Monitoring Pressure Augmentation in Patients With Ischemic Penumbra Using Continuous Electroencephalogram: Three Cases and a Review of the Literature

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Christopher R. Newey, DO, MS¹, Vikas Gupta, MD¹,
and Agnieszka A. Ardelt, MD, PhD²

Abstract

Background: Continuous electroencephalography (CEEG) is a sensitive, noninvasive surrogate monitor of cerebral blood flow (CBF). Changes in CBF can be seen as changes in the frequencies on the CEEG. This case series suggests that increase in CEEG frequencies may be used to detect improved CBF following pressure augmentation such as with treatment of vasospasm from subarachnoid hemorrhage (SAH) or acute thrombosis from ischemic stroke. The application of this observation to clinical decision-making has not been clearly defined and requires further study. **Methods:** Case series and imaging. **Results:** We present 3 patients with ischemic penumbras either from vasospasm from SAH or thrombosis from acute ischemic stroke. All patients were monitored on CEEG and found to have lateralized slowing. During pressure augmentation, the lateralized slowing improved in frequency, which corresponded with improvement in the patients' neurological examinations. **Conclusion:** Continuous electroencephalography may be used as a noninvasive monitor to allow for individualization of pressure augmentation in cases of vasospasm from SAH or in cases of acute ischemic strokes. This customized approach may allow for less morbidity associated with pressure augmentation in patients who otherwise may have dysfunction of their intracerebral autoregulation.

Keywords

continuous electroencephalography (CEEG), pressure augmentation, vasospasm, subarachnoid hemorrhage, acute ischemic stroke

Introduction

The ischemic penumbra is an area of hypoperfused tissue that has the potential to be salvaged if reperfused in a timely fashion.^{1,2} It classically develops in acute ischemic stroke where a vessel is completely or partially occluded, and it also can be seen in cases of vasospasm from subarachnoid hemorrhage (SAH). The duration of this penumbra is not known and likely individualized. It largely depends on the patient's physiologic milieu, specifically collateral circulation, and may be blood pressure-dependent. The human body typically elevates blood pressure in response to ischemia as a protective mechanism to preserve brain tissue from the risk of ischemia. This reflex is the basis of induced pressure augmentation in the management of vasospasm from SAH and also in the management of acute thrombosis from ischemic strokes. Blood pressure reduction in cases of acute ischemic stroke or vasospasm from SAH may lead to hypoperfusion of this penumbra and, thus, extend the core ischemia.³

Current clinical practice of pressure augmentation is to increase blood pressure in a stepwise manner while closely following the clinical examination.^{4,5} Blood pressure augmentation with intravenous (IV) vasopressors is not without risks. Complications include cerebral infarction, myocardial ischemia, and cerebral edema.⁶ These complications may be even more relevant in patients with dysfunction of intracerebral autoregulation that occurs with brain injury.⁷ Individualizing blood pressure augmentation is, therefore, an appealing option. To some extent, blood pressure augmentation is

¹ Department of Neurology, University of Missouri, Columbia, MO, USA

² Department of Neurology, The University of Chicago Medicine, Chicago, IL, USA

Corresponding Author:

Christopher R. Newey, Department of Neurology, University of Missouri, 5 Hospital Drive, CE 540, Columbia, MO 65211, USA.
Email: crnewey@gmail.com

individualized already by following the neurologic examination as an end point for vasopressor escalation. However, if the patient's neurologic examination is poor or if the area at risk is noneloquent, using the clinical examination to guide therapy may be difficult. Multimodality monitoring with brain tissue oxygen tension (PbtO₂) and microdialysis have been used in identifying ischemia by the changes that occur with brain metabolism and oxygenation.⁸ These monitors, however, only allow for global assumption from focal monitoring in addition to being invasive.⁹ Having a noninvasive monitor to guide blood pressure augmentation in real time is desirable.

Continuous electroencephalography (CEEG) may be a novel method of noninvasively monitoring pressure augmentation in real time. Continuous electroencephalography is sensitive to changes in cerebral blood flow (CBF).^{10,11} As CBF decreases, the faster frequencies are lost first and the slower frequencies become more prevalent.¹⁰ Similarly, CEEG may be used to monitor for improvement in CBF of the penumbra to gauge adequacy of induced hypertension along with the clinical examination in patients with vasospasm and/or vessel occlusion/stenosis from ischemic stroke.

We present 3 cases of symptomatic hypoperfusion who were monitored on CEEG before and during pressure augmentation.

Methods

Patients

Three adult patients were identified in this retrospective case series. Patients were included if requiring pressure augmentation for treatment of their ischemic penumbra (either from vasospasm or acute thrombosis) and concurrently being monitored on CEEG prior to the start of pressure augmentation and during pressure augmentation. Ischemic penumbra was identified by computed tomography perfusion (CTP) and/or by clinical examination. Penumbra on CTP is defined as an increase in mean transit time and cerebral blood volume with a decrease in CBF. If the clinical examination was worse than would be expected by neuroimaging, a penumbra was suspected. This study was approved by the institutional review boards of University of Chicago Medical Center and University of Missouri. A waiver of informed consent was granted.

Data Acquisition

Continuous electroencephalography monitoring in these 3 cases was initiated prior to the start of pressure augmentation and was continued during pressure augmentation. The decision to start and then wean the blood pressure augmentation was made on clinical grounds, that is, based on improvement in the neurologic examination and/or neuroimaging with CTP. The goal of pressure augmentation was to increase mean arterial pressure (MAP) by 10% to 20% above the patient's known baseline MAP, while following improvement in the clinical examination. The CEEG was also reviewed for improvement

in background frequency. The duration of the pressure augmentation and serial neuroimaging was at the discretion of the attending physician in the neurological intensive care unit guided by the patient's neurological examination, not CEEG. Continuous electroencephalography was recorded using 21 electrodes placed according to the International 10-20 System by certified electroencephalography technologists and interpreted by a board-certified electroencephalographer and neurointensivist (C.R.N.).

Data Interpretation

Continuous electroencephalography was reviewed for initial frequencies prior to augmentation and during augmentation. An arbitrarily increase of ≥ 2 Hz in background frequencies on CEEG was considered significant.

Results

Cases

Patient 1. This case was of a 27-year-old male with a medical history of hypertension, tobacco use, and alcohol abuse and a recent ankle injury for which he was taking daily nonsteroidal anti-inflammatory drug. He presented to the emergency department following 2 generalized tonic-clonic seizures lasting 1 to 2 minutes each. Phenytoin was administered and no further seizure activity occurred. Postictally, he complained of a severe right frontal headache with nausea and vomiting along with neck stiffness and paresthesias in the lower extremities. His blood pressure was 173/99 mm Hg. His neurological examination was nonfocal. Computed tomography (CT) of the head showed diffuse SAH with thick blood in the basal cisterns, right more than left (Fisher grade 3; Figure 1A). Computed tomography angiography (CTA) showed a 1.5 mm $\times$ 2 mm saccular aneurysm of the right distal internal carotid artery (ICA). He was started on nicardipine drip for his hypertension. He was taken to the endovascular suite but attempts to embolize a 2.5-mm right ICA terminus aneurysm failed. He remained intubated postprocedure. Serial CT of the head showed progression of ventriculomegaly of the temporal horns of the lateral ventricles and third ventricle. He was taken to the operating room on SAH day 2 for right ICA aneurysm clipping with a right frontal external ventricular drainage placement (open to drain at 10 mm Hg). He was extubated postoperatively and was neurologically unchanged. He was maintained at a euvolemic fluid balance and permissive hypertension. On bleed day 8, he developed restlessness and mild left hemiparesis. He also developed fever (38.4°C) with leukocytosis (elevation of white blood count from 8900 to 14 100 per microliter, with negative cultures), decreasing sodium from 139 to 134 mEq/L, and elevation of transcranial Doppler mean flow velocities to 127 cm/s (right middle cerebral artery [MCA]) and 146 cm/s (right terminal ICA) with pulsatility indices of 0.61 and 0.79, respectively. He was started on hypervolemia (increasing IV fluids along with 5% albumin),

Figure 1. Computed tomography (CT) of the head. A, Subarachnoid hemorrhage (SAH) day 0 showing diffuse SAH (Fisher grade 3) with basal cistern hemorrhage burden on right more than left. Reconstruction of CT angiography (CTA) showing patent vessels without evidence of vasospasm. B, Subarachnoid hemorrhage day 8 showing evolving patchy hypodensity in the right middle cerebral artery territory (MCA). Midline hyperdensity is the external ventricular drain (EVD) tip. C, Subarachnoid hemorrhage day 12 showing the evolving hypodensity in the right MCA territory. Reconstruction of CTA showing diffuse narrowing of vessels consistent with vasospasm.

hypertonic saline, and blood pressure augmentation (increase in systolic blood pressure of 35 mm Hg, ie, ~25% increase) using continuous IV phenylephrine. Noncontrast CT of the head showed patchy evolving ischemia in the right MCA distribution (Figure 1B and C), and CTA showed segmental narrowing consistent with mild vasospasm in the affected vascular territory (Figure 1C). Computed tomography perfusion showed a relative perfusion delay in the right inferior and middle frontal gyri. Continuous electroencephalography prior to pressure augmentation showed diffuse slowing with lateralized slowing (1.5-2 Hz) over the right hemisphere, maximum centrally (Figure 2A), that improved to 3.5 to 5 Hz over the right hemisphere during blood pressure augmentation (Figure 2B). Clinically, the left-sided weakness and restlessness soon improved with the concurrent improvement of frequencies on CEEG. The CEEG was discontinued after 48 hours for neuroimaging. He remained on blood pressure augmentation for 72 hours prior to weaning while following the neurological examination. His clinical examination remained improved following pressure augmentation.

Patient 2. This was a case of a 77-year-old female with a history of hypertension, mitral valve repair, and new-onset atrial fibrillation on enoxaparin. She presented with a right hemiparesis, left gaze preference, and aphasia consistent with a left MCA syndrome. Computed tomography of the head did

not show any early ischemic changes. Computed tomography angiography showed a left M1 occlusion. She was not a candidate for IV tissue plasminogen activator (tPA) since she was fully anticoagulated with enoxaparin. Clot retrieval was performed. Postprocedure, inferior division of the MCA remained occluded. She was admitted to the neurosciences intensive care unit. On examination, she continued to have the left gaze preference, right hemiparesis, and aphasia. She was placed on CEEG. It showed generalized slowing and lateralized left hemispheric slowing of 1.5 to 2 Hz (Figure 3A). Her systolic blood pressure was then augmented by 40 mm Hg (~25% increase) using continuous IV norepinephrine. Continuous electroencephalography showed an improvement in the left hemispheric slowing to a frequency of 5 to 6 Hz (Figure 3B). Closely paralleling the change in CEEG, the examination improved with her right arm spontaneously moving and briskly withdrawing to noxious stimulation. She remained on blood pressure augmentation and CEEG for 24 hours prior to discontinuing given a change in goals of care to comfort measures.

Patient 3. This patient was a 69-year-old female with a history of hypertension, hyperlipidemia, diabetes mellitus type 2, and chronic kidney disease. She presented with chest pain and found to have 4 vessel coronary artery disease. She underwent coronary artery bypass graft surgery at an outside facility.

Figure 2. Electroencephalography (EEG) in subarachnoid hemorrhage. A, Electroencephalography before continuous phenylephrine infusion showing generalized continuous slowing and lateralized right slowing (1.5-2 Hz), maximum centrally (red box). B, Electroencephalography during continuous phenylephrine infusion showing generalized continuous slowing but return of faster frequencies in the right hemisphere. Systolic blood pressure augmented 35 mm Hg (ie, ~25% increase) above baseline. Bitemporal montage, 15 seconds epoch, sensitivity at 10 μ V. Note: The color version of this figure is available in the online version at journals.sagepub.com/home/NHO

Postprocedure, she had moderate encephalopathy, requiring noxious stimulation to awaken, global aphasia, right hemiplegia, and left gaze preference. She was transferred to a tertiary care center. There was no acute ischemic process on noncontrast head CT (Figure 4A). However, CTA showed a subocclusive thrombus in her distal M1 of the left MCA (Figure 4B). Computed tomography perfusion showed a large left MCA penumbra (Figure 5A). She was placed on CEEG which showed a generalized continuous slowing with lateralized left slowing, maximum centrally, at 4 to 5 Hz (Figure 6A). Her systolic blood pressure was stepwise augmented while monitoring CEEG. Her systolic blood pressure was eventually increased to 45 mm Hg (~35% increase) above her baseline using continuous IV norepinephrine. Her CEEG showed immediate improvement in the left lateralized slowing to a frequency of 8 to 9 Hz (Figure 6B). Twenty-four hours postaugmentation, she would open her eyes spontaneously, and they were now midline. She was following simple commands, and her right hemiplegia had improved to at least antigravity strength. The CEEG was discontinued after 48 hours. She remained on blood pressure augmentation for 72 hours prior to weaning while

following neurological examination. The penumbra had resolved on repeat CTP obtained 8 days after the first CTP and pressure augmentation (Figure 5B). Her examination remained improved following weaning of pressure augmentation.

Discussion

Continuous electroencephalography is tightly linked to cerebral metabolism making it a sensitive tool to monitor CBF. Our cases suggest a role of using CEEG, along with the neurological examination, to monitor blood pressure augmentation goals in the ischemic penumbra that develops in aneurysmal SAH-related vasospasm and acute occlusive thrombosis.

The ischemic penumbra is a well-documented phenomenon with an evolving definition.¹² Criteria have been proposed to clinically identify the ischemic penumbra including “(1) an area of hypoperfused, abnormal tissue with physiological and/or biochemical characteristics consistent with cellular dysfunction but not death, (2) the tissue is within the same ischemic territory as the infarct core, (3) demonstration that the tissue can survive or progress to pan-necrosis, and (4)

Figure 3. Electroencephalography (EEG) in left middle cerebral artery occlusion. A, Electroencephalography before continuous infusion of norepinephrine showing generalized continuous slowing and lateralized left slowing (1.5-2 Hz). Left parasagittal chain highlighted in the red box. B, Electroencephalography during continuous norepinephrine infusion showing generalized continuous slowing but return of faster frequencies (6-7 Hz) in the left hemisphere. Systolic blood pressure augmented 40 mm Hg (~25% increase) above baseline. Bitemporal montage, 10 seconds epoch, sensitivity at 7 μ V.

Figure 4. Computed tomography (CT; A) and CT angiography (CTA; B). A, Computed tomography of the head showing no acute ischemic changes. B, Computed tomography angiography showing distal left M1 of middle cerebral artery (MCA) subocclusive thrombus.

salvage of this tissue is related to better clinical outcome.”^{2,12} In other words, the ischemic penumbra is the flow threshold between reversible functional failure and irreversible

functional failure.¹³ Different techniques have been developed to image the ischemic penumbra. These include various positron emission topography biomarkers, CT perfusion, and magnetic resonance imaging (MRI) diffuse weighted imaging (DWI)/perfusion weighted imaging (PWI).¹² These techniques each have disadvantages, which may include costs and resource availability, the need for contrast, and patient contraindication (eg, pacemaker and MRI), to name a few.¹² Furthermore, these images are stagnant and do not allow for clinical response to treatment in real time. Continuous electroencephalography may be a technique that can be used in real time to highlight response to therapy as our cases suggest.

Continuous electroencephalography is tightly yoked to cerebral metabolism making it sensitive to changes in CBF. We arbitrarily chose a frequency of 2 Hz or greater as being a significant improvement in frequency on CEEG and thus a significant improvement in CBF. This frequency change corresponds to $\sim 25\%$ of the frequency until a normal posterior dominant rhythm (ie, 8 Hz) is reached in an adult patient. Delta frequencies (ie, 1-4 Hz) on CEEG estimate a CBF of 12 to 18 mL/100 g/min.^{10,11} By increasing MAP and

Figure 5. Computed tomography perfusion (CTP). A, Computed tomography perfusion before continuous infusion of norepinephrine showing penumbra of the left middle cerebral artery (MCA) territory. There is decreased cerebral blood flow (CBF), increased mean transit time (MTT), and unchanged cerebral blood volume (CBV). B, Computed tomography perfusion showing improvement in the penumbra of the left MCA during continuous norepinephrine infusion.

subsequently CBF (eg, 18-25 mL/100 g/min), CEEG frequencies would increase (eg, from delta to possibly theta waves).^{10,11} The changes in CEEG frequencies concurrent with changes in CBF are the basis of its use for intraoperative monitoring during carotid endarterectomies.¹⁰ As CBF decreases below 35 mL/100 g/min, the faster frequencies are lost first and the slower frequencies become more prevalent, representing an ischemic penumbra.¹⁰ At CBF of <8 to 10 mL/100 g/min, there is suppression of all frequencies and may eventually reflect neuronal death.¹⁰ In the animal ischemic penumbra model, mild paresis can be seen at 22 mL/100 g/min to complete paralysis at 8 mL/100 g/min.¹⁴ Evoked potentials abolish at 15 to 20 mL/100 g/min.¹⁵ Cerebral adenosine triphosphate (ATP) content and metabolic rate of glucose exhibit a threshold similar to that of the electrophysiology variables.¹⁶ ATP depletion occurs at 18.5 mL/100 g/min and spontaneous neuronal activity ceases at 18 mL/100 g/min.¹⁶ Thus, it would seem prudent to monitor patients and keep CBF above these levels.

Preserving/improving the ischemic penumbra is associated with improved/favorable neurological outcomes.¹⁷⁻²⁰ Reperfusion is the basis of the Echoplanar Imaging Thrombolytic Evaluation Trial and Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution trial using MRI mismatch to identify patients for tPA^{19,21-25} and of the Interventional Management of Stroke 3 or Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy to identify patients for clot retrieval.^{26,27} Recently, the Extending the Time for Thrombolysis in Emergency Neurological

Deficits—Intra-arterial trial was published that showed in patients with salvageable tissue on CTP, early thrombectomy with stent retrieval after IV tPA improved neurologic recovery and functional outcome compared to IV tPA alone.²⁸ In any 1 patient, it is not known how long an ischemic penumbra will persist before irreversible failure. There has been suggestion it may last as late as 24 to 48 hours after stroke onset without intervention.^{29,30} The ischemic penumbra from vasospasm from patients with SAH is fundamentally different from the penumbra in acute thrombosis in patients with ischemic stroke. The penumbra from vasospasm is a slowly developing phenomenon allowing for some patients to have radiographic vasospasm but be clinically asymptomatic. In patients who are or will become symptomatic from their ischemic penumbra, whether it is from vasospasm or thrombosis, it is important to optimize CBF, which in some patients may require blood pressure augmentation. Our cases of pressure augmentation show changes in frequency on CEEG prior to changes in clinical examination. The increase in frequencies on CEEG may reflect optimization of CBF, which may not be immediately appreciated on neurological examination. Indeed, changes on CEEG as loss of faster frequencies have been shown to occur in a case of increased intracranial pressure (ICP) up to 24 hours prior to clinical change.³¹ Overall, the ischemic penumbra—whether from vasospasm or acute thrombosis—is likely individualized and depends on the patient's prior history, rapidity of occlusion, and collateral circulation.^{3,32}

Collateral circulation is the basis of the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times trial evaluating clot retrieval and patient outcomes.³³ Patients with moderate to good collaterals, defined as filling of 50% or more of the MCA pial arterial circulation on CTA, were found to have improved functional outcomes and reduced mortality after clot retrieval.³³ In those patients who were not candidates for clot retrieval or in those patients with vasospasm from SAH, induced hypertension may be required to prevent cerebral infarction. The theory behind pressure augmentation is that blood pressure reduction in the acute symptomatic setting may lead to hypoperfusion of the ischemic penumbra and thus extend the ischemia.³ The human body typically acutely elevates blood pressure in response to the developing ischemia. Studies have shown decreased likelihood of ischemia extension with elevated blood pressure.^{20,34} A retrospective study by Koenig et al^{3,35} showed that in patients with acute ischemic stroke, induced hypertension at a goal of 10% to 20% increase in MAP above baseline (average MAP of 103 ± 14 mm Hg compared to the control group MAP of 96 ± 13 mm Hg) improved neurologic function (median National Institute of Health Stroke Scale [NIHSS] of 7 preaugmentation compared to NIHSS of 3 by discharge after augmentation).³⁵ Similar results were found in an earlier study by Hillis et al who showed that patients with pressure augmentation compared to those who did not have

Figure 6. Electroencephalography (EEG) of left middle cerebral artery occlusion. A, Electroencephalography before continuous norepinephrine infusion showing generalized continuous slowing and lateralized left slowing (4-5 Hz), maximum parasagittal chain (red box). B, Electroencephalography during continuous norepinephrine infusion showing generalized continuous slowing but return of faster frequencies (8-9 Hz) in the left hemisphere, maximum parasagittal (red box). Systolic blood pressure augmented 45 mm Hg ($\sim 35\%$ increase) above baseline. Bitemporal montage, 10 seconds epoch, sensitivity at 7 μ V.

pressure augmentation had improved NIHSS by day 3 (5.6 vs 12.3) and at weeks 6 to 8 (2.8 vs 9.7).²⁰ Likewise, neurologic outcomes are worse with a decrease in blood pressure.³⁶⁻³⁸ Animal studies have shown that normally, CBF is maintained constant with fluctuating MAPs of 50 to 150 mm Hg.³⁹ This autoregulation may be lost with structural brain injury.⁴⁰ Induced hypertension may be necessary to preserve collateral circulation. Indeed, induced hypertension has been shown to decrease frequency of transient ischemic attacks in patients with large-vessel occlusions,⁴¹ directly increase cortical perfusion as observed through craniotomy,⁴¹ and increase CBF and improve functional outcome.^{38,42-45}

Phenylephrine has been the vasopressor of choice for induced hypertension.⁶ The reason for this preference is that the cerebral circulation has low density of α -1-receptors, and it does not cause tachycardia or tachyarrhythmias that may be seen with vasopressors that have β -adrenergic activity.⁶

Norepinephrine is another frequently used vasopressor for pressure augmentation. It is a potent α 1 agonist but also has some β 1 agonist activity. It will increase MAP by increasing systemic vascular resistance and cardiac output and ultimately improve cerebral hemodynamics.³

Pressure augmentation is not without risks. Pressure augmentation improves cerebral perfusion pressure by increasing MCA peak velocities to a higher degree ipsilateral to the ischemia without affecting ICP.⁴⁶ In the brain-injured patient, cerebrovascular autoregulation is disrupted.⁷ Consequently, pressure augmentation can result in intracerebral hemorrhage, particularly in the setting of reperfusion into an infarct and cerebral edema.^{3,6,46,47} Systemic complications of pressure augmentation include increased cardiac afterload, vagally induced reflex bradycardia, myocardial ischemia, and ischemic bowel and digits.^{3,6} Consequently, blood pressure augmentation should be individualized to the patient. The

duration for induced hypertension should also be individualized. Response can be observed as early as 2 minutes up to 3 days.^{3,6} Long-term benefit may require up to 6 days of induced hypertension.⁶ Weaning the pressure augmentation is typically guided by the clinical examination. Our cases suggest how CEEG along with the neurological examination may be used to noninvasively monitor pressure augmentation induction and weaning.

In summary, having a real-time surrogate monitor of CBF is important, particularly in cases where the neurological examination is not as reliable (eg, coma or noneloquent tissue at risk). In comparison with other real-time monitors of CBF as well as tissue oxygenation and microdialysis, CEEG is noninvasive. By being a real-time, noninvasive monitor, CEEG may be an ideal tool to gauge adequacy of induced hypertension in patients with vasospasm and/or vessel occlusion/stenosis. Unlike other surrogate monitors of CBF, such as brain tissue oxygenation and microdialysis, CEEG monitors global cerebral function.^{8,9} The increase of frequency of 2 Hz or greater on CEEG was noted prior to changes in clinical examinations in all 3 cases. The use of CEEG to noninvasively monitor CBF may then allow for optimizing pressure augmentation in patients whose neurological examinations cannot be reliably followed, such as in coma. This customization of pressure augmentation may allow for therapies to be individualized to the patient. A main drawback of using CEEG in all patients is that it is affected by sedation/anesthesia, which can make it unreliable in these patients. Future studies systematically evaluating CEEG in blood pressure augmentation and patient outcomes are needed. Studies should be designed evaluating the ideal duration and eventual weaning of augmentation using CEEG and ultimately long-term outcomes in patients whose neurological examinations can and cannot be reliably followed. A study should be designed comparing patients with an ischemic penumbra to those without while monitoring CEEG changes with time. Additionally, the ideal frequency change on CEEG should be systematically identified for optimal clinical improvement following pressure augmentation.

Authors' Note

Christopher R. Newey, Vikas Gupta, and Agnieszka A. Ardelt contributed equally to the writing of the case and formatting the images.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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