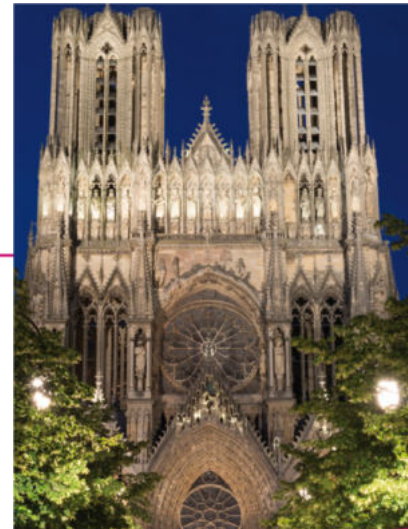


51^{ème} Congrès National
25 & 26 Mai 2018
du **Club d'Anesthésie-
Réanimation en Obstétrique**

Faculté de médecine de REIMS



Les Drogues Vasoactives

Pierre-Yves Dewandre, MD, PhD

Professeur de Clinique

Service Universitaire d'Anesthésie-Réanimation

CHU-CHR Liège

Hypotension & Rachianesthésie

- **Rachianesthésie : ➔ *HypoTA >50%***
 - **Bloc sympathique**
 - **↓ Résistances vasculaires périphériques,**
 - **↓postcharge**
 - **Veinodilatation, (+ CVCI)**
 - **↓précharge**
- **Réflexes via barorécepteurs**
 - **↑FC, ↑VES, ↑DC**
 - *Bloc étendu: pas de tachycardie*
 - *Bradycardie vasovagale possible*
 - *Bezold-Jarish (VG)*
 - *Bainbridge inversé (OD)*

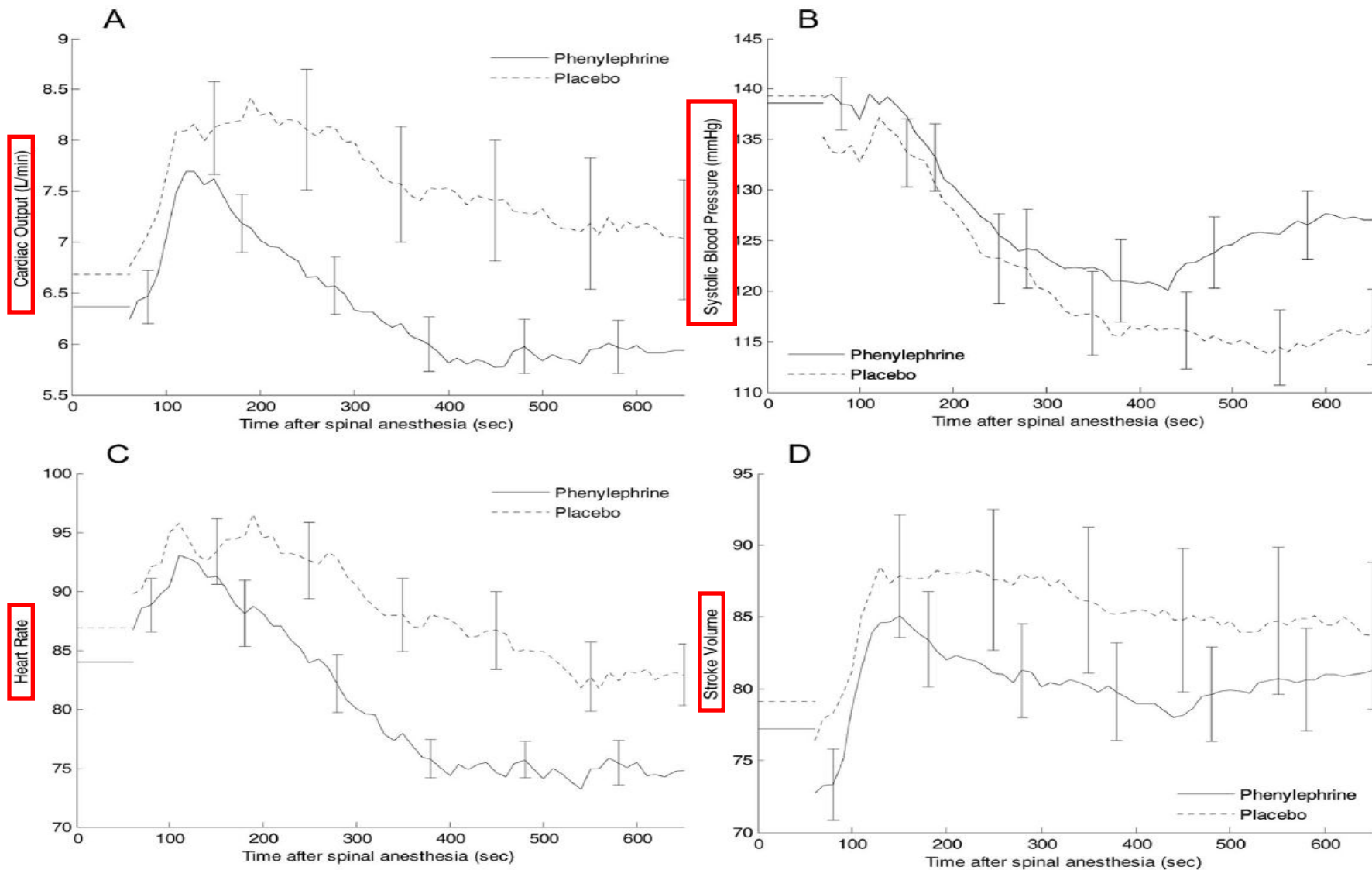


Fig. 3. Mean differences in hemodynamic variables between the phenylephrine groups and the placebo groups the first 11 min after spinal anesthesia. (A) Cardiac output. (B) Systolic blood pressure. (C) Heart rate. (D) Stroke volume. Baseline is marked on the y label. SE for each group is marked as error bars.

Traitement Vasopresseur

- **But**
 - Restaurer **résistance vasculaires périphériques**
 - **α -agonistes**
 - Sans diminuer **DC**
 - **β -agoniste ?**
 - En préservant la **balance DO_2/VO_2**

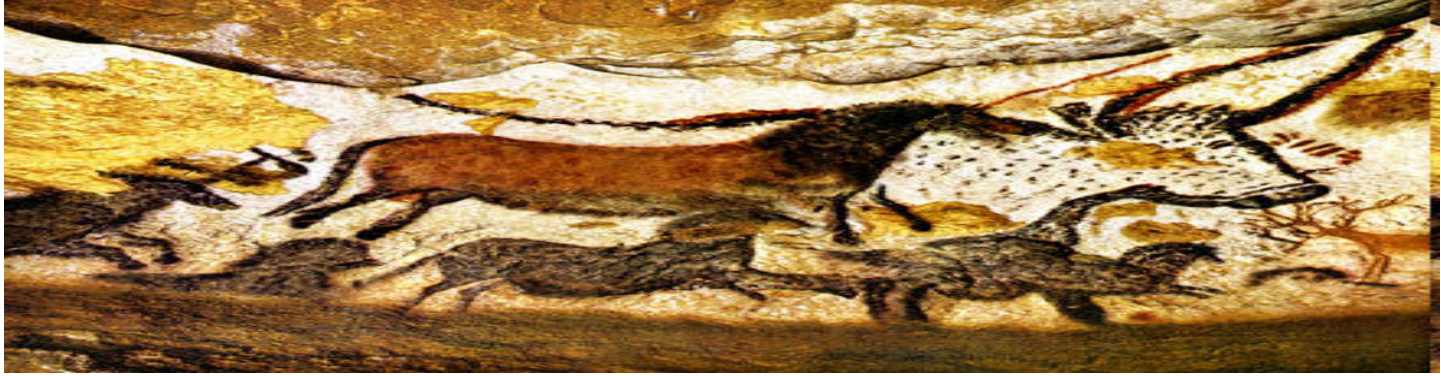
Table 1 Comparison of commonly used vasopressors.

	Ephedrine	Phenylephrine	Metaraminol	Noradrenaline	Adrenaline	Mephentermine
Receptor	β_1, β_2 , weak α	α_1	α_1 , weak β	α_1, β	α_1, β	α_1, β
Mechanism	Indirect, weak direct	Direct	Direct and indirect	Direct	Direct	Indirect
Onset	Slow	Immediate	1–2 min	Immediate	Immediate	Immediate
Duration	Prolonged	Intermediate	Prolonged	Short	Short	Prolonged

Anaesthesia 2018, 73, 71–92

Ephedrine vs Phenylephrine





- α -agonistes (phenylephrine)
- Correction de l'hypotension
- Hypoperfusion utéroplacentaire
- Aggravation de l'asphyxie foetale



A Quantitative, Systematic Review of Randomized Controlled Trials of Ephedrine Versus Phenylephrine for the Management of Hypotension During Spinal Anesthesia for Cesarean Delivery

Anna Lee, MPH, PhD, Warwick D. Ngan Kee, MBChB, MD, FANZCA, and Tony Gin, MBChB, MD, FANZCA, FRCA

Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, China

- Ephedrine vs Phenylephrine
- Efficacy & Safety
- 7 RCT (n= 292)
- Maternal
 - Hypotension
 - Hypertension
 - Bradycardia
- Foetal
 - pH
 - Apgar

For the management (prevention and treatment) of maternal hypotension, there was no difference between phenylephrine and ephedrine (relative risk [RR] of 1.00; 95% confidence interval [CI], 0.96–1.06). Maternal bradycardia was more likely to occur with phenylephrine than with ephedrine (RR of 4.70; 95% CI, 1.47–15.60). Women given phenylephrine had neonates with higher umbilical arterial pH values than those given ephedrine (weighted mean difference of 0.03; 95% CI, 0.02–0.04). There was no difference between the two vasopressors in the incidence of true fetal acidosis (umbilical arterial pH value of <7.2; RR of 0.78; 95% CI, 0.16–3.92) or Apgar score of <7 at 1 and 5 min. This systematic review does not support the traditional idea that ephedrine is the preferred choice for the management of maternal hypotension during spinal anesthesia for elective cesarean delivery in healthy, nonlaboring women.

(Anesth Analg 2002;94:920–6)

Phenylephrine

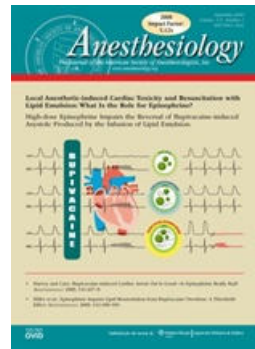
Anesthesiology 2009; 111:506-12

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Placental Transfer and Fetal Metabolic Effects of Phenylephrine and Ephedrine during Spinal Anesthesia for Cesarean Delivery

Warwick D. Ngan Kee, M.B.Ch.B., M.D., F.A.N.Z.C.A., F.H.K.A.M.,* Kim S. Khaw, M.B.B.S., F.R.C.A., F.H.K.A.M.,† Perpetua E. Tan, B.Sc., M.Phil.,‡ Floria F. Ng, R.N., B.A.Sc.,§ Manoj K. Karmakar, M.B.B.S., F.R.C.A., F.H.K.A.M.†

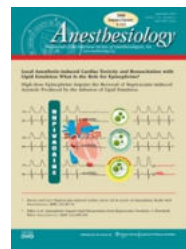
Anesthesiology, V 111, No 3, Sep 2009



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- **Ephedrine**
- Altération status acido-basique fœtal
- Passage transplacentaire & effets métaboliques (β -adrénergiques)
- **Méthode**
- N = 104 ASA 1 & 2
- Pas de pré-remplissage,
- co-remplissage cristalloïde (max 2L)
- Rachi: Bupi HB 10mg + Fenta.15 μ g
- Perf. vasopresseur $\Rightarrow$ PAS initiale
 - Phenylephrine 100 μ g /ml vs
 - Ephedrine 8mg/ml
 - 60 ml/h
 - Stop si PAS 20% > baseline
 - Poursuivie si PAS $\leq$ baseline
 - Si PAS < 80% baseline
 - Rescue phenylephrine 100 μ g
- Délivrance: Prélèvement sanguins
 - Artériel maternel
 - veineux et artériel ombilical
 - Gaz sanguins
 - Phenylephrine, Ephedrine
 - Lactate, Glucose
 - Epinephrine, Norepinephrine





Placental Transfer and Fetal Metabolic Effects of Phenylephrine and Ephedrine during Spinal Anesthesia for Cesarean Delivery

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Table 2. Blood Gases

	Phenylephrine Group	Ephedrine Group	P Value
Maternal arterial			
Number of samples	45	45	
pH	7.42 [7.41 to 7.44]	7.42 [7.41 to 7.43]	0.14
Pco ₂ , mmHg	33 [30 to 35]	34 [32 to 36]	0.15
Po ₂ , mmHg	111 [101 to 123]	112 [99 to 122]	0.68
Base excess, mmol/l	-2.3 [-2.9 to -1.5]	-2.3 [-3.1 to -1.3]	0.98
Umbilical arterial			
Number of samples	51	51	
pH	7.33 [7.30 to 7.35]	7.25 [7.14 to 7.29]	<0.001
Pco ₂ , mmHg	49 [42 to 54]	56 [48 to 66]	<0.001
Po ₂ , mmHg	20 [18 to 22]	20 [17 to 24]	0.57
Base excess, mmol/l	-1.9 [-3.2 to -0.6]	-4.8 [-8.7 to -3.0]	<0.001
Umbilical venous			
Number of samples	49	52	
pH	7.34 [7.33 to 7.35]	7.31 [7.26 to 7.34]	<0.001
Pco ₂ , mmHg	46 [43 to 49]	47 [42 to 51]	0.49
Po ₂ , mmHg	28 [25 to 32]	30 [27 to 33]	0.03
Base excess, mmol/l	-1.6 [-2.4 to -0.7]	-4.3 [-6.2 to -2.6]	<0.001

Placental Transfer and Fetal Metabolic Effects of Phenylephrine and Ephedrine during Spinal Anesthesia for Cesarean Delivery

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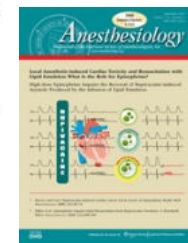


Table 3. Plasma Concentrations of Lactate, Glucose, Epinephrine, Norepinephrine, Phenylephrine, and Ephedrine

	Phenylephrine Group	Ephedrine Group	P Value
Maternal arterial			
Lactate, mmol/l	2.3 [2.0–2.7] (44)	2.4 [2.0–2.7] (45)	0.56
Glucose, mg/dl	80 [76–85] (44)	86 [80–94] (45)	0.003
Epinephrine, pg/ml	33.5 [19–54] (46)	47 [22–73] (50)	0.046
Norepinephrine, pg/ml	115 [92–178] (45)	297 [223–390] (50)	<0.001
Phenylephrine, ng/ml	8.2 [5.7–10.7] (47)		
Ephedrine, ng/ml		366.5 [306.5–523.5] (50)	
Umbilical arterial			
Lactate, mmol/l	2.2 [1.9–2.6] (52)	4.2 [3.0–6.7] (49)	<0.001
Glucose, mg/dl	55 [49–60] (52)	63 [59–71] (49)	<0.001
Epinephrine, pg/ml	525 [289–852] (45)	696 [507–1,291] (49)	0.019
Norepinephrine, pg/ml	2,158 [1,526–3,403] (46)	5,523 [3,066–9,538] (49)	<0.001
Phenylephrine, ng/ml	0.9 [0.6–1.2] (47)		
Ephedrine, ng/ml		355.2 [254.5–545.2] (47)	
Umbilical venous			
Lactate, mmol/l	2.2 [1.9–2.4] (51)	3.4 [2.7–5.1] (50)	<0.001
Glucose, mg/dl	66 [61–70] (51)	73 [68–79] (50)	<0.001
Epinephrine, pg/ml	97 [50–214] (50)	132 [84–226] (52)	0.039
Norepinephrine, pg/ml	446 [293–683] (50)	1,568 [812–2,940] (52)	<0.001
Phenylephrine, ng/ml	1.4 [0.8–1.9] (47)		
Ephedrine, ng/ml		434.5 [334.0–594.3] (52)	

Placental Transfer and Fetal Metabolic Effects of Phenylephrine and Ephedrine during Spinal Anesthesia for Cesarean Delivery

Warwick D. Ngan Kee, M.B.Ch.B., M.D., F.A.N.Z.C.A., F.H.K.A.M.,* Kim S. Khaw, M.B.B.S., F.R.C.A., F.H.K.A.M.,† Perpetua E. Tan, B.Sc., M.Phil.,‡ Floria F. Ng, R.N., B.A.Sc.,§ Manoj K. Karmakar, M.B.B.S., F.R.C.A., F.H.K.A.M.†

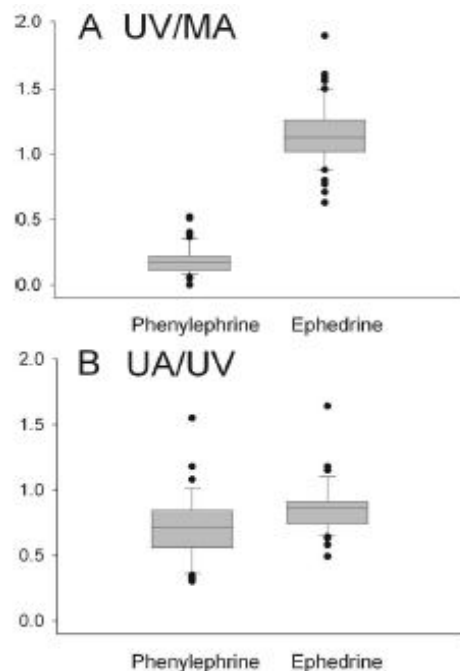
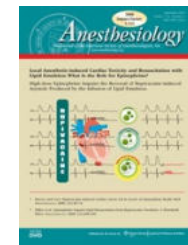


Fig. 1. Plasma concentration ratios for phenylephrine and ephedrine. Data are shown for (A) umbilical venous to maternal arterial (UV/MA) and (B) umbilical arterial to umbilical venous (UA/UV) ratios. Box plots display the 25th, 50th, and 75th percentiles as horizontal lines on a bar, whiskers above and below the box indicate the 90th and 10th percentiles, and data beyond the 10th and 90th percentiles are displayed as individual points. Data were significantly different between groups ($P \leq 0.001$) for both concentration ratios.

	Ephedrine	Phenylephrine	P
UV / MA	1.13	0.17	< 0.001
UA / UV	0.83	0.71	0.001

- Passage transplacentaire
 - Ephedrine > Phenylephrine
- Metabolisation ou redistribution foetale
 - Ephedrine < Phenylephrine

Table 4. Hemodynamic Changes, Intravenous Fluid, and Vasopressor Consumption

	Phenylephrine Group	Ephedrine Group	P Value
Total volume of vasopressor given, ml	13 [9.6–16.9]	7.7 [5.6–9.9]	<0.001
Total intravenous fluid, ml	1,725 [1,200–2,010]	1,800 [1,450–2,010]	0.36
Incidence of hypotension	2 (4%)	13 (25%)	0.002
Minimum recorded systolic blood pressure, mmHg	104 [96–109]	101 [87–108]	0.33
Rescue phenylephrine required	1 (2%)	11 (22%)	0.002
<u>Incidence of hypertension</u>	<u>21 (41%)</u>	<u>24 (47%)</u>	0.55
Maximum recorded systolic blood pressure, mmHg	134 [127–140]	139 [129–152]	0.044
Incidence of bradycardia (heart rate < 50 beats/min)	6 (12%)	0 (0%)	0.03
<u>Minimum recorded heart rate, beats/min</u>	<u>58 [54–65]</u>	<u>70 [63–78]</u>	<0.001
<u>Nausea or vomiting</u>	<u>1 (2%)</u>	<u>18 (35%)</u>	<0.001

- Confirmation pH et BE ephedrine < phenylephrine
 - Passage transplacentaire ephedrine > phenylephrine
 - Metabolisation et ou redistribution ephedrine < phenylephrine
 - Effet métabolique: Lactate, glucose, epinephrine, norepinephrine , UA PCO2

- Balance D02 (↓ par phenylephrine) - V02 (↑ par ephedrine)

- Quid si insuffisance placentaire chronique?

- Durée: Induction - incision: 20min, extraction 27 min

- Doses

- Ephedrine: 62 mg
- Phenylephrine: 1300 µg

mise, although in a recent comparison of ephedrine and phenylephrine in nonelective Cesarean delivery, we did not find that use of moderate doses of phenylephrine (median dose before delivery, 100 µg; range 0–1,200 µg) to be associated with any evidence of detrimental effects on the fetus.¹⁴

Anaesthesia, 2008, **63**, pages 1319–1326

Burden of Proof

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of Columbia University, New York, New York. rms7@columbia.edu

Titrated phenylephrine infusions minimize maternal nausea, vomiting, and episodes of hypotension, and they result in higher neonatal pH and lower base deficits. A variety of specific dosing strategies can be used and have been published,^{2,6,23,24} but doses in the range of 25–100 μ g/min titrated to maintain maternal blood pressure near baseline values appears to be very effective and relatively easy to employ. It is the therapeutic strategy that most anesthesiologists would want for themselves or family members as patients, and it should probably be the default choice for prevention and treatment of hypotension during spinal anesthesia for elective Cesarean delivery in the absence of a specific contravening rationale or contraindication. As the famous Alka-Seltzer ad from the 1970s said, “Try it, you’ll like it,” and so will your patients.

Continuous Invasive Blood Pressure and Cardiac Output Monitoring during Cesarean Delivery

A Randomized, Double-blind Comparison of Low-dose versus High-dose Spinal Anesthesia with Intravenous Phenylephrine or Placebo Infusion

Eldrid Langesæter, M.D.,* Leiv Arne Rosseland, M.D., Ph.D.,* Audun Stubhaug, M.D., Ph.D.†

- N= 80 elective CS
- CSE
 - +/- Phenylephrine 0.25 µg/kg/min
- Cohydration 750 ml Saline 0.9%
- LIDCO
- HypoTA: < 90 mmHg
 - θ 30µg phenylephrine
 - θ 5mg ephedrine si FC<55

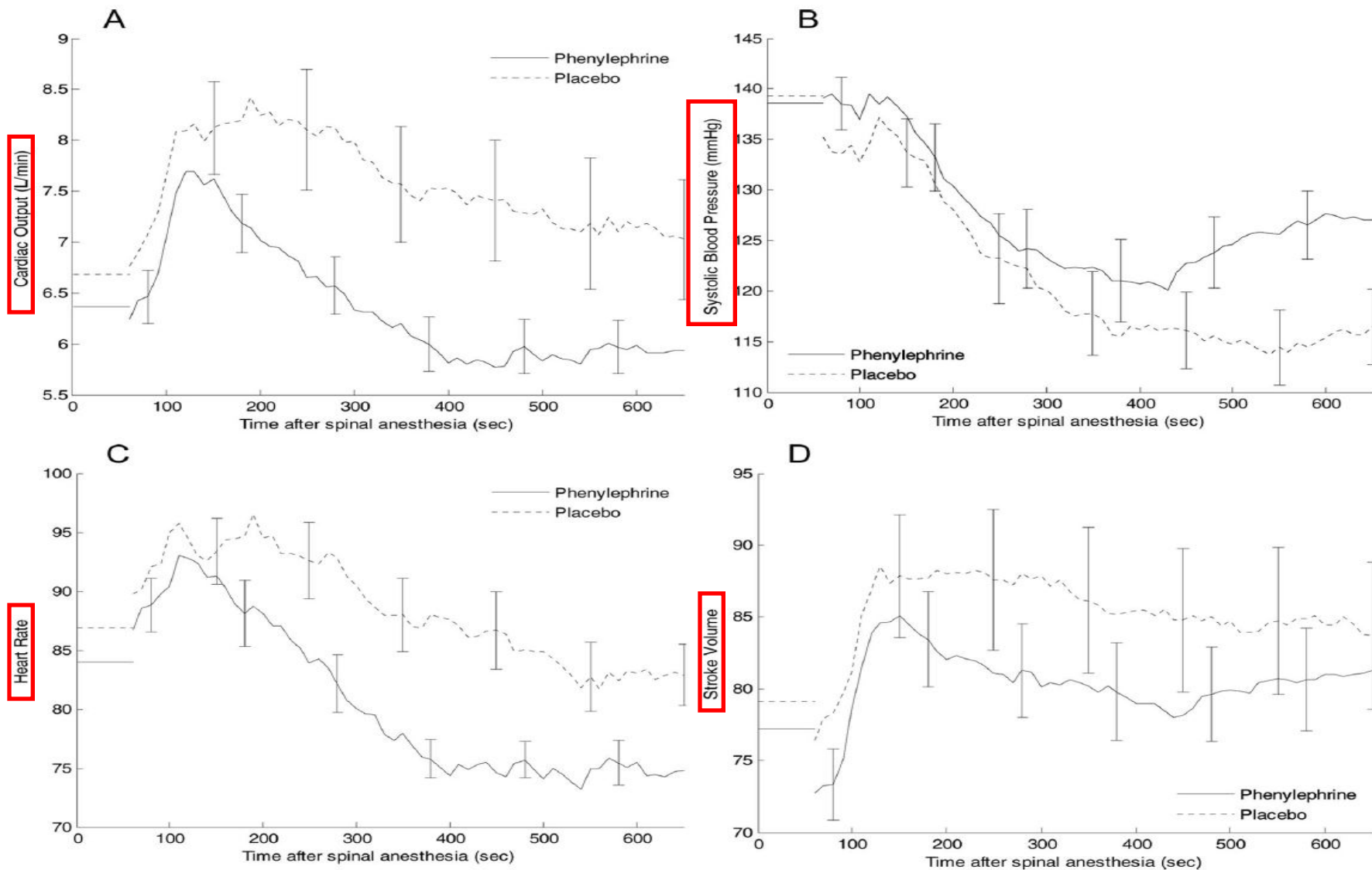


Fig. 3. Mean differences in hemodynamic variables between the phenylephrine groups and the placebo groups the first 11 min after spinal anesthesia. (A) Cardiac output. (B) Systolic blood pressure. (C) Heart rate. (D) Stroke volume. Baseline is marked on the y label. SE for each group is marked as error bars.

Continuous Invasive Blood Pressure and Cardiac Output Monitoring during Cesarean Delivery

A Randomized, Double-blind Comparison of Low-dose versus High-dose Spinal Anesthesia with Intravenous Phenylephrine or Placebo Infusion

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data show that there was a statistically significant lower heart rate and CO in the phenylephrine groups compared with the placebo groups, but all groups had an increase in heart rate and CO the first minutes (fig. 3). There was no statistically significant difference regarding stroke volume. Phenylephrine is an α_1 agonist that increases the blood pressure by increasing SVR. In addition, phenylephrine has a direct inotropic effect on the heart.¹³ The fact that the phenylephrine groups had lower heart rate and CO than the placebo groups can be explained by the arterioconstrictive effect of phenylephrine resulting in high SVR and therefore a simultaneous reduction of cardiac output. The approach of keeping the blood pressure at baseline by infusing high doses of phenylephrine might be questioned in daily clinically practice because of a negative effect on CO. Allowing 10–20% decrease in blood pressure, reducing the doses of bupivacaine, and thereby reducing the need for phenylephrine may be a better approach for hemodynamic stability during cesarean delivery.

In conclusion, this study shows that low-dose bupivacaine (with sufentanil) combined with a low-dose infusion of phenylephrine and moderate cohydration, gives the best hemodynamic stability during spinal anesthesia for cesarean delivery. This study supports the view that prophylactic phenylephrine infusion should be part of standard clinical practice during spinal anesthesia for cesarean delivery.

Vasopressors for the management of hypotension after spinal anesthesia for elective caesarean section. Systematic review and cumulative meta-analysis

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¹Department of Anaesthesiology, Klinikum am Bruderwald Sozialstiftung Bamberg, Bamberg, Germany and ²Department of Anaesthesiology, University of Aachen, Aachen, Germany

N= 20 études, 1069 patientes

Acidose fœtale : Epédrine vs Phényléphrine ($pH < 7.20$)

RR = 5.29

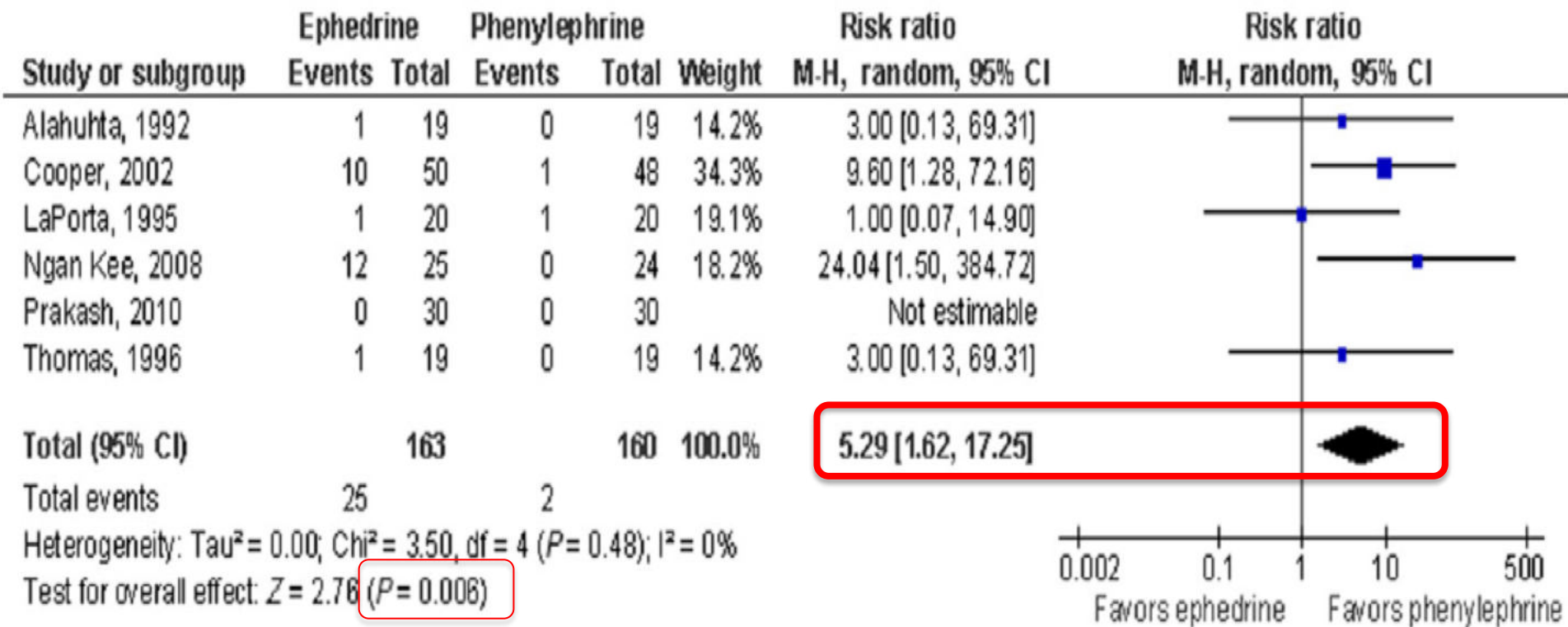


Fig. 2. Fetal acidosis after ephedrine or phenylephrine use. CI, confidence interval; M-H, Mantel-Haenszel Test.

BE éphédrine vs phényléphrine

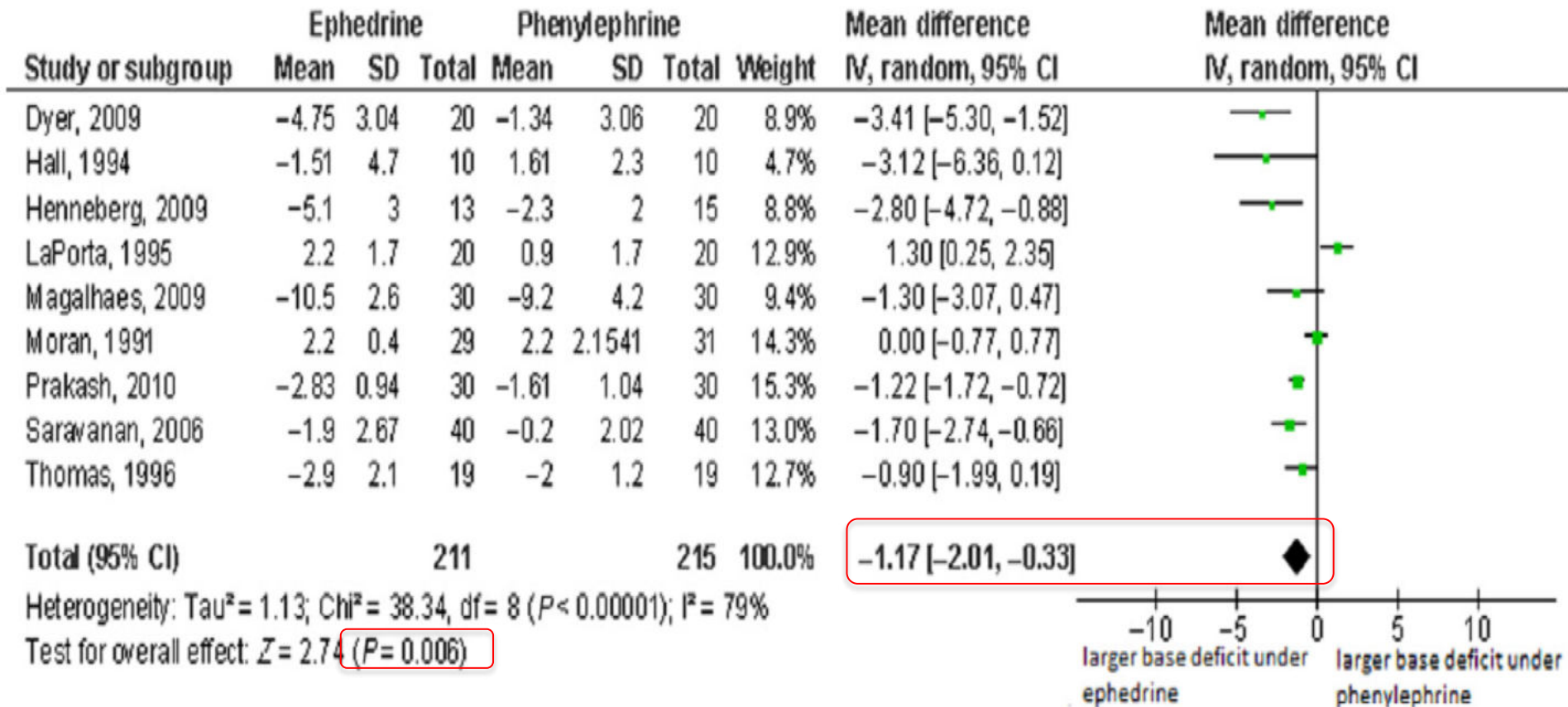


Fig. 3. Neonatal base excess after ephedrine or phenylephrine. CI, confidence interval; SD, standard deviation.

- **PCO₂: NS, Apgar: NS**

Bradycardie maternelle

éphédrine vs phényléphrine: **RR= 0.17**

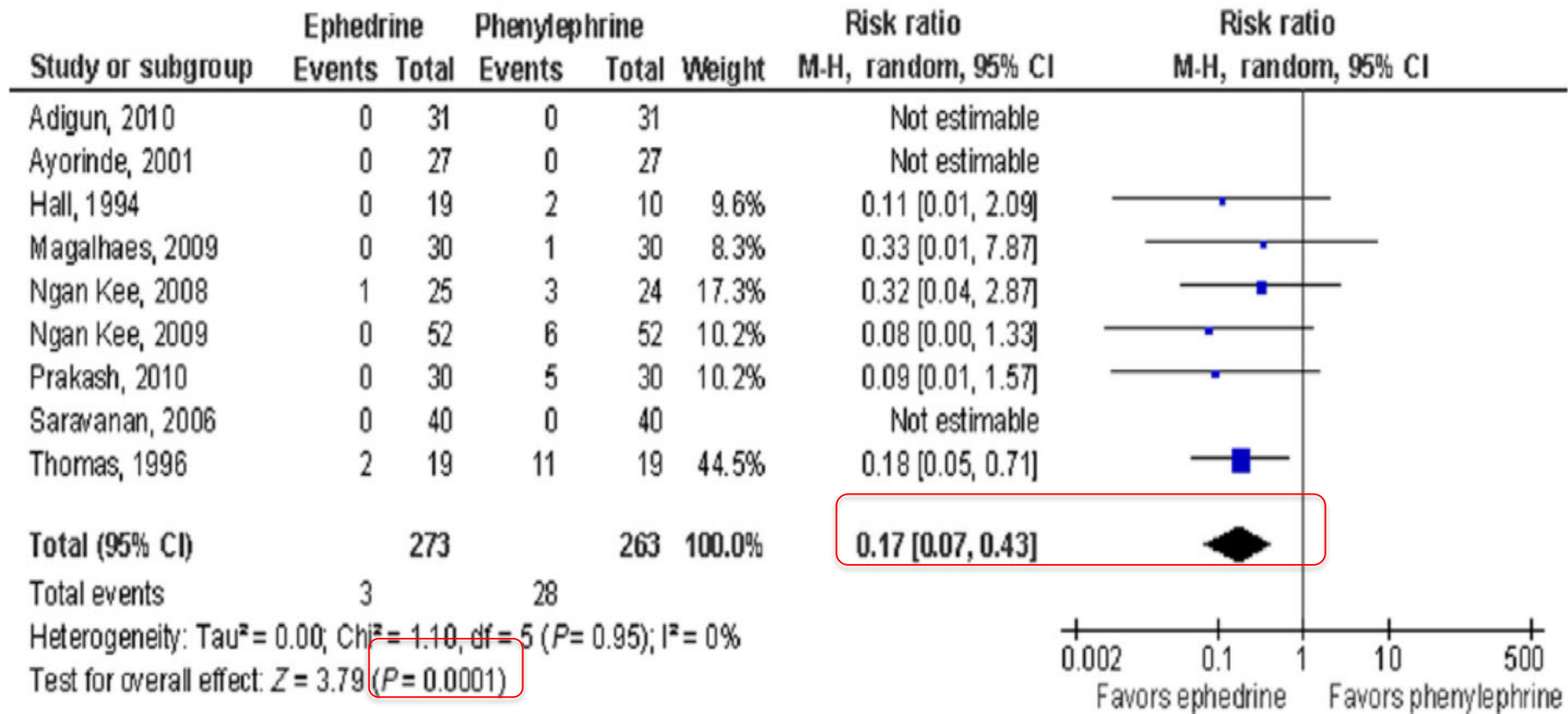


Fig. 4. Maternal bradycardia after ephedrine or phenylephrine. CI, confidence interval.

Vasopressors for the management of hypotension after spinal anesthesia for elective caesarean section.

Systematic review and cumulative meta-analysis

Conclusions: Our analysis could clearly demonstrate a decreased risk of fetal acidosis associated with phenylephrine use. In addition with our findings for BE, this suggests a favorable effect of phenylephrine on fetal outcome parameters. The mechanism of pH depression is not related to $p\text{CO}_2$.

Neonatal effects after vasopressor during spinal anesthesia for cesarean section: a multicenter, randomized controlled trial

K. Uerpaiojkit,^a R. Anusornthanawat,^b A. Sirisabya,^c M. Chaichalothorn,^a
S. Charuluxananan^a

International Journal of Obstetric Anesthesia (2017) 32, 41–47

- ***N = 354 elective CS***
- ***Ephedrine boluses 6 mg vs Phenylephrine 100 µg***
- ***Neonatal outcome***
 - ***HR 10, 30, 45 min***
 - ***SaO₂, capillary blood glucose 30 min, lactate,***
 - ***Urine metamphetamine***

Table 3 Neonatal vital signs and the incidence of tachycardia after birth at 10 and 30–45 minutes

	Ephedrine group (n=177)	Phenylephrine group (n=177)	Mean difference [95% CI]
At 10 min			
HR, beats/min	156 (14.4)	152 (13.8)	4.0 [0.6 to 7.3]*
Tachycardia, %	42.9%	43.5%	
SpO ₂ , %	94 (5.9)	95 (7.6)	−0.7 [−2.6 to 1.1]
At 30–45 min			
HR, beats/min	145 (13.5)	145 (13.2)	0.6 [−2.3 to 3.6]
Tachycardia, %	18.6	22.0	
SpO ₂ , %	98 (1.9)	98 (1.8)	0.2 [−0.6 to 0.2]
BP systolic, mmHg	69 (7.6)	70 (10.9)	−1.2 [−3.6 to 1.2]
BP diastolic, mmHg	37 (7.4)	37 (7.3)	0.3 [−1.8 to 1.9]
Hypertension, n (%)	1 (%)	2 (%)	
Respiratory rate, breaths/min	53 (7.0)	53 (7.4)	−0.2 [−1.8 to 1.4]
Tachypnea, n (%)	18/159 (11.3)	13/154 (8.4)	
Body temperature, °C	37.0 (0.4)	37.1 (1.1)	−0.1 [−0.2 to 0.1]

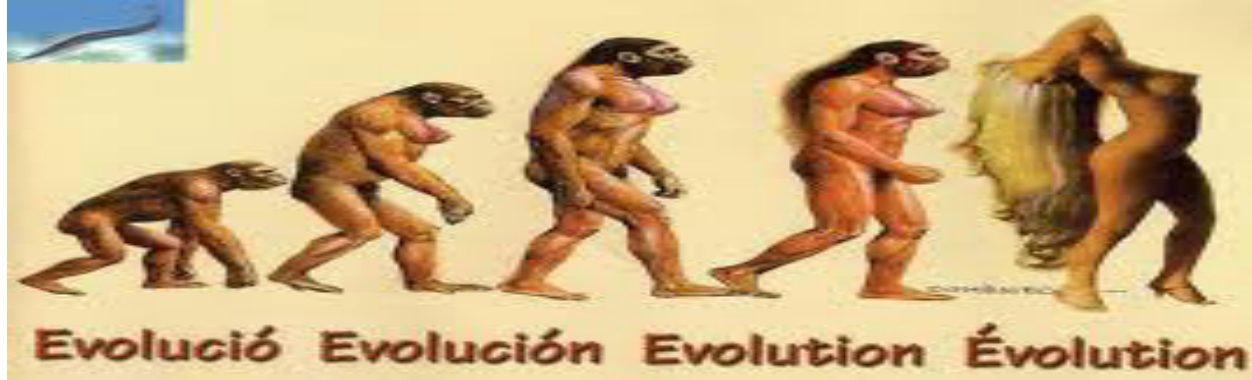
Values are mean (SD). HR: heart rate. BP: blood pressure. SpO₂: oxygen saturation by pulse oximetry. * $P < 0.05$. Tachycardia defined as HR > 160 beats/min; hypertension as systolic BP > 90 mmHg, tachypnea as respiratory rate > 60 breaths/min, hypoxia as SpO₂ $< 85\%$; hyperthermia as $> 37.5^{\circ}\text{C}$.

Table 4 Neonatal Apgar scores, movement, capillary blood glucose, capillary blood lactate, and urine amphetamine

	Ephedrine group (n=177)	Phenylephrine group (n=177)	<i>P</i> -value
1-min Apgar score (0–10)	9 (9–9)	9 (9–9)	0.92
5-min Apgar score (0–10)	10 (10–10)	10 (10–10)	0.41
Neonatal movement score (1–5)	1 (1–3)	1 (1–1)	0.06
Mean CBG, mg/dL	62 (16.4)	59 (13.5)	0.15
Minimum CBG, mg/dL	23	21	
Incidence of hypoglycemia, %	5.6	7.8	0.42
Capillary lactate, mmol/L	1.42 (0.55)	1.25 (0.38)	0.37
Maximum capillary lactate, mmol/L	3.0	1.8	
Positive urine metamphetamine, %	19.1		

Values are median (IQR) or mean (SD) for capillary samples. Neonatal movement score: 1=calm, 2=agitated, 3=crying, 4=critical, 5=intubated. CBG: capillary blood glucose.

Conclusions: Ephedrine, compared to phenylephrine as a vasopressor during cesarean delivery, was associated with higher neonatal heart rate in the early post-birth period, but without a significant difference in clinical outcomes in uncomplicated pregnancies.



Noradrenaline vs Phenylephrine



Randomized Double-blinded Comparison of Norepinephrine and Phenylephrine for Maintenance of Blood Pressure during Spinal Anesthesia for Cesarean Delivery

Warwick D. Ngan Kee

What We Already Know about This Topic

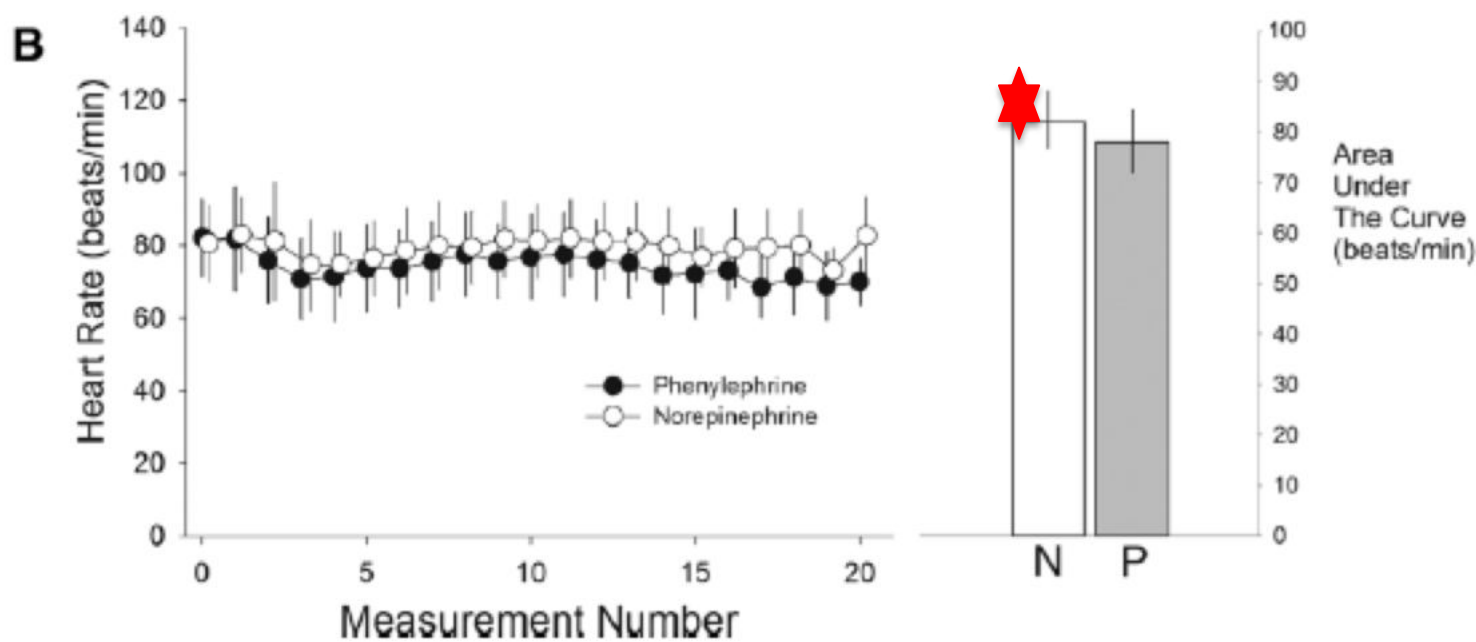
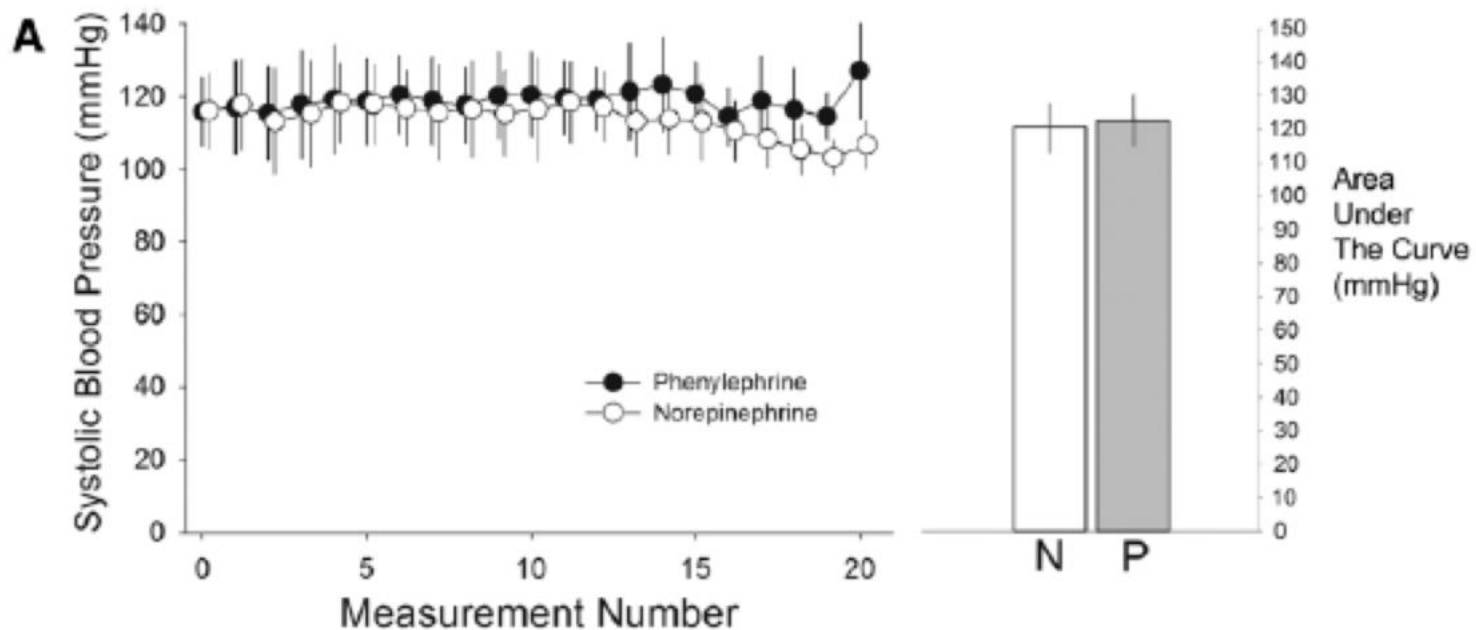
- Although norepinephrine has theoretical advantages over phenylephrine to treat spinal anesthesia-induced hypotension in obstetric patients, it has not been assessed in this setting

What This Article Tells Us That Is New

- In a randomized study of 104 healthy patients undergoing cesarean delivery under spinal anesthesia, maternal blood pressure and Apgar scores of neonates were similar whether norepinephrine or phenylephrine was administered
- Maternal cardiac output and heart rate were greater in women treated with norepinephrine compared with that in women treated with phenylephrine, but further work is needed to assess safety and efficacy of norepinephrine in this setting

Randomized Double-blinded Comparison of Norepinephrine and Phenylephrine for Maintenance of Blood Pressure during Spinal Anesthesia for Cesarean Delivery

- N= 104
- Computer-controlled vasopressor infusion
 - SBP
- Spinal: Hbupi 12mg + F 15 µg
- Coloadng Crystalloid
- **Phénylèphrine:** 0-100 µg/min
- **Norepinephrine:**0-5 µg/min
- **Suprasternal doppler**
 - CO,SV,SVR



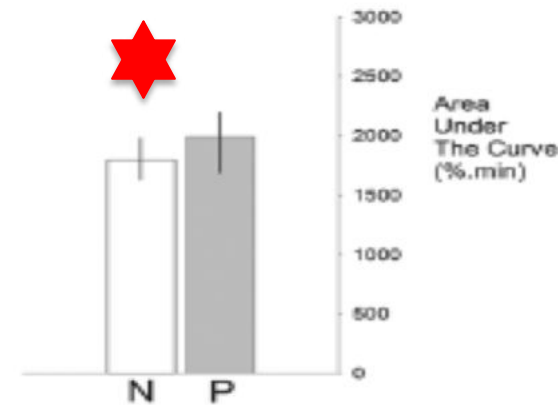
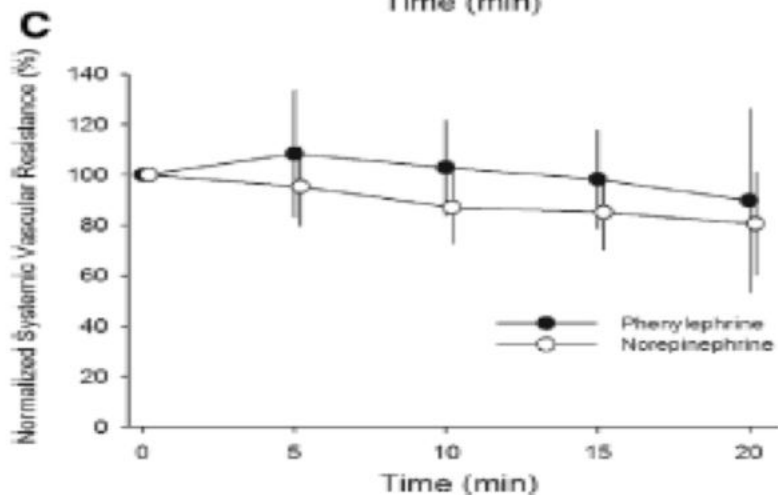
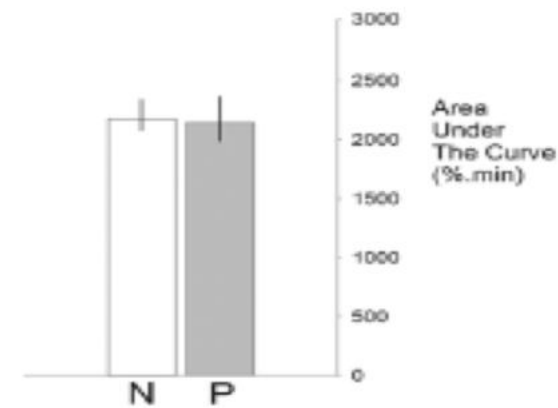
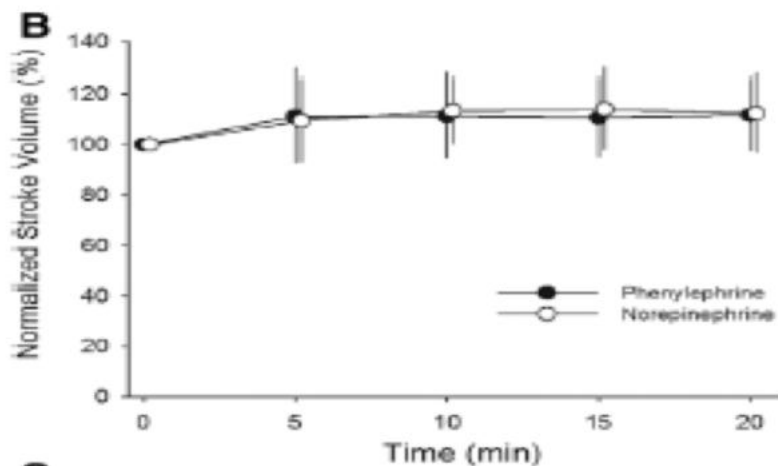
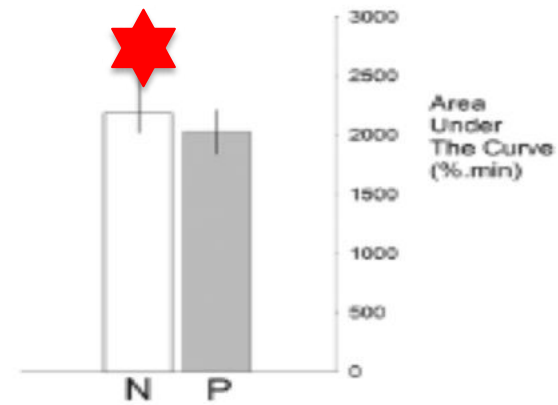
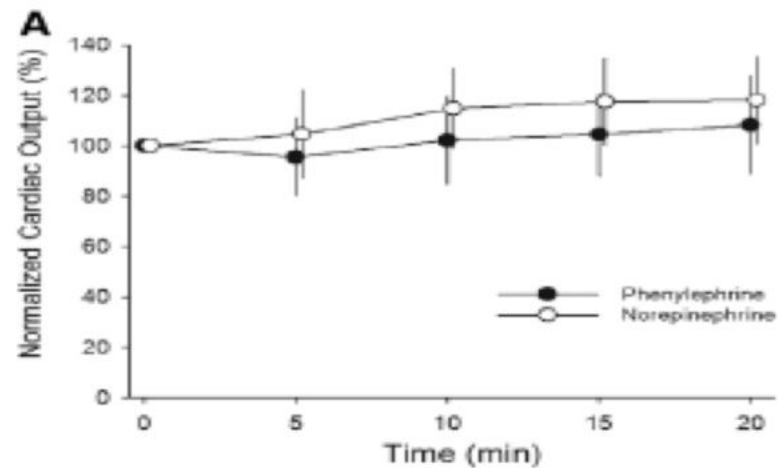


Table 2. Neonatal Outcome

	Norepinephrine Group	Phenylephrine Group	P Value
Birth weight (kg)	3.11 [2.85–3.37]	3.19 [3.04–3.36]	0.37
Apgar score at 1 min <8	0	0	
Apgar score at 5 min <8	0	0	
Umbilical arterial blood gases			
pH	7.30 [7.28–7.33]	7.29 [7.28–7.32]	0.45
Pco ₂ (mmHg)	50 [48–56]	52 [48–56]	0.77
Po ₂ (mmHg)	15 [13–18]	14 [11–16]	0.20
Base excess (mmol/l)	–2.0 [–3.7 to –1.0]	–2.4 [–4.2 to –0.8]	0.87
Oxygen content (ml/dl)	6.0 [4.4–7.7]	5.2 [3.8–7.0]	0.29
Umbilical venous blood gases			
pH	7.35 [7.34–7.37]	7.34 [7.32–7.36]	0.031
Pco ₂ (mmHg)	41 [38–43]	41 [38–45]	0.69
Po ₂ (mmHg)	27 [23–30]	26 [23–28]	0.23
Base excess (mmol/l)	–3.2 [–4.1 to –2.0]	–3.5 [–5.6 to –2.4]	0.06
Oxygen content (ml/dl)	12.7 [11.3–14.4]	11.8 [9.6–13.7]	0.047

Values are median [interquartile range] or number.

Table 3. Umbilical Cord Plasma Concentrations of Epinephrine, Norepinephrine, Glucose, and Lactate

	Phenylephrine Group	Norepinephrine Group	P Value
Umbilical arterial			
Epinephrine (pg/ml)	400 [227–700]	281 [78–491]	0.042
Norepinephrine (pg/ml)	2,178 [1,403–3,921]	1,756 [1,048–2,435]	0.035
Glucose (mg/dl)	46 [43–52]	53 [48–60]	<0.001
Lactate (mmol/l)	1.8 [1.6–2.0]	2.0 [1.7–2.4]	0.088
Umbilical venous			
Epinephrine (pg/ml)	40 [18–73]	23 [18–63]	0.16
Norepinephrine (pg/ml)	457 [281–647]	347 [225–486]	0.031
Glucose (mg/dl)	51 [44–56]	56 [51–62]	<0.001
Lactate (mmol/l)	1.8 [1.6–2.0]	2.0 [1.6–2.4]	0.33

Values are median [interquartile range].

An open-label randomized controlled clinical trial for comparison of continuous phenylephrine versus norepinephrine infusion in prevention of spinal hypotension during cesarean delivery

International Journal of Obstetric Anesthesia (2017) 29, 18–25

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G.R. Hobbs,^a R.E. Shapiro,^a P. Ranganathan^a

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^b*Duquesne University School of Business, Pittsburgh, PA, USA*

In summary, norepinephrine fixed-rate infusion has efficacy for preventing hypotension and can be considered as an alternative to phenylephrine. Future research is needed to assess the safety of norepinephrine, its potency compared to phenylephrine, its use in the parturient with other comorbidities, and to determine the optimal infusion rate and dosing strategy for maintaining maternal hemodynamics under spinal anesthesia for CD.

A Random-allocation Graded Dose–Response Study of Norepinephrine and Phenylephrine for Treating Hypotension during Spinal Anesthesia for Cesarean Delivery

Warwick D. Ngan Kee, M.D., F.A.N.Z.C.A., F.H.K.A.M.

What We Already Know about This Topic

- Norepinephrine is suggested as an alternative to phenylephrine for maintaining blood pressure during spinal anesthesia for cesarean delivery
- Although a recent dose-finding study reported 6 µg norepinephrine bolus injection effective for the purpose, the relative potencies of these two vasopressors have not been fully determined

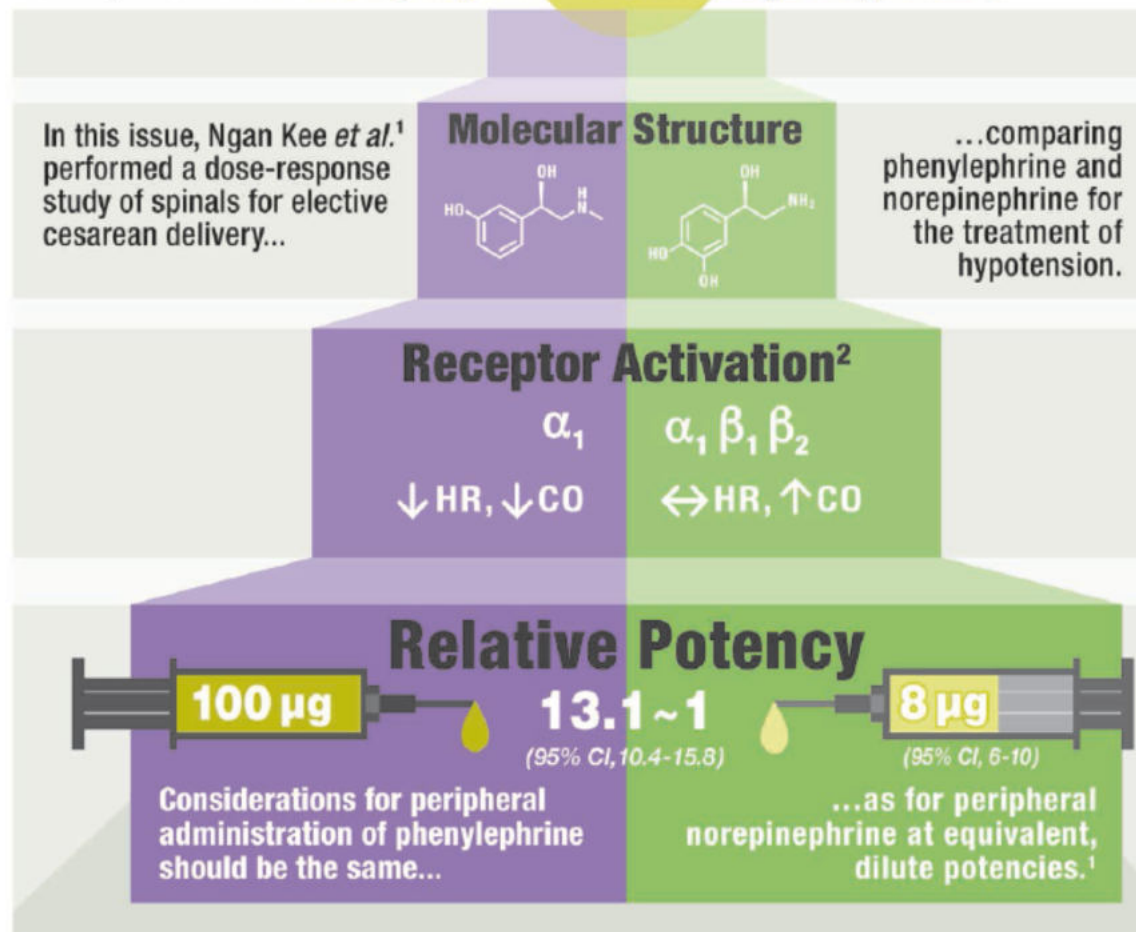
What This Article Tells Us That Is New

- In this random-allocation, graded dose–response study, the relative potencies of the vasopressors were assessed by the proportion of full restoration of systolic blood pressure to the baseline in response to a bolus injection of one of six different doses of the vasopressors in 180 healthy patients undergoing spinal anesthesia for elective cesarean delivery
- The estimated dose equivalent to phenylephrine 100 µg was norepinephrine 7.6 µg (95% CI, 6.3 to 9.6 µg)

Conclusions: Comparative dose–response analysis was completed for norepinephrine and phenylephrine given as a bolus to treat the first episode of hypotension in patients undergoing spinal anesthesia for cesarean delivery. The estimated dose equivalent to phenylephrine 100 µg was norepinephrine 8 µg (95% CI, 6 to 10 µg). These results may be useful to inform the design of future comparative studies. (ANESTHESIOLOGY 2017; 127:934-41)

Pressor *VS.* Pressor

A Comparison of: **Phenylephrine** & **Norepinephrine**



More perfect?

It is clear that the “burden of proof” has not been met to suggest a change from phenylephrine to norepinephrine as the standard approach to prevention and treatment of hypotension during cesarean delivery under spinal anesthesia. Current evidence and logic would suggest that phenylephrine infusion should still be the default approach, both because phenylephrine now has

- Phenylephrine:
 - 15 ans de recul efficacité-sécurité
- NA:
 - propriétés pharmacologiques intéressantes
 - résultats expérimentaux intéressants: DC, bradycardie
 - 1 seule étude avec méthodologie OK
 - Absence de bénéfice clinique démontré

Vasopresseurs & Prééclampsie

A randomised comparison of bolus phenylephrine and ephedrine for the management of spinal hypotension in patients with severe preeclampsia and fetal compromise

R.A. Dyer,^a A. Emmanuel,^a S.C. Adams,^a C.J. Lombard,^b M.J. Arcache,^a A. Vorster,^a C.A. Wong,^c N. Higgins,^c A.R. Reed,^a M.F. James,^a Y. Joolay,^d S. Schulein,^a D. van Dyk^a

Conclusions: In patients with severe preeclampsia and fetal compromise, fetal acid-base status is independent of the use of bolus ephedrine versus phenylephrine to treat spinal hypotension.

Methods

- **133 severe PE patient requiring CS for NRFHR**
 - **Exclusion:**
 - **Persitent bradycardia, GA < 28 W, EFW < 900 g, twin**
- **Spinal: HBupi 10mg + fentanyl 10µg**
- **Preload: 300 ml 6% HES**
- **O2 face mask**
 - **64 requiring vasopressor treatment randomized**
 - **↓ 20% MAP & MAP < 110 mmHg**
 - **32 Phenylephrine boluses 50 µg (X2 if ↓30% MAP)**
 - **32 Ephedrine boluses 7.5 mg (X2 if ↓30% MAP)**
 - **Cross over if Ineffective 45 mg ephedrine or 300 µg Phenylephrine**
 - **Ephedrine ± atropine for hypotension + bradycardia**

Table 1 Patient characteristics and intra-operative data

	Complete cohort (n=129)	Ephedrine (n=32)	Phenylephrine (n=32)
Age, y [mean (SD)]	26 (6)	24 (6)	26 (6)
BMI, kg/m ² [mean (SD)]	30 (6)	29 (6)	32 (6)
Gravidity, median (range)	2 (1–5)	1 (1–5)	2 (1–5)
Parity, median (range)	0 (0–4)	0 (0–4)	1 (0–3)
MgSO ₄ therapy (n)	115 (89%)	29 (90%)	31 (97%)
Hydralazine therapy (n)	58 (45%)	16 (50%)	17 (53%)
In labour (n)	25 (19%)	5 (15%)	9 (28%)
Baseline MAP, mmHg [mean (SD)]	127(14)	128 (14)	128 (15)
SBP >160 mmHg (n)	121 (94%)	30 (94%)	30 (94%)
Proteinuria 3–4 + (n)	98 (76%)	19 (60%)	28 (88%)
Gestational age, weeks [mean (SD)]	32.7 (3.3)	33.0 (3.7)	33.6 (3.6)
Neonatal weight, g [mean (SD)]	1676 (747)	1744 (787)	1988 (860)
Placental weight, g [mean (SD)]	380 (135)	392 (120)	420 (139)
TOTI, min	19 (6)	18 (5)	19 (5)
TIUI, min	12 (3)	12 (3)	12 (3)
TUID, s	57 (42)	54 (29)	66 (64)
D–D interval, min	67 (33)	62 (23)	70 (32)
Nausea (n)	5 (4%)	1 (3%)	2 (6%)
Vomiting (n)	9 (7%)	5 (15%)	2 (6%)
Ephedrine pre-delivery, mg [median (range)]	Nil in 65 cases	15 (7.5–45)	–
Phenylephrine pre-delivery, µg [median (range)]	Nil in 65 cases	–	100 (50–650)

BMI: body mass index; MgSO₄: magnesium sulphate; MAP: mean arterial pressure; SBP: systolic blood pressure; TOTI: time from arrival in theatre to induction of spinal anaesthesia; TIUI: time from induction of spinal anaesthesia to uterine incision; TUID: time from uterine incision to delivery; D–D: decision to delivery.

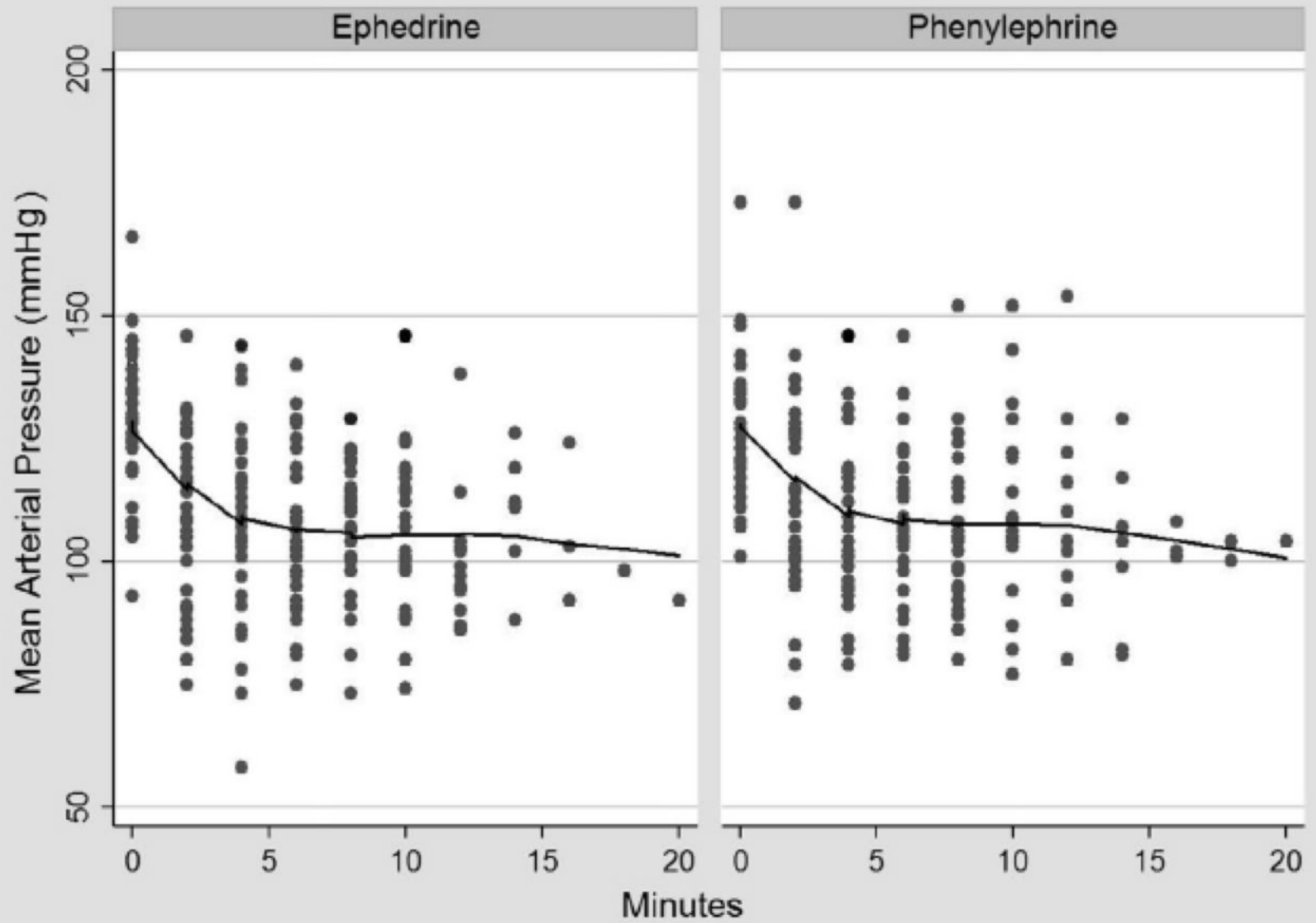


Table 2 Blood gas data and neonatal outcome

Blood gas parameters	Entire cohort (n=133)	Ephedrine (n=32)	Phenylephrine (n=32)	Mean difference	95% CI	P-value
Neonatal umbilical arterial mean (SD)]	Analysed: n=121	Analysed: n=31	Analysed: n=29			
pH	7.25 (0.09)	7.25 (0.08)	7.22 (0.10)	0.03	-0.02 to 0.08	0.22
PCO ₂ (kPa)	6.9 (1.37)	6.72 (1.29)	7.00 (1.58)	-0.28	-1.02 to 0.46	0.45
PO ₂ (kPa)	1.68 (0.69)	1.92 (0.78)	1.71 (0.76)	0.21	-0.19 to 0.62	0.30
Base excess (mmol/L)	-4.35 (4.08)	-4.81 (3.73)	-5.97 (4.60)	1.16	-1.00 to 3.32	0.29
Standard bicarbonate (mmol/L)	18.52 (3.06)	18.1 (3.02)	17.5 (3.48)	0.64	-1.04 to 2.32	0.45
Lactate (mmol/L)	3.56 (2.36)	3.76 (2.20)	3.82 (2.81)	-0.06	-1.37 to 1.25	0.93
Neonatal umbilical venous mean (SD)]	n=128	n=31	n=32			
pH	7.28 (0.08)	7.28 (0.07)	7.27 (0.10)	0.01	-0.03 to 0.06	0.55
PCO ₂ (kPa)	6.23 (1.3)	6.20 (1.24)	6.31 (1.34)	-0.11	-0.76 to 0.54	0.74
PO ₂ (kPa)	2.53 (0.73)	2.79 (0.68)	2.39 (0.62)	0.39	0.06 to 0.72	0.02
Base excess (mmol/L)	-4.48 (3.71)	-4.65 (3.89)	-5.36 (3.60)	0.72	-1.17 to 2.61	0.45
Standard bicarbonate (mmol/L)	19 (2.96)	18.9 (3.16)	18.2 (3.05)	0.64	-0.93 to 2.22	0.42
Lactate (mmol/L)	3.25 (2.29)	3.41 (2.18)	3.28 (2.44)	0.14	-1.04 to 1.32	0.81
Maternal arterial mean (SD)]	n=126	n=32	n=30			
pH	7.41 (0.03)	7.39 (0.04)	7.40 (0.03)	-0.01	-0.02 to 0.01	0.57
PCO ₂ (kPa)	4.07 (0.47)	4.11 (0.42)	3.94 (0.53)	0.17	-0.07 to 0.41	0.17
PO ₂ (kPa)	17.09 (5.92)	17.1 (5.07)	17.7 (6.62)	-0.60	-3.50 to 2.40	0.71
Base excess (mmol/L)	-4.8 (2.79)	-5.67 (2.57)	-6.05 (3.0)	0.38	-1.02 to 1.79	0.59
Standard bicarbonate (mmol/L)	20.87 (2.22)	20.1 (2.13)	19.9 (2.30)	0.30	-0.90 to 1.40	0.64
Lactate (mmol/L)	1.3 (0.6)	1.60 (0.53)	1.34 (0.55)	0.27	-0.01 to 0.54	0.06
Neonatal outcome						
UA pH <7.2 (n)	20/121 (16.5%)	6/31 (19%)	8/29 (28%)	-8.2%	-29.6 to 13.2%	0.45
UA base excess >10 mmol/L (n)	11/121 (9%)	4/31 (13%)	4/29 (14%)	-1.0%	-18.1 to 16.3%	0.92
1-min Apgar score (median [range])	8 [2-10]	8 [4-10]	8 [4-9]			
1-min Apgar score <7 (n)	41 (32%)	10 (31%)	12 (38%)	-6.3%	-29.5 to 17.0%	0.60
5-min Apgar score (median [range])	9 [4-10]	9 [7-10]	9 [7-10]			
5-min Apgar score <7 (n)	3 (2%)	0	0			
Intubation in OT (n)	0	1 (3%)	0			
Mortality prior to discharge NICU (n)	3 (2%)	0	0			
IVH grade 3 or 4 (n)	3 (2%)	0	0			
HIE (n)	0	0	0			

UA: umbilical arterial; OT: operating theatre; NICU: neonatal intensive care unit; IVH: intraventricular haemorrhage; HIE: hypoxic ischaemic encephalopathy.

In conclusion, the important finding of this study is that fetal acid-base status is independent of whether phenylephrine or ephedrine is used as a bolus to treat spinal hypotension in patients with severe preeclampsia. The choice of vasopressor should be based upon maternal haemodynamic responses in the individual case.

The Effect of Prophylactic Phenylephrine and Ephedrine Infusions on Umbilical Artery Blood pH in Women With Preeclampsia Undergoing Cesarean Delivery With Spinal Anesthesia: A Randomized, Double-Blind Trial

Nicole Higgins, MD,* Paul C. Fitzgerald, RN,* Dominique van Dyk, FCA (SA),† Robert A. Dyer, FCA (SA), PhD,† Natalie Rodriguez, BS,* Robert J. McCarthy, PharmD,* and Cynthia A. Wong, MD*

CONCLUSIONS: We were unable to demonstrate a beneficial effect of phenylephrine on umbilical artery pH compared with ephedrine. Our findings suggest that phenylephrine may not have a clinically important advantage compared with ephedrine with regard to improved neonatal acid-base status when used to prevent spinal anesthesia-induced hypotension in women with preeclampsia undergoing cesarean delivery. (Anesth Analg 2017;XXX:00–00)

- ***RCT , N= 110 (108 analyzed: 2 X 54)***
- ***Elective CS in PE Women (50% severe, GA 36W)***
 - ***Exclusion:***
 - *Labour, BMI > 40, emergency procedures, eclampsia*
 - ***Spinal:***
 - *Hbupi 12mg + Fentanyl 15 µg + M* 150*
 - *Coloading 500ml lactated Ringer*
 - *Nasal O2: 2-4 l/min*
 - ***Prophylactic vasopressor infusion***
 - *Phenylephrine (100 µg/ml)*
 - *Ephedrine (8 mg/ml)*
 - » *Potency ratio = 80/1*
 - *Infusion rate 1ml/min for 2 min then titrated for SBP ≥ 80% baseline*
 - *All women received study drug initially*
 - *30% stopped and not restarted after 2 min*

Table 3. Umbilical Blood Gases and Infant Outcomes

	Ephedrine (n = 74)	Phenylephrine (n = 72)	Difference ^a (95% CI of the Difference)	P
Umbilical artery blood gases				
pH	7.20 [0.10]	7.22 [0.07]	-0.02 (-0.06 to 0.07) ^a	.38
Paco ₂ (mm Hg)	58 (53, 70)	59 (55, 65)	-1 (-4 to 3)	.63
Pao ₂ (mm Hg)	18 (13, 24)	17 (13, 22)	1 (-1 to 5)	.20
Base excess (mEq/L)	-3.4 (-5.7, -2.0)	-2.8 (-4.6, -2.2)	-0.6 (-1.6 to 0.3)	.10
Umbilical vein blood gases				
pH	7.27 [0.08]	7.26 [0.07]	0.01 (-0.02 to 0.04) ^a	.17
Paco ₂ (mm Hg)	47 (40, 53)	53 (47, 59)	-6.5 (-11.5 to -1)	.007
Pao ₂ (mm Hg)	24 (19, 33)	21 (16, 27)	3 (-1.5 to 9.5)	.03
Umbilical artery pH <7.2, n (%)	24 (37)	18 (31)	6% (-12% to 24%)	.25
Apgar scores				
1 min	8 (7, 8)	8 (7, 8)	0 (0-0)	.51
5 min	9 (8, 9)	9 (9, 9)	0 (0-0)	.89
Neonatal intensive care unit admission, n (%)	37 (50)	31 (43)	7% (-10% to 24%)	.69

Table 4. Sensitivity Analysis for Umbilical Artery pH^a

	Ephedrine	Phenylephrine	Difference ^a (95% CI of the Difference)	P
Adjusted for gender and gestational age equal to 37 wk	7.18 [0.11]	7.20 [0.07]	-0.02 (-0.06 to 0.01)	.42
Magnesium therapy				
No	7.19 [0.10]	7.22 [0.07]	-0.03 (-0.07 to 0.01)	.10
Yes	7.20 [0.10]	7.20 [0.07]	0 (-0.06 to 0.06)	.34
Severity of preeclampsia				
Without severe features	7.17 [0.12]	7.21 [0.08]	-0.04 (-0.09 to 0.01)	.68
With severe features	7.21 [0.08]	7.22 [0.06]	-0.01 (-0.04 to 0.03)	.41

Maternal cardiac output response to colloid preload and vasopressor therapy during spinal anaesthesia for caesarean section in patients with severe pre-eclampsia: a randomised, controlled trial

Anaesthesia 2018, 73, 23-31

R. A. Dyer,¹ A. Daniels,² A. Vorster,³ A. Emmanuel,³ M. J. Arcache,³ S. Schulein,³ A. R. Reed,³ C. J. Lombard,⁴ M. F. James⁵ and D. van Dyk³

In conclusion, we found that cardiac output increased in response to spinal anaesthesia in women with severe early onset pre-eclampsia, and that a small dose of phenylephrine reversed the haemodynamic changes more effectively than ephedrine. Phenylephrine is an effective vasopressor in the management of spinal hypotension in patients with severe pre-eclampsia and preserved left ventricular systolic function. Colloid preload for spinal anaesthesia for caesarean section in treated severe pre-eclampsia was associated with a mean increase in cardiac index, but considerable variability in stroke volume responsiveness, suggesting that fluid restriction is preferable in the absence of cardiac output monitoring.

- N= 42 PE sévère & précoce
- CS rachianesthésie
- Colloid preload 300 ml
 - 20 hypotension
 - 10: boluses 50 µg phenylephrine
 - 10: boluses 7.5 mg ephedrine
- LiDCO
- Primary outcome:
 - % change CI (150 sec)

Post-spinal, Pre-vasopressor

Table 3 Comparison between baseline and pre-vasopressor haemodynamic values in 20 patients who developed spinal hypotension. Values are mean (SD) or mean (percentage change).

	Baseline	Pre-vasopressor	Mean difference	95%CI	p value
Cardiac output; $\text{l} \cdot \text{min}^{-1}$	9.7 (2.6)	10.8 (4.1)	1.1 (11.3%)	0.1 to 2.2	0.0362
Cardiac index; $\text{l} \cdot \text{min} \cdot \text{m}^{-2}$	5.2 (1.2)	5.8 (1.9)	0.6 (11.5%)	0.1 to 1.1	0.0379
Systemic vascular resistance; dyne.s.cm ⁻⁵	1132.0 (364.6)	833.6 (327.2)	-298.5 (-26.4%)	-359.9 to -237.0	< 0.0001
Systemic vascular resistance index; dyne.s.cm ⁻⁵ .m ⁻²	2093.9 (644.1)	1539.9 (604.7)	-554.0 (-26.5%)	-662.0 to -446.0	< 0.0001
Systolic arterial pressure; mmHg	190.7 (19.1)	151.5 (13.4)	-39.2 (-20.6%)	-46.4 to -32.0	< 0.0001
Mean arterial pressure; mmHg	134.5 (15.3)	105.5 (10.0)	-29.0 (-21.5%)	-33.6 to -24.5	< 0.0001
Diastolic arterial pressure; mmHg	103.2 (11.7)	83.3 (9.1)	-19.9 (-19.3%)	-23.3 to -16.5	< 0.0001
Stroke volume; ml	110.9 (18.0)	108.7 (26.3)	-2.1 (-1.9%)	-10.8 to 6.6	0.6173
Stroke volume index; $\text{ml} \cdot \text{m}^{-2}$	59.4 (8.8)	58.0 (11.4)	-1.4 (-2.4%)	-5.9 to 3.2	0.5302
Heart rate; beats.min ⁻¹	87.8 (17.7)	97.7 (19.8)	10.0 (11.4%)	6.3 to 13.7	< 0.0001

Post-vasopressor

pH, BE, lactate: NS

Table 4 Haemodynamic parameter means and mean changes in response to ephedrine and phenylephrine during the 150-s measurement period. Values are mean (SD) or mean (95%CI).

	Ephedrine n = 10	Phenylephrine n = 10	Difference	p value
Heart rate; beats.min ⁻¹	101.2 (17.8)	88.8 (16.3)	12.3 (-3.7 to 28.4)	0.1237
% change	5.3 (12.6)	-9.1 (3.4)	↓ 14.4 (5.7 to 23.1)	0.0027
Mean arterial pressure; mmHg	102.6 (16.1)	115.1 (11.2)	-12.5 (-25.5 to 0.5)	0.0590
% change	0.5 (13.1)	5.9 (7.8)	-5.4 (-15.6 to 4.7)	0.2764
Systolic blood pressure; mmHg	146.4 (16.9)	161.0 (16.8)	-14.5 (-30.4 to 1.3)	0.0701
% change	0.7 (12.5)	2.7 (9.3)	-1.9 (-12.3 to 8.4)	0.6917
Diastolic blood pressure; mmHg	82.2 (13.2)	90.9 (6.9)	-8.6 (-18.5 to 1.3)	0.0837
% change	1.6 (12.2)	6.5 (5.8)	-4.9 (-13.9 to 4.1)	0.2686
Stroke volume; ml	108.6 (31.0)	103.5 (20.2)	5.0 (-19.6 to 29.6)	0.6715
% change	-1.5 (10.6)	-3.0 (9.2)	1.5 (-7.8 to 10.8)	0.7402
Stroke volume index; ml.m ⁻²	57.9 (14.5)	55.3 (8.0)	2.6 (-8.4 to 13.6)	0.6284
Systemic vascular resistance; dyne.s.cm ⁻⁵	813.8 (383.7)	1031.8 (342.4)	↑ -218.0 (-559.7 to 123.7)	0.1968
% change	-1.9 (10.5)	22.3 (7.5)	↑ -24.2 (-32.7 to -15.6)	< 0.0001
Systemic vascular resistance index; dyne.s.cm ⁻⁵ .m ⁻²	1507.7 (724.5)	1888.9 (552.5)	-381.1 (-986.4 to 224.2)	0.2025
Cardiac output; l.min ⁻¹	11.1 (4.3)	9.3 (3.2)	1.8 (-1.7 to 5.4)	0.2910
% change	2.6 (6.0)	-12.0 (7.3)	↓ 14.6 (8.3 to 20.8)	0.0001
Cardiac index; l.min.m ⁻²	5.9 (2.0)	4.9 (1.3)	1.0 (-0.6 to 2.6)	0.2160



Conclusions



International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia

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Recommendations for best clinical practice

- 1 Hypotension following spinal or combined spinal-epidural anaesthesia at caesarean section causes both maternal and fetal/neonatal adverse effects.
- 2 Hypotension is frequent and, therefore, vasopressors should be used routinely and preferably prophylactically.

- 3 α -agonist drugs are the most appropriate agents to treat or prevent hypotension following spinal anaesthesia. Although those with a small amount of β -agonist activity may have the best profile (noradrenaline (norepinephrine), metaraminol), phenylephrine is currently recommended due to the amount of supporting data. Single-dilution techniques, and/or prefilled syringes should be considered.

- 4 Left lateral uterine displacement and intravenous (i.v.) colloid pre-loading or crystalloid coload, should be used in addition to vasopressors.
- 5 The aim should be to maintain systolic arterial pressure (SAP) at $\geq 90\%$ of an accurate baseline obtained before spinal anaesthesia, and avoid a decrease to $< 80\%$ baseline. We recommend a variable rate prophylactic infusion of phenylephrine using a syringe pump. This should be started at $25\text{--}50 \mu\text{g}\cdot\text{min}^{-1}$ immediately after the intrathecal local anaesthetic injection, and titrated to blood pressure and pulse rate. Top-up boluses may be required.

- 6 Maternal heart rate can be used as a surrogate for cardiac output if the latter is not being monitored; both tachycardia and bradycardia should be avoided.
- 7 When using an α -agonist as the first-line vasopressor, small doses of ephedrine are suitable to manage $SAP < 90\%$ of baseline combined with a low heart rate. For bradycardia with hypotension, an anticholinergic drug (glycopyrronium (glycopyrrolate) or atropine) may be required. Adrenaline (epinephrine) should be used for circulatory collapse.

- 8 The use of smart pumps and double (two drug) vasopressor infusions can lead to greater cardiovascular stability than that achieved with physician-controlled infusions.

A Randomized Double-Blinded Comparison of Phenylephrine and Ephedrine Infusion Combinations to Maintain Blood Pressure During Spinal Anesthesia for Cesarean Delivery: The Effects on Fetal Acid-Base Status and Hemodynamic Control

CONCLUSIONS: When varying combinations of phenylephrine and ephedrine were given by infusion to maintain arterial blood pressure during spinal anesthesia for cesarean delivery, as the proportion of phenylephrine decreased and the proportion of ephedrine increased, hemodynamic control was reduced and fetal acid-base status was less favorable. Combinations of phenylephrine and ephedrine appear to have no advantage compared with phenylephrine alone when administered by infusion for the prevention of hypotension associated with spinal anesthesia for cesarean delivery.

- 9 Women with pre-eclampsia develop less hypotension after spinal anaesthesia than healthy women. Abrupt decreases in blood pressure are undesirable because of the potential for decreased uteroplacental blood flow. A prophylactic vasopressor infusion may not be required but, if used, should be started at a lower rate than for healthy women.
- 10 Women with cardiac disease should be assessed on an individual basis; some conditions are best managed with phenylephrine (an arterial constrictor without positive inotropic effect), whereas others respond best to ephedrine (producing positive inotropic and chronotropic effect).

Merci



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