Photoplethysmography and Heart Rate Variability for the Prediction of Preeclampsia

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The focus of this study was to develop a non-invasive, inexpensive bedside test that can accurately predict which women are at risk for developing preeclampsia. Healthy controls and high-risk participants were monitored intermittently throughout their pregnancy (beginning before 24 weeks gestation). Three-lead electrocardiogram (ECG) recordings from the maternal chest and pulse oximetry waveforms (photoplethysmography, PPG) from the middle finger were obtained for 30 minutes with the patient at rest at each prenatal visit. Upon delivery, their preeclampsia status was recorded. The data were utilized as an indirect measurement of arterial compliance and used to train an Artificial Neural Network (ANN) to predict preeclampsia at delivery. Of the 20 subjects studied prior to the 3rd trimester, the system accurately predicted 5/6 that developed preeclampsia. Overall, the system had a sensitivity of 0.91 and specificity of 0.77.

INTRODUCTION

Preeclampsia is a hypertensive disorder that occurs in 3-5% of all pregnancies and can have serious consequences for both maternal and fetal health. Symptoms of the disorder include hypertension, proteinuria, edema, and neurological symptoms such as severe headaches, light sensitivity, nausea, and even seizures (eclampsia). Women are at higher risk for preeclampsia if they possess one or more of the following preexisting conditions: chronic hypertension, obesity, multiple gestation, diabetes, gestational diabetes, preeclampsia in a previous pregnancy, liver disease and/or kidney disease. According to the International Society for the Study of Hypertension in Pregnancy, a previously normotensive woman is determined to have preeclampsia if she has one systolic blood pressure reading ≥140 mmHg, two successive diastolic blood pressure readings ≥90 mmHg within a 4-hour period, and/or ≥300 mg of protein in the urine in a 24-hour urine collection.

The exact causes of preeclampsia are unclear, making it difficult to develop a treatment or cure. Studies have demonstrated placental endothelial dysfunction due to oxidative stress and irregular placental development as potential underlying causes. Currently, the only available cure for preeclampsia is delivery. When a woman is admitted to a hospital with preeclamptic signs and symptoms, physicians may administer magnesium sulfate to prevent seizures and steroids to mature the fetal lungs. Physicians are sometimes able to avoid preterm delivery if a woman is admitted before her symptoms become severe and is responsive to blood pressure control therapy.

Preeclampsia in the Third World

In underdeveloped countries, the prevalence of preeclampsia is approximately seven times greater than in the developed areas of North America and Europe. One factor contributing to the increased incidence is lack of education - expectant mothers are unaware of the signs and symptoms indicating that medical attention must be sought. Additionally, receiving medical attention is unaffordable and access is very limited. The majority of the population is located in remote areas and transportation is either impractical or unavailable. For example, in Nigeria 50% of women live more than 5 kilometers from the closest hospital. Additionally, if a woman is actually able to travel to the hospital, the quality of care provided may be extremely poor.

Prevention of the complications of preeclampsia requires the ability to predict which women are at high risk for developing the disorder. A simple, cost-effective, and reliable test that can predict these patients in underdeveloped countries could allow direction of education and resources to this most vulnerable group. Thus far, researchers have not found a test that can fulfill this need. If a woman’s relative risk of developing preeclampsia can be estimated, the total number of fetal and maternal deaths can be dramatically reduced, especially in the Third World.

Preeclampsia Prediction

Presently, there are two commonly studied methods of predicting preeclampsia before the onset of symptoms. Serum biomarkers have been studied based on their
involvement in placental dysfunction, specifically the concentration ratio of placental growth factor (PIGF) to soluble fms-like tyrosine kinase (sFlt-1). Uterine artery Doppler ultrasonography has also been considered by noninvasively searching for indications of placental dysfunction, such as resistance to blood flow in the uterine arteries and decreased placental volume. Although studies have shown that the two methods function more efficiently when used in conjunction, these tests remain very expensive and unable to be utilized outside of a clinical setting.

In recent years, researchers have attempted to study preeclampsia by non-invasive applanation tonometry, via a device placed on the wrist to extract the radial arterial pressure waveform, which alternately applies pressure to the artery and examines the reflecting waves. Although applanation tonometry is expensive, requires training, and suffers from reproducibility issues, the studies provide useful insight into the physiology: preeclamptic patients demonstrate an increase in arterial stiffness. Features of the photoplethysmogram have been correlated with arterial stiffness/compliance, therefore our study was interested in investigating the use of a pulse oximeter and an electrocardiogram for the detection of these vascular changes. Our findings illustrate the potential to accurately determine a woman’s risk of developing preeclampsia through a single test in a more economical and less invasive manner.

METHODS

After written, informed consent, 20 women receiving prenatal care at Women’s Health at Shands Medical Plaza, a high-risk prenatal clinic, participated in this observational prospective pilot study. Inclusion criteria consisted of women prior to 25 weeks of gestation with multi-fetal gestation, chronic hypertension, pre-gestational diabetes, and/or history of preeclampsia in a prior pregnancy. Three-lead electrocardiogram (ECG) recordings and pulse oximetry waveforms (photoplethysmography, PPG) were collected from the subjects for 30-minutes at their prenatal visits and again when they presented for delivery, if possible. Prenatal visit collections were performed at 2-4 week intervals depending on the women’s prenatal visit frequencies. Data were stored for subsequent analysis in light of delivery outcome. To date, the 20 women have delivered: 6 preeclamptics and 14 normotensives.

The maternal ECG was recorded using Convergent Engineering’s amplifier and software system. The ECG data were synchronized with PPG signals extracted in real time from a commercial pulse oximeter and logged with PC user-interface (UI) software. These recordings were all saved to databases along with patient information using the UI.

As with any signal processing approach, the first step involved understanding the underlying features exhibited by preeclampsia. Using a variety of techniques to extract the important features (described below), the features were refined based on simple clustering methods to reduce complexity given the size of the datasets. As more data were recorded, models with higher degrees of freedom were employed to model these data.

Data Collection Protocol

1. Four ECG electrodes were attached to the maternal chest for continuous ECG recording.
2. Pulse oximetry probe was attached to middle finger.
3. ECG and pulse oximetry waveforms were collected for 30-minutes after a stable tracing was achieved.
4. Blood pressure, weight and proteinuria (if available) measurements were recorded.

Feature Extraction

The current feature set consists of parameters from three different physiologic classes: A) heart rate, B) pulse transit time (PTT, correlates with blood pressure) and C) augmentation indices. Multiple parameters from each class capture different representations of the fundamental data (e.g. heart rate or PTT variability), and combinations of parameters are also derived (e.g. change in PTT per change in heart rate). Using the different covariates, a high-dimensional feature vector was assembled as input into our classifier. More importantly, performance of classifiers is often best improved by ensuring the features adequately represent the desired information in all possible situations. Refinement of the feature extraction software is very important to ensure that the model parameters do not contain excess noise or outliers during poor data collection conditions.

Classifier

Although traditionally a black box modeling tool, artificial neural networks (ANN) afford an increase in the degrees of freedom to model the aforementioned data nonlinearly. For this model, Levenberg-Marquardt training was used as a compromise between Gauss-Newton and gradient descent (for faster more robust error minimization). We used the logistic function (which we determined empirically) for the sigmoid function of our processing element (PE) and an 80/20 percent mixture of training/testing sets. The ANN was trained and tested with 1000 different trials using data acquired in a parallel study of the same equipment analyzing patients whose preeclampsia status was known (preeclampsia vs normotensive).
RESULTS

Figure 1 shows two features [Δ heart rate variability (Y-axis) vs. Δ pulse transit time (X-axis)] changing through the time of gestation for three patients. Darker colors indicate more observations of the particular variability measures. Looking at Patient #3, heart rate variability and pulse transit time variability did not change significantly as gestational age progressed. Ultimately, Patient #3 did not develop preeclampsia. When analyzing the figures for Patient #1 and Patient #2 at 27 and 26 weeks of gestation, respectively, a decrease in heart rate variability is clearly observed (reduce spread in the Y-axis). Both patients were diagnosed with preeclampsia at 38 weeks of gestation. We see from the figure that more than 10-12 weeks before a diagnosis is made there are fundamental changes that can be observed from the preeclampsia’s features (patient #1 and #2) vs. the patient without preeclampsia (patient #3).

Of the 20 subjects, the system accurately predicted 5 of the 6 patients that developed preeclampsia. Overall, across the 1000 randomized trials, the system had a sensitivity of 0.91 and specificity of 0.77.

DISCUSSION

The ability to predict preeclampsia before the onset of symptoms is not an innovative undertaking, but has proven challenging. The two most studied methods have been serum biochemical markers and uterine artery Doppler ultrasonography. Serum biochemical markers have been studied by researchers as potential predictors of preeclampsia based on their concentrations during pregnancy (i.e., first, second, or third trimester) and their involvement in placental dysfunction. Unfortunately, no single biomarker has been identified as a reliable indicator of predicting preeclampsia; rather a combination of biomarkers has been observed to be more dependable. The most promising combination is the concentration ratio of placental growth factor (PIGF) to soluble fms-like tyrosine kinase (sFlt-1). PIGF is an angiogenic factor that is responsible for “the development of new blood vessels from existing endothelium and is essential for normal placental development.” SFlt-1 is an anti-angiogenic factor that binds to and inhibits the function of PIGF. It has been determined that the levels of PIGF decrease and the levels of sFlt-1 increase in women who have been diagnosed with preeclampsia.

In Germany, a study was performed by Verlohren, et al. that tested the ability of the concentration ratio of PIGF to sFlt-1 to predict the occurrence of preeclampsia in 351 pregnant women after 20 weeks gestation. Overall, the test had a sensitivity of 82% and a specificity of 95%. Although these results indicate PIGF:sFlt-1 to be a reliable predictor of preeclampsia, the expense of running the test is not cost-effective, it can only be performed in a professional medical setting, and it is an invasive procedure.

Researchers have also studied Doppler ultrasonography as a method of predicting preeclampsia by noninvasively searching for indications of placental dysfunction, such as resistance to blood flow in the uterine arteries and decreased placental volume. One such study recruited 17,480 women and studied their uterine arteries via transvaginal sonography at 23 weeks of gestation. Ultimately, the test had a high false-positive rate of 25% and a low detection rate of 63.1%.

Doppler ultrasonography alone has not proven to be a reliable predictor of preeclampsia. Other studies, however, have combined Doppler with other clinical tests and have observed significant improvements in sensitivity, specificity and positive predictive values. These multiparameter tests include various combinations of Doppler ultrasonography, serum biomarkers, and maternal history. Although the statistics have improved, these tests remain expensive, invasive and impractical for our intended application.

The results of our study do not vary significantly from those of the multiparameter studies mentioned above. Our findings, however, illustrate the potential to accurately determine a woman’s risk of developing preeclampsia through a single test in a more economical and less invasive manner. More importantly, it provides an avenue for developing a device that can be used outside of the hospital setting and in areas with limited resources. The majority of expectant mothers in underdeveloped countries do not have immediate access to medical attention because the hospitals and facilities are located at great distances and transportation is either unavailable or limited. Sadly, most mothers will never even see a physician during their pregnancies. These impoverished living conditions demand an efficient method for predicting a woman’s risk of developing preeclampsia.

Collecting heart rate and pulse oximetry data is noninvasive and inexpensive - data collectors require very little training, while the equipment used is compact, easily
transported and reusable.

Currently, volunteers and technicians are dedicating their time providing minimal healthcare in underdeveloped countries through organizations such as the World Health Organization. Having a simple device that can quickly estimate a woman’s risk for developing preeclampsia will allow individuals, such as these volunteers, the opportunity to not only educate women about the dangers of preeclampsia, but also inform them of their risk of developing the disorder. Possessing the ability to determine a woman’s risk early in her pregnancy will also give her the extra time to travel and seek professional medical attention before symptoms emerge or worsen. Ultimately, the number of fetal and maternal deaths will be dramatically reduced.

In addition to its Third World applications, our study’s findings can also benefit the First World. In countries such as the United States, the majority of expecting mothers has immediate access to a hospital and receives prenatal care throughout their pregnancy; therefore, medical access is not a prevalent problem. The real issue is the time and money spent on admitting women for monitoring at hospitals. The simplicity of our test will potentially allow a woman to be monitored outside of the hospital and only be admitted if she is considered at high risk for preeclampsia. Additionally, it will permit researchers to conduct more efficient studies by only enrolling women who will show explicit signs and symptoms. Thus, the ability to determine a woman’s risk of developing preeclampsia will decrease the amount of money spent on healthcare and ensure a more efficient allocation of research funding.

FUTURE WORK

The study’s results demonstrate that economical, non-invasive and reusable ECG and PPG technology have potential as reliable tools in predicting preeclampsia. The eventual goal is to develop a small, inexpensive, portable device that employs smart phone technology to predict a woman’s risk of developing preeclampsia and appropriately recommend necessary level-of-care for delivery. Further data are necessary and data collection continues under a NIH-STTR grant.

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CONFLICT OF INTEREST

Tammy Y. Euliano, M.D., is the study principal investigator and is married to Neil Euliano, Ph.D., the president of the sponsoring company, Convergent Engineering. Any resulting patents and products could have financial implications.

ENDNOTES