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Research Article

SEQUENTIAL NEPHRON BLOCKADE IN THE TREATMENT OF RESISTANT HYPERTENSION

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ABSTRACT

To report the case of a patient with resistant hypertension, in whom antihypertensive therapy was instituted by sequential nephron blockade. After an initial evaluation, the patient received as an additional prescription to the baseline regimen (losartan, chlorthalidone and amlodipine), spironolactone, furosemide and lastly amiloride, sequentially to increase the natriuretic effect. The patient performed ambulatory blood pressure monitoring (ABPM) 24 hours before and 12 weeks after starting treatment.

A review of the literature and this case report revive the discussion of the treatment of a rather complex clinical entity, that is, resistant hypertension. When sequential nephron blockade is well instituted in patients with a correct diagnosis of resistant hypertension, excluding secondary causes, pseudo-resistance and associated factors such as poor adherence to treatment, it provides satisfactory and permanent control of blood pressure with improved quality of life.

INTRODUCTION

Systemic arterial hypertension (HTN) is a complex multifactorial clinical entity characterized by permanent and chronic elevation of systolic (SBP) and diastolic blood pressure (DBP) levels above the limits established by statistical and epidemiological criteria. This pathology is associated with functional and structural changes in target organs (heart, brain, kidneys and blood vessels), particularly in resistant hypertensive patients, [1] as well as metabolic abnormalities that increase the risk of unfavorable cardiovascular outcomes. [2]

The true prevalence of this disease is unknown; it is estimated that 30% of the adult population, that is, about 1.2 billion people worldwide, has HTN. [3-5] In Brazil, 14 population studies between 1994 and 2009 showed uncontrolled BP in about 19.6% of patients. [6] Regarding treatment, the number of drugs taken and the control of hypertension, data from the ALLHAT study, which prospectively monitored 40,000 patients, showed that only 49% of the patients had blood pressure (BP) controlled with one or two drugs; the other 51% required three or more antihypertensive medications to achieve the recommended goals. [7]

Thus, the high prevalence of HTN and the low rates of control of this significant modifiable risk factor for cardiovascular diseases represents a serious public health problem. It is well known that mortality due to cardiovascular diseases progressively increases with elevations in SBP and DBP from 115 and 75 mmHg, respectively, in a continuous and independent linear manner. [8]

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Resistant hypertension (RHTN) is defined as a BP that remains above the recommended targets (< 140/90 mmHg) with the use of three antihypertensive drugs with synergistic actions at maximum tolerated doses (one preferably being a diuretic) or with the use of four or more antihypertensive drugs, even when the BP is controlled. True RH should be differentiated from pseudo-resistance, which occurs due to non-adherence to treatment, inappropriate BP measurements, use of inappropriate doses or therapeutic regimens, or the presence of the white coat effect. [9-11]

RHTN treatment is difficult either because patients fail to compliance non-pharmacological and pharmacological therapies, because of the physician's difficulty to adjust antihypertensive medication owing to genetic factors that impede the effectiveness of treatment or due to medical inertia. [12-13]

A new therapeutic approach, sequential nephron blockade, was proposed by Bobrie *et al*. in 2012. [14] When a single high-dose diuretic is administered, a functional segment of the tubule is blocked and sodium reabsorption increases in other segments in a compensatory manner. The use of low doses of different diuretics acting on different segments of the collecting tubules reduces sodium absorption and decreases the incidence of adverse effects seen with single drugs administered in high doses. Hydrochlorothiazide acts on the distal convoluted tubule, furosemide on the ascending portion of the loop of Henle, spironolactone on the collecting tubule (cortical) and amiloride in the same way, acts on the proximal portion of the collecting tubule (Figure 1).

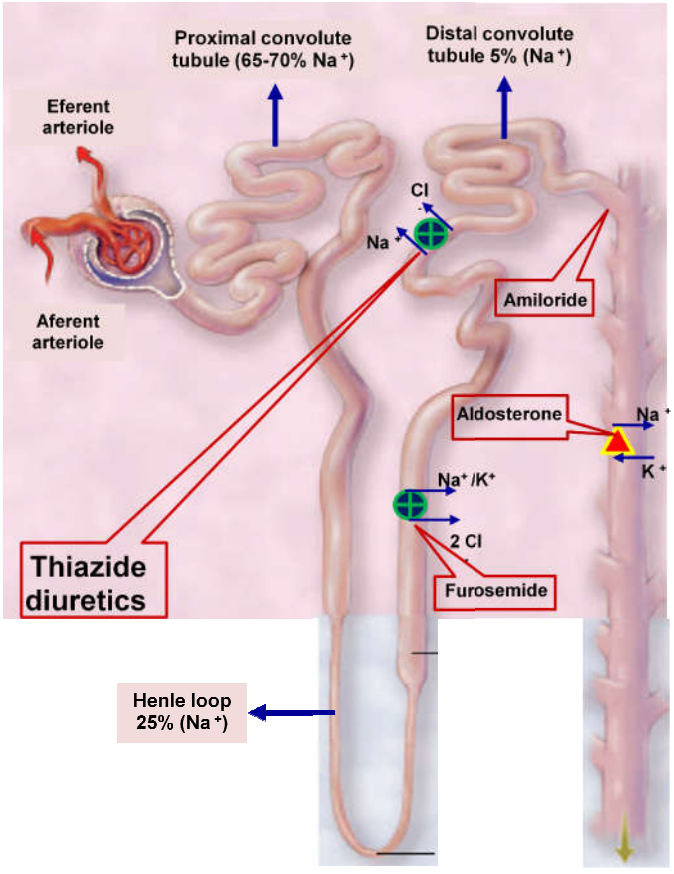

Figure 1 Mechanisms and sites of action of diuretics

In a prospective study, Bobrie *et al*. studied RHTN patients taking irbesartan (300 mg/day), hydrochlorothiazide (12.5 mg) and amlodipine (5 mg) who received the sequential addition of spironolactone (25 mg/day), furosemide (20/day), furosemide (40 mg/day) and finally amiloride (5 mg/day). In this study, 58% of the patients treated with sequential nephron blockade achieved the primary endpoint (home BP <135/85 mmHg) compared to only 20% with complete blockade of the renin-angiotensin system. This interesting scheme requires validation because this means that more than half of patients with RH can be treated satisfactorily with this therapeutic regimen.

Objective

To report the case of a patient with RHTN submitted to sequential nephron blockade who achieved adequate BP control.

METHOD

The patient was initially evaluated using the flowchart of the Brazilian Position in the Diagnosis of Resistant Hypertension of the Brazilian Society of Cardiology (Figure 2). [11]

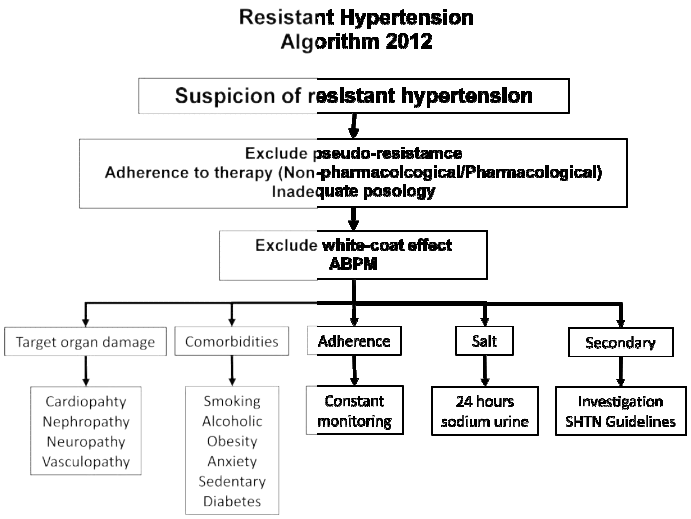

Figure 2 flowchart of the evaluation of resistant hypertension DHA-SBC 2012

The patient, who was receiving a conventional antihypertensive regimen (Losartan, Chlorthalidone and Amlodipine), was submitted to sequential nephron blockade consisting of a progressive increase in sodium depletion. Following the administration of a thiazide diuretic and blockade of the aldosterone receptor, low doses of furosemide and eventually amiloride were administered sequentially, potentiating the natriuretic effect (Figure 3).

The patient performed 24-hour ambulatory BP monitoring (ABPM) before and 12 weeks after starting treatment.

Case report

Medical history

A 53-year-old female Patient, MIF, sought out the hypertension outpatient clinic due to difficulty in controlling her BP over recent months despite of the use of three antihypertensive drugs according to medical prescription and reduced sodium intake.

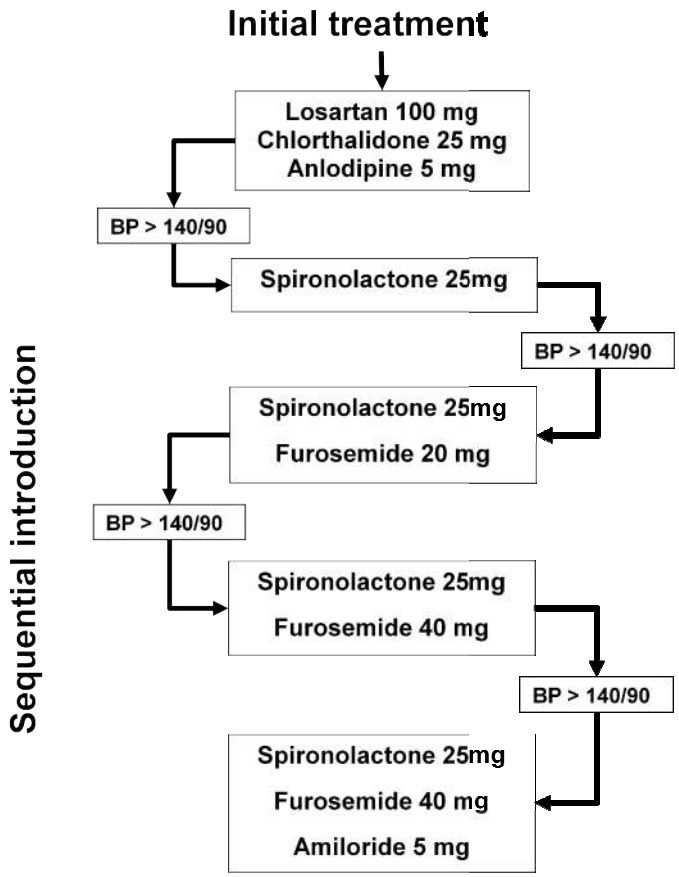

Figure 3 Sequential nephron blocking

She reported headache and dizziness usually in the morning, in addition to lower limb pain.

She denied alcoholism, but reported badly controlled diabetes mellitus, which she treated with oral hypoglycemic agents. Furthermore, she denied any history of surgeries, heart disease or stroke.

Physical examination

Good general condition with a heart rate of 72 beats per minute (bpm).
BP was measured using an automatic device (MicroMed):
1st measurement: 156 x 92 mmHg.
2nd measurement: 158 x 104 mmHg.
3rd measurement: 166 x 95 mmHg.
Carotid and extremity pulses were present and symmetrical.
Extremities without edema.
Neurological evaluation without alterations.

Diagnostic hypothesis

Resistant hypertension

Medical conduct

The patient received counseling for lifestyle changes with guidance on diet and physical activity.

Carotid Doppler ultrasound, 24-hour ABPM, ergometric test, echocardiogram, renal ultrasound with renal artery Doppler and electrocardiogram were performed.

In the re-evaluation, there was no improvement in the BP, although there was a change in lifestyle and so sequential nephron blockade was initiated.

Additional examinations

Table 1 Initial twenty-four hour ABPM

	SBP (mmHg)	DBP (mmHg)	HR (bpm)
24 hours	173	97	79
Awake	172	97	80
Sleep	176	95	77

Carotid Doppler ultrasound: Calibers and flow normal
Renal ultrasound with Doppler: Normal
Echocardiogram: Left ventricle function normal, slight hypertrophy of the left ventricle
Ergometric test: Inconclusive for ST.
Electrocardiogram: Normal

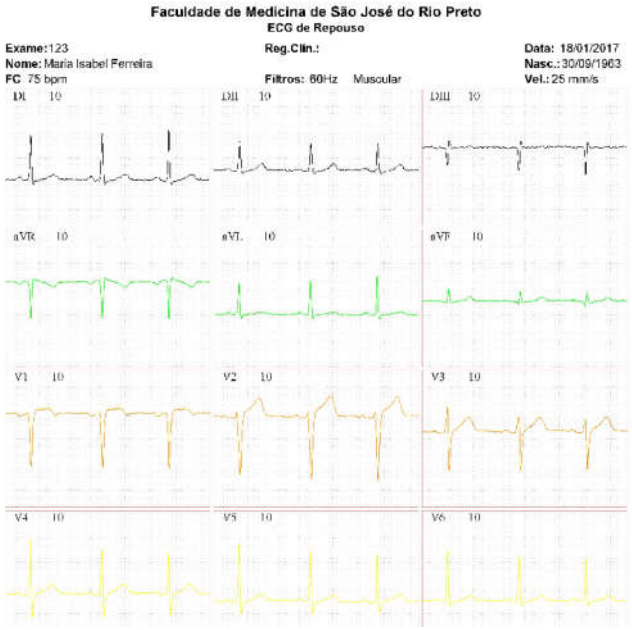

Figure 4 Electrocardiogram

Evolution and follow-up

The patient was followed up for 12 weeks with visits at 4-week intervals and sequential introduction of diuretics. Currently, her BP is controlled, but her diabetes is still uncontrolled.

She reported improvement of the lower limb pain and headache, as well as no new episodes of dizziness.

BP during her latest visit:
1st measurement: 130 x 81 mmHg.
2nd measurement: 123 x 87 mmHg.
3rd measurement: 123 x 88 mmHg.
Heart rate = 92 bpm

Table 2 Twenty-four hour ABPM at 12 weeks

	SBP (mmHg)	DBP (mmHg)	HR (bpm)
24 hours	128	78	106
Awake	126	78	110
Sleep	134	78	91

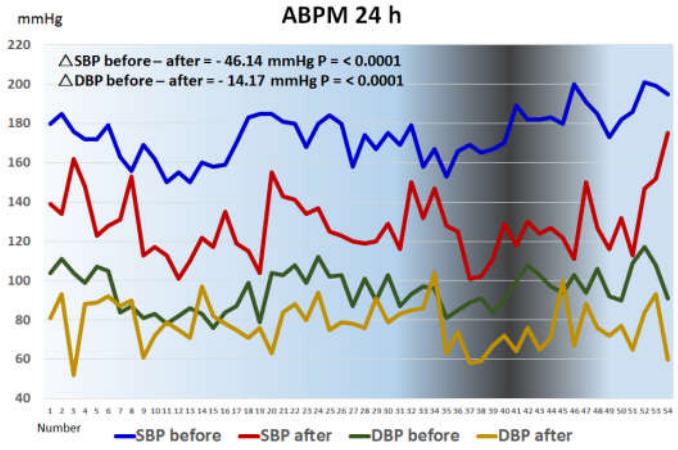

Figure 5 24-hour ABPM at 12 weeks

DISCUSSION

The knowledge that RHTN is a common entity with a prevalence of between 10 and 30% and a high risk for the occurrence of fatal and non-fatal cardiovascular events [15] has stimulated the investigation of new therapeutic regimens using drug combinations [9, 16-17]. RHTN presents a progressively increasing risk of target organ damage [1] and fatal cardiovascular outcomes. [15]

Among the mechanisms involved in the pathophysiology of RHTN are vascular smooth muscle tone and increased blood volume, an intensification of sympathetic nervous system activity, and hyperactivity of the renin-angiotensin-aldosterone system. Increased sensitivity to sodium seems to be the main factor in understanding the pathophysiology of this syndrome, not only because it combines the mechanisms described, but also because it partly explains the variability of the therapeutic response of patients with RHTN. [18-20]

An understanding of the contribution of volume to maintaining BP levels could help to adapt treatment with more effective choices to control hypertension [21]. Sequential nephron blocking causes a progressive increase in sodium depletion. [22]

One of the most common aspects in the treatment of hypertension is the low adherence to therapy especially by patients with RHTN. Reports on prevalence establish a range between 25 and 50% of resistant patients [13,23]. This fact has been associated with worse BP control [24] and consequently unfavorable outcomes. [25-26]

In the case we report herein, elevated BP levels persisted despite the optimization of the medication and the patient's apparent adherence to therapy and lifestyle changes. The adoption of sequential nephron blockade led to the progressive improvement of BP levels until normalization with consequent benefits in the quality of life of the patient.

Final considerations

A review of the literature and this case report revive the discussion of the treatment of a rather complex clinical entity, that is, RHTN. When sequential nephron blockade is performed in adequately selected patients, this approach can bring highly satisfactory and permanent results in respect to the control of BP and improvements to the quality of life of the patient.

References

1. Cuspidi, C., *et al*., *H*igh prevalence of cardiac and extracardiac target organ damage in refractory hypertension. *J Hypertens,* 2001. 19(11): p. 2063-70.
2. Kearney, P.M., *et al*., Worldwide prevalence of hypertension: a systematic review. *J Hypertens,* 2004. 22(1): p. 11-9.
3. Pereira, M., *et al*., Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. *J Hypertens*, 2009. 27(5): p. 963-75.
4. Crim, M.T., *et al*., National surveillance definitions for hypertension prevalence and control among adults. Circ Cardiovasc Qual Outcomes, 2012. 5(3): p. 343-51.
5. Nwankwo, T., *et al*., Hypertension among adults in the United States: National Health and Nutrition Examination Survey*, 2011-2012.* NCHS Data Brief, 2013(133): p. 1-8.
6. Rosario, T.M., *et al*., Prevalence, control and treatment of arterial hypertension in Nobres - MT. Arq Bras Cardiol, 2009. 93(6): p. 622-8, 672-8.
7. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*, 2002. 288(23): p. 2981-97.
8. Lewington, S., *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(9349): p. 1903-13.
9. Acelajado, M.C., *et al*., Refractory hypertension: definition, prevalence, and patient characteristics*. J Clin Hypertens (Greenwich),* 2012. 14(1): p. 7-12.
10. Calhoun, D.A., *et al*., Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation, 2008. 117(25): p. e510-26.
11. de Souza, W.S., *et al*., First Brazilian position on resistant hypertension. *Arq Bras Cardiol,* 2012. 99(1): p. 576-85.
12. Faselis, C., M. Doumas, and V. Papademetriou, Common secondary causes of resistant hypertension and rational for treatment. *Int J Hypertens,* 2011. 2011: p. 236239.
13. Tomaszewski, M., *et al*., High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart*, 2014. 100(11): p. 855-61.
14. Bobrie, G., *et al*., Sequential nephron blockade versus sequential renin-angiotensin system blockade in resistant hypertension: a prospective, randomized, open blinded endpoint study. *J Hypertens*, 2012. 30(8): p. 1656-64.
15. Daugherty, S.L., *et al*., Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation, 2012. 125(13): p. 1635-42.
16. Laurent, S., M. Schlaich, and M. Esler, New drugs, procedures, and devices for hypertension. *Lancet*, 2012. 380(9841): p. 591-600.

17. Mancia, G., *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 (ESH) and of the European Society of Cardiology *(ESC). Eur Heart J,* 2013. 34(28): p. 2159-219.
18. Pimenta, E., K.K. Gaddam, and S. Oparil, Mechanisms and treatment of resistant hypertension. *J Clin Hypertens* (Greenwich), 2008. 10(3): p. 239-44.
19. Pimenta, E. and D.A. Calhoun, Treatment of resistant hypertension. *J Hypertens*, 2010. 28(11): p. 2194-5.
20. Dudenbostel, T. and D.A. Calhoun, Use of Aldosterone Antagonists for Treatment of Uncontrolled Resistant Hypertension. *Am J Hypertens,* 2017. 30(2): p. 103-109.
21. Alvarez-Alvarez, B., *et al*., Management of resistant arterial hypertension: role of spironolactone versus double blockade of the renin-angiotensin-aldosterone system. *J Hypertens,* 2010. 28(11): p. 2329-35.
22. Knauf, H. and E. Mutschler, *S*equential nephron blockade breaks resistance to diuretics in edematous states. *J Cardiovasc Pharmacol,* 1997. 29(3): p. 367-72.
23. Jung, O., *et al*., Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens,* 2013. 31(4): p. 766-74.
24. 24.DiMatteo, M.R., Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care,* 2004. 42(3): p. 200-9.
25. Burnier, M., *et al*., Measuring, analyzing, and managing drug adherence in resistant hypertension. *Hypertension*, 2013. 62(2): p. 218-25.
26. Irvin, M.R., *et al*., Prevalence and correlates of low medication adherence in apparent treatment-resistant hypertension. *J Clin Hypertens (Greenwich),* 2012. 14(10): p. 694-700.

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