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**Editorial**

# Angiotensin converting enzyme inhibitors stimulate cerebral arteriogenesis

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A potent stimulatory effect of Angiotensin-converting-enzyme inhibitors (ACEI) on cerebral arteriogenesis, involving bradykinin, was recently demonstrated by Hillmeister *et. al*, in a rat model of three-vessel occlusion.[1] The evidences presented by the authors show clearly that the collateral growth in the posterior cerebral artery occurs, resulting in blood supply and cerebral autoregulation recovery.

The brain is an organ with a high-rate metabolism supported by constant glucose and oxygen supply through blood vessels. The normal blood perfusion is involved not only in neurons and glia viability but also in their communication and activity, since it allows to reverse ion movement that underlie synaptic transmission[2]. Furthermore, cerebral constant blood flow is maintained by cerebrovascular autoregulation, compensatory hemodynamic responses in larger conductance vessels, resistant arteries and microvessels in response to changes to perfusion pressure.

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Brain ischemic event (ischemic stroke), is among the most relevant cause of death and a leading cause of disability. The important paths of collateral perfusion for the injured brain tissue are the circle of Willis, leptomeningeal anastomoses, and the microvasculature in the periinfarction area[3]. Ischemic cerebral tissue received bulk blood flow from collateral vessels that could replace the stroke-induced loss of perfusion. However, in ischemic stroke increasing additional collateral circulation is an important potential treatment[3]. Collateral circulation and new capillaries can be stablished through neovasculogenesis, which involves the development of a new vascular network by two different processes: arteriogenesis and angiogenesis[4]. Arteriogenesis takes place when preexisting collateral arterioles turn into functional collateral arteries, whereas angiogenesis is the expansion of the vascular network via sprouting in the ischemic border[3]. Improvement of local perfusion during ischemia is a rational approach to rescue brain tissue.

On the other hand, selection of antihypertensive medications that inhibit the brain angiotensin II system may result in significant end organ protection during brain ischemia. ACEI and angiotensin II AT1 receptor blockers (ARBs) are the principal pharmacological tools in the treatment of hypertension, coronary artery disease, peripheral artery disease and heart failure. Moreover, the efficiency of ACEI and ARBs in arteriogenesis modulation remains under discussion. Both ARBs and ACEI, have relevant roles in improving cerebral blood flow (CBF) in hypertensive patients. In accordance to this effect, it has been shown that ARB and ACEI pre-treatment maintain CBF and protects against cerebral ischemia in hypertensive rats[5]. However, Ito *et. al* found antiproliferative properties of ARBs that protects against hypertension-induced pathological increase in vascular wall thickness and reduced vascular capacity, after 28 days of treatment[5]. These findings could be explained by AT1 receptor stimulation-induced expression of various growth promoting factors. Although, Hillmeister *et. al*, found that the AT1 receptor blockade by ARB has no stimulatory nor an inhibitory effect on arteriogenesis. In contrast, regarding ACEI they found properties that seem to be beneficial for arteriogenesis, showing a pro-arteriogenic effect after 7 days of ACEI administration. These results were obtained measuring the cerebral collateral growth post three-vessel occlusion, by using the cerebrovascular reserve capacity technique to quantify blood flow and latex angiographies to evaluate the posterior cerebral artery vessel diameter. Moreover, the immunohistological imaging analysis showed significant increased number of smooth muscle cell layers in the growing posterior cerebral artery in ACEI treated animals.

The results obtained by Hillmeister *et. al*, can be explained by the ACEI and ARBs particularities in their mechanism of actions and the associated responses. To this respect, it is well known that

ACE modulates the Renin Angiotensin System (RAS) through angiotensin I conversion to angiotensin II. However, it is known that ACE plays a major role in activating Kallikrein-Kinine system (KKS) and its signaling pathways, via bradykinin receptors activation by bradykinin increase resulting from ACE substrate (kinase II) degradation. Indeed, ACE has a higher affinity for bradykinin than for angiotensin I, suggesting that ACEI are more effective in activating KKS than for RAS. Therefore, it is currently postulated that ACEI cardiovascular protective effect is largely mediated by bradykinin signaling. Supporting this view, Hillmeister *et. al*, when evaluating the bradykinin receptors role on cerebral arteriogenesis, found that ACEI exerts their effects presumable via B1R. Moreover, they previously demonstrated that kininogen is a highly effective biomarker for cerebral arteriogenesis in the three-vessel occlusion model, since it is highly expressed in the growing ipsilateral posterior cerebral artery [6]. To this respect, it is known that kallikrein acts on kininogen to release vasoactive kinin-related peptides, the downstream effectors of bradykinin receptor, modulating arteriogenesis and playing an important role in cardiovascular homeostasis. Kinin derivatives stimulate two bradykinin receptors (B2R) and (B1R). B1R expression increases during inflammation in several tissues but remains lower under physiological conditions, while B2R are expressed in the cardiovascular system and participate in blood pressure regulation[7]. Considering the available evidences, B1R could represent an interesting target for pharmacologic modulation since B2R undergoes rapid desensitization upon stimulation[6, 8].

Taking all together, the results presented by Hillmeister *et. al*, prompt us to revise our knowledge regarding ACEI effects and their therapeutic use. Selecting ARBs or ACEI is more than a different way to reduce the angiotensin II actions. It is possible, perhaps, to propose a combination of both to obtain a better clinical result. Facing the high risk for an ischemic stroke in hypertensive patients, or even if this event occurs, ACEI should be administered to induce arteriogenesis, recovering and improving tissue perfusion. ARBs could be indicated for brain artery remodeling prevention and CBF improvement.

In my opinion, Hillmeister *et. al*, findings are highly relevant bringing better understanding and opening new therapeutic possibilities in the treatment of brain ischemic events, in order to avoid or diminish their deleterious consequences.

## CONFLICT OF INTEREST

The author declare no conflicts of interest.

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