The blood-brain barrier disruption after syncope: a dynamic contrast-enhanced magnetic resonance imaging study

A case report

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Abstract
Rationale: Using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), we demonstrated blood-brain barrier (BBB) disruption following syncope.

Patient concerns: A 45-year-old man experienced syncope with a chief complaint of syncope (duration: 1 minutes), 1 day before visiting a university hospital for examination. He had no history of medical problems and was not taking any medications. This episode was the first in his lifetime.

Diagnoses: After syncope, the patient did not have any illnesses or symptoms, such as headache, cognitive deficits, or somnolence.

Interventions: Cardiac evaluation did not reveal any abnormal findings. In addition, in conventional brain and chest computed tomography and brain MRI, no abnormal lesions were observed.

Outcomes: DCE-MRI of the patient showed bright blue colored lines within the sulci throughout the cerebral cortex. The regions of interest, including bright blue colored lines, had significantly higher Ktrans values (6.86 times higher) than those in healthy control participants. These findings are indicative of BBB disruption of the vessels in the sulci.

Lessons: Using DCE-MRI, we demonstrated BBB disruption following syncope. DCE-MRI is a useful tool for the detection of BBB disruption following syncope.

Abbreviations: BBB = brain-brain barrier, DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging.

Keywords: blood-brain barrier, brain damage, hypoxia, magnetic resonance imaging, syncope

1. Introduction
Syncope is an abrupt and transient loss of consciousness, which is induced by a drop in blood flow to the brain due to low blood pressure.[1] There are various causes of syncope, including reflex-mediated syncope, cardiac, drug-induced, psychiatric syncope, orthostatic hypotension, hypoglycemia, and cerebral ischemia.[1] Of these, reflex-mediated syncope is the most common.[2] Although syncope is short, impaired blood supply during syncope reduces the delivery of oxygen and other essential nutrients, such as glucose, to the brain.[3] We believe that this may damage brain structures and impair brain function. It has been reported that recurrent syncope episodes can lead to impairment...
of short-term memory.\textsuperscript{[4]} However, to date, the exact evidence of structural brain damage after syncope has not been reported.

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a noninvasive perfusion MRI technique that enables evaluation of damage to the microcirculatory structure and dysfunction of the brain-brain barrier (BBB).\textsuperscript{[5–8]} Several previous DCE-MRI studies have shown BBB disruption in various neurological disorders, including stroke, traumatic brain injury, dementia, mild cognitive impairment, and brain tumors.\textsuperscript{[5–8]}

In this case report, we demonstrate BBB disruption after syncope using DCE-MRI.

2. Case presentation

A 45-year-old man (occupation: medical doctor) visited a university hospital with a chief complaint of fainting 1 day back. He had no history of medical problems and was not taking any medications. He had hiked 4 to 5 times a week for 2 years. Syncope occurred while hiking on a cold winter night (temperature: \textdegree8°C). He fainted while resting for a while in a standing position after hiking at a fast speed for an hour. The witness reported that he lost consciousness for about 1 minutes, and no head strike or seizure-like activity was observed. Upon awakening from syncope, the patient had no syncope recollection. After syncope, the patient did not have any illnesses or symptoms, such as headache, cognitive deficits, or somnolence. He had no prior episodes of syncope or fainting.

At the time of examination (the day after the syncope), his blood pressure was 122/77 mm Hg, and his resting heart rate was 75 beats per minute. Electrocardiogram, 24 hours ambulatory electrocardiogram monitoring, echocardiogram, tilt table test, and exercise tolerance test showed no abnormal findings. In addition, in conventional brain and chest computed tomography and brain MRI, no abnormalities were observed. All blood test results, such as electrolyte level, hemoglobin level, erythrocyte sedimentation rate, and C-reactive protein level, were normal. In the physical examination, he did not show any neurological symptoms, including motor, sensory, or cognitive deficits.

At the time of examination, the patient had no history of medical problems and was not taking any medications. He had hiked 4 to 5 times a week for 2 years. He had no prior episodes of syncope or fainting. The patient was normoactive in all the extremities. The deep tendon reflex was normoactive in all the extremities. Based on the patient’s history and examination results, the cardiologist diagnosed the patient with transient loss of consciousness due to syncope. In addition, considering that syncope occurred during excessive physical activity at cold temperatures, the possibility of vasovagal syncope was thought to be high.

DCE scans were acquired using a 3T system (Skyra, Siemens Healthcare, Erlangen, Germany). In addition to the patient, a DCE scan was obtained from a healthy control participant (42-year-old man) who volunteered for the study. Seven pre-contrast sets of DCE-MRI (echo time = 1.92 ms, repetition time = 5.46 ms, the field of view = 230 × 135 mm\textsuperscript{2}, matrix size of 256 × 150, and slice thickness of 3 mm), followed by an additional 114 sets under the physical examination, he did not show any neurological symptoms, including motor, sensory, or cognitive deficits.

Figure 1. T2-weighted magnetic resonance imaging (MRI) and \(K_{\text{trans}}\) map of dynamic contrast-enhanced MRI of the healthy control participant (the 42-year-old man) and the patient (the 45-year-old man). (A) The T2-weighted MRI of the healthy control participant and (B) that of the patient show no abnormal finding. Ten round regions of interest (5 on each hemisphere) are depicted on the \(K_{\text{trans}}\) map of dynamic contrast-enhanced (DCE)-MRI of the healthy control participant and the patient (dotted circles in Figure c). (C) \(K_{\text{trans}}\) map of DCE-MRI of the healthy control participant shows no abnormal finding; however, (D) \(K_{\text{trans}}\) map of DCE-MRI of the patients shows bright blue colored lines throughout the overall sulcus.
patient was 6.86 times higher than that of the healthy controls, and the difference was statistically significant \((P = .003409)\).

### 3. Discussion

In the current report, using DCE-MRI, we investigated BBB disruption following syncope. On DCE-MRI of the patient, bright-blue colored lines were observed in the overall sulci, although conventional MRI did not show any remarkable lesions. These findings indicate BBB disruption. Considering that the red, light green, and bright colors in DCE-MRI indicate severe, moderate, and mild BBB disruption, respectively, the degree of BBB disruption in our patient is thought to be mild.\(^{[11]}\)

Additionally, the values of average \(K_{\text{trans}}\) in the ROIs depicted, including the bright blue colored lines, were significantly higher in the patient than in the normal control. \(K_{\text{trans}}\) is one of the most frequently used values for assessing BBB disruption, which indicates volume transfer contrast from the plasma into the extracellular extravascular space.\(^{[10]}\) Therefore, BBB disruption increased \(K_{\text{trans}}\). The increased value of \(K_{\text{trans}}\) in our patient is a quantitative finding confirming BBB disruption.

BBB disruption occurs in the vessels of the sulci throughout the cerebral cortex. This phenomenon appears to be correlated with the fact that the brain cortex is particularly vulnerable to hypoxic conditions.\(^{[12]}\) The insufficient supply of oxygen and glucose at the time of syncope inhibits ATP production. Reduced ATP levels in the brain impair the function of Na\(^+\)-K\(^+\)-ATPase and Ca\(^{2+}\)-ATPase activity in the cellular membrane.\(^{[13,14]}\) This results in the accumulation of Na\(^+\) in the endothelial cells of the BBB, which leads to endothelial cell swelling and BBB breakdown.\(^{[13,14]}\)

Vasovagal syncope is the most common type of reflex syncope induced by a sudden drop in blood pressure.\(^{[15]}\) It causes a drop in blood flow in the brain, resulting in an abrupt and transient loss of consciousness. The cause of vasovagal syncope is unclear. However, it has been suggested that vasovagal reaction is an exaggerated adaptive response for assisting hemostasis, such as lowering blood pressure and heart rate to reduce the bleeding volume, in the setting of physical trauma.\(^{[15]}\) Vasovagal syncope occurs frequently, with a lifetime incidence of more than 30%.\(^{[16]}\)

The etiology of vasovagal syncope is often unidentifiable; however, pain or emotional stress is known to be a frequent cause of vasovagal syncope.\(^{[17]}\) In addition, central hypovolemia from dehydration or upright posture increases the risk of vasovagal syncope.\(^{[15]}\) This state increases cardiac contractility, which can trigger mechanoreceptors in the cardiac ventricle that stimulate vagal afferents to the central nervous system.

Some previous studies reported that alterations in DCE-MRI parameters, such as \(K_{\text{trans}}\), were significantly correlated with poor cognitive performance following traumatic brain injury.\(^{[18,19]}\) We believe that BBB disruption can indirectly implicate microscopic injury to the brain parenchyma.\(^{[9]}\) We showed that syncope can result in BBB disruption. In our case, as the syncope duration was short, the degree of BBB disruption was mild, and specific neurological symptoms did not manifest. However, if the syncope duration is long or repetitive, the degree of BBB disruption can be moderate or severe, causing various neurological deficits.

### 4. Conclusion

In the current report, using DCE-MRI, we demonstrated BBB disruption following syncope. DCE-MRI is a useful tool for the detection of BBB disruption following syncope. This is the first report to show that BBB disruption occurs after syncope. However, our study is limited in that it was a case study. Further studies involving a larger number of participants are required.

### Author contributions

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### References

\[1\] Runser LA, Gauer RL, Houser A. Syncope: evaluation and differential diagnosis. Am Fam Physician 2017;95:303–12.

\[2\] Kidd SK, Doughty C, Goldhaber SZ. Syncope (Fainting). Circulation 2016;133:e600–2.

\[3\] Wieling W, Thijss RD, van Diijk N, et al. Symptoms and signs of syncope: a review of the link between physiology and clinical clues. Brain 2009;132:2630–42.

\[4\] Jedrzejczyk-Spaho J, Pietrucha AZ, Borowiec A, et al. Influence of the recurrent syncope episodes on neurocognitive functions in patients with vasovagal syncope. Pol Merkur Lekarski 2017;42:106–9.

\[5\] Jin T, Zhang H, Liu X, et al. Enhancement degree of brain metastases: correlation analysis between enhanced T2 FLAIR and vascular permeability parameters of dynamic contrast-enhanced MRI. Eur Radiol 2021;31:5595–604.

\[6\] Raja R, Rosenberg GA, Caprihan A. MRI measurements of blood-brain barrier function in dementia: a review of recent studies. Neuropharmacology 2018;134:259–71.

\[7\] Ulas C, Das D, Thrippleton MJ, et al. Convolutional neural networks for direct inference of pharmacokinetic parameters: application to stroke dynamic contrast-enhanced MRI. Front Neurol 2019;10:1147.

\[8\] Wang H, Golob EJ, Su MY. Vascular volume and blood-brain barrier permeability measured by dynamic contrast enhanced MRI in hippocampus and cerebellum of patients with MCI and normal controls. J Magn Reson Imaging 2006;24:695–700.

\[9\] Oh S5, Lee EH, Kim JH, et al. The use of dynamic contrast-enhanced magnetic resonance imaging for the evaluation of blood-brain barrier disruption in traumatic brain injury: what is the evidence? Brain Sci 2021;11:775.

\[10\] Keil VC, Mäddler B, Gieseke J, et al. Effects of arterial input function selection on kinetic parameters in brain dynamic contrast-enhanced MRI. Magn Reson Imaging 2016;40:192–7.

\[11\] Li KL, Zhu X, Zhao S, et al. Blood-brain barrier permeability of normal-appearing white matter in patients with vestibular schwannoma: a new hybrid approach for analysis of \(T_1\)-W DCE-MRI. J Magn Reson Imaging 2017;46:79–93.

\[12\] Huang BY, Castillo M. Hypoxic-ischemic brain injury: imaging findings from birth to adulthood. Radiographics 2008;28:417–39. quiz 617.

\[13\] Qiao M, Malvisa KL, Del Bigio MR, et al. Transient hypoxia-ischemia in rats: changes in diffusion-sensitive MR imaging findings, extracellular...
space, and Na+-K+ -adenosine triphosphatase and cytochrome oxidase activity. Radiology 2002;223:63–75.

[14] Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a “two-hit” model. Crit Care 2017;21:90.

[15] Jeanmonod R, Sahni D, Silberman M. Vasovagal Episode. [Updated 2021 Jul 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470277/.

[16] van Dijk N, Sprangers MA, Boer KR, et al. Quality of life within one year following presentation after transient loss of consciousness. Am J Cardiol 2007;100:672–6.

[17] Alboni P, Alboni M. Typical vasovagal syncope as a “defense mechanism” for the heart by contrasting sympathetic overactivity. Clin Auton Res 2017;27:253–61.

[18] Yoen H, Yoo RE, Choi SH, et al. Blood-brain barrier disruption in mild traumatic brain injury patients with postconcussion syndrome: evaluation with region-based quantification of dynamic contrast-enhanced MR imaging parameters using automatic whole-brain segmentation. Korean J Radiol 2021;22:118–30.

[19] Yoo RE, Choi SH, Oh BM, et al. Quantitative dynamic contrast-enhanced MR imaging shows widespread blood-brain barrier disruption in mild traumatic brain injury patients with post-concussion syndrome. Eur Radiol 2019;29:1308–17.