Research Article

ISSN 2639-8486

Cardiology & Vascular Research

The Double Sequential Actions of the Angiotensin II Receptor Blockers and Mineralocorticoid Receptor Antagonists Therapy on the Renin Angiotensin Aldosterone System Produce a Better Reduction of Both Blood Pressure and Central Haemodynamic Parameters and Can Prevent the Appearance of the Atrial Fibrillation

Carlos Alberto Paterno Marchioli*

Via Camillo Benso Conte di Cavour, Castiglion Fiorentino, Italy.

***Correspondence:**
Carlos Alberto Paterno Marchioli, Fellow of the European Society of Cardiology, Via Camillo Benso Conte di Cavour, Castiglion Fiorentino, Italy, E-mail: carlos_paterno@tiscali.it.

Received: 11 May 2023; **Accepted:** 16 Jun 2023; **Published:** 22 Jun 2023

Citation: Paterno Marchioli CA. The Double Sequential Actions of the Angiotensin II Receptor Blockers and Mineralocorticoid Receptor Antagonists Therapy on the Renin Angiotensin Aldosterone System Produce a Better Reduction of Both Blood Pressure and Central Haemodynamic Parameters and Can Prevent the Appearance of the Atrial Fibrillation. Cardiol Vasc Res. 2023; 7(3): 1-12.

ABSTRACT

Hypertension is a complex, multifactorial disease that has a significant positive association with adverse cardiovascular outcomes, such as myocardial infarction, stroke, kidney disease, and death. Research studies on hypertension have, so far, generally focused on vascular resistance and small arteries. The development of hypertension is usually accompanied by arterial structural remodelling, such as large artery stiffness, and increased both central systolic blood pressure and pulse pressure. Also, is well-established that hypertension is an important risk factor for atrial fibrillation. The goal of antihypertensive therapy is to prevent cardiovascular complications. Therefore, treatment with combination of antihypertensive agents acting on multiple targets is necessary for successful in the majority of patients. New therapeutics models are necessary to reduce both arterial stiffness and volume cardiovascular to ameliorate the stress of the arterial-ventricular-atrial dynamic coupling and the abnormal pulsatile system.

The objective of the study was to assess the levels reached on both the systolic and diastolic blood pressure, and the central haemodynamic parameters into each one of the three groups of patients during the angiotensin II receptor blockers therapy alone, associated with hydrochlorothiazide or mineralocorticoid receptor antagonists, and observing the presence of episodes of atrial fibrillation during 24-hour Holter monitoring.

The results suggest that the latter association of sequential double blockade on the renin angiotensin aldosterone system achieves the best haemodynamic conditions to avoid or reduce the presence of brief phases of atrial fibrillation on hypertensive patients with normal kidney function.

Keywords

Hypertension, Blood pressure, Angiotensin II receptor blockers.

Abbreviations

ARB: Angiotensin Receptors Blockers, MRA: Mineralocorticoid Antagonists, Hct: Hydrochlorothiazide, CCB: Calcium Channel Blocker, RAAS: Renin Angiotensin Aldosterone System, ESC: European Society of Cardiology, ISH: International Society of Hypertension, ESH: European Society of Hypertension, HF: Heart Failure.

Objective of This Study

The aim of this study was to know whether the simultaneous and sequential actions by the association of the Angiotensin Receptors

Blockers and Mineralocorticoid Antagonists therapy on the Renin Angiotensin Aldosterone System in hypertensive patients with normal kidney function could obtain a better benefit as synergy therapy than the Angiotensin Receptor Blockers alone or when it is associated with hydrochlorothiazide, according on both Systolic and Diastolic Blood Pressure values and the central haemodynamic parameters assessed with the non-invasive applanation tonometry's measures. In addition, it was important to know in which therapy group the presence of brief episodes of atrial fibrillation is lowest during 24-hour Holter monitoring.

Background

Normal blood pressure is a level that does not cause cardiovascular injuries. Arterial hypertension is a complex, multifactorial, and chronic disease, frequently beginning during childhood or adolescence, that it has a significant positive association with adverse cardiovascular outcomes, such as myocardial infarction, stroke, kidney disease, and death [1,2]. It has been shown that even in the normotensive range (Box 2-J), the incidence of cardiovascular disease progressively increases from optimal to normal to high-normal blood pressure values [3]. Labeling an individual as "hypertensive" or "normotensive" is dependent on the cut-off values, and as suggested by the 2007 European Society of Hypertension/European Society of Cardiology guidelines" the threshold for hypertension, and the need for drug treatment, should be considered as flexible based on the level and profile of total cardiovascular risk".

The hypertensive disease can exist without an increase in blood pressure, for this reason, we show the clinical case (Box 4-2) of a patient who presents the stigmata of the natural history of the disease with habitual normal blood pressure. The last Guidelines on hypertension (ESH-ISH 2018) fixed the new limits into 130/80 mmHg, but maybe it is not definitive probably because should it be less [4].

Hypertensive cardiovascular disease has innumerable causes in variable proportions and onset times, with an irreversible evolution, it develops from an early age with a paucisymptomatic evolution (Box 1 & 2). In the last decades, the pulsatile arterial function has been increasingly recognized as a major determinant of cardiovascular risk.

The pathophysiology of hypertensive cardiovascular disease shows increased peripheral vascular resistance, and increased sodium and water retention, with elevated cardiac output. An increase in arterial stiffness is regarded as a direct measure of target organ damage, indicating the occurrence of pathological changes in large artery walls under the action of cardiovascular risk factors [5].

The development of the clinical evolution of hypertension is usually accompanied by arterial structural remodelling, increasing large artery stiffness, and central systolic blood pressure arising are well documented [6-8].

It is known that hypertension is the most prevalent independent risk factor for atrial fibrillation in the population and that this is due to atrial enlargement caused by the increased pressure induced in the atrium by left ventricular hypertrophy [9-12].

Both structural remodelling and subsequent electrophysiological changes by atrial fibrosis constitute an arrhythmogenic substrate for the induction and maintenance of atrial fibrillation. In 2010, 8.8 million adults in the European Union were estimated to suffer from atrial fibrillation, and this number is expected to more than double by the year 2060 [13-15]. Tissue RAAS is involved in numerous physiological and pathological processes, such as growth and remodelling [16], development [17], inflammation and cardiac hypertrophy (18), vascular hypertrophy and thrombosis [19], and obesity [20] (Box 2-I). Undoubtedly, Angiotensin II is one of the most potent vasopressor substances known, it is able to regulate cardiac contractility [21], cell coupling, and impulse propagation [22-25], as well as being responsible for remodeling and the induction of apoptosis [26,27].

Lastly was demonstrated that Angiotensin II may directly cause podocyte injury [28]. A cross-talk has been demonstrated between Angiotensin II and Aldosterone, because some of the cellular effects of Angiotensin II occur through aldosterone-dependent pathways [29].

The phenomenon of "aldosterone escape" or "aldosterone breakthrough" occurs even in the presence of combination therapy with Angiotensin Converting Enzyme inhibitors, regardless of the doses used [30]. A diminishment in aldosterone level during therapy with ARB was no longer observed by 43 weeks, then these data provided an additional physiological rationale for the use of a direct aldosterone receptor blocker [31]. Aldosterone is now considered a major cardiovascular-risk steroid hormone, it exerts its effects through genomic and nongenomic pathways. The harmful effects of aldosterone are innumerable (Box 3) known since the early work of Laragh et al. [32]. Aldosterone activates the mineralocorticoid receptor in principal cells and plays a vital role in regulating extracellular volume homeostasis and blood pressure by inducing sodium reabsorption and potassium excretion. The MRAs are not recommended as first-line drugs. The European Society of Hypertension/European Society of Cardiology guidelines actually placed them as fourth-line agents to be used in resistant hypertension [33].

On other hand, thiazide diuretics are one of the most commonly prescribed antihypertensive drugs worldwide, but the major concern is that can activate the neurohormonal system through volume depletion and could release aldosterone. In addition, can develop hyperuricaemia, impair glucose tolerance, and produce hypokalaemia and hyponatraemia, which are potentially arrhythmogenic.

Changes in atrial electrical properties occur early in hypertension heart disease, preceding the appearance of left ventricular and left

atrial enlargement [34], and this electrical instability was shown to promote the development of atrial fibrillation [35,36]. The research of non-antiarrhythmic drugs that act both on the electrical and mechanical atrial remodelling, that constitutes the substrate of arrhythmia, is a new and very interesting field of challenge to prevent its onset and to control recurrences.

BOX 1

The main causes and consequences of hypertensive cardiovascular disease.

1 – Main Causes

Renin Angiotensin Aldosterone System
Autonomic Nervous System
Metabolic and Endocrinology Factors
Inflammatory Systemic Diseases
Genetics, Behaviours, Lifestyles, Dependencies & Environmental factors.

2 – Major Consequences

Increases Systolic and Diastolic Blood Pressure, but "normal" blood pressure data should not always negate hypertensive heart disease, therefore, they should be considered relatives values, that produce serious complications and that can lead to significant disability or death. We learned that: "in Medicine, an isolated negative result is not capable to negate an illness". It is not an asymptomatic illness because we can observe many early symptoms and signs even before the measurements are higher than the levels accepted today as "normal".

a - Frequent symptoms (Box 2-C)

Headache (Box 2-A), palpitations, sweating, thoracic pain, breathlessness, throat tightness, asthenia, mental confusion.

b - Early signs

Minimal mitral regurgitation (Box 2-B 1 & 2), loud P2 sound, wandering atrial rhythm (Box 2-D).

c - Late signs

Atrial enlargement, left ventricular hypertrophy, ventricular arrhythmias (Box 2-E), atrial fibrillation (Box 2-F), ascending aorta ectasia, abdominal aortic aneurysm, stenosis renal artery, are among the most important.

"In Medicine, clinical data are always sovereign"

BOX 2

Posters presented by the author preceded and gave the bases for this presentation.

A – Migraine.

ESH 2012: Relation between angiotensin receptor blocker candesartan cilexetil treatment and chronic migraine on central haemodynamic parameters.

B – Minimal Mitral Regurgitation.

1 - ESH-ISH 2020: What does the finding of minimal mitral regurgitation mean?
2 - ESC 2021: Is the minimal mitral regurgitation a marker of high blood pressure,
and can predispose to the appearance of atrial fibrillation?

C – Symptoms.

ESH 2022: The importance of the symptoms for diagnosing and treating of hypertension in children, adolescents and young-aged, assessed with applanation tonometry.

D – Wandering atrial rhythm.

ESH 2022: What is the significance and the meaning from finding a wandering atrial rhythm.

E - Ventricular extrasystoles.

ISH 2022: Benefit of ranolazine added to angiotensin receptor blockers plus mineralocorticoid receptor antagonists therapy for ventricular extrasystoles treatment in hypertensive patients.

F – Hydrochlorothiazide.

ISH 2022: The use of hydrochlorothiazide for the treatment of hypertension increases the cardiovascular risk according to the central haemodynamic parameters.

G – Angiotensin II Receptors Blockers + Calcium Channel Blockers.

ESH 2019: Differences of angiotensin receptor blockers therapy associated to mineralocorticoid receptor antagonists or calcium channel blockers according to central haemodynamic parameters.

H – ARB vs ARB + MRA vs ARB + Hct.
ESH 2016: Benefit in central haemodynamic parameters by association angiotensin II receptor blockers and canrenone therapy in hypertensive patients with normal kidney function.

I – ARB + MRA in obese hypertensive patients.

HF 2016: Improvement in central haemodynamic parameters by association of Angiotensin II Receptors Blockers and canrenone therapy in obese hypertensive patients.

J – Hypertensive disease with normal blood pressure.

ESH 2023: Early diagnosis of hypertensive disease in youth with normal systolic and diastolic blood pressure levels.

BOX 3

Aldosterone exerts its deleterious effects at several levels
Increase sympathetic nervous system activation [37], induced metabolic effects such as glucose intolerance, insulin resistance, and cardiac [38,39] and renal [40-43] inflammation and fibrosis [44,45].

Increases expression of COX-2 and modulating oxidative stress through induction of NADPH oxidase, contribute to the development of left ventricular interstitial fibrosis and myocardial apoptosis, that involved in arterial and myocardium remodelling [16,46], impairs endothelial function by reducing the bioavailability of nitric oxide which alter diastolic function [47,48].

Decrease sodium and water excretion with concomitant increase plasma volume and increase the filling pressure, and induce to heart failure, increases sodium influx in vascular smooth muscle cells, leads to vascular wall inflammation [49] and cell hypertrophy, with reduction in vascular compliance, and produce a prothrombotic state [50].
Enhance vascular responsiveness to pressor agents such as norepinephrine and angiotensin [51].
Developed arrhythmias by hypokalaemia and myocardial calcium channel expression [52,53], increases atrial fibrosis with subsequent structural remodelling developing a substrate for atrial arrhythmias [54] by electrical instability that promotes the new-onset atrial fibrillation [35,36].

Design & Methods

For this retrospective cross-sectional and observational study entering 1500 hypertensives patients, both sexes, with normal kidney function, without antiarrhythmic drugs, and without decompensated diseases, were divided into three therapy groups.

Group 1: Angiotensin Receptor Blockers + Mineralocorticoid Receptor Antagonists
Group 2: Angiotensin Receptor Blockers alone
Group 3: Angiotensin Receptor Blockers + Hydrochlorothiazide

In this study, the patients were entered from the beginning of the year 2007 to the end of the year 2021, both sexes females 879 (58.6%) and males 621 (41.4%).

Table 1: The Distribution of the Patients by Sex, Age, and Therapy Group.

	Females			Males		
	ARB+MRA	ARB	ARB+Hct	ARB+MRA	ARB	ARB+Hct
n	**388**	**238**	**253**	**239**	**215**	**167**
Age	**60.1**	**62.4**	**65.2**	**58.9**	**58.5**	**62.0**
SD	**12.7**	**13.0**	**11.2**	**12.8**	**13.6**	**12.5**

ARB: Angiotensin Receptor Blockers. MRA: Mineralocorticoid Receptor Antagonists.
Hct: Hydrochlorothiazide. SD: Standard Deviation.

The average age, both sexes, was highest in the group with ARB + Hct therapy.

In Table 2 it can be seen all of the ARBs used according to sex and group of therapy.

Table 2:

	ARBs	CANDES	OLMES	IRBES	VALS	TELMIS	LOS	EPROS	Total
F	**ARB +MRA**	**344**	**11**	**18**	**11**	**1**	**3**	**0**	**388**
M	**ARB +MRA**	**209**	**11**	**12**	**7**	**0**	**0**	**0**	**239**
F	**ARB**	**85**	**50**	**35**	**34**	**20**	**14**	**0**	**238**
M	**ARB**	**90**	**44**	**39**	**18**	**15**	**9**	**0**	**215**
F	**ARB +Hct**	**34**	**45**	**59**	**54**	**19**	**41**	**1**	**253**
M	**ARB +Hct**	**23**	**34**	**31**	**37**	**22**	**19**	**1**	**167**
	Total	**785**	**195**	**194**	**161**	**77**	**86**	**2**	**1500**

F: Females. M: Males. ARB: Angiotensin Receptor Blockers. MRA: Mineralocorticoid Receptor Antagonists. Hct: Hydrochlorothiazide.

All patients included in the registry were treated at least for 3 months. The patients of the group ARB and ARB + Hct were being treated by their physicians when they were entered into this study. Most of the patients treated with ARB + MRA belong to our laboratory of hypertension. The first communication about this no-traditional association therapy was presented in the year 2011 [55].

When began to use the applanation tonometry in the year 2007 we observed that frequently the patients treated with antihypertensive drugs such as ARB alone (Box 2-H) or in combination with thiazide diuretics (Box 2-F) and/or Calcium Channel Blockers (Box 2-G) they did not reach normal values according to the central haemodynamic parameters.

In our previous study, unpublished data (Iannacone C, D'Alonzo L. Statisticians - Milan, 2011), hypertensive patients treated with all of the above ARBs were evaluated with non-invasive arterial tonometry, observing a slight superiority of candesartan cilexetil, which predominantly we used for association with MRAs. For the patients, each visit had an average duration between 60-90 minutes, in which the patient received precise information about his disease, the current state, and the modifications that they should make to improve the symptoms and restore the lost haemodynamic balance.

The patients were highly encouraged to suppress or diminished salt intake in the diet to the lowest tolerable quantity, a very important variable considering that aldosterone exerts its deleterious action principally in the presence of sodium chloride. Also, patients received information about to moderating the consumption of alcohol and give up the habit of smoking, absolutely, in addition, they were advised to maintain regular physical activity according to sex and age. The patients were informed that they should have their renal function checked regularly. Thus, when the MRA was added to ARB therapy considering could be a rationale possibility by a double sequential blockade over the RAAS even knowing that the serum potassium level could increase in patients with a previous normal kidney function with an occult injury. Developing precise communication between patients and physicians, no serious problems were observed in a long time of therapy.

Sphygmomanometers ERKA N° 7102869 & 18031068 were used to measure the blood pressure according to standard methods.

Brief phases of atrial fibrillation in the 24hs-Holter monitoring (Spacelabs) were defined as registration at least of runs of 5 or more supraventricular heartbeats without imaging of sinus or atrial rhythm, observed one or more times during the test. Considering that the atrial tissue of hypertensive patients can develop a minimum of brief phases of atrial fibrillation, it is very probable that an electrical remodeling process already established could trigger the appearance of threatening atrial arrhythmias during the natural evolution of the cardiovascular hypertensive disease. Combination therapies should be based on complementary pathophysiological mechanisms of action. The combination of ARB + ARM was used with the aim of achieving both an arterial elasticity and a normal plasma volume in order to avoid both an overload of work on the arterial-ventricular-atrial coupling and the increase in volume/pressure in the left atrium, which is the potential site where atrial fibrillation is triggered

Applanation Tonometry

The Central Haemodynamic Parameters such as Central Aortic Pressure (CAP), End-Systolic Pressure (ESP), Mean Arterial Pressure (MAP), Pulse Pressure (PP), and Augmentation Pressure (AP) were measured in mmHg. The Augmentation Index adjusted to 75 beats/minute was measured in percentage.

All data were registered by the SphygmoCor PVX device (AtCor Medical, Inc, Australia), software version 9, a validated pulse wave analysis system that employs the high-fidelity technique of non-invasive applanation tonometry of the radial artery and an appropriate computer software for pressure wave analysis with a generalized transfer function that assesses the central augmentation index as a surrogate value of the arterial wall stiffness, according to established protocols with an operator index ≥ 85%.

In addition, the differences between the observed values and the normal levels of Augmentation Index (Diff-AIx) were assessed according to normal ranges by gender and age. The Augmentation Index is calculated as a ratio of the difference between the second and the first systolic peaks (Ps) to the pulse pressure (PP). AIx = Ps 2 – Ps 1 / PP. The resultant reduction in the buffering effect on pulsatile pressure and increased amplification of pressure waves reflected from the periphery may increase end-systolic pressure in the left ventricle, causing an increase in left ventricular work and hypertrophy.

Statistical Analysis

Continuous variables were summarized by descriptive statistics. Data are expressed as mean + standard deviation. Categorical variables were summarized using counts of patients and percentages. Differences between means of both systolic and diastolic blood pressure, and central haemodynamic parameters in three groups of therapy, both sexes, were compared by Student's t-test for independent samples. Statistical tests were two-sided and the alpha level was set at 0.05. all analyses were performed using SAS software version 9.4.

Results

Mild side effects were observed in all groups. During systematic control, few cases of mild hyperkalaemia were observed that did not cause discontinuation of therapy, in a few cases the MRA dose was reduced. In rare cases of gynecomastia among men, they improved with diminished doses of MRA or changed to Eplerenone. All patients with ARB and MRA association therapy had strict control of electrolytes and renal function during all times of therapy with adequate information to patients. The patients had permanent telephone communication. The height, weight, body mass index, and waist circumference, of both sexes, were similar in the three groups of therapy (Tables 3 and 4).

Table 3

Females	Height	Weight	B M I	W C	SBP	DBP	H R
ARB+ MRA	155.8	77.2	31.7	99.2	119.0	73.7	70.9
SD	6.4	15.6	6.1	12.9	16.0	8.7	10.0
ARB	154.0	73.3	31.0	98.0	134.1	79.4	71.4
SD	6.9	14.7	5.6	13.5	23.8	10.3	10.5
ARB+Hct	154.0	77.6	32.8	101.8	143.0	83.4	73.2
SD	6.5	16.0	6.2	13.3	22.5	10.5	11.5

BMI: Body Mass Index. WC: Waist Circumference. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. HR: Heart Rate.

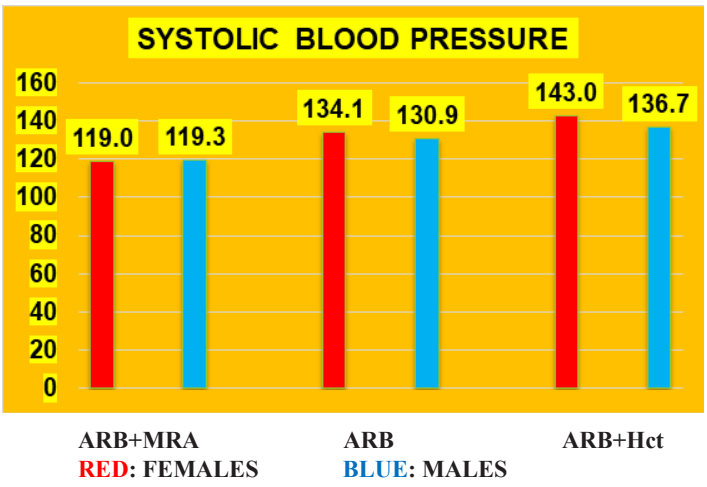
Table 4

Males	Height	Weight	B M I	W C	SBP	DBP	H R
ARB+ MRA	170.3	87.0	30.1	105.0	119.3	75.2	69.4
SD	6.9	14.3	4.5	10.6	14.8	8.6	10.9
ARB	169.6	85.1	29.5	103.5	130.9	80.6	71.0
SD	7.5	15.6	4.7	11.7	19.4	11.0	11.1
ARB + Hct	169.1	87.4	30.5	106.6	136.7	84.3	72.2
SD	7.4	15.0	4.4	10.5	17.9	11.2	12.5

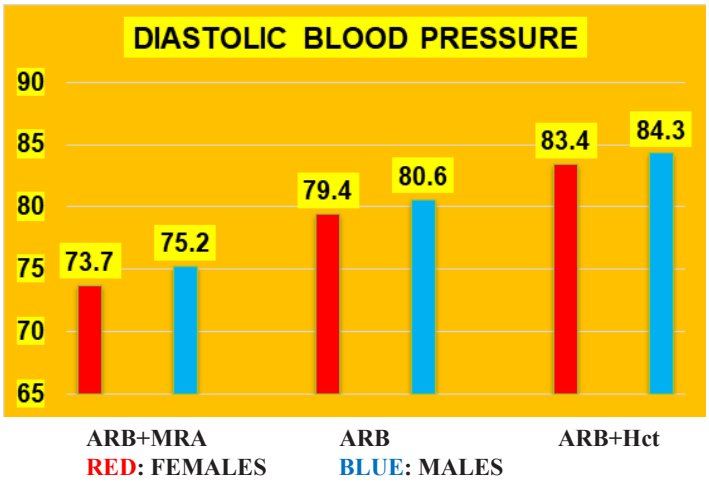
BMI: Body Mass Index. WC: Waist Circumference. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. HR: Heart Rate.

In the group ARB + MRA therapy the Systolic and Diastolic Blood Pressures of both sexes were observed to be lower, reaching optimal levels, compared to the other two therapy groups with a statistically significant difference while the heart rate was observed also lower in the ARB + MRA group compared to the MRA + Hct group with a statistically significant difference (Tables 3,4 and Graphics 1-3).

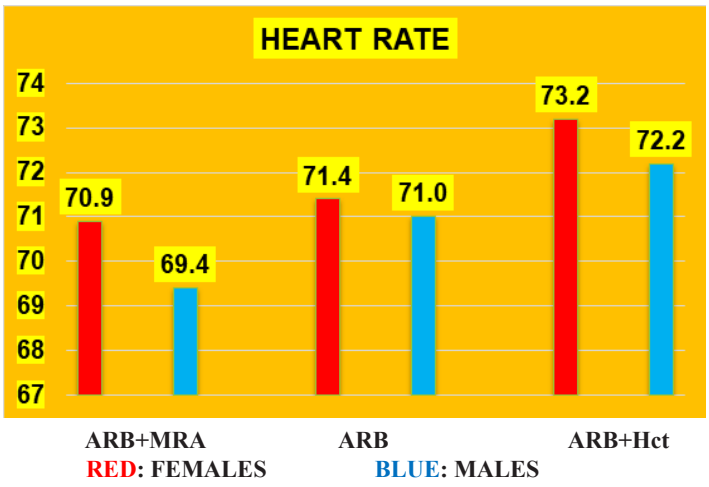
Graphic 1



Graphic 2



Graphic 3



The same results were obtained comparing the systolic and diastolic blood pressures among the ARB group versus ARB + Hct in both sexes (Tables 3 and 4). While the heart rate of the group ARB + MRA versus ARB, and ARB versus ARB + Hct in both sexes did not show significant changes (Tables 3,4).

Tables 5 and 6 show the central haemodynamic parameters of the 3 therapy groups of both sexes.

Table 5

Females	CAP	ESP	MAP	PP	AP	AIx	Diff-AIx
ARB+ MRA	110.8	102.7	90.0	36.3	10.9	27.1	-2.0
SD	15.0	12.9	10.5	11.3	5.5	7.9	7.4
ARB	125.4	115.0	99.6	45.0	15.1	30.2	0.4
SD	22.6	18.9	14.4	17.3	8.8	7.4	7.1
ARB+Hct	133.4	122.1	105.5	48.8	17.2	33.3	2.6
SD	21.1	17.2	13.7	17.0	8.9	8.5	8.6

CAP: Central Aortic Pressure. ESP: End-Systolic Pressure. MAP: Mean Arterial Pressure. PP: Pulse Pressure. AP: Augmentation Pressure. Diff-AIx: Difference Augmentation Index.

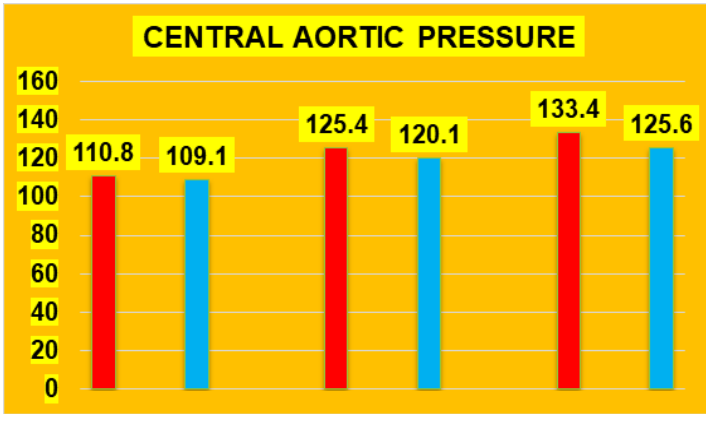
Table 6

Males	CAP	ESP	MAP	PP	AP	AIx	Diff-AIx
ARB+ MRA	109.1	101.0	90.0	33.0	7.2	17.6	-1.9
SD	13.2	11.4	9.6	10.5	4.9	7.9	6.7
ARB	120.1	110.3	97.4	38.3	9.9	21.1	2.0
SD	18.5	16.5	14.3	14.0	7.0	8.8	6.1
ARB + Hct	125.6	116.2	102.4	40.3	10.8	23.9	3.5
SD	16.5	14.1	12.6	12.9	6.6	7.9	7.1

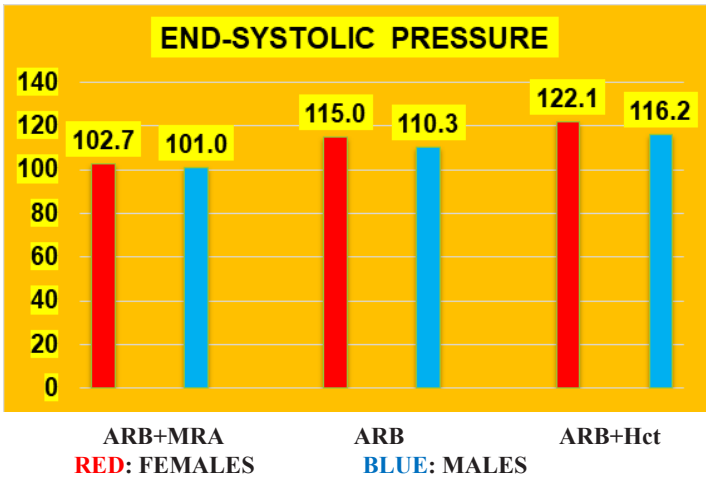
CAP: Central Aortic Pressure. ESP: End-Systolic Pressure. MAP: Mean Arterial Pressure. PP: Pulse Pressure. AP: Augmentation Pressure. Diff-AIx: Difference Augmentation Index.

Considering the central hemodynamic parameters such as CAP, ESP, MAP, PP, AP, and the difference in the augmentation index, lower values were observed in the ARB + MRA group in relation to the other two therapy groups with statistical significance (Tables 7,8 and Graphics 4-10).

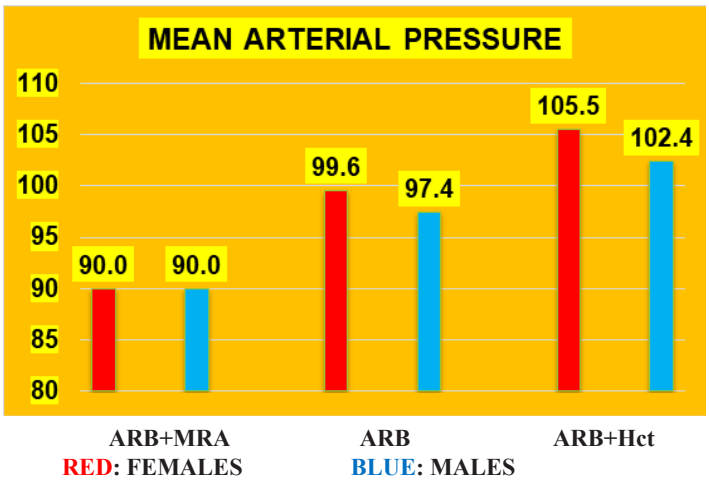
Graphic 4



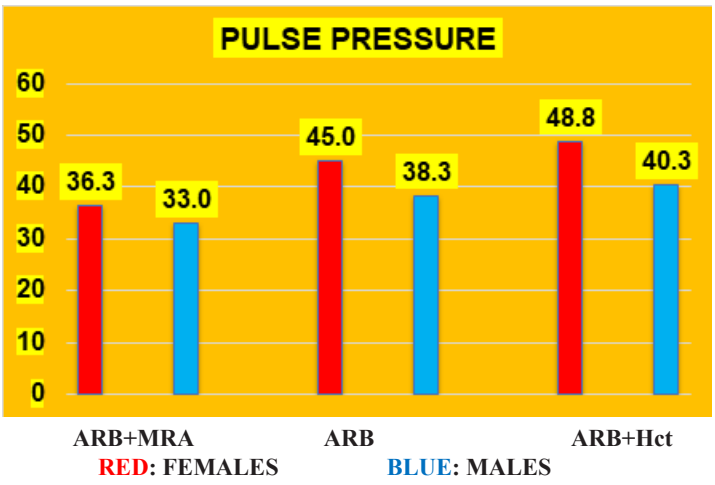
Graphic 5



Graphic 6



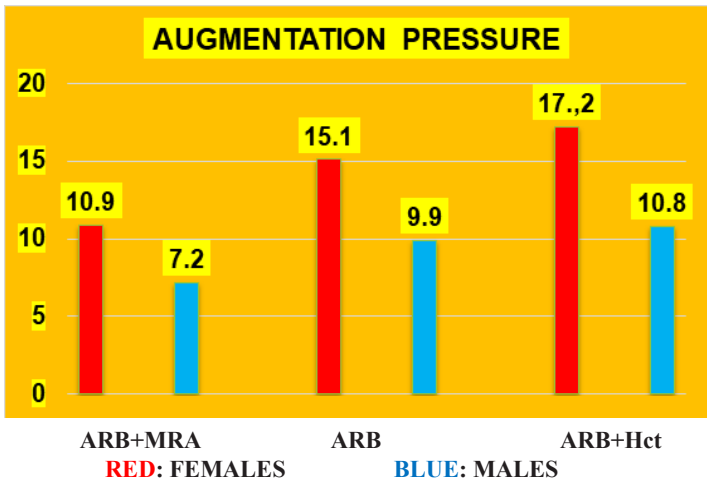
Graphic 7



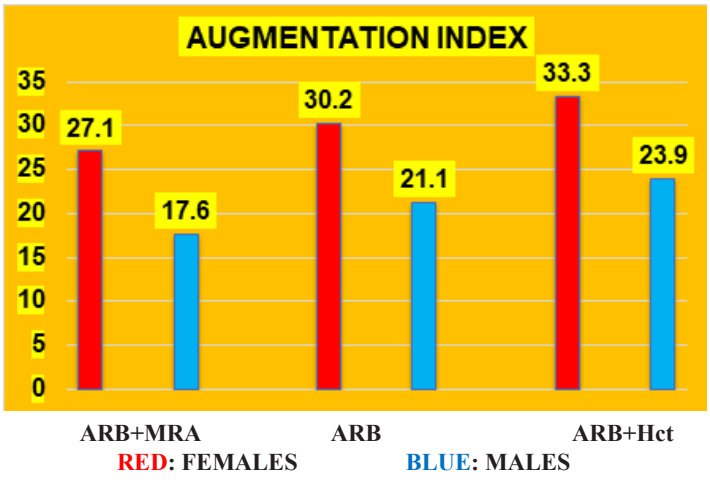
The normal end-systolic pressure should be no more than 100 mmHg, therefore the association therapeutic abovementioned show that achieves more effective results.

In the ARB group compared to the ARB + Hct group, only CAP, ESP, MAP, and the difference in the augmentation index had statistical significance (Tables 7,8).

Graphic 8



Graphic 9



Graphic 10

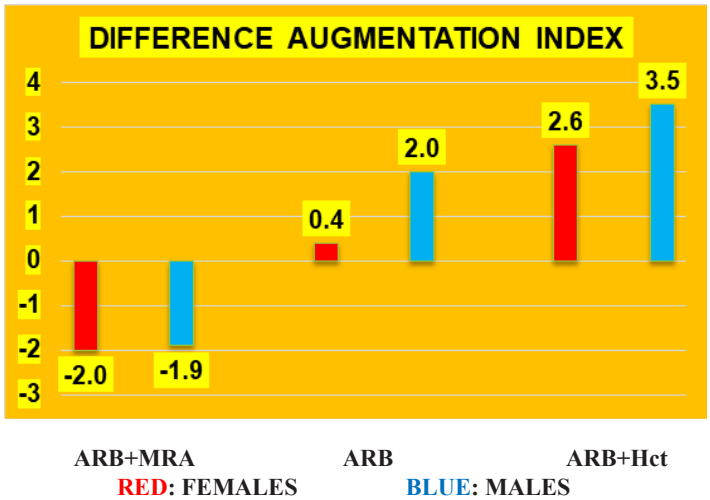


Table 7

Females	ARB+MRA vs ARB	ARB vs ARB+HCT	ARB+MRA vs ARB+Hct
CAP	<0.001	<0.001	<0.001
ESP	<0.001	<0.001	<0.001
MAP	<0.001	<0.001	<0.001
PP	<0.001	<0.01	<0.001
AP	<0.001	<0.01	<0.001
Diff-AIx	<0.001	0.01	<0.001
Heart rate	<0.5	<0.1	<0.01
SBP	<0.001	<0.001	<0.001
DBP	<0.001	<0.001	<0.001

CAP: Central Aortic Pressure. ESP: End-Systolic Pressure. MAP: Mean Arterial Pressure. PP: Pulse Pressure. AP: Augmentation Pressure. DIFF-AIx: Difference Augmentation Index. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. HR: Heart Rate.

Table 8

Males	ARB+MRA vs ARB	ARB vs ARB+HCT	ARB+MRA vs ARB+Hct
CAP	<0.001	<0.001	<0.001
ESP	<0.001	<0.001	<0.001
MAP	<0.001	<0.001	<0.001
PP	<0.001	0.1	<0.001
AP	<0.001	0.2	<0.001
Diff-AIx	<0.001	<0.03	<0.001
Heart rate	0.1	0.3	<0.02
SBP	<0.001	<0.003	<0.001
DBP	<0.001	<0.001	<0.001

CAP: Central Aortic Pressure. ESP: End-Systolic Pressure. MAP: Mean Arterial Pressure. PP: Pulse Pressure. AP: Augmentation Pressure. Diff-AIx: Difference Augmentation Index. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. HR: Heart Rate.

Increased pulse pressure, defined as the difference between systolic blood pressure and diastolic blood pressure, is a marker of arterial stiffness [56], and is an independent predictor of new-onset atrial fibrillation in hypertensive populations [57].

Tables 9 and 10 show the follow-up of each group, the history of atrial fibrillation episodes, the quantitative and the percentage of patients who were monitored with a 24-hour Holter monitor, and those who did present or did not have brief episodes of atrial fibrillation after therapy.

Table 9: FEMALES.

Groups of therapy	n	Months of therapy (Range)SD	Ex Atrial fibrillation	With Holter	Atrial fibrillation positive	Atrial fibrillation negative
ARB+ MRA	388	13 (3-60) 7	64 (16.5%)	117 (30%)	5 (4%)	112 (96%)
ARB	238	23 (3-180) 28	21 (8.8%)	27 (11%)	17 (63%)	10 (37%)
ARB+ Hct	253	31 (3-240) 34	30 (12.0%)	29 (12%)	14 (48%)	15 (52%)

Table 10: MALES

Groups of therapy	n	Months of therapy (Range) SD	Ex Atrial fibrillation	With Holter	Atrial fibrillation positive	Atrial fibrillation negative
ARB+MRA	239	12 (3-83) 11	33 (13.8%)	77 (32%)	1 (1%)	76 (99%)
ARB	215	22 (3-240) 26	13 (6.0%)	23 (11%)	8 (35%)	15 (65%)
ARB+Hct	167	30 (3-180) 31	28 (16.8%)	26 (16%)	19 (73%)	7 (27%)

ARB: Angiotensin Receptor Blockers. MRA: Mineralocorticoid Receptor Antagonists. Hct: Hydrochlorothiazide.

Table 11

Brief phases of AF	ARB+MRA vs ARB	ARB+MRAvsARB+Hct	ARB vs ARB+Hct
Females p	<0.0001	<0.0001	0.3
Males p	0.0006	<0.0001	<0.004

AF: atrial fibrillation. ARB: Angiotensin Receptor Blockers. MRA: Mineralocorticoid Receptor Antagonists. Hct: Hydrochlorothiazide.

In the tables 9 & 10 we can observe the shortest-time therapy was observed among the ARB + MRA group (women/men 13/12 months), and the largest time in the ARB + Hct group (women/men 31/30 months.

The percentage of patients that had been controlled with 24-h Holter monitoring varied between 11% to 30% among of women group, and from 11% to 32% in the men group. Patients who presented a history of episodes of atrial fibrillation before this study varied between 8.8% and 16.5% among women and 6.0% and 16.8% in the group of men. The lowest percentage of brief phases of atrial fibrillation was found in the group treated with ARB + MRA, both sexes, compared to the other two groups, with a statistically significant difference while the highest percentage was found in the group treated with ARB among women and in the group treated with ARB + Hct in the men's group. Evaluating groups ARB versus ARB + Hct, an increase of brief phases of atrial fibrillation was observed only in the second group among men with a statistically significant difference. (Tables 9-11).

The MRAs that were used were canrenone 25/50 mg (41%), potassium canreonate 25/50/100 mg (37%), spironolactone 25 mg (14%), and eplerenone 25 mg (8%) which 3% were men who have developed gynecomastia.

The longest-time treatment observed with the association of ARB + MRA in women was 60 months (5 years) and in men 83 months (~7 years), with no evidence of heart failure, hospitalization, or appearance of atrial fibrillation. Among the older, good evolution was recorded, and sporadically slight hyperkalemia was observed in the frequent controls that were resolved by reducing the dose of the MRA, and eventually furosemide 12.5 mg once or twice a day was added with good tolerance. We must consider that 420 patients were previously treated with Hct, which could have caused kidney

damage. Hyperkalaemia in older patients was interpreted as a previous sign of kidney damage as a result of hypertension treated late or not treated correctly, added to a drop in volume/pressure of the glomerular filtration because of the specific effects of the MRA. The decrease in pressure/volume due to the use of MRAs results from the intention to protect organs such as the heart and brain from hypertensive disease.

Discussion

In this study, we can see that the simultaneous and sequential action of the non-traditional association of ARB + MRA therapy to treat cardiovascular hypertension disease in patients with normal kidney function and without use of antiarrhythmic drugs manages to reduce both systolic and diastolic pressures as well as central hemodynamic parameters with efficacy and safety, improving the pressure/volume curve with the reduction of parietal stress of the arterial-ventricular-atrial coupling, and thus can significantly avoid or diminish the appearance of brief phases of atrial fibrillation.

Hypertension is a prevalent, independent, and potentially modifiable risk factor for atrial fibrillation development, it is originally a clinical disease with a high impact on the cardiovascular system then the goal of the therapy is to prevent its complications. Historically, the knowledge and the research of the relation of causal-effect between high blood pressure and atrial fibrillation begin before the year 2000. Today it has become an undeniable challenge. This tells us that the true treatment must be oriented to recognize the beginning of their causes, and not only to treat its consequences. In other words, in Medicine, how to occur in all diseases is opportune to define their origins in order to abolish their complications. High Blood Pressure starts by neurohormonal and RAAS activation producing inflammation, arterial stiffness, water and sodium retention developing increased blood pressure that achieves to the left atrium manifesting as regurgitation of the mitral valve (Box 2-B) conducing to atrial dilatation, triggering atrial extrasystoles (Box 2-D) that in turn its deleterious natural evolution, can lead to the establishment atrial fibrillation. Several epidemiological studies have reported that increased arterial stiffness predicts morbidity and mortality.

In human heart failure, cardiac aldosterone production is increased in relation to the degree of ventricular failure. About these facts, it would be possible to think that in an early stage of hypertension, increasing the mechanical work of the myocardium above the physiological threshold, could produce an incipient state of heart failure stimulating a small but sustained increase of aldosterone release, just to produce its deleterious effect. This enabled us to impute atrial structural remodelling and disturbed electrical conduction as an atrial fibrillation substrate directly to aldosterone, independent of haemodynamic changes. During the action of Aldosterone low potassium levels or clear hypokalemia is observable which reduces cellular resting membrane potential thereby favouring increased automaticity [15] and coincides with the symptom asthenia (Box 1-a) lamented frequently by hypertensive young people. Several drugs were used to decrease elevated systolic and diastolic values according to current guidelines. The cardioprotective effects of RAAS blockade have been repeatedly reported to be at least partially independent of the antihypertensive action. The ARBs are widely used in patients with arterial hypertension, however, there are several mechanisms by its efficacy can be limited, for example, aldosterone levels increase in about 50% of patients during treatment with ARBs, a phenomenon called aldosterone-breakthrough. An important number of clinical studies, have yielded contrasting results, have evaluated the role of RAAS inhibition in Atrial Fibrillation such as TRACE (Trandolapril & AF - 1999), Stop-H2 (Old & new antihypertensive drugs – 1999/2001), SOLVD (Enalapril & AF - 2003), Val-HeFT (Valsartan & AF - 2005), LIFE (ARB & AF – 2005), GISSI-AF (Valsartan & AF – 2009), ANTIPAF (ARB & AF – 2012), among others.

The study of drugs with action on atrial structural and electrophysiological changes, that constitute the substrate for the induction and maintenance of atrial fibrillation, is a new and very interesting field of challenge and research. Since 2007, evaluating patients during ARB + Hct therapy with the applanation tonometry we have been able to observe that central hemodynamic parameters are higher than those indicated as normal by this method, for example, the augmentation index was above the normal level, and the end-systolic pressure was not less than 110 mmHg. (See Tables 5 & 6). It is known that normal end-systolic pressure should be no more than 100 mmHg. Even one must be considered that the effect of the hydrochlorothiazide diuretic could be harmful to the metabolism of carbohydrates and uric acid, and the possibility be the cause of the release of aldosterone.

At the same time, we observed that diastolic blood pressure and end-systolic pressure increased due to the increase of cardiovascular volume, which could be caused by aldosterone, and both decreased during the association of ARB + MRA therapy. Using the same technique were assessed patients with ARBs alone therapy, observing that the central hemodynamic parameters did not reach the normality. Additionally, although it does not belong to this study, a personal observation with the association of ARB + CCB therapy, measuring with applanation tonometry do not obtaining efficacy results, considering that these two drugs had no action on cardiovascular volume nor a synergistic effect on arterial stiffness (Box 2–G).

Chronic kidney disease is prevalent in undiagnosed and prehypertension. Earlier identification and treatment of both these conditions may prevent or delay morbidity and mortality from chronic kidney disease. Subclinical renal suffering due to damage caused by hypertension not early diagnosed or with insufficient treatment could be evidenced during ARB + MRA therapy that produces a considerable drop in blood pressure in order to protect the heart and brain. Renal failure and secondary hyperkalemia are frequently attributed to the direct effect of the drugs when it is an indirect effect. Considering the difficult to detect hypertension early, the kidney damage produced by aldosterone during the

evolution of the hypertension disease, it could be theorized that the early MRAs therapy would be opportune. The MRAs could be as an alternative antihypertensive treatment, although not devoid of knowing adverse effects such as an excess of hyperkalaemia-associated hospitalizations and deaths following the publication of the RALES trial [58].

The MRA had received much attention in the past, but in 2013 years they are recommended as third or fourth-line therapy in hypertension. However, the MRAs demonstrated a significant and safe Blood Pressure-lowering effect compared with other active drugs in hypertensive patients, it improves diastolic dysfunction because of reduced arterial stiffness, decreased plasma volume, collagen/elastin ratio, and vascular/myocardial fibrosis. Based on a rational association of drugs that sequentially block the RAAS, such as ARB + MRA therapy, we have managed to obtain normal systolic-diastolic values and central hemodynamic parameters with the benefit of obtaining a significant decrease in the presence of brief phases of atrial fibrillation and to be able to compare the data with ARB therapy alone and the ARB combined with Hct.

The knowing undesirable effects of MRAs such as hyperkalemia, renal failure, gynecomastia, and sexual impotence in men, decided how to choose MRAs and their doses, in addition, were made the necessary clinical and laboratory controls with the aim to avoid complications. Recently, in patients with chronic kidney disease and type 2 diabetes was observed that the MRA finerenone reduced the risk of new-onset Atrial Fibrillation o Flutter [59].

The ESC 2020 guidelines recommend the restoration of the heart rhythm in order to improve the individual symptoms and the quality of life of the symptomatic patient for atrial fibrillation (class of recommendation I, level of evidence A).

Early use of MRAs as first-line antihypertensives would avoid the harmful action of aldosterone, thus preventing its serious consequences such as heart failure. At the last ISH 2022 congress, Prof Shibata Hirotaka said that it is conceivable that MRA should be included in the first-line therapy for hypertension. Maybe in a short time, a renaissance of MRA for the treatment of hypertensive disease can be expected.

BOX 4

1 - Clinical case

Name: V.F. male, 73 years old. Body mass index 34. Type 2 DM, Hyperlipidaemia IIa, Arterial Hypertension.
2006, 1° episode of Atrial Fibrillation.
2020 Echocardiogram: IVS 14 mm, Left Atrium 48 mm, Diastolic Dysfunction, minimal mitral regurgitation.
02-2021: 1st visit, TA 160/100 mmHg. Therapy: Olmesartan 20 mg, Hydrochlorothiazide 25 mg Atorvastatin 10 mg, Rivaroxaban 20 mg.
ECG: Rhythm of atrial fibrillation (RFA), persistent since 11-2020.
Non-invasive applanation tonometry: high Augmentation Index (AIx) 44%, High End-Systolic Pressure (ESP) 139 mmHg.
New therapy: Olmesartan 40 mg, Canreonate 100 mg, Rivaroxaban 20 mg, Furosemide 25 mg 2/d (only 1st week), Nebivolol 5 mg 1/2x2.
04-2021: 2nd visit. TA 130/80 mmHg. High AIx 33%, high ESP 115 mmHg.
ECG: RFA, HR 72'.
07-2021: 3rd visit. TA 112/70 mmHg. AIx: 27% slightly high, normal ESP 97 mmHg. ECG: Sinus Rhythm (SR). 24-hs Holter: SR, heart rate 53-66-103, Ventricular Extrasystoles 3, Supraventricular Extrasystoles 51, without anti-arrhythmic drugs.

2 - Clinical case

Name: GA, male. 68 years old. Height 160 cm, Weight 53 Kg. Former smoker, COPD. CCAG normal.
Long-life TA 90/60 mmHg.
Echocardiogram: diastolic dysfunction FE 25% Aortic ectasia. Aortic and mitral regurgitation mild/moderate, tricuspid regurgitation mild.
24-h Holter monitoring: complex ventricular extrasystoles.
Two weeks before the medical visit, the patient was implanted a cardioverter defibrillator to treat ventricular extrasystoles resistant to anti-arrhythmic drugs.
Creatinine 0.9, LDL-C 85, Glycemic 107.
Non-Invasive Applanation tonometry: AIx 44% very high arterial stiffness, End-Systolic pressure 79 mmHg.

Conclusions

The findings of this study suggest that with the simultaneous and sequential double blocking with ARB + MRA therapy, a non-traditional therapeutic association, both the systolic and diastolic blood pressure levels, and central hemodynamic parameters were optimized, because improves arterial stiffness, reducing the stress of the pressure/volume system into the arterial-ventricular-atrial dynamic coupling, ameliorating the whole heart electrical structure without added of antiarrhythmic drugs avoiding the presence of brief phases of atrial fibrillation. The best therapy for atrial fibrillation is Prevention, which is safer, effective, and economic.

References

1. Psaty BM, Furberg CD, Kuller LH, et al. Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality: the cardiovascular health study. Arch Intern Med. 2001; 161: 1183-1192.
2. Lewington S, Clarke R, Qizilbash N, et al. 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: 1903-1913.
3. Vasan RS, Larson MG, Leip EP, et al. Impact of the high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med. 2001; 345: 1291-1297.

4. Bryan Williams, Giuseppe Mancia, Wilko Spiering, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J. 2018; 33: 3021-3104.
5. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the Management of Arterial Hypertension: the Task Force for the Management of Arterial hypertension of the European Society of Hypertension and of the European Society of Cardiology. J Hypertens. 2007; 25: 1105-1187.
6. Liao D, Arnett DK, Tyroler HA, et al. Arterial stiffness and the development of hypertension.The ARIC study. Hypertension. 1999; 34: 201-206.
7. O'Rourke MF, Adji A. An updated clinical primer on large artery mechanics: implications on pulse waveform analysis and arterial tonometry. Curr Opin Cardiol. 2005; 20: 275-281.
8. Melenovsky V, Borlaug BA, Fetics B, et al. Estimation of central pressure augmentation using automated radial artery tonometry. J Hypertens. 2007; 25: 1403-1409.
9. Cuspidi C, Negri F, Zanchetti A. Angiotensin II receptors blockers and cardiovascular protection: focus on left ventricular hypertrophy regression and atrial fibrillation prevention. Vasc Health Risk Manag. 2008; 4: 67-73.
10. Gerdts E, Wachtell K, Omvik P, et al. Left atrial size and risk of major cardiovascular events during antihypertensive treatment: losartan intervention for endpoint reduction in hypertension trial. Hypertension. 2007; 49: 311-316.
11. Gupta S, Matulevicius SA, Ayers CR, et al. Left atrial structure and function and clinical outcomes in the general population. Eur Heart J. 2013; 34: 278-285.
12. Sardana M, Lessard D, Tsao CW, et al. Association of left atrial function Index with atrial fibrillation and cardiovascular disease: the Framingham offspring study. J Am Heart Assoc. 2018; 7: e008435.
13. Chan PH, Wong CK, Pun L, et al. Diagnostic performance of an automatic blood pressure measurement device, microlife WatchBP home A, for atrial fibrillation screening in a real-world primary care setting. BMJ Open. 2017; 7: e013685.
14. Himmelreich JCL, Lucassen WAM, Harskamp RE. CHARGE-AF in a national routine primary care electronic health records database in the Netherlands: validation for 5-year risk of atrial fibrillation and implications for patient selection in atrial fibrillation screening. Open Heart. 2021; 8: e001459.
15. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: an increasing epidemic and public health challenge. Int J Stroke. 2021; 16: 217-221.
16. Tamura T, Said S, Harris J, et al. Reverse modeling of cardiac myocyte hypertrophy in hypertension and failure by targeting of the renin-angiotensin system. Circulation. 2000; 102: 253-259.
17. Guron G, Friberg P. An intact renin-angiotensin system is a prerequisite for renal development. Journal of Hypertension. 2000; 18: 123-137.
18. Schieffer B, Schieffer E, Hilfiker-Kleiner D, et al. Expression of angiotensin II and interleukin6 in human coronary atherosclerotic plaques. Potential implications for inflammation and plaque instability. Circulation. 2000; 101: 1372-1378.
19. Brown NJ, Vaughan DE. Prothrombotic effects of angiotensin. Advances in Internal Medicine. 2000; 45: 419-429.
20. Engeli S, Negret R, Sharma AM. Physiology and pathophysiology of the adipose tissue renin-angiotensin system. Hypertension. 2000; 35: 1270-1277.
21. Koch Weser J. Nature of inotropic action of angiotensin on ventricular myocardium. Circulation Research. 1995; 16: 230-237.
22. De Mello WC. Is an intracellular renin angiotensin system involved in the control of cell communication in heart?. Journal of Cardiovascular Pharmacology. 1994; 23: 640-646.
23. De Mello WC. Renin angiotensin system and cell communication in the failing heart. Hypertension. 1996; 27: 1267-1272.
24. De Mello WC, Cherry R, Mannivanan S. Electrophysiologic and morphologic abnormalities in the failing heart; effect of enalapril on the electrical properties. Cardiac failure. 1997; 3: 53-62.
25. De Mello WC. Cell coupling and impulse propagation in the failing heart. Journal of Cardiovascular Electrophysiology. 1999; 10: 1409-1430.
26. Harada K, Sugaya T, Murakami K, et al. Angiotensin II type 1A receptor knockout mice display less left ventricular remodeling and improved survival after myocardial infarction. Circulation. 1999; 100: 2093-2999.
27. Horiuchi M, Ashita M, Dzau VJ. Recent progress in angiotensin II type 2 receptor research in the cardiovascular system. Hypertension. 1999; 33: 613-621.
28. Che G, Gao H, Hu Q, et al. Angiotensin II promotes podocyte injury by activating Arf6-Erk1/2-Nox4 signaling pathway. PLos One. 2020; 15: e0229747.
29. Virdis A, Neves MF, Amiri F, et al. Spironolactone improves angiotensin-induced vascular changes and oxidative stress. Hypertension. 2002; 40: 504-510.
30. Pitt B. "Escape" of aldosterone production in patients with left ventricular dysfunction treated with an angiotensin converting enzyme inhibitor: implications for therapy. Cardiovascular Drugs Therapy. 1995; 9: 145-149.
31. Cohn JN, Anand IS, Latini R, et al. Glazer R and for the Valsartan Heart Failure Trial Investigators. Sustained Reduction of Aldosterone in Response to the Angiotensin Receptor Blocker Valsartan in Patients with Chronic Heart Failure. Results from the Valsartan Heart Failure Trial. Circulation. 2003; 108: 1306-1309.

32. Laragh JH, Angers M, Kelly WG, et al. Hypotensive agents and pressor substances. The effect of epinephrine, norepinephrine, angiotensin II, and others on the secretory rate of aldosterone in man. JAMA. 1960; 174: 234-240.
33. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of Arterial Hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and of the European Society of Cardiology. Eur Heart J. 2013; 34: 2159-2219.
34. Madu EC, Baugh DS, Gbadebo TD, et al. Effect of ethnicity and hypertension on atrial conduction: evaluation with high-resolution P-wave signal averaging. Clin Cardiol. 2001; 24: 597-602.
35. Touyz RM, Schiffrin EL. Left ventricular hypertrophy in hypertension: its arrhythmogenic potential. Heart. 2005; 91: 250-256.
36. Lendeckel U, Dobrev D, Goette A. Aldosterone-receptor antagonism as a potential therapeutic option for atrial fibrillation. Br J Pharmacol. 2010; 159: 1581-1583.
37. MacFadyen RJ, Barr CS, Struthers AD. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. Cardiovasc Res. 1997; 35: 30-34.
38. Horisberger JD, Rossier BC. Aldosterone regulation of gene transcription leading to control of ion transport. Hypertension. 1992; 19: 221-227.
39. Weber KT. Aldosterone in congestive heart failure. New England Journal of Medicine. 2001; 345: 1689-1697.
40. Barrera-Chimal J, Girerd S, Jaisser F. Mineralocorticoid receptor antagonists and kidney disease: pathophysiological basis. Kidney Int. 2019; 96: 302-319.
41. Epstein M. Aldosterone and mineralocorticoid receptor signaling as determinants of cardiovascular and renal injury: from Hans Selye to the present. Am J Nephrol. 2021; 52: 209-216.
42. Hollenberg NK. Aldosterone in the development and progression of renal injury. Kidney Int. 2004; 66: 1-9.
43. Nishiyama A. Pathophysiological mechanisms of mineralocorticoid receptor-dependent cardiovascular and chronic kidney disease. Hypertens Res. 2019; 42: 293-300.
44. Brown NJ. Aldosterone and vascular inflammation. Hypertension. 2008; 51: 161-167.
45. Robert V, Besse S, Sabri A, et al. Differential regulation of matrix metalloproteinases associated with aging and hypertension in the rat heart. Laboratory Investigation. 1997; 76: 729-738.
46. Brilla CG, Pick R, Tan LB, et al. Remodelling of the rat right and left ventricles in experimental hypertension. Circ Res. 1990; 67: 1355-1364.
47. Brilla CG, Janicki JS, Weber KT. Impaired diastolic function and coronary reserve in genetic hypertension. Role of interstitial fibrosis and medial thickening of intramyocardial coronary arteries. Circulation Research. 1991; 69: 107-115.
48. Funder J. Mineralocorticoids and cardiac fibrosis: the decade in review. Clin Exp Pharmacol Physiol. 2001; 28: 1002-1006.
49. Rocha R, Funder JW. The pathophysiology the aldosterone in cardiovascular system. Annals of the New York Academy Science. 2002; 970: 89-100.
50. Sechi LA, Novello M, Colussi GL, et al. Relationship of plasma renin with a prothrombotic state in hypertension: relevance for organ damage. Am J Hypertens. 2008; 21: 1347-1353.
51. Ullian ME. The role of corticosteroids in the regulation of vascular tone. Cardiovasc Res. 1999; 41: 55-64.
52. Benitah JP, Vassort G. Aldosterone upregulates Ca2+ current in adult rat cardiomyocytes. Circulation Research. 1999; 85: 1139-1145.
53. Carmeliet E, Vereecke J. General description of electrical activity. In: Carmeliet E, Vereecke J, eds. Cardiac Cellular Electrophysiology. Boston, Dordrecht/London: Kluwer Academic Publishers Group. 2002: 1-7.
54. Reil JC, Hohl M, Selejan S, et al. Aldosterone promotes atrial fibrillation. Eur Heart J. 2012; 33: 2098-2108.
55. Paterno CA, Franciolini E. Essential hypertension and organ damage: the benefits of antialdosterone therapy. Italian J of Hypertension. 2011; 18: 2-8.
56. Darne B, Girerd X, Safar M, et al. Pulsatile versus steady component of blood pressure: a cross-sectional analysis and a prospective analysis on cardiovascular mortality. Hypertension. 1989; 13: 392-400.
57. Ciaroni S, Bloch A, Lemaire MC, et al. Prognostic value of 24-hour ambulatory blood pressure measurement for the onset of atrial fibrillation in treated patients with essential hypertension. Am J Cardiolm. 2004; 94: 1566-1569.
58. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with ventricular dysfunction after myocardial infarction. N Engl J Med. 2003; 348: 1309-1321.
59. Filippatos G, Bakris GL, Pitt B, et al. FIDELIO-DKD Investigators. Finerenone Reduces Risk of New-Onset Atrial Fibrillation in Patients With Chronic Kidney Disease and Type 2 Diabetes. J Am Coll Cardiol. 2021; 78: 142-152.