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J Eng Sci Med Diagn Ther. 2019 November ; 2(4): . doi:10.1115/1.4045203.**Toward Automation of the Supine Pressor Test for Preeclampsia****Hamna J. Qureshi¹,**

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Abstract

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

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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 nonpregnant women and demonstrated the feasibility of an autonomous 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) nonpregnant 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 Introduction

Preeclampsia, a condition associated with hypertension during pregnancy, affects between 5 and 8% of pregnant women worldwide and leads to upward 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].

Although maternal vascular endothelial factors, proinflammatory cytokines, and abnormal trophoblast invasion in the placenta are all thought to contribute to preeclampsia formation [3,6], 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 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 [7]. 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 [8,9]. Additionally, this vein is subject to anatomic variability between patients [10]. Connections from the left renal vein to other branches can vary [10,11], and flow through collateral veins can be beneficial under certain hemodynamic circumstances [12]. However, these connections are not adequate in all women [10], 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 intrarenal 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].

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 1970s. This test was shown to predict a pregnant women's risk of developing preeclampsia with a 93% positive predictive value [13]. 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 and 32 weeks gestation, which is a timeframe that does not accommodate the variable venous anatomy that pregnant women exhibit [1].

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. This tool could potentially direct pregnant women identified as being at risk for developing preeclampsia to seek further clinical care. Patients could also work to rest in a therapeutic position (i.e., on their side) in order to mitigate some of the effects of renal vein compression and potentially prevent preeclampsia from developing. A fully automated SPT could include a wearable 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, both in resource-limited areas and 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 autonomous SPT may have utility for this population without the need for expensive equipment or frequent clinical visits.

2 Methods

2.1 Animal Study

2.1.1 Surgical Procedure.—Female C57BL/6J mice were used for this 2-week study and were divided between two groups (Jackson Laboratory, Bar Harbor, ME). 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 [14]. 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 (Fig. 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). All procedures were approved by the Purdue Animal Care and Use Committee.

2.1.2 Ultrasound.—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 postsurgical 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 (Supplementary Fig. 2 which is available in the Supplemental Materials on the ASME Digital Collection) and pulsed wave (PW) Doppler along the vein. PW Doppler images were analyzed for all animals at baseline and postsurgical 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.

2.1.3 Blood Pressure.—A noninvasive tail cuff system (Supplementary Fig. 1 which is available in the Supplemental Materials on the ASME Digital Collection) was used to acquire blood pressures of conscious mice at baseline and postsurgical 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.

2.1.4 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 1× phosphate-buffered saline for up to 72h before being transferred to 4% paraformaldehyde for all animals.

2.1.5 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 40× magnification and analyzed by a veterinary pathologist certified by the American College of Veterinary Pathologists.

2.2 Nonpregnant Human Pilot Study

2.2.1 Screening Subjects.—A nonpregnant 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. Nonpregnant women 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 (Figs. 2(a) and 2(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 (CV) conditions such as hypertension or history of sudden cardiac death in immediate family members (Supplementary Table 5 which is available in the Supplemental Materials on the ASME Digital Collection). Total measurement duration per participant was roughly 30–40 min. All study procedures were approved by the Purdue University Institutional Review Board.

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 (Supplementary Table 6 which is available in the Supplemental Materials on the ASME Digital Collection). 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 [15]. Subjects then performed light exercise by walking up and down three flights of stairs before immediately lying down in the left lateral recumbent position (Fig. 2(a)). Five serial BP measurements were taken in this position before the subject rotated to the supine position (Fig. 2(b)) where five more BP measurements were acquired by the cuff. Each measurement was acquired in roughly 90s, with at least 30s 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 (Supplementary Table 6, which is available in the Supplemental Materials on the ASME Digital Collection). 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 (Fig. 2(c)). Subjects then placed their right arm on their right side for the last five measurements (Fig. 2(a)). Body angle measurements (Fig. 2(d)) 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 [16] and short free response questions evaluating their experience (Supplementary Table 6 which is available in the Supplemental Materials on the ASME Digital Collection).

2.3 Pregnant Women Study

2.3.1 Screening Subjects.—Pregnant volunteers ($n = 25$) at or past 20 weeks gestation were recruited from the antenatal clinic at Indiana University (IU) Health University Hospital in Indianapolis, IN. 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 (Supplementary Table 7, which is available in the Supplemental Materials on the ASME Digital Collection). 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.

2.3.2 Procedure.—Pregnant women were provided a booklet of printed instructions that was created based on feedback from the initial nonpregnant women study (Supplementary Fig. 3, which is available in the Supplemental Materials on the ASME Digital Collection). 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 nonpregnant women but excluded the exercise component. BP measurements were acquired three times in a seated position, five times in a left lateral recumbent position (Fig. 2(a)), and five times in a supine position (Fig. 2(b)). In the left lateral recumbent orientation, women placed their right arms along the side of their bodies as depicted in Fig. 2(a). Body angle measurements were also obtained in the same manner as in the nonpregnant women study (Fig. 2(d)). 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 (Supplementary Table 8, which is available in the Supplemental Materials on the ASME Digital Collection).

2.4 Analysis.

For the animal study, significant differences among time points and groups were determined using a one-way repeated measure ANOVA with Tukey or Dunnett's post hoc tests (Minitab v18, State College, PA; GraphPad Prism v8, San Diego, CA). For the PW Doppler data, the number of samples in each group varied since it was not always possible to detect flow due to image artifacts. Thus, a mixed-model analysis was used to analyze differences instead of an ANOVA. 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 two-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 (systolic blood pressures of pregnant women taken in the supine position).

3 Results

3.1 Animal Study

3.1.1 Blood Pressure Increases After Renal Vein Stenosis.—All female mice in this study were between 8 and 15 weeks of age to ensure sexual maturity and weighed $21.6 \pm$

2.1 g. An average stenosis of $53 \pm 26\%$ 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 (Fig. 3(b)). For the control group, BPs fluctuated and were within 20 mmHg of the baseline measurements for both day 14 systolic and diastolic BP (Fig. 3(b)).

3.1.2 Peak Renal Vein Blood Velocity Increases After Stenosis.—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.

3.1.3 Renal Vein Stenosis Leads to Renal Necrosis.—The left kidney of the experimental group was necrotic (Fig. 3(a)) 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 (Fig. 4). Proteinaceous material was often present in the 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 (Fig. 4).

3.2 Nonpregnant Human Pilot Study

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 body mass index (BMI) range of $18.5\text{--}24.9$ kg/m² (68%; 22.32 ± 3.41 kg/m²). Blood pressure measurements stabilized after roughly 5 min, which corresponded to two BP readings (Fig. 5(a)). As such, the first two measurements taken in the left lateral recumbent position were excluded from the average measurement (Fig. 6(a)) in order to account for only stable postexercise measurements. In nonpregnant women, 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 (Fig. 6(a)). BPs increased significantly when shifting between left lateral recumbent and supine positions ($p < 0.001$). Nonpregnant women naturally rested at an average angle of 78.5 ± 9.0 deg in the left lateral recumbent position (Fig. 2(d)).

3.2.2 User Feedback Suggests General Ease of Use.—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 (Supplementary Table 1 which is available in the Supplemental Materials on the ASME Digital Collection).

3.3 Pregnant Women Study

3.3.1 Blood Pressure Increases Between Left Lateral and Supine Positions in Pregnant Women.—The mean age of the women in this portion of the study was 31.5 ± 4.7 years. The mean gestational age was 29.7 ± 6.6 weeks with 2.4 ± 2.3 gravidity and 1.2 ± 2.1 parity. When averaging all five measurements taken in both body positions, pregnant subjects experienced an average increase of 14.0 ± 4.0 mmHg in systolic BP and 12.5 ± 4.8 mmHg in diastolic BP while shifting from left lateral recumbent position to supine position (Fig. 6(b)). In the left lateral recumbent position, women naturally rested at an angle of 72.6 ± 6.3 deg measured from the bed to their back. The change in systolic and diastolic BPs between positions was 3.4 mmHg and 2.1 mmHg greater, respectively, in pregnant women than in nonpregnant women, but only the systolic BP increase between positions was significantly different between pregnant and nonpregnant women ($p < 0.05$).

3.3.2 Lateral Position Is More Comfortable Than Supine.—Almost all 25 pregnant women (88%) agreed that the instructions were easy to follow. Additionally, most subjects (92%) 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 (96%), while only 52% of these women agreed that it was comfortable for them to take BP measurements on their back (Supplementary Table 2 which is available in the Supplemental Materials on the ASME Digital Collection). These women were also asked in which position they tended to sleep and rest, and all women responded that they sleep on their side.

4 Discussion and Conclusions

Overall, these data suggest that an autonomous SPT is feasible for pregnant women at risk for preeclampsia. The results of our nonpregnant and pregnant women studies both suggest that the autonomous 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 nonpregnant women 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 intrarenal 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 fourth 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 [17]. 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 [1,18]. 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. Although the tail-cuff system used to obtain murine BP measurements can produce noisy data, previous validation studies comparing tail-cuff measurements to radio telemetry suggest that general trends in data are reliable and accurate [19]. 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 could be considered 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 [20,21] and in cases of Page kidney [18]. 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 [18]. Additionally, renal obstruction leads to decreased perfusion to blood vessels in the kidney [22]. 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 [23,24], albeit to different degrees likely based on cuff position relative to the heart. We controlled for this factor in the clinical study with pregnant women 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 (Fig. 6(c)). 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 nonpregnant women. This change is important because the difference between stages 1 and 2 hypertension is only 10 mmHg [25]. While clinical BP measurements are typically acquired in a seated position, our data suggest that it may be worthwhile to consider body position as a variable when acquiring BP, especially when diagnosing hypertension. American Heart Association (AHA) guidelines indicate that home-based ambulatory BP monitoring can be used to acquire accurate BP measurements outside of the clinic [26], but our data indicate 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 5 min 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 1970s focused on diastolic BP as it was considered the best

predictor of CV health [13], perhaps due to decreased effects of pressure distortion in this phase [27]. 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 [28].

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 women were increased as compared to differences in nonpregnant women, which could indicate that the gravid uterus does have some effect on BP in supine position as demonstrated in Ref. [9]. 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 Fig. 2(a). When they did not naturally lie 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 [9,29]. 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 [30].

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 [31]. 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 [26]. 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 [26]. This previous work, combined with the results of this study, suggests that home-based BP monitoring for pregnant populations could be beneficial to overall maternal health.

A workflow diagramming how the automated supine pressor test could work is presented in Supplementary Fig. 4, which is available in the Supplemental Materials on the ASME Digital Collection. This tool has the potential to allow pregnant women to conduct the SPT throughout their pregnancies with a home-monitoring strategy that eliminates the need for frequent clinic visits. The automated test will need to integrate an automatic blood pressure cuff and Bluetooth inertial measurement unit (IMU) position sensor through the interface of

an application to guide the patient through the supine pressor test. A smartphone app can help guide patients through self-administering the supine pressor test using the wearable sensors, including an automated blood pressure cuff and a nine-axis IMU sensor capable of communicating angular and positional data throughout the duration of the SPT. These data could be transmitted to a secure, cloud-based server from which the app could both upload and retrieve information. The data from the IMU can be processed through an extended Kalman filter in real-time to provide greater accuracy in guiding the patient to a desired orientation [32]. Throughout the duration of the SPT, the app can communicate to the patient whether or not she is in the correct position. If the patient happens to orient herself out of the specified range of acceptable values, the app sends out an alert that will help her return to the desired posture. Through this integrated system, women can guide themselves through the steps of a SPT without having a clinician present. This automated tool can also serve as more than just a diagnostic tool, especially since it has the potential to become a management device that helps ensure that pregnant women are resting in the lateral recumbent position when sleeping. Such a tool could mitigate the effects of left renal vein compression from the gravid uterus and help prevent renal outflow obstruction and resulting renal compartment syndrome.

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 before proceeding to more aggressive clinical intervention. In lower resource settings, an automated SPT could serve as monitoring tool between clinical visits, which are not as frequent. This would be particularly beneficial in areas of Africa where up to 10% of pregnancies are affected by preeclampsia, compared to the global average of 2–8% [33]. 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 [34]. 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 women 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 [30].

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.

In conclusion, this study 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 women 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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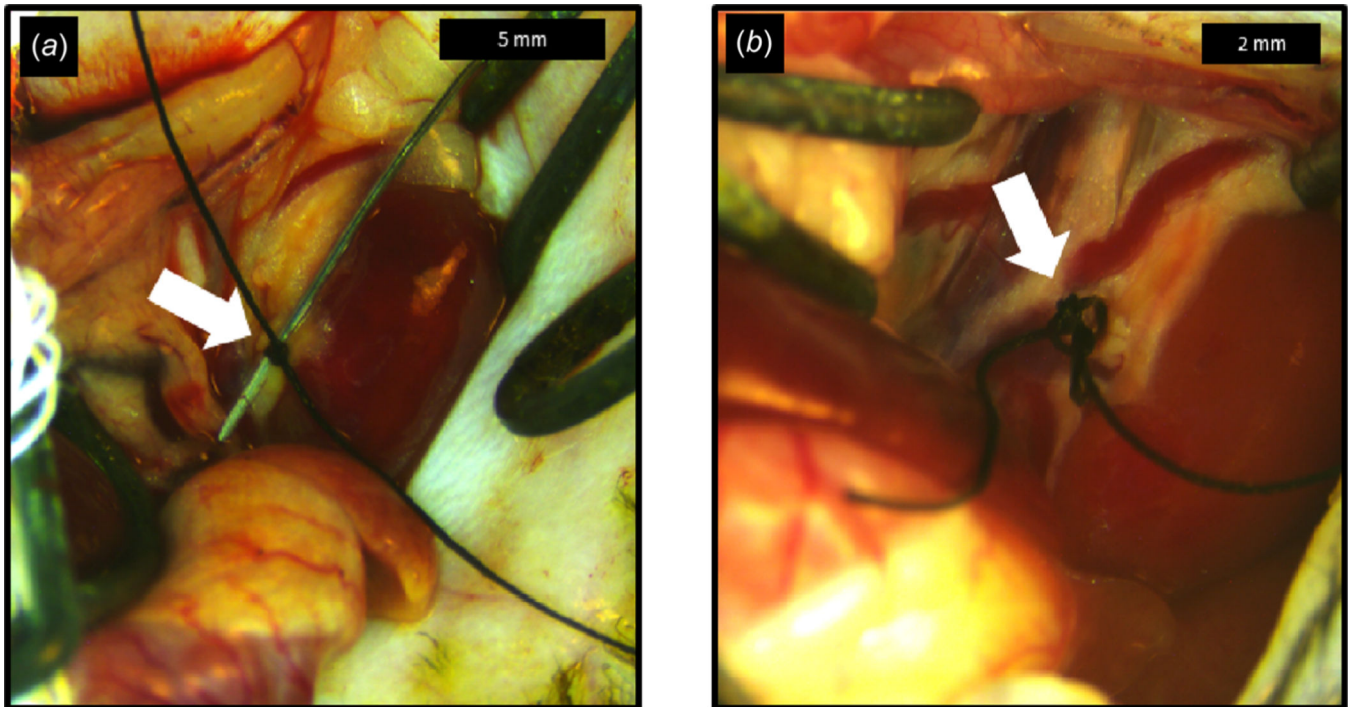


Fig. 1.

(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.

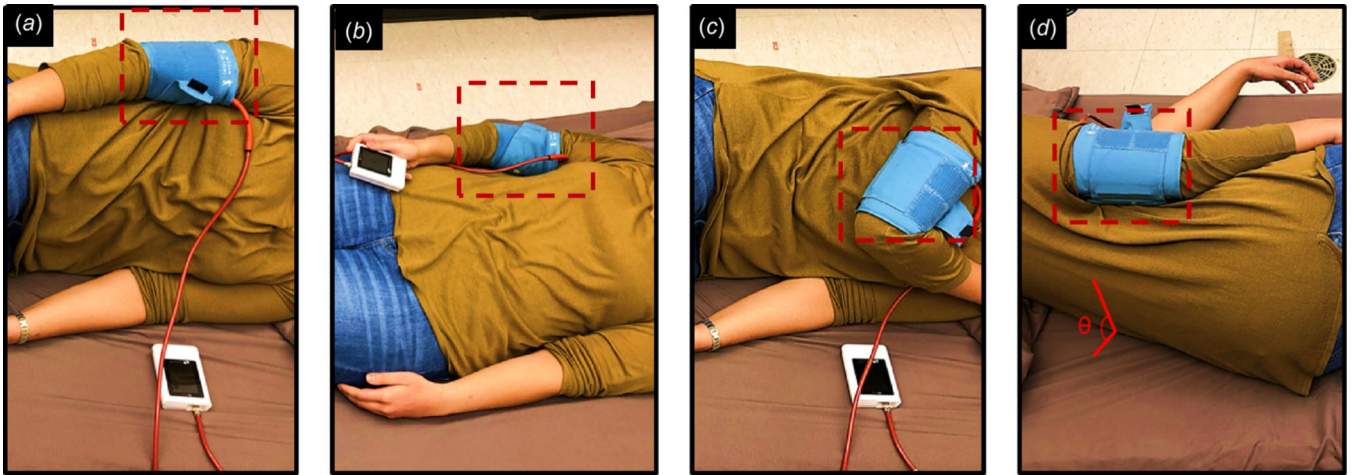


Fig. 2.
(a) Left lateral recumbent position with arm lying along the side of the patient. (b) Supine position. (c) Left lateral recumbent position with arm across subject with cuff positioned near heart. (d) Body angle is measured from bed to back.

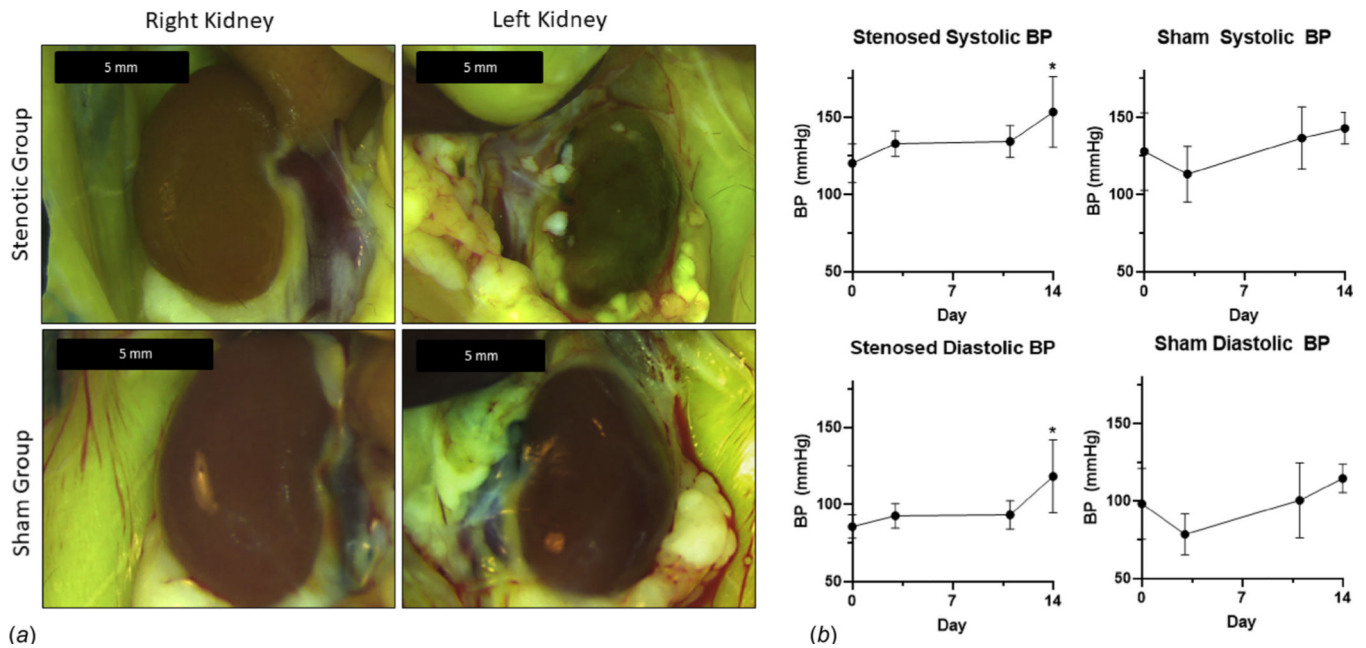


Fig. 3. (a) Right and left murine kidneys at day 14. Top row: kidneys from mice after inducing left renal stenosis reveals ischemic injury (left kidney) and contralateral control (right kidney). Bottom row: kidneys from mice that underwent a similar sham procedure where no stenosis was created. (b) BPs of stenosed/experimental group (left) and sham/control group (right). BP of stenosed group increased over the 2-week study period ($p = 0.05$). The increase in BP of sham group by day 14 also trended toward significance ($p = 0.071$). Statistical analysis was performed with one-way repeated measures ANOVA with Dunnett’s post hoc analysis.

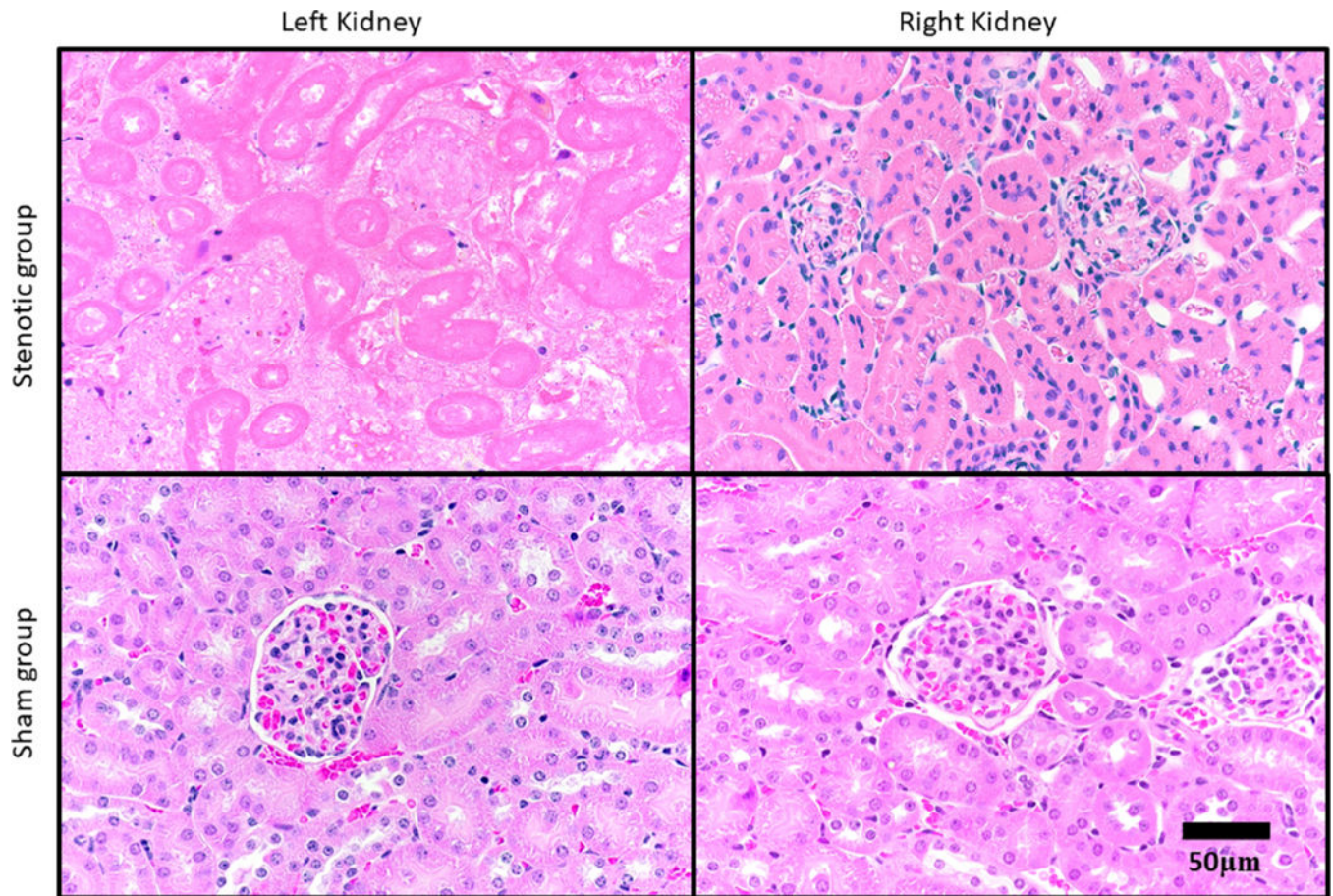


Fig. 4. Representative images of histology of kidneys from stenosed group (top) and sham group (bottom). In stenosed group, left kidney (top left) glomeruli lacked red blood cells and demonstrated endothelial swelling. Glomeruli from right kidney of stenosed group appeared typical, as did both kidneys from sham group. Images acquired at 40× magnification.

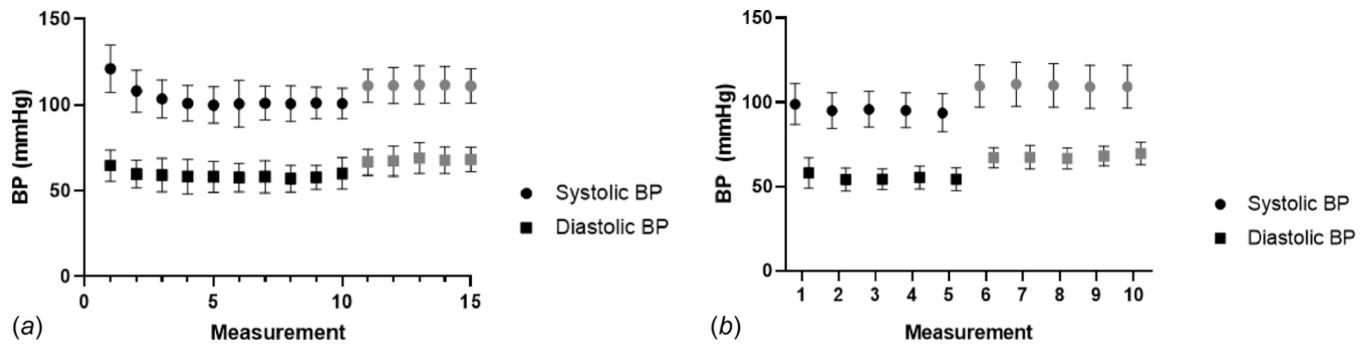


Fig. 5.
 (a) All 15 sequential BP measurements taken in left lateral recumbent (black dots) and supine (gray dots) positions in nonpregnant women. First 2–3 measurements in lateral position are higher than other measurements because they were taken immediately after exercise. BPs stabilized after first few measurements. (b) All ten sequential BP measurements taken in left lateral recumbent (black dots) and supine (gray dots) positions in pregnant women.

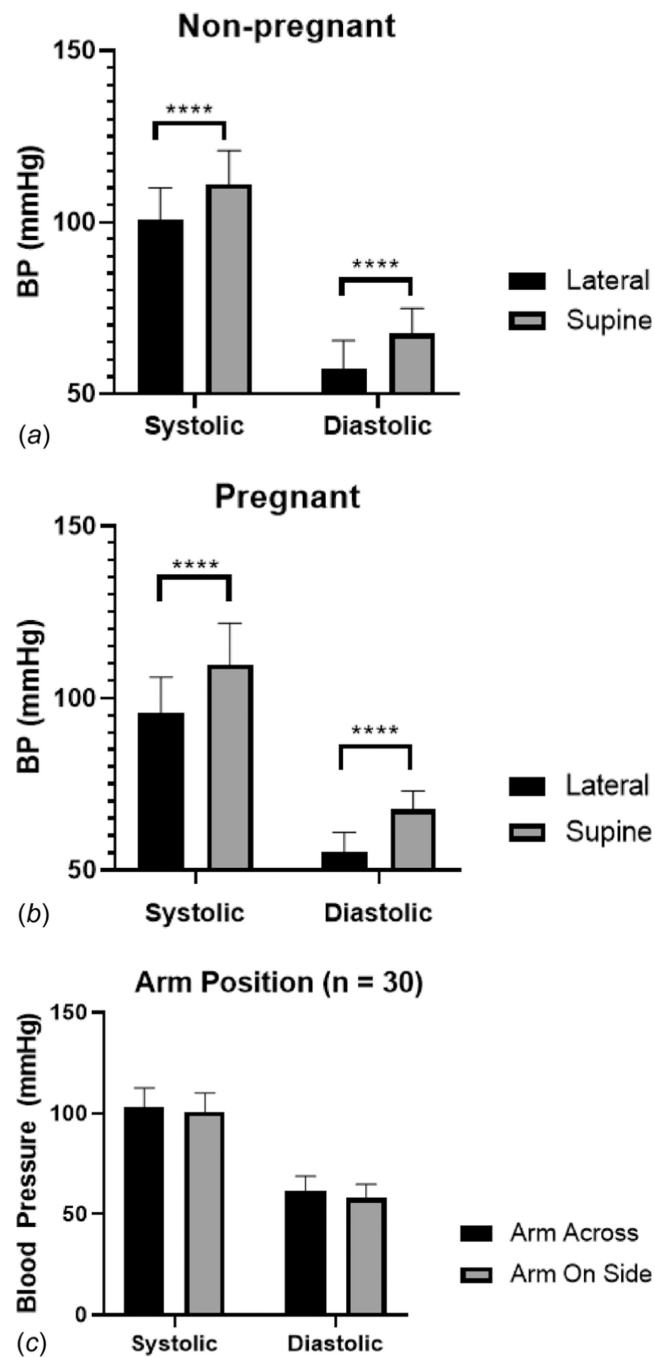


Fig. 6.

(a) Comparisons of BPs in both positions for nonpregnant women. 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 ($p < 0.0001$). (b) Comparison of BPs in both positions for pregnant women. Systolic BP increased by 14.0 ± 4.0 mmHg and diastolic BP increased by 12.5 ± 4.8 mmHg. BPs in supine position were higher 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 along the side of the 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.

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