Hypertonicity Following Selective Angiocardiography

By Samuel T. Giammona, M.D., Paul R. Lurie, M.D., and William E. Segar, M.D.

Selective angiocardiography as a practical means of delineating anatomic details of cardiac malformations has been advanced by the development of contrast agents with greater radiopacity, lower viscosity, and less apparent toxicity. The severe immediate reactions of collapse, so common with older media, are rarely seen today; many patients, however, still have vomiting, intense headache, and other symptoms during the first few hours after the procedure. Occasional deaths that occur within the first few hours after angiocardiography are usually attributed to the severity of the cardiac lesion rather than directly to the procedure.

The present study was prompted by observation of a four-month-old infant weighing 4.8 Kg. with tricuspid atresia who underwent a routine cardiac catheterization with selective angiocardiography. As the child was quite ill, sedation was obtained with only 10 mg. of methohexitol sodium (Brevital) intramuscularly, and the procedure was carried out expeditiously. Four injections of sodium and methylglucamine diatrizoate (Renovist), each of 1.25 ml./Kg., were given at intervals of two to four minutes. Each injection was tolerated well, and the infant was awake and normally responsive at the completion of the last injection. The fontanel had been noted by the anesthesiologist to be normally full during the early part of the procedure. Ten minutes after the last injection, the infant began to have severe respiratory distress and aggravation of cyanosis. Within ten more minutes, she was unconscious with clonic twitching followed by generalized convulsions. The fontanel was deeply sunken, and cupping of the optic disc was extremely deep. Serum sodium 75 minutes later was 169 mEq./L. and the chloride was 140 mEq./L. Despite intravenous therapy with hypotonic fluid and moderate amounts of barbiturates, the convulsions continued and the infant died ten hours after the catheterization had been completed. No autopsy was permitted but it was believed that this death represented a Renovist reaction. This investigation was then undertaken in order to clarify the role of contrast media in producing changes in the tonicity of body fluids during angiocardiography.

Methods

Thirty patients with varied forms of congenital heart disease were investigated. Of the children studied, eight were infants under one year of age; six were from one to three years of age; nine were from four to ten years; and seven were over ten years old. The patients were selected at random, independent of the type of malformation present and their clinical status.

Selective angiocardiography was performed in various cardiac sites by rapid catheter injections with a Picker pressure injector at a pressure of 750 p.s.i. The contrast medium, Renovist*, was drawn from a freshly opened vial which had been prewarmed to body temperature.

Blood samples were obtained before and after the injection of contrast on 48 separate occasions. In four patients, multiple samples were taken over a 30-minute to 60-minute interval following angiocardiography. This study was designed to evaluate changes in osmolality during routine diagnostic angiocardiography and thus the only change made in the laboratory procedure was the obtaining of blood samples for analysis. The timing of the injection of contrast medium and the collection

* Renovist, a product of E. R. Squibb & Sons, New Brunswick, New Jersey.
of blood samples were dictated by the particular diagnostic requirements of the catheterization. Although the initial blood specimen was always obtained before the injection of contrast agent, subsequent samples were obtained after various lengths of time and after one or more injections of varying amounts of contrast medium. The average time after a single injection or the last one of a rapid series of injections and the subsequent drawing of a blood sample was four minutes. The blood samples were centrifuged immediately and the plasma was separated. Osmolality was determined cryoscopically with a Fiske Osmometer with an accuracy of ± 2 mOsm./L. Sodium analyses were made on the Baird flame photometer with an accuracy of ± 2 mEq. of sodium.

Renovist was analyzed in this laboratory and found to have an osmolality of 1,815 mOsm./L. and a sodium concentration of 755 mEq./L. A solution of 25 ml. of Renovist was compared to an equiosmolar solution of sodium chloride with regard to their diffusion rates. Cellophane membranes* were used as separators and the two solutions were placed in distilled water baths of similar dimensions. The sodium chloride solution reached osmotic equilibrium in six hours, whereas the Renovist required 24 hours to attain equilibrium.

Results

Prior to the injection of the contrast medium the mean osmolality of the plasma was 287 mOsm./L. (S.D. ± 6 mOsm./L.) with a range from 268 to 298. The mean initial plasma osmolality was the same for the four age groups studied.

When the dosage of contrast media was less than 1 ml./Kg., there was a mean rise in osmolality of 8.8 mOsm./L. corresponding to a 3 per cent increase over initial plasma levels. No child having less than 1 ml./Kg.

*Manufacturer, Visking Corporation, Chicago, Illinois.

![Figure 1](http://circ.ahajournals.org/)

Relationship of osmolality increase to dosage of contrast medium. Each symbol represents the percentage increase in osmolality following the injection of contrast media at different dosage levels.

dose had a rise greater than 18 mOsm./L. or a 6 per cent increment in osmolality.

For those injections greater than 1 ml./Kg., there was a mean rise in osmolality of 26.8 mOsm./L. corresponding to a 9 per cent rise over initial plasma levels. Due to the large variation within this group it was not possible to quantitate further the dose-osmolality relationship. Twelve of the 26 injections in this dosage level resulted in more than a 10 per cent increase in osmolality. The greatest increment was 72 mOsm./L. corresponding to a 25 per cent increment over initial plasma osmolality (fig. 1 and table 1).

In those cases in which the effects of widely spaced multiple injections were evaluated, the cumulative change in osmolality did not exceed 10 per cent of initial plasma levels. No age difference was apparent in the dosage-osmolality relationship; the largest dosages, however, were given chiefly to small infants who required more complete selective cham-

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Number of injections</th>
<th>Mean Increase in Osmolality*</th>
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<tr>
<td></td>
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<td>mOsm./L.</td>
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<tr>
<td>&lt; 1 ml./Kg.</td>
<td>22</td>
<td>8.8 ± 6</td>
</tr>
<tr>
<td>&gt; 1 ml./Kg.</td>
<td>26</td>
<td>26.3 ± 21</td>
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*The probability that the mean of the two groups is the same for both absolute and percentage increase is less than 0.001.
were greater all children of injection headaches after severe patients (14) had peak values from 320 mOsm./L. Twelve of the patients had a 10 per cent or greater increase in osmolality following injection of contrast media. This included all children whose peak levels of osmolality were greater than 320 mOsm./L. Seventy-eight per cent of the patients with osmolality rises of 10 per cent or more exhibited vomiting, lethargy, severe headaches, or extreme irritability, whereas only 33 per cent of those with less than a 10-per cent rise had similar symptoms.

There was no death in this series of 30 children following angiocardiology. The only immediate reaction was an episode of dyspnea and coughing in a 4-year-old patient after a small dose of Renovist. The fatality commented upon initially, however, is thought to be an example of the adverse effects of hypertonicity produced by an unusually large total of Renovist.

In the four instances in which osmolality was followed by repeated sampling for 30 to 60 minutes, there was a rapid fall over a five-minute period after the peak. This was followed by a much slower decline, with a significant residual increment over the baseline value at the end of the observation period (fig. 3).

The changes in sodium concentration in the blood following angiocardiology were minimal, transitory, and highly variable. The mean initial sodium concentration was 142 mEq./L and the mean sodium concentration following angiocardiology was 144 mEq./L, which was not significantly different. There was no correlation between the sodium change and the age of the patient, the magnitude of change of plasma osmolality, or the

Figure 2
Plasma osmolality in 30 children before and immediately after selective angiocardiology. Mean level before injection was 287 mOsm./L for the entire group.

Figure 3
Changes in plasma osmolality and serum sodium levels during the course of a routine series of selective angiocardiographic injections and for one hour after the procedure. Each arrow represents an injection of contrast media of 0.5 mL/Kg.

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Dosage of contrast media. Even when a significant rise in sodium concentration occurred (greater than 5 mEq./L.), return to baseline value was observed in five to 10 minutes in the cases studied by repeated samplings.

Discussion

This clinical study demonstrated that significant changes in body fluid osmolalities are produced by the injection of Renovist for selective angiocardiography in children. The changes in osmolarity, when related to the dosage of contrast medium, revealed the greatest increase in osmolarity occurring in those receiving more than 1 mL./Kg. of Renovist. No significant change in sodium concentration was observed. The observation of a significant increase in osmolarity without a marked change in sodium concentration may be explained by the demonstrated difference in diffusion rates of sodium chloride and Renovist.

Renovist is a combination of the sodium and methylglucamine diatrizoates, and the commercial preparation contains 69 per cent diatrizoate salts. Renovist has approximately six times the osmolality of plasma and five times the concentration of serum sodium found in normal children. Its protein-binding capacity is unknown but data on a closely related parent compound, diatrizoate methylglucamine (Renografin)* indicate that it is minimal. An in vitro study in this laboratory suggested that no measurable binding to plasma occurred. Renal tubular excretion is largely responsible for the removal of Renovist from body fluids so the rate of excretion is dependent upon the functional capacity of this system. All the presently available contrast media are hypertonic solutions with osmolalities greater than 1,500 mOsm./L. in the concentrations commonly used for angiocardiography. Toxic effects produced by these agents have been investigated in experimental animals and in clinical studies with the finding that toxicity is related to the concentration of the media and the total amount injected.

All hypertonic solutions, including contrast agents, induced profound changes in the cardiovascular and central nervous systems when injected intravascularly. Read has demonstrated an acute systemic hypotension with transitory pulmonary hypertension occurring immediately after injection of hypertonic solutions. He related these findings to systemic vasodilatation and intravascular red blood cell agglutination. Cotrim found that single rapid injections of contrast media or other hypertonic solutions produced central nervous system damage and led to the death of many of his animals from acute respiratory failure. Zinner and Gottlob have shown that following the injection of hypertonic solutions endothelial damage occurs in the peripheral vessels which was greater with the contrast media than with glucose solutions of identical osmolality. Bromman and Olsson found that 10-second exposure of the brain to hypertonic solutions of contrast media resulted in transitory alteration of the blood-brain barrier as reflected by Trypan blue staining of the brain.

With hyperosmolality of longer duration, permanent damage to the central nervous system can be experimentally produced. Sotos et al. reported that an increase of osmolality of 10 per cent, or a plasma level in excess of 330 mOsm./L. was the critical point at which continued exposure would produce pathologic lesions in cats. Luttrell, Finberg, and Drawdy made the interesting observation that the development of symptoms in cats rendered hypertonic was related to the fall in cerebrospinal fluid pressure which did not begin until hypertonicity had been present at least five minutes. The duration of minimum cerebrospinal fluid pressure, although affecting the continuation of clinical symptoms, did not influence pathologic damage. Thus they reasoned the pathologic damage must occur during the initial rapid fall in spinal fluid pressure. The fall in cerebrospinal fluid pressure was caused by intracel-

*Renografin, a product of E. R. Squibb & Sons, New Brunswick, New Jersey.

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lular dehydration and was manifested pathologically by the shrinkage of the brain from the dura, intra- and subdural hemorrhage, and by intracerebral hemorrhage with softening.

The experimental data demonstrate an immediate effect on blood vessels with instantaneous damage to endothelium at the moment of initial peak concentration of contrast in the cerebral capillaries. There are also later effects on the brain cells, resulting in central nervous system dysfunction. Both the immediate effect on vessels and the later effect on brain cells are due primarily to extracellular hyperosmolality. The studies of Broman and Olsson demonstrate that the contrast agents have inherent chemotoxic properties making them more damaging to the cerebral blood vessels and brain cells than glucose and electrolyte solutions of identical osmolality. Persistence of a plasma osmolality above 10 per cent of baseline levels has been shown experimentally to induce cerebral dehydration often resulting in irreversible brain damage if not corrected. In this group of 30 patients, 12 had levels exceeding 10 per cent of initial values and many of the symptoms noted in this group such as headache, lethargy, and vomiting may be accounted for by brain cell changes.

Since the toxicity of body fluids is chiefly maintained by the kidneys, impairment of their excretory capacity will be reflected in a prolongation of the hyperosmolality induced by administered hypertonic solution. In children undergoing angiocardiography, the hypertonic effects of the contrast media may be augmented and prolonged by pre-existing renal disease and by dehydration. Therefore, patients undergoing angiocardiography should be kept well hydrated and hypotonic electrolyte solutions should be used for infusions required during and after the procedure.

Although no injection of contrast media can be considered completely innocuous, in this study, total dosages of 1 ml./Kg. or less of Renovist were not associated with significant increases in plasma osmolality or important clinical reactions.

Special precautions must be taken with total dosages larger than 1 ml./Kg., which produce unpredictable increments in osmolality. In the present study, 46 per cent of the children receiving this dosage had a rise of 10 per cent or more above their initial osmolality level.

The ideal means of assessing the relative safety of injections of contrast material beyond 1 ml./Kg. is the determination of plasma osmolality. Such determinations on an emergency basis can be made available to laboratories performing selective angiocardiography.

Since the mean initial plasma osmolality of children is 287 mOsm./L., a 10 per cent increase results in general in an absolute level of approximately 315 mOsm./L. This level is suggested as an arbitrary danger point above which one should delay further injections until lower levels are reached or else terminate the procedure.

Fluoroscopic examination of the renal collecting system cannot be quantitatively related to clearance of the plasma osmotic load produced by the contrast medium. If osmolality determination cannot be obtained, it is suggested that further injections beyond 1 ml./Kg. be delayed 20 to 30 minutes to permit some renal elimination of the contrast medium and reduction of plasma osmolality.

Conclusions

The attention that has been accorded toxicity of contrast media in the past has been mainly centered upon reactions occurring at the moment of injection. Newer, less toxic media that have produced fewer and less severe reactions at comparable dosages have led to a sense of confidence, yet their osmolality is no lower than that of older media. Therefore, in repetitive dosage in such procedures as selective cineangiocardiography, the danger of cumulation resulting in delayed manifestations of hypertonicity must be considered. Awareness of this danger will help prevent accidents of this kind and will aid.
in the understanding and treatment of the symptoms that may appear if such an untoward reaction occurs. Furthermore, in the continuing development of new contrast agents there should be additional effort made to lower their osmolality values.

Summary
Plasma osmolality and serum sodium concentrations were studied in 30 children with a variety of cardiac abnormalities who underwent selective angiocardiography. A significant increase of osmolality occurred, but there were no significant changes in sodium concentration. The pathologic effects of hypertonic solutions including contrast media are discussed and it is concluded that hypertonicity is a preventable factor in serious reactions seen after angiocardiography.

Acknowledgment
We wish to thank Mr. Charles Hancock, who assisted in the laboratory determinations.

References

Medical Etymology
An amusing example is found in the history of the word astragalus which today is the name of a bone in the foot. It started off in Greek to mean a vertebra, especially in the neck of sheep. How it moved from the neck of sheep to the foot of man is interesting. The Greeks of the Iliad carved their dice from the astragalos of the neck of sheep and so the term came to designate one of a set of dice. The Roman soldiers much later took over the word with this latter meaning but applied it to the heel bone of horses from which they were accustomed to carve their dice—and from this it came into human anatomy. Whichever bone was used the resulting dice must have been very uneven, and to risk much on the rolling of such "bones" might prove expensive.—O. H. PERRY PEPPER, M.D. Opuscula Medica. (Reprinted from Transactions & Studies of the College of Physicians of Philadelphia, 4 Ser., 18: 31, April, 1950).
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