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Biomarkers of activation of renin-angiotensin-aldosterone system in heart failure: how useful, how feasible?

Michele Emdin [a,b,*], Cinzia Fatini [c], Gianluca Mirizzi [a], Roberta Poletti [a,b], Chiara Borrelli [b], Concetta Prontera [a], Roberto Latini [d], Claudio Passino [a,b], Aldo Clerico [a,b], Giuseppe Vergaro [a,b]

[a] Division of Cardiology and Cardiovascular Medicine, Fondazione Toscana G. Monasterio, Pisa, Italy
[b] Scuola Superiore Sant'Anna, Pisa, Italy
[c] Department of Medical and Surgical Critical Care, University of Florence, Italy
[d] Istituto Mario Negri, Milan, Italy

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ABSTRACT

Renin-angiotensin-aldosterone system (RAAS), participated by kidney, liver, vascular endothelium, and adrenal cortex, and counter-regulated by cardiac endocrine function, is a complex endocrine system regulating systemic functions, such as body salt and water homeostasis and vasomotion, in order to allow the accomplishment of physiological tasks, such as orthostasis, physical and emotional stimuli, and to react towards the hemorrhagic insult, in tight conjunction with other neurohormonal axes, namely the sympathetic nervous system, the endothelin and vasopressin systems. The systemic as well as the tissue RAAS are also dedicated to promote tissue remodeling, particularly relevant after damage, when chronic activation may configure as a maladaptive response, leading to fibrosis, hypertrophy and apoptosis, and organ dysfunction. RAAS activation is a fingerprint of systemic arterial hypertension, kidney dysfunction, vascular atherosclerotic disease, and is definitely an hallmark of heart failure, which rapidly shifts from organ disease to a disorder of neurohormonal regulatory systems. Chronic RAAS activation is an indirect or direct target of most effective pharmacological treatments in heart failure, such as beta-blockers, inhibitors of angiotensin converting enzyme, angiotensin receptor blockers, direct renin inhibitors, and mineralocorticoid receptor blockers. Biomarkers of RAAS activation are available, with different feasibility and accuracy, such as plasma renin activity, renin, angiotensin II, and aldosterone, which all accompany the increasing clinical severity of heart failure disease, and are well recognized prognostic factors, even in patients with optimal therapy. Polymorphisms influencing the expression and activity of RAAS pathways have been recognized as clinically relevant biomarkers, likely influencing either the individual clinical phenotype, or the response to drugs. This solid, growing evidence strongly suggests the rationale for the use of biomarkers of the RAAS activation, as a guide to tailor individual therapy in the current practice, and their implementation as a rule-in marker for future trials on novel drugs in the heart failure setting.

1. Do we need a renin-angiotensin-aldosterone system? The biological and physiological background

Renin-angiotensin-aldosterone system (RAAS) is a complex endocrine system that regulates salt-water homeostasis, circulating plasma volume, arterial vascular myogenic tone, and blood pressure in healthy humans [1,2], and has been largely recognized to play a central role in the development and progression of cardiovascular diseases, in particular of atherosclerosis and heart failure [3,4]. The kidney secretory iuxtaglomerular cells release the aspartyl-protease renin (MW 48 000 Dalton) in response to: a) a decrease in pressure (below 100 mmHg with a maximum at 60 mmHg level) at the distal portion of the afferent glomerular arteriola, as well as to: b) a decrease in salt content in macula densa perfusion, and to: c) neurohormonal modulation, such as a positive influence on secretion determined by an increase of sympathetic drive, and a negative feed-back sustained by increasing levels of angiotensin II. Renin acts (in a pH range 5–7.5, in the presence of a H_2O molecule) cleaving a decapeptide, called angiotensin I, from its unique substrate, the circulating N-terminal portion of an inactive peptide, angiotensinogen, a 452-amino acid alpha2-globulin, produced by the liver. Human kidney renin is synthesized as pre-prorenin: in mammals two forms of renin are produced into the bloodstream in mammals, a mature, active one, secreted by granula of myoepithelioid cells, and an immature one (prorenin, circulating inactive renin, without enzymatic activity), mostly produced by extrarenal organs (female genitals, retina). Chronic stimulation induces an hyperplasia of iuxtaglomerular apparatus, with a net increment in the ability of

* Corresponding author at: Division of Cardiology and Cardiovascular Medicine, Fondazione Toscana Gabriele Monasterio CNR-Regione Toscana, Via Giuseppe Moruzzi 1, 56124 Pisa, Italy. Tel.: +39 050 3152189; fax: +39 050 3152109.
E-mail address: emdin@ftgm.it (M. Emdin).

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synthesis, storage, and secretion of renin (Fig. 1). Angiotensin I is a peptide with little biological activity, and is converted to angiotensin II, the active 8-amino acid peptide, by the angiotensin I converting enzyme (ACE), a zinc metallopeptidase, which is widely distributed on the surface of endothelial and epithelial cells [5], and is present particularly at the endothelial level of pulmonary capillaries. Angiotensin II is then cleaved into the eptapeptide angiotensin-III, with some possible action on angiotensin receptors AT1, and then into the esapeptide angiotensin IV (Fig. 1). Angiotensin II is the principal hormone produced by RAAS and has endocrine, paracrine and autocrine functions, and primarily acts through two types of receptors: angiotensin II type 1 and type 2 receptors. Angiotensin II is a potent vasoconstrictor that, at the kidney level, acts on both afferent and efferent arteriola: at the afferent level it determines an increase in arteriolar resistance and hence an increase in systemic arterial pressure and a reduction in glomerular blood flow. Acting on the efferent level it buffers intraglomerular blood pressure, in order to counterbalance the eventual reduction in flow caused by the action on the afferent arterioles. Furthermore, it stimulates: a) the secretion of the water-retaining hormone vasopressin in the pituitary gland; b) the sympathetic nervous system and the medullary portion of the adrenal cortex to secrete norepinephrine and epinephrine; c) the glomerular cells of the adrenal cortex to produce and release aldosterone, a steroid hormone whose principal action is to increase sodium reabsorption and potassium excretion from the distal convoluted part of Henle loop.

Angiotensin I is also a substrate for ACE2, a carboxypeptidase enzyme and homologue of ACE, expressed in heart, kidney, and vessels, that produces angiotensin [1–9] (Fig. 1). ACE2 has a high affinity for angiotensin II to form angiotensin [1–7], which is also being formed by the action of ACE on angiotensin [1–9] (Fig. 1). Angiotensin [1–7] is reported to have functions opposite to angiotensin II, counteracting the adverse actions of angiotensin II on the heart, kidney and blood vessels. The physiological actions of angiotensin [1–7] are mediated through the Mas receptor (Mas R), a G protein-coupled receptor [6] (Fig. 1).

AT1 receptor is ubiquitously distributed in adult tissues, as it promotes cell growth and regulates the expression of bioactive substances such as vasoconstrictive hormones, growth factors, cytokines, aldosterone, and extracellular matrix components [7], and therefore it is believed to mediate most of the atherogenic effects of angiotensin II. The angiotensin II receptor type 2 (AT2) is mainly limited to myocardium, vascular endothelium, uterus, ovary, brain, pancreas, and adrenal medulla. It often counterbalances the effects of AT1 by inhibiting the growth of vascular smooth muscle and cardiomyocytes [8].

AT2 receptors are more plentiful in the fetus and neonate, but scantily in adult tissues, except brain, adrenal medulla, and atretic ovary. This receptor has been shown to mediate programmed cell death and this apoptotic function may play an important role in developmental biology and pathophysiology. The angiotensin AT2 receptor mediates tissue protective actions. Its regenerative potential has been tested in multiple disease models including models of myocardial infarction. The so-called protective arm of the RAAS includes AT2-receptors and MasR, and is characterized by effects different from and often opposing those of the AT1 receptor. These include anti-inflammation, anti-fibrosis, anti-apoptosis and neuroregeneration that can counterbalance pathological processes and enable recovery from disease [9] (Fig. 1). The AT2 receptor, while being only sparsely expressed in most healthy tissues, is strongly up-regulated following tissue damage, such as vascular and neuronal injury, myocardial infarction, and brain ischemia. The recent development of novel, small-molecule AT2 agonists offers a therapeutic potential in humans with a variety of clinical indications [9].

Other poorly characterized subtypes include the AT3 and AT4 receptors. The AT4 receptor is activated by the angiotensin II metabolite angiotensin IV, and may play a role in regulation of the central nervous system extracellular matrix, as well as modulation of oxytocin release.

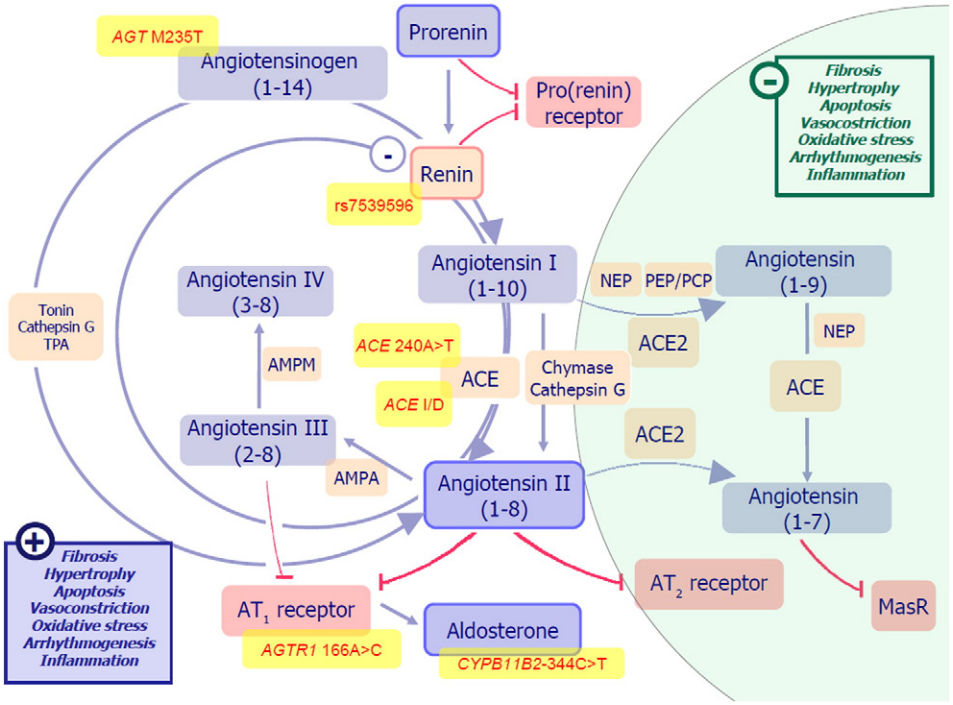

Fig. 1. Pathways and effectors of the renin-angiotensin-aldosterone system (RAAS). Effectors and enzymathic pathways of the renin-angiotensin-aldosterone system (RAAS). Enzymes are labelled in orange, receptors in light red, gene polymorphisms in yellow. Arrows indicate the conversion from one effector into another; red lines indicate binding to receptors. Pathways mediating the detrimental profibrotic, prohypertrophic and vasoconstrictive actions RAAS are on white background; pathways with putative or ascertained anti-remodeling effects are shaded in green. ACE, angiotensin convertying enzyme; ACE2, angiotensin convertying enzyme 2; ACE I/D, insertion/deletion polymorphism of the gene encoding for ACE; ACE −240A > T, polymorphism of the promoter region of ACE gene; AGT M235T, polymorphism of the exon 2 of gene encoding for angiotensinogen; AGTR1 1166A > C, polymorphism of the 3′-UTR region of the gene AGTR1, encoding for angiotensin II receptor type 1; AMPA, aminopeptidase A; AMPM, aminopeptidase M; AT1, angiotensin II type 1 receptor; AT2, angiotensin II type 2 receptor; CYP11B2 −344C > T, polymorphism of the gene encoding for aldosterone synthase; MasR, Mas receptor; rs7539596 polymorphism downstream from renin gene enhancer element; NEP, neutral endopeptidase (neprilysin); PEP/PCP, prolyl endopeptidase and prolyl carboxypeptidase; TPA, tissue plasminogen activator.