical research to discover the pressor effect of renal extracts (ascribed to renin) in 1898 and another 10 decades of imaginative work by many to culminate in the discovery of angiotensin II (Ang-II), the primary effector peptide of the RAS, and its receptors (AT1R and AT2R) in 2000. Since then, expansion of the RAS to the renin-angiotensin-aldosterone (RAAS) system and discovery of several bioactive peptides produced through Ang-II degradation has contributed to the increasing complexity of the RAS (Figure), and the search continues.

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with a favorable outcome, and combination therapies are often needed. Over the last 2 decades, several laboratories have been searching for specific molecular targets that may lead to the development of therapies and strategies to optimize therapy of hypertension, heart failure, and chronic renal disease, prevent adverse remodeling, and improve outcome. Many studies have been conducted in experimental animal models and humans. However, therapy to limit adverse remodeling in patients with these diseases, especially the elderly, remains suboptimal, and hearts continue to enlarge after hypertension and heart failure.
In this issue of Circulation, Salem and colleagues\textsuperscript{14} tested the provocative and bold hypothesis that a novel peptide acts as an endogenous cofactor in Ang-II–mediated vasoregulatory effects. The observation that plasma Ang-II concentrations were not increased in patients with heart failure and chronic kidney disease triggered the idea that unknown endogenous cofactors may be involved in the action of Ang-II.\textsuperscript{14,15} They present a large volume of compelling data suggesting that this peptide, a fragment of chromogranin-A that they named vasoconstriction inhibiting factor (VIF), modulates vasoconstrictive effects of Ang-II and exerts vasodilator effects mediated by AT\textsubscript{2}R, and may provide a potential counter-regulatory mechanism against hypertension.\textsuperscript{14} This interesting non-RAS peptide acting through AT\textsubscript{2}R further underscores the complexity of the RAS/RAAS (Figure, B) and need for more research to establish its importance as a potential target for the prevention and therapy of cardiovascular disease. Marie Curie, winner of separate Nobel Prizes for Physics and Chemistry, is credited with saying "be more curious about ideas.”

It is known that chromogranin-A is produced by chromaffin cells of the adrenal medulla and other tissues and is elevated in pheochromocytomas. It serves as precursor to several functional peptides, including vasostatin I, vasostatin II, pancreaticostatin, catestatin, and parastatin, which negatively modulate autocrine and paracrine functions.\textsuperscript{16–18} Some of these peptides, such as vasostatin I and vasostatin II, inhibit vasoconstriction while concentrations of catestatin are reduced and those of chromogranin-A are increased in hypertensive patients. Here Salem et al\textsuperscript{15} report at least 7 important findings. First, they nicely demonstrated that VIF released from the adrenal glands and derived from chromogranin-A modulates Ang-II–induced vasoconstriction by testing different VIF concentrations on Ang-II–induced vasoconstriction and calculating the EC\textsubscript{50}. Second, they probed mechanisms and showed that VIF impairs Ang-II–induced phosphorylation of p38MAPK but not extracellular signal–regulated kinase 1/2. Third, they present evidence suggesting that elevated plasma VIF may modulate the harmful effects of Ang-II in chronic renal disease and heart failure patients, especially since chromogranin-A is also elevated in these patients. Fourth, they showed that VIF reduced Ang-II–induced increase in blood pressure in vivo. Fifth, they confirmed absence of homology in amino acid sequences between VIF and the other main Ang peptides. Sixth, they confirmed that VIF but neither scrambled nor truncated peptides caused a significant effect on Ang-II–induced vasoconstriction. Seventh, they addressed the affinity of VIF for AT\textsubscript{2}R by showing that VIF inhibits Ang-II–induced vasoconstriction in a large physiologically relevant range, and maintains its effect in the presence of L-\textsuperscript{NO}-Nitro arginine methyl ester (hence independent of nitric oxide), but its effect is abolished by the AT\textsubscript{2}R blocker PD 123,319. These findings unmasking the nitric oxide–independent effect of VIF on the AT2 receptors further underscore the importance of AT\textsubscript{2}R in the regulation of blood pressure.

The overall findings of Salem et al\textsuperscript{14} underscore the complexity of vasoregulation as pointed out by the authors. Importantly, the findings suggest a potentially novel strategy for promoting counterregulatory vasodilation thereby limiting hypertension, adverse remodeling, and heart failure. Whether targeting the VIF/AT\textsubscript{2}R pathway might be a potential approach for preventing adverse remodeling and improving outcome in hypertension warrants study. Whether VIF levels are decreased with aging and explain the poorer outcome in older patients also deserves study. The authors deserve to be applauded for the idea that non-RAS–derived peptides may interact with 2\textsuperscript{1} of the 3 major RAS receptors (AT\textsubscript{1}R, AT\textsubscript{2}R, and Mas) and produce significant physiological and pathophysiological effects. This possibility opens up a new area of research into other biologically active peptides. The authors have suggested testing for interactions of VIF with other angiotensin peptides (such as angiotensinogen, Ang-II, Ang-III, Ang-IV, and Ang-[1–7]), angiotensin-converting, and alamandine.\textsuperscript{14} However, the possibility that peptide interactions may not always be beneficial but rather might be harmful and contribute to disease progression should also be considered.

Sources of Funding
This work was supported in part by grant IAP99003 (2010-2012) from the Canadian Institutes of Health Research.

Disclosures
None.

References


**KEY WORDS:** Editorials ◼ angiotensin ◼ hypertension ◼ peptides ◼ receptors ◼ renin-angiotensin system
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Circulation. 2015;131:1380-1383; originally published online March 25, 2015;
doi: 10.1161/CIRCULATIONAHA.115.016328
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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