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Original article

Effects of carotid baroreceptor stimulation on retinal arteriole remodeling evaluated with adaptive optics camera in resistant hypertensive patients

Effets de la stimulation du barorécepteur carotidien sur le remodelage artériolaire rétinien évalué par l'optique adaptative chez l'hypertendu résistant

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Abstract

Background and aim. – Baroreceptor activation therapy (BAT) leads to a decrease in blood pressure (BP) in patients affected by resistant hypertension (RH) by reducing sympathetic outflow. This study aimed at evaluating the effects of BAT on RH patients' retinal arteriolar microvasculature, a territory devoid of adrenergic innervation.

Patients and methods. – Five patients defined as affected by RH after excluding secondary causes of hypertension and based on number of antihypertensive treatments, underwent the implantation of BarostimTM neoTM. Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were assessed by office and 24-hours ambulatory BP monitoring (ABPM). Adaptive Optics Camera RTX1[®] (ImagineEye, Orsay, France) was used to measure wall thickness (WT), internal diameter (ID), wall cross-sectional area (WCSA) and wall-to-lumen ratio (WLR). A cohort of 21 not-controlled hypertensive patients matched for age, gender and follow-up time, undergoing standard-antihypertensive therapy changes, was selected as a control group. SBP and DBP were assessed by office and home BP monitoring (HBPM). Evaluations were performed at baseline and after 6 months mean follow-up.

Results. – Office SBP decreased by $9.7 \pm 12.3\%$ and $29.7 \pm 12.4\%$ in standard-therapy and BAT group respectively, while office DBP decreased by $7.6 \pm 17.4\%$ and $14.8 \pm 15.7\%$. Concerning ABPM/HBPM, a mean reduction of both SBP and DBP of $7.9 \pm 11\%$ was observed for the standard-therapy while a reduction of $15.8 \pm 10.5\%$ and $15.8\% \pm 5.3\%$ was observed for SBP and DBP respectively in BAT group. While in the standard-therapy group a significant reduction in WLR (-5.9%) due to both ID increase ($+2.3\%$) and WT reduction (-5.7%) was observed, without changes in WCSA (-0.3%), RH patients had a significant reduction in WCSA (-12.1%), due to a trend in both WT and ID reduction (-6.5% and -1.7% respectively), without significant changes in WLR (-2%).

Conclusion. – While a reverse eutrophic remodeling was observed in patients undergoing a standard-antihypertensive treatment, hypotrophic changes were found in RH patients undergoing BAT. Despite the lack of adrenergic receptors on retinal vessels, chronic baroreflex stimulation may exert an effect on retinal microvasculature in RH patients by more systemic than local mechanisms.

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Keywords: Adaptive optics camera; Resistant hypertension; Retina; Arteriolar remodeling; Microcirculation

Résumé

Contexte et but de l'étude. – La thérapie de stimulation des barorécepteurs (TSB) conduit à une diminution de la pression artérielle chez l'hypertendu résistant par une réduction de la décharge du système sympathique. Cette étude a comme objectif l'évaluation des effets de la TSB sur la microcirculation rétinienne, un territoire dépourvu d'innervation adrénergique, dans l'hypertension résistante (HR).

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Patients et méthode. – Cinq patients atteints d'une HR, définie sur la base du nombre de médicaments, ayant exclu toute cause secondaire d'hypertension, ont eu l'implantation du Barostim™ *neo*™. La pression systolique (PAS) et diastolique (PAD) ont été mesurées en consultation et par MAPA. La caméra d'optique adaptative RTX1® (ImagineEye, Orsay, France) a été utilisée pour calculer l'épaisseur de paroi (WT), la lumière (ID), l'aire cross-sectionnelle (WCSA) et le rapport paroi-lumière (WLR). Vingt et un hypertendus non contrôlés appariés pour âge, sexe et temps de suivi ont été recrutés en tant que témoins, ayant une adaptation du traitement antihypertenseur. La PAS et PAD ont été mesurées en consultation et au domicile. Les évaluations tensionnelles et rétinienues ont été réalisées avant le début de la TSB où de l'adaptation du traitement, et après 6 mois de suivi.

Résultats. – Après 6 mois, on a observé une diminution moyenne de PAS en consultation de $29,7 \pm 12,4$ % et $9,7 \pm 12,3$ % chez les patients TSB et les témoins respectivement et une diminution moyenne de PAD de $14,8 \pm 15,7$ % et $7,6 \pm 17,4$ % respectivement. Une diminution moyenne de $15,8 \pm 10,5$ % pour la PAS et $15,8 \pm 5,3$ % pour la PAD a été observée pour les MAPA chez les patients TSB et chez les témoins il y a eu une diminution de PAS et PAD de $7,9 \pm 11$ % pour les automesures. Les témoins ayant eu une adaptation standardisée du traitement antihypertenseur ont montré une baisse significative du WLR ($-5,9$ %) en rapport à une augmentation de l'ID ($+2,3$ %) et à une réduction du WT ($-5,7$ %), sans modification du WCSA ($-0,3$ %). Par contre, les patients avec HR ont montré une diminution significative du WCSA ($-12,1$ %) liée à une tendance à la baisse du WT et du ID ($-6,5$ % et $-1,7$ %, respectivement), sans modification du WLR (-2 %).

Conclusion. – Un remodelage eutrophique inverse est observé chez l'hypertendu non contrôlé ayant une adaptation classique du traitement antihypertenseur, alors que l'on a un pattern de modification hypotrophique chez l'hypertendu résistant. Malgré l'absence de récepteurs adrénergique sur les vaisseaux rétinienues, une stimulation chronique du baroreflex chez l'hypertendu résistant a un effet sur la microcirculation rétinienne dont les mécanismes sont systémiques plutôt que locaux.

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Mots clés : Optique adaptative ; Microcirculation ; Hypertension résistante ; Rétine ; Remodelage artériolaire

1. Introduction

Novel strategies for a better management of resistant hypertension (RH) are being sought. Apart from pharmacologic treatment, which by definition should already be at adequate dose, novel invasive therapeutic strategies have been introduced lately, among which the baroreflex activation therapy (BAT).

RH is characterized by an increased sympathetic activity that regulates vascular smooth muscle tone by increased circulating levels of noradrenaline [1]. Simultaneously, a decrease in parasympathetic activity is found. By stimulating the afferent nerve fibers of carotid sinus baroreceptors, BAT determines a central reduction in sympathetic outflow with an increased parasympathetic activity [2].

Apart from the renovated interest in sympathetic nervous system (SNS) activity in arterial hypertension, solid evidences exist about micro- and macrovascular remodeling taking place in arterial hypertension. Effects on large vessels like an increase in wall thickness and a reduction in lumen diameter, as well as an increased stiffness have been shown early in hypertension, independently from aging effects [3].

Retinal microvasculature is the only microvascular territory directly approachable in a non-invasive fashion. Retinal arteriolar remodeling has been found to have the same characteristics of large vessel remodeling, with an increase in wall-to-lumen ratio (WLR) observed in hypertensive patients, representing an inward eutrophic remodeling. A reverse remodeling process has also been shown after the start of standard-antihypertensive therapy in newly diagnosed or non-controlled non-resistant hypertensive patients [4,5]. As retinal vessels are typically devoid of adrenergic receptors and are not directly influenced by SNS, no direct effects of acute BAT-induced BP changes are expected on retinal microcirculation. Long-term BAT effects on retinal arterioles in RH have never been analyzed.

Hence, the main objectives of our study were:

- to study the effects of BAT on retinal microcirculation in patients with RH;
- to compare them with a group of not-controlled hypertensive patients undergoing an adaptation of antihypertensive therapy.

2. Materials and methods

2.1. Study population

Between June 2015 and December 2015 in the Cardiovascular Prevention Unit of Pitié-Salpêtrière University Hospital, Paris, we consecutively enrolled 5 patients affected by RH (as defined by 2013 ESC guidelines), aged from 20 to 60 years old, without contraindication for the implantation of the device, with no recent history of cardiovascular disease.

In the same time period, 21 not-controlled not-RH patients without recent history of cardiovascular disease were recruited. They were matched for age, gender and follow-up time.

Exclusion criteria were refusal to give consent and technical obstacles to AOC assessment.

The study was carried out according to the principles outlined in the Declaration of Helsinki. Approval of the local Ethics Committee was obtained and informed consent was given by all participants.

2.2. BP measurements

Office brachial blood pressure (BP) was assessed in standard conditions in seated position during the outpatient visit using an oscillometric device simultaneously to AOC assessment.

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