HEMODYNAMIC AND GEOMETRIC CHANGES OF THE FEMALE REPRODUCTIVE SYSTEM IN HEALTH AND DISEASE

by

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To my family,

For their constant love and support.

Thank you to my mom for her patience,

My grandma for her inspiration,

My sister for her guidance,

My aunt for her encouragement,

My cousins for their words of wisdom,

And my uncle for his loyalty.

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ABSTRACT

Preterm birth is the leading cause of newborn mortality, with 15 million babies born premature worldwide every year. Children that do survive early delivery are more likely to develop cognitive abnormalities, motor deficits, heart disease, cerebral palsy, and more. While little is known about the pathophysiology of preterm birth, several pregnancy-related complications are related to preterm birth, namely cervical insufficiency and preeclampsia. In the former, premature cervical remodeling and softening can result in the shortening of the cervix, increasing a woman's risk of preterm birth; this condition is called cervical insufficiency (CI), which is the inability of the cervix to remain closed as a result of weakened tissues. CI is currently measured by a one-dimensional sonographic cervical length, where < 25 mm indicates shortening. Preeclampsia is a disorder that can be explained through the Page kidney phenomenon: compression of the left renal vein (LRV) causes renal venous outflow obstruction, leading to elevated intrarenal pressure and hypertension. The supine pressor test (SPT) is a diagnostic tool for preeclampsia where a positive test is defined by an increase of 20 mmHg in diastolic blood pressure (BP) when shifting from the left lateral recumbent to the supine position. Due to the intense risk of morbidity and mortality for both the mother and the fetus, the need to monitor BP changes is critical. Currently, there is an unmet clinical need to characterize the hemodynamic and geometric properties of the female reproductive organs throughout gestation. Utilizing ultrasound imaging can increase our knowledge about the 3D anatomy and systemic changes during pregnancy, unravel risk factors, establish preventative methods, and standardize treatment plans. In this thesis research, we developed a murine model to 1) examine the pathophysiology of renal vein stenosis, and 2) investigate the effects of stenosis on various cervical dimensions. Renal vein stenosis was found to greatly impact blood flow velocities, as well as cervical width ($p<0.05$). LRV and cervical area and height also trend towards significance, and there is negative damage to the left kidney and placentae within the stenosed cohort. We also conducted a human study that showed reduced change in postural BP in patients with higher body mass index (BMI). Systolic and diastolic BP in the supine position was significantly greater than in the lateral position for all BMIs with a baseline increase in BP of approximately 9-14 mmHg. These findings suggest that therapeutic positioning and close monitoring of BP could mitigate the risk of developing related disorders in pregnancy.

1. HEMODYNAMIC AND GEOMETRIC CHANGES OF THE FEMALE REPRODUCTIVE SYSTEM IN HEALTH AND DISEASE

1.1 Introduction

1.1.1 Preterm Birth

Any birth of a human baby that occurs fewer than 37 weeks' gestational age is deemed a preterm or premature birth [1]. Prematurity is the most common cause of infant death with over 1.1 million babies affected every year [2], [3]. This syndrome impairs up to 11% of births worldwide, complicating one in every ten deliveries in the United States alone [4]. Unfortunately, while further investigations are needed to determine the etiology, there are several risk factors known that may indicate prematurity: multiple gestations, stress, issues with the uterus/cervix/placenta, diabetes, hypertension, and obesity [5]. Many psychosocial, biological, environmental, and socioeconomical factors often combine to influence the probability of preterm birth occurrence, especially afflicting expecting mothers in low-resource settings with lack of proper access to healthcare. The health outcomes of those born preterm include an increased risk of long-term disability, sepsis, developmental delays, cerebral palsy, or even death [5]. Current solutions include taking progesterone supplements or undergoing cervical cerclage, but much debate remains regarding their effectiveness [6]. The economic burden of preterm birth is also a critical aspect to consider when focusing on future preventive or treatment interventions [7]. Premature births require effective public health strategies to target risk factors and populations and reduce perinatal morbidity and mortality [8].

1.1.2 Cervical Insufficiency

Cervical insufficiency (CI) is the inability of the cervix to retain a pregnancy in the second trimester by remaining closed, specifically when the cervical length <25 mm or if it undergoes drastic physical changes before 24 weeks gestation [9]. A pregnant mother's cervix attaches to the fetal membranes and serves to protect and maintain the fetus until conception [10]. Throughout pregnancy, the uterine cervix adjusts for compressive and tensile loads induced by a growing fetus by dilating, deforming, or shortening [11]. An early onset of cervical shortening causing a mechanically weak/incompetent cervix can put pregnant mothers at risk for preterm birth [11].

Currently cervical length serves as a clinical marker for the risk of prematurity and is measured on the ultrasound; however, length is a 1D dimension measuring a 3D anatomical organ. CI has been attributed to genetic variation, uterine overdistension, collagen vascular disorders, or infected amniotic fluid and is diagnosed using transvaginal ultrasound (TVU) [9]. Currently, diagnosis of CI remains problematic due to the sonographic limitations of quantifying cervical shortening [12]; likewise, the sole preventive measure for CI and thereby preterm birth is also controversial because the efficacy and safety of cervical cerclage has yet to be adequately assessed outside of emergency cases [13], [14]. Despite various studies exploring the cervical mechanical and material properties [15], [16] there is much unknown regarding cervical function, the three-dimensional (3D) anatomy, and how to analyze its data longitudinally throughout pregnancy.

1.1.3 Preeclampsia

Preeclampsia is a pregnancy complication characterized by proteinuria, hypertension, and multi-organ failure [17]. This disorder causes up to 75,000 maternal deaths and over 250,000 neonatal premature deaths worldwide [18]. Since the increase in blood pressure (BP) commonly leads to early delivery, preeclampsia accounts for 18% of premature births [19]. As one of the top three leading causes of maternal morbidity and mortality, preeclampsia significantly affects those in underdeveloped countries due to lack of access to proper healthcare and management interventions [20]. In low-resource settings, preeclampsia accounts for one-quarter of all neonatal deaths, and infant mortality rates are three times higher than in high-income countries. There are several potential etiologies that are considered in the medical community: placental ischemia, compression of the left renal vein (LRV) by the gravid uterus, or a hyperinflammatory state [18], [21] [22]. The pathogenesis is complicated and involves things like abnormal remodeling of placental spiral arteries, defective trophoblast differentiation, placental hypoperfusion and endothelial disfunction. Preeclampsia is currently diagnosed by a BP $\geq$ 140 mmHg systolic or $\geq$ 90 mmHg diastolic and/or urine protein excretion > 0.5 g [19]. Expecting mothers are more at risk if they have diabetes, obesity, and previous pregnancies. As symptoms do not often present until the third trimester or at least 20 weeks gestation, monitoring for fluctuations in blood pressure is critical. Eclampsia is a life-threatening condition that often follows preeclampsia, which can cause damage to the brain, including seizures or coma. While there are no definitive cures, except

delivery, there are currently few methods to alleviate the progression of preeclampsia such as close monitoring, antihypertensive medications, and therapeutic positioning [17], [21], [23].

1.1.4 Mechanisms of Page Kidney

A mechanism potentially contributing to preeclampsia is called Page kidney, first described by Irvine Page in 1939 [24]. Essentially, when the left renal vein is compressed by something external—in this case, the gravid uterus—renal venous outflow is obstructed, activating the renin-angiotensin-aldosterone system (RAAS), thereby increasing blood pressure. Renal compartment syndrome, caused by persistent obstruction, leads to preeclampsia. The vessel experiences a long-term response from vasoconstriction and undergoes renal ischemia. While the Page kidney phenomenon has been studied through various imaging studies; using ultrasound has proven to be inexpensive, noninvasive, and relatively quick. This hypothesis of the LRV being compressed and causing hypertension could strongly tie into the early stages of preeclampsia (gestational hypertension), particularly since intrarenal pressure increases as preeclampsia progresses.

1.1.5 Automation of the Supine Pressor Test

In the 1970s, the supine pressor test (SPT) was invented by Norman Gant to address the need for predicting the risk of developing preeclampsia. This BP test, more commonly referred to as the roll-over test, consisted of a subject switching from the left lateral recumbent position to the supine position and proved to have a positive predictive value of 93% [25]. Gant et al., observed that pregnant women experienced an increase in diastolic blood pressure of at least 20 mmHg when they shifted positions. While this test demonstrated its potential utility, there were still repeatability and reproducibility issues. The SPT came to clinical disuse largely because it was not associated with a standardized procedure, leading to reduced specificity possibly due to the manual testing approach that made reproducibility challenging. Currently, people are not even aware that the SPT even compares BP in various positions and the lack of knowledge has prevented it to be properly evaluated.

To combat this, we aim to highlight the physiological insights and automate the diagnostic tool to better integrate it for the target audience of pregnant women. Our approach, or the AUTO-SPT, combines an automatic BP cuff and Bluetooth inertial measurement unit (IMU) position

sensor through a smartphone application to guide the patient through the test. Our version of this tool will allow users to take their own blood pressure in different body positions away from clinical settings to determine their risk for developing preeclampsia later in their pregnancy. An algorithm will detect blood pressure and body position in real-time and then will transmit this information to a smartphone application. The smartphone application could then share the results with the user as well as with a clinician who will be able to review these results to determine if the user needs further monitoring and care. By automating the process, we are implementing a more standardized procedure, potentially resulting in the improved prediction of who is at increased risk for developing preeclampsia during their pregnancy. We also make use of wireless technology to enable patients to use telemedicine to communicate with their physicians about their results. This device could address a huge concern because women in low-resource settings encounter healthcare barriers such as minimal prenatal education and transportation difficulty, causing them to be at greater risk for preeclampsia due to deficient monitoring during pregnancy. Our uniquely discovered understandings drove us in the direction to re-invent the SPT and make it more useful, hopefully changing the lives of mothers and children.

1.2 Materials and Methods

1.2.1 Animal Study

Overview

Eight- to ten-week old nulligravida female C57BL/6J wild-type mice (n = 12, initial body mass = 19.63g ± 1.26g) from The Jackson Laboratory (Bar Harbor, ME) underwent LRV procedures as approved by The Purdue Animal Care and Use Committee. When the mice arrived, they underwent imaging and blood pressure measurements for baseline values before being paired for breeding. When paired, the cages were arranged with a 1:2 ratio of 1 male to 2 female mice. Mice were separated into stenosis (n = 8) and sham (n = 4) groups. Throughout the study, missing data points arose due to mice unexpectedly giving birth, issues with their tails that prevented us from obtaining BP data, etc. As a result, there is a range of 3-8 stenosed mice and 1-4 sham mice used to analyze BP data, and a range of 5-8 stenosed mice and 3-4 sham mice used to analyze ultrasound data. All animals were anesthetized during the imaging and surgery sessions, and

aseptic technique was used during the procedure. The mice weights were tracked throughout the study to provide an additional metric when determining pregnancy stage.

Ultrasound Imaging

The mice were imaged using a high-resolution small animal ultrasound system (Vevo3100 Imaging System, FUJIFILM VisualSonics, Inc., Toronto, ON, Canada) with a 32-55 MHz range 256-element array transducer (MX550D; 40 MHz center-frequency). As previously noted, we acquired complete imaging datasets for all mice before they were even paired—once acclimating to the new environment, they were imaged and then paired with males. Imaging was conducted on day 0, and approximately on embryonic (E)/gestational day E7.5, E14.5, and E17.5. Rather than timed pregnancies, we continually kept the males and females paired until confirmed to be pregnant. Therefore, if after being paired for 7 days with still no sign of pregnancy, we checked every 3-4 days to ensure the mice were within the proper range of days and thereby not make a measurement too late in a pregnancy. The timelines were extremely important to manage because a mouse's entire gestational period is about 18-21 days, such that a late prediction of a stage could result in an unexpected birth, causing the loss of valuable data. We established pregnancy by comparing our ultrasound images to previous reports of mice embryos in utero [26]. Accurate dating of the pregnancy was determined by ultrasound images of the gestational sacs, decidualization, and features observed in the developing fetuses.

During each imaging session, mice were placed on a heated stage after being anesthetized with ~1.8% isoflurane. Each was imaged in the supine position and to ensure clear images, a depilatory cream was applied to remove any abdominal hair (Nair, Church & Dwight Co., Inc. Ewing, NJ). Ultrasound conductive gel was then applied to the pelvis and 3D gated acquisitions of the cervix were performed using a stepper motor that translated across the abdomen on the animal with a step size of 0.1 mm. The DC motor was utilized to acquire serial ECG and respiration-gated B-mode images. We aimed to acquire images from the vaginal canal, tracking the development of the cervix until it bifurcates into the uterine horns. Both short- and long-axis images were collected using two-dimensional B-mode, EKG, color Doppler, and pulse wave (PW) Doppler. Most notably, we analyzed long-axis images of the left renal vein to determine how the vessel diameter and mean and peak blood flow velocities change after undergoing stenosis. All analysis was conducted using VevoLAB and SimVascular software. Cervical width, posterior and

anterior height, and maximum dimensions were calculated at all timepoints from three-dimensional volumetric models and B-mode images of the cervix's widest point. Building 3D models consisted of creating a path line, segmenting, and then exporting the model to determine different metrics as pregnancy progresses.

Left Renal Vein (LRV) Stenosis

To anesthetize all animals, a small animal anesthesia system (SomnoSuite, Kent Scientific) was used with 1-3% isoflurane and 0.5 L/min medical grade air. To ensure the mouse was properly under anesthesia, a toe pinch was administered, and vital signs were closely monitored. The female mice were placed in the supine position on a heated surgical suite (SurgiSuite, Kent Scientific) with both eye lubricant and depilatory cream applied; the former to prevent corneal desiccation and the latter to remove hair from the abdomen. To clean and sterilize both the animal and the tools, aseptic technique was used.

Based on how many mice were pregnant at a time, we attempted to obtain an even number of mice undergoing both the stenosis procedure and the sham surgery. Regarding the LRV stenosis group (n = 8), they were subject to a partial ligation to simulate the mechanisms of the Page Kidney, compared to a sham surgery group (n = 4), where they were simply meant to observe if a surgical procedure alone caused any changes. Surgery was performed on E10.5, which represented the halfway point, or 20 weeks gestation, normally when a preeclamptic pregnancy would present itself with hypertension.

A small mid-line incision was made through both the skin and muscle layers. A surgical scope (M60, Leica Microsystems, Wetzlar, Germany) was used to perform the procedure. By performing laparotomy, the kidney and LRV were exposed and isolated. Once the abdominal cavity was open, a partial ligation was created by aligning a 30-gauge needle parallel to the vessel of interest. The needle was used to establish a consistent procedure for the stenosed cohort (percent stenosis 90.1 ± 2.1%). Then, a silk 6-0 suture was tied around both the LRV and the needle. To set up the sham surgery, the same process was conducted, but the suture was now loosely tied around the LRV, instead of truly constricting it. The incision was then closed using 5-0 prolene sutures and the mouse was monitored until it became fully ambulatory. Buprenorphine was subcutaneously injected near the surgical site at a dose of 0.05 mg 0.03 mg/mL and antibiotic ointment (Neosporin, Johnson & Johnson, Skillman, NJ) was applied to reduce pain. Post-ops were

performed for 48 hours, where the mouse's weight, sutures, and diet were evaluated, medication was provided, and any problems were assessed.

Blood Pressure Measurements

To acquire the blood pressures of the mice, a noninvasive tail cuff system (2 Channel CODA System, Kent Scientific Corp., Torrington, CT) was employed. The mice were conscious and had measurements taken at baseline, and E7.5, E14.5, and E17.5 after becoming accustomed to the restraining tubes. The set-up includes an occlusion cuff at the base of the tail and VPR (volume pressure recording) cuff behind it. At the start of the measurement cycle, blood is pushed from the tail by the VPR cuff and then the occlusion cuff inflates to prevent blood flow back into the tail. When the occlusion cuff deflates, blood begins to flow back into the tail, increasing the tail volume. The occlusion cuff pressure at which the tail volume increases is the systolic BP. The tail volume will continue to increase as the occlusion cuff deflates until blood flows into and out of the tail equalizes; the occlusion cuff pressure at this point is the diastolic BP. To ensure we acquired a proper amount of data, we ran the BP test several times; we aimed to have approximately 25 clear BP readings per mouse per time point.

Euthanasia and Dissection

To properly euthanize the mice, each underwent carbon dioxide asphyxiation and then cervical dislocation. Subsequently, another incision was created to access the abdominal cavity. Both kidneys were removed, and the fetuses and placentae were carefully extracted. The fetuses and placentae were then weighed on a plastic weigh boat. All organs were placed in 4% paraformaldehyde (PFA) to fixate and then transferred to 70% ethanol for histology.

Histology

The tissues of the kidneys and placentae were processed using hematoxylin and eosin (H&E) staining. For the kidneys, we chose to focus on the glomerular structure when determining the effects of stenosis. For the placentae, we chose to focus on the vascular network near the fetal side (chorionic plate + labyrinth sections) and trophoblasts. Images were acquired at 40X magnification.

1.2.2 Body Mass Index (BMI) vs Blood Pressure Study

Volunteer Recruitment

A non-pregnant human study was previously conducted at Purdue University to determine the feasibility and usability of the automated SPT by establishing a baseline increase in BP and measuring stability and comfort. This thesis research was undertaken to expand upon this work by utilizing the similarity between pregnancy and central obesity; both scenarios having an abdominal mass could mean that excess weight would compress the left renal vein, potentially contributing to renal venous outflow obstruction. To test for the effects of body mass index (BMI) and gender on changes in blood pressure, we designed another study at Purdue University with both males (n = 50) and non-pregnant females (n = 70). The 70 women included the data from the 50 non-pregnant females as conducted in the earlier study [17]. We aimed to gather a heterogenous population of varying BMI values, so we posted advertisements around Purdue University and contacted Metabolic Research centers to recruit for diverse populations. The subjects were between the ages of 18-43 years old and were asked to self-report any previous history of chronic hypertension or heart disease to uphold to the exclusion criteria. Once verbal and written consent was obtained, the study procedures were performed. All study procedures were approved by the Purdue University Institutional Review Board.

Procedure

All subjects were provided a set of instructions that we re-personalized and were subsequently asked to perform the SPT as autonomously as possible. One of the team members was always present to provide any assistance if necessary. The subjects were provided with an automated ambulatory BP cuff (OnTrak 90227 Ambulatory BP Monitor, SpaceLabs, Seattle, WA) and asked to follow the directions. BP measurements were taken 13 times, 3 sitting down to get a baseline value, 5 in the left lateral recumbent position, and 5 in the supine position. To standardize the procedure, subjects had their back supported such that their legs were uncrossed when sitting down. After the baseline measurements, subjects were asked to perform light exercise by walking up and down three flights of stairs. Then, they continued the SPT by laying on their left side and taking 5 serial BP measurements, and the same repeated while lying on their back. Each measurement took about 90 seconds, with an automatic 30 seconds included between

measurements for reperfusion. After the study, participants were asked to complete two surveys: one focused on their feedback and experience with the SPT and the other focused on their sleep habits. All procedures were approved by the governing Institutional Review Board.

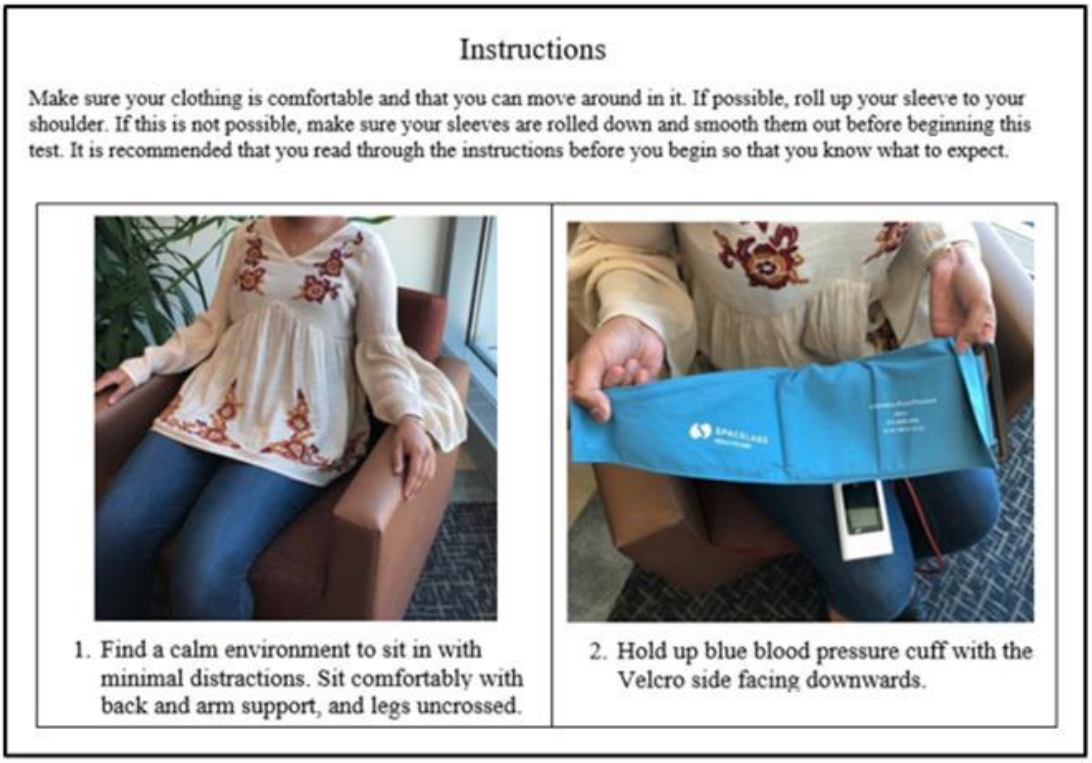


Figure 1. Set of written and visual instructions distributed to each subject for BMI study.

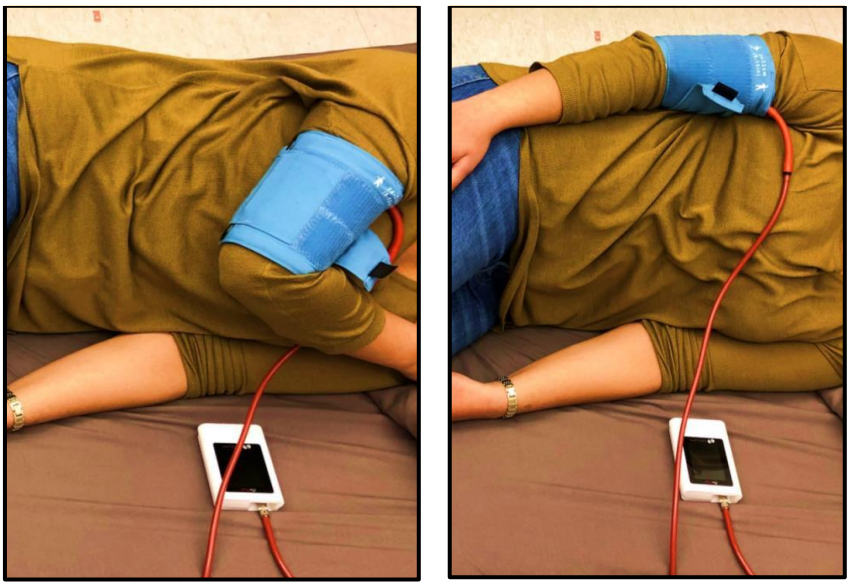


Figure 2. A) Left lateral recumbent position. B) Supine position.

1.2.3 Device Development

Overview

To detect the early onset of preeclampsia in pregnant women, the team worked to create a cohesive device; this device integrates a Bluetooth blood pressure cuff and an inertial measurement unit (IMU) with a smartphone app, which guides the patient through the supine pressor test. The app, 'AUTOSPT', monitors patient position in real-time and communicates through an interactive UI (user interface) with the patient as they undertake the SPT. While there are BP cuffs out there already, the novelty of the position sensor when integrated into one device leads to future preventative alerts. This can help track the expecting mother is in the right range for the SPT, especially long-term when sleeping to ensure that they stay on the left side with a little buzz or physical notification. In accordance with iOS development, the app was written in Swift, communication with the Next-Generation IMU (NGIMU) was through a Python script, and cloud configuration was in JavaScript. Platforms Firebase and Google Cloud Platform (GCP) were used to securely store user data and to communicate from the IMU to the app.

Data Acquisition and Processing – Inertial Measurement Unit (IMU) Algorithm

An inertial measurement unit, or IMU, was used in order to detect body position in real time. The IMU used was the NGIMU from x-IO Technologies. The device connects to the processor through a wireless, Wi-Fi connection. Although, it features a barometric pressure sensor, humidity sensor, triple-axis gyroscope, accelerometer, magnetometer, only the last three were incorporated into the system. The gyroscope and accelerometer were used in tandem to detect body position through angles and velocities. The magnetometer was used to calibrate any magnetic radiation from smartphones, laptops, implants, or any other material exhibiting a magnetic on the IMU. The combination of sensors aids the patient in minimizing movement during the SPT and warns them if they shift out of the appropriate angle ranges. While the main data stream is acquired from the gyroscope, accelerometer data is taken as an average over a larger frame of datapoints and is then used to correct for gyroscope wander. This aids the patient in minimizing movement during the SPT and warns them if they shift out of the appropriate angle ranges.

In order to accurately detect user body position, data acquired from the IMU was put through an extended Kalman filtering (EKF) algorithm. Kalman filtering, also known as linear

quadratic estimation, takes measurements over a certain period, calculates statistical error terms and other sources of variability from this dataset, and uses this to predict the next set of measurements. Then, the next round of measurements is acquired by the device and compared to the set predicted by the Kalman filter; error terms are calculated again. The raw data matrices used in three-dimensional Kalman filters are processed into quaternions, with one scalar and three vector components in the complex domain. The three-dimensional Kalman filtering used in the IMU algorithm was a nonlinear, extended Kalman filter. The main difference between Kalman and extended Kalman filtering is the ability of the EKF to use either differential or linear functions of state. Since patient body position can be modeled by a differential function [27], the Jacobian, a matrix of partial derivatives is used to update the covariance terms. Since the patient's body position is assumed to be still, the initial estimate of state is obvious and thus makes it possible for the EKF to act as an optimal estimator. Thus, due to the nature of the problem in the development of the AUTO-SPT, the EKF greatly resembles the normal, linear model used by the Kalman filter. This algorithm can be seen in Figure 3 below.

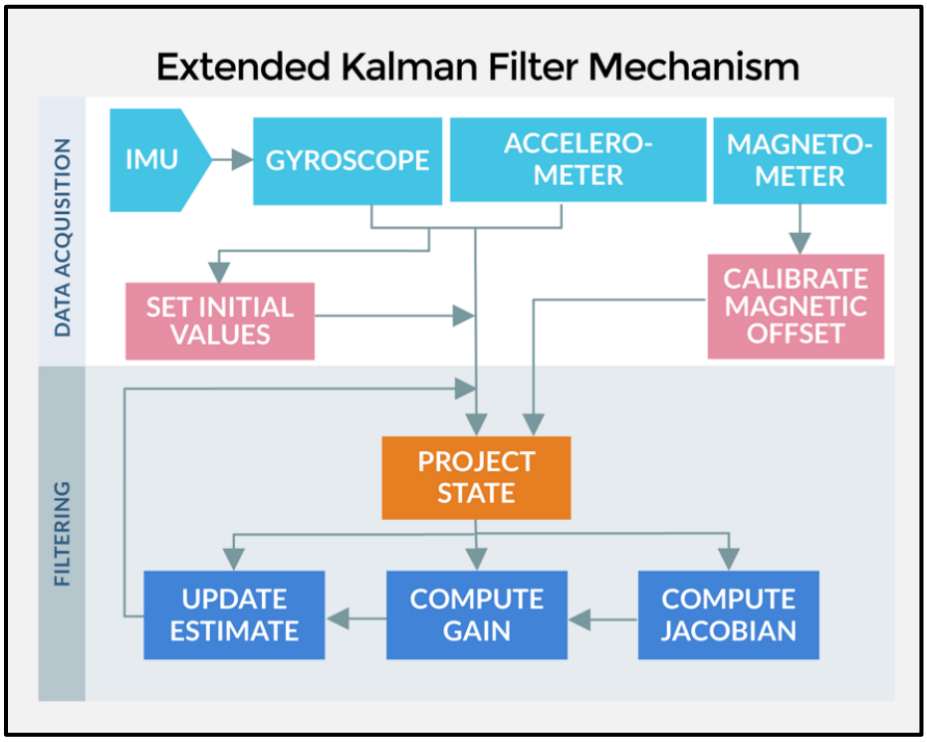


Figure 3. Flowchart of the EKF algorithm. Light blue: inputs, pink: initialization of all sensors, orange: theoretical estimate, dark blue: adjusting predicted values by using measured values.

User Interface

The user interface is currently able to be viewed on two platforms: a laptop or PC, and an iPhone. Data from the NGIMU, encoded in open sound control (OSC) packets, is transmitted to one of the platforms, which functions as an OSC client. OSC is an open, message-based protocol developed for communications between multimedia devices. The NGIMU, connected through Wi-Fi to a laptop or PC device, takes part in this. First, the data is collected from the magnetometer for a duration of 12 seconds. After the calibration period, the user is instructed to start the test and the script collects data from the gyroscope. Here, the device algorithm collects gyroscope and accelerometer values through frames of 200 datapoints in order to make a more robust visual. From these data, statistical calculations are made as per the algorithm and used to predict and accurately display user position. This data stream is then viewed in a window on a laptop in an interactive graph with two horizontal asymptomatic boundaries. The patient is instructed to remain within these boundaries throughout the duration of the test.

Market and Customer Discovery

Our research team applied for the Purdue NSF I-Corps: Introduction to Customer Discovery in Fall 2019. It was desired to learn more about the commercialization process for our prototype via best practices for conducting customer discovery and identifying key stakeholders. We traveled and networked with physicians, nurses, mothers, and even clients in Kenya to acquire as much data about the need for this product. The following questions asked during the interviews are outlined in the Appendix.

1.2.4 Statistical Analysis

All datasets were assessed assuming normality and homogeneity of variance using Shapiro-Wilk tests due to limited, uneven sample sizes. Regarding the animal study, to determine differences between the LRV stenosis and sham surgery, a one-way ANOVA with Tukey and Dunnett post-hoc tests was completed for the BP, LRV, and cervical analysis. To compensate for massive anatomical variation between animals, the data was normalized to access if there was a difference from baseline. Additionally, many mixed-effects models were performed on systolic and diastolic BP, LRV area, blood flow velocities, and cervical area, width, height, and effective

diameter. With respect to the human BMI study, a paired t-test was used to determine significant differences in BMI groups of “less than 25” or “greater than or equal to 25” groups. A two-way ANOVA with Tukey post-hoc analysis was performed to determine differences for subjects’ systolic and diastolic BP measurements when shifting positions. To assess the relationship between gender and BMI on BP, a one-way ANOVA with Tukey and a two-way ANOVA with Tukey were used, respectively. For all the models, p-values are defined at $p<0.05$. All analyses were performed in GraphPad Prism.

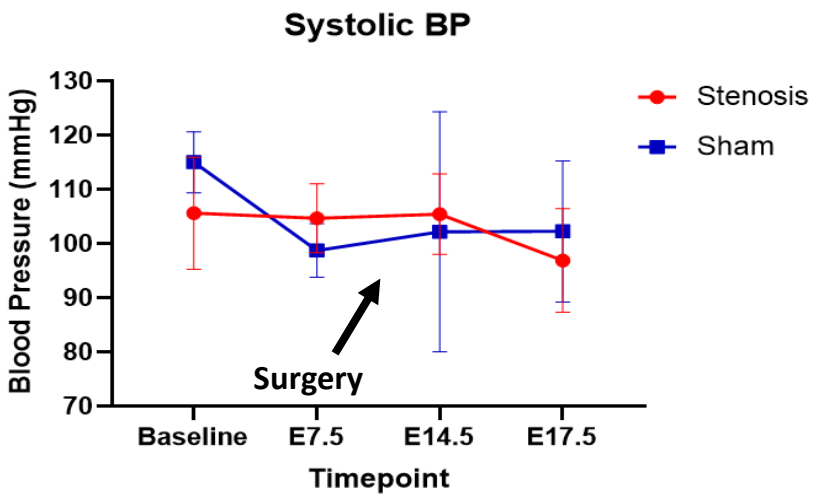
1.3 Results

1.3.1 Animal Study

BP does not significantly change due to LRV stenosis in pregnant mice

As aforementioned, mice were paired at about 8-10 weeks of age to ensure sexual maturity. An average stenosis of 91 ± 2.7% was created by using a 30-gauage needle. The surgeries were carried out at E10.5, and since the mice were euthanized at E17.5, there were only about 7 days to observe any distinct differences from the procedure. The differences in systolic BP, diastolic BP, and the mean arterial pressure over time were observed to not be statistically significant from baseline measurements.

A)



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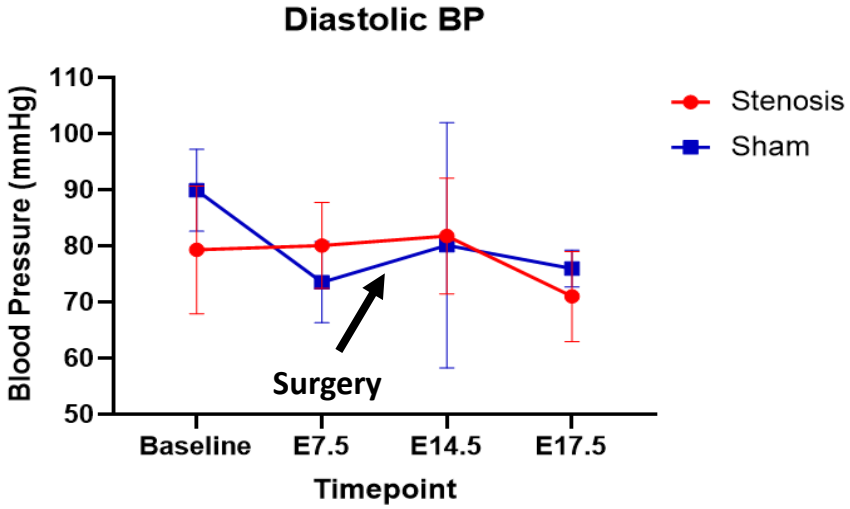

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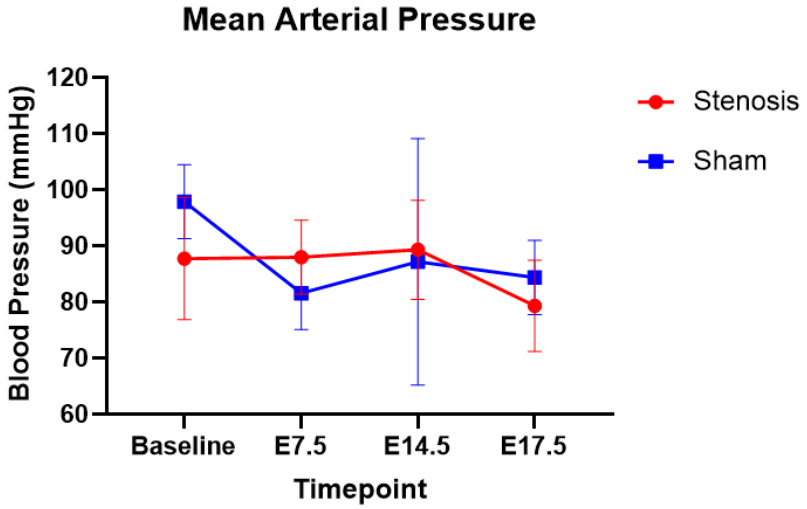


Figure 4. Normalized blood pressures of stenosed vs sham group: A) Systolic BP, B) Diastolic BP, C) Mean Arterial Pressure

LRV area and velocities are negatively affected by stenosis

All the measurements collected from the left renal vein decreased as the pregnancy progressed compared to baseline measurements. The area was not statistically significant (p=0.051) from stenosis, but it did show a decreasing trend by E17.5 (Figure 5A). Both peak and mean velocities of the left renal vein were measured near the aorta at the same timepoints. There is an effect of time on velocity in the stenosed group. A one-way ANOVA with post-hoc Dunnett's test showed a significant decrease in velocities from the baseline and E17.5 groups (p<0.05).

In the stenosed groups, blood flow velocities significantly decrease in the kidney potentially as an effect of morphological damage from stenosis.

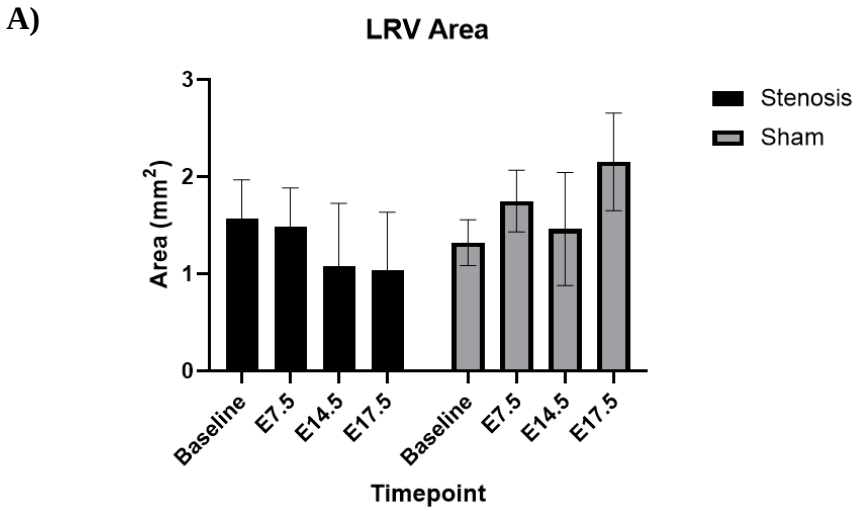
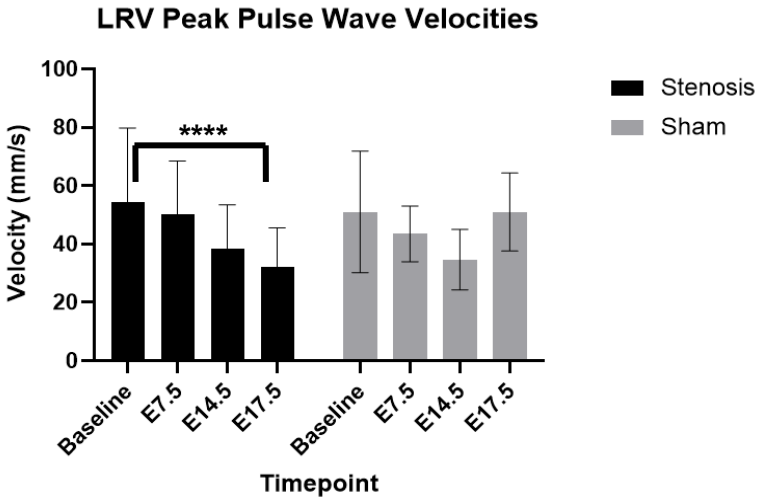


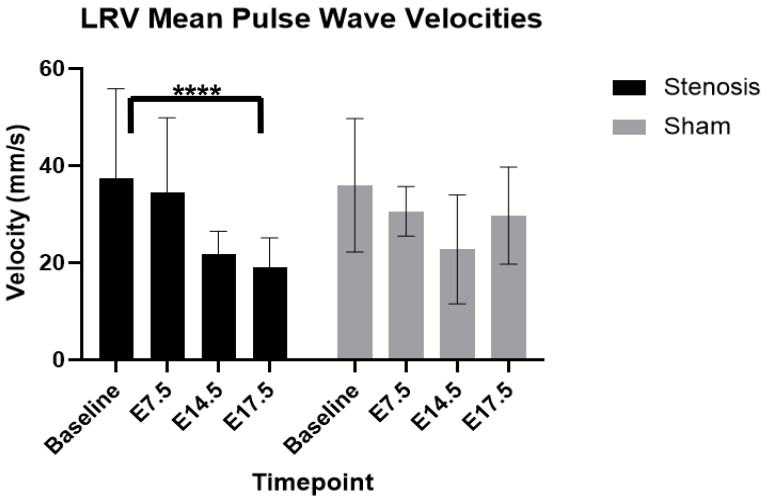
Figure 5. A) LRV area changes throughout pregnancy compared to stenosed and sham group, trending towards significance. B) LRV peak pulse wave velocities significantly different between E17.5 and baseline (p<0.05). C) LRV mean pulse wave velocities significantly different between E17.5 and baseline (p<0.05). For both B) and C), sham group also decreases afterwards, indicating that surgery could potentially affect blood flow velocities, but they return to normal levels by the end of pregnancy. Statistical analysis was done with one-way ANOVA post-hoc Dunnett's test.

Figure 5 continued

B)



C)



Cervical dimensions are impaired after stenosis

To observe the morphological changes as a mouse goes through pregnancy, the cervical area, width, effective diameter, and cervical height were assessed. For the mice undergoing LRV stenosis, there was not a statistically significant effect of time on cervical area, effective diameter, and cervical height (Figure 6A-C). Cervical width significantly increases as gestational age increases and these measurements correspond to trends seen in human pregnancies, which is useful for clinical applications (Figure 6D). Despite not being statistically significant, there is a clear trend that shows stenosis impairs cervical changes. Multiple comparisons with post-hoc Dunnett's

test revealed a significant increase between the non-pregnant state, and E7.5 and E17.5 in the stenosed group for cervical width (p<0.05).

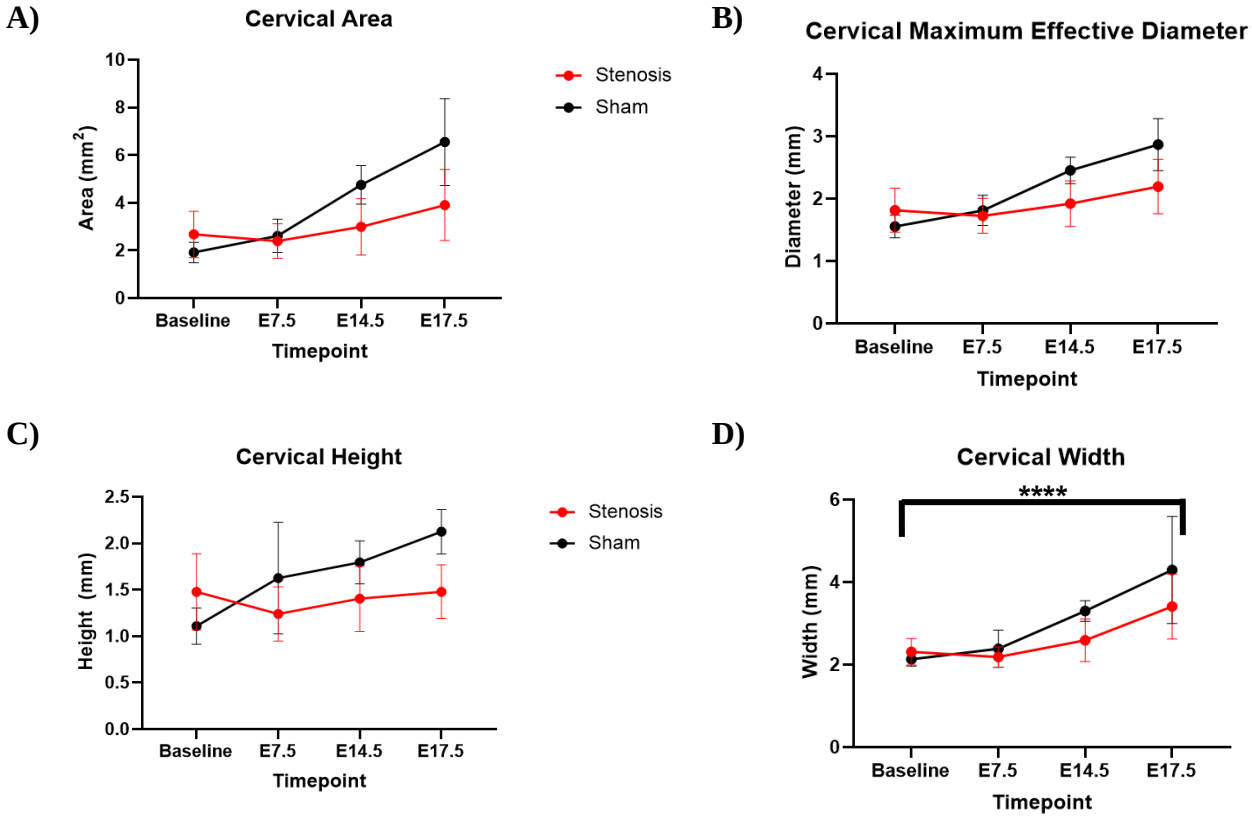


Figure 6. A) Cervical area. B) Cervical maximum effective diameter. C) Cervical height. D) Cervical width (p<0.05) is statistically significant when comparing between baseline and E17.5. A), B), and C) are not statistically significant, but they are clearly affected by stenosis.

Creating 3D models to assess the biomechanical state of the cervix in mice

Three-dimensional models were also created on SimVascular to monitor the changes in the murine cervical geometry and mechanics throughout the pregnancy cycle. For the longitdinal *in vivo* study, the murine cervix revealed patterns of geometric developments similar to changes in humans during pregnancy. We tracked the cervix starting in the vagina and continuned until the bifurcation into uterine horns. Using the Vevo3100 Ultrasound system allowed for the collection of volumetric data, and from that, building the models on SimVascular can predict cervical length, area, etc. These models can then accurately depict how these dimensions develop throughout the pregnancy (Figure 7). Instead of acquiring normal 2D images, we can acquire multiple slices across the cervical region that leads into an accurate 3D model. To reconstruct the images, we

needed to created pathlines, segment the vessel of interest, and then export the model to analyze the different metrics in different points of time (Figure 8). 3D ultrasound imaging can help provide a fuller understanding of the spatial anatomic relationship in real-time by visualizing detailed features in an additonal viewing plane.

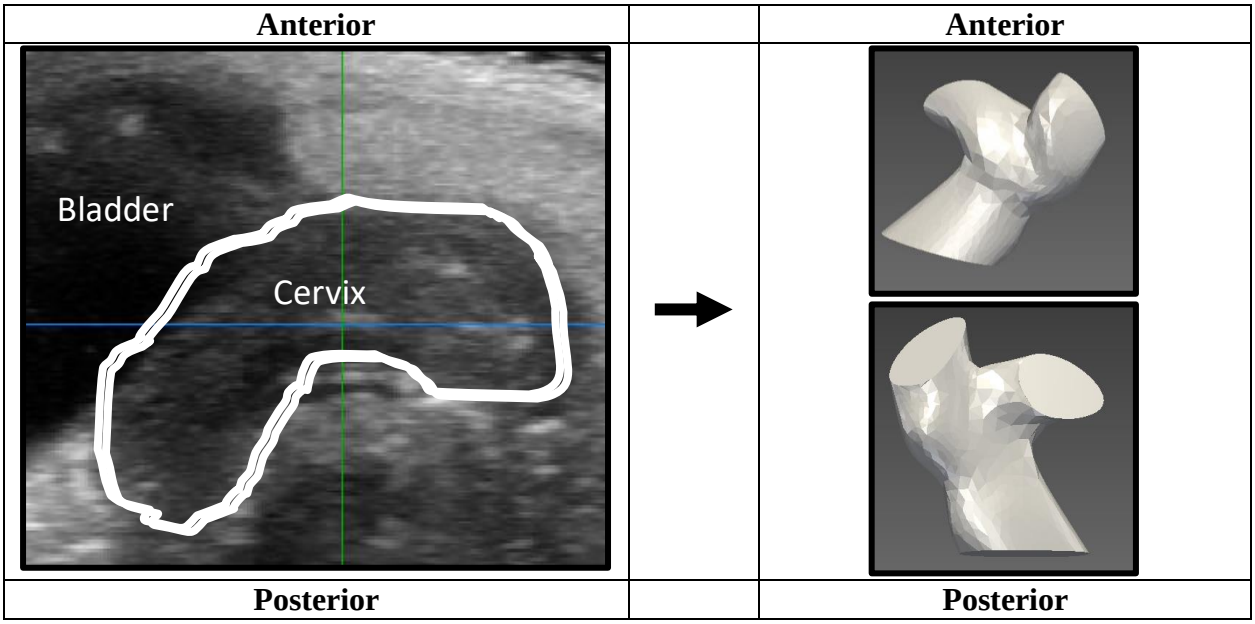


Figure 7. From volumetric data gathered on the ultrasound to creating 3D models on SimVascular, this demonstrates how multiple slices of these images can create an accurate representation of the cervix and the uterine horns.

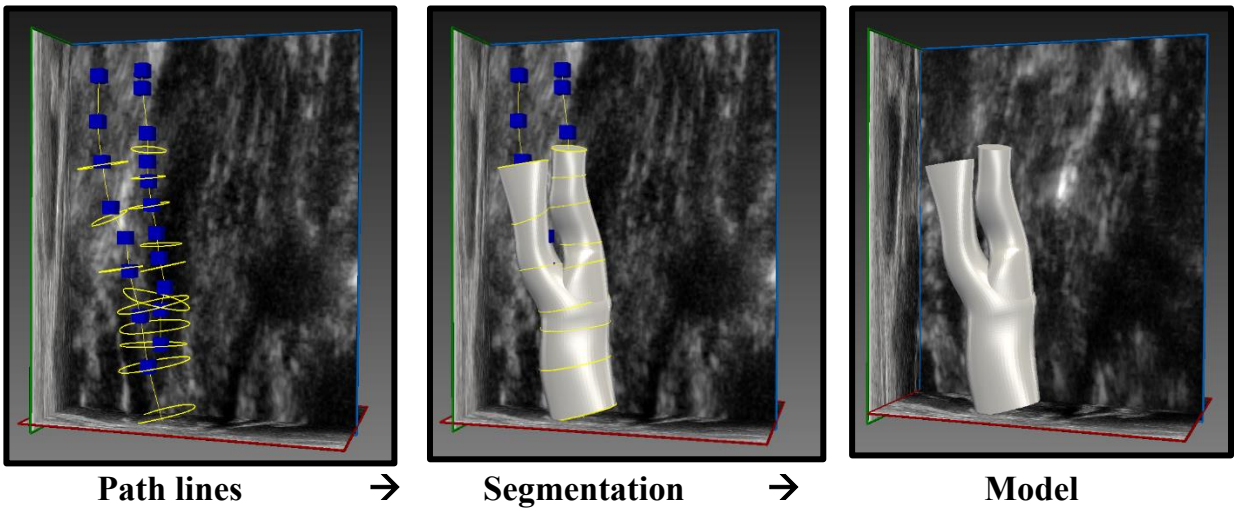
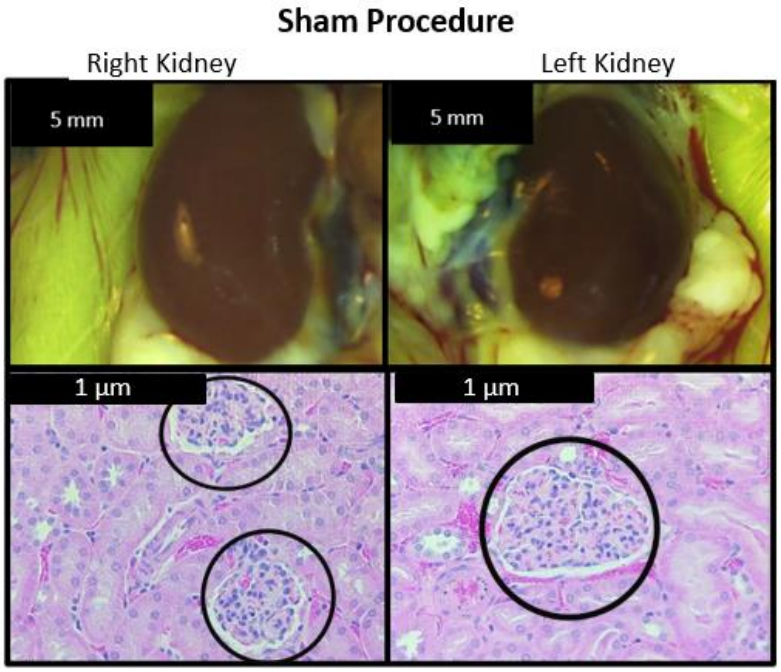


Figure 8. 3D ultrasound images have been segmented and built to create 3D volumetric models. They were created by making a path line, segmenting the regions of interest, and then smoothing the model. Created on SimVascular software.

Renal vein stenosis leads to renal and placental damage

After undergoing stenosis, the left kidney experienced damage compared to the right kidney and compared to both kidneys in the sham group (Figure 9). For the kidneys, we chose to focus on the glomerular structure when assessing effects of stenosis. Firstly, the size of the left kidney became noticeably smaller, potentially due to the atrophy of the renal tissue. A healthy kidney is characterized by many erythrocytes, nuclei of renal tubular epithelial cells, and an overall compact proximal and distal tubular network. However, histologic samples of the renal glomeruli from the left kidney demonstrated necrotic tubules, swollen endothelial cells, and an absence of many nuclei and red blood cells. The differences were prominent, when especially compared to the sham group; the kidneys not affected by LRV stenosis right showed a normal, healthy glomerular network.

A)



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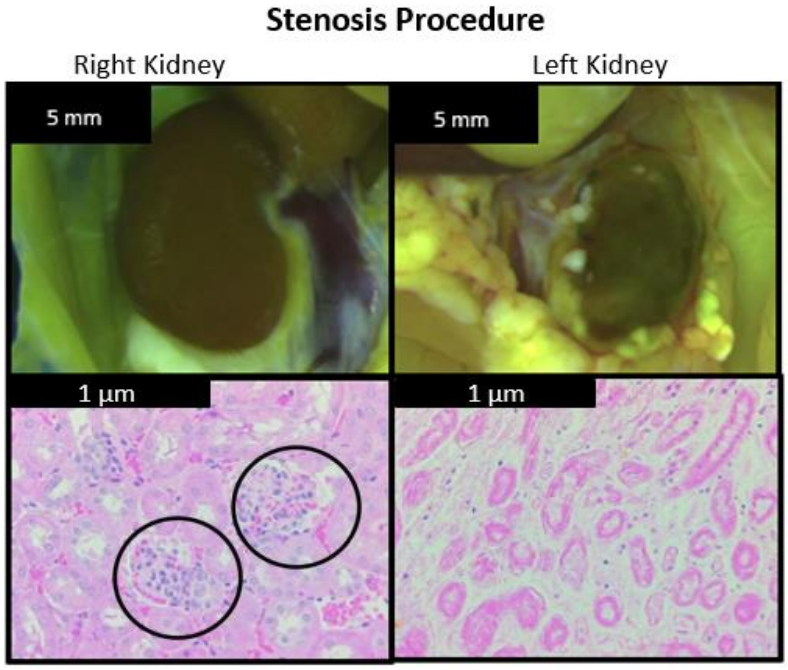

Figure 9. A) Histological samples from the sham procedure show that there is plenty of RBCs, nuclei, and an extensive tubular network. B) Left kidney glomeruli from stenosis showed endothelial swelling and lack of RBCs. Histological assessment confirmed LRV stenosis caused necrotic kidneys.

Placenta samples were also analyzed through histology. For the placentae, we chose to focus on the vascular network near the fetal side (chorionic plate + labyrinth sections). A placenta that is unaffected has healthy trophoblasts, red blood cells, chorionic villi, and a compact labyrinth section. The labyrinth is the functional structure where gas and nutrient exchange occurs. Compared to the healthy placenta, one that experienced stenosis had a weakened vascular network with prominent spaces, decreased number of nuclei, and poorly branched villi. The primary pathology is characterized by poor trophoblastic occurrence of the uterus, causing a "widening of the pathway." Based off several literature articles, our pathologic findings represent how an inflamed placenta would look. One of the biggest determinants is quantity and quality of labyrinth trophoblasts; as stained blue, the placenta in the sham group have abundant nuclei in the trophoblast cells compared to the stenosed group. Atrophy was observed when the trophoblasts were damaged/inflamed, and prominent vascular spaces were widened when the placenta was damaged (Figure 10B).

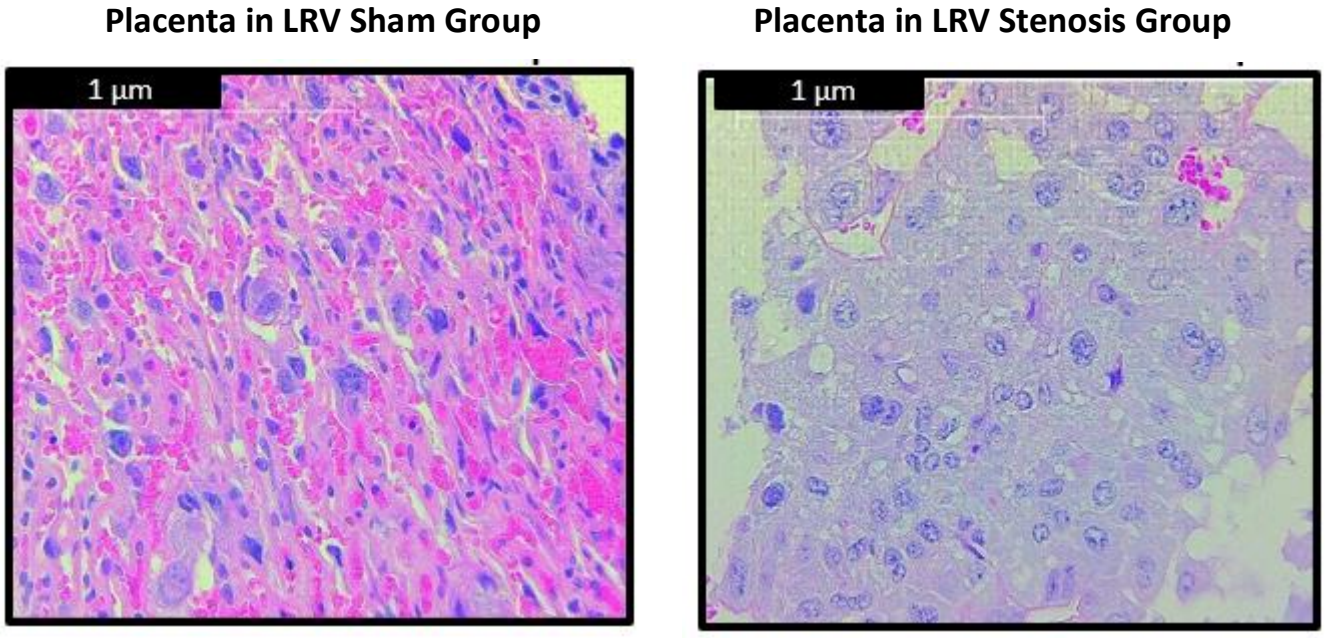

Figure 10. A) The placenta in the sham group showed plenty of RBCs and nuclei and an overall tight vascular network. B) The trophoblasts' nuclei are atrophied, and this sliced sample shows negative impact from stenosis.

1.3.2 BMI vs BP Study

Both systolic and diastolic BP differences are significant when shifting positions

The human study at Purdue University comprised of 120 participants: 70 women and 50 men. The mean age was 23.98 ± 3.77 years and 62% of them were in the healthy BMI range (average was 24.35 ± 4.11 kg/m^2). The subjects' BP measurements were averaged for both body positions and then compared. When shifting from left lateral recumbent to supine position, systolic blood pressure increased by an average of 9.17 ± 5.64 mmHg and diastolic blood pressure increased by an average of 9.04 ± 5.38 mmHg (Figure 11). BPs increased significantly when shifting between positions (p<0.0001). Overall, change in position affects BP because BPs in the supine position are significantly greater than in lateral.

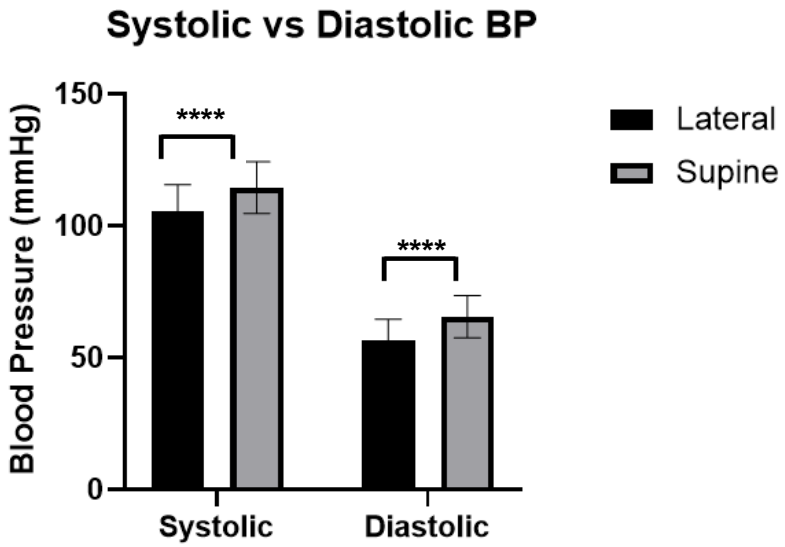

Figure 11. Blood pressure is significantly higher in the supine position than the left lateral position (p<0.0001).

A lower BMI value leads to a larger change in BP

To obtain as much useful information as possible, we divided the cohort into two BMI groups: greater than or less than 25 and greater than or less than 30. A BMI value of 25 kg/m^2 or higher is in the unhealthy range, or overweight. When the BMI is 30 kg/m^2 or higher, a person is obese (11% of our participants fall under this category). Utilizing the BMI value of 30 would better represent a pregnancy with a larger abdominal mass. It was observed that when a subject has a

smaller BMI value, the difference in BP when shifting positions is significantly greater *(p<0.0001*; Figure 12).

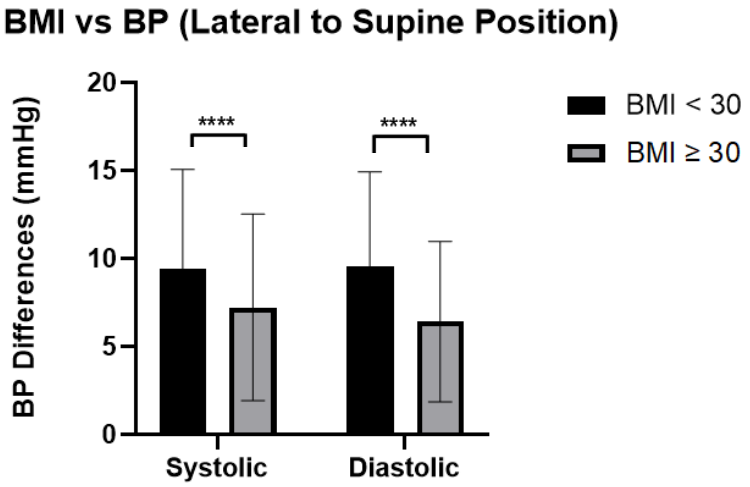

Figure 12. When subjects have a higher BMI value, there is less of a change in BP. For both cohorts of BMI less than or greater than 25 or 30, there is a significant impact on BP ($p<0.001$).

There is a significant difference in BP due to gender

When dividing the groups into males and females and comparing their effect on systolic and diastolic BP, the differences were not significant (p = 0.596). Considerable variability between groups was observed, obscuring the data. Therefore, we separated males and females into systolic and diastolic BP groups (BMI vs Gender for Systolic BP and BMI vs Gender for Diastolic BP; Figure 13). While there is a significant effect of gender on BP for both males and females, where smaller BMI values show less of a change in BP, there is an exception for both males and females when they have a BMI < 25 kg/m^2 (p = 0.99). This supports the previous data that people with larger BMI have less of a change in BP, despite gender. However, there is a significant difference between sex in the cohort with larger BMIs, especially for females. Women with a greater BMI value do see a greater change in BP. Since women are our target audience, they are more likely to be susceptible to changes in BP from this switch in position. When pregnant, women will definitely have a BMI greater than 25 due to increase in adipose tissue and a growing fetus that emphasizes the relevance to the SPT and its target users because they are more sensitive to this change. We aimed to determine 1) if the change in BP is significant and 2) how much does the BP increase or decrease from BMI groups. Comparing between a smaller to greater BMI in females, systolic BP drops from 10.04 ± 0.180 mmHg to 8.84 ± 0.060 mmHg and diastolic BP drops from 10.21 ± 0.76

mmHg to 8.26 ± 0.29 mmHg. In males, systolic BP drops from 10.13 ± 1.650 mmHg to 7.28 ± 2.240 mmHg and diastolic BP drops from 10.20 ± 1.33 mmHg to 6.43 ± 0.37 mmHg.

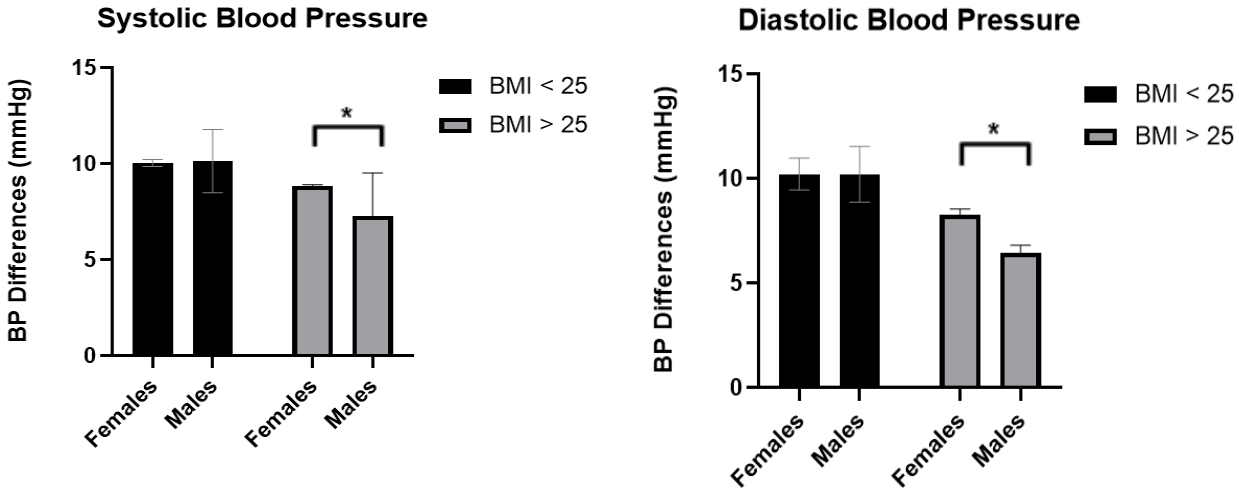

Figure 13. A) Difference in systolic BP impacted by gender and B) Difference in diastolic BP impacted by gender. Both are statistically significant from gender ($p<0.05$).

Automated SPT received with positive feedback

Out of all the 120 participants, most user feedback suggests a general ease-of-use. Subjects were given two surveys to complete at the end of the study. They were asked to evaluate the feasibility and user-friendliness of performing the AUTO-SPT, along with a sleep habit survey to better understand their body positioning throughout the night. An average of 73% of people thought the device was comfortable to wear, 76% thought our customized instructions were easy to understand, and majority of subjects thought it was comfortable to take BP measurements in both positions (Figure 14).

	Device was comfortable to wear	Instructions were easy to interpret / follow	Comfortable to take BP on side	Comfortable to take BP on back
Agree	73%	76%	73%	78%
Neither	15%	6%	12%	8%
Disagree	13%	19%	15%	14%

Figure 14. Selected survey results from BMI study

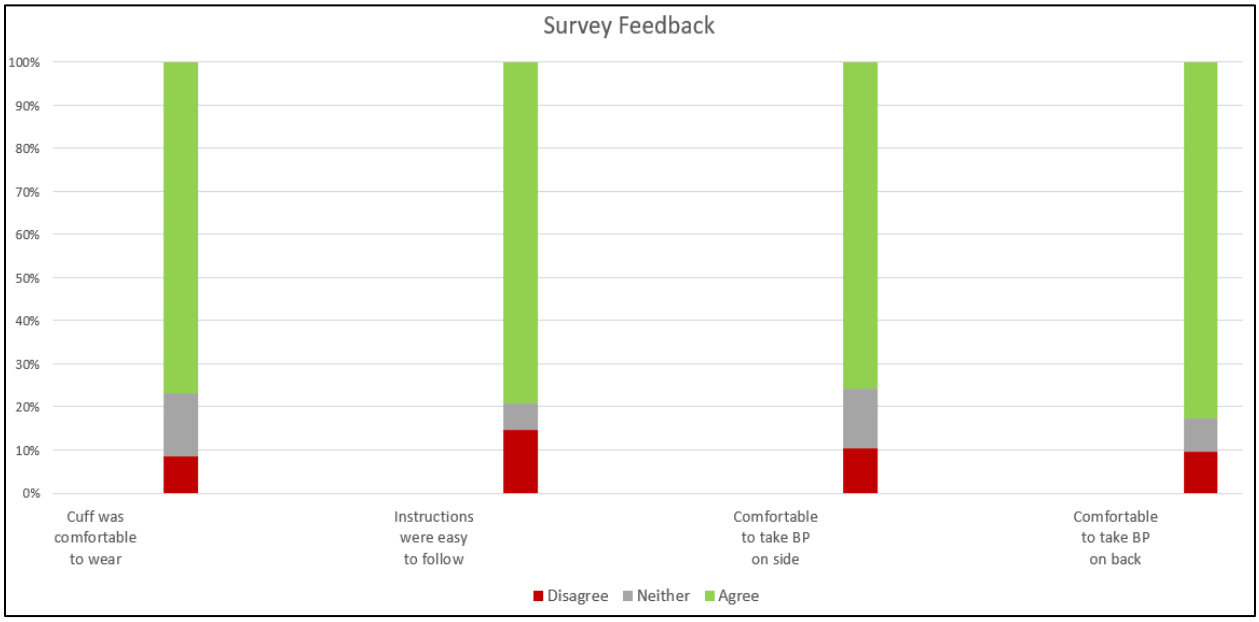

Figure 15. Survey feedback from 120 participants organized in a visual graph: red means disagree, gray means neither agree or disagree, and green means agree.

1.3.3 Device Development

Successful development of smartphone application and position sensor

The method of calculating an error, predicting the next dataset, and comparing the prediction matrix to the true data matrix results in an algorithm that improves over time. The NGIMU, through its own built-in extended Kalman filtering algorithm, outputs quaternions. Through testing, it was found that the NGIMU's quaternion outputs work well in the AUTO-SPT automated device application. The algorithm processes these quaternions in order to obtain an output value that suited the needs of the device. In the application of the Kalman filter algorithm used in the automated device, the gyroscope and accelerometer data both had statistical error

values calculated from their respective quaternion datasets. Factoring both measurements into an equation provided a workable dataset less affected by noise. These final numbers were used to detect user angular position. By testing out the position sensor, we used our team members as the subject by strapping the NGIMU to our stomachs. From this, the graphs showed that the values stabilized and varied accordingly with the magnitude of the subject's movements. During the test, the graph was not excessively affected by acute movements movement, allowing about 25 degrees of leeway in how much the IMU or the patient could rotate, but still be within the green, positive range of correct positioning (Figure 16). Also, the results stabilized fairly quickly after experiencing abrupt movement.

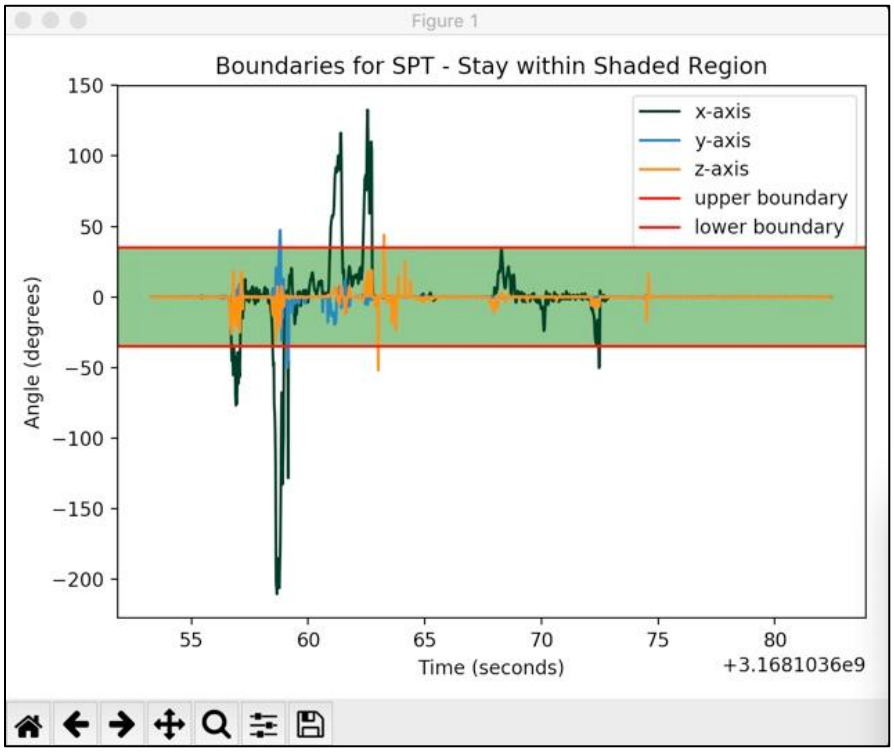

Figure 16. Real-time graph guiding users in positioning themselves for IMU. Green bar is acceptable range for users to lie in and be in optimal position.

Through platforms Firebase and GCP, in the future the app will also be able to display results from current and past measurements and store these results to track changes over longer periods of time. User information in the app will be password protected and the data will be encrypted, so access to patient information will only be provided to those who can securely access the device. The iOS app guides the patient through the AUTO-SPT through visual feedback. After each reading, the patient will then be prompted to enter their results from the device to the app.

These results are then relayed to a secure database and stored with the patient's encrypted User ID. The readings for each day could be accessed by the patient once they enter their User ID and password on the app, allowing the patient to track their readings over longer periods of time. After all readings required for the SPT are taken, the app will inform the patient and show them their results. We intend for the splash page to be able to eventually load potential educational tips or fun facts for the user.

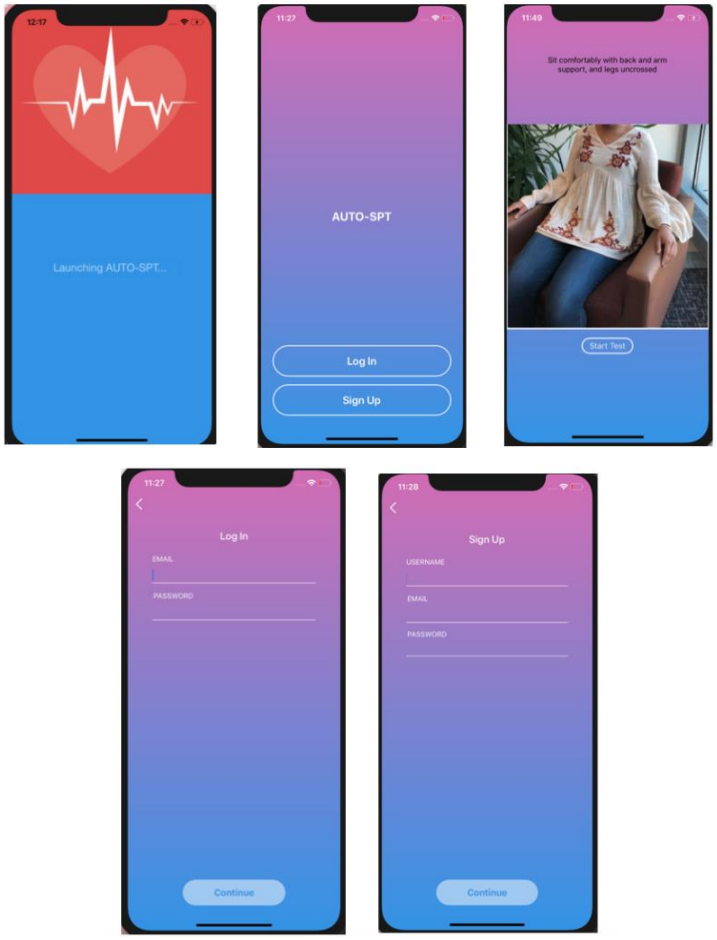

Figure 17. Displays of the app's authentication screen, splash page, login screen, and the first page of instructions for AUTO-SPT.

Defining unmet user needs from cross-functional stakeholders

Our experiences in customer discovery allowed us to network with valuable stakeholders and identify gaps in the current healthcare system and how our product can alleviate those issues. Through I-Corps, we connected with physician-scientists in Kenya to get a genuine testament as to how they operate when dealing with preeclamptic patients and risk of preterm births. One doctor

stated that only when mothers show extremely high BP measurements, do they become admitted for close monitoring due to lack of proper resources. We also saw pictures of some living situations in Kenya that gave us more things to consider when developing a prototype.

Figure 18. Multiple homes are clustered together, and many people lack essentials like blankets, pillows, etc. that may prevent them from consistently performing the SPT.

However, all the interviews resulted in one common lesson: monitoring pregnancy is the best method to detect abnormalities; all kinds of stakeholders agreed there was a need for this product. After this program, the Director of Growth at Purdue Foundry, reached out to us to learn more about our prototype and help us build a business model in the future.

1.4 Discussion

Overall, this research has reinforced the need for constant monitoring throughout a woman's pregnancy, and that this can could be accomplished through an automated supine pressor test (AUTO-SPT). The animal study suggested that renal vein stenosis impairs many different parameters of the mouse's pregnancy: blood flow velocities, cervical area, width, and height. Histology suggested renal and placental damage that leads for future opportunities to explore biomarkers, and placenta and umbilical blood flow. Venous hemodynamics were able to affect both the kidney and uterus in an analogous manner. The human study suggests the AUTO-SPT will fulfill the major healthcare gap of tracking one's BP and educating users how to best position themselves to alleviate any risk of developing pregnancy disorders, namely preeclampsia. Thus, a future goal is to further develop the prototype in order to manufacture it and deploy it into low-resource settings.

To better understand the mechanisms and pathways underlying these pregnancy complications, small mouse models have been created to simulate human pathologies. These models provide insights due to their similar resemblance to humans by being able to rapidly replicate the disorder and manipulate desired factors. There are many differences between humans and mice, but several features are similar to make the models relevant, i.e. stenosis mimics pressure of the gravid uterus on the LRV. The murine model was created to observe hemodynamic and geometric changes before and after stenosis during the entire gestational period. The Page kidney [24] explains how a reduced vessel diameter could greatly affect the tissue and entire system. Specifically, the left renal vein was discovered to be vulnerable to compression because it undergoes anatomic variability and distension in women with preeclampsia [18], [28]. When women are pregnant, they usually experience a protective mechanism with an increase in cardiac output and blood volume, preventing any hypertension from occurring; therefore, the ~25% of women affected by venous outflow obstruction most likely have inadequate ipsilateral collaterals that fail to provide alternative drainage from the left renal vein to the inferior vena cava [29], [30]. Ipsilateral collaterals are blood vessels that allow for additional blood flow paths, when the main vessel of interest is compromised. Collateral circulation has the potential to protect against these ischemic injuries by maintaining blood flow. While this research did not show any noticeable changes in BP, this could be due to the mouse's protective mechanism of pregnancy; the collateral

network is working in effect. This finding could translate to clinical work suggesting that the developmental anatomy of a robust collateral network can prevent changes in BP vs inadequate ipsilateral collaterals, causing venous outflow obstruction. The BP measurements might have fluctuated too much from potential noise. The tool to measure BP is inherently noisy and when combined with isoflurane potentially decreasing BP, the results can be cluttered. When determining the effect of stenosis on BP, a previous study had extended the study until 14 days after the surgery [17], which is something to take into consideration for future animal work. There was not enough time for hypertension to develop with our timeline, so we could in the future attempt to carry out the murine model for a longer duration; even after the mother gives birth as she would still have the suture that could replicate LRV compression. One could also ideally implant a BP tracking device into mice for a longitudinal study, but it is extremely expensive and still not guaranteed to accurately detect changes in BP.

Throughout gestation, the pregnant mice exhibited a significant decrease in anatomical changes. Surprisingly, the change in LRV area was only trending to significance, but it had a consistent 90% stenosis throughout the entire cohort. Given such a high percent stenosis, the area should have significantly decreased from baseline. It would be interesting to perform another iteration with varying percent stenosis to observe the effects. A 90% LRV stenosis would basically mean that the kidney is completely necrotic in a human, since that is what we saw in the murine model; this could lead to dangerous consequences as necrotic debris builds up, leading to sepsis. Regardless, there were significant decreases in mean and peak pulse wave velocities throughout pregnancy. Given Poiseuille's Law, as radius decreases (from the compression), velocity should increase, contrary to what we observed. We believe that had we measured the velocity waveforms immediately before and after surgery, velocity would have dramatically increased. However, by the time we measured at E14.5, there was already morphological changes and ischemia causing velocity to decrease from renal damage. Also, there was noticeable impairment from stenosis on the cervix; while cervical measurements continued to increase as pregnancy progresses (similar to human pregnancy), the stenosed group experienced a significant decrease in cervical width on E17.5 from day 0. Histology samples of the kidneys and placentae exhibited results that represented renal congestion and ischemia. While renal compartment syndrome leads to hypoperfusion and renal injury in preeclampsia, our data showed necrosis; the various stenosis

levels would be interesting to learn more about if it could be a factor. Given such significant differences in the histology of the placentae, there is opportunity for future experiments by focusing on the umbilical and placental blood flow in stenosed vs sham groups. One could also investigate different biomarkers to diagnose preeclampsia; however, acquiring enough blood samples remains a challenge.

In order to develop methods to detect preterm birth, we focused on characterizing cervical biomechanics through 3D high resolution ultrasound imaging and volumetric modeling. This novel method would enhance clinical understanding of how to address different issues when the cervix is anatomically or functionally impaired. Infection and inflammation could lead to premature cervical softening [31]. While we were not able to image during labor, E14.5 and E17.5 corresponded to the later trimesters of pregnancy, when CI becomes a more common complication [32]. In order to create accurate 3D models, we tracked the cervix starting the in vagina and continued until the bifurcation into the uterine horns. If we were able to assess traumatic change to the cervix, we would ideally be able to determine the retaining strength of the organ and supporting structures. Because traditional metrics are insufficient to measure all dimensions, we must explore all the options: maximum effective diameter, anteroposterior height, width, area, etc. Our results demonstrate that ultrasonography can accurately show pathological cervical changes during pregnancy by considering multiple metrics. While cervical length is one of the common clinical markers to use for preterm birth, it is a one-dimensional metric of a three-dimensional anatomical part and undergoes many changes throughout pregnancy. This marker is only one component of a larger and complex syndrome of preterm birth; given that cervical length naturally shortens in a healthy pregnancy, there is a need for discovering more precise metrics as the unifying etiology of CI. It is only valid to use a method that includes multiple ways to assess for morphological changes. Our results suggest three-dimensional ultrasound imaging and volumetric assessment of the cervix could be useful for analysis of geometric and mechanical changes during pregnancy, which is an extremely novel use of the method. Utilizing advanced imaging modalities and hemodynamic models, we can construct accurate models with intricate geometry and analyze how mapping risk predictors impacts the blood flow and how various dimensions change throughout pregnancy. This is critical because while we cannot guarantee that CI causes preterm birth, we can constantly image, monitoring for abrupt changes throughout pregnancy and can

determine if CI can contribute to prematurity. Overall, 3D modeling suggests to have strong potential applications.

BMI became an important variable to consider because we were trying to investigate if central obesity can also contribute to renal venous outflow obstruction like pregnancy can. If the biomechanics are similar enough through this excessive abdominal weight compressing the renal vein, a medical device that could detect the risk of hypertension would provide much peace and stability to the user. Since obesity can affect both men and women, we had to include a sizeable population of men and have them perform the SPT to determine if they experienced any changes in BP. While this human BMI study was an expansion upon another study [17], it continued to show that both systolic and diastolic blood pressures increased when shifting from the left lateral recumbent to the supine position. We had removed many confounding variables such as arm position, body angle, etc. to standardize the procedure. Due to adding men, the average increase in systolic and diastolic BP difference widened from approximately 10-14 mmHg to 9-14 mmHg. This baseline increase in BP in non-pregnant subjects is critical to consider when creating a device that needs a consistent diagnostic criterion to assess the results. Regarding the diagnosis criteria, the original SPT stated that an increase in diastolic BP of more than 20 mmHg would result in a positive test. Our data shows that we have more to consider since there is a baseline increase in both non-pregnant and pregnant women. For the BMI study, we tested both cohorts with a BMI value of 25 and 30; 25 means the subject is overweight and 30 means the subject is obese. Testing both showed that they were statistically significant on blood pressure changes. To test the effects of BMI, we used the BMI value of 30 because that is the standard for obesity and would represent a pregnant state better (large abdominal mass). Since preeclampsia presents itself during the latter half of pregnancy, we thought there would be a greater statistical impact on BP if the BMI was more like obesity and pregnancy. It would enable us to see the effects of venous outflow obstruction from the mechanical compression. Interestingly, we initially thought a high BMI value would see a greater change in BP, like we saw in pregnant women. However, the opposite occurred: a greater BMI value saw less of a change in BP. Subjects could have an extensive collateral network that negates any effect of mass; if the subjects have robust alternative drainage paths, their BP will not be affected as much. This point drives a dual insight that highlights the importance of predicting and preventing preeclampsia: 1) there is underlying anatomy independent of BMI

(ipsilateral collaterals work regardless of mass) and 2) BP is driven by both RAAS and ischemia. The implications of disturbed renal perfusion are huge and continue to illuminate upon the fact that protective collaterals are the potential key variable as to why some people (and mice) experience increased BP when compressing the LRV and why some do not.

In a healthy cohort, there are still profound physiological alterations that differ from at least each other between renal blood flow and glomerular filtration rate (GFR) [23]. For an uncomplicated pregnancy, those with underlying renal disease will experience a self-improvement in renal function by accommodating for the gravid uterus, placenta, and fetus. For those who develop preeclampsia, the GFR and renal blood flow decline, and experience glomerular endotheliosis, which illustrates the condition heavily involve the kidney [23]. When pregnant women undergo extreme vasoconstriction, endothelial "activation" and dysfunction are shown. Altered hemodynamics can affect endothelial cells (which sense blood flow) and can trigger RAAS. These differences and changes throughout pregnancy are critical to spot and avoid deviations because they often precede the risk of preeclampsia. This disorder is both renin- and ischemia-mediated implying that they are greatly involved in RAAS and altered hemodynamics. Essentially, RAAS is activated to compensate for when the kidney experiences increased intrarenal pressure as a short-term response, but then constant compression results in renal ischemia as a long-term response. The persistent outflow obstruction decreases blood perfusion to kidneys, leading to drastic damage. The degree of renal vein constriction and necrosis of renal tissue could affect renin levels, and thereby BP, because the renin would eventually start to decrease as ischemia takes over and can lead to tissue damage. This causes dysfunction in juxtaglomerular cells and kidneys overall, preventing them from sensing changes in pressure anymore. Subjects with a higher BMI value also had an average higher systolic BP, so the change in position might not have had as much of an impact. However, they had an unusually lower diastolic BP, which might be due to improper method of wearing the BP cuff. Wearing a BP cuff that is too large will give false low readings, while an overly small cuff will give false high readings.

We looked to consider all potential sources of variation to reduce effects of confounding factors, so we investigated gender. To test the effects of gender on BP, we used the BMI value of 25 because there were more data points; only 10% of the study's population was > 30. The data analysis was more robust because there was a greater sample size. The significance means gender

is critical to consider because this project is meant to create a medical device for pregnant women, but the data showed men clearly drove differences in BP.

We also investigated the correlation between age and BP increase due to position change. While our study subjects ranged from 18 to 43 years old, the mean subject age was 23.98 ± 3.77 years old, with most participants being younger students. Given this, it is difficult to conduct any type of regression analysis that could help determine if subject age influences the SPT. For future studies, a larger subject pool with a more heterogenous spread in ages would be used for determining any correlation between age on acute BP changes due to body position.

Automating the SPT has its own set of complications and factors to consider. The SPT in the 1970s said its main diagnostic criteria was an increase in diastolic BP of more than 20 mmHg, but our work has debated how effective it is as a clinical metric. There is a baseline increase in non-pregnant women and men of about 9-14 mmHg, and in pregnant women of about 12-18 mmHg [17], so adjustments on how to properly diagnose a risk for preeclampsia is yet to be defined. To help pregnant women in low-resource settings, we had to learn about the customers and their resources. Pregnant women in these target areas could greatly benefit from an AUTO-SPT because many studies suggest that home-based BP monitoring is beneficial to maternal and neonatal health [17], [33]. After conferring with collaborators and completing the Customer Discovery course, we gathered a sense of the living situation in rural areas with the lack of resources and difficulty to implement a device without stable source of electricity. In high-income settings, pregnant women often get weekly appointments with their physician or OBGYN; however, in many rural regions, pregnant women fail to have the proper finances, transportation, or other means to receive reliable healthcare. These numerous barriers lead to high maternal mortality rates, with as many as 90% of global maternal deaths in Sub-Saharan Africa and South Asia [34]. In some rural areas, to combat the distant healthcare services, there are community healthcare workers that care for groups of pregnant women. This customer discovery program taught us that these people would also be important target users, since they would be the ones helping pregnant women use this device. Essentially, there could be two types of users: the one physically handling the device and the patient in need of the test (end-user).

Clinical communities believe that the main cause of preeclampsia is placental ischemia. However, our work has shown that the kidneys and the left renal vein specifically, are potentially large contributors to this disorder. Previous work was supported by our murine model that all fetal growth parameters, such as blood flow redistribution, were positively linked with kidney volume and the overall kidney anatomy and physiology [35]. The fact that our results show renal blood flow is connected to placental blood flow when observing stenosis vs control groups is truly significant—this highlights that Page Kidney is very likely to contribute to pathophysiology of preeclampsia. The variations of the renal venous anatomy recommend that therapeutic treatments ought to correlate with the underlying anatomy. Because there are distinct differences between late-term and pre-term preeclampsia, understanding those changes is critical. For women at risk of late-term preeclampsia, they often have small collaterals sufficient enough to provide partial protection from renal compartment syndrome, compared to women at risk of preterm preeclampsia, where no ipsilateral collaterals exist. For these target patients, identifying the risk early enough using the SPT is crucial to prevent the progression of renal compartment syndrome. Our mouse work had many interesting discoveries and especially tying in with our BMI study and the explanation of collateral circulation and renal ischemia, all of which could lay the groundwork for future clinical studies and human applications.

In conjunction to our scientific progress, our team is attempting to enhance our grass roots, global advocacy campaign of educating pregnant women to “Sleep Sideways.” Ideally, by increasing prenatal education, pregnant women can decrease prematurity due to preeclampsia with simple therapeutic positioning. Identifying these women at high-risk allows for greater monitoring and a more thorough opportunity to develop preventative strategies [36]. In the future, the novelty of the AUTO-SPT incorporates a long-term position sensor. The IMU portion of the device will provide preventative alerts to ensure users are in the right range of the SPT, and in the long-term could potentially be used during sleeping. It would ensure users stay on their left side throughout the night, which will not only predict, but prevent preeclampsia. To accommodate the underlying variable anatomy and dynamic physiology would be to perform serial SPTs; this would also increase test sensitivity and identify women at risk proactively. From a physiologic standpoint, the need for constant monitoring aims to target how early vs late changes in vasculature and their impact on BP could be evaluated as pregnancy progresses.

1.5 Limitations

Despite much progress, these studies have inherent limitations that should be considered. For the mouse model, we did not use timed pregnancies because we had considerable challenges with breeding. Thus, we had to estimate what stages of pregnancy the mice were at based off previous work, wherein there is a risk of inaccurately assuming the stage. This prevented us from tracking fetal development and being able to qualitatively draw conclusions from the results. We initially hoped to see the effects of stenosis on pup weight, but there is a potential we euthanized the mice a few days earlier to prevent spontaneous birth, which led to inaccurate times for dissection. Also, with the BMI study, while we aimed to gather heterogenous data, there was still room to improve and gain a more diverse population. BMI has also proven to rarely have been an effective metric, so a higher BMI value does not guarantee that the distribution of mass is directly centered in in the abdominal area, meaning the anatomy is not compressing the vessel of interest. Although more difficult to manage, body fat could be a more telling metric for future work. Additionally, the BP cuff is not the most user-friendly and could cause human error when taking measurements. Future research is needed to follow subjects throughout the longitudinal clinical study and to assess the AUTO-SPT with a more effective BP cuff.

1.6 Conclusion

In conclusion, this thesis research has increased our understanding of the biomechanisms during pregnancy and reinforced the need for the AUTO-SPT. Our studies suggest that LRV stenosis negatively alters hemodynamics and impairs morphology in kidneys and placentae. We are also able to build 3D ultrasound volumetric models to help quantify cervical changes during pregnancy. Our human studies showed that there is a significant baseline increase in BP, and that BMI and gender both impact changes in BP. Aside from the scientific progress, we have identified and interviewed various stakeholders, proving that completing the AUTO-SPT could fulfill a clinical need to diagnose and proactively monitor the risk of preeclampsia. There is still much work to be done, but the results demonstrated that this device would help both maternal and fetal health worldwide. Too many expecting mothers have minimal prenatal education and are unable to monitor their risk for developing this disease. Greater knowledge about reproductive system and how its dimensions change during pregnancy will help develop preventative strategies. We

need to understand the pathophysiological changes during pregnancy and explore diagnostic and therapeutic treatment modalities. Thus, we are encouraged to continue to build the framework for improving outcomes for children born preterm.

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APPENDIX

Table A.1. Subject information from human BMI study

ID	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)
1	22	145	69	21.41
2	26	165	66	26.63
3	25	125	67	19.58
4	24	150	66	24.21
5	20	145	67	22.71
6	22	130	64	22.31
7	18	108	65	17.97
8	21	150	64	25.74
9	30	118	62	21.58
10	22	120	62	21.95
11	20	140	69	20.67
12	20	107	60	20.89
13	24	95	60	18.55
14	26	200	68	30.41
15	22	110	65	18.30
16	24	128	66	20.66
17	21	130	69	19.20
18	23	140	67	21.92
19	43	134	64	23.00
20	19	150	65	24.96
21	23	150	65	24.96
22	21	150	67	23.49
23	21	117	67	18.32
24	20	135	62	24.69
25	25	125	64	21.45
26	23	100	62	18.29
27	21	138	64	23.69
28	25	140	66	22.59
29	22	130	67	20.36
30	23	136	67	21.30
31	18	120	69	17.72
32	21	125	67	19.58
33	21	165	67	25.84
34	21	130	62	23.77
35	22	154	71	21.48
36	24	120	65	19.97
37	23	135	66	21.79
38	19	179	65	29.78
39	22	180	68	27.37
40	25	125	64	21.45
41	22	131	66	21.14
42	25	117	63	20.72
43	22	150	67	23.49
44	19	127	65	21.13
45	27	135	64	23.17
46	26	140	64	24.03

Table A1. continued

47	22	120	61	22.67
48	21	180	64	30.89
49	21	155	64	26.60
50	23	108	63	19.13
51	28	94	62	17.19
52	24	150	68	22.80
53	27	224	70	32.14
54	27	165	68	25.09
55	23	169	72	22.92
56	21	160	72	21.70
57	23	196	68	29.80
58	23	190	65	31.61
59	26	160	65	26.62
60	24	160	64	27.46
61	22	235	72	31.87
62	28	212	74	27.22
63	27	150	72	20.34
64	24	127	62	23.23
65	28	150	70	21.52
66	28	105	63	18.60
67	28	140	70	20.09
68	22	185	65	30.78
69	22	119	61	22.48
70	24	165	70	23.67
71	22	165	70	23.67
72	29	159	69	23.48
73	30	162	70	23.24
74	22	123	66	19.85
75	22	155	70	22.24
76	24	180	71	25.10
77	24	136	65	22.63
78	33	235	70	33.72
79	30	147	67	23.02
80	25	151	61	28.53
81	24	185	70	26.54
82	23	165	68	25.09
83	23	230	72	31.19
84	26	185	70	26.54
85	19	135	68	20.52
86	22	165	70	23.67
87	28	165	69	24.36
88	25	200	72	27.12
89	24	176	69	25.99
90	23	143	67	22.39
91	29	160	67	25.06
92	22	125	63	22.14
93	21	135	71	18.83

Table A1. continued

94	22	180	68	27.37
95	21	220	75	27.50
96	27	237	68	36.03
97	36	150	68	22.80
98	23	135	63	23.91
99	25	250	72	33.90
100	23	132	59	26.66
101	22	250	71	34.86
102	21	150	63	26.57
103	22	140	61	26.45
104	21	135	67	21.14
105	25	170	71	23.71
106	22	150	66	24.21
107	39	185	73	24.41
108	23	190	72	25.77
109	23	166	68	25.24
110	29	154	64	26.43
111	24	250	69	36.91
112	26	160	69	23.63
113	29	195	68	29.65
114	24	180	71	25.10
115	22	170	69	25.10
116	21	240	74	30.81
117	25	190	65	31.61
118	26	160	70	22.96
119	25	195	70	27.98
120	23	182	71	25.38

Table A.2. Sleep Questionnaire

1. What position are you typically in when you fall asleep? (Check **one** box)
□ On my back □ On my stomach □ On my left side □ On my right side

2. What position are you typically in when you wake up? (Check **one** box)
□ On my back □ On my stomach □ On my left side □ On my right side

3. How many hours per day do you spend resting or sleeping?
(Check **one** box)

□ 0-2 hours	□ 4-6 hours	□ 8-10 hours
□ 2-4 hours	□ 6-8 hours	□ 10 or more hours

4. How many hours per day do you spend resting or sleeping in a reclined position, such as in a recliner, during both day and/or night?
(Check **one** box)

□ 0-2 hours	□ 4-6 hours	□ 8-10 hours
□ 2-4 hours	□ 6-8 hours	□ 10 or more hours

5. Do you use extra pillows to help you sleep? □ Yes □ No

If you answered Yes, how do you usually use extra pillows? (check all that apply)
□ Under head □ Under legs □ Between legs □ Between arms □ I use a body pillow

□ Other (please specify): _____

6. Have you heard about or been talked to about different sleep positions and whether one position is better than the other? □ Yes □ No
If you answered Yes, where did you get the information from? (check all that apply)
□ Nurse, doctor, or other healthcare provider
□ Friend or family
□ Website or social media site
□ Other (please specify): _____

7. Has anyone told you that you snore while you are sleeping?
□ Yes □ No

8. Do you wake up during the night while sleeping? □ Yes □ No
If Yes, what is the typical cause of waking up?
(Please select **any** you experience)
□ I have to use the bathroom to urinate or have a bowel movement
□ I am uncomfortable in general
□ Nausea or vomiting
□ Other: _____

Table A1. continued

9. Have you experienced increased swelling of your ankles and/or feet during the past six months?

□Yes □ No

If Yes, how would you best describe this swelling?

□ Mild
□ Moderate
□ Significant

10. Have you been to see a dentist during the past six months or are you planning to see one during the next six months? (Check **one box**)

□ Yes, I have already seen one during the past six months
□ Not yet, but I am planning to see one in the next six months
□ No, I am not planning to see a dentist in the next six months
□ No, I do not typically get dental care

11. Do you own and use a smart phone or similar device? □ Yes □ No

If you answered Yes, are you able to download apps and other programs to it? □Yes □ No

12. How old are you? _____ years

13. What group(s) would you use to describe yourself?

□ African-American/black
□ Asian/Pacific Islander
□ Caucasian/white
□ Hispanic/Latinx
□ Other: _____
□ I prefer not to answer

Table A.3. Human BMI feedback survey about BP cuff

Please rate your experiences on a scale of 1 to 5, with 1 being strongly disagree and 5 being strongly agree.

1. The device was comfortable to wear:

   1 2 3 4 5

2. The device was challenging to use:

   1 2 3 4 5

3. The instructions for the device were easy to interpret and follow:

   1 2 3 4 5

4. It was comfortable to take blood pressure while lying on my back:

   1 2 3 4 5

5. It was comfortable to take blood pressure while lying on my side:

   1 2 3 4 5

6. Do you have any other comments or concerns regarding the device and its usage that were not covered above?

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