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Sonographic Ventriculography: A New Potential Use for Sonographic Contrast Agents in Neonatal Hydrocephalus

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BACKGROUND AND PURPOSE: **Sonographic identification of communicating and noncommunicating forms of posthemorrhagic hydrocephalus can be difficult. This study evaluates the feasibility of using sonographic contrast agents to determine ventricular patency in a newborn animal model.**

METHODS: **A craniotomy was performed and a catheter was placed under sonographic guidance into the lateral ventricle in five anesthetized newborn piglets. Sonograms were obtained before and after intraventricular injection of 0.01 mL of a sonographic contrast agent (Imagent, formulation AF0150; Alliance Pharmaceutical Corp, San Diego, CA) diluted in 1 mL normal saline, and images were assessed for presence and location of echogenic contrast material.**

RESULTS: **Flow of contrast material was identifiable from the ipsilateral lateral ventricle into the contralateral lateral ventricle, and through the third and fourth ventricles into the basal cisterns during real-time sonography in every animal. Ventricular and cistern echogenicity remained increased for approximately 4 minutes after injection.**

CONCLUSION: **Contrast-enhanced sonographic ventriculography has the potential to identify patency of CSF pathways in newborns with hydrocephalus and an indwelling ventricular catheter.**

Intracranial hemorrhage in the premature infant is one of the more common causes of acute hydrocephalus in the neonatal period (1). Blood may cause impairment of CSF flow by a variety of mechanisms, including mechanical obstruction of the ventricular system, obliterative ventriculitis or arachnoiditis at the level of the aqueduct of Sylvius, at the outflow of the fourth ventricle, or at the level of the subarachnoid space (1–3). Initial medical management of both slowly and rapidly progressive forms of ventricular dilatation often involves serial lumbar punctures for temporary improvement of ventricular size (3–5). However, this technique is useful only when there is a communication between the lateral ventricles and the spinal subarachnoid space, allowing relatively large volumes of CSF to be removed by this approach. Sonographic identification of communicating and noncommunicating forms of posthemorrhagic hydrocephalus can be difficult, and techniques to determine patency of the ventricular system in premature infants that are safe, able to be performed at the bedside, and are not user-intensive are currently lacking. Results of recent work with experimental microbubble-based sonographic contrast agents have shown their potential for the creation of regional blood flow maps in the neonatal brain (6). In addition to increasing backscatter from blood vessels, these contrast agents also produce a high degree of reflectance in gray-scale images. This study evaluates the feasibility of using contrast agents for direct sonographic visualization of ventricular patency in a newborn animal model.

Methods

Five newborn Yorkshire piglets were anesthetized with 20 mg/kg of ketamine hydrochloride (Ketalar; Parke-Davis, Morris Plains, NJ) and 5 mg/kg of xylazine (Rompun; Miles, Shawnee, KA) by intramuscular injection, followed by 1% halothane (Fluothane; Wyeth-Ayerst, Philadelphia, PA) inhalation anesthetic until venous access could be secured. Thereafter, a continuous IV infusion of diprivan 1% (Propofol; Stuart Pharmaceuticals, Wilmington, DE) diluted in 5% dextrose at a dose of 0.02 mg/kg per minute was used for the remainder of the experiment. A heating lamp and warming blanket were used to prevent loss of body temperature during anesthesia.

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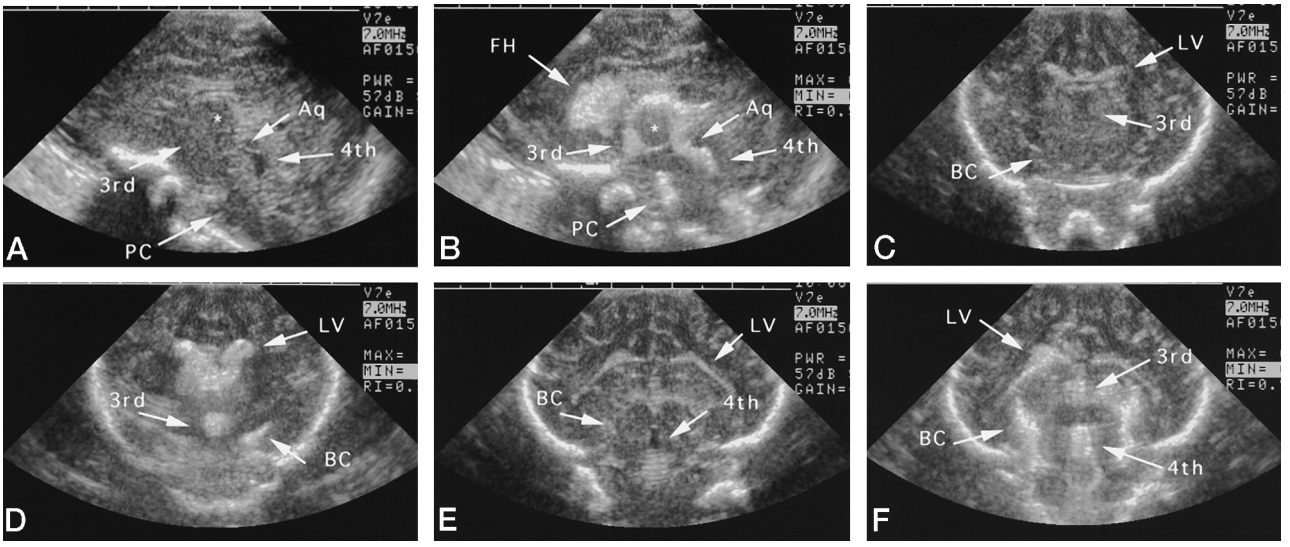

FIG 1. *A–F*, Sagittal midline images before (*A*) and after (*B*) intraventricular contrast administration, coronal images at the level of the anterior horns before (*C*) and after (*D*) intraventricular contrast administration, and at the level of the occipital horns before (*E*) and after (*F*) intraventricular contrast administration show improved visibility of the ventricular system and basal cisterns with contrast material. FH, frontal horn; LV, lateral ventricle; 3rd, third ventricle; Aq, aqueduct of Sylvius; 4th, fourth ventricle; PC, prepontine cistern; AC, ambient cistern; BC, basal cistern. *Asterisk* denotes massa intermedia.

Controlled ventilation was maintained via an oral endotracheal tube, and supplemental oxygen was administered. Polyvinyl chloride catheters were placed in the left femoral artery for continuous blood pressure monitoring and in both femoral veins for administration of IV fluid and medications. A 1 × 2-cm craniotomy was performed across the midline at the level of the coronal suture, leaving the dura intact for sonographic access. A second 2-mm burr hole was created in the right occipitoparietal area, and a 27-G catheter was placed into the occipital horn of the lateral ventricle under sonographic guidance. A 7.0-MHz vector transducer (model 128 XP; Acuson Corp, Mountain View, CA) was used for guidance and imaging studies.

Arterial blood pressure and heart rate were monitored continuously with a Hewlett Packard model 76 physiological monitoring system (Hewlett Packard, Andover, MA). The contrast agent Imagent (formulation AF0150; Alliance Pharmaceutical Corp, San Diego, CA) was reconstituted according to the manufacturer's directions. A dispersion of surfactant-coated perfluorohexane/nitrogen–containing microbubbles with a median diameter of approximately 5 μm is formed after reconstitution. Elimination from the blood is accomplished by evaporation through the lungs (7). Contrast material was administered into the occipital horn of the lateral ventricle through the indwelling catheter using a tuberculin syringe. In one animal, three serial intraventricular injections were performed using a 0.1-mL, a 0.05-mL, and a 0.01-mL volume of contrast agent diluted with sterile water into a total volume of 1.0 mL. The smallest dose (0.01 mL) allowed marked echogenic enhancement without persistent shadowing of deeper structures by overly echogenic contrast material and was used for subsequent studies. Sonograms were obtained in the coronal and sagittal planes before and after contrast administration and were analyzed for presence and location of echogenic contrast material. Only the fourth ventricle could be confidently identified on precontrast images. The exact boundaries of the lateral and third ventricles were not identifiable. As a result, we were only able to provide subjective estimates of the degree of ventricular dilatation after contrast injection. Transverse measurements of the lateral ventricles were obtained at the level of the foramen of Monro on postcontrast images.

These studies were performed as part of a related experiment on changes in cerebral blood flow during acute elevations of intracranial pressure. At the conclusion of the study, the animals were killed using an IV injection of 100 mg/kg of pentobarbital sodium. This study was approved by our institutional Animal Care and Use Committee and complied with the guidelines of the National Institutes of Health for the care and handling of animals.

Results

The presence of contrast material in the ventricular system was identifiable by a marked increase in echogenicity and swirling motion at real-time sonography. Flow of contrast material was identifiable from the ipsilateral lateral ventricle into the contralateral lateral ventricle and through the third and fourth ventricles into the basal cisterns in four animals (Fig 1). Ventricular and cistern echogenicity remained increased for approximately 4 minutes after injection. Mild (<5 mm Hg) transient elevations in intracranial pressure were observed during injection, but intracranial pressure returned to baseline in every animal at the end of injection. Mild transient dilatation (<4 mm transverse dimension) of the lateral ventricles was observed in all four animals. No dilatation of the fourth ventricle was seen during injection and no detectable changes in heart rate or mean arterial blood pressure were observed during or after intraventricular injection. In one animal, the tip of the catheter was inadvertently dislodged from the lateral ventricle. Serial sonograms showed the rapid appearance of echogenic contrast material in the basal cisterns without ventricular opacification (Fig 2).

Discussion

Several imaging methods have previously been described for the evaluation of CSF flow dynamics. Winkler (8) has reported that Doppler examination

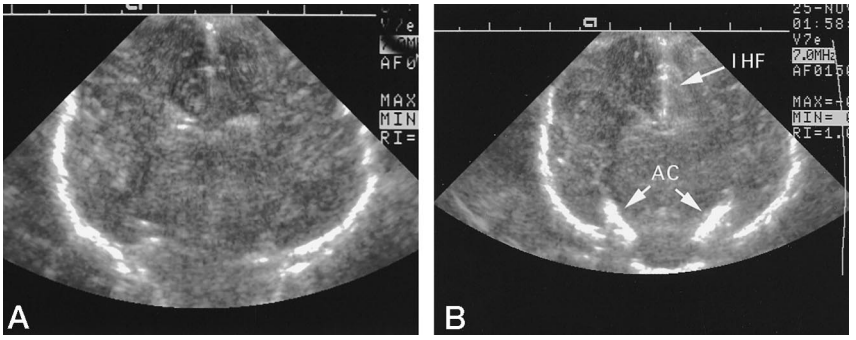

FIG 2. *A* and *B*, Coronal images at the level of the basal ganglia before (*A*) and after (*B*) intraventricular contrast administration show echogenic contrast material outlining only the interhemispheric fissure (IHF) and the ambient cisterns (AC). Note the absence of contrast material in the lateral ventricles.

of the ventricular system during cranial or abdominal compression may induce movement of CSF detectable with color or duplex Doppler sonography. Particulate debris within the CSF form reflective surfaces that cause a transient flash artifact on color Doppler images if retrograde flow is present. If no flow or debris is present, then abdominal compression does not result in the expected color flash. These dynamic techniques have been used to show obstruction at the foramina of Monro and the aqueduct of Sylvius. However, the accuracy, sensitivity, and specificity of this method have not been reported.

Radionuclide lumbar cisternography and, more recently, MR imaging have been used to measure CSF flow direction and velocity and to distinguish between obstructive and nonobstructive forms of hydrocephalus in preterm infants (8–11). Although these methods are accurate and clinically useful, they are difficult to implement in premature or critically ill infants, or in the operating room.

The findings of this preliminary study show the feasibility of using newly developed sonographic contrast agents to outline the ventricular system in a newborn animal model. Patency of the ventricular system was easily definable at real-time sonography by monitoring the progression of echogenic contrast material throughout the ventricular system into the basal cisterns.

In this study, a 0.01-mL dose of contrast agent diluted into a total volume of 1.0 mL was sufficient to opacify the entire ventricular system and determine its patency. Echogenic contrast material was detectable for approximately 4 minutes, after which ventricular echogenicity returned to normal. However, ventricular volumes and CSF dynamics in infants with hydrocephalus are quite different from those of normal newborn piglets, and it is likely that modifications will have to be made in both the concentration of contrast agent and the total volume of fluid injected to optimize the degree and duration of ventricular opacification.

An obvious limitation of this technique is that it requires direct access to the ventricular system. However, a significant proportion of premature infants with posthemorrhagic hydrocephalus will require a ventricular access device for temporary drainage of obstructed ventricles when medical management of rapidly progressive ventricular dilatation fails. Ventricular access devices are often indicated in premature infants who are too small to accept a permanent ventriculoperitoneal shunt and in infants treated with intraventricular fibrinolytic agents (12). Sonographic ventriculography might be useful during initial placement of ventricular access devices or before conversion to a permanent shunt to assess the presence and location of ventricular obstruction by clot or ventriculitis. Additional potential applications of this technique include the assessment of ventricular patency in infants with various forms of hydrocephalus, the identification of potential communication between bilateral subdural collections before drainage, and as an intraoperative technique to define the presence of communication between posterior fossa or interhemispheric cysts and dilated lateral ventricles to determine the need for additional shunt catheters.

Over the last few years, sonographic contrast agents have steadily evolved to the point where they are now clinically feasible. Most of the contrast agents currently under development consist of a surfactant or otherwise stabilized shell that encapsulates air or an inert gas. These agents exert their effect by increased ultrasound backscatter; bubble properties, such as strength and elasticity of the shell, and solubility of the encapsulated gas all affect reflectivity and longevity in the circulatory system (13). Most research studies with these agents have concentrated on intravascular enhancement or tissue characterization (7, 13). This class of agent has undergone extensive safety testing for intravascular use as part of the approval process by the U.S. Food and Drug Administration for new drugs. Although we know of no information on potential adverse effects or reactions related to intrathecal injection of sonographic contrast agents, additional studies are necessary to determine their safety for intraventricular and intrathecal use.

Conclusion

Our findings establish the feasibility of using sonographic contrast agents for the real-time evaluation of ventricular patency in a newborn animal model. Although these results are promising, they are preliminary in nature. Sonographic contrast agents will require extensive safety and efficacy testing before they are approved for intrathecal use in humans.

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