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Non-invasive sensor shows correlation between blood pressure and intracranial pressure

The discovery, made possible by a partnership between a research group and a startup in São Paulo state (Brazil), could lead to novel treatments for intracranial hypertension and its complications, such as stroke

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IMAGE: RESEARCHERS HAVE SIMULTANEOUSLY DEMONSTRATED THE MECHANISM LINKING HIGH BLOOD PRESSURE TO ELEVATED INTRACRANIAL PRESSURE. THE DISCOVERY CAN LEAD TO NOVEL TREATMENTS FOR INTRACRANIAL HYPERTENSION AND ITS COMPLICATIONS, SUCH AS STROKE view more ›

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Brazilian researchers have simultaneously demonstrated the mechanism linking high blood pressure to elevated intracranial pressure, validated a non-invasive intracranial pressure monitoring method, and proposed a treatment for high blood pressure that does not affect intracranial hypertension.

The study was **supported by FAPESP** and involved collaboration between researchers at São Paulo State University (UNESP) and **Brain4care**, a startup based in São Carlos. It could result in novel treatments for intracranial hypertension and its complications, including stroke. The main findings are **reported** in the journal *Hypertension*.

The researchers monitored blood pressure and intracranial pressure in rats for six weeks. “We set out to investigate what happened to intracranial pressure during the period in which the animals were becoming hypertensive. We were the first to succeed in monitoring this process non-invasively, tracking changes in the shape of the intracranial pressure curve. Our study suggests that intracranial hypertension can be

prevented if diagnosed early and treated with losartan, a drug widely used by patients with high blood pressure. It blocks the action of angiotensin II [*a naturally occurring peptide that can cause vasoconstriction and an increase in blood pressure*], which we also show to be important to control intracranial pressure," said **Eduardo Colombari**, principal investigator for the study. Colombari is a professor at UNESP's Dental School in Araraquara (FOAr).

Intracranial pressure typically increases because of a tumor, encephalitis, meningitis, aneurysm or similar problems, but the researchers showed that chronic high blood pressure can also impair cerebral compliance, leading to a rise in intracranial pressure.

In the study the researchers used vascular clips to simulate renal artery obstruction in rats, restricting the flow of blood to one kidney. The reduced irrigation triggered the pressure-controlling renin-angiotensin system, leading the kidney to release peptides, enzymes and receptors that constrict the blood vessels and raise blood pressure throughout the organism. In the third week of monitoring, when the rats were considered hypertensive, blood pressure rose even more, causing fluid retention and above all boosting cerebral blood flow.

"If the hypertension isn't treated, the disorder can worsen," Colombari said. "The rise in intracranial pressure caused by systemic hypertension impairs the brain's ability to stabilize the pressure [*cerebral autoregulation*]. This can also lead to blood-brain barrier rupture. Our study showed that the rats' blood-brain barrier was compromised in the third week. When the barrier is breached, substances and products from the renin-angiotensin system as well as pro-inflammatory substances present in the blood vessels can enter the interstitial space, where the neurons reside, especially regions important to integrative neurohumoral adjustment, such as the cardiovascular, respiratory, and renal systems, among others."

Treating intracranial hypertension

Blood-brain barrier disruption endangers areas of the nervous system that are important to control cardiovascular pressure as a whole. "How is intracranial hypertension treated now? By inducing a coma or administering a diuretic to resolve fluid retention in the skull. These methods are relatively unspecific and highly systemic. Deeper understanding of the link between high blood pressure and intracranial hypertension points to the possibility of a new field of study in pharmacology," said **Gustavo Frigieri**, Brain4care's Scientific Director.

Part of the study involved a comparison between intracranial pressure measured by the non-invasive sensor and by the invasive method. The wearable sensor developed by Brain4care has been used to measure intracranial pressure in patients with systemic impairments and has been licensed by the National Health Surveillance Agency (ANVISA) in Brazil and the Food and Drug Administration (FDA) in the United States.

Frigieri also sees plenty of opportunities for applications in basic research. "By comparing the non-invasive and invasive methods, we validated our technology for use in scientific research with small animals," he said. "It can close gaps left open owing to the aggressiveness of the conventional method, which entails a significant risk of infection because a hole is drilled in the skull to insert a sensor."

Blood flow and hormones

At the end of the study, the researchers treated the animals with losartan, reducing blood pressure and intracranial pressure. “It’s not a cause-and-effect relationship because intracranial pressure wasn’t affected when we lowered blood pressure with a vasodilator [*hydralazine*]. We observed a major impairment of the brain, and the angiotensin inhibitor [*losartan*] improved both blood pressure and cerebral blood flow,” Colombari said.

In the sixth week of the experiment, before administration of any drugs, blood pressure was high (190 per 100 mmHg) and intracranial pressure had risen significantly. The researchers discovered alterations in the intracranial pressure pulse waveforms. Each heartbeat (systolic or diastolic) pumps blood to the brain, originating the first peak (P1). A second wave (P2) correlates directly with intracranial arterial volume and cerebral compliance, important factors observed immediately before ventricular diastole.

According to the researchers, the second wave is associated with brain tissue compliance and arterial elasticity in the skull so that the energy of the first wave is absorbed. However, blood-brain barrier disruption and loss of cerebral compliance hinders control of P2, and the first wave becomes stronger than the second.

“At this point we found P2 to be higher than P1, which is the opposite of the normal situation. This is due to loss of protection by the blood-brain barrier so that the brain expands and fluid leaks into the interstitium,” Colombari said.

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