Finite element analysis of periventricular lucency in hydrocephalus: extravasation or transependymal CSF absorption?

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OBJECTIVE Periventricular lucency (PVL) is often observed in the hydrocephalic brain on CT or MRI. Earlier studies have proposed the extravasation of ventricular CSF into the periventricular white matter or transependymal CSF absorption as possible causes of PVL in hydrocephalus. However, there is insufficient evidence for either theory to be conclusive.

METHODS A finite element (FE) model of the hydrocephalic brain with detailed anatomical geometry was constructed to investigate the possible mechanism of PVL in hydrocephalus. The initiation of hydrocephalus was modeled by applying a transmante pressure gradient (TPG). The model was exposed to varying TPGs to investigate the effects of different geometrical characteristics on the distribution of PVL. The edema map was derived based on the interstitial pore pressure.

RESULTS The model simulated the main radiological features of hydrocephalus, i.e., ventriculomegaly and PVL. The degree of PVL, assessed by the pore pressure, was prominent in mild to moderate ventriculomegaly. As the degree of ventriculomegaly exceeded certain values, the pore pressure across the cerebrum became positive, thus inducing the disappearance of PVL.

CONCLUSIONS The results are in accordance with common clinical findings of PVL. The degree of ventriculomegaly significantly influences the development of PVL, but two factors were not linearly correlated. The results are indicative of the transependymal CSF absorption as a possible cause of PVL, but the extravasation theory cannot be formally rejected.

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KEY WORDS biomechanics; finite element model; transmante pressure gradient; hydrocephalus; periventricular lucency; intracranial pressure

PERIVENTRICULAR lucency (PVL) refers to the decreased attenuation level, or “blurring,” around the periventricular area on CT, or T2 hyperintensity on MRI. This radiological phenomenon is a common finding not only in various neurological or cardiovascular disorders, but also in the general elderly population.^{21,22,29,47} Although widely researched and documented, the pathogenesis and clinical significance of PVL are still inconclusive, especially for PVL associated with hydrocephalus. Hydrocephalus is defined as the excessive accumulation of CSF in the brain due to various causes. The disease is

considered to be caused by an imbalance between the formation and reabsorption of CSF, due to the disturbance in CSF dynamics.²⁸ Considering the site of the obstruction in the flow of CSF, two types of hydrocephalus have been defined: communicating and noncommunicating. PVL in hydrocephalus was first documented by Naidich et al.²⁷ PVL and enlarged ventricles are typical radiological signs of acute or noncommunicating hydrocephalus.³⁰ However, these two signs also exist in chronic or communicating hydrocephalus, although the prevalence is relatively lower.^{25,34} In either case, the pathogenesis of PVL remains

ABBREVIATIONS FE = finite element; ICP = intracranial pressure; ISF = interstitial fluid; PVL = periventricular lucency; TPG = transmante pressure gradient.

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controversial. Naidich et al. speculated that PVL may occur due to the disruption of the ventricular wall and the subsequent extravasation of CSF into the periventricular region, or the transependymal absorption of CSF. Since then, several studies have been conducted and have yielded conflicting findings.^{2,8,15,23,40,47} Currently, the dominant theory involves extravasation of CSF.³⁴ However, this assertion is still disputable, for it cannot explain why PVL seldom occurs in severe ventricular enlargement,² or why PVL occurs quite extensively around the lateral ventricles, with typically localized ventricular rupture.¹⁵

The relationship between ventricular enlargement and PVL can be investigated via finite element (FE) analysis.^{5,30} FE analysis enables the numerical approximation of the mechanical behavior of a structure under stress, by development of a 2D or 3D model that is composed of numerous, yet finite, smaller elements. The method has been increasingly used to assess the biomechanical behavior of the hydrocephalic brain since the pioneering study of Nagashima et al. in 1987.²⁶ The present study was based on the hypothesis that the changes in geometrical characteristics of the brain induced by ventricular enlargement could affect aspects of PVL. This possible relationship was investigated with a geometrically detailed FE hydrocephalic brain model, thereby providing insights into the clinical significance of PVL.

Methods

This study investigated the effects of structural characteristics of enlarged ventricles on the severity of PVL, by executing a series of FE simulations of hydrocephalus with varying degrees of ventricular enlargement. FE analysis of the hydrocephalic brain can simulate the main features of hydrocephalus, such as structural deformation, ventricular enlargement, PVL, and cerebral edema; thus, it is widely considered a valid approach to assess biomechanical changes in the hydrocephalic brain.^{5,6,9,19,26,30,39,42,43,45}

Construction of the FE Model

To minimize clinical factors that may affect the simulation results, an MR image of a young (30-year-old) healthy adult was used as a template for the model (Siemens Magnetom Trio, at Korea University Brain Imaging Center, Korea University). The use of MR imaging was approved by the local ethics committee. Although simplifying the anatomical geometry would yield decreased computational complexity, recent studies suggest that details of anatomical geometry may influence the results of FE simulations.^{7,14} We decided that because the present study was highly oriented toward the structural features of the brain, geometrical details should be implemented. The FE model used in this study was designed to have detailed geometrical information for the sulci, gray and white matter, falx cerebri, and cranium. ScanIP (Simpleware Software Ltd.) enabled segmentation of the region of interest. ScanFe (Simpleware Software Ltd.) and Hypermesh (Altair Engineering) were used for the fine meshing (i.e., the transformation of the structure into numerous small elements). The actual analysis of the model was performed with ABAQUS (Abaqus/Standard, Dassault Systèmes). As

the obtained geometry was symmetric, only one half of the slice was used for analysis (Fig. 1).

Initiation of Ventricular Enlargement

The mechanism underlying ventricular enlargement has been extensively researched. The increase in intracranial pressure (ICP), ICP pulse pressure, changes in brain tissues characterized by a nonlinear constitutive relationship, or the transmante pressure gradient (TPG) are proposed causes of ventricular deformation.³¹ The intracranial system is encased by an effectively rigid body, and the brain itself is based on a pore structure fully saturated by incompressible fluid, which makes it nearly incompressible. Although the ventricles are perceived as expanding (or collapsing) entities, they are, in fact, not independent structures and are only spatial concepts.⁴⁴ Therefore, the enlargement of ventricles should be understood as a volumetric reduction of brain parenchyma.^{10,11} This volumetric reduction is only possible by the outflow of interstitial fluid (ISF), which makes the change in the TPG the most plausible explanation for the ventricular enlargement in hydrocephalus. The change in the TPG can be due either to the increased ventricular CSF pressure or the abnormal absorption of CSF.⁴ Conventionally, the TPG is defined as the pressure difference between the ventricles and cerebral convexity. Given that this study embraces the idea of capillary absorption of CSF/ISF,¹² the TPG was defined as the pressure difference between capillary blood pressure and ventricular fluid pressure (Fig. 1 left).

Material Properties and Biomechanical Assessment of Simulations

The tissue property of the parenchyma is modeled as isotropic, poro-hyperelastic material with 2 phases, consisting of a solid hyperelastic matrix (i.e., porous solid exhibiting nonlinear stress-strain relationship), saturated with fluid.^{3,35} In contrast, the falx cerebri and the cranium are modeled as linear elastic materials. The interface between structures includes the capillaries on the outer layer of the cerebral cortex, as well as the ependymal and dura mater. The details of the material properties in the FE model are listed in Table 1.

Previous studies by Peña et al.³⁰ and Cheng and Bilston⁵ accurately described the degree and pattern of the stress distribution caused by brain deformation in the hydrocephalic brain using various biomechanical parameters. For the purpose of this study, only the changes in pore pressure were analyzed. Pore pressure is defined as the pressure of the fluid filling the pore space.⁴¹ The concept is frequently used in soil mechanics to describe the status of fluid saturation; the unsaturated soil has a negative pore pressure, thus causing a suction effect.¹³ In this context, the negative pore pressure at a given point can be interpreted as the fluid inflow, while a zero or positive pore pressure represents the free or outflow of fluid.

Results

The brain FE model successfully simulated core features of hydrocephalus, namely ventricular enlargement and PVL. The degree of ventricular enlargement was

FIG. 1. Schematic diagram of the FE model incorporating detailed anatomical geometry. The skull, cerebral cortex, falx cerebri, parenchyma, ventricle, and interface area are shown. The transmantle pressure (P_{TPG}) is derived from capillary blood pressure at the exterior of the cortex (P_c) and ventricular fluid pressure at the ependymal membrane (P_{vf}). Copyright Dong-Joo Kim. Published with permission.

closely associated with the degree of the TPG. As the TPG increased, the distribution of pore pressure showed interesting changes (Fig. 2). The pore pressure decreased at the nearby anterior and posterior horns of the lateral ventricles, and retained a certain level along the centrum semiovale.

The change in the TPG was found to have a close relationship with the change in pore pressure. The trends in pore pressure were plotted in terms of TPG increase (Fig. 3). The pore pressures at the anterior and posterior horns of the lateral ventricles initially decreased as the TPG increased. When the TPG reached approximately 2.5 mm Hg, the pore pressures at the two horns became positive.

The contour plots showing actual simulations are presented in Fig. 4. The color gradient indicates the distribution of the pore pressure. The round-shaped configu-

rations of the negative pore pressure resemble the PVL. With the escalation of the TPG, the negative-pressure area primarily increased and then successively decreased. As the TPG reached 3.0 mm Hg and the degree of ventricular expansion was most severe, a region with a negative pore pressure was rarely observed.

To be more specific, the proportion of the area with a highly negative pore pressure (-0.1 to -10.0 mm Hg) increased to 3.8% of the total area when the TPG reached 1.0 mm Hg (Fig. 5). The proportion became higher (4.8%), until the TPG reached 1.5 mm Hg. The proportion of the area with a slightly negative pore pressure ($-1.0 \times 10^{-0.5}$ to -0.1 mm Hg) was dominant (37.5%) when the TPG remained relatively low (0.5 mm Hg). However, the proportion markedly decreased with the increase in the TPG. Meanwhile, the area with a positive pore pressure gradu-

TABLE 1. Material properties utilized for the FE model

Components	Young's Modulus (Pa)	Poisson's Ratio	Density (kg ⁻³)	Reference
Parenchyma	420	0.35	1040	9,17,24,26,30
Falx cerebri	3.4×10^6	0.45	1130	16,38,46
Skull	14×10^9	0.23	1412	16,38,46

The void ratio of parenchyma is 0.2.²⁶ The permeability of white and gray matter is 1×10^{-7} and 1×10^{-9} , respectively.¹⁷ The compressibility parameter D_1 (224 Pa) and shear parameter C_{10} (77.9 Pa) of the parenchyma were calculated from Young's modulus and Poisson's ratio, in accordance with the neo-Hookean model for describing compressible biological tissue. Further details of the derivation of parameters can be found in a previous study (Kim et al., 2015¹⁸) and the ABAQUS user manual.³⁷

ally expanded, eventually spanning the majority of the area (97.8% when TPG = 3.0 mm Hg).

Discussion

Several FE studies that focused on the effects of geometrical details of ventricles on mechanical changes in the periventricular region have been conducted.^{5,30} Despite the advances reported in these studies, the models used omitted other important geometrical details, such as sulci. Additionally, there has been no attempt to investigate the effect of the degree of ventricular deformation on the biomechanical changes in the brain. The present study is the first to investigate the mechanisms of PVL using an FE model that incorporated ventricular and sulcal geometry. The results are consistent with common clinical findings, and possibly can be understood as indirect counterevidence to the extravasation theory. As the disruption of the ependymal wall is bound to be dependent on the degree of ventricular enlargement, the proportion of the area with

FIG. 3. Graph of the trends in pore pressure as a function of the increase in TPG. The pore pressures at the posterior and anterior horns reach their lowest, negative value at approximately TPG of 1.0 mm Hg. As the TPG reached 2.0 to 2.5 mm Hg, the pore pressures reached zero, before becoming positive. In contrast, the pore pressure at the centrum semiovale linearly increased with the TPG.

a negative pore pressure should increase as the degree of ventricular enlargement increases, according to the extravasation theory. However, our findings do not support this theory.

The ventriculomegaly in the present study was induced by raising the TPG. Although the TPG is widely considered an important concept for explaining ventriculomegaly in hydrocephalus, some recent studies have questioned its existence, or its effect on brain deformation.^{32,37} However, brain deformation may not necessarily require a large TPG.²⁰ Moreover, once the change in the TPG induces ventricular enlargement, the pressure can be uniformly distributed throughout the intracranial system, per the Pascal principle; the ventricular enlargement can be sustained, even after the disappearance of the TPG.³⁶ Unless proven otherwise, the concept of the TPG should be considered as the main cause of brain deformation in hydrocephalus. Inducing the increased TPG and thereby facilitating ventricular enlargement is a valid approach in the FE analysis of the hydrocephalic brain.^{5,30}

Periventricular Lucency in the FE Hydrocephalic Brain Model

PVL is commonly found in patients with hydrocephalus, regardless of the underlying causes. The prevalence of PVL is associated with the degree of ventricular enlargement, but these factors are not linearly correlated. In fact, an early report indicates otherwise. Asada et al.² reported that among 53 patients with PVL, 60% exhibited normal or mildly enlarged ventricles, and 25% of patients exhibited moderate ventriculomegaly. Interestingly, PVL was barely observed in severe ventriculomegaly. This discordance between the degree of ventricular enlargement and the prevalence of PVL is common (Fig. 6). Similar results were obtained in the present study, as illustrated in Fig. 4. The negative pore pressure (i.e., the fluid influx) in the periventricular region was visible when the degree of

FIG. 2. Graph of the trends in pore pressure along the ependymal wall with an increasing TPG (0.01, 1.5, and 3.0 mm Hg). A TPG of 0.01 mm Hg can be considered as 0 mm Hg, which indicates minimal or no change in TPG (i.e., there is no change in pore pressure). As per the increase in TPG, the pore pressure becomes negative at first (TPG = 1.5 mm Hg), and later becomes positive as the TPG increases to 3.0 mm Hg. a.u. = arbitrary units.

FIG. 4. Contour plots depicting the distribution of pore pressure. The initial TPG was set as 0, and continuously increased until it reached 3.0 mm Hg. The increase in the TPG induced increased ventricular enlargement. The anterior and posterior horns of the lateral ventricle retain negative values until the TPG becomes 2.0 mm Hg. As the TPG reaches 2.5, the pore pressure at the posterior horn becomes positive, and when the TPG reaches 3.0 mm Hg, the anterior horn also shows positive pore pressure. HNP = severe negative pore pressure; HPP = severe positive pore pressure; MNP = moderate negative pore pressure; MPP = moderate positive pore pressure.

ventriculomegaly was mild or moderate. As the degree of ventriculomegaly increased above a certain level (approximately 1.0 mm Hg in the presented results), the proportion of the area with a negative pore pressure was reduced.

Influence of Geometrical Characteristics of the Hydrocephalic Brain on PVL

The results are indicative of transepandymal CSF absorption as the cause of PVL in hydrocephalus, but the possibility of CSF extravasation cannot be dismissed, given the number of experimental studies supporting this theory.³⁴ Moreover, the ependymal wall of the lateral ventricles is constantly under mechanical stress in the hydrocephalic brain, indicating that structural damage does occur, especially in the acute stage of hydrocephalus.³³ Considering the fact that PVL exists in various types of hydrocephalus, it may be possible that the extravasation

and transepandymal absorption of CSF coexist, because the structural characteristics of the deformed brain allow both processes to occur. Nonetheless, the results of the simulations can be better explained by the transepandymal CSF absorption theory, rather than the extravasation theory.

Currently, the mechanism for the fluid accumulation in the periventricular region is unknown. However, a previous FE simulation study suggested that geometrical characteristics may play a major role in PVL in hydrocephalus.³⁰ In that study, Peña et al. found that the distribution of PVL is affected by ventricular geometry, and considered their findings to be evidence supporting the extravasation theory. In contrast, the present study further investigated the effects of the degree of structural deformation, and the results led to opposite conclusions. While the degree of deformation was mild or moderate, the pore pressure at the anterior and posterior horns of the lateral ventricle

FIG. 5. Graph of the proportional change in area associated with 5 different degrees of pore pressure according to the increase in the TPG. HNP = high negative pore pressure (-0.1 to -10.0 mm Hg); HPP = high positive pore pressure (0.1 to 10 mm Hg); MNP = moderate negative pore pressure (0 to -0.1 mm Hg); MPP = moderate positive pore pressure (0 to 0.1 mm Hg); none = zero pore pressure.

became negative, thereby allowing an inflow of CSF/ISF, which caused the accumulation of fluid. However, when the degree of structural deformation exceeded certain values, the geometrical change induced the positive pore pressure at the two horns of the lateral ventricles, which caused fluid outflow from those regions, and the disappearance of PVL.

According to the transependymal CSF absorption theory, PVL in hydrocephalus is, effectively, the edema in the periventricular region.¹⁵ There is ample evidence to support the transependymal CSF absorption theory, such as that derived from MR diffusion imaging studies reporting increased diffusion in the periventricular region, in both animal experiments and clinical case reports.⁴⁰ In addition, a recent study reported that low-dose acetazolamide, which is frequently used to treat cerebral edema, can also reduce PVL in idiopathic normal pressure hydrocephalus.¹ Notably, patients with severe ventriculomegaly were more responsive to acetazolamide compared with the patients with moderate ventriculomegaly. The results of the present study indicate that the pore pressure around the ventricular horns becomes positive in severely enlarged ventricles, thus enhancing the drainage of PVL by acetazolamide. In contrast, in moderate ventriculomegaly, the pore pressure in the periventricular region remains negative, thereby retaining the suctioning effect. This effect leads to relatively poor responses of PVL to acetazolamide. The results of this study indicate that PVL can persist even after the disappearance of the TPG because the pore pressure around the ventricular horns is affected by geometrical characteristics (i.e., the degree of ventricular deformation).

Limitations and Suggestions

The model used for the simulations shares the major limitation of current FE hydrocephalic brain models. The important drawback of this study is the lack of experimental evidence to support the conclusion. In addition, the

FIG. 6. Actual CT axial images of patients with hydrocephalus. **A:** Ventricular enlargement can be observed, but without signs of PVL. **B:** Severe hydrocephalus. The patient received a ventriculoperitoneal shunt after admission and suffered from excessive ventricular enlargement, did not show PVL. **C and D:** Hydrocephalic patients with PVL.

rupture of the ependymal wall, which would be the single most important consequence of the ventricular enlargement in the context of PVL pathogenesis, is not allowed by the model. Also, the model is a 2D approximation of a 3D brain; the stress and strain distributions associated with the ignored dimension are overlooked. While the model used in this study successfully simulated the radiological features of hydrocephalus, the results only indicate the tendency of biomechanical changes and, therefore, should be interpreted with caution. Additionally, the acuteness of the hydrocephalus initiation was not considered. Future studies should further explore the nature of PVL. A 3D FE model, with detailed geometrical information and the capability to simulate tissue disruption, is now required to fully investigate the biomechanical changes of the brain associated with PVL in hydrocephalus. A well-designed laboratory study may also be helpful in validating the findings of this study.

Conclusions

PVL is often observed in acute or subacute obstructive hydrocephalus with moderate ventricular enlargement. An FE model of a hydrocephalic brain can provide some insights into the pathogenesis of PVL. The increase in the TPG resulted in increased ventricular enlargement. However, the degree of PVL was not linearly proportional to the degree of ventricular deformation. The results of the simulations are in accordance with the clinical findings of PVL, i.e., the prevalence of PVL is higher in moderate

ventriculomegaly and relatively lower in severe ventriculomegaly. Nevertheless, the results should not be considered as definitive counterevidence to the CSF extravasation theory, as they only indicate that the rupture of the ependymal wall is not necessary for the development of PVL.

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Conception and design: DJ Kim. Acquisition of data: Park. Analysis and interpretation of data: DJ Kim, H Kim. Drafting the article: DJ Kim, H Kim, Jeong. Critically revising the article: Z Czosnyka, Yoon, K Kim, M Czosnyka. Reviewed submitted version of manuscript: DJ Kim, H Kim. Approved the final version of the manuscript on behalf of all authors: DJ Kim. Statistical analysis: H Kim, Park. Study supervision: DJ Kim.

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