AUTOMATION OF THE SUPINE PRESSOR TEST FOR PREECLAMPSIA

by

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To my parents,

For their support and for exemplifying resilience through challenging times.

I am forever grateful for their love and encouragement.

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ABSTRACT

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Preeclampsia leads to increased risk of morbidity and mortality for both mother and fetus. Most previous studies have largely neglected mechanical compression of the left renal vein by the gravid uterus as a potential mechanism. In this study we first used a murine model to investigate the pathophysiology of left renal vein constriction. The results indicate that prolonged renal vein stenosis after 14 days can cause renal necrosis and an increase in blood pressure (BP) of roughly 30 mmHg. The second part of this study aimed to automate a diagnostic tool, known as the supine pressor test (SPT), to enable pregnant women to assess their preeclampsia development risk. A positive SPT has been previously defined as an increase of at least 20 mmHg in diastolic BP when switching between left lateral recumbent and supine positions. The results from this study established a baseline BP increase between the two body positions in non-pregnant female subjects and demonstrated the feasibility and utility of an automated SPT in pregnant women. Our results demonstrate that there is a baseline increase in BP of roughly 10-14 mmHg and that pregnant women can autonomously perform the SPT. Overall, this work in both rodents and humans suggests that 1) stenosis of the left renal vein in mice leads to elevation in BP and acute renal failure, 2) non-pregnant women experience a baseline increase in BP when they shift from left lateral recumbent to supine position, and 3) the SPT can be automated and used autonomously.

1. AUTOMATION OF THE SUPINE PRESSOR TEST FOR PREECLAMPSIA

1.1 Introduction

1.1.1 Preeclampsia

Preeclampsia, a condition associated with hypertension during pregnancy, affects between 5-8% of pregnant women worldwide and leads to upwards of 70,000 deaths from related complications [1-3]. This condition typically presents after 20 weeks gestation and can cause multi-organ failure in the expecting mother, leading to premature birth and thereby increasing risk of morbidity and mortality to both the fetus and the expecting mother [2]. Preeclampsia is diagnosed by 1) the presence of a systolic blood pressure (BP) greater than or equal to 140 mmHg or diastolic BP greater than or equal to 90 mmHg and 2) another symptom such as thrombocytopenia, renal insufficiency, or proteinuria [3]. This condition is also more likely to occur in subsequent pregnancies if a woman had preterm preeclampsia in a previous pregnancy [4, 5]. Currently, the standard treatment for preeclampsia is to induce delivery, but there may be recommended steps expecting mothers can take to mitigate the risk for developing this condition which could be as simple as resting in the left lateral recumbent position during pregnancy [6-8].

1.1.2 Preeclampsia Pathophysiology

Although maternal vascular endothelial factors, proinflammatory cytokines, and abnormal trophoblast invasion in the placenta are all thought to contribute to preeclampsia formation [3, 9], another possible mechanism contributing to the development of preeclampsia is the compression of the left renal vein by the gravid uterus [1]. This mechanical compression leads to left renal venous outflow obstruction and acute activation of the renin-angiotensin-aldosterone system (RAAS) followed by chronic ischemia-mediated hypertension [1]. The release of pro-inflammatory cytokines associated with renal ischemia may contribute to the multi-organ system dysfunction [1]. The venous outflow obstruction from compression of the left renal vein can cause increased intra-parenchymal renal pressure, which can then cause persistent arterial hypertension as described in the 1930s by Irvine Page in a phenomenon known as Page kidney [10]. The left

renal vein is of particular interest because studies have shown that this vessel is dilated in women with preeclampsia and that it is especially vulnerable to compression by the gravid uterus where it crosses the aorta [11, 12]. Additionally, the this vein is subject to anatomic variability between patients [13]. Connections from the left renal vein to other branches can vary [13, 14], and flow through collateral veins can be beneficial under certain hemodynamic circumstances [15]. However, these connections are not adequate in all women [13], and blood pressure elevation in pregnant patients may be due to the acute renal venous outflow obstruction in women with inadequate ipsilateral collateral veins. This outflow obstruction can cause increased intra-renal pressure that may lead to acute changes in vasoactive compounds. Animal models can be useful to study varying degrees of left renal vein constriction as it is difficult to fully examine the effects of venous constriction in humans. Recent preeclampsia mouse models, however, focus on placental ischemia and neglect renal vein compression issues [3].

1.1.3 The Supine Pressor Test

In order to predict preeclampsia before it develops, a method known as the supine pressor test (SPT), or roll-over test, was developed by N.F. Gant in the 1970's. This test was shown to predict a pregnant women's risk of developing preeclampsia with a 93% positive predictive value [16]. A positive SPT is defined as an increase in diastolic BP of at least 20 mmHg when shifting from the left lateral recumbent position to the supine position. However, the specificity of the SPT was variable, possibly due to the inconsistent methodology between clinics. Key variables of the methodology include arm position and duration of time spent in supine position. The SPT also fell out of favor due to its poor sensitivity, likely due to its performance between 28-32 weeks gestation, which is a timeframe that does not accommodate the variable venous anatomy that pregnant women exhibit [1].

1.1.4 Automation of the SPT

In this study, we aimed to begin automating the SPT in order to improve execution with the ultimate goal of optimizing specificity and providing a tool that would allow serial assessments in the second half of pregnancy. A fully automated SPT could include an automated BP cuff with a position sensor that could guide users to position themselves correctly. While physicians promote regular check-ups for pregnant women ranging from monthly to weekly depending on gestational

age, medicine in rural areas both domestically and globally is often limited by resources that prevent access to quality care. As such, this type of cost-effective, robust, and straightforward diagnostic tool could be useful for pregnant women to track their risk for developing preeclampsia, in both resource-limited areas as well as in developed regions. The purpose of this study was 1) to further elucidate potential mechanisms of preeclampsia by investigating the effects of renal vein stenosis in a murine model of Page kidney and 2) to determine the feasibility and utility of an automated tool with a simplified procedure that allows pregnant women to accurately conduct a SPT. The results suggest an automated SPT may have utility for this population without the need for expensive equipment or frequent clinical visits.

1.2 Materials and Methods

1.2.1 Animal Study

1.2.1.1 Maintenance

Female C57B1/6J mice (n = 13; 21.6±2.1 g) were used for this 2-week study (Jackson Laboratory, Bar Harbor, ME). Animals were between 8-15 weeks to ensure sexual maturity. Animal weights were tracked throughout the study, both before and after surgical procedures. All procedures were approved by the Purdue Animal Care and Use Committee.

1.2.1.2 Surgical Procedure

The first group was subject to a partial left renal vein stenosis to mimic aspects of Page kidney (n = 6), while the second group underwent a sham surgery (n = 7). Briefly, all mice were anesthetized using 3% isoflurane delivered in 0.5 L/min medical grade air before they were switched to 1.5-2% isoflurane throughout the surgery. The abdominal cavity was exposed via laparotomy, and the left kidney and renal vein were isolated. In the stenosed group, a 30-gauge needle was aligned parallel to the left renal vein and a silk 6-0 suture was tied around both the needle and the vein as done previously [17]. The needle was then removed to create a stenosis. In the control group, a sham procedure was performed where the suture was loosely tied around the renal vein without constriction (Figure 1). Buprenorphine (0.03 mg/mL) was administered before the first incision to

minimize pain and discomfort. Antibiotic ointment was applied after the surgery (Neosporin, Johnson & Johnson, Skillman, NJ).

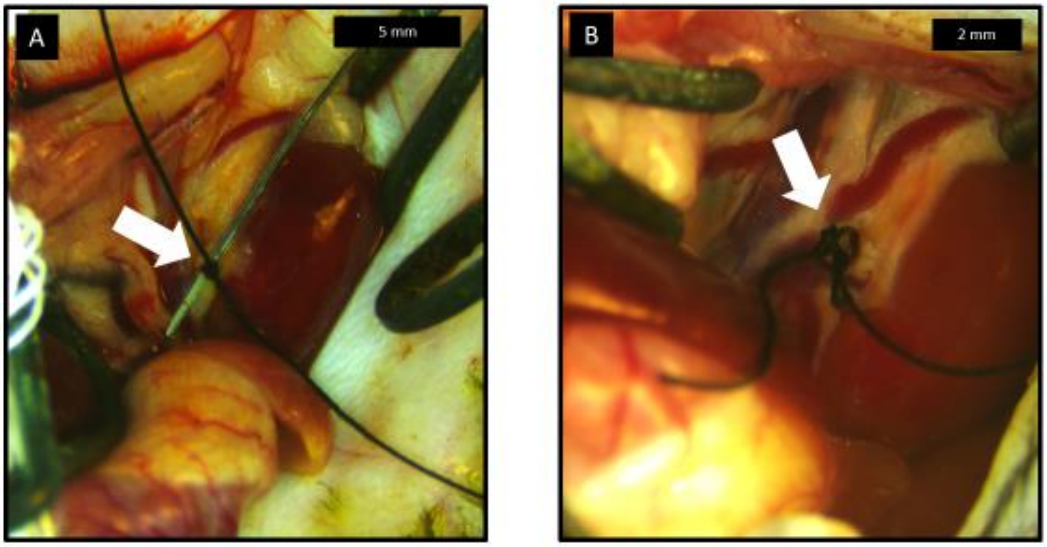

Figure 1. A) Experimental procedure with left kidney is shown. Black silk 6-0 suture is tied around a 30-gauge needle and the renal vein. Needle was removed and excess suture was cut off prior to closing the abdominal cavity. B) Sham surgery procedure on left kidney with black silk 6-0 suture depicted. Suture was loosely tied around vein and not tightened enough to create a stenosis. Excess suture was cut off prior to closing abdominal cavity.

1.2.1.3 Ultrasound & Image Analysis

All mice were imaged using high-frequency ultrasound imaging (Vevo3100 Imaging System, FUJIFILM VisualSonics, Inc., Toronto, ON, Canada) with a 32-55 MHz range 256-element array transducer (MX550D, 40 MHz center-frequency). Imaging was performed the day before their surgeries as well as on post-surgical days 3, 11, and 14. Animals anesthetized with isoflurane were imaged in the supine position on a heated stage after a depilatory cream was applied to remove abdominal hair (Nair, Church & Dwight Co., Inc. Ewing, NJ). Long-axis images of the left renal vein were collected using two-dimensional B-mode as well as color Doppler (Figure 6) and pulsed wave (PW) Doppler along the vein. PW Doppler images were analyzed for all animals at baseline and post-surgical day 14 to identify changes in flow and velocity. The PW Doppler images were analyzed using both the VevoLAB Software (FUJIFILM VisualSonics) and a custom MATLAB code for determining blood flow velocity waveforms.

1.2.1.5 Blood Pressure

A noninvasive tail cuff system (Figure 2) was used to acquire blood pressures of conscious mice at baseline and post-surgical days 3, 11, and 14 (2 Channel CODA System, Kent Scientific Corp., Torrington, CT). Between 20 and 40 BP readings per mouse were collected during each time point. Readings were plotted to identify regions of stable measurements after mice became comfortable in the restraining tubes.

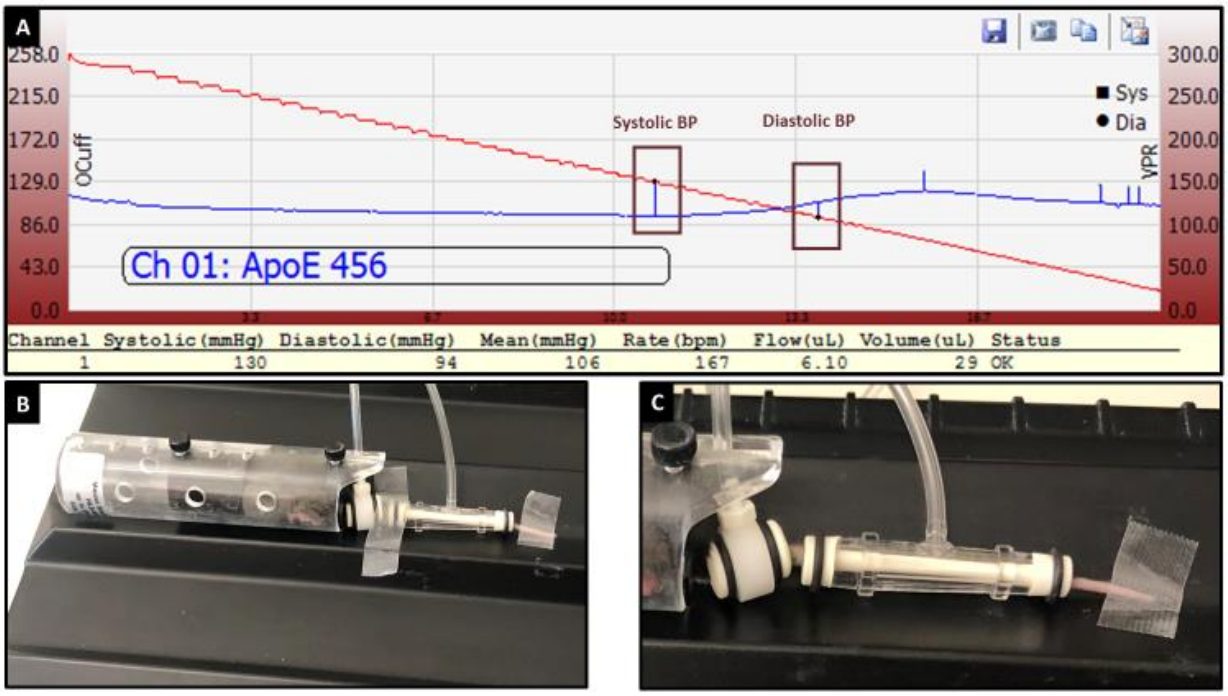

Figure 2. A) Example systolic and diastolic murine blood pressure measurements. Measurements are obtained by the Kent Scientific CODA system from this graph, with the red curve representing the occlusion cuff pressure and the blue curve representing the volume-pressure recording (VPR) sensor curve. The intersection of the inflection points of the blue curve with the red curve are used to calculate systolic and diastolic pressure. B) Set-up of noninvasive tail-cuff BP system with mouse comfortably positioned inside restrainer. C) Cuffs on mouse's tail. Occlusion cuff is at base of tail and VPR cuff is behind it.

1.2.1.6 Euthanasia and Dissection

Animals were euthanized via isoflurane overdose inhalation, and the kidneys were removed on day 14 of the study. Isoflurane overdose was followed by cardiac puncture to collect blood. Then both the left and right kidneys were removed and placed in 1X phosphate-buffered saline (PBS) for up to 72 hours before being transferred to 4% paraformaldehyde (PFA) for all animals.

1.2.1.7 Histology

Tissues were processed for standard histology. Paraffin-embedded coronal sections of each kidney were analyzed using hematoxylin and eosin (H&E) staining, with focus on glomerular structure. Images were acquired at 40X magnification and analyzed by a veterinary pathologist certified by the American College of Veterinary Pathologists.

1.2.2 Non-Pregnant Human Pilot Study

1.2.2.1 Screening Subjects

A non-pregnant cohort (*n*=50) was recruited to help refine the functionality of the automated SPT in terms of measurement stability and comfort prior to testing in pregnant women. Non-pregnant females were asked to participate in this study to establish a baseline increase in blood pressure when shifting from the left lateral recumbent position to the supine position (Figure 3A-B) and to determine how long it takes for BP readings to stabilize after a period of light exercise. Subjects were provided a questionnaire to screen for exclusion criteria including previous cardiovascular conditions such as hypertension or history of sudden cardiac death in immediate family members (Appendix Table 3). Total measurement duration per participant was roughly 30-40 minutes. All study procedures were approved by the Purdue University Institutional Review Board.

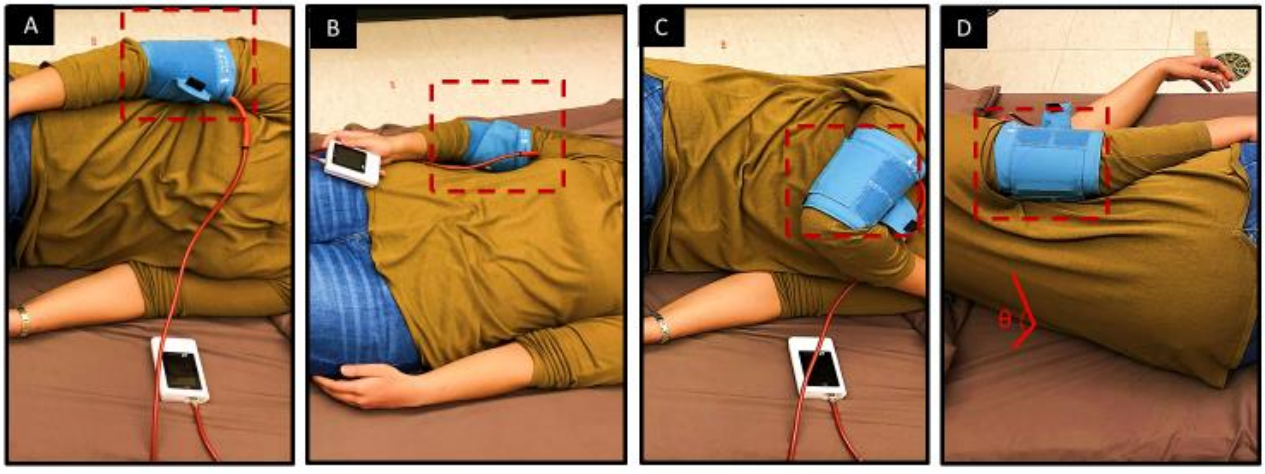

Figure 3. A) Left lateral recumbent position with arm lying along side. B) Supine position. C) Left lateral recumbent position with arm across subject with cuff positioned near heart. D) Body angle is measured from bed to back.

1.2.2.2 Procedure

Blood pressure measurements were acquired using a noninvasive ambulatory BP cuff (OnTrak 90227 Ambulatory BP Monitor, SpaceLabs, Seattle, WA). Subjects were given a set of one-page instructions which detailed the study procedure and how to use the automated cuff. The study was divided into two phases. The first phase included 20 subjects and was used to verify the validity of the procedure itself by gathering survey feedback and identifying issues (Appendix Table 4). This phase of the study asked subjects to first take three BP measurements while seated with their legs uncrossed and their back supported to establish a baseline BP [18]. Subjects then performed light exercise by walking up and down three flights of stairs before immediately lying down in the left lateral recumbent position (Figure 3A). Five serial BP measurements were taken in this position before the subject rotated to the supine position (Figure 3B) where five more BP measurements were acquired by the cuff. Each measurement was acquired in roughly 90 seconds, with at least 30 seconds of reperfusion time between measurements. Once the study procedure was complete, subjects were asked to complete a short, anonymous survey with questions about their experience (Appendix Table 4). Based on the data from the first 20 subjects, phase two of the study was slightly modified to control for the effects of arm positioning and to assess body position angle in the left lateral recumbent position. In addition to the steps in the first phase, the participants were asked to take additional serial BP measurements in the left lateral recumbent position with varying arm positions. For the first five measurements, subjects rested their right arm across their chest (Figure 3C). Subjects then placed their right arm on their right side for the last five measurements (Figure 3A). Body angle measurements (Figure 3D) were also acquired five times in the left lateral recumbent position concurrent with BP measurements by placing a smartphone against the subject's abdomen and using a mobile application to acquire position information (SomnoPose, Proximal Box Software, Eagan, MN). Subjects were also asked to complete a survey with Likert scale-type questions [19] and short free response questions evaluating their experience (Appendix Table 4).

1.2.3 Pregnant Women Study

1.2.3.1 Screening Subjects

Pregnant volunteers (n = 20) at or past 20 weeks gestation were recruited from the antenatal clinic at Indiana University (IU) Health University Hospital in Indianapolis, Indiana. Prior to starting study procedures, all subjects were asked to self-report previous history of chronic hypertension and chronic kidney disease as these were exclusion criteria (Appendix Table 5). Study procedures were performed after subjects met eligibility criteria and once their verbal consent was obtained. All procedures were approved by the governing Institutional Review Board.

1.2.3.2 Procedure

Pregnant women were provided a booklet of printed instructions that was created based on feedback from the initial non-pregnant female study (Figure 4). These women were also provided with an automated ambulatory BP cuff (OnTrak 90227, SpaceLabs) and were asked to follow the directions to perform the SPT autonomously using the instructions to the best of their abilities. Research team members recorded data and clarified questions about the procedure as needed. The procedure was similar to the one conducted with non-pregnant women but excluded the exercise component. BP measurements were acquired three times in a seated position, five times in a left lateral recumbent position (Figure 3A), and five times in a supine position (Figure 3B). In the left lateral recumbent orientation, women placed their right arms along the side of their bodies as depicted in Figure 3A. Body angle measurements were also obtained in the same manner as in the non-pregnant female study (Figure 3D). While the procedure requested that these women lie in the supine position with their legs extended, many of the study participants laid in this position with their knees bent and feet planted as they felt more comfortable this way. After the study, participants were asked to complete a survey about their experience (Appendix Table 6)

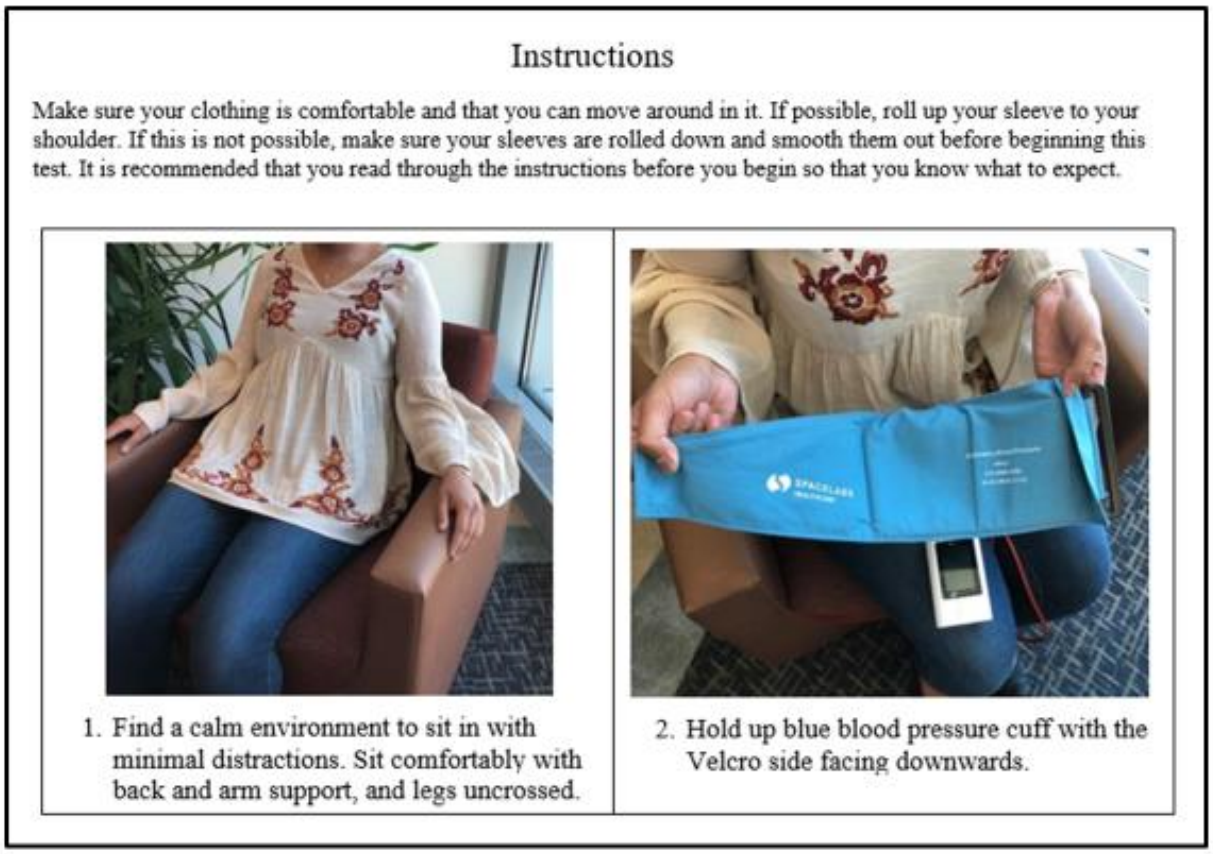

Figure 4 First page of instructions that patients in the pregnant female study received. Instructions were printed and bound into a booklet that was provided to each patient in the study for the duration of the procedure. All steps in the instruction booklet included both a visual graphic and a short, written description of the step

1.2.4 Statistical Analysis

For the animal study, significant differences among time points and groups were determined using a one-way ANOVA with Tukey or Dunnett's post hoc tests (Minitab v18, State College, PA). For both human studies, subjects' BP measurements were averaged for both body positions and compared between positions. A one-way ANOVA with Tukey's post-hoc analysis and 2-sample t-tests were both used to determine differences between groups. Statistical significance for all comparisons was considered at $p < 0.05$. For both animal and human data, assumptions of normality and homogeneity of variance were tested using Bartlett's test and Ryan-Joiner test.

Groups were homogenous ($p > 0.05$), and all but one group followed a normal distribution. This group was of systolic blood pressures of pregnant women taken in the supine position.

1.3 Results

1.3.1 Animal Study

1.3.1.1 Blood pressure increases after renal vein stenosis

Mice in this study were between 8-15 weeks of age to ensure sexual maturity and weighed 21.6±2.1 g. An average stenosis of 53±26% was created after the 30-gauge needle was removed as measured from long-axis, B-mode ultrasound images. Day 14 systolic BPs for the stenosed group were significantly different from baseline BP measurements ($p < 0.05$). At the end of the study, the average BPs of all animals in the stenosed group increased by 33.3±25.0 mmHg for systolic BP and by 32.7±26.9 mmHg for diastolic BP (Figure 5A). For the control group, BPs fluctuated and were within 20 mmHg of the baseline measurements for both day 14 systolic and diastolic BP (Figure 5B).

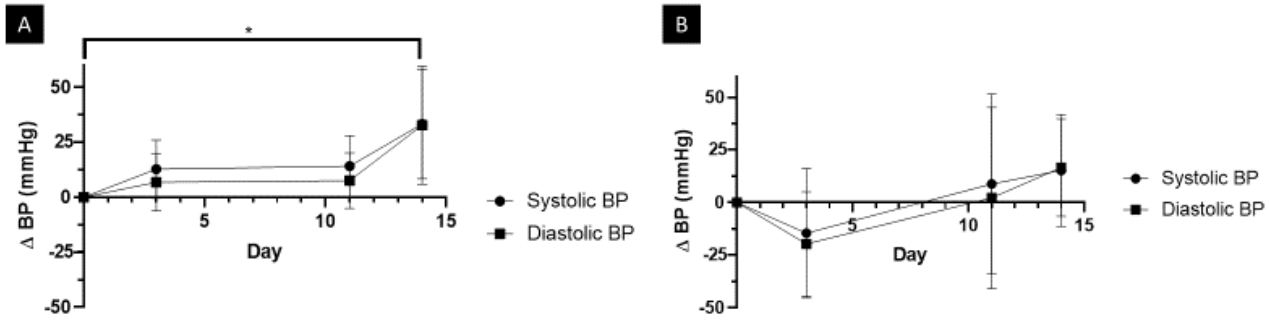

Figure 5. A) Normalized blood pressures of stenosed/experimental group B) Sham/control group normalized BPs. BP of experimental group increased more than that of control group over 2-week study period. Statistical analysis performed with ANOVA with Dunnett's post-hoc analysis ($p < 0.05$).

1.3.1.2 Peak renal vein blood velocity increases after stenosis

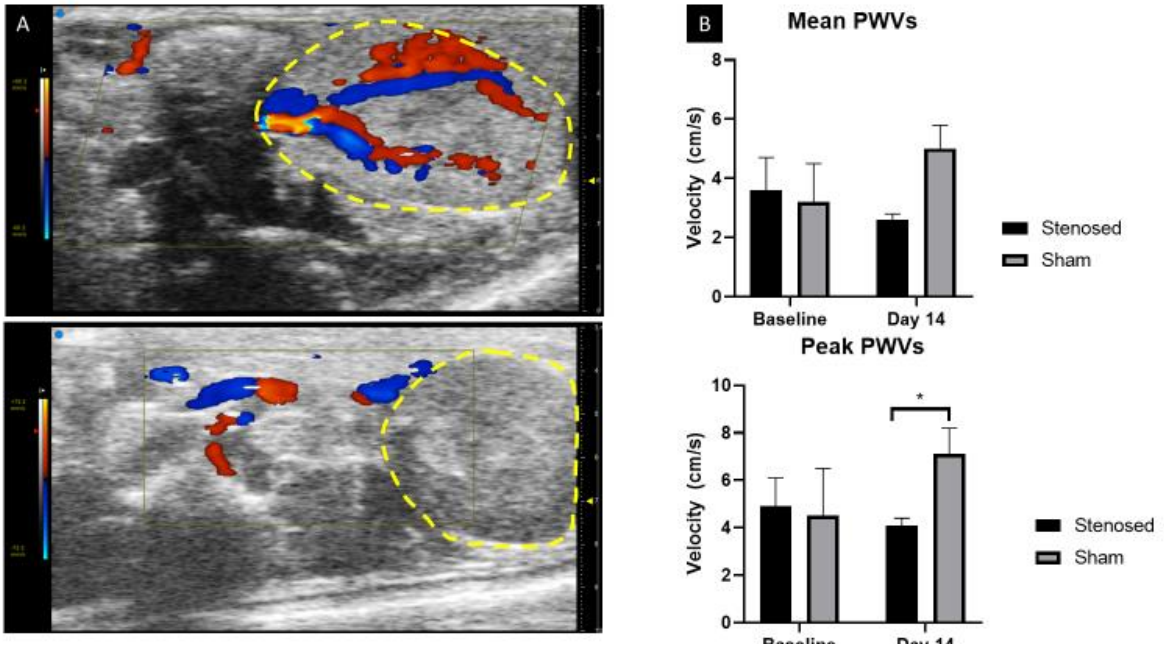

Figure 6. A) Representative color Doppler results from baseline (top) and day 11 (bottom) in the left kidney (circled in yellow dashed line) in the stenosed group. There is decreased flow in kidney on day 11 compared to baseline. B) Mean pulsed wave velocities & peak pulsed wave velocities (cm/s) of the left renal vein close to the inferior vena cava at baseline and day 14. Peak velocities (bottom) of sham and experimental group are significantly different from each other ($p < 0.05$). Number of samples in each group vary because it was not always possible to detect flow in desired area of vessel, oftentimes due to artifact.

Both peak and mean velocities of the left renal vein measured near the inferior vena cava were lower at day 14 compared to baseline measurements in mice with the stenosis. These velocities measured at the same region in mice from the sham group showed an increasing trend over two weeks. Peak velocities on day 14 were lower in the stenosed group compared to the sham group ($p < 0.05$; Figure 6).

1.3.1.3 Renal vein stenosis leads to renal necrosis

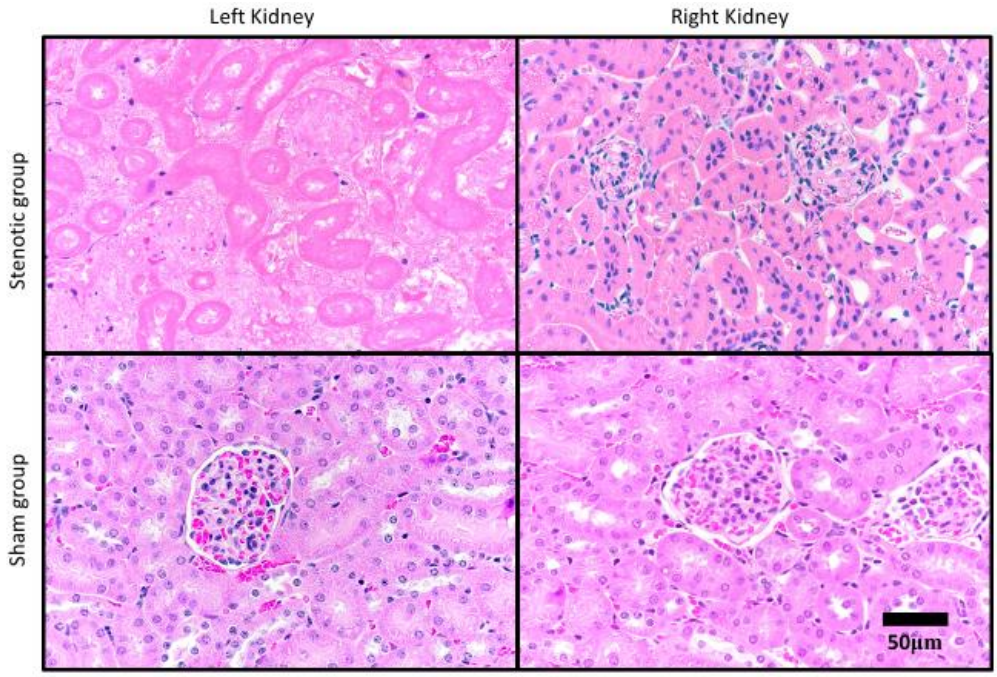

Figure 7. Representative images of histology of kidneys from stenosed group (top) and sham group (bottom). In stenosed group, left kidney (top left) glomeruli lacked red blood cells and demonstrated endothelial swelling. Glomeruli from right kidney of stenosed group appeared typical, as did both kidneys from sham group. Images acquired at 40X magnification.

The left kidney of the experimental group was necrotic (Figure 8) compared to the right kidney in the same group as well as to both kidneys in the sham group. Renal necrosis was characterized by increased cellular eosinophilia as well as pyknotic or absent nuclei of renal tubular epithelial cells, glomeruli, and interstitial vessels. More specifically, capillary lumina of affected glomeruli were obscured by swollen endothelial cells and lacked erythrocytes (Figure 7). Proteinaceous material was often present in Bowman's space in affected glomeruli suggesting dysfunctional glomerular filtration. Interstitial hemorrhage and thrombosis of a few medium-sized arteries were also apparent in some specimens. The right kidneys in the experimental group and both kidneys in the sham group had typical healthy glomeruli (Figure 7).

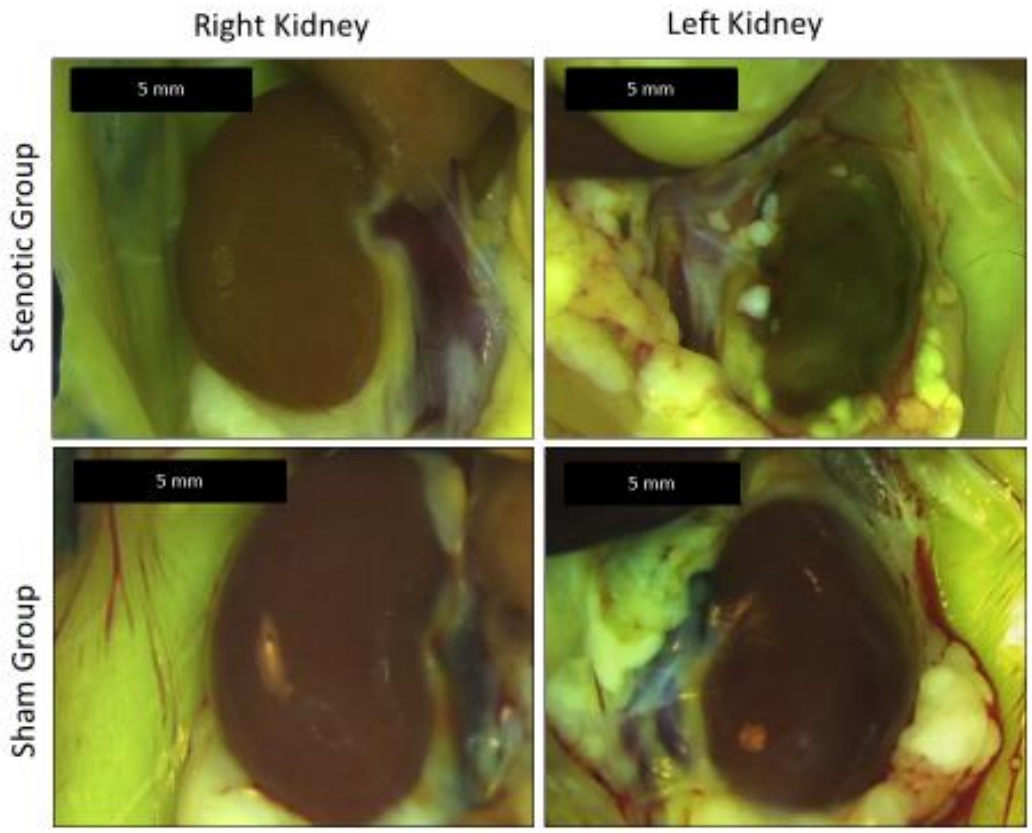

Figure 8. Left and right kidneys at day 14. Top row: right kidney without stenosed vein from experimental procedure (left) and left kidney with stenosed vein from experimental procedure (right). Bottom row: right kidney from sham procedure (left) and left kidney from sham procedure (right).

1.3.2 Non-Pregnant Human Pilot Study

1.3.2.1 Blood pressure increased when subjects shifted from left lateral to supine position

The mean age of the 50 participants in this study was 22.8±3.8 years. Most participants were in the healthy BMI range of 18.5-24.9 kg/m^2 (68%; 22.32±3.41 kg/m^2). Blood pressure measurements stabilized after roughly five minutes, which corresponded to two BP readings (Figure 9A). As such, the first two measurements taken in the left lateral recumbent position were excluded from the average measurement (Figure 9B) in order to account for only stable post-exercise measurements. In non-pregnant females, BPs increased by an average of 10.6±5.7 mmHg and by 10.4±6.0 mmHg for systolic and diastolic BPs, respectively, when shifting from left lateral recumbent to supine position (Figure 9B). BPs increased significantly when shifting

between left lateral recumbent and supine positions ($p < 0.001$). Non-pregnant females naturally rested at an average angle of 78.5±9.0° in the left lateral recumbent position (Figure 3D).

1.3.2.2 User feedback suggests general ease of use

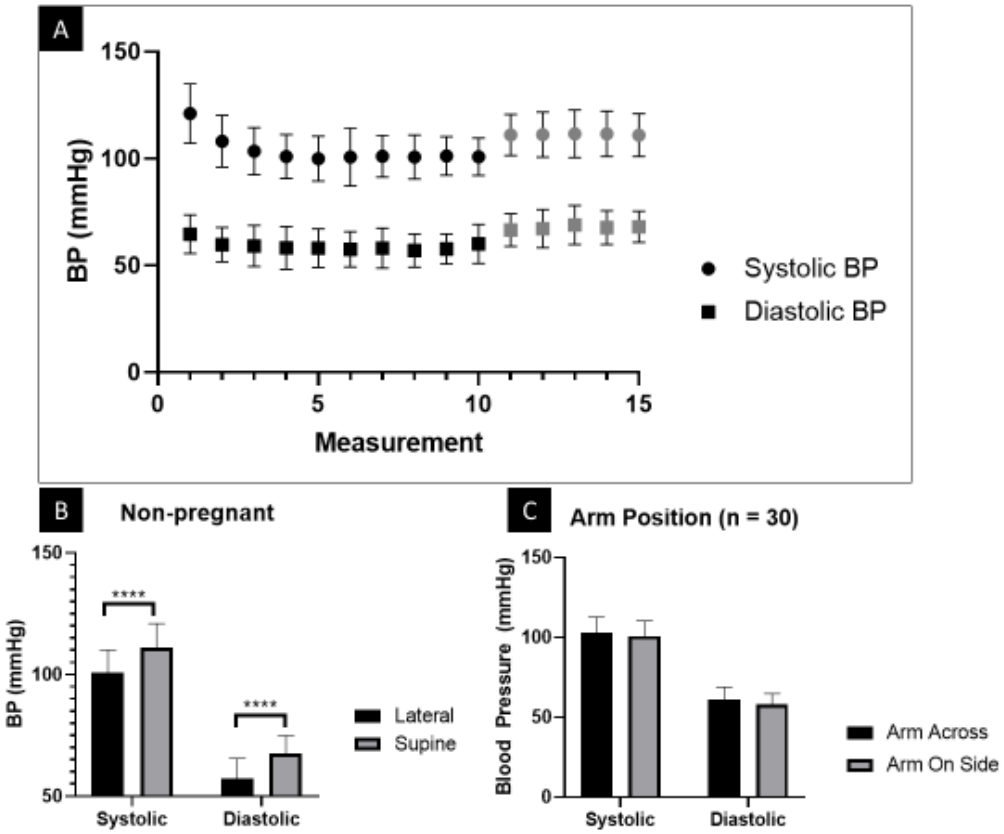

Figure 9. A) All 15 sequential BP measurements taken in left lateral recumbent (black dots) and supine (gray dots) positions in non-pregnant females. First 2-3 measurements in lateral position are higher than other measurements because they were taken immediately after exercise. BPs stabilized after first few measurements. B) Comparisons of BPs in both positions for non-pregnant females. Systolic BP increased by an average of 10.6±5.7 mmHg. Diastolic BP increased by an average of 10.4±6.0 mmHg. BPs in supine position were statistically different than in left lateral recumbent position ($p < 0.0001$). C) BPs acquired in left lateral recumbent position taken with arm across chest are typically higher than when arm is lying across side of body. There is a 2.2±6.1 mmHg difference in systolic BP and a 3.2±4.8 mmHg difference in diastolic BP between arm positions.

Subjects were asked to complete a survey at the conclusion of the study assessing factors such as their comfort and user-friendliness of the instructions and device. Most of the subjects agreed that the instructions they were given were easy to follow (64%), while 32% disagreed. Regarding comfort during the actual procedure, 66% of subjects indicated that it was comfortable for them to

acquire BP measurements on their left side, and 60% of subjects said the same for acquiring BPs on their backs (Table 1).

Table 1. Selected survey results from non-pregnant female pilot study

	Cuff was comfortable to wear	Instructions were easy to interpret/follow.	Comfortable to take blood pressure while laying on side.	Comfortable to take blood pressure while laying on back.
Agree	58%	64%	66%	60%
Disagree	26%	32%	30%	30%
Neither	16%	4%	4%	10%

1.3.3 Pregnant Female Study

1.3.3.1 Blood pressure increases between left lateral and supine positions in pregnant women

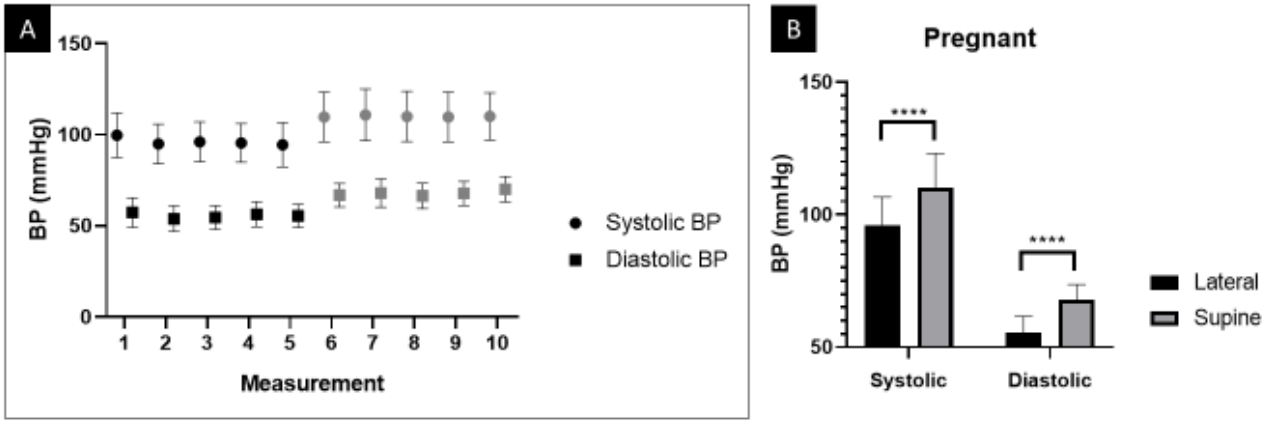

Figure 10. A) All 10 sequential BP measurements taken in left lateral recumbent (black dots) and supine (gray dots) positions in pregnant females. B) Comparison of BPs in both positions for pregnant females. Systolic BP increased by 14.0±4.3 mmHg and diastolic BP increased by 12.3±5.2 mmHg. BPs in supine position were higher than in left lateral recumbent position ($p < 0.0001$).

The mean age of the women in this portion of the study was 31.4±4.6 years. The mean gestational age was 29.5±6.8 weeks with 2.4±2.5 gravidity and 1.1±2.3 parity. When averaging all five measurements taken in both body positions, pregnant subjects experienced an average increase of 14.0±4.3 mmHg in systolic BP and 12.3±5.2 mmHg in diastolic BP while shifting from left lateral recumbent position to supine position (Figure 10B). In the left lateral recumbent position, women naturally rested at an angle of 73.2±6.2° measured from the bed to their back. The change in systolic and diastolic BPs between positions was 3.4 mmHg and 1.9 mmHg greater, respectively, in pregnant females than in non-pregnant females, but only the systolic BP increase between positions was significantly different between pregnant and non-pregnant females ($p < 0.05$). Blood pressure difference was plotted against gestational age, and there was no correlation between these two factors ($p > 0.05$; Supplementary Figure 1).

1.3.3.2 Lateral position is more comfortable than supine

Almost all 20 pregnant women (95%) agreed that the instructions were easy to follow. Additionally, most subjects (90%) agreed that the BP device was comfortable for them to wear throughout the procedure. Pregnant women in the study generally agreed that it was comfortable to take BP on their left side (95%), while only 55% of these women agreed that it was comfortable for them to take BP measurements on their back (Table 2). These women were also asked in which position they tended to sleep and rest, and all women responded that they sleep on their side.

Table 2. Selected survey results from pregnant female usability study

	Cuff was comfortable to wear	Instructions were easy to interpret/follow.	Comfortable to take blood pressure while laying on side.	Comfortable to take blood pressure while laying on back.
Agree	90%	95%	95%	55%
Disagree	5%	--	--	10%
Neither	5%	5%	5%	35%

1.4 Discussion

Overall, these data suggest that an automated SPT is feasible for pregnant women at risk for preeclampsia. The results of our non-pregnant and pregnant female studies both suggest that the automated SPT procedure will be feasible for pregnant women to perform throughout their pregnancy, either autonomously or with minimal assistance. The results also suggest that a baseline increase in BP between positions in non-pregnant females will need to be considered in further development of an automated version of the SPT. From the animal study, severe stenosis of the left renal vein for a period of two weeks led to severe damage to the left kidney as well as to increased BP. Studying the effect of varying degrees of renal vein constriction on intra-renal pressure and vasoactive compounds is warranted.

Blood pressures in animals increased overall in both groups but to varying degrees. Given that Poiseuille's law approximates that pressure difference in flow through a pipe is related to radius to the 4^{th} power, then we can expect that venous outflow obstruction could have a substantial effect on intrarenal pressure. In other words, a small reduction in diameter can have a large effect on pressure as well as on the health and viability of upstream tissue. In a previous rodent study, the left renal vein was ligated leading to increased flow through collateral vessels; mortality, though, increased when important collateral vessels were not preserved [20]. The overall BP change in the stenosed group was about 10 mmHg higher in both systolic and diastolic BP than in sham controls. Hypertension is expected as a result of Page kidney, which previous work has linked to preeclampsia [1, 21]. The slight increase in the sham group by day 14 may be due to general stress from the procedure or from typical variation in tail-cuff BP measurements. Variations in BP among animals in the same procedural group may also have been due to the degree of stenosis they experienced. Even though the same size of needle was used when creating each stenosis, there was variation in baseline vessel diameter among animals, likely due to the differences in ages and body mass. Still, there was no strong correlation found when age was plotted against percent stenosis. While factors such as age and percent stenosis should be taken into account in future iterations of this model, mice in the stenosed group did indeed experience necrotic tubules. Tubular injuries are in line with results seen in similar renal obstruction procedures [22, 23] and in cases of Page kidney [21]. The mice in this study also exhibited other physiologic and histologic changes that result from renal congestion and are also similar to those of Page kidney. Animals in the stenosed group

experienced increased eosinophilia, which has also been reported in cases of Page kidney [21]. Additionally, renal obstruction leads to decreased perfusion to blood vessels in the kidney [24]. This decrease may explain the observed necrosis, but clinically, renal injury is more common than renal necrosis. Overall, these murine data suggest that animals with severe renal vein stenosis sustain substantial kidney injury and develop hypertension.

In the human pilot study, subjects shifting from the left lateral recumbent position to the supine position experienced an increase in BP similar to previous studies [25, 26], albeit to different degrees likely based on cuff position relative to the heart. We controlled for this factor in the clinical study with pregnant females based on literature and the results from phase two of this pilot study, which demonstrated that, although not statistically significant, arm position can vary the BP in the left lateral recumbent position (Figure 9C). Moreover, the difference in BP taken between the lateral recumbent and supine positions was at least 10 mmHg for both systolic and diastolic BP in both pregnant and non-pregnant women. This change is important because the difference between stage 1 and stage 2 hypertension is only 10 mmHg [27]. While clinical BP measurements are typically acquired in a seated position, our data suggests that it may be worthwhile to consider body position as a variable when acquiring BP, especially when diagnosing hypertension. AHA guidelines indicate that home-based ambulatory BP monitoring can be used to acquire accurate BP measurements outside of the clinic [28], but our data indicates that it may also be useful to ensure consistent body positioning when acquiring measurements. We also assessed the amount of time it took BP to stabilize after light exercise. BP stabilized after roughly five minutes in most subjects. This is notable because a fully automated SPT will need to incorporate a signal detection feature to ensure that stable BP measurements are being collected in the lateral recumbent position prior to shifting into the supine position in order to optimize test sensitivity.

Another factor to consider with automating the SPT is whether an increase in diastolic BP is still the best metric to use to determine a positive SPT. The initial work that led to the development of the SPT in the 1970's focused on diastolic BP as it was considered the best predictor of cardiovascular (CV) health [16], perhaps due to decreased effects of pressure distortion in this phase [29]. However, since the development of the SPT, more recent studies have shown that systolic BP may actually be a better predictor of CV status than diastolic BP [30]. Additionally,

because each subject experienced different degrees of change when shifting between positions, the positive SPT criteria could potentially be adjusted based on baseline increase data for better prediction value. Further longitudinal studies will be needed to explore these possibilities and optimize diagnosis criteria.

The pregnant subjects in this study were asked to follow a set of instructions with both text and visual aids provided to them. The research team clarified questions and helped as needed, but for the most part, the pregnant women were able to follow directions autonomously, indicating that they would be able to perform the SPT without the help of a clinician. Differences in BP between positions for pregnant females were increased as compared to differences in non-pregnant females, which could indicate that the gravid uterus does have some effect on BP in supine position as demonstrated in [12]. In this portion of the study, most women naturally laid their arm across their side when they were in the left lateral recumbent position as depicted in Figure 3A. When they did not naturally lay in this position, we asked them to adjust to it in order to keep cuff position consistent. Some women needed assistance sitting up from the supine position after they were done with the procedure, especially if they were past 30 weeks gestation. As such, pregnant women in their third trimester may need additional assistance in order to perform this procedure. It is also important to note that disturbed venous flow has been implicated with kidney and liver failure in patients with preeclampsia, as well as with dysfunction in venous return when pregnant patients are supine [12, 31]. The position in which pregnant women rest has been studied since this can influence venous blood flow. Previous work noted that patients resting in the supine position experienced an elevation of renal pressure in their lower limbs but that this elevation was reduced when the patients were on their side [32].

Other studies have also asked pregnant women to acquire their own BPs by following a set of instructions. A previous study screened for preeclampsia in the first trimester of pregnancy by having patients record their own BPs at stations (not ambulatory cuffs) and compare these measurements to ones acquired by clinicians [33]. The results helped lead to the current understanding that ambulatory BP monitoring should be considered the reference standard, as per updated 2019 American Heart Association guidelines [28]. These ambulatory BP devices take measurements based on an automated approach that is thought to reduce the white coat effect and

human errors associated with the traditional in-office BP acquisition methods requiring sphygmomanometers [28]. This previous work, combined with the results of this study, suggest that home-based BP monitoring for pregnant populations could be beneficial to overall maternal health.

Additional considerations include the end users of these devices and the locations where it would be most useful. Pregnant women in developed countries as well as in low- and middle- income countries could benefit from an automated SPT. In developed regions, if the SPT is employed early in the pregnancy, a positive test could allow for closer longitudinal surveillance of both mother and fetus. If positive, therapeutic resting positions (i.e. left lateral recumbent) could be recommended for the duration of the pregnancy. In lower resource settings, an automated SPT could serve as monitoring tool between clinical visits, which are not as frequent. In areas of Africa, for example, up to 10% of pregnancies are affected by preeclampsia, compared to the global average of 2-8% [34]. Sub-Saharan Africa and south Asia have especially high maternal mortality rates, with as many as 90% of global maternal deaths occurring in these areas [35]. In some of these regions, pregnant women are only advised to see their physicians a few times throughout their pregnancies, and transportation expenses are often a barrier to receiving reliable healthcare. An automated SPT tool could be potentially useful in these areas to monitor preeclampsia progression without frequent travel to a clinic. Some regions of Kenya have community health-care workers who can be trained to help administer the automated SPT in rural areas where pregnant females do not have the resources to regularly get their BP checked throughout their pregnancy. There are, however, certain limitations to be considered before implementation. Currently, many automated systems are battery-operated, and these batteries need to be replaced frequently. People in resource-limited areas may not have access to a large supply of batteries or to reliable electrical outlets for charging. It is also important to consider that a positive SPT would indicate that preeclampsia may develop, but effective comprehensive treatments for this condition are still needed. Identifying high-risk pregnant women, though, may lead to increased surveillance and a better opportunity to develop preventative strategies. An educational campaign about safe sleeping practices during pregnancy, for example, may still be beneficial by encouraging pregnant women to sleep on their sides as the best resting position [32].

1.5 Limitations

These studies are not without their limitations. First, the mouse model does not mimic all of the physiologic changes associated with preeclampsia in humans. Further efforts are needed to create animal models that better reproduce the human condition where renal changes could be investigated. Additionally, neither varying gestational ages nor longitudinal data were included during the pregnant human studies. Future work with a larger human study will be needed to follow subjects throughout pregnancy and to determine the efficacy of an automated SPT.

1.6 Conclusions

In conclusion, this series of studies helps to lay the groundwork for an automated SPT that pregnant women could use for monitoring, early detection, and eventually, prediction of preeclampsia. Our studies indicated that females would largely be able to perform this test autonomously given descriptive visual instructions and that there is a significant baseline increase in BP when shifting from the left lateral recumbent position to the supine position of 10-15 mmHg. Additionally, we investigated the pathophysiology of left renal vein stenosis using an animal model, which confirms a relationship between renal vein obstruction and hypertension. The results demonstrated that stenosis in the vein can lead to kidney injury and increased BP. While further work will be needed to evaluate the efficacy of an automated SPT, our hope is to eventually develop and distribute a combined device and data system that can be implemented in a wide range of settings, eventually improving both maternal and fetal health worldwide.

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APPENDIX

Table 3 Subject information from non-pregnant female pilot study

Subject	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
1	22	175.3	65.8	21.4
2	26	167.6	74.8	26.6
3	25	170.2	56.7	19.6
4	24	167.6	68.0	24.2
5	20	170.2	65.8	22.7
6	22	162.6	59.0	22.3
7	18	165.1	49.0	18.0
8	21	162.6	68.0	25.7
9	30	157.5	53.5	21.6
10	22	157.5	54.4	22.9
11	20	175.3	63.5	20.7
12	20	152.4	48.5	20.9
13	24	152.4	43.1	18.6
14	26	172.7	90.7	30.4
15	22	165.1	49.9	18.3
16	24	167.6	58.1	20.7
17	21	175.3	59.0	19.2
18	23	170.2	63.5	21.9
19	43	162.6	60.8	23.0
20	19	165.1	68.0	25.0
21	23	165.1	68.0	25.0
22	21	170.2	68.0	23.5

Table 3 continued

23	21	170.2	53.1	18.3
24	20	157.5	61.2	24.7
25	25	162.6	56.7	21.5
26	23	157.5	45.4	18.3
27	21	162.6	62.6	23.7
28	25	167.6	63.5	22.6
29	22	170.2	59.0	20.4
30	23	170.2	61.7	21.3
31	18	175.3	54.4	17.7
32	21	170.2	56.7	19.6
33	21	170.2	74.8	25.8
34	21	157.5	59.0	23.8
35	22	180.3	69.9	21.5
36	24	165.1	54.4	20.0
37	23	167.6	61.2	12.8
38	19	165.1	81.2	29.8
39	22	172.7	81.6	27.4
40	25	162.6	56.7	21.5
41	22	167.6	59.4	21.1
42	25	160.0	53.1	20.7
43	22	170.2	68.0	23.5
44	19	165.1	57.6	21.1
45	27	162.6	61.2	23.2
46	26	162.6	63.5	24.0
47	22	154.9	54.4	22.7
48	21	162.6	81.6	30.9

Table 3 continued

49	21	162.6	70.3	26.6
50	23	160.0	49.0	19.1
AVG	22.8	165.7	61.7	22.3
STDEV	3.8	6.2	9.7	3.4

Table 4 Subject information from pregnant female study

Patient	Age (years)	Gestational Age (weeks)	Gravidity	Parity	Height (cm)	Weight (kg)	BMI (kg/m^2)
1	34	36	1	0	163.8	82.1	31.1
2	32	39	1	0	180.3	104.3	32.1
3	29	22	1	0	162.6	65.8	24.9
4	27	28	2	1	173.0	78.0	26.2
5	33	39	4	3	182.9	83.0	24.8
6	36	25	2	1	167.6	90.7	32.3
7	34	35	1	0	172.7	84.0	28.1
8	38	30	12	10	158.8	91.0	36.0
9	27	23	1	0	162.6	68.0	25.7
10	26	22	3	0	175.3	104.3	34.0
11	38	36	1	0	162.1	64.4	24.5
12	35	20	1	0	160.0	58.0	22.7
13	28	36	1	0	160.0	88.9	34.7
14	37	28	2	1	170.4	84.4	29.0
15	32	24	2	1	149.9	98.0	43.6
16	34	38	3	0	157.5	76.7	30.9
17	31	38	1	0	160.0	54.7	21.3
18	28	26	1	0	160.0	79.4	31.0
19	28	22	4	2	165.1	74.8	27.5
20	21	23	4	3	170.2	101.6	35.1
AVG	31.4	29.5	2.4	1.1	165.7	81.6	29.8
STDEV	4.6	6.8	2.5	2.3	8.2	14.6	5.4

Table 5. Non-pregnant female screening questionnaire

Pre-Study Questionnaire
What is your age?
What is your weight?
What is your height?
What is your ethnicity?
Are you pregnant?
Have you previously been pregnant?
To your knowledge, has there been a history of cardiac death in any of your family members under the age of 50?
Do you have a history of heart palpitations?
Do you have a history of syncope/loss of consciousness?
Do you have any form of cardiovascular disease?
Do you have any form of pulmonary disease?
Are you able to perform light exercise (i.e. walking up and down stairs)?
Is there anything you would like the study coordinators to know that was not listed here?

Table 6. Non-pregnant female screening questionnaire

Post Non-Pregnant Study Survey
The device was comfortable to wear. Please rate from 1-5, with 1 being strongly agree and 5 being strongly disagree.
The cuff was challenging to use. Please rate from 1-5, with 1 being strongly agree and 5 being strongly disagree.
The instructions for the cuff were easy to interpret and follow. Please rate from 1-5, with 1 being strongly agree and 5 being strongly disagree.
It was comfortable to take blood pressure while lying on my back. Please rate from 1-5, with 1 being strongly agree and 5 being strongly disagree.
It was comfortable to take blood pressure while lying on my side. Please rate from 1-5, with 1 being strongly agree and 5 being strongly disagree.
Do you have any other comments or concerns regarding the devices and their usage that were not covered above?
For how long do you typically sleep at night?
What type of bed do you sleep on? (i.e. size, mattress type, etc.)
Do you typically sleep on your side or on your back?
Do you use a pillow or any other sleep/body position devices?
What would make resting on your back more comfortable?
What would make resting on your side more comfortable?
Do you think you would be able to repeat this procedure without help? Why/why not?

Table 7. Inclusion/exclusion criteria for pregnant woman study

Pregnant Woman Study Inclusion/Exclusion Criteria Checklist
Is patient over 18?
Is patient currently pregnant?
Is patient at least at or past 20 weeks gestation?
Is this a singleton pregnancy?
Is patient taking medication for high blood pressure?
Does patient have chronic kidney disease?
Does patient have chronic hypertension, or did she have it before pregnancy?
Was patient involved in any accident that resulted in a head injury?
Has patient ever had a blood clot or deep vein thrombosis?
Is patient able to lie flat on her back?
Is patient able to lie on her side?

Table 8. Post-study survey for pregnant women

Post Pregnant Woman Study Survey
The device was comfortable to wear. Please rate from 1-5, with 1 being strongly agree and 5 being strongly disagree.
The device was challenging to use. Please rate from 1-5, with 1 being strongly agree and 5 being strongly disagree.
The instructions for the device were easy to interpret and follow. Please rate from 1-5, with 1 being strongly agree and 5 being strongly disagree.
It was comfortable to take blood pressure while lying on my back. Please rate from 1-5, with 1 being strongly agree and 5 being strongly disagree.
It was comfortable to take blood pressure while lying on my side. Please rate from 1-5, with 1 being strongly agree and 5 being strongly disagree.
The device was convenient to use. Please rate from 1-5, with 1 being strongly agree and 5 being strongly disagree.
Do you have any other comments or concerns regarding the device and its usage that were not covered above?
What were the main challenges of using the device? What did you like best about the device?
Would you buy this device for a future pregnancy? Please elaborate?
How do you rest/position when sleeping?

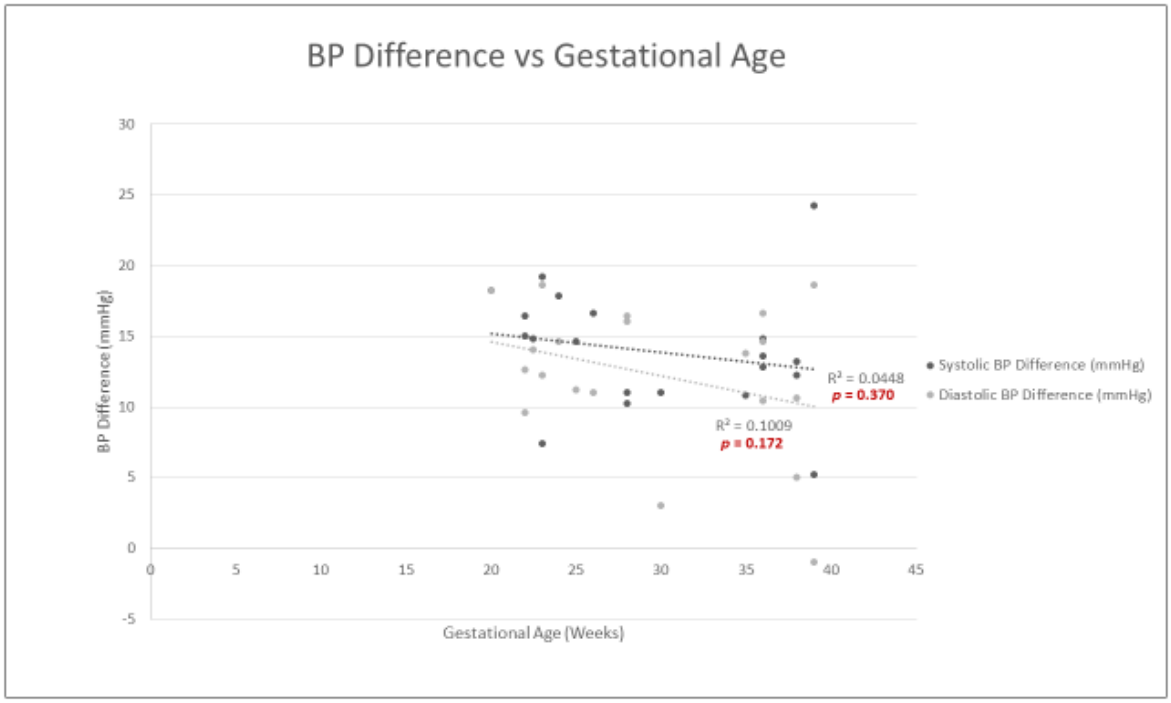

Figure 11 BP Difference plotted against gestational age. No correlation was found for either systolic of diastolic BP difference ($p > 0.05$).

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