

4-12-2009

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**Ultrasound measurement of the inferior vena cava diameter in the assessment of
pediatric dehydration**

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Yunie Kim

2008

ULTRASOUND MEASUREMENT OF THE INFERIOR VENA CAVA DIAMETER IN THE ASSESSMENT OF PEDIATRIC DEHYDRATION

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Dehydration is a common pediatric condition, but limitations exist with current methods of assessing pediatric fluid status, particularly with interobserver variabilities in clinical assessment and the inaccuracy and questionable validity of laboratory tests. Bedside ultrasonography (US) measurement of the inferior vena cava (IVC) and aorta (Ao) may be useful in objectively assessing children with suspected dehydration. The objectives of this study were 1) to compare the IVC and Ao diameter (IVC/Ao) ratio of dehydrated children with euvoletic controls and 2) to compare the IVC/Ao ratio before and after intravenous (IV) rehydration in children with clinical dehydration. This prospective observational study was performed in an urban pediatric emergency department. Children between 6 months and 16 years of age with clinical evidence of dehydration and who were to receive IV fluid hydration were enrolled. Bedside US measurements of the IVC and Ao were taken pre- and post-IV fluid hydration administration. An age-, gender-, and weight-matched control was enrolled for each subject. The IVC/Ao ratios of subjects and controls were compared using the Wilcoxon signed rank test, as were the ratios before and after IV hydration for each subject. Thirty-six pairs of subjects and matched controls were enrolled. The IVC/Ao ratios in the subjects were lower as compared with controls (mean of 0.75 vs. 1.01), with a mean difference of 0.26 (95% confidence interval = 0.18 to 0.35, $p < 0.001$). In subjects, the IVC/Ao ratios were significantly lower before IV hydration (mean of 0.75 vs. 1.09), with a mean difference of 0.34 (95% confidence interval = 0.29 to 0.39). As measured by bedside US, the IVC/Ao ratio is lower in children clinically assessed to be dehydrated. Furthermore, it increases with administration of IV fluid boluses. The IVC/Ao ratio, as determined by bedside US, is an objective and noninvasive method of evaluating fluid status in children.

ACKNOWLEDGEMENTS

I would like to extend gratitude to the following people: Dr. Lei Chen for allowing me the opportunity to be involved in this project and for his kind mentorship and guidance throughout the process, from the inception of the project to the writing of this thesis; Dr. Melissa Langan for her review of this thesis; Dr. Karen Santucci and other members of the faculty in the Department of Pediatrics in the Yale-New Haven Pediatric Emergency Department for their support and comments; Dr. Norman Siegel for his review and input into the research proposal and my summer research grant application; and Dr. Howard Pearson and the Pediatrics Departmental Thesis Committee. And finally, I would like to thank the Office of Student Research, Yale University School of Medicine, for a summer student research grant in support of this work.

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INTRODUCTION

I. Clinical Assessment of Dehydration in Children

A common pediatric condition is dehydration, often an accompaniment to symptoms of diarrhea and vomiting. Children, especially those younger than four years of age, tend to be more susceptible to dehydration because of significant fluid loss in a short amount of time. In the U.S., there are ~220,000 hospitalizations each year for children younger than five years due to gastroenteritis and dehydration (1).

Accurate assessment of the degree of dehydration in children is important in appropriately managing these patients in the emergency department (ED). Dehydration, if unrecognized and untreated, can lead to profound shock and even death. On the other hand, overestimation of the severity of dehydration might result in inappropriate utilization of limited resources such as prolonged care in the ED and hospitalization. Furthermore, aggressive intravenous (IV) rehydration is a known cause of iatrogenic morbidity and even mortality (2-4).

Symptoms of dehydration in children may be subtle and variable, and many of them are nonspecific. For example, children with hypovolemia might present with fatigue, weakness, muscle cramps, thirst, and postural dizziness. In extreme hypovolemia, end-organ ischemia can occur, resulting in oliguria, cyanosis, abdominal and chest pain, and confusion. Hypotension is a late finding; a child can lose up to 25% of their circulating fluid volume before hypotension is detected (5). Other clinical indications of

hypovolemia are delayed capillary refill, weak pulses, cool or clammy skin, dry mucous membranes, tachycardia, and decreased skin turgor and tears (6, 7).

Steiner et al., in a meta-analysis on assessment of pediatric dehydration, wrote that the clinical finding that is the best predictor of “significant” dehydration (loss of $\geq 5\%$ of body weight) is increased capillary refill time (8). But despite good specificity (0.85), it is not very sensitive (0.60). Some texts and earlier studies also suggest capillary refill time might be affected by both ambient and body temperature, which makes it susceptible to variation (7, 9, 10). These findings are contradicted by more contemporary studies, which have shown that capillary refill time is not affected by these variables or is affected in an insignificant way (11, 12). Gorelick et al. reported in a study of children (one month to five years of age) that a temperature ≥ 38.3 degrees Fahrenheit had no clinically important effect on capillary refill time (11). Shavit et al. reported in a limited cohort from a study of children ages one month to five years with gastroenteritis presenting to a pediatric ED no significant correlation between ambient, skin, or core temperature and capillary refill time (12).

Interestingly, in this study by Shavit et al., the capillary refill time was measured in a novel manner with digital videography (12). The authors compared digitally measured capillary refill time with clinical assessment and conventional capillary refill, finding that the digitally measured capillary refill time better predicted significant dehydration than overall clinical assessment.

But, despite the fact that capillary refill time might be the best clinical sign of significant dehydration, it is unclear what role this variable plays in impacting outcomes. Leonard and Beattie performed a study where capillary refill time was measured in 4,878 children, and found that although a “prolonged” time set at three seconds or greater was associated with fluid bolus administration, overall, capillary refill time was a poor predictor of administration of IV fluids or admission (13).

The clinical assessment of hypovolemia involves taking into account a variety of symptoms and signs, many of which are considered subjective or unreliable (8, 14). Only when a number of particular criteria are used and in certain combinations does the sensitivity and specificity of detecting dehydration enter a useful range (15). One method, and currently the most objective means of making a determination of the degree of dehydration, is to know the change in body weight that has occurred over a limited period of time (7). This gold standard of assessing degree of dehydration is the calculation of the difference between the well and ill weights of the child as a percentage of the well weight (8, 15). However, the problem that arises with children is that their body weight is constantly changing. In addition, accurate measurement of weight loss is even more difficult in an ED setting where children can usually be weighed only during their acute presentation.

One way of circumventing this issue in the emergent setting is the use of rehydration weight as a surrogate for well weight in studies on pediatric dehydration (16, 17). Friedman et al. used rehydration weight as a surrogate for well weight, but did not study

the validity of this surrogate value. Steiner et al., in an investigation of urinary indices as diagnostic tests for dehydration, also chose to use immediate rehydration weights of their subjects to determine their volume status. In addition, they studied a small subset of their study population to validate the use of this surrogate. By finding previously documented well weights for a small subset and comparing them to the rehydration weights, the authors found a high degree of correlation (16). However, the authors acknowledge their small population size in this validation of using rehydration weight as a surrogate for well weight and that this criterion standard should be confirmed.

A clinical scoring method for determining the degree of dehydration has been evaluated. In a prospective study by Gorelick et al., diagnosis of dehydration using the presence of three or more from a list of clinical findings has a sensitivity of 0.87 and a specificity of 0.82. The sensitivity and specificity of using these clinical findings was validated against a gold standard of change in body weight of $\geq 5\%$ body weight (8, 15). An often-used scale of assessment is the placement of children into three categories of dehydration: mild, moderate and severe. In the literature, there is categorization of mild dehydration as body weight loss of $< 5\%$ and $< 3\%$ for infants and children, respectively. Moderate dehydration is a loss of 5-10% and 3-6% for infants and children, respectively. And, severe dehydration is a loss of 10-15% and 6-9% for infants and children, respectively (7). However, the limitation of this scale is the overlap of signs and symptoms ascribed to each of these categories that occur in the real world. The signs and symptoms associated with these levels of dehydration are not always clear cut and this has led to attempts to developing more objective criteria for assessment (17). Despite the attempts to find the

best models for assessing pediatric dehydration, there is neither a uniformly nor a universally employed way as of yet of objectively and noninvasively measuring intravascular status.

II. Laboratory Values in Assessing Pediatric Dehydration

Laboratory values can also be used to help judge the severity of dehydration in children (18). However, laboratory studies have limited sensitivity and specificity in their ability to detect hypovolemia (5, 7, 16).

Wathen et al. asked the question of whether routine serum electrolyte panels (SEP) would be useful in treating pediatric patients with dehydration and assessing the need for IV fluid hydration (19). In their study in a pediatric ED, all subjects had an SEP performed. Physicians were asked to comment on whether or not they would have ordered the SEP after taking a history and physical, but before the results of the SEP was made available. In addition, the physicians were asked how often the SEP results changed management. The authors concluded that attending physicians did not have a good rate of predicting which children would have serum electrolyte abnormalities. This conclusion was based on a 58% sensitivity of predicting which children would have clinically significant results (results that changed management). Thus, ordering an SEP could be useful. However, Steiner et al. as well as Rhee and Silverstein pointed out in commentaries on this study that Wathen et al. failed to note that only 6.6% of patients for whom the attending physician would not have planned on ordering an SEP had clinically significant results (20, 21). In other words, most of the time (93%), the clinical management was unchanged

by the SEP when the physician would have felt it unnecessary to order one. In addition, Steiner et al. note that the retrospective nature of having physicians commenting on whether the SEP results changed management introduced bias.

The literature on serum bicarbonate values is growing and some studies have shown that bicarbonate values can be useful, but the data can be conflicting. In children with gastroenteritis, Vega and Avner suggested that serum bicarbonate values <17 mEq/L were helpful in the assessment of moderate to severe dehydration (percent loss of body weight of 6-10% and $>10\%$, respectively) (22). In contrast, Yilmaz et al. found that a lower level of bicarbonate was not helpful in assessing degree of dehydration in children with gastroenteritis, but interestingly, that higher levels of bicarbonate (>15 mmol/L) in children with levels of urea >100 mg/dL were negatively correlated with severe dehydration (23). In a study by Wathen et al. that did not limit their subjects to children presenting with gastroenteritis, only 29% of their study population (children between 2 months to 9 years of age who were receiving intravenous fluids because of dehydration) had bicarbonate levels <16 mmol/L (19). A recent study by Nagler et al. demonstrated that serum bicarbonate concentration is lower in children with vomiting and diarrhea and can be detected noninvasively by end-tidal CO_2 measurement (24).

Blood urea nitrogen (BUN) and creatinine might be helpful in the child with preserved renal function, as a disproportionate rise in BUN might indicate volume depletion (18). However, the BUN level of any patient is affected by not only by volume status, but a host of other factors, including anything affecting the urea cycle. For example, poor

nutritional status (poor protein intake), increased urea production from a gastrointestinal bleed or high cell turnover, or any high-catabolic state could alter BUN (18).

Teach et al. explored serum anion gap in assessing dehydration in children (25). Serum anion gap could be considered as a marker for dehydration, as unmeasured anions that could arise in the face of decreased PO intake could elevate the gap. However, Teach et al. did not find an elevated anion gap to be a good diagnostic test for dehydration in children with gastroenteritis (25). Additionally, children can have multiple contributing mechanisms to their dehydration. For example, a child might have volume depletion secondary to diarrhea, and secondary renal insufficiency. With the potential for more than one mechanism to be present, confounding of the acid-base status may occur (18).

Increased urine specific gravity and decreased urinary output are frequently taught as indicators of dehydration, and perhaps even severity of dehydration (7, 18). For example, children's urinary outputs have been roughly described to be normal, decreased, and anuric with mild, moderate, and severe dehydration, respectively (7). However, a meta-analysis showed that one could not predict dehydration by a history of decreased urinary output (8).

Urine specific gravity is described as being more useful than urinary output by popular reference, with one unvalidated cutoff criteria being a specific gravity of 1.020 to delineate children with mild or no dehydration (18). But even the use of specific gravity comes with caveats: urinary concentrating ability is low in infants and can also be

affected by an intrinsic urinary concentrating defect such as diabetes insipidus (18). A recent study by Steiner et al., aforementioned as the study utilizing rehydration weights in lieu of well weights for determining dehydration status, investigated the validity of urinary indices in the evaluation of dehydration in children ages 3-36 months (16). Others had previously found there to be no relationship between urine specific gravity and degree of dehydration, but Steiner et al. were the first to attempt to correlate cutoff values of urine specific gravity with dehydration data (16, 25, 26). In a prospective study of children presenting with gastroenteritis and dehydration and who received IV fluid rehydration, they found that urinary indices such as specific gravity, ketones, and output during rehydration were not predictive of severity of dehydration. Urine specific gravity did decrease after rehydration and most of the subjects did have an increase in urinary output in a three-hour period post-rehydration. But as a diagnostic test of children presumed to be dehydrated, the authors were unable to correlate urine specific gravity values with degree of dehydration. The authors concluded that, given that these indices have never previously been shown by a clinical study to be valid in the assessment of children with dehydration, one should not use these indices. Like many of the other studies that were referenced in this literature evaluation on dehydration in children, this study is limited by the fact that the study subjects were only children with gastroenteritis.

Therefore, no clear and clinically useful relation between laboratory values and intravascular volume depletion independent of etiology has been shown. The literature is replete with studies, but none have robustly demonstrated the utility of obtaining routine SEP or urinalysis on pediatric patients suspected to have dehydration.

III. Bedside Ultrasonography in Assessment of Fluid Status

Bedside ultrasonography is a relatively novel imaging modality in the pediatric ED setting (27, 28). Ultrasonography has been gaining popularity as a diagnostic modality as it is rapid, painless, noninvasive, and increasingly accessible, especially in the ED. In recent years, many new indications for ultrasonography in the pediatric ED have been explored (27, 29, 30). Ultrasonography may be a noninvasive and objective way to assess intravascular status and confirm a diagnosis of dehydration in children.

Ultrasound assessment of the inferior vena cava has been used for over three decades as its utility as a noninvasive diagnostic tool has become apparent. Most of the earliest studies that utilized ultrasonography to visualize the IVC came from the field of cardiology. Areas studied included assessing patients for tricuspid regurgitation, presence of atrial septal defects, and IVC diameter and collapsibility as examined in relation to cardiac function (31-37). Moreno et al., in the early 1980s, noted that the IVC is a highly compliant vessel whose size varied with central venous pressure. They studied its size and dynamics in adult patients, finding that IVC diameter correlated well with its collapsibility index (32). Additionally, there was a difference in IVC diameter and collapsibility between the group with normal right atrial pressures and those with elevated right atrial pressures. Thus, this study showed that IVC assessment via ultrasound could be useful in identifying patients with right-sided cardiac disease.

Recently, use of IVC diameter and collapsibility has extended to more acutely ill patients, whether in emergency medicine or surgical patients in the intensive care unit (ICU) (38-

40). In a prospective observational study performed in an adult ED setting, both IVC diameter and IVC collapsibility index were correlated with volume status in adult trauma patients. Yanagawa et al. reported IVC diameter to correlate with hypovolemia in trauma patients (40). Similarly, Sefidbakht et al. found that in adult trauma patients with shock secondary to hemorrhage, compared with control patients who were normotensive, there was a negative correlation between IVC diameter and the presence of shock. There was also a higher mean IVC collapsibility index in the shock group (38).

Carr et al. found that IVC diameter and collapsibility indices as measured by bedside ultrasound in a surgical ICU were good surrogates for central venous pressure (CVP) (39). They found that ultrasound data and CVP were comparable with expert clinical judgment. Lorsomradee et al. found that IVC diameter correlated with CVP well only when CVP was ≤ 11 mmHg (39, 41). However, Lorsomradee et al. used a study population of pre-surgery cardiac patients who had their IVC measured via transesophageal echocardiography (TEE). This raises questions of the variability and precision of measuring IVC diameters with different ultrasound modalities, namely, TEE versus transthoracic or transabdominal measurement, as well as the portion of the IVC measured. Carr et al. measured IVC diameter 2 cm below the junction of the hepatic veins, an abdominal measurement commonly utilized in the literature, whereas Lorsomradee et al. measured IVC diameter at the point of entry in the right atrium.

Sonogram has been used to measure the diameter of the inferior vena cava (IVC) in acute blood loss in adults (40, 42). In this study, volume contraction of the intravascular space

resulted in a measurable decrease in IVC diameter. In volunteer blood donors, IVC diameters were measured pre- and post-donation. After a donation of 450 ml of whole blood, an approximate reduction in IVC diameter of 5 mm was measurable. Thus, the authors reported that even a small reduction in intravascular volume could result in a measurable change in IVC diameter and that this information might be useful in assessing volume depletion in patients (42).

IVC diameter has also been shown to be a way of assessing fluid status in adults and children on hemodialysis (40, 43-48). Avoiding post-dialysis dehydration as well as hypervolemia is a concern for patients on hemodialysis. Cheriex et al. described a method of determining dry weight in hemodialysis patients by using an index of IVC diameter to body surface area, and found this IVC index more accurately determined dry weight than clinical judgment (43). Yanagiba et al. found that IVC diameter could be a useful measurement of dry weight as well, confirming this in nonoliguric patients (44). Krause et al. and Dietel et al. found similar efficacy of using IVC diameters in relation to body surface areas in a pediatric population (46). After these studies, Mandelbaum and Ritz attempted to characterize the clinical relevance of IVC data by comparing them with central venous pressure and atrial natriuretic peptide (ANP) (48). Given that there was low interobserver and intraobserver variability in IVC diameter measurements, but higher variabilities with IVC collapsibility measurements, the authors focused their analyses on IVC diameters only. Of note, Mandelbaum and Ritz found that IVC diameter significantly correlated to heart rate, thus corrected for heart rate when doing their data analysis (48). In the patients on dialysis, they saw decreases in ANP and IVC diameters.

Although “dehydration,” “volume depletion,” and “hypovolemia” are often used interchangeably in the clinical literature, Mandelbaum and Ritz suggested serial measurements of IVC diameters can, with a few caveats, estimate intravascular status, but cannot accurately estimate interstitial volume (8, 48). Mandelbaum and Ritz also reported that measurements of the IVC diameter were reproducible (48).

HYPOTHESIS/SPECIFIC AIMS

The purpose of this study was to obtain and evaluate data on IVC diameter, measured by bedside US, as a possible objective measurement of intravascular status in infants and children. This may eventually offer an additional objective measure to assist physicians in their assessment of children suspected to be dehydrated.

AIM 1: Evaluating IVC diameter in relation to fluid status

Aim 1.1: Given the literature on IVC diameter as a measurement of intravascular status in adults and selected pediatric populations, and also that the IVC is a vessel of relatively high compliance, we hypothesized that IVC diameter is reduced in children who are judged to be dehydrated and to need IV rehydration in the ED setting.

Aim 1.2: We also proposed that after rehydration to the extent deemed necessary by the attending physician, a measurable increase in IVC diameter occurs.

Aim 1.3: And finally, we hypothesized that the IVC diameter is measurably reduced in dehydrated children when compared to age-, gender-, and weight-matched controls.

Because the sizes of the IVC and Ao in pediatric patients vary with their ages and sizes, our study utilized the ratio between the IVC and Ao diameters, rather than the IVC diameter alone (49). This is using the premise that the Ao diameter can serve as an internal control for each patient because it should be constant regardless of hydration status. For the clinician to be able to apply data on IVC/Ao ratio to patients suspected to be dehydrated, it is essential that there are not confounding effects of age, gender, weight, or other unforeseen variables on the IVC/Ao ratio. If so, a study with a larger sample size would be necessary to determine a normogram for IVC diameters, Ao diameters, and IVC/Ao ratios for the pediatric population.

AIM 2: Evaluate IVC diameter in relation to commonly used clinical descriptors of severity of dehydration

Since children are often classified in a rather subjective manner into the categories of none/mild, moderate, or severe dehydration, a secondary of this study was to assess if these clinical descriptors were associated with IVC diameter (7, 15).

METHODS

This was a prospective observational study carried out in an urban pediatric emergency department between June 2006 and July 2007. The study was approved by the Human Investigations Committee (HIC) at Yale University School of Medicine. Informed written consent was obtained from a parent or guardian for each subject and control. Written assents were obtained from children ages 7-16. The HIC protocol was written conjointly by both the main investigators, Lei Chen, MD (LC) and Yunie Kim, BS (YK). Written consents and assents were obtained by both LC and YK.

The study was conducted at the Pediatric Emergency Department at Yale-New Haven Hospital. Children between 6 months and 16 years of age were eligible to be enrolled as subjects if they presented with clinical evidence of dehydration and were judged to need treatment with IV fluids by the attending physician. They were approached to be enrolled as study subjects when one of the investigators was available.

Children were excluded from the study if they had a history of congenital heart disease, Marfan syndrome, or acute blood loss. In addition, children for whom there was a suspicion for multi-systemic illness or inflammation were excluded as to avoid the unknown magnitude of the effects of cytokines on vascular compliance, intravascular volume, and overall body fluid distribution.

As a control group, euvolemic children were enrolled in this study. Patients with minor complaints and subsequently judged as euvolemic were approached to be controls. The same exclusion criteria for subjects applied to the controls. In addition, two other exclusion criteria were applied to the controls: fever and placement under nil per os orders upon entering the ED. For each subject, an age-, gender-, and weight-matched control was enrolled. Age was matched within 15% of the subject's age and weight within 20% of the subject's weight. Children entering the ED had their fluid status clinically assessed by an attending physician.

If a child was clinically assessed as dehydrated and IV fluids were ordered, the attending physician was also asked to make a clinical judgment of whether they believed the patient was mildly, moderately, or severely dehydrated.

Bedside ultrasound measurements of the IVC and aorta were taken before and immediately after IV fluids were administered (within thirty minutes of bolus completion). For controls, bedside ultrasound was performed once. The equipment used in this study was the Sonosite 180 plus portable ultrasound machine (Sonosite, Bothell, Wash.) with the C60 curvilinear probe. Measurements were taken with the subjects and controls placed in the supine position. The probe was placed at the subxiphoid region, just rostral or caudal to the insertion of the left renal vein into the IVC (Fig.1).

In this view, the liver could be used as an acoustic window. No graded compression was used to displace intestinal gas. In addition, we took great care not to compress the

abdomen to avoid compressing the vessels being measured. A transverse view of the IVC and Ao was imaged using cine-loop capture (a feature that allows a number of frames to be stored and scrolled through). Images were recorded over several respiratory and cardiac cycles. The maximal anterior-posterior IVC diameter and descending Ao diameter were measured, placing calipers at the anterior and posterior midpoints of each vessel (Fig. 2A). After the initial bedside US examination, the subjects underwent bolus IV fluid infusion with normal saline, as is the standard of care in the Yale-New Haven Hospital Pediatric ED. The amount of fluid administered in the IV fluid boluses varied and was determined by the treating physician. Immediately after the first bolus infusion, the measurements were repeated in the same region of the abdomen (Fig. 2B).

Two investigators performed the US measurements during the course of the study. One (LC) was a pediatric emergency attending physician who attended an American College of Emergency Physicians–sponsored two-day ultrasound workshop, in addition to spending a six-week period in an emergency ultrasound (EUS) rotation in an academic ED. The other operator (YK) was a medical student who underwent training given by LC.

The sample size calculation was performed using previous pilot data, which indicated that a difference of up to 40% can be detected between normal and dehydrated subjects. In order to detect a 20% change in IVC diameter in dehydrated children compared to controls, we used the following:

Alpha = 0.05

Power = 0.80

Effect size = 0.23 cm

Standard deviation of IVC difference = 0.4 cm

Standardized effect size = $0.23/0.4 \text{ cm} = 0.575$

Patients needed to detect a difference between groups: $n = 36$

The IVC/Ao ratios of subjects and controls were compared using the Wilcoxon signed rank test, as were the ratios pre- and post-IV hydration for each subject. Data acquisition was performed by both LC and YK, and statistical analyses were performed by LC.

RESULTS

A total of 36 pairs of subjects and controls were enrolled. There were 10 male subjects and 26 female subjects with a mean (\pm SD) age of 7.3 years (\pm 5.0 years) (range: 9 months to 16 years) compared with 10 male controls and 26 female controls with a mean (\pm SD) age of 8.0 years (\pm 5.3 years) (range: 8 months to 16 years) (Table 1).

TABLE 1. Patient Demographics

| | Subjects | Controls |
|---------------------|-----------|-----------|
| <i>N</i> | 36 | 36 |
| Female (<i>n</i>) | 26 | 26 |
| Male (<i>n</i>) | 10 | 10 |
| Age range (yr) | 0.8-16 | 0.7-16 |
| Mean age (yr) | 7.3 | 8.0 |
| Weight range (kg) | 10.0-65.5 | 10.6-68.5 |
| Mean weight (kg) | 30.0 | 35.6 |

Among the subjects, ultimate diagnoses from the ED were predominantly viral gastroenteritis (53%). However, other reasons for subject presentation of dehydration included peritonsillar abscess, urinary tract infection, post-operative tonsillectomy, and heat exhaustion.

As mentioned in the Methods section, the volume of normal saline of the IV fluid boluses was determined by the treating physician. The amounts that subjects in this study received ranged from 15 to 50 cc/kg. The median bolus was 20 cc/kg.

In the subjects, there was a measurable difference in the mean IVC diameter pre- and post-IV hydration. The mean IVC diameter pre-hydration was 0.75 cm. The mean IVC

diameter post-hydration was 1.12 cm. The mean difference in IVC diameter pre- and post-hydration was 0.27 cm (95% confidence interval [CI] = 0.24 to 0.32 cm, $p < 0.05$).

In the subjects, Ao diameters did not vary significantly pre- and post-hydration. The mean Ao diameter in study subjects pre-hydration was 0.99 cm. The mean Ao diameter post-hydration was 1.02 cm. The mean difference in Ao diameter pre- and post-hydration was 0.03 cm (95% CI = -0.04 cm to 0.10 cm, $p < 0.05$).

The IVC/Ao ratios were significantly different pre- and post-hydration. The mean IVC/Ao ratio in study subjects pre-hydration was 0.75 cm. The mean IVC/Ao post-hydration was 1.09 cm. The mean difference in IVC/Ao ratio pre- and post-hydration was 0.34 cm (95% CI = 0.29 cm to 0.39 cm; $p < 0.001$) (Fig. 3).

In the matched controls, the IVC/Ao ratio did not vary appreciably with age in the controls, with a mean ratio (\pm SD) of 1.01 cm (\pm 0.15 cm). The mean difference between the IVC/Ao ratio of the controls with the pre-hydration IVC/Ao ratio of the study subjects was 0.26 (95% CI = 0.18 cm to 0.35; $p < 0.001$) (Fig. 3).

Using the clinical judgment of dehydration as the standard, the test characteristics of the IVC/Ao ratio were calculated. A receiver operator characteristics curve was constructed (Fig. 4). The area under the curve was 0.91 (95% CI = 0.84 to 0.98). With a cutoff ratio of 0.72, the test had a sensitivity of 39% and a specificity of 100%. On the other hand, with a cutoff ratio of 1.0, the test had a specificity of 58% and a sensitivity of 97%.

The attending physician was asked to make a clinical assessment of whether the subject was mildly, moderately, or severely dehydrated. 23 subjects were described as mildly dehydrated. 13 subjects were described as moderately dehydrated. No children were described as severely dehydrated. The IVC/Ao means (\pm SD) for these two groups were identical at 0.75 cm (\pm 0.12 cm). For the group described as mildly dehydrated, the mean age (\pm SD) was 7.3 years (\pm 5.1 years). For the group described as moderately dehydrated, the mean age was 7.6 years (\pm 5.0 years).

DISCUSSION

As measured by bedside US measurement, the IVC/Ao ratio is lower in children clinically assessed to be dehydrated and this ratio increases with administration of IV fluid boluses. Thus, the IVC/Ao ratio, as determined by bedside US, is an objective and noninvasive method of evaluating fluid status in children.

This study confirms some earlier pilot data showing that IVC diameters are lower in children with dehydration. Furthermore, this study is the first to demonstrate increases in IVC diameter resulting directly from increases in intravascular volume in children with dehydration. We designed the study around a novel parameter: the ratio between the IVC and Ao diameters. The premise stems from the fact that the IVC and Ao diameter will be different in each child, possibly correlating with such factors as age, gender, weight, height, and body surface area (49). However, Ao diameter was predicted to be fairly

stable within each child despite hydration status because it is a vessel of low compliance, especially when compared with the IVC. To address the question if Ao diameter could be affected by intravascular depletion and resultant tachycardia and activation of the sympathetic system, Sonesson et al. found that sympathetic stimulation did not alter the mechanical properties of the abdominal aorta (50). We therefore predicted that Ao diameter should not change much with changes in intravascular volume. In our study, the Ao diameter was found to remain stable in each subject pre- and post-hydration. Thus, our assumption that the Ao diameter could serve as an internal control for each child appears, thus far, to hold true.

That Ao diameter was not associated with intravascular status is consistent with other previous research. Yanagawa et al. reported a study of adults in hypovolemic shock in which the diameter of the abdominal Ao remained constant despite large volumes of blood loss (40). In our study, the IVC/Ao ratio, as measured by bedside US examination, appeared to be consistent in the euvolemic controls regardless of age and weight. In contrast, we were able to demonstrate a correlation between the IVC/Ao ratio in our study subjects and intravascular volume. This ratio is smaller in children clinically assessed to be dehydrated as compared with controls. Furthermore, IV fluid rehydration in the subjects resulted in measurable increases in their IVC/Ao ratios.

The combination of clinical findings used for assessing pediatric dehydration with the best sensitivity and specificity was reported by Gorelick et al. Yet, their criteria with the fairly good sensitivity and specificity for detecting dehydration would still miss 13% of

children with dehydration (15). A clinician might also employ an often-used scale of assessing severity of dehydration by regarding children as mildly, moderately, or severely dehydrated. Friedman et al. attempted to develop criteria for less subjective use of these descriptors of severity, but their analysis was limited to children 36 months of age or less (17). In addition, these descriptors, like the optimal combination of clinical findings described by Gorelick et al., are neither uniformly nor universally applied in the assessment of pediatric dehydration.

Given the subjectivity of these descriptors, we attempted to see if IVC diameter was at all associated with their use. Attending physicians assigned descriptors “mildly” and “moderately” to describe the severity of dehydration for subjects in this study (none were described as “severely” dehydrated). The IVC/Ao means (\pm SD) for these two groups were identical at 0.75 cm (\pm 0.12 cm). Thus, clinician assessment of severity of dehydration using subjective descriptors appears to have no association with IVC/Ao ratios. A main limitation of this study, to be more fully discussed shortly, was that the current gold standard for assessing dehydration in children was not used to identify patients as hypovolemic versus euvoletic in the two groups of the study (subjects and controls). Thus, either rehydration weight or knowing pre-illness weights would be essential to prove that children who were deemed to be “dehydrated” were in fact so, as well as the severity of dehydration. Since physicians might judge how much IV fluid to bolus as well as how many boluses to give based on their gestalt of severity of dehydration, being able to more objectively characterize severity would be useful. If

IVC/Ao ratio could not only objectively identify children with dehydration, but also classify their severity, it would be useful in treatment decisions.

These findings are of importance as dehydration is a common diagnosis in the pediatric ED. Assessment of dehydration has been extensively studied partly because the appropriate recognition and management of dehydration in children may result in avoidance of iatrogenic harm and better allocation of resources. Studies and meta-analysis have attempted to discern the most sensitive and specific findings, or combinations thereof, that would best predict dehydration (8, 15). But despite best efforts to describe the most objective findings and values that characterize a child with dehydration, it is most likely that most physicians treat and order tests based on clinical acumen and institutional norms (21). Steiner et al. undertook a systematic review of the assessment of pediatric dehydration since “most teaching regarding the assessment of dehydration is based on clinical experience and medical tradition” (8).

Current methods of assessing fluid status encompass laboratory values, clinical findings, and history. Laboratory testing is invasive and has not been shown not to change clinical management when routinely ordered for children thought to need IV fluids. There is still a need for more rigorous studies to discern if it has a clinically significant role in addition to history and physical examination (19-21, 51). In addition, dehydration can have multiple different causes. Thus, certain laboratory cutoff values, even when validated in a particular subset of the population, might very well be insensitive for dehydration in the rest. There still exists the question of whether or not laboratory testing would add to clinical decision-making and improve actual patient outcomes (19, 21).

Clinical signs and symptoms of dehydration can be subjective and sometimes neither sensitive nor specific (8, 25). Historical information such as oral intake, reports of dehydration symptoms, stool and urine output, and well weight are difficult to obtain, not always accurate, or just nonspecific (8). Capillary refill time is one example of a clinical finding that has been studied in association with clinical outcomes. Despite being the clinical finding that is best predictive of significant dehydration, Leonard and Beattie found capillary refill time to be a poor predictor of need for IV fluids or admission (8, 13). However, perhaps the advent of digital videography that was developed and studied by Shivat et al. will prove otherwise with more accurate and/or precise data acquisition (12).

In addition to the measurement of capillary refill time with digital videography, the measurement of IVC parameters such as diameter and collapsibility might add to the existing methods of assessing intravascular status. Studies using IVC measurements to assess intravascular volume status have been conducted in adults (40, 42). In addition, multiple other studies have been conducted in patients on hemodialysis, including one study that compared IVC diameters in children of various ages undergoing hemodialysis (40, 43-48). The use of ultrasonography has extended to the critical care setting as well, where often volume status is inferred from central venous pressure, the acquisition of which involves invasive central venous access (39). The pilot study by Carr et al. suggests that bedside ultrasonography to estimate volume status is feasible (39).

A strength of this study is that patients with multiple etiologies for their dehydration were enrolled, instead of just subjects with gastroenteritis. Many previous studies of the assessment of children with dehydration have limited their subject population to children with gastroenteritis, some even more specifically limiting their group to very young children (both Gorelick et al. and Shavit et al. enrolled children in their studies aged one month to five years) with gastroenteritis (12, 16, 22, 23, 52). However, one could also view this strength as a weakness because the electrolyte abnormalities and fluid shifts that occur in children with a wide variety of etiologies for their dehydration could be a confounding factor. However, given that we did not exclude any diagnoses save for acute causes of intravascular losses and hypovolemia, such as acute blood loss through trauma, as well as parameters that change intravascular status independent of overall volume status, such as sepsis, we were able to see if our method was still applicable to the general presenting pediatric population. Our enrolled subjects had a variety of mechanisms for dehydration, including decreased intake (due to oral lesions and postoperative pain) and increased losses (vomiting and diarrhea). Thus, this method may potentially be more generalizable than other methods that limit their results to children affected by gastroenteritis, which is certainly very common, but not the only cause of pediatric dehydration.

A facet of this study that could be further expounded is the timing of IVC diameter measurement. The subjects in this study received normal saline IV rehydration therapy, which provides good intravascular and extracellular rehydration, thus allowing us to have the ability measure IVC diameter changes. However, Katzarski et al. found in a study of

IVC diameter in adult patients on hemodialysis that measurements taken shortly after hemodialysis might not accurately assess dry weight (53). This raises the questions of the accuracy of assessing IVC diameter at a period just post-IV rehydration. Practically, it would not be very feasible to keep patients in the ED several extra hours to assess IVC diameter as it changes after some of the normal saline equilibrates within the body compartments. However, if a study of pediatric inpatients could be performed that would follow IVC diameter measurements from just post-IV fluid administration to several hours out, that might provide more information on overall fluid status and not purely intravascular status.

Other possible future studies of the use of IVC/Ao ratios in the assessment of children with dehydration include using rehydration weight as a surrogate for well weight in studies on pediatric dehydration (16, 17). Steiner et al., in an investigation of urinary indices as diagnostic tests for dehydration, chose to use immediate rehydration weights of their subjects to determine their volume status. They also studied a small subset of their study population to validate the use of this surrogate. By finding previously documented well weights for a small subset and comparing them to the rehydration weights, Steiner et al. found a high degree of correlation (16).

As mentioned previously, one of the reasons for conducting this study is to contribute to the goal of appropriate assessment and treatment of children presenting with dehydration. It is important to be able to accurately identify those patients who are truly dehydrated and in need of IV rehydration therapy. In a system with limited resources and excessive

costs associated with prolonged care in the ED and hospitalization, it may be cost-effective to more objectively assess dehydration. Furthermore, one may be able to avoid iatrogenic morbidity, such as IV therapy-associated phlebitis, and even mortality (2-4, 54).

Oral rehydration therapy (ORT) has been found to be a good alternative to intravenous fluids in the rehydration of moderately dehydrated children due to gastroenteritis, if not a preferable option for most patients (1, 52, 55). A recent Cochrane analysis by Hartling et al. comparing oral versus intravenous rehydration therapy found that although there were no clinically important differences found between the two, ORT is associated with shorter hospital stays (54). However, ORT is often underutilized. In cases of only moderately reduced IVC/Ao in addition to clinical assessment, perhaps emergency care providers will be more likely to consider alternatives to IV fluid hydration. In light of the utility of ORT, if pediatric patients could be further be more accurately stratified in terms of degree of intravascular depletion, perhaps IVC diameter measurements could also help in the decision-making process of who might be trialed on ORT first in the ED (55). Because repeated bedside US examinations do not incur significant additional cost, this modality might also be used to follow ongoing fluid losses as well as to follow the efficacy of rehydration.

In a study by Chang et al. of periodic echocardiographic measurement of the IVC diameter and its effects on quality of life in patients on chronic hemodialysis, the authors found that by better maintenance of dry weight, quality of life was improved (56). Other

beneficial uses of bedside US in assessing fluid status might include pediatric patients who present in sickle cell crises or diabetic ketoacidosis. These are patients for whom accurate fluid status assessment can be critical. Given that Carr et al. and Lorsomradee et al. report that IVC diameter and collapsibility might be surrogates for CVP in adults, bedside ultrasound might be of use in pediatric patients in the intensive care setting in whom volume status monitoring is important (39, 41).

It is relevant to mention that this technique evaluates only intravascular fluid status. It does not detect other metabolic derangements common to children with dehydration, such as hyponatremia, hypoglycemia, and acidosis.

LIMITATIONS

Study Size

We enrolled a relatively small number of subjects. We enrolled the minimum number of subjects and controls to have statistically significant results (see Methods). The main reason for that was the difficulty in matching the subjects with appropriate controls as we wished to find age-, gender-, and weight-matched controls for the subjects. Our results are encouraging in that the IVC/Ao ratio remained consistent in the group of control subjects and suggest that if this ratio is eventually proven to be of a relatively constant value, future studies would not need to be encumbered by matching for so many variables. More data are needed, however, to establish normal values in children with euvolemia and no normograms yet exist for the IVC/Ao ratio in either children or adults.

Need of Gold Standard

We did not attempt to correlate our measured deficits with the gold standard of assessing fluid deficits. Ideally, having both the ill and well weights of the subjects would be helpful to calculate and assess fluid status in a manner other than just clinical assessment. This pilot study was designed to demonstrate a correlation between IVC/Ao ratio and intravascular fluid status. This relationship was shown by our preliminary data. To further investigate the validity of this preliminary data, future plans could include longitudinal studies of children with dehydration. For example, one could correlate repeat measurements of the IVC/Ao with weight changes during acute illness and convalescence.

Another possibility could be to use, as mentioned earlier, rehydration weights of children as a measure of fluid deficits against which to compare IVC/Ao data (16, 17). As used by Friedman et al. and validated by Steiner et al. in a small sample size, if rehydration weights can be confirmed as surrogate for the current gold standard of using well and ill weights, a future study of IVC/Ao ratios in assessing fluid status would be much more easily performed in an ED setting. These studies would help establish the validity of this modality to prospectively identify patients with dehydration.

Feasibility and Precision of Ultrasonography

Throughout the research study, two operators performed the ultrasonographic studies. One operator was a pediatric emergency attending physician who underwent formal EUS training with an American College of Emergency Physicians–approved EUS course, in

addition to spending six weeks on an EUS rotation in an adult ED. The other operator was a medical student with no previous training. She received a limited amount of training by the first operator. Intraobserver and interobserver variabilities were not measured, although previous research has demonstrated good interobserver agreement in the measurement of the IVC as performed by pediatric emergency physicians, even when they were as a group compared to experienced pediatric echocardiography providers (33).

In addition, studies have shown that bedside ultrasonography can be quickly learned to be used by housestaff. Hellmann et al. found that internal medicine residents could learn to use hand-held ultrasonography equipment in conventional transthoracic echocardiograms at a “reasonably rapid rate” (57). Medical students are increasingly having ultrasound training integrated into their education as the value of this imaging modality is becoming increasingly apparent (58). Decara et al. found that it was feasible to teach fourth year medical students to use hand-carried ultrasounds, and that its use also helped in bedside diagnoses. This trend in using portable ultrasonography as a method of teaching medical students combined with the present integration of this education at the resident level ensures that if IVC diameter measurement can provide for more accurate diagnoses, including that of intravascular status, that the next generation of future physicians will be well-equipped to use this technology.

But, despite the increasing incorporation of handheld ultrasound and bedside ultrasonography in multiple areas of medicine, formal evaluation in methods to generalize this technique is warranted. Future studies incorporating multiple

measurements taken by separate operators on pediatric subjects and controls would be useful to assess the intra- and interobserver variability that might exist with this technique. However, the drawback of that additional component could be introduction of increased inconvenience to pediatric patients and perhaps even delay of care despite the rapidity of the imaging technique.

Imaging Limitations

Subjects and controls enrolled in the study with larger amounts of adipose tissue often revealed poorer image quality on bedside ultrasound, which is an intrinsic limitation of ultrasonography. To best accommodate for this limitation, cine-loop was not saved until we obtained a series of images of sufficient quality from which measurements could be taken. However, even then, the image quality was relatively diminished owing to the larger amount of material through which the ultrasound waves must penetrate.

Intravenous Fluid Bolus Standardization

One facet of this study that was not studied was the effect of fluid bolus size and number of boluses. Although most of the patients received a standard bolus of close to 20 cc/kg, the fluid quantity per mass varied and was not standardized as physicians administered fluids and managed patients as they would have done normally. In addition, a few patients received more than one fluid bolus based on clinical judgment by the physician. Standardization of fluid bolus quantity was not necessary for our study to demonstrate that there is a measurable change in IVC diameter with a change in intravascular volume. However, future studies measuring IVC diameter change in relation to specific quantity

per mass boluses might be of use to determine which patients might actually need larger boluses or more than one bolus, and thus greater time spent in the ED.

Accuracy of IVC Diameter Measurement—The Elliptical IVC

Besides the location of the body at which the IVC is measured, the angle at which the IVC is measured can also be raised as a future point of study. In this study, the IVC diameter was measured in a transverse view in the subxiphoid region. Naruse et al. point out that in some cases, IVC diameters might be different depending on whether it is measured in a sagittal or cross-sectional view (59). Noting that several severely dehydrated adult patients still had abnormally high IVC diameters, they observed that in certain patients the IVC did not collapse in a horizontal fashion (did not collapse into a horizontal ellipse due to gravity despite a supine position), but in a vertical fashion. This data was recently published, and introduces an interesting question of an unexplored variable of variations in IVC collapsibility. Thus, Naruse et al. suggest measuring the IVC from two angles, getting both the major and minor axes and calculating what they term a “flat ratio,” or a ratio of the two axes, to better assess hydration status. They hypothesize that this flat ratio might provide for a more accurate assessment of fluid status since there may be variations in IVC collapsibility. This may warrant further study in and of itself, but a future study of IVC diameters in a pediatric population could include not only transverse measurements of the IVC, but also measurements of the short axis and calculation of the flat ratio to see if this is applicable to the pediatric population as well. The authors noted that this method of measuring the IVC may be best suited for

dry weight assessment of patients on hemodialysis and that the method has not been statistically proven.

Exclusion of Patients with Systemic Illness

Another limit of this study was the fact that children for whom there was a suspicion for multi-systemic illness or inflammatory response were excluded. This was to avoid unknown confounding effects of cytokines on vascular compliance and intravascular volume and distribution. This allowed us to utilize the intrinsic compliance of the IVC and aorta in otherwise healthy children with dehydration, but clearly limiting the data to children not meeting systemic inflammatory response criteria is a deficit. This exclusion criterion makes the data less generalizable and perhaps non-applicable to children with both systemic illness and dehydration. Future studies of IVC measurement and fluid status in both adults and children in whom systemic inflammatory response syndrome is suspected would be useful.

CONCLUSION

In summary, assessment of pediatric dehydration in an acute care setting is a clinical judgment that can vary from one observer to another due to the subjective nature of many of the signs and symptoms of dehydration. Bedside US is rapid, noninvasive, painless, and inexpensive. We found that the IVC/Ao ratio as measured by bedside US is lower in children clinically assessed to be dehydrated compared to euvolemic controls. In addition, increases in the ratios were measured after IV hydration. Measurement of the IVC/Ao ratio is an objective method of evaluating children with dehydration. Bedside US should

be further studied for its use in assessing fluid status in pediatric patients. These further studies should include the use of gold standards of assessing dehydration to validate this pilot data, as well as consider the enrollment of a large patient cohort so that a normogram of IVC/Ao might be developed to further understand the size and compliance of these vessels in children.

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FIGURES



Figure 1. Placement of the probe in the subxiphoid region.

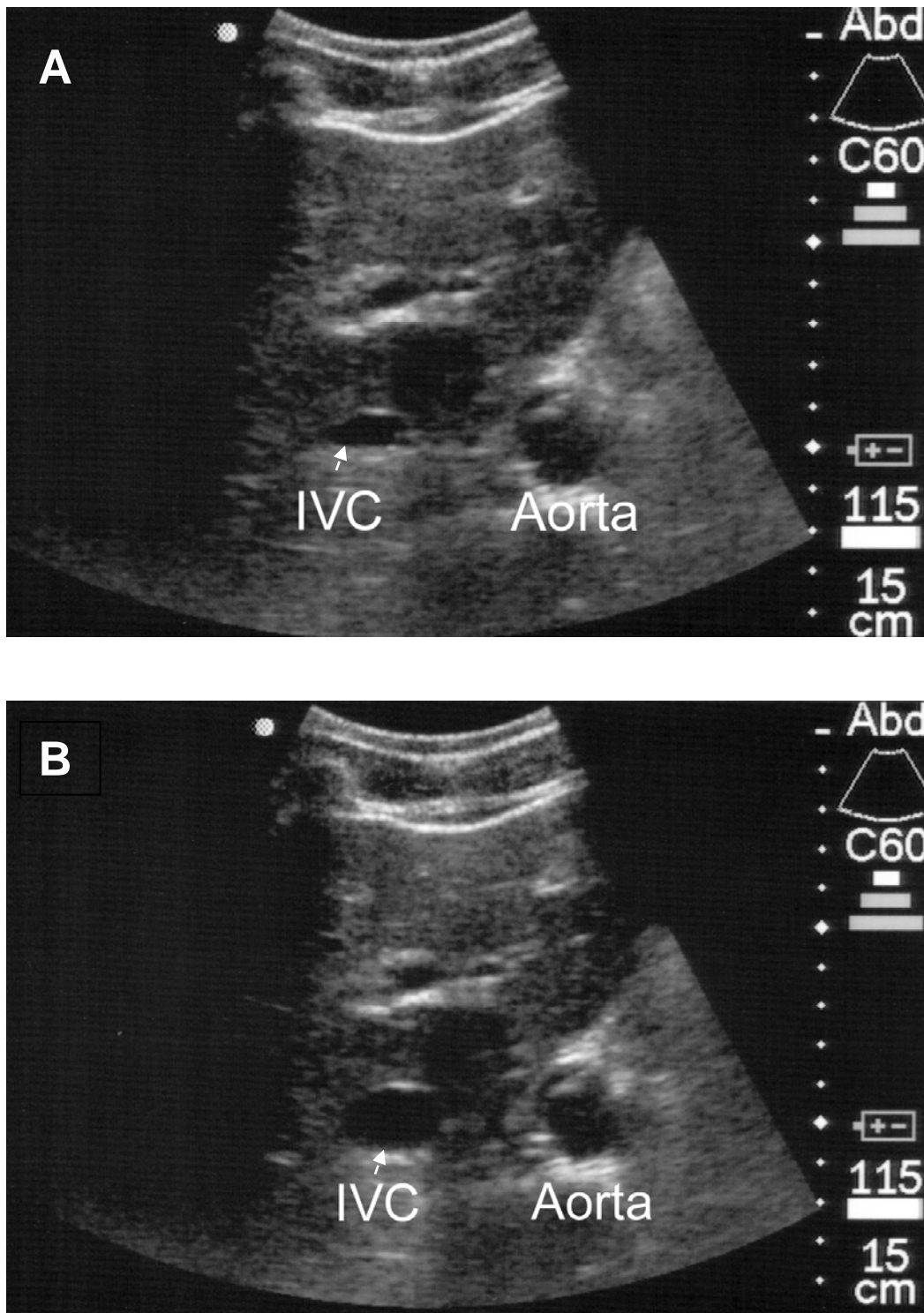


Figure 2. Transverse views of the abdomen (A) before and (B) after administration of IV fluid administration in a 16-year-old subject with viral gastroenteritis.

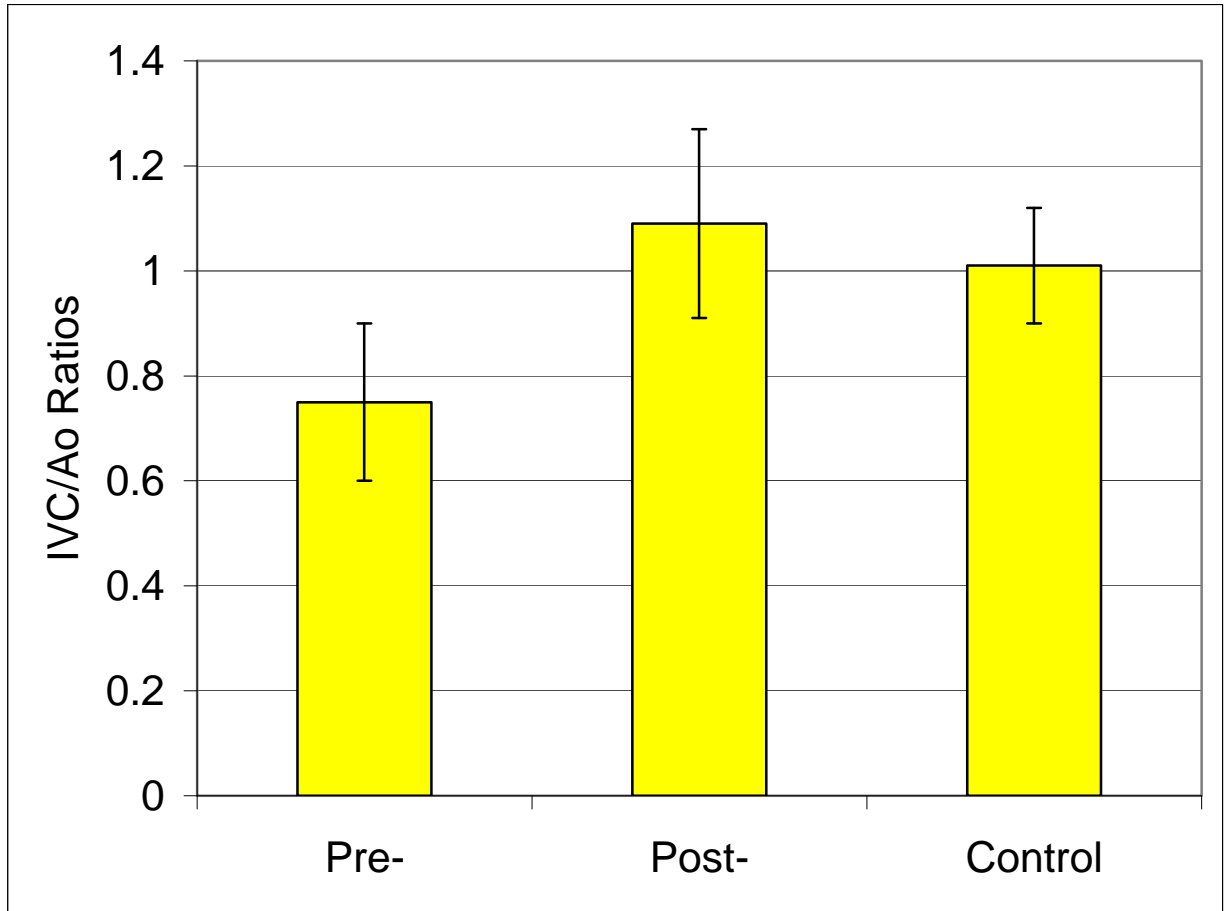


Figure 3. Mean inferior vena cava/aorta ratios in subjects before (pre-) and after (post-) hydration as compared with controls. Error bars represent 1 SD.

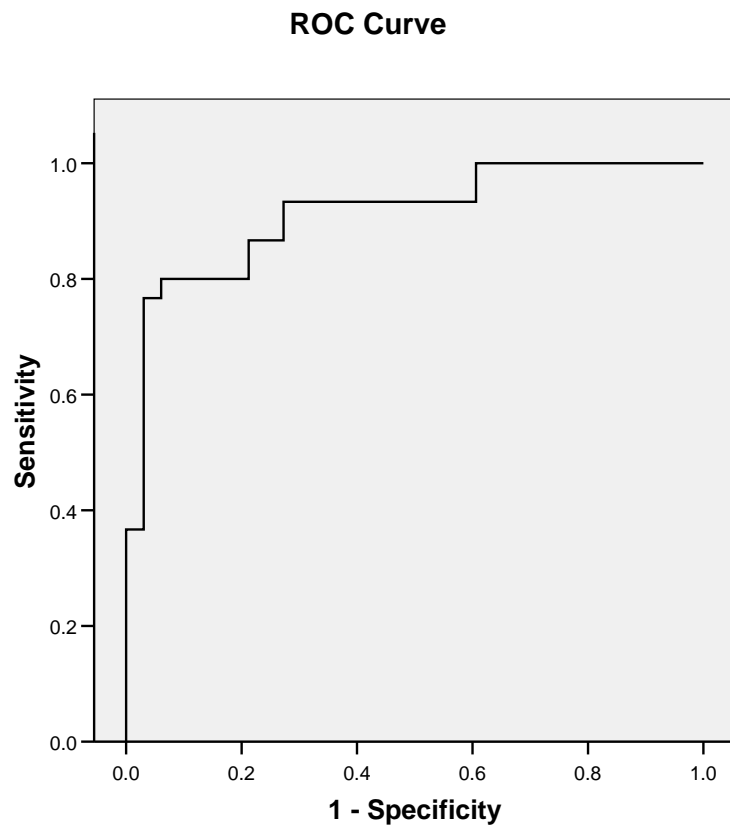


Figure 4. Receiver operator characteristic (ROC) curve of interior vena cava/aorta ratio and clinical assessment of dehydration. Area under the curve is 0.91.