Comparison of the vasoconstriction effect of phenylephrine and ephedrine on the uterine arteries of pregnant rabbits: A CT imaging-based study

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Abstract

Introduction: Hypotension is one of the most common complications during perioperative obstetric surgery and can cause serious adverse reactions in mothers and infants. Phenylephrine and ephedrine are the most widely used vasoconstrictors for preventing and controlling hypotension. However, which of them is the best choice remains unclear due to the lack of solid data on the effects of phenylephrine and ephedrine on uterine placental blood flow. This study aims to investigate the vasoconstriction effect of phenylephrine and ephedrine on the uterine arteries of pregnant rabbits via computed tomography (CT) imaging.

Methods: Fifteen near-term pregnant rabbits at 27–29 days of pregnancy were randomly divided into Group P, Group E and Group C. Phenylephrine, ephedrine and normal saline were injected. CT imaging was performed, and the diameters of the uterine arteries were measured to evaluate the contractile response to different drugs.

Results: Both phenylephrine and ephedrine induced a similar degree of vasoconstriction on peripheral resistance of the vessels (rostral arteries) ($p > 0.05$). At 5 min and 10 min, the uterine arteries contracted more strongly in response to phenylephrine than ephedrine ($p < 0.01$); after that, there was no significant difference in the diameters of the uterine arteries with the administration of phenylephrine and ephedrine ($p > 0.05$).

Conclusion: In summary, compared with ephedrine, phenylephrine had a faster effect, and resulted in stronger contraction of the uterine arteries, indicating a greater impact on placental perfusion. Therefore, in clinical practice, ephedrine has more favorable effects than phenylephrine on uterine and placental circulation.

Introduction

Hypotension is one of the most common complications during perioperative obstetric surgery. Studies have shown that the incidence of hypotension after spinal anesthesia can reach 80%^[1–4].

When hypotension is severe and persistent, it can easily lead to impaired uterine and placental blood flow, fetal hypoxia, and acidosis, which can cause serious adverse reactions in mothers and infants. Common clinical prevention and treatment methods include fluid therapy, posture adjustment, and the use of vasoconstrictors^[5–7]; of these, vasoconstrictors are the preferred therapy due to their fast action and effectiveness. Ephedrine and phenylephrine are widely used vasoconstrictors. A series of studies has proven the efficacy of phenylephrine and ephedrine for preventing and controlling hypotension; however, which of them is the best choice remains unclear due to the lack of solid data on the effects of phenylephrine and ephedrine on uterine placental blood flow^[1,7–9]. Therefore, it is of great clinical significance to identify a vasoconstrictor that can maintain the stability of the maternal circulation while having the least effect on placental perfusion.

Most of the published research on placental perfusion and uterine vascular resistance is based on Doppler ultrasound technology. Although ultrasound scanning can reflect the direction of blood flow, it cannot accurately measure the diameter of the uterine artery due to color expansion; in addition, the angle of the ultrasonic probe and the experience of the operator have a great influence on the accuracy of measurement^[10–13]. Therefore, the results of Doppler evaluation of the effect of vasoconstrictors on uterine blood vessels are controversial, which makes a consensus difficult to reach. Computed tomography (CT) angiography is a good method for visualizing the different branches of arteries and studying anatomic variations in their origin. In addition, computed tomography image reconstruction technology provides an accurate way to simultaneously evaluate the overall contractile movement of different blood vessels and their upstream and downstream branches^[14–16]. Whether CT angiography is a useful tool for studying the effect of vasoconstrictors on uterine arteries is still unclear. In this study, we aimed to evaluate the quality of CT imaging of the uterine arteries of pregnant rabbits. CT imaging was performed, and the diameters of the rostral artery of the ear were measured to evaluate the effect of the vasoconstrictors on resistance vessels; the diameters of the uterine arteries were measured to determine placental perfusion.

Materials And Methods

Animals

This study was approved by the Animal Care and Use Committee of Wannan Medical College with the license number LLSC-2020-111 and conducted under their supervision. In addition, all animal experiments in the study were followed the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines (<https://arriveguidelines.org/>). Fifteen near-term pregnant (27-29 days) New Zealand rabbits, which purchased from Qinglongshan Experimental Animal Breeding Center in Nanjing were randomly divided into three groups: Group P (phenylephrine), Group E (ephedrine) and Group C (normal saline).

Drug dose calculation

The doses of the vasoactive drugs selected for this study were the most commonly used single intravenous dose for parturients (100 µg phenylephrine or 5 mg ephedrine to a parturient of 70 kg). According to the guidance of the USFDA, the animal equivalent dose was calculated on the basis of body surface area by multiplying the human dose (mg/kg) by the K_m ratio. The equivalent dose ratio for the rabbit and human body surface area was 3.1, and the rabbit dose = human dose (mg/kg) $\times 3.1$ ^[17]. After calculation, phenylephrine (phenylephrine hydrochloride injection, 10 mg/ml, Shanghai Harvest Pharmaceutical, Shanghai) was administered at 4.4 µg/kg, and ephedrine (ephedrine hydrochloride injection, 30 mg/ml, Shenyang Northeast Pharm, Shenyang) was administered at 0.22 mg/kg.

CT scanning

Two peripheral venous accesses were routinely established on the same side of the ear: one was for injecting anesthetics and drugs, and the other was for injecting contrast agent. After anesthesia was

administered, the rabbits were fixed on the operating table in the supine position with all four limbs fully symmetrically stretched and the neck extended. A 17F central vein catheter was placed into the bladder to drain urine to reduce the influence of an enlarged bladder covering the uterine artery during CT scanning. After the pelvic cavity was opened, the uterine artery was exposed and marked. Contrast agent (IOVERSOL INJECTION, 350 mg I/ml, Hengrui Pharmaceuticals, Jiangsu) was injected with a power syringe at a rate of 1 ml/s. CT images were taken with a flash 128 dual-source X-ray CT scanner. The rabbits were injected with 1.5 ml phenylephrine in Group P, ephedrine in Group E, and normal saline in Group C. CT images were scanned and recorded 5 min, 10 min, 15 min, 30 min, 45 min and 60 min after drug administration. All of the rabbits were euthanized with a lethal dose of pentobarbital at the end of the experiment.

Diameter measurement

The diameters of the uterine artery and rostral artery were measured to reflect uterine blood flow and peripheral resistance. All of the measurements were performed by the same imaging physician, who was unaware of the medication used; the measurements were repeated three times, and the average of the three measurements was used^[14,18].

Statistical analysis

Data are presented as the mean $\pm$ standard error of the mean and were calculated with GraphPad Prism 6 software. Statistical significance was determined with one-way ANOVA, and Tukey's test was applied for post hoc multiple comparisons. A value of $p < 0.05$ was considered statistically significant.

Results

Identify uterine artery under CT scanning

In this study, we first attempted to visualize and identify the uterine artery under CT. According to published data^[19,20], the uterine artery of female rabbits originates from the umbilical artery, which stems from the external iliac artery, a branch of the common iliac artery, which in turn is derived from the abdominal aorta. In this research, we observed the same anatomical distribution of arteries (Fig. 1A). After trying a series of combinations of parameters of the CT machine, we finally obtained clear images of the uterine artery and its upstream and downstream branches with CT (Fig. 1B) and 3D image reconstruction (Fig. 1C).

Phenylephrine And Ephedrine Trigger The Same Degree Of Peripheral Artery Contraction

To ensure that equivalent dosages of phenylephrine and ephedrine were used in this research, we determined the degree of peripheral artery contraction via CT to reflect the changes in peripheral

resistance. We chose the rostral artery in the ear as the resistance vessel because of its convenience and distinctiveness. The contractile response was evaluated according to the changes in artery diameters. The CT images showed that phenylephrine and ephedrine produced similar degrees of artery contraction (Figs. 2 and 3A). After the administration of vasoconstrictors, the rostral arteries began to contract at 5 min compared to their baseline levels (5 min: 87.7% $\pm$ 2.7% in Group P vs. 94.5% $\pm$ 0.8% in Group E, N = 5/group, $p > 0.05$; 10 min: 84.0% $\pm$ 2.9% in Group P vs. 83.9% $\pm$ 7.1% in Group E, N = 5/group, $p > 0.05$; 15 min: 86.3% $\pm$ 2.9% in Group P vs. 81.6% $\pm$ 9.1% in Group E, N = 5/group, $p > 0.05$). After 15 min, the diameter of the rostral artery began to recover and showed a trend of gradual increase (30 min: 97.4% $\pm$ 6.6% in Group P vs. 87.4% $\pm$ 10.3% in Group E, N = 5/group, $p > 0.05$; 45 min: 103.7% $\pm$ 9.7% in Group P vs. 110.7% $\pm$ 0.8% in Group E, N = 5/group, $p > 0.05$; 60 min: 104.2% $\pm$ 10.8% in Group P vs. 114.2% $\pm$ 3.2% in Group E, N = 5/group, $p > 0.05$). From 5 min to 15 min, both Group P and Group E showed significant vasoconstriction ($p < 0.05$) compared to Group C. In addition, there was no significant difference between Group P and Group E at any time point ($p > 0.05$) (Fig. 3B, Table 1).

Table 1 Percentage change in rostral artery diameter							
	0 min	5 min	10 min	15 min	30 min	45 min	60min
Group C	100%	102.7% $\pm$ 1.7%	106.3% $\pm$ 1.8%	108.2% $\pm$ 2.5%	109.4% $\pm$ 3.1%	113.8% $\pm$ 3.1%	119.0% $\pm$ 3.7%
Group P	100%	87.7% $\pm$ 2.7%	84.0% $\pm$ 2.9%	86.3% $\pm$ 2.9%	97.4% $\pm$ 6.6%	103.7% $\pm$ 9.7%	104.2% $\pm$ 10.8%
Group E	100%	94.5% $\pm$ 0.8%	83.9% $\pm$ 7.1%	81.6% $\pm$ 9.1%	87.4% $\pm$ 10.3%	110.7% $\pm$ 1.8%	114.2% $\pm$ 3.2%

Phenylephrine And Ephedrine Demonstrate Different Vasoconstriction Effects On The Uterine Artery

From CT images, we observed different vasoconstriction effects of phenylephrine and ephedrine on the uterine artery. In summary, phenylephrine elicited a strong but short duration vasoconstriction effect, while ephedrine triggered a mild but long-lasting duration vasoconstriction effect (Fig. 4, Fig. 5 and Table 2). At 5 min, the uterine arteries were 85.8% $\pm$ 0.8% in Group P, 97.4% $\pm$ 3.4% in Group E, and 103.3% $\pm$ 0.9% in Group C, N = 5/group, compared to their baseline levels. At 10 min, uterine arteries was 75.7% $\pm$ 2.8% in Group P, 97.2% $\pm$ 1.5% in Group E, 105.4% $\pm$ 2.1% in Group C, N = 5/group. CT scanning indicated a stronger vasoconstriction effect in Group P than in Group E at 5 min ($p < 0.01$) and 10 min ($p < 0.0001$). Although uterine arteries were still contracted in Group E as compared with Group C at 15 min, 30 min and 45 min ($p < 0.05$), there was no statistical significance between Group P and Group E ($p > 0.05$) (15 min: 92.6% $\pm$ 3.9% in Group P, 86.8% $\pm$ 2.6% in Group E, 106.4% $\pm$ 1.3% in Group C, N = 5/group; 30 min: 95.7% $\pm$ 6.7% in Group P, 91.9% $\pm$ 2.5% in Group E, 109.5% $\pm$ 1.5% in Group C, N = 5/group; 45 min: 108.4% $\pm$ 2.7% in Group P, 100.5% $\pm$ 1.6% in Group E, 109.7% $\pm$ 1.1% in Group C, N = 5/group). At 60 min, the

effect of ephedrine on the uterine artery vanished, and the uterine artery returned to baseline levels (60 min: 112.0% $\pm$ 3.4% in Group P, 108.7% $\pm$ 0.8% in Group E, 113.1% $\pm$ 1.3% in Group C, N = 5/group).

Table 2
Percentage change in uterine artery diameter

	0 min	5 min	10 min	15 min	30 min	45 min	60min
Group C	100%	103.3% $\pm$ 0.9%	105.4% $\pm$ 2.1%	106.4% $\pm$ 1.3%	109.5% $\pm$ 1.5%	109.7% $\pm$ 1.1%	113.1% $\pm$ 1.3%
Group P	100%	85.8% $\pm$ 0.8% ^a	75.7% $\pm$ 2.8% ^a	92.6% $\pm$ 3.9% ^a	95.7% $\pm$ 6.7%	108.4% $\pm$ 2.7%	112.0% $\pm$ 3.4%
Group E	100%	97.4% $\pm$ 3.4%	97.2% $\pm$ 1.5% ^b	86.8% $\pm$ 2.6% ^a	91.9% $\pm$ 2.5% ^a	100.5% $\pm$ 1.6% ^a	108.7% $\pm$ 0.8%
Compared to Group C a, ^a p <0.05; Compared to Group P, ^b p <0.05							

Discussion

Our experiments demonstrated that 4.4 μ g/kg phenylephrine (equal to a single shot of 100 μ g phenylephrine to a parturient of 70 kg) and 0.22 mg/kg ephedrine (equal to a single shot of 5 mg ephedrine to a parturient of 70 kg) resulted in a similar degree of increase in peripheral vascular resistance. However, the contraction effect on the uterine artery was weaker in ephedrine, particularly at 5 min and 10 min after i.v. injection. Although uterine arteries were still contracted under challenge with ephedrine after 15 min, compared with the control group, there was no statistical significance between the phenylephrine and ephedrine groups. These results suggest that compared with phenylephrine, ephedrine can provide the same degree of increase in peripheral vascular resistance while inducing a weaker uterine artery contraction effect, which makes it a better choice for treating hypotension during perioperative obstetric surgery.

Hypotension remains a frequent complication during perioperative obstetric surgery, often leading to placental hypoperfusion that endangers the life of the fetus^[21–24]. Common clinical strategies for preventing and treating this hypotension include fluid therapy, posture adjustment, and the use of vasoconstrictors^[5–7], in which vasoconstrictors are the most preferred therapy due to their fast action and effectiveness. The vasopressors ephedrine and phenylephrine are the two most commonly used drugs in the clinic. However, which one is the better choice for providing enough peripheral resistance vessel contraction while imposing the least effect on uterine placental perfusion remains elusive. Due to ethical reasons and limits of research methods and equipments, previous researchers prefer to study indirect indicators as vital signs of the mothers, blood gas analysis and Apgar score of the infants to reflect the effect of vasopressors on uterine placental perfusion. Therefore, the research conclusions remain controversial^[22,25–28].

Doppler ultrasonography is routinely employed as a convenient and safe method for evaluating placental circulation and fetal safety during gestation period examination. Ultrasound Doppler flow imaging technology reflects blood flow through color blood flow signals, monitors the vascular resistance index, and indirectly reflects placental perfusion^[29–31]. However, ultrasonography cannot accurately reflect the diameter of the uterine artery due to color expansion, and the angle of the ultrasonic probe and equipment has a great influence on measurement accuracy. Therefore, choosing a suitable measurement method to evaluate the impact of vasopressors on placental perfusion via an animal model is of great significance.

Placental perfusion depends on maternal uterine perfusion: Uterine blood flow = uterine perfusion pressure/uterine vascular resistance. In other words, in efforts to ensure uterine perfusion pressure, vascular resistance can accurately reflect uterine blood flow. According to Ohm's law, $Q = \Delta P/R$; Q: Blood flow, R: Resistance of blood flow. Because most blood flows in a laminar manner, its resistance according to Poiseuille theorem is $R = 8\eta l/\pi r^4$; L: Length of the blood vessel, η : Blood viscosity, R: Resistance of the vascular lumen. In most cases, the blood viscosity and vessel length do not change significantly, and the vascular diameter is changed through the relaxation and contraction of vascular smooth muscle to adjust the regulation of blood flow resistance. Therefore, the change in uterine placental flow can be directly reflected by the change in the diameter of the uterine artery.

As shown in previous studies, CT angiography is a good exam for visualizing the different branches of arteries and studying the anatomic variations in their origin, especially in the case of uterine arteries^[14, 32]. CT demonstrates good penetration, can clearly show certain organs and arteries, has great potential for exploring smaller branches of blood vessels, and can be used to diagnose vascular diseases such as stenosis and occlusion^[33–34]. Therefore, in this study, we used CT imaging to observe changes in the diameter of the uterine and peripheral arteries to evaluate changes in placental perfusion and peripheral resistance.

Studies have shown that compared with ephedrine, phenylephrine is more likely to cause uterine artery contraction and increase vascular resistance, reduce uterine placental perfusion, and adversely affect the fetus^[10, 35]. In our study, both phenylephrine and ephedrine induced the same degree of peripheral vasoconstriction; however, the vasoconstriction effect on the uterine artery was different. In short, phenylephrine elicited a strong but short duration vasoconstriction effect, while ephedrine triggered a mild but long-lasting duration vasoconstriction effect, which was consistent with the aforementioned studies.

There are several limitations of our study that must be considered. First, the anatomical structure of the placenta is different in pregnant rabbits than in parturients. Accordingly, differences in the placental transfer of vasopressors may exist. In addition, human and rabbit responses to vasopressors may vary because there are species-specific differences in α - and β -adrenergic receptor distribution. Second, the drug doses used in this study are commonly used clinical single doses, and we did not carry out research using other doses of each drug. Third, the anesthesia method used for pregnant rabbits is general anesthesia, which is different from the intraspinal anesthesia used in clinical practice. The effect of

intraspinal anesthesia on uterine artery diameter in pregnant rabbits needs further study. This study comprised only observation of the phenomenon and did not study the underlying mechanism.

Conclusion

In summary, CT imaging of the uterine arteries showed that, compared with ephedrine, phenylephrine had a faster effect, resulting in stronger contraction of the uterine arteries, indicating a greater impact on placental perfusion. Therefore, in clinical practice, ephedrine has more favorable effects than phenylephrine on uterine and placental circulation.

Declarations

Ethics approval and consent to participate

This study was approved by the Animal Care and Use Committee of Wannan Medical College with the license number LLSC-2020-111 and conducted under their supervision. All procedures were performed in accordance with relevant guidelines.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's Contributions

Can Liu designed and performed the research, analyzed the data and corrected the manuscript; Jingjing Li performed the animal experiment and wrote the manuscript; Guangjian Gao performed the CT scanning, 3D reconstruction and measurement; Yibo Yin, Zhangrui Hu, Xuechen Long, Zixuan Guo and Xiaoju Jin performed the animal experiment; Wenjun Guo designed the research, analyzed the data and corrected the manuscript. All authors have read and approved the final manuscript for publication.

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Figures

Figure 1

Images of uterine arteries distribution of pregnant rabbits. A. Representative photograph of the uterine artery of pregnant rabbits. B. Representative CT image of the uterine artery of pregnant rabbits. C. 3D-images of uterine artery of pregnant rabbits.

Figure 2

CT images of rostral arteries of pregnant rabbits. Representative CT images of rostral arteries at 0 min, 15 min and 60 min after administering normal saline, phenylephrine and ephedrine. Arrow indicates the rostral artery.

Figure 3

Contractile responses of rostral arteries in pregnant rabbits. Contractile responses of rostral arteries of pregnant rabbits under stimulation with normal saline (N=5), phenylephrine (N=5) and ephedrine (N=5). A. Continuous changes in contraction to normal saline, phenylephrine and ephedrine in rostral arteries of pregnant rabbits. B. Percent change in the diameters of rostral arteries of pregnant rabbits at different time points after injection of normal saline, phenylephrine and ephedrine. Data are presented as the mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. NS, No statistical significance.

Figure 4

CT images of uterine arteries of pregnant rabbits. Representative CT images of uterine arteries at 0 min, 15 min and 60 min after administering normal saline, phenylephrine and ephedrine. Arrow indicates the uterine artery.

Figure 5

Contractile responses of uterine arteries in pregnant rabbits. Contractile responses of uterine arteries of pregnant rabbits under stimulation with normal saline (N=5), phenylephrine (N=5) and ephedrine (N=5). A. Continuous changes in contraction to normal saline, phenylephrine and ephedrine in uterine arteries of pregnant rabbits. B. Percent change in the diameters of uterine arteries of pregnant rabbits at different time points after injection of normal saline, phenylephrine and ephedrine. Data are presented as the mean $\pm$ SEM. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$. NS, No statistical significance.