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The role of aldosterone receptor blocker therapy in hypertension and heart failure

Giuseppina Santese, Cosimo Stefanio, Gianluca Belletti, Maria Boiani, Antonietta Schipani, Rosanna Trane, Fabio Zacà

Villa Torri Hospital Bologna, GVM, Italy

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ABSTRACT

The aldosterone receptor blocker therapy as an "add-on" to hypotensive therapy is an excellent therapeutic strategy that has proved to be particularly effective in treating refractory hypertension, hypertension with organ damage and overweight hypertensive patients. Aldosterone receptor blockers are extremely useful in inhibiting hormonal activation linked with heart failure: they have cardioprotective effects not only during full-blown heart failure, but also in its early stages, and this effect can be observed even more frequently in heart failures with metabolic syndrome. The use of molecules such as canrenone with a favorable tolerability profile ensures a better tolerability ratio by providing benefits linked to fewer drug interactions, lower incidence of side effects and improved therapy adherence.

1. Aldosterone receptor blocker and hypertension: why, when?

One of the main challenges of modern medicine is to achieve an adequate monitoring of the population's blood pressure: despite multiple therapeutic choices; in fact, current data show that a large proportion of patients do not reach target blood pressure.

Recent observations are not encouraging: in the US less than 50% of patients undergoing hypertensive treatment reach the target and the percentage is even lower in high risk patients [1]. A recent study carried out by Dr. Volpe in Italy on 50,000 subjects in several Italian regions, has proved how in treated patients, only 1/5 of the hypertensive ones arrives at pressure values <140/90 mm Hg and, among these, only half the cases reached the target blood pressure [2].

This phenomenon needs to be explained. The recent European Guidelines on Arterial Hypertension [3,4] have introduced the concept of Resilient Hypertension, i.e. the failure of target blood pressure despite the administration of at least three drugs including a diuretic and an adequate change in life style. The causes that can explain this state of things are multiple: *inter alia* an important role is played by poor adherence to therapy, inadequate modification of lifestyle, a concomitant drug administration that may lead to blood pressure increase as in glucocorticoids and NSAIDs (non-steroidal anti-inflammatory drugs), also associated with obstructive sleep apnea syndrome.

A decisive role is definitely represented by an overload of volume due to inadequate diuretic therapy, progressive renal failure, increase of sodium intake and presence of high aldosterone values. In recent years there has been abundant evidence of the role of aldosterone in the development of arterial hypertension. One of the main effects is hypervolemia which is linked to the increase in the reabsorption of sodium and water, as well as augmented kidney level [5].

Furthermore, aldosterone induces the formation of collagen in the heart as well as in the peripheral vessels with a consequent remodeling of tissue and increase in peripheral vascular resistance. Besides that, it alters the endothelial function and by binding itself to the smooth vascular muscle receptors, it may alter the pressure response to adrenergic stimulation.

It is interesting to observe how aldosterone levels are connected to the severity of sleep apnea syndrome in patients with obstructive sleep apnea, a condition that has been underestimated for years and is now considered one of the most common causes of resistant hypertension.

Over the years, knowledge of the harmful role of aldosterone has meant that the main therapeutic strategies against hypertension control were based on an Angiotensive Renin Aldosterone system, using drugs such as ACE inhibitors, ARBs, and more recently, Renin inhibitors. However, the modulation of such a system is often insufficient: several clinical trials have in fact underlined that after an initial reduction of the aldosterone levels during the administration of ACE-I, after a period of time from 3 to 12 months, the plasma levels of the hormone tend to rise again. This phenomenon, known as aldosterone "Escape" is evident both with the ACE-I inhibitors as well as with the Angiotensin Receptive Blockers (ARBs) and can also take place during the double block of the RAA system with ACE and ARBs. The extent of the phenomenon is not negligible: several studies have proved that the escape is present in over 40% patients treated with ACE and/or ARBs (Fig. 1).

The causes of this phenomenon are multiple: an important role is certainly played by the production of angiotensin II. Through mechanisms

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L'escape dell'aldosterone si verifica in una significativa percentuale di pazienti in terapia con ACE-I e Sartani

Studio	Pz	Insuff. cardiaca congestizia	M. renale cronica	Blocco del RAAS	Definizione escape aldosterone	Incidenza di escape
Lee, et al (1999)	22	SI	No	ACE-I titolato alla per 18 mesi	> 80 pg/ml dopo 18 mesi	23% (5/22)
Mac Fadyen, et al (1999)	91	SI	No	ACE-I per 4 settimane	> 144 pg/ml dopo almeno 4 settimane	38% (35/91)
Sato and Saruta (2001)	75	No	No	ACE-I per 40 settimane	Ald > ai livelli basali dopo 40 settimane	51% (38/75)
Tang, et al (2002)	75	SI	No	Enalapril 2.5 o 20 mg/bid per 6 mesi	Ald > 160 pg/ml dopo 6 mesi	35% (26/75)
Sato, et al (2003)	45	No	SI	Trandolapril per 40 settimane	Ald > ai livelli basali dopo 40 settimane	40% (16/45)
Schjoedt, et al (2004)	63	No	SI	Losartan 100 mg per 24-42 mesi	Ald > ai livelli basali dopo 24-42 mesi	41% (26/63)
Harita, et al (2006)	43	No	SI	Temocapril 1 mg/die, losartan 12.5 mg/die o entrambi per 12 mesi	Ald > ai livelli basali dopo 12 mesi	53% (23/43)

Fig. 1.

which are independent of ACE; the chymase enzyme generates angiotensin I in the brain, heart and blood vessels through non-ACE paths and contributes to the production of aldosterone. There is also evidence that the "Escape" of aldosterone in turn may promote the release of angiotensin II through a feedback control that stimulates ACE in the blood vessels.

Furthermore, the phenomenon can also occur in the absence of a rise in angiotensive II because of alternative stimuli to angiotensin which induce the production of aldosterone. These stimuli include increased K+ induced by ACE-I, ACTH, adipokines and vasopressin (Fig. 2).

On the basis of these findings both the pathogenic role played by aldosterone receptor blockers in the development of resistant hypertension, and the rationale of the therapy with drugs that are antagonists of the aldosterone receptors when dealing with this clinical reality are evident.

A growing number of studies confirm the antihypertensive effectiveness of aldosterone receptor blocker in addition to treatment with ACE-I or ARBs with or without thiazide in resistant hypertension. The mean dosage prescribed was 50 mg/day. The results of the studies demonstrated a significantly greater control of pressure values (with a decrease in PAS approximately equal to 22 mm Hg and DBP of 10 mm Hg), which was obtained only when the drug "added" was the aldosterone receptor blockers and not another class of hypotensives. The addition of aldosterone receptor blockers is therefore a rational therapeutic choice in patients with uncontrolled hypertension (Fig. 3) [7].

To this end, the ESCAPE study (Efficacy and Safety of Canrenone Add on in Patients With Essential Hypertension) was designed and is still in progress to define the therapeutic efficacy, tolerability and safety of the use of aldosterone receptor blocker canrenone in addition to therapy with ACE-I or ARBs and diuretics in patients with uncontrolled hypertension comparing two different doses of canrenone, 50 mg/day versus 100 mg/day.

Patients included were hypertensive outpatients, aged between 45 and 75 years of age, with uncomplicated hypertension and BP values >140.90 mm Hg but <180/100 despite therapy with ACE-I/ARBs and diuretics. Begun in 2011, the study will end in the first half of 2012. Canrenone treatment for each patient is scheduled for 3 months.

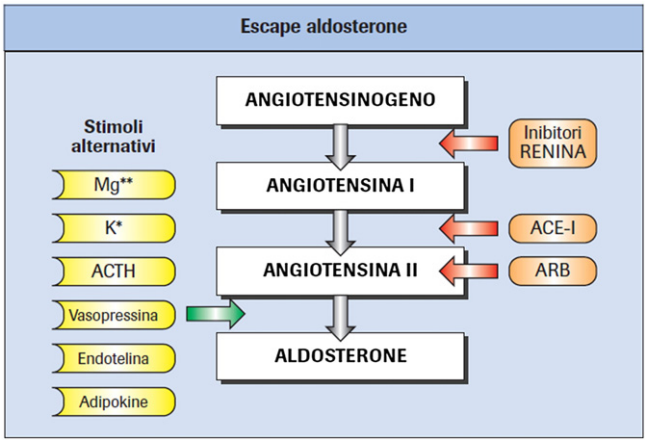

Fig. 2.

Cosa succede se ad una terapia ipotensiva standard aggiungiamo l'antialdosteronico?

Antialdosteronico

2.337 pazienti ipertesi non controllati con uno o più farmaci. **Add on** di un **Antialdosteronico**

Studio	Δ PAS/PAD (mm/Hg)	Studio	Δ PAS/PAD (mm/Hg)
ASCOT	-22/-10	Ouzan	-24/-10
Nishizaka	-25/-12	Ramsay	-30/-12
Lane	-22/-9	Krum	-16/-13
Sharabi	-24/-13	Rodilla	-28/-12

Dosaggio medio = **50 mg/die** *(range 12.5-100 mg/die)*

Fig. 3.