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Antihypertensives and Cerebral Autoregulation: Historical Perspectives and Pathophysiological Insights

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Research Article

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ABSTRACT

Background: Cerebral Autoregulation (CA) consists of a complex mechanism characterized by the ability of the cerebral microcirculation to contract and dilate in response to variations in Blood Pressure (BP), aiming to keep Cerebral Blood Flow (CBF) constant. Systemic arterial hypertension lead to an increase in cerebrovascular resistance, which can negatively influence this vasomotor response, shifting the CA curve to the right. Thus, a slight hypotension could compromise the CBF and cause damage to brain tissue.

Objective: From a brief historical perspective, the physiological mechanisms by which Antihypertensive (ASAH) contribute to maintaining the integrity of cerebral CA will be reviewed.

Methods: The material for this review was taken mostly from electronic journals. To collect publications, PubMed e Cochrane database of systematic reviews were used.

Results: Studies have shown that the ability of CA remains unchanged in hypertensive, since ASAH is capable of promoting a variable readaptation of CA. This beneficial effect on CA has been verified over the years through experimental and clinical models and occurs through different mechanisms of action.

Conclusion: The human brain is one of the organs that most benefit from ASAH. Short- or long-term BP control does not cause brain hypo perfusion and does not compromise CA.

Keywords: Antihypertensive agents; Arterial hypertension; Blood cerebral flow; Cerebrovascular autoregulation; Cerebrovascular reactivity

INTRODUCTION

The process by which Cerebral Blood Flow (CBF) remains relatively constant despite changes in Cerebral Perfusion Pressure (CPP) and which depends on the degree to which vascular smooth muscle cells are stretched in response to changes in Blood Pressure (BP) is known as Cerebral Autoregulation (CA) or autoregulatory pressure [1]. The vascular changes induced by Systemic Arterial Hypertension (SAH), such as the thickening of the smooth muscle layer and intimal hyperplasia, promote a reduction in luminal diameter and an increase in Cerebrovascular Resistance (CVR). This pathophysiological process corresponds to one of the mechanisms by which SAH can affect microvascular reactivity, shifting the CA curve towards higher values of its lower limit, which in certain situations favors an increase in oxygen extraction fractions and reduction in CBF and can result in neuronal electrical and metabolic failure [2,3]. However, in hypertensive individuals, the resulting CBF is also influenced by the pharmacological effect of antihypertensive (ASAH) treatment on the Blood Vessels (BV) [4].The influence of ASAH on CBF can occur in a way: (a) indirectly, through BP control and reversal of adaptive structural alterations in the BV wall; (b) direct, through the action of pharmacological agents on the BV [5]. From a brief historical perspective, the physiological mechanisms by which ASAH agents contribute to maintaining the integrity of CA will be reviewed.

MATERIALS AND METHODS

Antihypertensive drugs as cerebral blood flow regulators: An interesting relationship

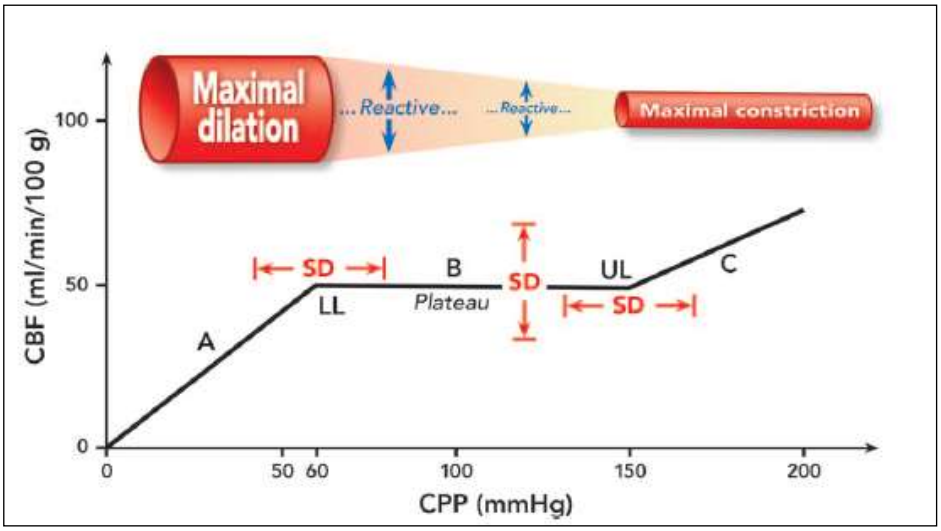
Nearly a century after William Harvey's discovery and shortly after Stephen Hales performed the first known BP measurement in history, a young professor of medicine in Berlin, Samuel Schaarschmidt, who expired prematurely in 1747, identified and suggested how to treat a definite clinical condition as “spastic constriction of the arteries”, what is now called “essential” or “primary” hypertension. However, the histological bases of Schaarschmidt's discovery were already known even before BP was measured in humans, as Richard Bright and George Johnson showed that chronic "Bright's disease" was characterized by hypertrophy and remodeling of the heart wall, arteries and arterioles [6].

This adaptive response reduces stress on the arterial wall and protects arterioles, capillaries and venules from this increase in BP. Over time, additional changes occur, including the accumulation of fibrous proteins, elastin and collagen and degeneration of smooth muscle cells [7,8]. Depending on the severity, these changes can influence several hemodynamic variables, including CA [9].

Since the studies developed by Lassen [10], it has been known that the lower limit of CA pressure is the value beyond which compensatory vasodilation becomes inadequate and CBF decreases, causing neurological symptoms. In hypertensive individuals, this “lower” pressure value is higher, due to a chronic adaptation, which shifts pressure to the right in the CA curve, causing neurological symptoms to appear earlier [11]. Therefore, even with BP at even slightly higher levels, neurological symptoms could already arise in some hypertensive individuals, making ASAH treatment apparently challenging.

In addition to the increase in transmural pressure, some intracellular signaling cascades activated by the Renin Angiotensin Aldosterone System (RAAS) may also contribute to the arterial histological changes present in hypertensive patients [12,13]. The RAAS influences the CA response through vasoconstriction secondary to the stimulation of Angiotensin 1 (AT1) receptors of smooth muscle cells, present in the cerebral microcirculation [14]. As a result, over many years, the potential therapeutic benefits have been evaluated of Angiotensin-Converting Enzyme (ACE) inhibitors or AT1 Receptor Blockers (ARB) on CA (Figure 1).

Figure 1. AR visualized as a graph of correlation between Cerebral Blood Flow (CBF) and Cerebral Perfusion Pressure (CPP). CBF remains stable between Lower Limit (LL) and Upper Limit (UL) (portion B, plateau), however, it undergoes passive modifications below the LL (part A) and above the UL (part C) according to the changes in the CPP. The limits vary (SD) between and within individuals depending on a variety of factors. The reflex response of the cerebrovascular reactivity is also illustrated.



Angiotensin-converting enzyme inhibitors and angiotensin 1 receptor blockers

Captopril was one of the first drugs to maintain CBF even when BP was reduced beyond the lower limit of CA. Using an experimental model of spontaneously hypertensive rats, Strandgaard et al. [15] evaluated the acute cerebrovascular effect of medication, applied intravenously or intraventricularly, and showed that intravenous use reduced the lower and upper limits of CA by 20% mmHg -30% mmHg and 50 mmHg-60 mmHg, respectively. The authors suggested that this response was mediated by the RAAS of the endothelial surface, mainly in the resistance vessels (where the ACE is located), rather than the brain RAAS per se, since the same results were not observed when the application was intraventricular.

Muller found that chronic antihypertensive treatment with ACE inhibitors also restored CA. The authors evaluated the effects of perindopril on mean blood pressure, CBF and CA pressure in rats with renovascular hypertension (induced by clipping of the left renal artery) and normotensive rats. Their experiment consisted of administering either ASAH or saline intraperitoneally to animals in both groups for 11 weeks. At the beginning of treatment, the hypertensive rats had Systolic Blood Pressure (SBP) between 150 mmHg -250 mmHg and the lower limit of their CA pressure was 150 mmHg. Chronic treatment led to a reduction of 36% ($p<0.05$) and 60 mmHg in SBP and lower CA level, respectively, possibly due to the reversal of adaptive arterial changes and did not compromise CBF [16].

The benefit of pharmacological intervention on the RAAS extended beyond experimental models. Moriwaki studied the effects of losartan on the CBF of hypertensive patients with a previous history of ischemic stroke, using ambulatory BP measurements and Single Photon Emission Computed Tomography (SPECT) [17]. Initially, the dose of losartan administered was 25 mg/day and titrations were performed with the aim of maintaining BP<130 mmHg × 85 mmHg. Thus, the authors monitored BP and CBF of 16 patients before starting treatment and 2 and 4 weeks later. At the end of this period, both SBP (Δ=13 mmHg) and diastolic BP (Δ=8.1 mmHg) showed significant reductions, on the other hand, CBF increased by 7.7%

($p<0.05$). Thus, in a joint evaluation, the benefit of medication can be explained both by its chronic effect on resistance arteries, improving their structure and function [17], and by its acute effect, which is similar to that of ACE inhibitors [15].

Another study that also evaluated the relationship between cerebral hemodynamics parameters and RAAS blockade, but with the use of lisinopril, did not identify a change in CBF, possibly due to the compensatory increase in the CVR index (+8.1%, $p<0.05$) in response to dilation of the large cerebral arteries, and there was also an improvement in vasodilator reserve (+24.8%, $p<0.05$) [18].

Lipsitz recorded hemodynamic parameters such a Cerebral Blood Flow Velocity (CBFV) of the middle cerebral artery, CA index and CVR in three groups of patients (normotensive [n=19]; hypertensive with SBP<140 mmHg [n=18]; hypertensive with SBP>160 mmHg [n=14]). In relation to baseline parameters this last group of patients showed a significant increase in CBFV ($p<0.003$) and reduction in CVR ($p<0.001$) after 6 months of rigorous treatment, which was not observed in the other groups, without any damage to their CA [19].

Unlike those studies that evaluated the effects of long-term treatment, in their clinical trial Zhang investigated whether ASAH could compromise CPP and dynamic CA in the early stages of treatment [20]. For this, among other parameters, CBFV and BP were measured in patients with mild (n=12) and moderate (n=9) hypertension and in healthy volunteers (n=9), both at baseline of the study and 1-2 weeks after administration of the losartan-hydrochlorothiazide combination. All the hypertensive in the sample had been newly diagnosed and was not yet using hypotensive drugs. Before treatment, CBFV were similar between the three groups and remained so at the end of the follow-up period, despite a significant reduction in BP (143 ± 7/88 ± 4 to 126 ± 12/77 ± 6 mmHg *vs.* 163 ± 11/101 ± 9 to 134 ± 17/84 ± 9, respectively, mild *vs.* moderate hypertensive groups, $p<0.05$). In view of this, the authors suggested that this maintenance of CBFV, despite the significant reduction in BP, was due to a rapid adaptation of the cerebral vasculature to protect the brain from hypo perfusion, even in the early stages of treatment.

However, the benefit of pharmacological intervention on BP, in the short or long term, goes beyond the functioning and modulation of the RAAS. SAH can also be successfully treated with a variety of other antihypertensive agents without harming CBF [21-25].

Calcium channel blockers

Regarding Calcium Channel Blockers (CCB), previous studies show that there are also different effects on CBF and CA. Ikeda [26] found that, in relation to untreated controls, hypertensive rats treated with benidipine or amlodipine had better BP control (184 ± 2 vs. 138 ± 1, $p<0.01$) and CA curve shifted towards lower limits (142 ± 4 vs. 91 ± 4, $p<0.01$), when evaluated under conditions of gradual pressure control, postulating that long-term CCB treatment would have a favorable effect for maintenance of CBF during BP reductions and that would be safe medications in patients with SAH, because CCB preserve CA. Similar results, however, were not found by Höllerhage who found that nimodipine, a first-generation CCB, compromised the CA capacity of rats with induced hypertension [27]. Among other reasons, this discrepancy may be due to the route and time of administration used and the pharmacological properties of the different CCB(s), which differently influence the CA control.

β -adrenergic receptor blockers

β -adrenergic receptor blockers are inhibitors of renin secretion, the precursor of Angiotensin II (AT2), and presumably of RAAS activity. A study that investigated the interaction between treatment with these medications and the RAAS in hypertensive humans showed a reduction in urinary aldosterone levels by 35% ($p<0.001$) and plasma levels of renin and AT2 by 80% ($p=0.002$) and 44% ($p<0.02$), respectively, confirming the high positive correlation between renin and AT2 ($R^2=0.05$, $p<0.001$) and, therefore, the potential effect of Beta Blockers (BB) on RAAS inhibition [28]. Thus, by contributing to the

suppression of the known deleterious action of RAAS hormones on the arterial wall and CVR, providing adequate BP control and minimizing transmural stress, BB can also participate in the control of the CA [29,30].However, BB do not seem to improve arterial structure. Chillon and Baumbach evaluated the effects of perindopril and propranolol on arterial remodeling in spontaneously hypertensive rats.

Diuretics

Diuretics have some vasodilating activity, either through their effect on the endothelium (release of Nitric Oxide [NO] and endothelium-derived relaxing factor) or on smooth muscle cells (opening of Ca^{2+} channels activated by K^{+} or by the desensitization of Ca^{2+} channels linked to the Rho-RhoA kinase pathway). Likewise, α-2 agonists and BB also promote peripheral vasodilation through central sympathetic block of α-1 receptors, increased availability of NO and/or intrinsic sympathomimetic activity.

RESULTS AND DISCUSSION

Thus, these agents also reduce vascular resistance by their direct action, favoring blood flow, which is especially important in the case of parenchymal or perforating arterioles, as they are naturally high-resistance vessels due to their greater tonus myogenic. And if, on the one hand, in the chronic stages of SAH, cerebral arterioles hypertrophy, on the other hand, they become more distensible, in part due to an increase in the thickness of the internal elastic lamina, which results in greater attenuation and less transmission of pulse pressure, minimizing damage related to hyperdynamia.

This adaptive response is further potentiated with the use of ASAH. In a comparative study, for a similar reduction in BP, the increase in carotid artery compliance was more pronounced with ACE inhibitors than with diuretics, which may suggest a direct effect of ACE inhibitors on arterial compliance. This same positive effect was also observed with CCB and with ARB, particularly due to its action on arterial distensibility. Therefore, as it attenuates remodeling concentric hypertrophy of the parechymal arterioles, antihypertensive treatment and long-term BP control contribute to reduce CVR and thus the lower limit of the CA curve shifts back to the left, which increases the safety margin with which the BP can go down without compromising the CBF.

CONCLUSION

The human brain is one of the organs that most benefit from ASAH. Short- or long-term BP control does not cause brain hypoperfusion, does not compromise CA and has a positive effect on some structural and functional changes in the brain. The structure of cerebral arterioles was examined in animals untreated or treated for 3 months with different doses of ACE inhibitors and/or the same dose of BB. Employing the reduction in External Arterial Diameter (EAD) as a remodeling marker, the authors observed that any dose of ACE inhibitors significantly attenuated the EAD reduction, which did not happen when BB was used. The ACE inhibitor, unlike BB, inhibits the inactivation of bradykinins, and it is not possible to exclude, therefore, that the remodeling is also related to an increase in bradykinins activity, rather than just a blockade of AT2 functions.

CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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CONSENT FOR PUBLICATION

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PATIENT AND PUBLIC INVOLVEMENT

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