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Venous Physiology Predicts Dehydration in the Pediatric Population

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ABSTRACT

Background: No standard dehydration monitor exists for children. This study attempts to determine the utility of Fast Fourier Transform (FFT) of a peripheral venous pressure (PVP) waveform to predict dehydration.

Materials and methods: PVP waveforms were collected from 18 patients. Groups were defined as resuscitated (serum chloride $\geq$ 100 mmol/L) and hypovolemic (serum chloride $<$ 100 mmol/L). Data were collected on emergency department admission and after a 20 cc/kg fluid bolus. The MATLAB (MathWorks) software analyzed nonoverlapping 10-s window signals; 2.4 Hz (144 bps) was the most demonstrative frequency to compare the PVP signal power (mmHg).

Results: Admission FFTs were compared between 10 (56%) resuscitated and 8 (44%) hypovolemic patients. The PVP signal power was higher in resuscitated patients (median 0.174 mmHg, IQR: 0.079-0.374 mmHg) than in hypovolemic patients (median 0.026 mmHg, IQR: 0.001-0.057 mmHg), ($P < 0.001$). Fourteen patients received a bolus regardless of laboratory values: 6 (43%) resuscitated and 8 (57%) hypovolemic. In resuscitated patients, the signal power did not change significantly after the fluid bolus (median 0.142 mmHg, IQR: 0.032-0.383 mmHg) ($P = 0.019$), whereas significantly increased signal power (median 0.0474 mmHg, IQR: 0.019-0.110 mmHg) was observed in the hypovolemic patients after a fluid bolus at 2.4 Hz ($P < 0.001$). The algorithm predicted dehydration for window-level analysis (sensitivity 97.95%, specificity 93.07%). The algorithm predicted dehydration for patient-level analysis (sensitivity 100%, specificity 100%).

Conclusions: FFT of PVP waveforms can predict dehydration in hypertrophic pyloric stenosis. Further work is needed to determine the utility of PVP analysis to guide fluid resuscitation status in other pediatric populations.

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Introduction

Dehydration is common and sometimes life-threatening in children. Clinicians use vital signs, urine output, physical examination findings, and laboratory values to estimate the level of dehydration and intravascular volume status; however, determining level of dehydration is still difficult as there is no standard dehydration monitor in children.[1] Scales have been developed to classify dehydration; however, they are not accurate, and more precise predictors are still needed.[2,3] The lack of a suitable gold standard has been a barrier to clinical research and may have hampered good clinical care.

Analysis of peripheral venous pressure (PVP) waveforms is a novel method of monitoring intravascular volume, which may provide earlier sensitivity in detection of volume depletion.[4] Fast Fourier Transform (FFT) is a powerful technique, which facilitates analysis of hemodynamic signals in the frequency domain.[5] Previous work in a young porcine model has demonstrated that FFT of a PVP waveform correlated with volume status more sensitively than standard vital sign monitoring.[4] The use of PVP waveforms could represent a significant advance in the field, particularly, as most children with severe dehydration often require intravenous rehydration.

Hypertrophic pyloric stenosis (HPS) is a common pediatric condition in which patients present with varying degrees of dehydration and marked biochemical derangement.[6-8] Electrolytes are used as a marker of resuscitation. Fluid replacement corrects the hypochloremic, hypokalemic metabolic alkalosis to avoid postoperative apnea.[9] Typically, if electrolyte abnormalities ($Cl^- < 100$ mmol/L, $HCO_3 \geq 30$ mmol/L) are present on diagnosis of HPS, aggressive intravenous fluid (IVF) resuscitation is given.[10-12] Dalton *et al.* found chloride to be the most sensitive and specific indicator of the need for multiple saline boluses.[10] Identifying a noninvasive monitor via a PVP waveform that correlates with hydration status and the presently used chloride values could be beneficial in determining adequate resuscitation.

In this study, we use PVP waveform analysis via a standard peripheral intravenous (PIV) catheter to study dehydration in children. We hypothesized that FFT could predict dehydration in patients with HPS.

Materials and methods

This study was performed in accordance with the University of Arkansas for Medical Sciences Institutional Review Board, IRB# 206193. After obtaining informed parental consent, PVP waveforms were collected from 32 patients with ultrasound-proven HPS.

Patients with cardiac defects, patients who were previously admitted to an outside hospital and received IVF, and patients receiving mechanical ventilation were excluded from the study. Of 32 patients, 29 (91%) had a 24-gauge Insyte-N Autoguard PIV catheter (Becton Dickinson Infusion Therapy Systems, Sandy, UT) placed in the upper or lower extremity at time of emergency department admission. The PIV was connected to a Deltran II pressure transducer (ADInstruments, Colorado Springs, CO) interfaced with a PowerLab (ADInstruments) data acquisition system via 48-inch arterial pressuring tubing (Smiths Medical, Dublin, OH).

A standard algorithm for fluid resuscitation was used based on the initial chloride and carbon dioxide laboratory values.[10] Groups were defined as resuscitated (i.e., ready for the operating room) when serum chloride was ≥ 100 mmol/L or bicarbonate < 30 mmol/L and hypovolemic when serum chloride < 100 mmol/L or bicarbonate ≥ 30 mmol/L. Data were collected on emergency department admission and after a 20 cc/kg fluid bolus.

The data collected before and after bolus were analyzed by using signal processing algorithms developed in the MATLAB (MathWorks, Natick, MA) software. The objective of this analysis was to identify a quantitative relationship between the PVP waveforms and the intravascular volume status of patients.

Signal processing algorithm

Sampling

For each patient, the entire PVP waveform was divided into nonoverlapping windows of 10 s, with a sampling rate of 1000 Hz. There are total 329 windows from all hypovolemic patients, and 343 from all resuscitated patients. FFT was performed over the time domain signals in each window to obtain the frequency domain signal representation of components between 0 and 20 Hz.[13] A window size of 10 s yields a frequency domain resolution of $1/10 = 0.1$ Hz, meaning the space between two adjacent frequency domain samples is 0.1 Hz. Thus, there are a total of 200 frequency domain samples in each window between 0 and 19.9 Hz.

Logistic regression

Logistic regression with LASSO (Least Absolute Shrinkage & Selection Operator), Ridge, and Elastic-net are performed over the frequency domain data to establish the correlation between the frequency domain PVP waveform signals and the hypovolemic or resuscitated status of a patient.[14-16] Denote the frequency domain samples in the i^{th} window as a 201-dimension vector X_i, with the first element being 1 and the other 200 elements corresponding to the frequency domain samples between 0 and 19.9 Hz. Define a binary variable Y_i to represent the hypovolemic or resuscitated status of the i^{th} window, with $Y_i = 1$ for hypovolemic and $Y_i = 0$ for resuscitated. For each window, the logistic regression model can be used to calculate its probability of being in one of the two categories, as

$$P(Y_i = 1) = \frac{1}{1 + e^{-\beta^T X_i}}$$

$$P(Y_i = 0) = \frac{e^{-\beta^T X_i}}{1 + e^{-\beta^T X_i}},$$

where β is a 201-dimension regression coefficient vector to be determined through training and β^T is the matrix transpose.

The coefficient vector β can be calculated by minimizing the following negative log likelihood function during the training process:

$$l(\beta) = \sum_{i=1}^{n}\left[(1-y_i)\beta^T X_i + \ln\left(1+e^{\beta^T X_i}\right)\right] + \lambda P_\alpha(\beta),$$

where

$$P_\alpha(\beta) = \frac{1-\alpha}{2}\left|\left|\beta\right|\right|_2^2 + \alpha\left|\left|\beta\right|\right|_1$$

n is the total number of training windows, $||\beta||_1$ and $||\beta||_2$ are theL_1 and L_2 norms of β, respectively, and λ is a tuning parameter that can be selected using cross-validation (CV). If $\alpha = 1$, this regression becomes LASSO; if $\alpha = 0$, this becomes Ridge. Both LASSO and Ridge regressions are special cases of Elastic-net regularization that basically mixes LASSO and Ridge using the parameter$\alpha \in [0, 1]$.

Among all the windows, 70% from each category were randomly chosen as the training data, and the remaining 30% were used for testing. Specifically, in our experiment, 232 widows with $Y = 1$ and 242 windows with $Y = 0$ were used for training. We performed 5-fold CV with these training data to tune the parameter λ. Within each CV, 80% of the training data have been used for training purpose and 20% have been used to find the deviance for selecting proper λ. For our case, $\lambda = 0.0055$ gives the minimum deviance during CV, and it is used during the testing process for logistic regression with LASSO (Fig. 1). The optimum λ forced 158 of the 201 coefficients of β to be zero.[13]

Window-level classification

Once the coefficient vector β was estimated through the training process, the probability $P(Y = 1)$ for each window in the testing data was then calculated, and the calculated probabilities were thresholded at 0.5, that is, the window was classified as dehydrated if $P(Y_i = 1) > 0.5$ and hydrated otherwise. We evaluated 101 windows from resuscitated patients and 97 windows from hypovolemic patients. The classification results were compared with their true values for each window.

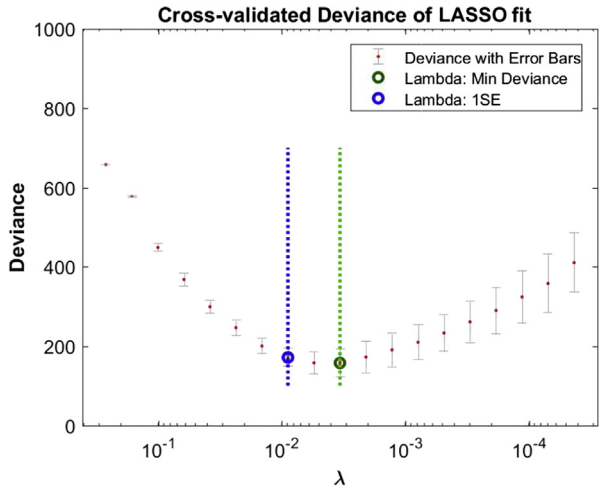

Fig. 1 – Cross-validation for optimizing the tuning parameter λ. The minimum deviance is obtained at $\lambda = 0.0055$. (Color version of figure is available online.)

Patient-level classification

Patient-level classification was determined as whether a patient is hypovolemic or resuscitated by using a collection of multiple PIV windows from the same patient. The patient-level classification was performed with a majority decision rule, which classifies a patient as hypovolemic if this patient has more windows classified as hypovolemic than resuscitated, and vice versa.

Comparison of study groups

The Kolmogorov-Smirnov (KS) two-sample test has been used to test the significance of the difference in frequency domain PVP data from hypovolemic or resuscitated patients.[17] The KS two-sample test is a nonparametric test that quantifies the difference between the empirical distribution functions of two group of data, which are the frequency domain PVP data from hypovolemic and resuscitated patients, respectively. To study the impact of the signals at different frequencies, the KS two-sample test is performed for signals at each frequency separately.

The setup of this hypothesis testing is H_0: hypovolemic and resuscitated samples have the same distribution at a frequency f Hz; H_1: hypovolemic and resuscitated samples have different distributions at f Hz. The KS two-sample test has been performed over the frequency range from 1.5 Hz to 5.5 Hz.

Results

Clinical demographics

Thirty-two patients were enrolled. Sixteen patients were excluded: 5 for incorrect PIV type, 9 for incorrect data collection times, and 2 for incorrect PIV location (scalp, hand).

Eighteen patients were compared in which 89% (16/18) were male and 39% (7/18) the first-born son. There was family history of HPS in 28%. The mean gestational age was 38 4/7 wk, mean age at study enrollment was 37.2 d, and mean admission weight was 3.93 kg. The mean days of projectile vomiting symptoms was 4.28 d. Average ultrasound measurements for width and length were 4.4 mm and 18.9 mm, respectively. No PIV infiltration occurred during data collection, which was monitored by the authors during each data point collection. No PIVs were lost during system setup.

Classification

Window-level classification

When the classification was performed on the window level, the logistic regression LASSO algorithm yielded a 97.95% sensitivity and a 93.07% specificity. Other models such as Ridge and Elastic-net shows almost similar performances

Table 1 – Summary of results for Elastic-net, LASSO, and Ridge regression.

α	Training sensitivity, (%)	Training specificity, (%)	Testing sensitivity, (%)	Testing specificity, (%)	Non-zero coefficients
0.0001	94.40	95.87	97.94	93.07	201
0.5	99.57	99.59	96.91	93.07	73
0.75	99.57	100	96.91	92.08	64
1	99.57	99.17	97.95	93.07	43

(Table 1). The LASSO model is more significant than others because it offers a sparse solution with the coefficients at many frequencies to be 0; thus, it helps us understand the impact of the PVP signals on the dehydration level at different frequencies.

Patient-level classification

Patient-level classification was determined as whether a patient is hypovolemic or resuscitated by using a collection of multiple PIV windows from the same patient. The patient-level classification was performed with a majority decision rule, which classifies a patient as hypovolemic if this patient has more windows classified as hypovolemic than resuscitated, and vice versa.

Peripheral venous waveform signal analysis

The KS two-sample test was performed over the frequency domain data from all patients to test the difference between the PVP waveforms of the hypovolemic and resuscitated patients at different frequencies. The results of the KS two-sample test are depicted in Figure 2, where the logarithm of the *P*-value is shown as a function of the frequency (Fig. 2). The *P*-value is defined as the probability that the null hypothesis H_0 is true; thus, a small *P*-value means a bigger difference between the two distributions. It is clear from this figure that the two samples have different distributions (reject H_0). Specifically, the smallest *P*-values are observed around the f_1 frequency at 2.4 Hz, which corresponds to the heart rate of 144 bps of pediatric patients. The corresponding empirical cumulative distribution functions of the two groups of data at 2.4 Hz are shown in Figure 3, which again clearly shows the difference in distributions between the two groups of data (Fig. 3).

A similar KS two-sample test with resuscitated patients was performed at the frequencies $f_2 = 4.8$ Hz and $f_3 = 7.2$ Hz, respectively. These two frequencies are the second and third harmonics of f_1. The KS two-sample test was performed between signals collected from resuscitated patients before and after bolus. This KS two-sample test yields a *P*-value of 0.0053 at f_2, and a *P*-value of 0.5154 at f_3. For comparison, the *P*-value obtained from the same test at f_1 is 0. With a significance level of 0.5%, it can be concluded that there is no significant correlation between the volume status of resuscitated patients and the signals f_2 and f_3. On the other hand, strong correlation is observed between volume status and the PVP signals at the heart rate frequency f_1.

To further highlight the difference in PVP signals, the admission PVP signals were compared between 10 (56%) children and 8 (46%) hypovolemic patients. The PVP signal power was higher in resuscitated patients (median 0.174 mmHg, IQR: 0.079-0.374 mmHg) than in hypovolemic patients (median 0.026 mmHg, IQR: 0.001-0.057 mmHg), ($P < 0.001$).

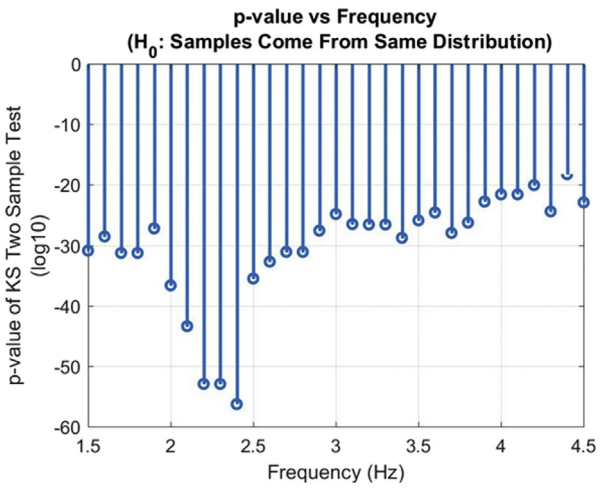

Fig. 2 – P-value of the Kolmogorov-Smirnov two-sample test over frequency range 1.5 to 4.5 Hz. (Color version of figure is available online.)

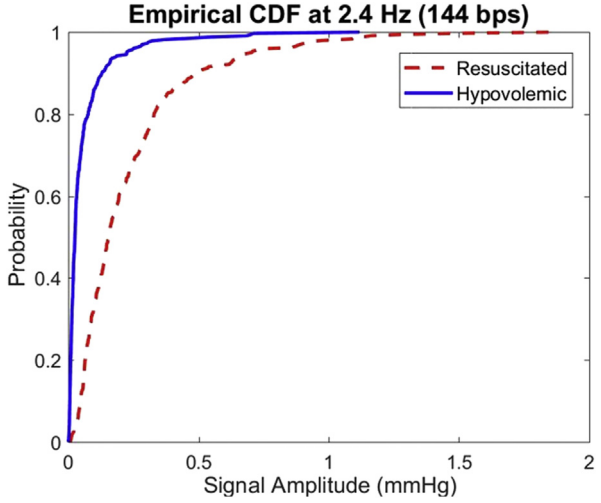

Fig. 3 – The empirical cumulative distribution functions (CDFs) of data from hypovolemic or resuscitated patients at 2.4 Hz. (Color version of figure is available online.)

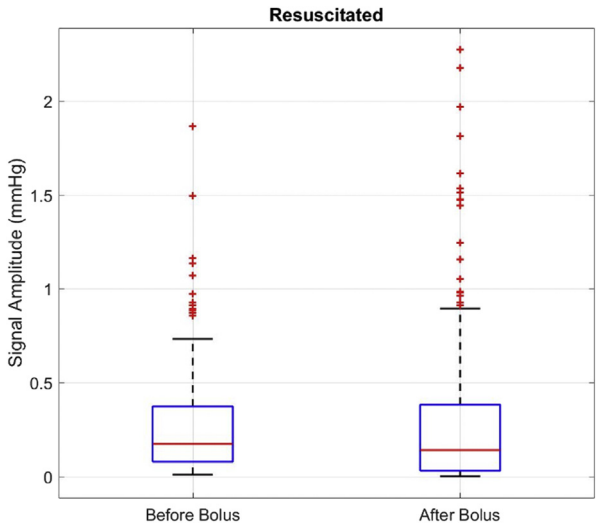

Fig. 4 – Box plot of peripheral venous pressure (PVP) signal amplitude at 2.4 Hz for resuscitated patients before and after bolus. The signal amplitude does not change significantly. The outliers are plotted using "+" symbol in the figure. (Color version of figure is available online.)

A total of 14 patients received a bolus regardless of laboratory values: 6 (43%) resuscitated and 8 (57%) hypovolemic. The box plots of the PVP signal power at 2.4 Hz for resuscitated and hypovolemic patients are shown in Figures 4 and 5, respectively. In resuscitated patients, the signal power did not change significantly after the fluid bolus (median 0.142 mmHg, IQR: 0.032-0.383 mmHg) ($P = 0.019$), whereas significantly increased signal power (median 0.0474 mmHg, IQR: 0.019-0.110 mmHg) was observed in the hypovolemic patients after a fluid bolus. ($P < 0.001$) (Figs. 4 and 5).

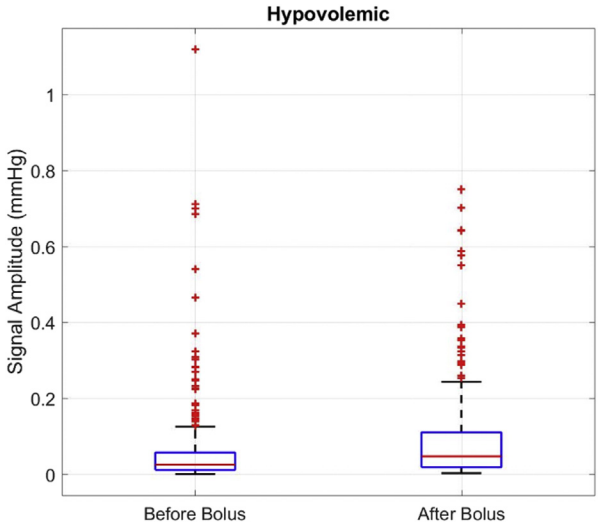

Fig. 5 – Box plot of peripheral venous pressure (PVP) signal amplitude at 2.4 Hz for hypovolemic patients before and after bolus. The signal amplitude changes significantly due to bolus. The outliers are plotted using "+" symbol in the figure. (Color version of figure is available online.)

Discussion

In this proof of concept study, PVP waveform analysis determined volume status by predicting dehydration. We found that the PVP waveforms have higher amplitudes when comparing resuscitated patients with hypovolemic patients, which associated to above and below a chloride value of 100 mmol/L. In addition, we found the PVP signal power changed significantly after IVF bolus in hypovolemic patients. These findings may guide physicians using a noninvasive venous waveform to assess volume status and direct resuscitation in an awake pediatric patient via a PIV.

In the United States alone, dehydration affects 30 million children annually and accounts for 400,000 pediatric emergency room visits.[1,16] Several existing studies have attempted to define level of dehydration.[18-22] In children, there is no standard of care for volume status measurement and is still a diagnostic challenge. Unrecognized dehydration or incorrect estimation of its degree can adversely affect the morbidity and mortality of a dehydrated infant.[23,24] On presentation, the degree of dehydration was traditionally assessed based on history and physical examination findings alone; however, this practice was called into question as being too subjective.[18] Measurements of body weight, use of clinical scales, physical examination, urine output, and laboratory values have been studied. The difference in body weight between the ill weight and the pre-illness or baseline weight of the patient is used; however, these weights may not always be available to the clinician and variation among different weight scales used can make it challenging to apply clinically.[19] In response, more objective clinical scales were developed and patients were stratified into severity groups.[2,3] Based on this stratification, many patients are resuscitated with IVF; however, endpoints of resuscitation remain subjective. Some clinicians rely on physical examination findings such as skin turgor and capillary refill. Unfortunately, these are less precise and cannot be monitored continuously. Urine output can be monitored in real time but requires invasive catheter placement into the bladder or weighing of diapers. Many clinicians also use laboratory values including sodium, bicarbonate, lactate, and urine specific gravity to assess adequacy of resuscitation[20-22]; however, reliance on these values have several drawbacks: invasive venipuncture is required, the dehydrated state can lead to difficulty accessing small caliber veins for blood draws, and specimens can be hemolyzed. In addition, serum electrolytes can vary depending on the disease state, which caused the dehydration and may be of limited value for detecting the degree of dehydration.[20] In selected cases, electrolyte abnormalities may exist including derangements in sodium levels or acidosis characterized by low bicarbonate levels or elevated lactate levels. Urine specific gravity and presence of ketones can assist in the evaluation of dehydration.[21] End-tidal carbon dioxide measurements have been studied in an attempt to assess degrees of dehydration in children but as of now have not proven to be an effective tool in determining the level of dehydration.[22] A gold standard assessment of dehydration is still lacking.[18-22]

Recent attempts have been made to use existing technology as an objective, noninvasive means of assessing

intravascular volume status in real time. Assessment by near-infrared spectroscopy has been studied using regional oxygen saturation as a surrogate for intravascular volume status.[24] However, there are no accepted normal standards for children of varying ages and body mass indices. Use of point-of-care bedside ultrasound has shown the most promise. Although assessment of inferior vena cava (IVC) collapsibility during inspiration has been less reliable, measurement of the IVC to aortic ratio (IVC/Ao) using this modality allows the user to more objectively assess adequacy of resuscitation.[21,25] In a previous study of HPS patients, Wyrick *et al.* found that as hydration status improved, IVC/Ao ratio approached 1. Specifically, a ratio of 0.75 correlated to a serum bicarbonate level of 30 mmol/L, an accepted endpoint of resuscitation for this disease process.[25] This ratio is similar to values found by other groups when ultrasound was used for assessment of dehydration from acute gastroenteritis.[25-28] The search for a rapid, noninvasive, and accurate method for assessing the degree of hydration in infants is mandatory especially in countries with limited resources.[28] Analysis of PVP waveforms could represent a modality to assess volume status via noninvasive means.

The venous system is a highly compliant system that can accommodate large changes in volume with minimal changes in pressure. Compensatory venous vasoconstriction to volume depletion diverts blood from the periphery to the central vasculature to maintain cardiac output and ultimately end-organ perfusion.[29] This may explain the insensitivity of arterial blood pressure, pulse rate, and PVP to initial volume depletion. PVP waveform analysis of the venous system was not rigorously examined until appropriate sensing and amplifying technologies became available.[29,30] PVP is measured after PIV catheter insertion, the most common procedure performed in the United States.[31] Detection of these small changes in PVP became possible through analysis of FFTs, which are highly sensitive to changes in venous compliances due to volume.[32,33] PVP waveform analysis of compensatory venous changes represents a significant paradigm shift from dynamic arterial-based measurements.[34] Venous waves are generated by the cardiac cycle and propagated as harmonics.[32] The f_1 waveform that correlates with the heart rate is affected by mild hypovolemia.[33] Alian *et al.* proposed that f_1 was associated with a decreased venous blood volume so that the venous waveform is no longer transmitted back from the right atrium.

For hydrated patients, a strong correlation was found at the frequency near the heart rate of the patients (f_1). Our analysis proposes an additional mechanism of hydromechanical interaction to explain the change in f_1 that correlates the heart rate with hypovolemia. In the hydrated patient, the signal from arterial pulse pressure waveform crossover to the venous side of the systemic circulation becomes stronger (Fig. 6). The hydromechanical interaction between the arterial and the venous side of the circulation depends on the diameter of the veins and arteries, which in the dehydrated state is lower than in the hydrated state. Hence, in the hydrated state, the direct physical interaction or at least the increase in proximity between the veins and arteries is responsible for the crossover of the pulse pressure waveform. The most demonstrative frequency was 2.4 Hz, equaling 144 beats per minute,

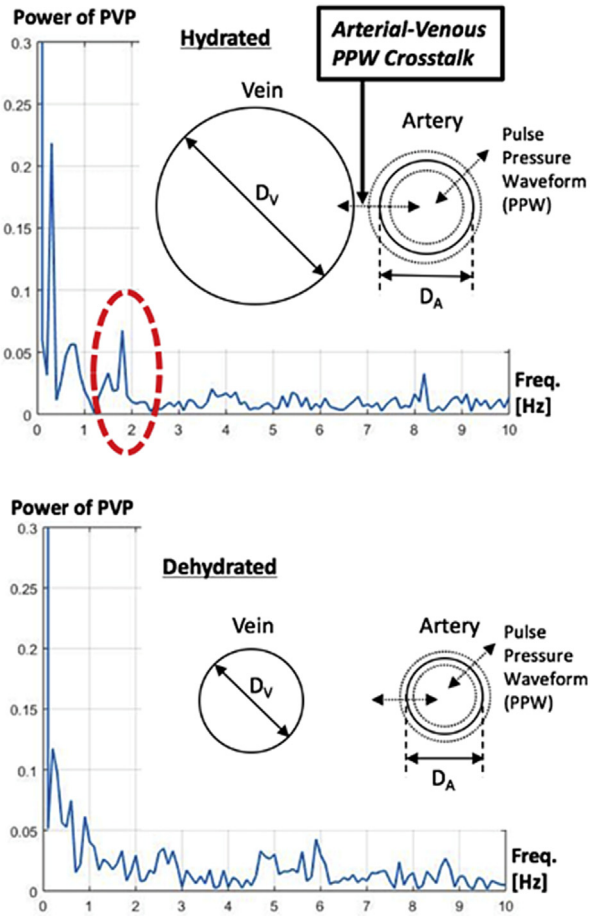

Fig. 6 – The power spectral density (PSD) of peripheral venous pressure (PVP) for the hydrated patient (top) identifies a peak at frequencies around the heart rate (red dotted line). In this example, the peak is shown at approximately 1.8 Hz = 108 bpm. In the same patient during dehydration (bottom), this phenomenon does not exist. The vein diameter (D_V) is significantly larger in the hydrated state. The arterial diameter (D_A) changes slightly between hydration and dehydration. Combined, this causes the hydromechanical interaction of pressure signals between the arterial and the venous side of the circulation to be stronger when the patient is hydrated. (Color version of figure is available online.)

which is a very realistic heart rate for dehydrated pediatric patients. This hydromechanical crossover interaction may be impacting the change in f_1 in a combination with the theory proposed by Alian *et al.* described previously.

There were study limitations. The study was of a limited number of patients with HPS who were categorized as resuscitated or hypovolemic based on laboratory values. The laboratory values provided an objective means of comparison; however, no absolute values of volume status could be determined. Chloride has not been a validated marker of dehydration but is an accepted endpoint of resuscitation in HPS, and its use in more critically ill children with other causes of dehydration is unknown.[10,12] The study only assessed a change in the PVP waveform signal from baseline

to after fluid bolus. This limitation is documented in other PVP waveform analysis articles; however, finding a strong correlation between fluid bolus given and change in the PVP waveform signal is evident.[34] Another limitation of the study was waveform variation based on type of PIV, PIV location, clots or air in arterial tubing, and inability to collect proper waveforms.[35] One physician was responsible for accurate waveform collection, and those patients were excluded from the study; however, some variation may still exist.

HPS was chosen as the model because laboratory values have been used as a predictive marker for the level of dehydration and subsequent volume needed for resuscitation. All HPS patients are hypovolemic and received some level of IVF resuscitation. This allows us to compare the dehydrated state with a more hydrated state within an individual and determine if there are changes in the PVP signal that reflect the amount of rehydration. Future models considered are dehydrated patients secondary to diabetic ketoacidosis or severe gastroenteritis. Our fundamental hypothesis is that the absolute pressure is not as relevant as the signal from venous augmentation during circulation. Static measures of fluid responsiveness such as central venous pressure (CVP) may not be the most appropriate and may be less accurate physiologically than dynamic measures.[36,37] No age-specific CVP norms have been defined, and the comparison of CVP to FFT of the PVP waveforms has not been performed in the pediatric population. Moreover, CVP may be less accurate in the infant population specifically those that require central venous access for resuscitation, that is, patients with complex congenital heart disease or chronic lung disease. Those patients with abnormal cardiopulmonary systems would introduce more variability into the experimental model.

This clinical model represented a homogenous group of awake patients without comorbidities and were dehydrated. Results from this study shows that PVP waveforms can be performed and predict dehydration. The ideal modality to determine dehydration in the pediatric age group would be reproducible, noninvasive, user-independent, and provide a real-time assessment of volume status which this study supports. PVP waveform analysis has the potential to monitor volume status in other clinical conditions such as perioperative goal-directed fluid therapy, congestive heart failure optimization, acute kidney injury, trauma, and hemorrhage.[34] This description and utilization of PVP waveforms in pediatric patients could significantly change the evaluation and management of volume status in children using a future technology that can adjust the rate and volume of fluid administration based on continuous PVP waveform analysis. This novel approach to a more objective assessment of dehydration in the pediatric population serves as an interesting pilot study for a hypothesis generating data in future studies and more general populations.

Conclusion

FFT of PVP waveforms is a novel modality that can assess volume status and predict dehydration in HPS. PVP waveform analysis can predict dehydration with a 97.75% sensitivity and a 93.07% specificity. We showed that fluid bolus administration in an awake pediatric patient can be performed possibly offering a significant advantage over dynamic monitoring modalities. Further work is needed to determine the utility of PVP analysis to guide fluid resuscitation status in children, which could profoundly impact treatment of dehydration in children.

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Authors' contributions: Study conception and design was performed by P.C.B., K.W.S., J.M.B., and M.S.D. Acquisition of data was performed by P.C.B. Analysis and interpretation of data was performed by P.C.B., M.A.H., J.W., H.K.J., M.O.J., and M.S.D. Drafting of manuscript was performed by P.C.B. and M.A.H. Critical revision was performed by all authors. Statistical expertise was provided by M.A.H., J.W., H.K.J., and M.O.J. Supervision was by M.S.D.

Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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