

Cortical Neural Damage Associated with Cerebral Hyperperfusion after Reperfusion Therapy for Acute Ischemic Stroke: ¹²³I-iomazenil Single-photon Emission Computed Tomography Findings

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Abstract

We present an 88-year-old man with cerebral hyperperfusion (CH) after acute reperfusion therapy. He developed acute cerebral ischemia as a result of occluded middle cerebral artery that was subsequently recanalized with endovascular thrombectomy. I-123 *N*-isopropyl-*p*-iodoamphetamine single-photon emission computed tomography (SPECT) after reperfusion therapy showed increased cerebral blood flow (CBF) in brain areas that exhibited no abnormal findings on magnetic resonance imaging (MRI). Follow-up MRI did not demonstrate structural brain damage associated with CH. However, later I-123 iomazenil SPECT imaging showed a reduction in benzodiazepine receptor binding potential (BRBP) in these areas, a finding that correlates with cortical neural damage. CH is being increasingly observed after endovascular treatment for acute stroke. However, little is known about CH when not associated with cerebral hemorrhage or infarction. The role of CH after reperfusion therapy in causing brain damage remains unclear. BRBP on I-123 iomazenil SPECT images is useful to evaluate brain neural density: a reduction in cortical BRBP indicates cortical neural damage or loss. Our findings suggest that post-reperfusion hyperperfusion induces cortical neural damage even in the absence of associated brain infarction or hemorrhage on MRI. Early postoperative SPECT is recommended to detect CH after acute reperfusion therapy. CH should be considered when the recovery from stroke is unexpectedly poor for a patient.

Keywords: cerebral hyperperfusion, cortical neural damage, endovascular reperfusion therapy, iomazenil, single-photon emission computed tomography

Introduction

Cerebral hyperperfusion (CH) is a rare complication of carotid endarterectomy (CEA) and carotid artery stenting (CAS) that is being increasingly observed after endovascular treatment for acute stroke.^{1,2)} Although CH after reperfusion therapy is associated with hemorrhagic transformation,^{1,3)} little is known about it when it occurs alone and not accompanied

by cerebral hemorrhage or infarction. For example, its role in causing brain damage after reperfusion therapy remains unclear. Therefore, this study aimed to evaluate cortical neural damage in areas of CH by measuring benzodiazepine receptor binding potential (BRBP), a parameter related to brain neural density, on I-123 iomazenil single-photon emission computed tomography (SPECT).

Case Report

An 88-year-old man with a history of atrial fibrillation and right frontal lobe infarction experienced sudden onset of right-sided weakness and disturbed consciousness. His National Institute of Health stroke

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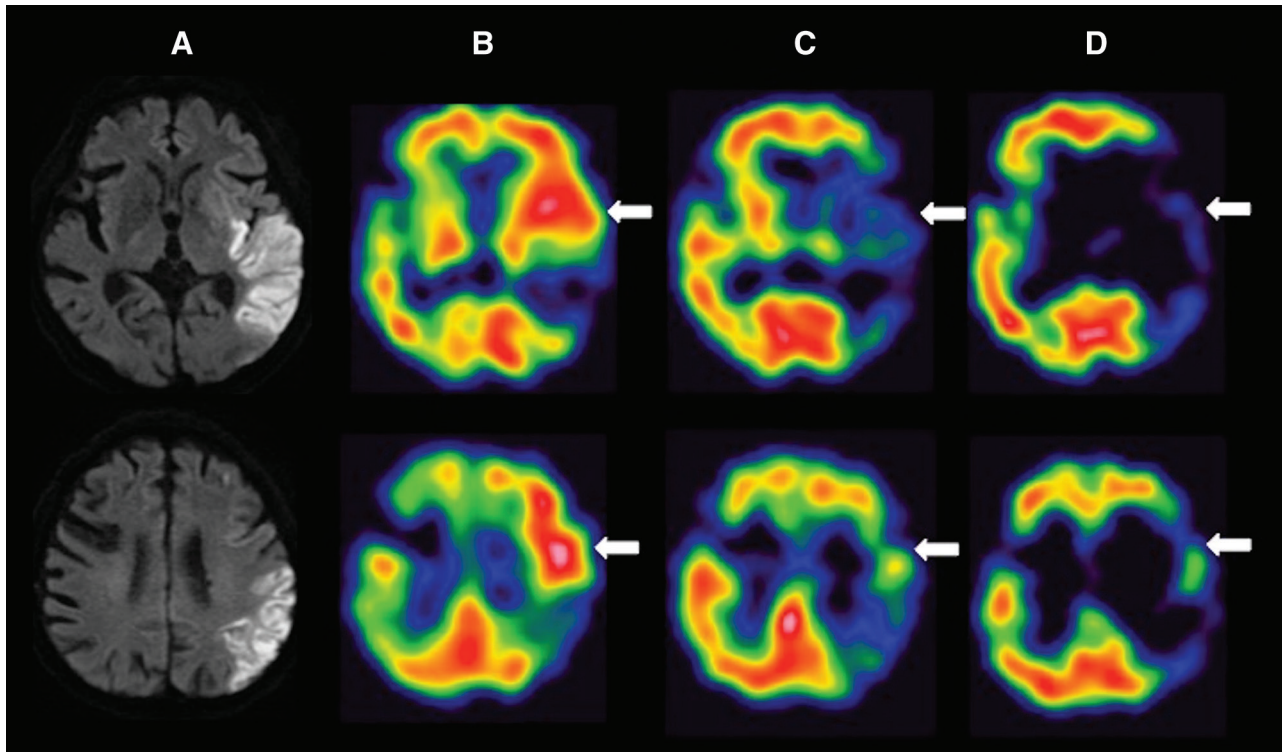


Fig. 1 (A) Postoperative diffusion-weighted MRI showed areas of high-intensity signal in the left temporal and parietal lobes, and areas of slightly high-intensity signal in the left frontal cortex and basal ganglia compared to the contralateral side. (B) ^{123}I -*N*-isopropyl-*p*-iodoamphetamine SPECT obtained 3 days after reperfusion therapy showed increased CBF in the left frontal lobe (arrows). Early (C) and late (D) ^{123}I -iomazenil SPECT obtained 1 month after reperfusion therapy showed a reduction of tracer uptake in the previously demonstrated areas of hyperperfusion (arrows) and cerebral infarction. CBF: cerebral blood flow, MRI: magnetic resonance imaging, SPECT: single-photon emission computed tomography.

scale (NIHSS) score was 33. Acute cerebral ischemia developed due to left middle cerebral artery occlusion, which successfully recanalized after thrombectomy (thrombolysis in cerebral infarction 2b). Postoperative diffusion-weighted magnetic resonance imaging (MRI) showed areas of high-intensity signal in the left temporal and parietal lobes, and areas of slightly high-intensity signal in the left frontal cortex and basal ganglia compared to the contralateral side (Fig. 1A). Three days after reperfusion therapy, brain perfusion SPECT using *N*-isopropyl-*p*- ^{123}I -iodoamphetamine showed increased cerebral blood flow (CBF) in the left frontal lobe (Fig. 1B), suggesting post-reperfusion CH. One month after thrombectomy, ^{123}I -iomazenil SPECT was performed. Immediately after injection of 167 MBq of I-123 iomazenil, scans were initiated (early images), and 180 min later, scans were also initiated (late images). Tracer uptake had decreased in the previously demonstrated areas of hyperperfusion (Figs. 1C and 1D); the corresponding area on follow-up MRI was structurally intact. Two months later, he was

transferred to another hospital with expressive aphasia and right hemiparesis (NIHSS score 28).

Discussion

CH is increasingly observed after endovascular treatment for acute stroke. Clinical features of CH following CEA and CAS are different, and those following endovascular reperfusion therapy remain unclear. Little attention has been paid to the significance of post-reperfusion therapy CH when not accompanied by cerebral hemorrhage or infarction. Therefore, we examined cortical neural damage in areas of the brain that exhibited CH after endovascular reperfusion therapy. To our knowledge, this is the first report of evaluating cortical neural damage in areas of CH after thrombectomy using I-123 iomazenil SPECT. Images obtained at 180 min after the administration of I-123 iomazenil using brain SPECT (late image) are proportional to BRBP.⁴⁻⁷ BRBP on late I-123 iomazenil SPECT images correlates with neural density in the cerebral cortex and a reduction

in cortical BRBP indicates cortical neural damage or loss.^{4–8)} Furthermore, early images on I-123 iomazenil SPECT correlate with CBF images on positron emission tomography.⁹⁾ A previous study showed that post-CEA hyperperfusion was significantly associated with postoperative hemispheric reduction of BRBP: $\geq 80\%$ of the pixels with reduced BRBP also exhibited hyperperfusion.¹⁰⁾ Another study indicated that iomazenil SPECT is useful for evaluating loss of neuronal integrity in patients with traumatic brain injury without brain MRI abnormalities,¹¹⁾ as MRI cannot always demonstrate selective neuronal loss.^{7,10–13)} The above findings and our data indicate that CH after endovascular reperfusion therapy results in postoperative cortical neural damage, even in a region where MRI abnormalities were not found.^{4,5,7,10,11)} However, cortical neural loss, and thus reduced BRBP on later I-123 iomazenil SPECT imaging, may have occurred secondary to hypoperfusion before reperfusion therapy if the hypoperfusion was significant enough to damage the cortical neurons.⁷⁾ In the previous study, post-CEA hyperperfusion was significantly associated with postoperative hemispheric reduction of BRBP; the duration of internal carotid artery clamping did not correlate.¹⁰⁾ This report supports the hypothesis that CH after reperfusion therapy may reflect cortical neural damage. Previous studies suggested that ischemic brain tissues might have undergone changes in blood–brain barrier permeability and loss of CBF autoregulation (or vasoparalysis), both of which could lead to CH after reperfusion.^{14,15)} Thus, all areas of CH were also exposed to hypoperfusion already. It is possible that both hyperperfusion and hypoperfusion cause cortical neural damage. The incidence of CH after reperfusion therapy was 48% in patients with acute ischemic stroke¹⁵⁾; not all areas of CH could lead to neural damage. Areas of CH can be divided into two groups based on pathophysiology: those with neural damage and those without neural damage. Similar to ischemia, extent of neural damage may depend on both duration and intensity of hyperperfusion. It is presumed that cytotoxic edema owing to CH results in neural damage secondarily.¹⁶⁾ In this study, early images on I-123 iomazenil SPECT demonstrated hypoperfusion in the previously demonstrated areas of CH, suggesting matched hypometabolism due to cortical neural damage. Although we could not conclude whether additional brain atrophy occurred because he already had advanced cerebral atrophy due to aging, most areas of CH with neural damage would show atrophy on chronic stage.^{16,17)} Furthermore, CH after CEA results in postoperative cortical neural loss that correlates with postoperative cognitive impairment.¹⁰⁾ Cortical neural damage associated

with post-reperfusion CH may be responsible for cognitive impairment and adversely affect stroke recovery. Thus, early postoperative SPECT is recommended to detect CH after acute reperfusion therapy.

Optimal postoperative management after endovascular thrombectomy has not been established. Recent studies reported that lowering blood pressure after this treatment might have a positive impact on clinical outcome in acute ischemic stroke patients.^{18,19)} We speculate that lowering blood pressure may prevent exacerbation of CH after recanalization, so this could prevent neural damage. Another theory on the formation of CH is damage from free radicals. Reactive oxygen species can damage the cerebrovascular endothelium, resulting in CH, which can be prevented by administration of free radical scavenger.²⁰⁾ Administration of minocycline may represent secure and effective postoperative management to prevent CH after extracranial-intracranial bypass for moyamoya disease.²¹⁾ Minocycline, a neuroprotective antibiotic agent, plays a role in blocking matrix metalloproteinase 9, which contributes to edema formation and hemorrhagic conversion after cerebral ischemia–reperfusion.²¹⁾ Those agents have a possibility to prevent CH after endovascular thrombectomy for acute ischemic stroke, but further research is needed.

In conclusion, CH after endovascular reperfusion therapy may result in cortical neural damage, even when structural brain damage is not shown on MRI. Thus, early postoperative SPECT is recommended to detect CH after acute reperfusion therapy. This phenomenon should be considered when the recovery from stroke is unexpectedly poor for a patient.

Conflicts of Interest Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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