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Using Peripheral Venous Pressure Waveforms to Predict Key Hemodynamic Parameters

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Using Peripheral Venous Pressure Waveforms to Predict Key Hemodynamic Parameters

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Abstract

Analysis of peripheral venous pressure (PVP) waveforms is a novel method of monitoring intravascular volume. Two cohorts were used to study the hemodynamics change of the body state and its influence on the PVP using (1) dehydration setting with infants suffering from pyloric stenosis and (2) hemorrhage setting during a craniosynostosis elective surgery. The goal of this research is to develop a minimally invasive method of analyzing the PVP waveforms and find correlations with volume loss.

Twenty-three pyloric stenosis patients PVP were acquired at five stages and were divided into euvolemic, normal fluid volume, and hypovolemic, significant fluid loss. Seven craniosynostosis patients were enrolled and the PVP was acquired at the intervention to explore if the isoflurane dosage influences the PVP. A multivariate analysis of variances (MANOVA) was used to test if the PVP was influenced by the volume change and the anesthetic drugs effect. Prediction algorithms based on Fast Fourier Transform were utilized at the two cohort patients analyses to classify an arbitrary PVP into its correct classification.

Our research found that PVP signal is influenced by the different hemodynamics states of the body. Based on MANOVA outcomes, we built prediction systems and they were able to categorize an arbitrary PVP signal into its correct classification. The k-nearest neighbor (k-NN) model correctly predicted 77% of the data in the euvolemic and hypovolemic groups. The k-NN models of the anesthetic drugs were able to correctly predict correctly at least 85% of the preoperative and intraoperative signals of the pyloric stenosis patients and the different isoflurane dosages of the craniosynostosis patients.

Analyzing the PVP signal is a promising tool for measuring the dehydration level in acute settings. Our results imply that the subsequent changes in vascular resistance due to inhaled and

infused anesthetics are reflected in the peripheral veins. A technology that would accurately assess the volume status of a patient to guide triage and treatment would be a significant improvement in various care settings. This minimally invasive technology utilizes a standard peripheral intravenous line and a commercial pressure-monitoring transducer, which exist today and requires no new clinical skills.

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Author

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Chapter 1: Introduction

Dehydration occurs when the amount of fluid entering the body is less than the amount that the body loses. Dehydration affects everyone differently and rehydrating the tissues differs based on the dehydration symptoms. For example, an athlete would be dehydrated during workout session but drinking water helps to restore the lost fluid. Another example of dehydration is when an infant is born with pyloric stenosis, which causes forceful vomiting because the pylorus muscle is stenosed and food cannot enter the intestine. A surgery is required to widen the pylorus muscle and resolve dehydration (Steele and Humphries, 2012). The human body contains approximately 60% water, making it difficult for the body to function with less fluid especially when there are sores or injuries. The body needs to be hydrated to keep the heart in a regular state since undergoes stress when the fluid amount goes below the normal level of the body. When there is less fluid volume, the heart rate increases to inject more blood through arterial vessels to deliver more blood to the organs which do not function well without the oxygen within the blood (Joyner and Casey, 2015). Moreover, dehydration changes the mechanical properties of the biological tissues. Not only outer skin is affected by dehydration, but also the internal organs are disrupted. Thus, the response to the occurred deformation between hydrated and dehydrated tissues is different depending on how dehydrated they were and the time to recover (Suchý et al., 2018). The tissues are in danger of being damaged if there is not enough fluid volume during the stress for a long time.

In order to emphasize the dehydration risks, we implemented a biaxial test experiment that compares between dehydrated and hydrated tissues in terms of their response to stress. The expectation results of this experiment are to have higher deformation degree in the dehydrated sample which reflects the actual damage that happens to the human body if the dehydration was

not treated. Moreover, the hydrated tissues should show less destructive mechanism under stress because of the amount of fluid in them. The experiment steps are explained in **Appendix A**.

In figure 1, the curve of the dehydrated sample is inclined resulting in having more stiffness in the tissue whereas the hydrated sample has less stiffness. As the tissue loses water, the possibility of damaging the tissue permanently is higher. Also, the hydrated tissue can handle more stress and pressure without getting damaged comparing to the dehydrated sample.

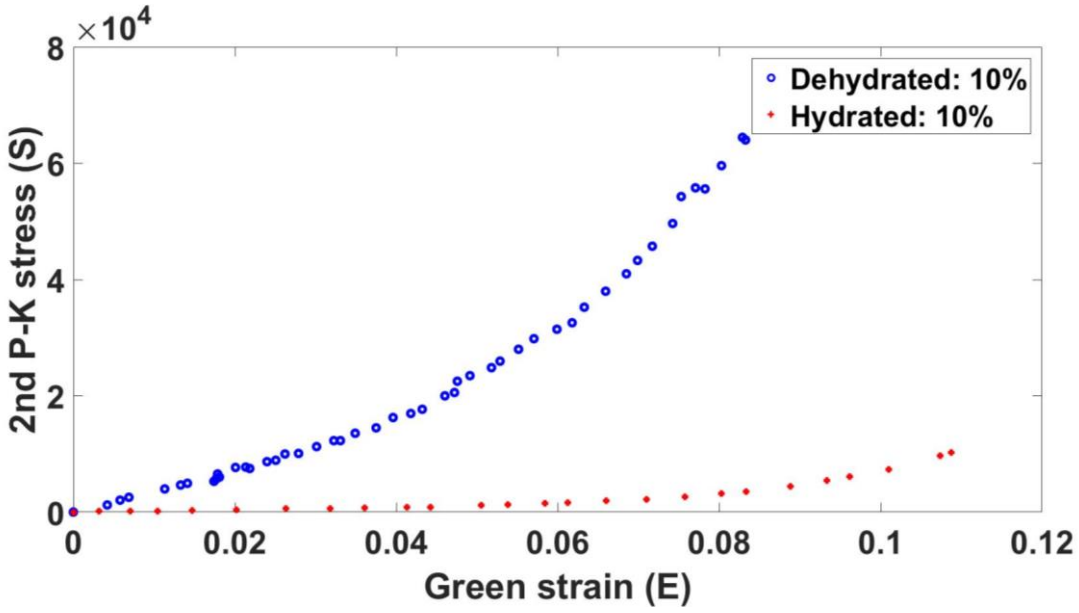

Figure 1: The strain-stress curves of hydrated and dehydrated samples at 10% stretch ratio

The results from the previous experiment showed that dehydration has to be treated as soon as possible to avoid tissue damage. However, dehydration is subjective and depends on many factors including age, body weight, and physical activity (Riebl and Davy, 2013). The proper way to measure the amount of fluid loss is to calculate the weight difference between before and after the symptom's appearance (Yang, Jeon, Min, & Lee, 2017). However, it is not necessary that all the patients have a medical record in the hospital and in some cases the patient needs an immediate care in the emergency room which makes it inconvenient to only depend on the weight difference.

Thus, there are many studies that are trying to use the engineering perspective to find different ways to quantify dehydration such as blood sample test and other non-invasive methods.

1.1. Literature Review

The levels of electrolytes in the blood can be used as a dehydration indicator and it requires blood sample test. However, in some cases it might be difficult to draw blood from the patients because dehydration causes vasoconstriction, especially in pediatrics, and sometimes it is not easy to find the vein (Yang et al, 2017; Bonasso, 2016).

Biological components, plasma, saliva, body mass, and urine output, were hypothesized to assess dehydration (Cheuvront, Ely, Kenefick, & Sawka, 2010). Eighteen soldiers volunteered in the study and they were given a specific diet instruction for two weeks. During the first week, participants were asked to drink 3 liters of water during the day to stay hydrated over three days. Simultaneously, the biological parameters were measured over the three-day period. In the second week of the study, the biological parameters were measured while participants were dehydrated and exercising for 50 minutes with 10 minutes rests over four hours. After that, study participants had a regular-size meal with small amount of water and the parameters were measured again. The study found that the biological parameters for both weeks were almost identical except for Plasma Osmolality (P_{osm}) which showed to be a promising tool for estimating dehydration. However, blood samples do not provide a continuous dehydration assessment and it is difficult to rely on the electrolyte levels to assess dehydration.

Non-invasive methods are preferred to avoid interfering with the patient's internal organs and exposure to the outside surrounding. Also, it helps to assess the volume change in the patient without surgical intervention. Non-invasive methods also save the trouble of finding the vein to take blood samples, especially in pediatric patients.

A non-invasive dehydration indicator was proposed by Yang et al (2017), and in their observational study they were testing the relationship between end-tidal carbon dioxide ($ETCO_2$) and fluid loss in the patients. The investigators used bicarbonate concentration (HCO_{3-}) in the blood and clinical dehydration scale (CDS) score as the control parameter that validate the $ETCO_2$ results. 105 pediatric patients with acute gastroenteritis were enrolled in the study and the level of HCO_{3-} was measured and CDS score was computed individually for each patient. The study showed a weak correlation between $ETCO_2$ and HCO_{3-} and the relationship between CDS score and $ETCO_2$ was uncertain. This means that $ETCO_2$ may not be used as a dehydration assessment parameter and more research is required in this area.

The ratio between Inferior Vena Cava (IVC) and aorta (Ao) diameters is a non-invasive method to quantify dehydration. Mazza et al (2019) investigated if the IVC/Ao ratio is less in the dehydrated patients than hydrated patients. 24 hydrated and 35 dehydrated patients were enrolled in the study. The researchers placed the array transducer on the patients in a way the aorta and IVC could be observed in a cross-section view. The cutoff point of the IVC/Ao fraction to determine the hydration status was 0.8 as suggested by previous researchers who did their research with American pediatric patients. The results of this study showed that the IVC/Ao ratio did not support the study hypothesis and their results were not as expected because they did the study in rural Panama cities. Also, the IVC/Ao threshold that they picked might not have been appropriate for Panama society.

Terahertz (THz) radiation is a type of magnetic wave and it has been used in different fields such as chemical material identification. In 2017, Guo et al hypothesized that THz technology is sensitive to water content in biological tissues. They used six samples of muscle and adipose tissues from three different animals: porcine, cattle, and mutton. The samples were dehydrated at

different levels and images were taken to the samples. Then, the quality of the THz images was improved using a reconstruction algorithm. Researchers were able to observe the differences between the dehydration levels between the two different tissue types, muscle and adipose, due to their differences in the histological properties. Adipose tissues have less water compared to the muscle tissues. They also noticed that as the adipose tissues became more dehydrated, the waves absorption decreased. Moreover, as the amount of water within the biological tissues increased, the THz wave absorption becomes higher whereas THz waves were transmitted through the tissues that have less water content.

Refilling time (RT) is another technique used to assess dehydration. It is a fast method and depends on the time it takes the skin to return to its original color. If the time is more than two seconds, the patient is considered dehydrated (Caruggi et al., 2018; "Capillary nail refill test", 2017). In 2018, the RT approach was tested by Caruggi et al on 242 pediatric patients who suffered from vomiting and/or acute diarrhea in the study. The procedure that was followed in this study was to apply a gentle pressure on the patient's finger for five seconds and then measured the time it took the skin color to be restored. They used other parameters to validate their RT results such as weight difference percentage and clinical dehydration scale score. However, not all the patients' previous weight information was recorded in their report, so the study investigators could not verify the hypothesis among all the enrolled patients; it is one of the study limitations. In this study, they also were trying to compare between how subjective the RT method was, and they compared between the nurse and physicians' RT evaluations. They found that in most of the cases there were no difference between the two evaluations meaning that there is no subjectivity variable in the RT exam.

Another study by Visser, Kieser, Dellimore, Heever, & Smith used four non-invasive sensors: Capillary Refill Time (CRT), Skin Recoil Time (SRT), Skin Temperature Profile (STP), and Infrared Spectrometry (ISP) to assess dehydration (2017). A CRT sensor was connected to a pressure pad that puts pressure on the patient's skin and a camera was used to record the time from releasing the pressure pad till the skin color was restored. The SRT sensor was placed on the sternum of the patient while the physician was performing a skin recoil test on the patient's abdomen while the camera started to capture the skin images. A STP sensor was used to measure the temperature of the skin to test if it was related to the dehydration. An ISP sensor was used to measure the amount of water in the biological tissues and the wavelength was short to ensure a deep skin penetration. The results from the four sensors were compared to the percentage of weight loss of the patients to evaluate the outcomes accuracy. The study resulted in having weak or no correlation between the hydration status and the CRT, ISP, and STP sensors. Nevertheless, the SRT sensor was the only sensor that showed a correlation with the volume changes in the body.

Although the previously described non-invasive methods have advantages, they all have some drawbacks and they may not be appropriate to quantify volume change. First, some of these tools are subjective which makes it difficult to confirm the dehydration results. Not only are they subjective, but also, they do not provide a continuous dehydration assessment which is important in some clinical settings to see the improvement of the patient's health. Furthermore, some non-invasive methods require advance knowledge about running the device and obtaining the results, which may not be applicable in emergency cases.

Central venous pressure (CVP) is a common method in intensive care unit to measure circulatory or preload blood volume (Desjardins et al., 2004) and it can be used to monitor blood volume change. CVP is measured from Superior Vena Cava using a catheter that is inserted

through subclavian or external or internal jugular veins. Consequently, it is not a convenient tool to be used due to its invasiveness and its impractical at the emergency room situations. Thus, studies were focusing on another point in the vein circulation which is peripheral venous pressure (PVP) that can be measured from the limbs' veins. PVP has the advantages of being less invasive method and it is easy to access (Munis, Bahatia, & Lozada, 2001; Desjardins et al., 2004; Tugrul, Camci, Pembeci, Darsani, & Telci, 2004).

Munis et al. (2001) hypothesized that CVP and PVP are correlated and using one of them would provide the same results. In their research, they enrolled 15 patients undergoing complex spine surgery or craniotomy. They measured the PVP and CVP during the surgery and then used regression to calculate the Pearson's correlation coefficient, which was strong among all the patients except two which had approximately 20% correlation coefficient. The researchers commented on these two patients and said that the correlation between PVP and CVP was weak because of the small changes in PVP measurement that was caused by the hemodynamics instability. Also, they noticed that the difference between PVP and CVP measurements in these two patients was higher than the other patients which they hypothesized that this was one of the reasons that the correlation was weak.

In another setup, the PVP and CVP correlation hypothesis was tested by Desjardins et al., (2004) in a cardiopulmonary bypass operation at which they were trying to test whether PVP provides the same conclusion as CVP regarding the volume change. The study concluded that both measurements, PVP and CVP, had a maintained relationship in irregular cardiac function patients. The researchers noticed that the CVP and PVP difference was within 3 mmHg range which supported the Munis et al. (2001) explanation.

Measurements using the blood pressure in the veins CVP and PVP provides a continuous dehydration assessment and both of them eliminate the subjectivity variable to assess the volume change. However, PVP has the advantage of being minimally invasive compared to the CVP and according to the previous studies, PVP can replace CVP in most cases.

1.2. Research Objective

Venous circulation does not have much research focus even though it is as important as the arterial circulation and provides volume status assessment. The purpose of this research is to use the peripheral venous pressure (PVP) to quantify the volume change at different hemodynamic settings. Making a decision about the fluid that the body lost as fast as possible and precisely helps to determine how much fluid the patient needs especially in emergency cases such as car accidents and military uses. The data used in this research is clinical data from Arkansas Children's Hospital and we are collaborating with the University of Arkansas for Medical Sciences (UAMS). Two cohorts of patients, pyloric stenosis and craniosynostosis, were used in the analysis after obtaining a formal consent from the patients' guardians. Based on the measured PVP data, we have two main hypotheses that are the core of this research:

1) The first hypothesis is that the volume status of the body influences the PVP signal. This proposition is influenced from the research that concluded that PVP can be used as a volume change indicator. This hypothesis was tested using the recorded PVP signal of the pyloric stenosis cohort patients.
2) The anesthetic drugs that patients receive before any intervention change the physiology of the blood circulation in the vessels causing vasodilation to the vessels. Our second hypothesis was that anesthetic drugs, inhaled or infused, influence the PVP signal significantly. The hypothesis was tested using both cohorts. The first setting is

during the pyloromyotomy at which the patients are under infused anesthetic, propofol, and the PVP signal during the operation was compared to the preoperative PVP signal. The second setting is during craniosynostosis surgery at which the inhaled anesthetic, isoflurane, was used and the PVP signal was measured during the intervention. The craniosynostosis cohort patients were used to test how varying the inhaled anesthetic dosages change the PVP significantly.

Chapter 2: Methods

2.1 Data Acquisition

Peripheral venous pressure (PVP) was measured with a 24-gauge Insyte-N Autoguard peripheral intravenous catheter (Becton Dickinson Infusion Therapy Systems, Sandy, Utah, USA) and it was linked by a 48-inch arterial pressure tubing (Smiths Medical, Dublin, Ohio, USA) to a Deltran II pressure transducer (ADInstruments, Colorado Springs, CO, USA). The hardware system was connected with the *LabChart* program (ADInstruments) (Bonasso, Dassinger, Jensen, Smith, Burford, & Sexton, 2018).

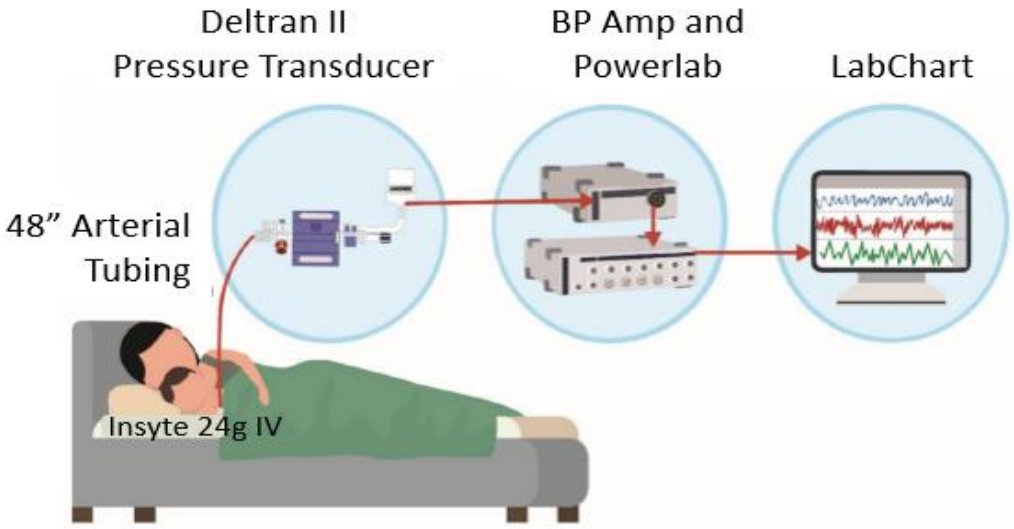

Figure 2: Acquiring PVP data setup. From "Optimizing peripheral venous pressure waveforms in an awake pediatric patient by decreasing signal interference," by P. Bonasso et al., 2018, Journal of Clinical Monitoring and Computing, 32(6), p. 1150.

The pressure transducer is sensitive to situations such as bed movement, infant’s crying, or apparatus errors, causing big spikes in the recorded PVP waveform (Figure 3) (Bonasso et al., 2018).

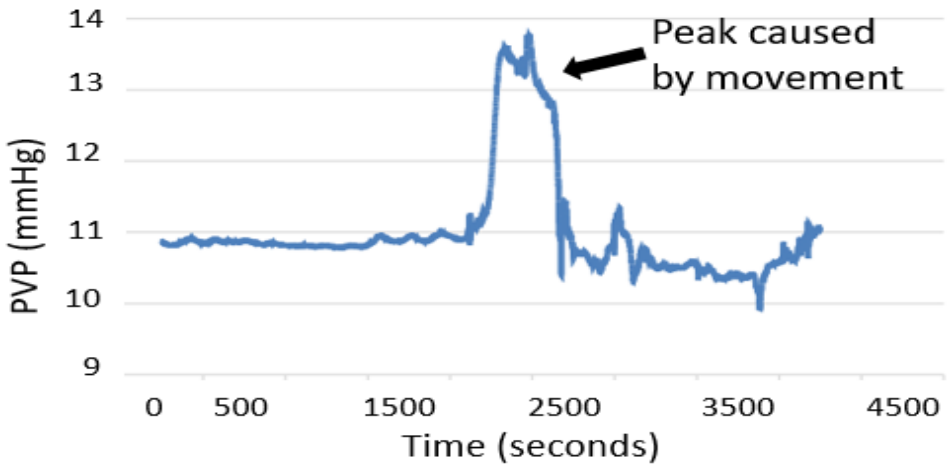

Figure 3: Example of spikes in the PVP signal

Those unwanted parts of the signal can be removed via manual or automated methods. However, adding two signals together after removing an unwanted part between them may result in artifacts in the frequency domain. To resolve this issue, the recorded PVP signal was divided into 10-second segments and any segment with spikes would be discarded from the analysis. Therefore, all the used segments in this research do not have any spikes within them.

2.2 Data Cleaning

2.2.1 Manual Cleaning

The manual cleaning method to get rid of the spikes is subjective and the person who is removing the spikes has to start from the beginning of the recorded PVP signal and highlight the parts that do not have any noise. However, the selected parts have to have a continuous 10-second length without spikes which consumes time and it might take 2 hours to clean a 10-minute PVP signal, especially if some recorded PVP signal is more than three hours.

2.2.2 Auto-Cleaning Algorithm

The algorithm takes sections of the PVP data at a user-selected length of time to evaluate. The algorithm calculates the remainder of the PVP signal divided by pre-selected time length, the

length of the segment, and then remove the last points of the signal that are equal to the PVP signal remainder. These two steps assure that every single segment has the same duration for all the patients. The next step is to take a segment at a time and calculate the mean and the standard deviation. The criteria to keep or remove the segments is to check if there is at least one point that is outside the range that the user has selected before based on their preferences.

$$mean \pm n * standard\ deviation$$

In the previous equation, *n* represents the number of standard deviations that the user has chosen for the data to fall into and be kept. If the data in a segment goes above or below *n* standard deviations from the mean, the algorithm discards that entire section of data (Figure 4).

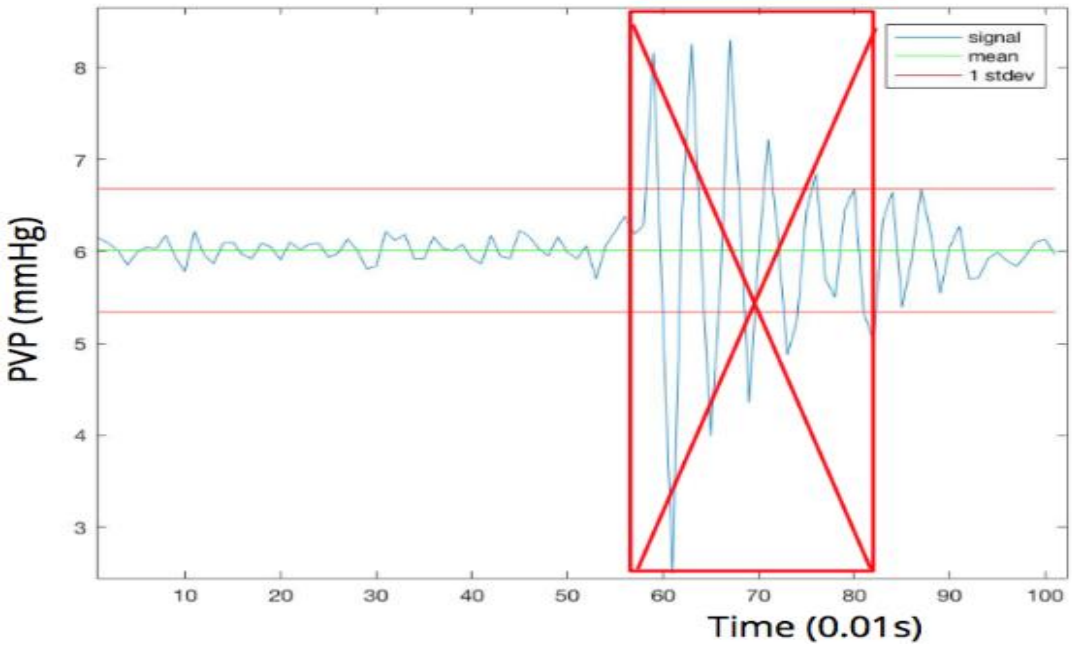

Figure 4: Cleaning algorithm criteria

2.2.3 Comparison between Auto and Manual Cleaning Methods

Cleaning the venous pressure, PVP, manually is not convenient because it is time consuming and is subjective. Not only that, but also it might lead to data loss if the computer breaks due to large amount of data stored in the temporary memory.

On the other hand, the developed cleaning algorithm undergoes the total PVP waveform which is in some recorded PVP longer than an hour in less than a minute. Also, cleaning the signals using the algorithm removes the subjectivity variable. The automated cleaning algorithm usually removes more sections of the data than manual cleaning, so it is more restricted tool than the manual cleaning. The restriction level of the cleaning can be changed by adjusting the number of standard deviations.

2.3 Fast Fourier Transform

Each segment of the PVP signal is transformed into the frequency domain using a built-in Fast Fourier Transform (FFT) function in *Matlab, fft*. The analyses in this research were in the frequency domain because it reduces the cost and time of the testing and it is more stable because of the absence of the negative feedback. Also, frequency domain is used to check the dominant amplitudes that reflects many factors such as the heart pulse and respiratory rate (Hocking et al., 2017).

The resolution of the frequency domain is 1 divided by the window length which is 10 seconds in this research. Thus, the frequency domain resolution is 0.1 Hz which represents the distance between two frequency samples (Bonasso et al., 2019). Furthermore, it is more helpful if we use only up to 20Hz and get rid of the rest of the frequencies. When converting the data to the frequency domain, the result is two mirrored values at different frequencies, so using just the first 20Hz makes sure that the used bins do not belong to the same frequencies. Furthermore, there is no useful information after the 20^{th} bins since nobody can have a heart rate that is greater than 20Hz. Thus, the total number of bins is 200 and each bin is a feature of the PVP signal at different frequency with 0.1 step frequency size. However, we down sampled the 200 features by a factor of 4 leading to have a 0.4 step frequency size with 50 points for each 10-second segment. The

down sampling ensures that the number of observations is more than the number of variables to get reliable results because having 200 frequency features in our research may not be fulfilled in some recorded PVP waveforms due to the small number of observations, less than 200.

2.4 Pyloric Stenosis Patients

Thirty-nine pyloric stenosis patients were admitted into the emergency room (ER) and went through the regular dehydration procedure that ER follows. Three patients were excluded because of the use of a different catheter leading to have different PVP waveforms (Bonasso, Dassinger, Jensen, Smith, Burford, & Sexton, 2018). Two patients were removed because the catheter was connected to the patient's foot. Five patients were excluded from the study as a result of having flat waveforms. Six more patients were discarded as advised from the University of Arkansas for Medical Sciences.

After getting admitted into the ER, the patients received a bolus depending on how dehydrated they were, and a blood sample was taken to measure the bicarbonate (HCO^3) and chloride (Cl^-) levels. The PVP waveforms were measured through five stages after the patients' guardians' consent was obtained. The first PVP measurement was when the patient arrived at the ER and the second measurement was after they received the required amount of fluid to rehydrate them if needed. Before the pyloromyotomy intervention, the PVP was recorded and again during the operation; the last recorded PVP stage was after the operation. The recorded waveforms were labeled in this research as:

Signal Name	Abbreviation
Before Bolus	BB
After Bolus	AB
Preoperative	Pre-op
Intraoperative	OR
Postoperative	Post-op

Based on the hypotheses that this research is investigating, the pyloric stenosis PVP data was divided into different analyses and were tested separately.

2.4.1 Hypovolemic and Euvolemic Analysis

The hypovolemic and euvolemic analysis tests whether the PVP is influenced by the intravascular volume change. To achieve this goal, the enrolled patients were divided into two groups based on the level of dehydration upon admission determined by blood samples in the ER: euvolemic (normal fluid volume) and hypovolemic (significant fluid loss). The Cl^- and HCO^3 concentrations are being used to indicate the dehydration which can be measured from the blood sample (Dalton, Gonzalez, Boda, Thomas, Sherman, & St. Peter, 2016; Aspelund and Langer, 2007).

When the level of HCO^3 is less than 30mmol/L or Cl^- is larger than100 mmol/L, the patient is classified as *euvolemic*. Whereas if the level of HCO^3 is greater than 30mmol/L or Cl^- is less than100 mmol/L, the patient is classified as *hypovolemic* (Bonasso et al., 2019).

Multivariate Analysis of Variance (MANOVA) tests the difference in means between two or more continuous dependent variables and more than two categorical independent variables (Aelst and Willems, 2011). In MANOVA, the null hypothesis states that all means from different responses are equal meaning that all the curves are overlapping each other. As a result, there is no significant influence on the PVP signal among the different volume status. On the other hand, the alternative hypothesis states that there are at least two groups that do not have the same mean leading the PVP data of the groups to be different curves. Thus, the PVP waveform is influenced by the intravascular volume change. The p-value is the key parameter that helps to reject or fail to reject the null hypothesis, α=0.05.

$$H_0: \mu_1 = \mu_2 = \cdots = \mu_m$$

$$H_0: \mu_1 \neq \mu_m \qquad ; for\ at\ least\ one\ l \neq m$$

MANOVA was first conducted to test if the two groups, hypovolemic and euvolemic, were significantly different. *0* and *1* were assigned to the hypovolemic and euvolemic groups, respectively. Next, machine learning models, logistic regression, Least Absolute Shrinkage and Selection Operator (LASSO) regression, and k-nearest neighbor (k-NN), were created based on Fast Fourier Transform (FFT) to attempt to predict the volume status from an arbitrary PVP waveform. The difference between logistic regression and LASSO regression is that the former takes all frequencies into account, even if some of them are not dominant. On the other hand, LASSO regression, which is a selection model tool, sets those unimportant parameters to zero. Therefore, the LASSO model provides the best performance with as small prediction error as possible (Ranstam and Cook, 2018).

A total of 23 patients' waveforms were cleaned using the automated cleaning algorithm and then converted to the frequency domain. The FFT segments for eight hypovolemic patients were combined together whereas 15 euvolemic patients were added together. Then, the windows of each category were divided into 70% to train and 30% to validate the models. When building a prediction model, the input and the output of the system is known. However, the model parameters, β, are unknown, and are being calculated. The training data is used to calculate the β coefficients and then the validation data is used to test if those calculated parameters are reliable to predict the output of the testing data correctly. The correct prediction percentages for the three models were calculated and compared against each other to pick the model that has the best performance.

2.4.2 Intraoperative and Preoperative Analysis

During the pyloromyotomy surgery, the patients received propofol which is an anesthetic drug that causes immediate vasodilation and relaxes the patient's vessels, which decreases the

pressure in the vessels (Sinha, Sinharoy, Bratz, & Damron, 2015). In order to test if the Propofol influences the PVP, the intraoperative PVP signal was tested against the preoperative PVP signal when the patient had not received any propofol. The hypothesis that we tested was if the intraoperative and the preoperative PVP waveforms were significantly different; MANOVA was used to test the hypothesis. Furthermore, three prediction models were built after checking if the preoperative and intraoperative PVP signals were significantly different using logistic regression, LASSO regression, and k-nearest neighbor.

Twenty-three patients were included in the propofol analysis, 15 euvolemic and 8 hypovolemic. In the proposed machine learning algorithms, the data was divided into 70% and 30% to train and validate the models, respectively. The accuracy of the systems was compared against each other.

2.5 Craniosynostosis Patients

Craniosynostosis PVP waveforms were collected from nine patients during the corrective surgery at which the minimum alveolar concentration (MAC) dosage was being changed as required by the physicians. Two patients were removed from the analysis because of data loss relating between real operation time and its corresponding *LabChart* time.

In the craniosynostosis cohort, we tested if the different levels of inhaled anesthetic, isoflurane, influenced the PVP due to the physiological change in the blood vessels, since isoflurane causes vasodilation in the peripheral blood vessels and alters the blood flow (Akata, 2007). Also, we constructed a prediction system to test if an arbitrary PVP signal could be classified to its correct MAC dosage.

The data presented for the isoflurane patients contains a continuous PVP measurement during the craniosynostosis operation while the MAC dosage is changing over time. Linear

regression and MANOVA were used to test if PVP signal is influenced by MAC. Machine learning was used to build MAC prediction models from an arbitrary PVP signal using multiple logistic regression and k-nearest neighbor.

The linear regression model fit requires the input and the output to be continuous to examine the data linearity. One of the parameters to look at in linear regression is the coefficient of determination (R-squared) which measures how close the fitted line is to the data. As R-squared increases, the model shows a more linear relationship between the two continuous variables.

To perform MANOVA, the MAC dosages, which are the independent variables, were categorized into subgroups to make them categorical variables and they were categorized as follows:

$$Group\ 1: MAC\ [0 - 0.9]$$

$$Group\ 2: MAC\ [1 - 1.9]$$

$$Group\ 3: MAC\ [2 - 2.9]$$

$$Group\ 4: MAC\ [3 - 3.9]$$

The null hypothesis in the craniosynostosis cohort patients is that as MAC dosage changes, there is no significant influence on the PVP signal. On the other hand, the alternative hypothesis states that the PVP waveform significantly changes as MAC dosage varies. For the patients whose MAC dosages were categorized into more than two MAC groups, a MANOVA pairwise test was needed to check which groups are different and which groups are the same.

After testing the MAC influence on the PVP, multiple logistic regression and k-nearest neighbor (k-NN) were used as machine learning algorithms to build prediction models for the MAC dosage. Both models were compared against each other.

Chapter 3: Results

3.1 Pyloric Stenosis Patients

3.1.1 Euvolemic and Hypovolemic Analysis

The MANOVA test showed that the hypovolemic and euvolemic PVP waveforms were significantly different with p-value = 0.02.

The k-nearest neighbor (k-NN) algorithm was able to classify 94 datapoints out of 122, 77%, for the testing data of the hypovolemic group. For the euvolemic group, the k-NN model was able to predict correctly 38 datapoints out of 50, 76%. Also, the algorithm was able to predict 243 datapoints out of 285, 85%, for the training data of the hypovolemic group and 100 datapoints out of 118, 85%, of the euvolemic group (Table 1).

Table 1: Confusion matrix using k-nearest neighbor

Testing data			**Training Data**		
	Hypovolemic	Euvolemic		Hypovolemic	Euvolemic
Hypovolemic	94	28	Hypovolemic	243	42
Euvolemic	12	38	Euvolemic	18	100

The logistic regression and LASSO regression did not result in better results (**Appendix B**).

3.1.2 Preoperative and Intraoperative Analysis

The MANOVA test showed that the intraoperative and preoperative PVP waveforms were significantly different for hypovolemic and euvolemic groups with p-value = 0.02.

The k-NN model was able to predict 78 windows out of 81, 96%, of the Preop signal for the hypovolemic group. On the other hand, the model was able to classify 20 windows out of 23, 87%, of the OR signal correctly. Also, the k-NN model was able to predict 115 out of 118, 97%, and 43 out of 54, 80%, for the training data of the Preop and OR signals, respectively (Table 2).

Table 2: Hypovolemic group confusion matrix using k-nearest neighbor

Testing data			**Training Data**		
	Preop	OR		Preop	OR
Preop	78	3	Preop	115	3
OR	3	20	OR	11	43

The k-NN model was able to predict 96 windows out of 109, 88%, of the Preop signal for the euvolemic group. Likewise, the k-NN model predicted 37 windows correctly out of 45, 82%, of the OR signal (Table 3).

Table 3: Euvolemic group confusion matrix using k-nearest neighbor

Testing data			**Training Data**		
	Preop	OR		Preop	OR
Preop	96	13	Preop	244	11
OR	8	37	OR	25	80

The logistic regression and LASSO regression results are in **Appendix C**.

3.2 Craniosynostosis Patients

The p-value was significant among all the craniosynostosis enrolled patients, p-value<0.01 meaning that MAC influences the PVP signal. The p-values of MANOVA pairwise test for the patients who received more than two MAC dosages are reported in Table 4. Patient 5 and 6 received only two MAC dosages and a pairwise test was not necessary for these patients.

Table 4: MANOVA pairwise test of craniosynostosis cohort patients

Patient #	**Testing data**			
3		MAC 1	MAC 2	
	MAC 2	0.02	-	
	MAC 3	0.02	NA	
4		MAC 1	MAC 2	
	MAC 2	0.02	-	
	MAC 3	0.02	0.02	
7		MAC 1	MAC 2	
	MAC 2	0.029	-	
	MAC 3	0.029	0.255	
8		MAC 1	MAC 2	MAC 3
	MAC 2	0.02	-	-
	MAC 3	0.02	0.02	-
	MAC 4	0.02	0.02	NA
9		MAC 1	MAC 2	MAC 3
	MAC 2	0.029	-	-
	MAC 3	0.02	0.137	-
	MAC 4	0.029	0.039	NA

The correct and mismatch predictions at different isoflurane dosages for the testing and training data using k-NN are in Table 5.

Table 5: Confusion matrices of k-NN algorithm

Patient #	**Testing data**			**Training Data**		
3		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	60	10	MAC 1	164	0
	MAC 2	6	6	MAC 2	0	29
4		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	28	8	Group 1	83	0
	MAC 2	4	27	Group 2	0	74
5		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	0	1	MAC 1	1	0
	MAC 2	0	89	MAC 2	0	209
6		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	97	3	MAC 1	234	0
	MAC 2	8	78	MAC 2	0	202
7		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	17	3	MAC 1	48	0
	MAC 2	5	10	MAC 2	0	35
8		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	1	3	MAC 1	10	0
	MAC 2	2	22	MAC 2	0	57
9		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	25	12	MAC 1	87	0
	MAC 2	6	39	MAC 2	0	104

The linear regression and multiple logistic regression results are in Appendix D.

Chapter 4: Discussion

4.1 Pyloric Stenosis Patients

4.1.1 Euvolemic and Hypovolemic Analysis

Multiple Analysis of Variance (MANOVA) test of the hypovolemic and euvolemic groups showed a significant p-value, less than $\alpha=0.05$, meaning that the PVP waveforms at the two volume states are different. In other words, the PVP signal is influenced by changing the amount of fluid flows in the blood vessels. To test MANOVA effectiveness, it was utilized for hypovolemic and euvolemic groups individually and each group was divided into two arbitrary subgroups even though they belong to the same classification. The p-values between the subgroups that were tested were not significant, greater than $\alpha = 0.05$, leading to fail to reject the null hypothesis which states that the two subgroups have the same mean and they belong to the same set of data (Table 6).

Table 6: Same group analysis of euvolemic and hypovolemic groups

Group name	**P-value**
Euvolemic (BB)	0.6284
Hypovolemic (BB)	0.3342

Since the euvolemic and hypovolemic groups are significantly different, we conducted machine learning using different algorithms, logistic regression, LASSO regression, and k-nearest neighbor, to test whether the algorithms can predict the classification of an arbitrary PVP waveform.

Logistic regression and LASSO regression models had a large misclassification in the euvolemic group whereas these models were able to predict the hypovolemic group correctly at least 89% of the time. In other words, the PVP signal of the euvolemic group was mostly classified as hypovolemic even though the two groups are clearly different based on the MANOVA test results.

The k-nearest neighbor model showed that the PVP signals, euvolemic and hypovolemic, can be differentiated 76% of the time. Being able to predict the class of an arbitrary PVP indicates that any volume change in the body state is detectable by the peripheral veins and machine learning can be implemented to predict the intravascular volume status of future patients without having any further information about the patient's medical record.

4.1.2 Preoperative and Intraoperative Analysis

The infused anesthetic, propofol, which was used in the pyloromyotomy intervention, caused vasodilation. As a result, the vessels physiologically changed and had an impact on the blood pressure. This variation in the vessel characteristic was tested using MANOVA to see if there is a significant difference between the normal and the dilated vessels in terms of blood pressure. The MANOVA resulted in a significant difference between the preoperative and intraoperative PVP signals, p-value less than $\alpha=0.05$. The results showed that the PVP would be different when the patient was under anesthesia.

To check the MANOVA performance, we conducted the same group analysis in the propofol interpretation by dividing the data from the same group randomly into two subgroups and performing MANOVA test. The same group analysis results showed that there was not enough evidence to reject the null hypothesis (Table 7).

Table 7: Same group MANOVA analysis: Intraoperative and Preoperative

Group Name	**P-value**
Euvolemic (Preop)	0.38
Euvolemic (OR)	0.95
Hypovolemic (Preop)	0.77
Hypovolemic (OR)	0.96

In the machine learning algorithms, logistic regression and LASSO regression showed weak performance by producing a large mismatch in the intraoperative signal which was classified

as preoperative signal even though MANOVA test demonstrated that the intraoperative PVP waveform is different from the preoperative PVP waveform. Nevertheless, k-nearest neighbor (k-NN) was carried out and k-NN had a better functionality on distinguishing between the preoperative and intraoperative PVP signals. K-NN was able to predict 87% and 96% of the intraoperative and preoperative PVP signals, respectively.

Our MANOVA results imply that the changes in vascular resistance that is caused by propofol are detectable in the peripheral veins. Likewise, machine learning can be used to predict the volume status of future patients using only the PVP signal without the need to know the patient's medical records.

4.2 Craniosynostosis Patients

The MANOVA test for all the craniosynostosis patients had p-values that are less than $\alpha=0.05$, meaning that the PVP signal is influenced by minimum alveolar concentration (MAC) dosage. However, a MANOVA pairwise test was an important step to check if there are any MAC groups that are not significantly different. This extra step is only necessary for patients whose PVP signal was divided into more than two MAC groups.

The comparison between MAC group 2 and group 3 for patient 3 and MAC groups 3 and 4 for patient 9 were not calculated due to the smaller number of observations to have sufficient MANOVA results.

The p-value between MAC groups 2 and group 3 for patients 7 and 9 was greater than α, 0.05, which was unlike the other patients. These two patients' results showed that PVP was not influenced by changing MAC dosage. The reason for not having a clear relationship in these two patients is due to the small recorded time of PVP when MAC was changed from [1–1.9] to [2–2.9]. The physicians might have increased the MAC dosage for a short time and then it lowered

back to the previous MAC. Thus, the residuals from before changing the MAC was still dominant in the PVP waveform even after changing the MAC dosage. In case that the recorded PVP signal was measured for a longer time, then the relationship between PVP and MAC would be significant in these two cases. As a result, PVP is not sensitive to the sudden MAC changes.

To verify the MANOVA results, a MANOVA test was done for each MAC group of each patient individually. This step was necessary to make sure that MANOVA can differentiate between the two different groups and the same group analyses. The PVP signal that belongs to the same MAC group was divided into two arbitrary signals even though both signals belong to the same MAC group. The MANOVA test results showed that the p-value of each MAC group among all the patients was greater than α, 0.05, meaning that there is not enough evidence to reject the null hypothesis (Table 8). Not all the MAC groups from the patients were tested because the minimum number of observations to have adequate results was 50 and in some MAC groups there was less than the minimum number in some groups.

Table 8: Same group MANOVA analysis: Craniosynostosis patients

Patient #	**Group 1**	**Group 2**	**Group 3**
3	0.45	-	-
4	0.059	0.65	-
5	-	0.95	-
6	0.86	0.91	-
7	0.96	0.77	-
8	0.18	-	0.19
9	0.87	0.43	-

The performance of linear regression over all did not result in a linear relationship because the average R-squared among all the seven craniosynostosis patients was 0.55 meaning that the relationship between PVP and MAC did not follow a linear relationship.

In the prediction models, the performance of multiple logistic regression was moderate in average. Nevertheless, it did not perform well for patient 5 because of the lack number of

observations of MAC group 1. Also, in some other patients, like patient 3, the number of observations in one MAC group was smaller than the other MAC groups. This issue led to have inequivalent distribution between the groups and less robust prediction model for the group that has a smaller number of observations. The k-NN performance was similar to the multiple logistic regression performance. However, k-NN had better results than multiple logistic regression in four patients.

Isoflurane causes vasodilation, and our results illustrate that the change in vascular resistance is detectable in the venous circulation and the PVP signal. We were also able to show that the machine learning system was able to accurately distinguish between the PVP waveforms of each MAC group and predict the correct MAC classification for an arbitrary PVP at least 77% of the time.

Chapter 5: Conclusion

In conclusion, we are interested in assessing the volume change of the patients immediately and precisely since this assessment is vital for emergency settings when the patient needs urgent treatment. To achieve this goal, we measured the peripheral venous pressure (PVP) from two cohorts of patients: pyloric stenosis and craniosynostosis and then started the study by investigating two hypotheses.

The first hypothesis is that the volume status of the body influences the PVP. In other words, the vein pressure would change according to the volume status of the body. As the anesthetic drugs change the blood vessels physiology, we explored whether the infused and inhaled anesthetic drugs affect significantly the vein pressure. In the infused anesthetic, propofol, we compared between the preoperative and intraoperative PVP signals. In the inhaled anesthetic, isoflurane, we examined if different minimum alveolar concentration (MAC) would result in different PVP signal.

Being able to see a significant difference in the PVP signal at different hemodynamic states has an important impact to the medical field. First, it helps the physicians to make an immediate decision in emergency situations. Also, showing a significant relationship between the anesthetic drugs, inhaled and infused, and the PVP implies that the consequent changes in vascular resistance due to the anesthetic drugs are reflected in the vein circulation and in the peripheral veins. A technology that would accurately estimate the volume status of a patient to guide triage and remediation would be a significant enhancement in various care settings, including but not limited to surgery, pediatrics, and military use. This minimally invasive technology utilizes a standard peripheral intravenous line and a commercial pressure-monitoring transducer, which exist today and requires no new clinical skills.

5.1 Limitation

The research cannot prove causality because of the small number of participants in the research. Moreover, the PVP waveform and the body hemodynamics could be affected by other cofounding parameters in the clinical setting. However, this research is a novel study that points out the correlation between the different hemodynamics states and the PVP and everyone who is exploring the PVP are encouraged to include more than one factor to the PVP analysis.

5.2 Future Work

In future work, other cofounding factors that influence PVP will be taken into consideration, such as cardiac index and arterial oxygen saturation (Masutani et al., 2016). Also, new pediatric patients will be enrolled to increase the robustness and accuracy of the machine learning prediction models. Lastly, a separate controlled study will be designed to simulate the vascular volume change at different states to produce new data to test the hypotheses; one such case will test the effect of different anesthetic drugs.

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Appendices

Appendix A

To begin the experiment, a fresh kidney was taken from a pig and cut into two 10mm by 10mm pieces and the fat around them was snipped as much as possible. After that, one piece was submerged in rubbing alcohol solution to dehydrate it whereas the other tissue was immersed in a saline solution to keep it hydrated (Figure 1). Both samples were left in the refrigerator for seventeen hours to ensure that the samples are saturated with the fluid especially the dehydrated sample.

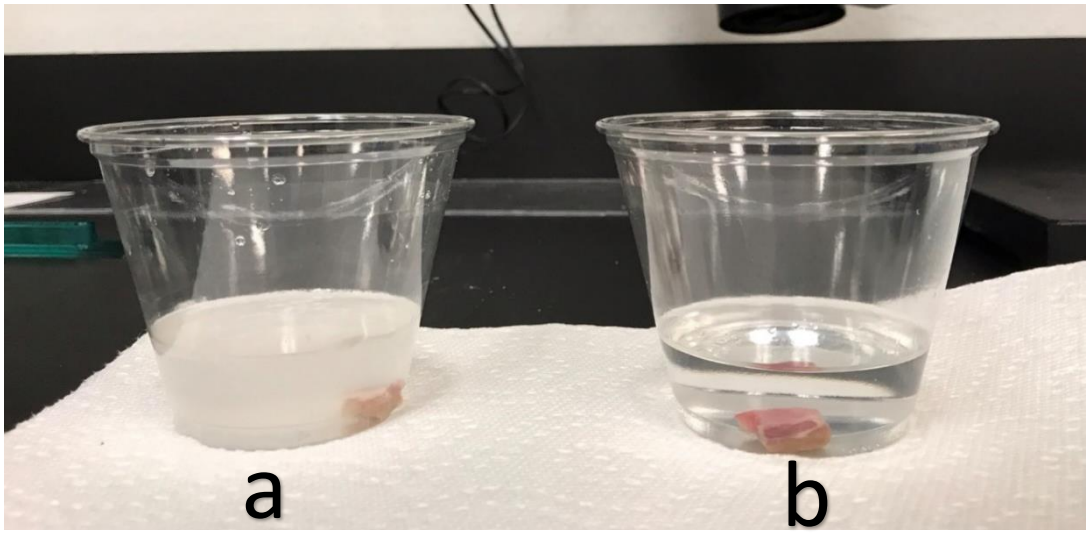

Figure 1: Immersing the kidney samples into saline solution (a) and rubbing alcohol (b)

On the day of the experiment, the samples were mounted on the biaxial machine followed by a 10-cycle preconditioning (Figure 2). These preconditioning cycles are important before the actual test because when a piece of an organ is cut, the tissue's fibers shrink and makes the tissue behaves in a random pattern (Giles, Black, and Bischoff, 2007). Consequently, preconditioning cycles help to retrieve the rhythmic behavior of the tissue. The kidney samples were tested on the biaxial machine at a 10% stretch ratio. The stress- strain curves illustrate the tissue behavior during stress (Figure 3). Also, it represents the mechanical properties of the tissues.

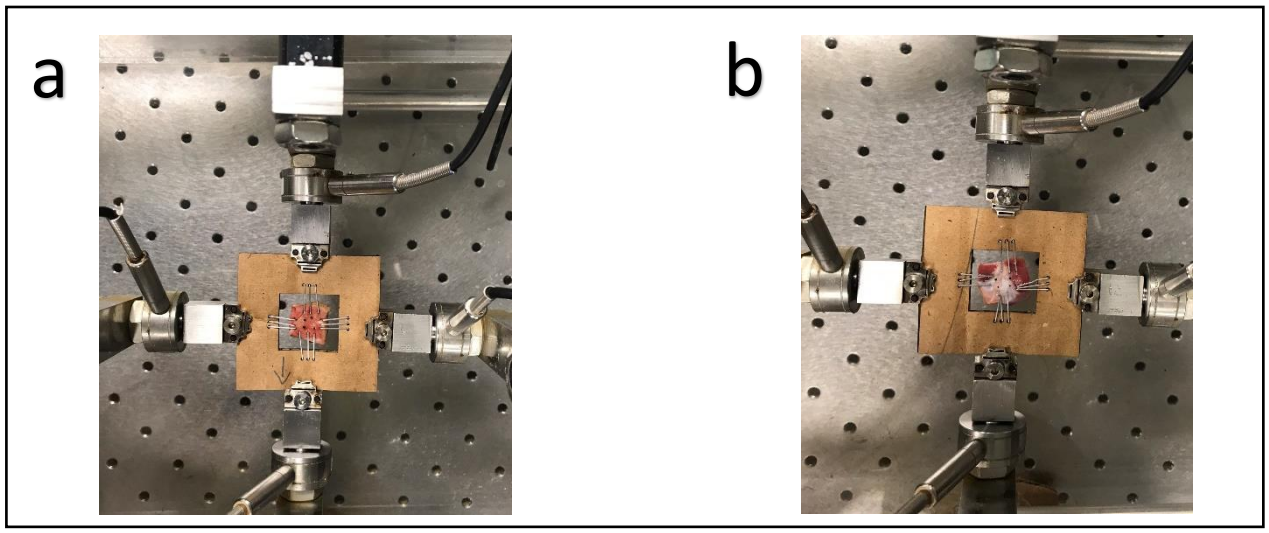

Figure 2: Mounting the sample on the Biaxial machine. (a): Dehydrated; (b): Hydrated

Appendix B

The LASSO algorithm predicted correctly all the testing and training data for the hypovolemic group whereas the LASSO model did not predict correctly any data for the euvolemic group (Table 1).

Table 1: Confusion matrix using LASSO regression

Testing data			**Training Data**		
	Hypovolemic	Euvolemic		Hypovolemic	Euvolemic
Hypovolemic	122	0	Hypovolemic	285	0
Euvolemic	50	0	Euvolemic	118	0

The logistic regression algorithm predicted correctly 109 out of 122 for the testing data of the hypovolemic group whereas 11 were correctly predicted out of 50 for the euvolemic group. The training data was used as an input to the logistic regression system to check if the machine learning model is able to predict the data that was originally used to train the model. The algorithm predicted correctly 260 out of 285 for the training data of the hypovolemic group whereas 76 datapoints out of 118 were correctly predicted for the euvolemic group (Table 2).

Table 2: Confusion matrix using logistic regression

Testing data			**Training Data**		
	Hypovolemic	Euvolemic		Hypovolemic	Euvolemic
Hypovolemic	109	13	Hypovolemic	260	25
Euvolemic	39	11	Euvolemic	76	42

Appendix C

The logistic regression model was able to predict all the datapoints, testing and training data, correctly for the Preop signal of the hypovolemic group. However, the prediction accuracy for the OR signal for the testing and the training data was 0% (Table 1).

Table 1: Hypovolemic group confusion matrix using logistic regression

Testing data			**Training Data**		
	Preop	OR		Preop	OR
Preop	81	0	Preop	188	0
OR	23	0	OR	54	0

For the testing data of the euvolemic group, the Preop signal had 91% prediction accuracy, whereas, the OR prediction accuracy was approximately 50%. For the training data, The Preop was able to predict 250 datapoints correctly out of 255, 98%. Whereas 91 datapoints out of 105 were predicted correctly for the OR signal, 87% (Table 2).

Table 2: Euvolemic group confusion matrix using logistic regression

Testing data			**Training Data**		
	Preop	OR		Preop	OR
Preop	99	10	Preop	250	5
OR	21	24	OR	14	91

The LASSO regression model of the hypovolemic and euvolemic groups was able to predict correctly all the Preop datapoints for the training and testing data. However, the LASSO algorithm failed to predict correctly any datapoints of the testing and training data of the euvolemic and hypovolemic groups for the OR signal (Table 3 and 4).

Table 3: Hypovolemic group confusion matrix using LASSO regression

Testing data			**Training Data**		
	Preop	OR		Preop	OR
Preop	81	0	Preop	188	0
OR	23	0	OR	54	0

Table 4: Euvolemic group confusion matrix using LASSO regression

Testing data			**Training Data**		
	Preop	OR		Preop	OR
Preop	109	0	Preop	255	0
OR	45	0	OR	105	0

Appendix D

The R-squared values for all the patients are in the Table 1 and the mean absolute error of linear regression was calculated and listed in Table 2.

Table 1: R-squared for the linear regression of the craniosynostosis patients

Patient #	R^2
3	0.583
4	0.387
5	0.329
6	0.634
7	0.565
8	0.784
9	0.512

Table 2: Mean absolute error of linear regression for the craniosynostosis patients

Patient #	**Linear Regression**
3	17.38 %
4	44.33 %
5	3.09 %
6	9.06 %
7	14.88 %
8	19.06 %
9	13.58 %

The correct and mismatch predictions at different isoflurane dosages for the testing and training data using multiple logistic regression are in Table 3.

.

Table 3: Confusion matrices of craniosynostosis using multiple logistic regression

Patient #	**Testing data**			**Training Data**		
3		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	60	10	MAC 1	163	1
	MAC 2	6	6	MAC 2	12	17
4		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	29	7	MAC 1	83	0
	MAC 2	13	18	MAC 2	11	63
5		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	0	1	MAC 1	1	0
	MAC 2	0	89	MAC 2	0	209
6		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	93	7	MAC 1	225	9
	MAC 2	8	78	MAC 2	9	193
7		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	14	6	MAC 1	48	0
	MAC 2	5	10	MAC 2	0	35
8		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	1	3	MAC 1	10	0
	MAC 2	3	21	MAC 2	0	57
9		MAC 1	MAC 2		MAC 1	MAC 2
	MAC 1	24	13	MAC 1	74	13
	MAC 2	12	33	MAC 2	12	92