Use of vasopressor during spinal anesthesia for cesarean delivery: from ephedrine to norepinephrine

Jose Carvalho MD PhD FANZCA FRCPC

Director of Obstetric Anesthesia, Mount Sinai Hospital

Professor of Anesthesia and Obstetrics and Gynecology, University of Toronto

No disclosures related to this lecture

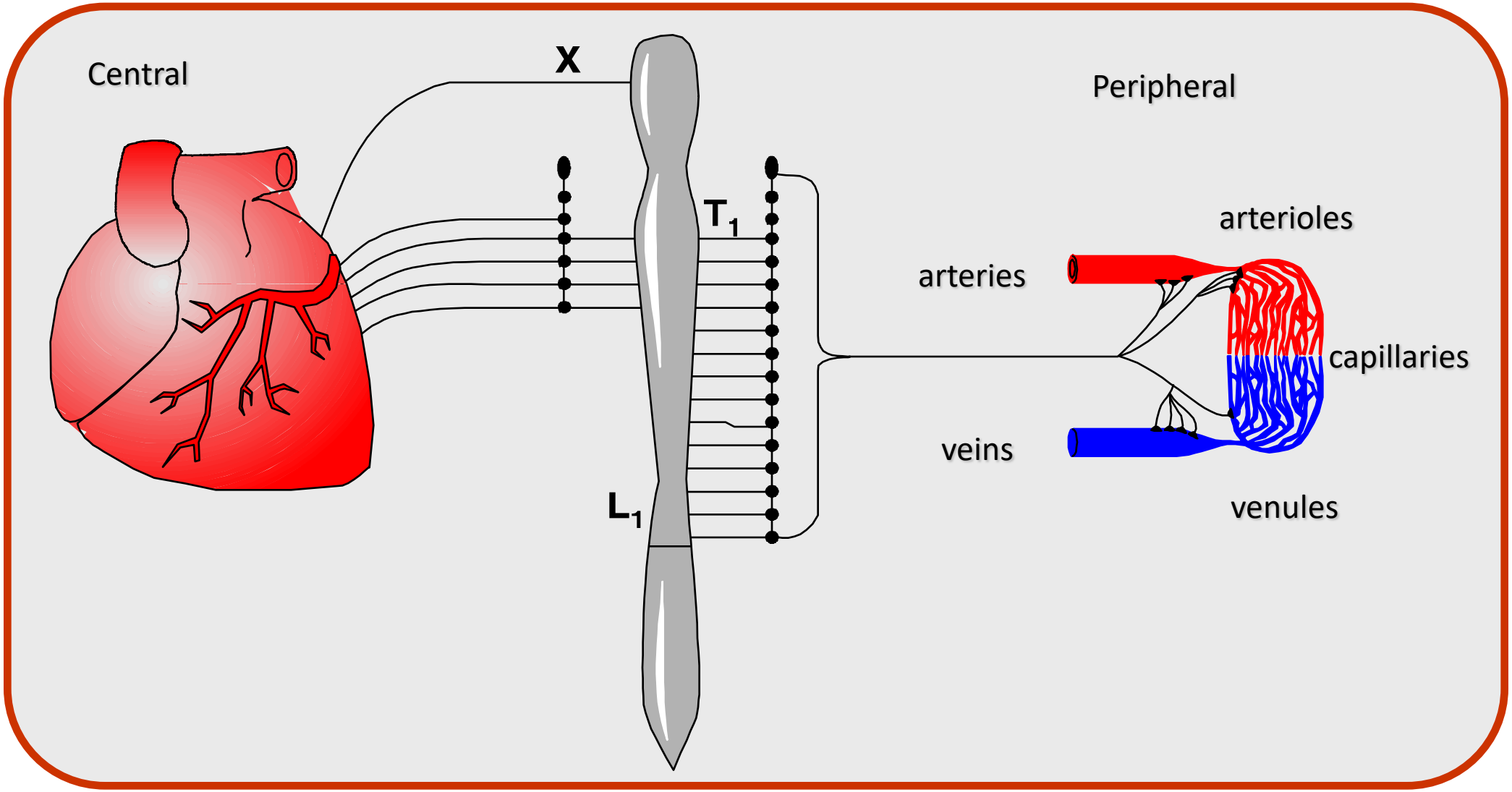
Objectives:

- Physiology of spinal anesthesia
- Maintenance of uteroplacental blood flow
  - aortocaval compression alleviation
  - acute volume expansion with crystalloid/colloid
  - vasopressors
    - ephedrine
    - phenylephrine/metaraminol
    - norepinephrine
  - Best practices

Maintenance of Uteroplacental Blood Flow (1980's)

Acute preload
Left uterine displacement
Trendelenburg
Short induction-delivery time
Normoglycemia
Vasopressors (ephedrine)

Cardiovascular Effects of Neuraxial Anesthesia



Anesthesiology 2008; 109:856–63 Copyright © 2008, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

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.†*

Bupivacaine 10 mg - phenylephrine 0.25 mcg/kg/min

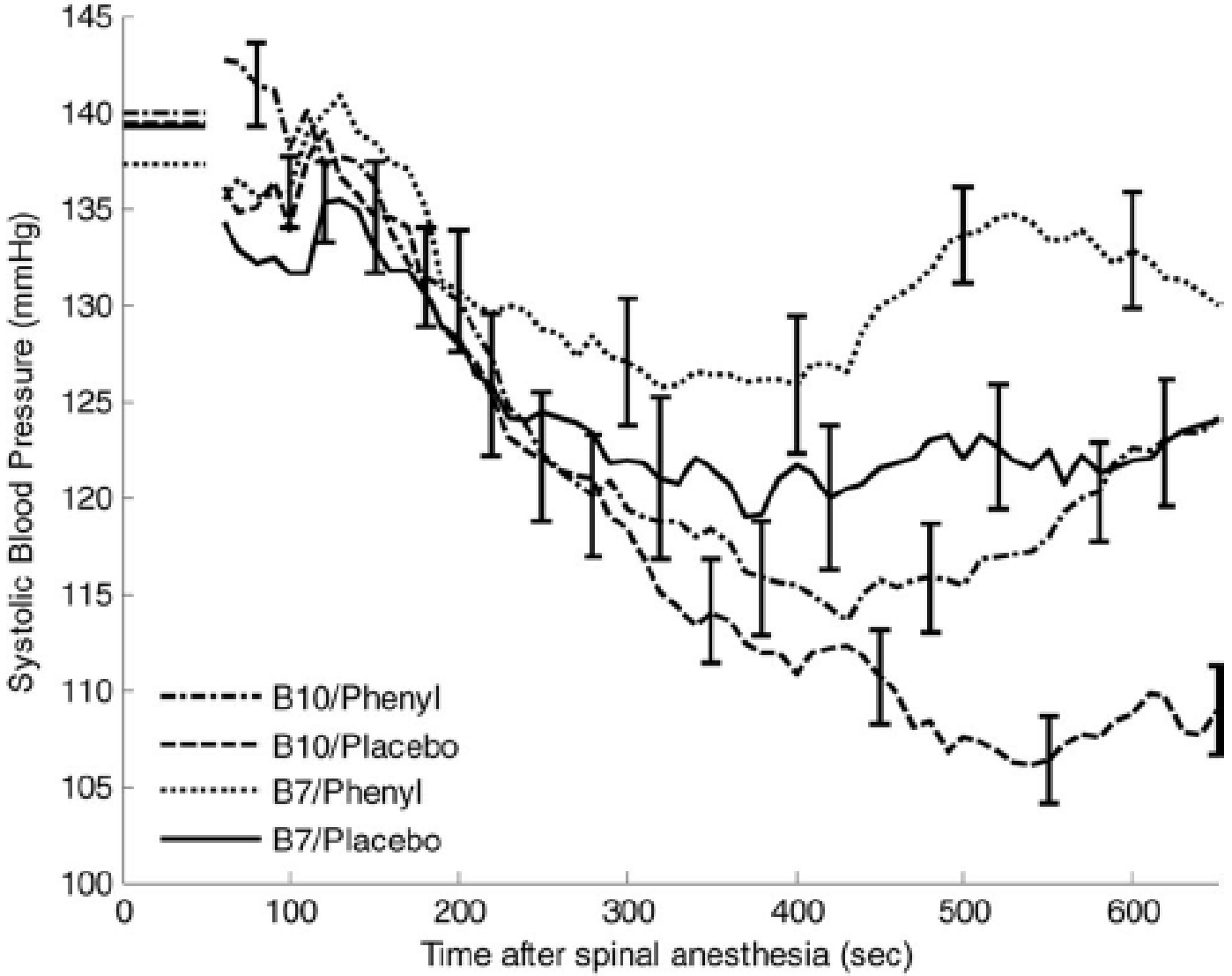
Bupivacaine 10 mg - placebo

Bupivacaine 7 mg - phenylephrine 0.25 mcg/kg/min

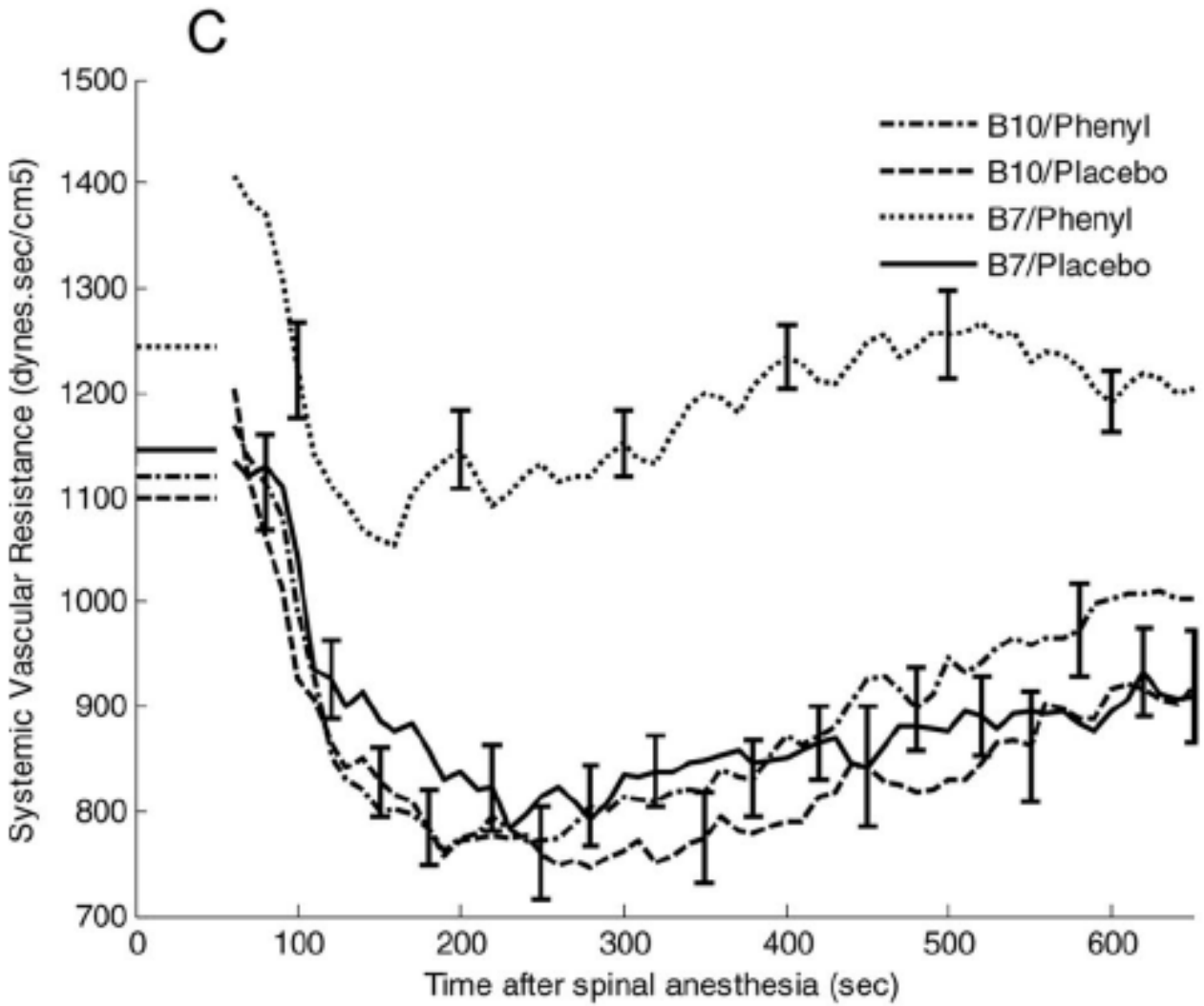
Bupivacaine 7 mg – placebo

* All groups received sufentanil 4 mcg

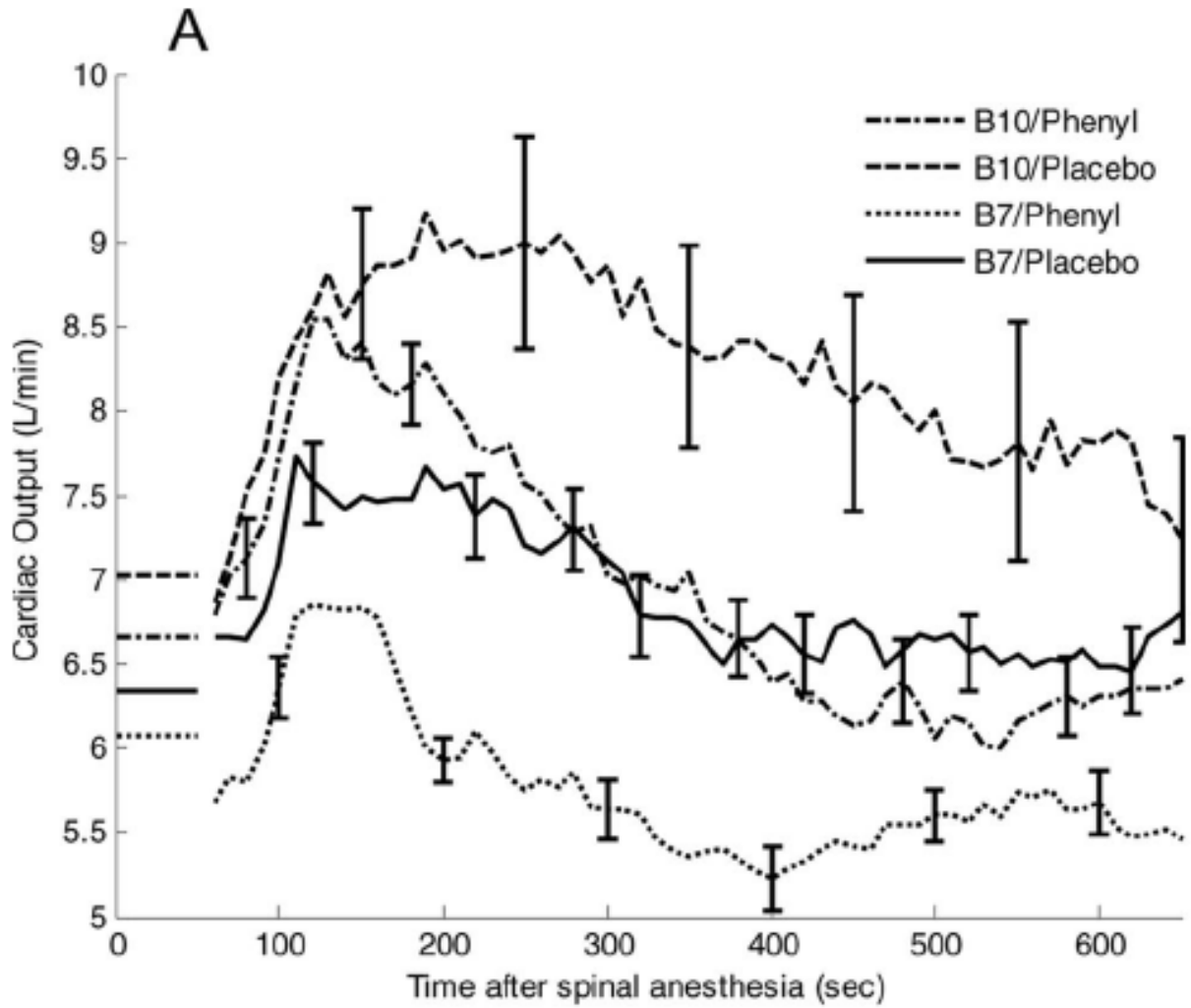
Hemodynamic trends with Lidcoplus



Langesaeter et al. Anesthesiology 2008;109:856-63

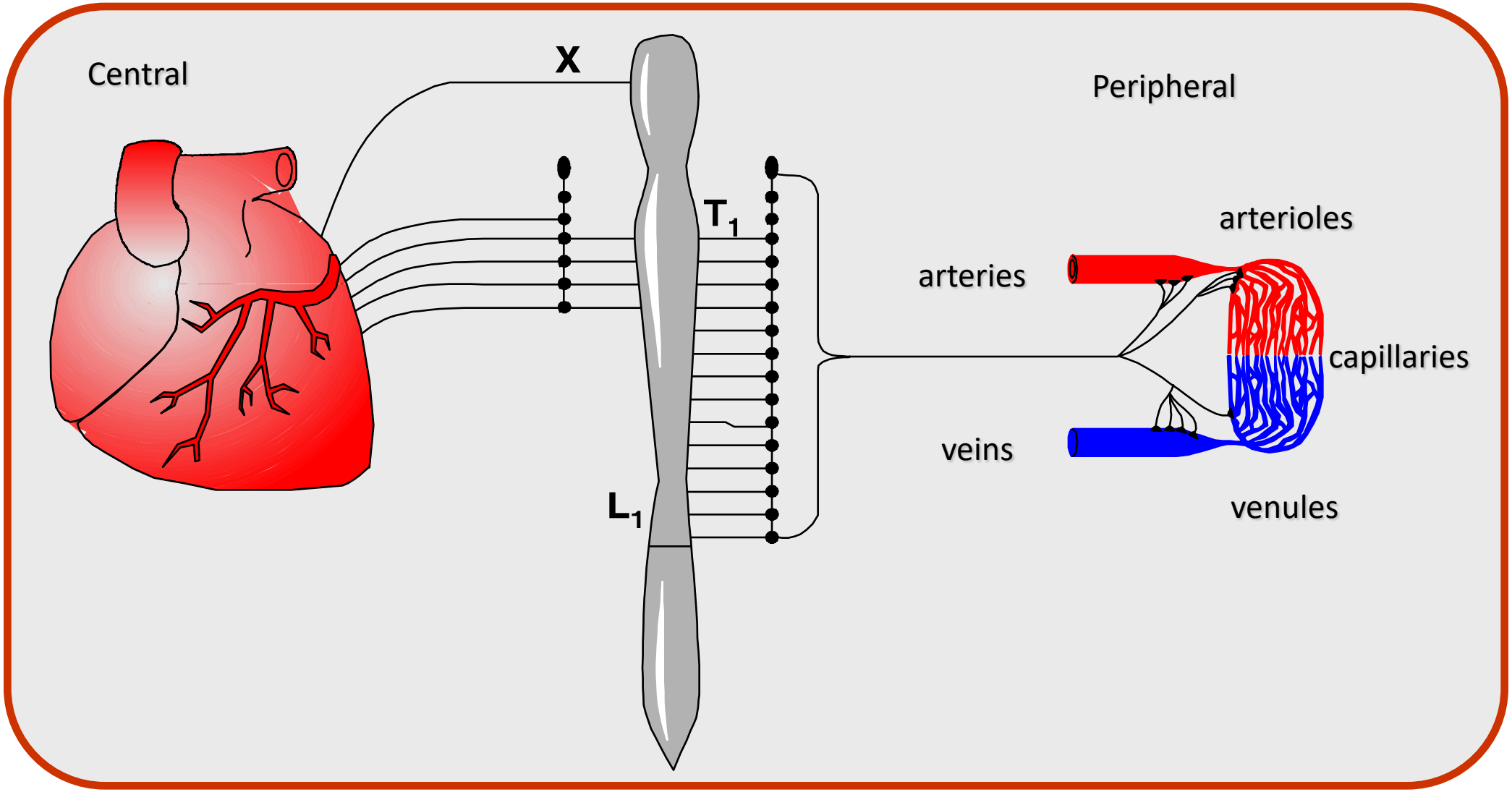


Langesaeter et al. Anesthesiology 2008;109:856-63



Langesaeter et al. Anesthesiology 2008;109:856-63

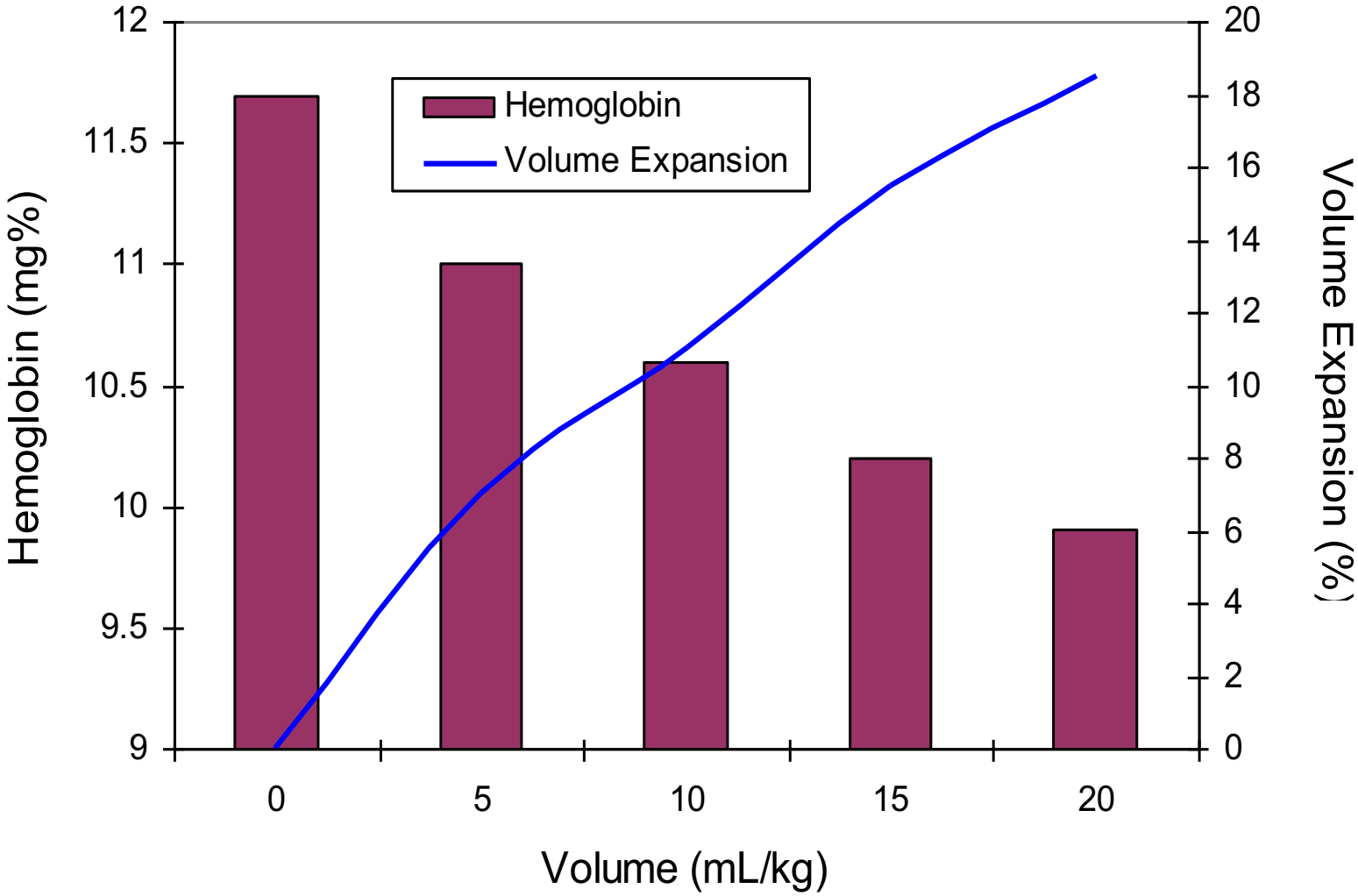
Cardiovascular Effects of Neuraxial Anesthesia



Fluid administration at Cesarean Delivery
Current Concepts

- ✓ Reduced volumes of crystalloid
- ✓ Co-loading has replaced pre-loading

Crystalloid Preload at Cesarean Delivery



Carvalho JCA et al. Int Anesthesiol Clin,1994;32(2):103

Co-loading for Spinal Anesthesia for Cesarean Section

50 patients, elective CS under spinal anesthesia

Preload: 20 ml/kg Ringer's lactate over 20 minutes preceding the spinal

Coload: 20 ml/kg Ringer's lactate under pressurized giving set @ spinal tap

	Preload	Coload
Volume infused (ml)	1474	1386
Duration of infusion (min)	20	10 *
Ephedrine predelivery (mg)	10	0 *
Pts not requiring ephedrine pre del	9/25	16/25 *
UA base deficit (mmol/l)	0.32	1.11

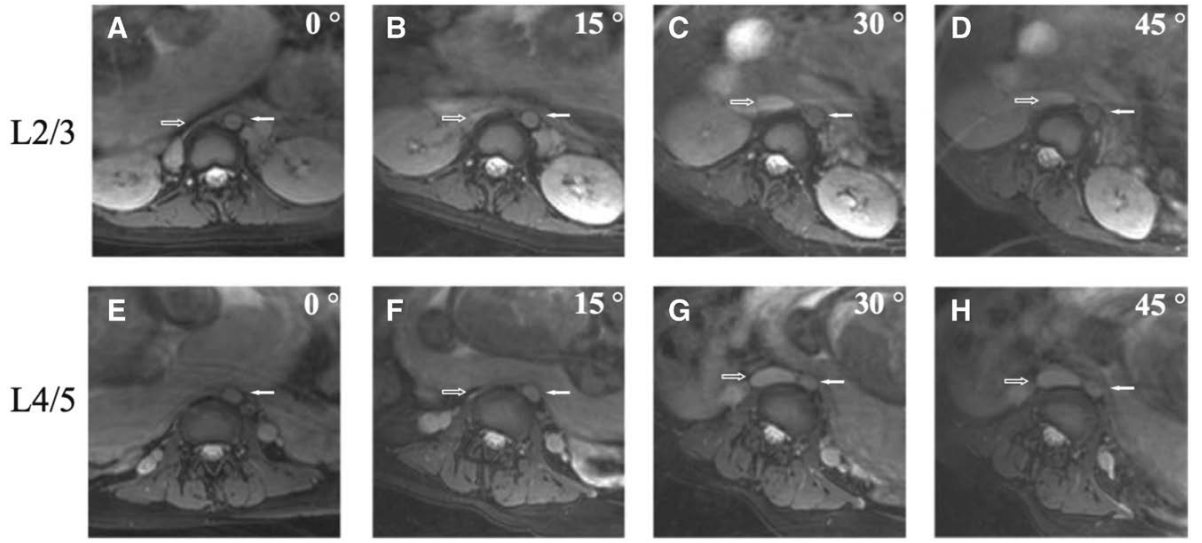
Dyer RA et al. Anaesth Intens Care 2004; 32:351-7

NARRATIVE REVIEW ARTICLE

Aortocaval Compression Syndrome: Time to Revisit Certain Dogmas

Allison J. Lee, MD, and Ruth Landau, MD

Anesth Analg 2017; 125:1975-85



EDITORIAL

The Aortocaval Compression Conundrum

David H. Chestnut, MD

Anesth Analg 2017; 125:1838-9

Anesthesiology
V 40, No 4, Apr 1974

Effects of Equipotent Ephedrine, Metaraminol, Mephentermine, and Methoxamine on Uterine Blood Flow in the Pregnant Ewe

David H. Ralston, M.D.,* Sol M. Shnider, M.D.,† Alfred A. deLorimier, M.D.‡

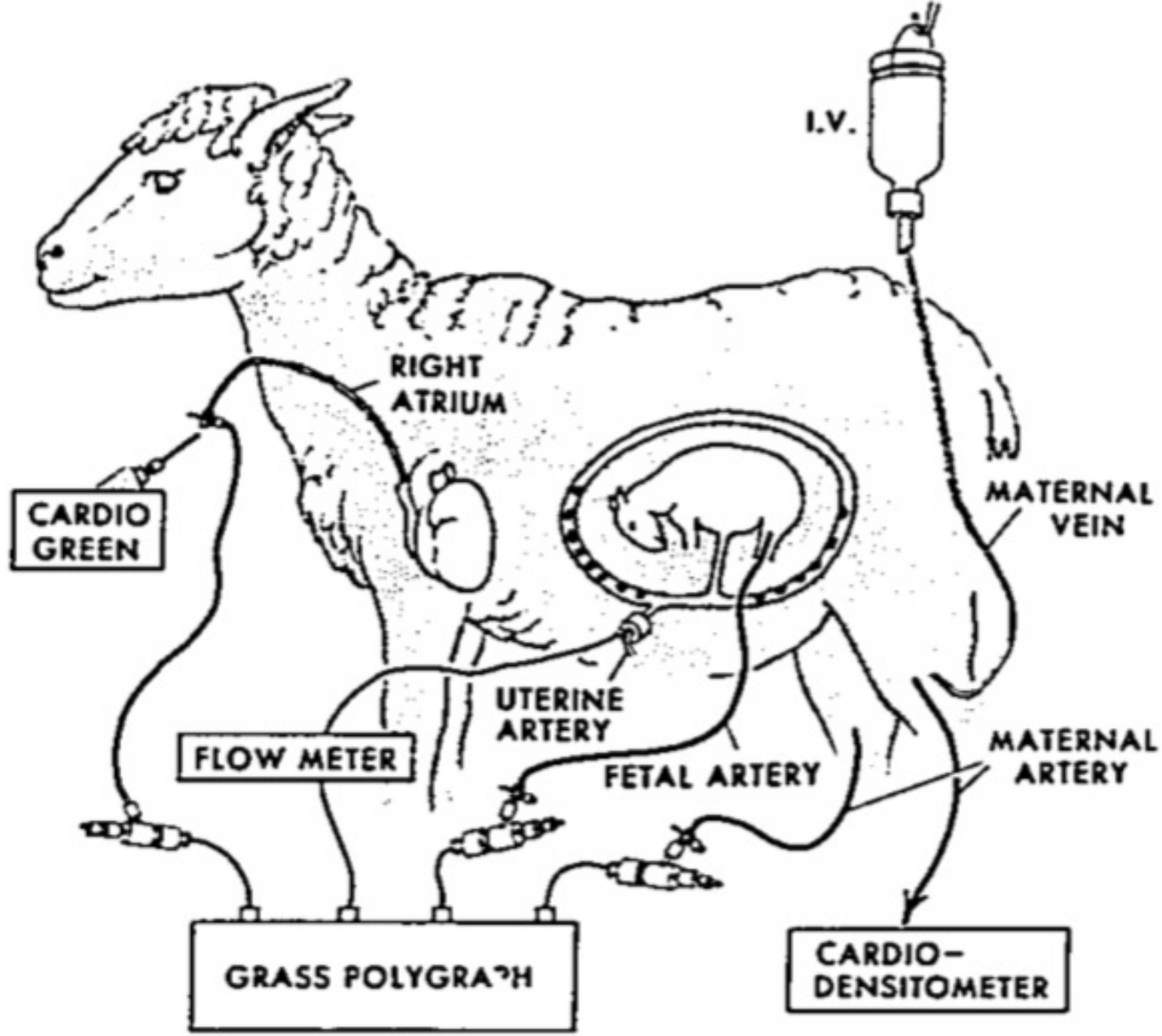


FIG. 1. Diagram of sheep experimental preparation with chronically implanted maternal and fetal intravascular catheters and an electromagnetic flow probe around a branch of a uterine artery.

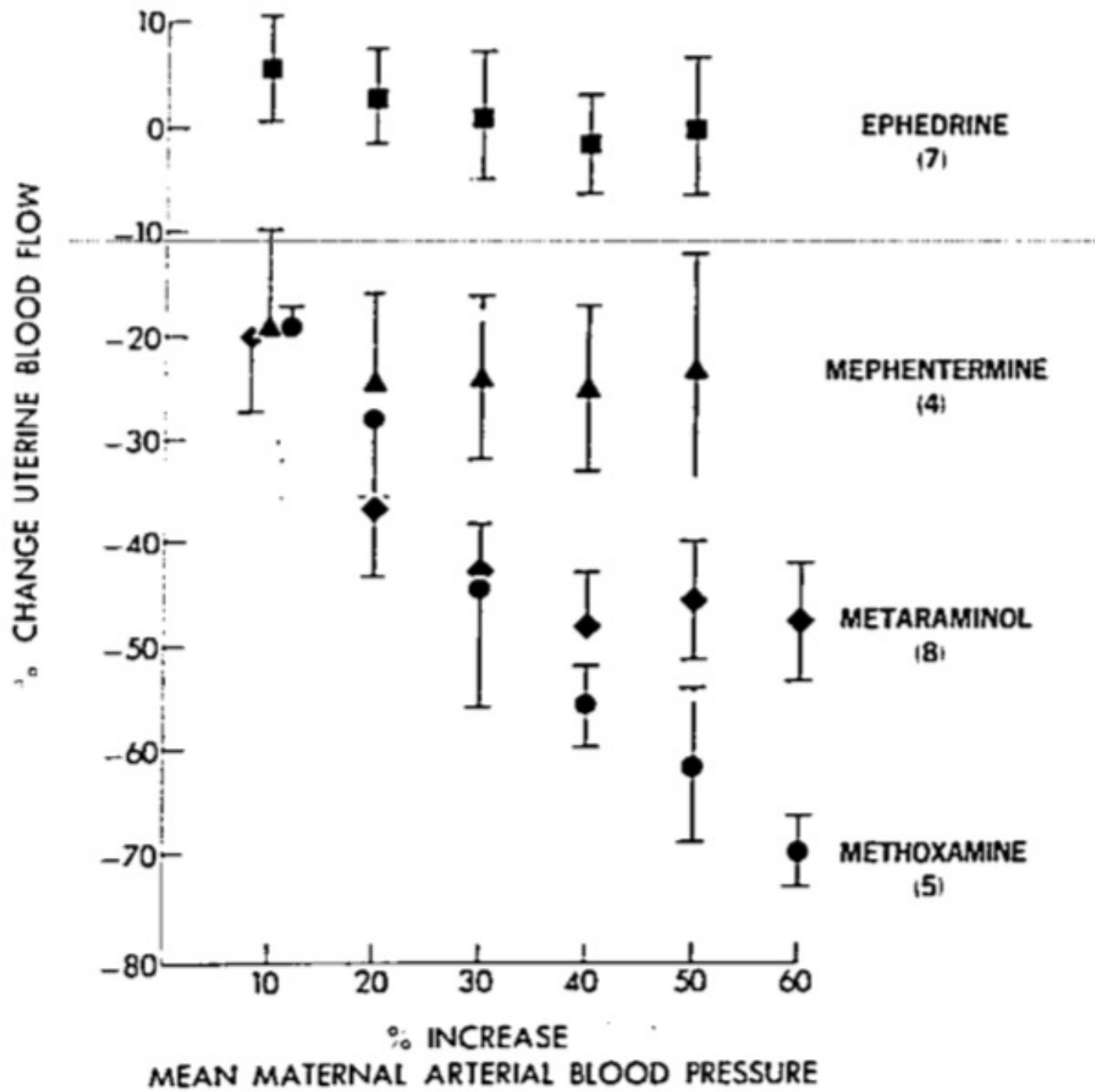


FIG. 5. Mean changes in uterine blood flow at equal elevations of mean arterial blood pressure following vasopressor administration.

Metaraminol (0.5mg/ml) vs Ephedrine (10mg/ml)
1 ml bolus followed by infusion of 0.5 ml/min

	Ephedrine N=25	Metaraminol N=25
Induction-delivery time (min)	24.8	28.5
Hypotension n (%)	10 (44)	8 (35)
Vasopressor consumption (mg)	50	3.1
Nausea n(%)	5 (20)	1(4) *
UA pH <7.2 n(%)	9 (39)	0 (0) *
UA pulsatility index	no change	no change

Ngan Kee et al. Anesthesiology 2001; 95:307

Phenylephrine versus Ephedrine: Systematic Review

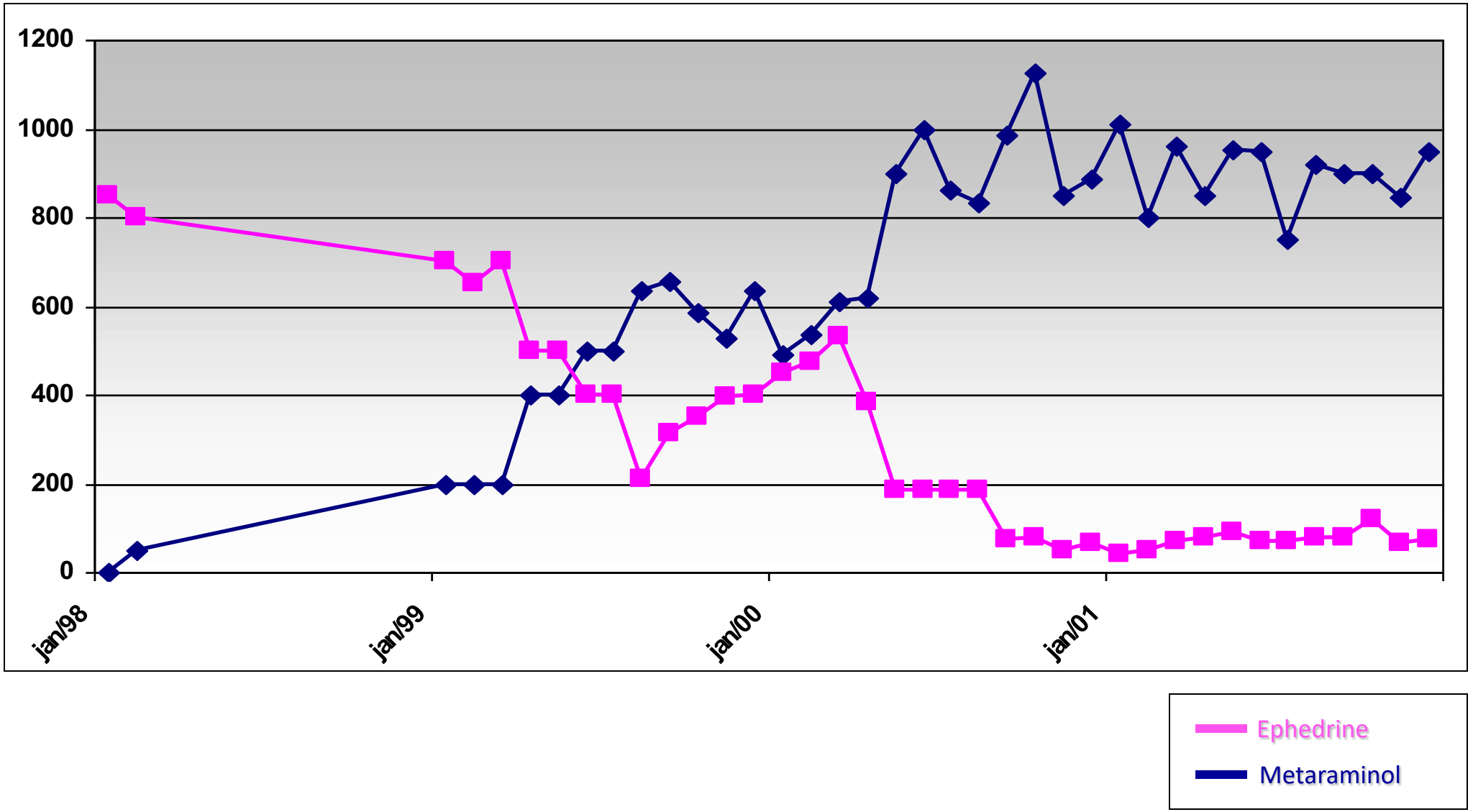
7 RCT (n=292)

		RR	95% CI
Hypotension		1.00	0.96-1.06
Hypertension		0.65	0.08-5.13
Maternal bradycardia		4.79	1.47-15.6
Higher UA pH	WMD	0.03	0.02-0.04
UA pH < 7.20		0.78	0.16-3.92

Lee A et al. Anesth Analg 2002;94:920-6

Vasopressor Consumption at Santa Joana Maternity Hospital (São Paulo, Brazil)

(montly # of ampoules requested from pharmacy)



Phenylephrine Infusion during Spinal Anesthesia for Cesarean Delivery

75 patients undergoing elective CS

No acute preload – Bupivacaine 0.5% 10 mg plus fentanyl 15 µg

Phenylephrine 100 µg/min titrated to 100%, 90% or 80% baseline SBP. Rescue 100 µg

	Group 80	Group 90	Group 100
Hypotension (%)	96	72	29 *
Hypertensive episodes (n)	5	2	0 *
Nausea or vomiting (%)	40	16	4 *
Fetal acidosis (UA pH < 7.20)	0	0	0
Bradycardia < 50 (%)	20	32	8

Ngan Kee WD et al. Br J Anaesth 2004; 92: 469-74

Phenylephrine Infusion Versus Bolus Regimens During Cesarean Delivery Under Spinal Anesthesia: A Double-Blind Randomized Clinical Trial to Assess Hemodynamic Changes

Anne Doherty, MD,* Yayoi Ohashi, MD, PhD,* Kristi Downey, MSc,* and Jose C. A. Carvalho, MD, PhD*

(Anesth Analg 2012;115:1343–50)

Double blind RCT, 60 women

Elective cesarean delivery under spinal anesthesia

Randomized into 2 groups

- bolus of 120 mcg
- infusion of 120 mcg/min (fixed rate)

Any decrease in SBP below baseline was treated

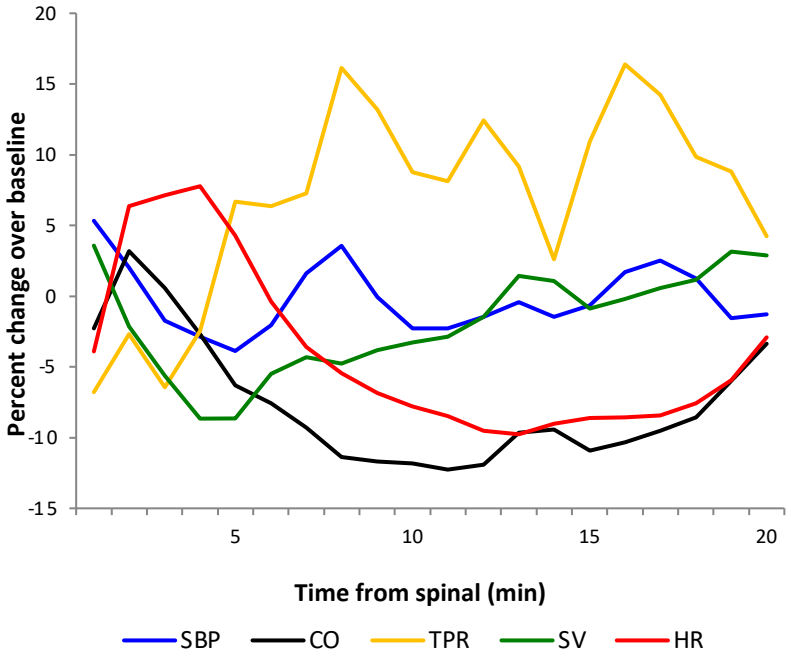
Bio-reactance monitor: SBP, DBP, HR, SV, CO, SVR

Primary outcome: maximum change in CO

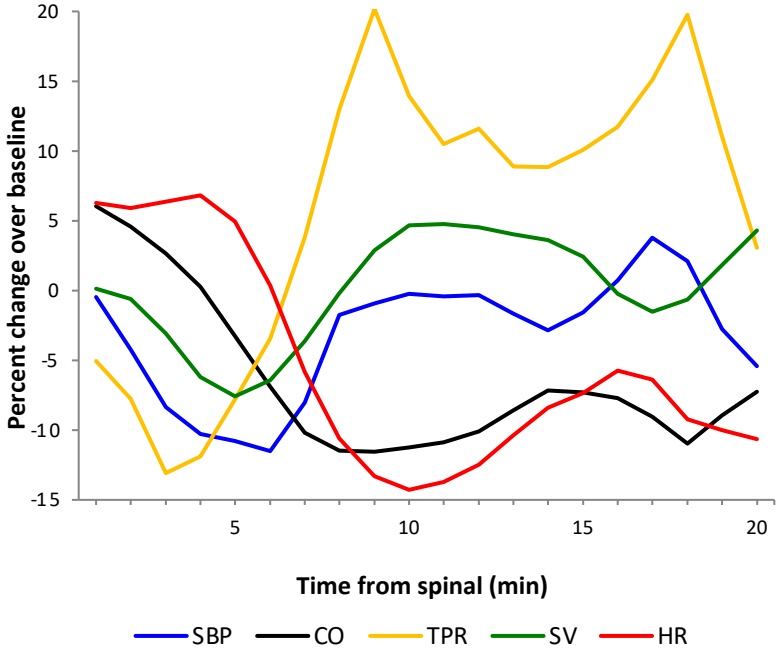
Secondary outcomes: Hemodynamic profile, nausea/vomiting

Hemodynamic profile in the pre-delivery period

Percent change over baseline



Bolus Group



Infusion Group

Doherty et al. Anesth Analg 2012; 115:1343-50

Side Effects and Consumption of Phenylephrine

	Bolus	vs	Infusion	
Hypotension (%)	23		26	ns
Hypertension (%)	40		30	ns
Nausea/Vomiting(%)	36		16	ns
Bradycardia (%)	30		36	ns
Phenylephrine (mcg)	964		1740	<0.001

Doherty et al. Anesth Analg 2012; 115:1343-50

Anesthesiology 2009; 111:753–65
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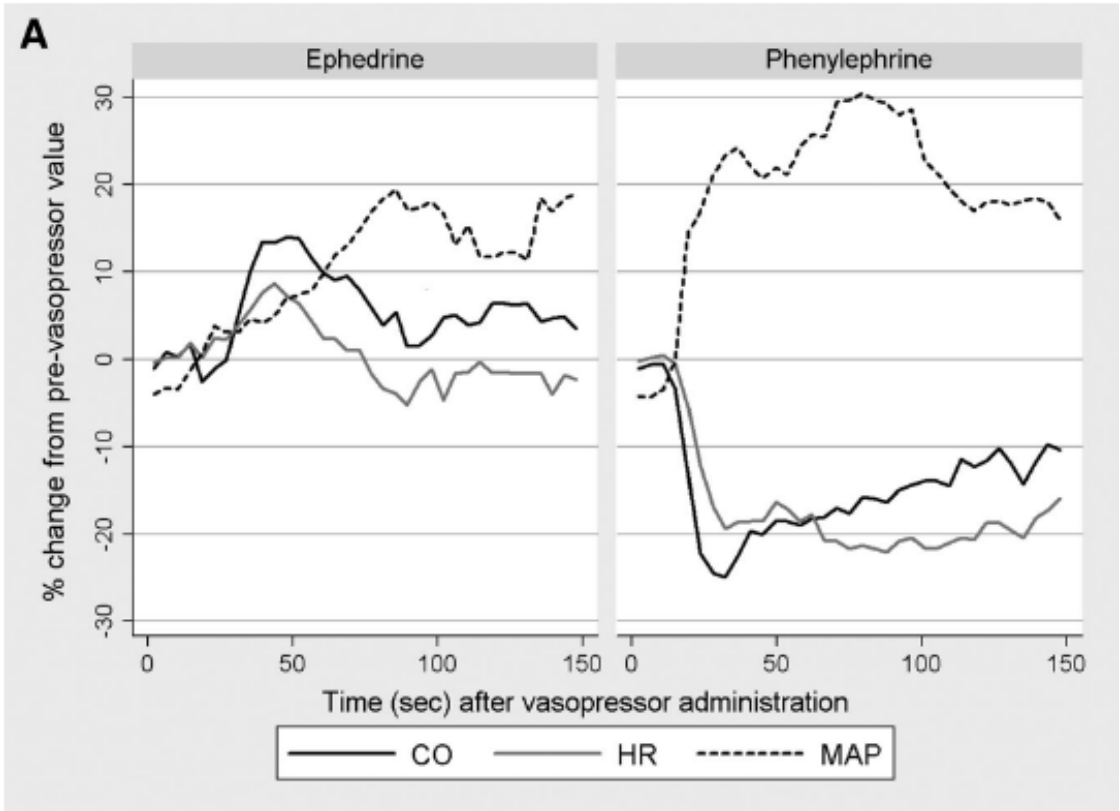
Hemodynamic Effects of Ephedrine, Phenylephrine, and the Coadministration of Phenylephrine with Oxytocin during Spinal Anesthesia for Elective Cesarean Delivery

Robert A. Dyer, F.C.A.(S.A.), Anthony R. Reed, F.R.C.A.,† Dominique van Dyk, F.C.A.(S.A.),‡ Michelle J. Arcache, F.C.A.(S.A.),‡ Owen Hodges, F.C.A.(S.A.),‡ Carl J. Lombard, Ph.D.,§ Jaime Greenwood, F.R.C.A.,‖ Michael F. James, Ph.D.#*



Randomized Double-blinded Comparison of Norepinephrine and Phenylephrine for Maintenance of Blood Pressure 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.,
Shara W. Y. Lee, B.Sc.(Hons.), M.Sc., Ph.D., Floria F. Ng, R.N., B.A.Sc.,
Perpetua E. Tan, B.Sc., M.Phil., Kim S. Khaw, M.B.B.S., M.D., F.R.C.A., F.H.K.A.M.

104 women under spinal for cesarean delivery
Co-hydration up to 2 L crystalloid + vasopressor infusion
- Phenylephrine 100 mcg/ml
- Norepinephrine 5 mcg/ml
  - start dose 30 mL/h until first BP
  - computer controlled closed-loop feedback system
  - vasopressor dose between 30 and 60 mL/h
  - default to 0 mL/h if HR less than 50/min

CO assessed by suprasternal doppler
Primary outcome was changes in CO

Anesthesiology 2015; 122:736-45

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

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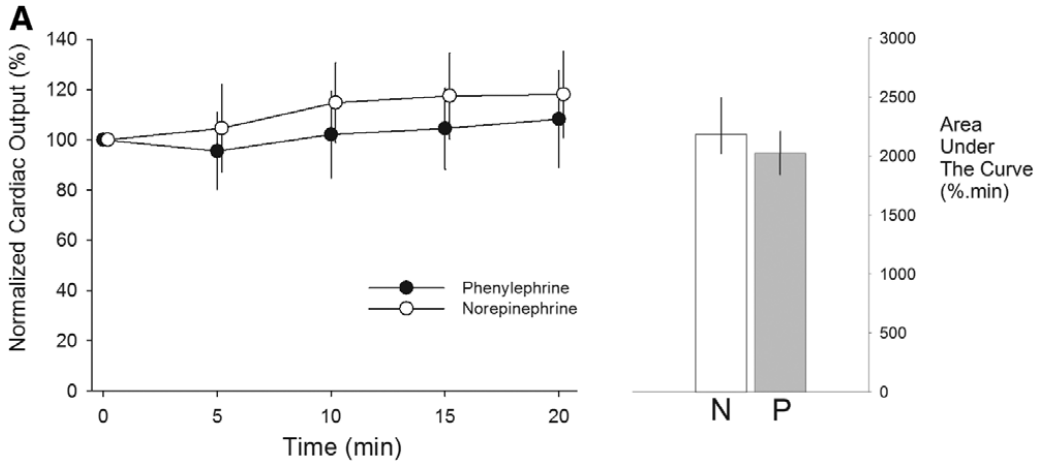
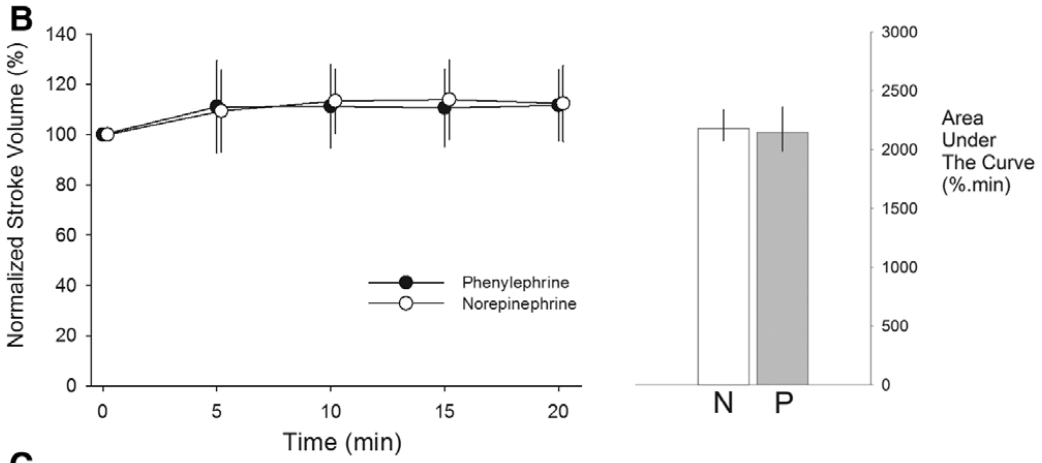
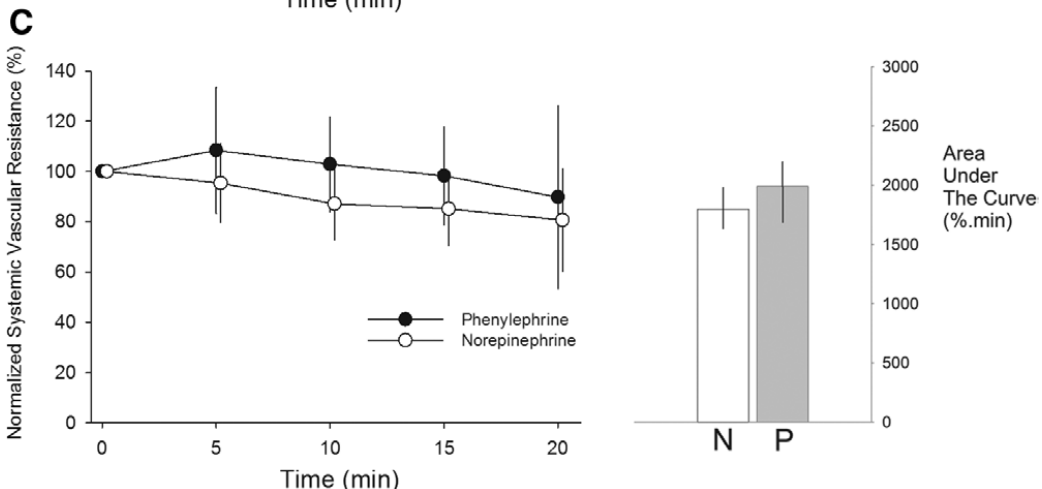
Anesthesiology 2015; 122:736-45

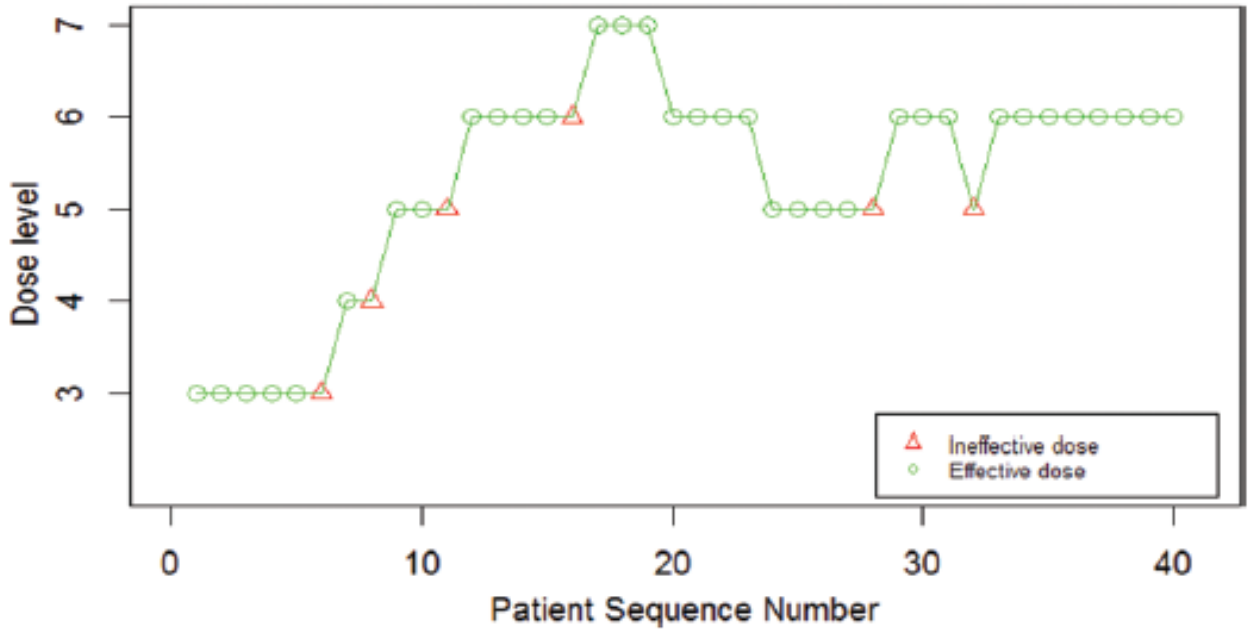






Norepinephrine Intermittent Intravenous Boluses to Prevent Hypotension During Spinal Anesthesia for Cesarean Delivery: A Sequential Allocation Dose-Finding Study

Desire N. Onwochei, MBBS BSc (Hons), FRCA,* Warwick D. Ngan Kee, MBChB, MD, FANZCA, FHKCA,†
Lillia Fung, MD, FRCPC,* Kristi Downey, MSc,* Xiang Y. Ye, MSc,‡
and Jose C.A. Carvalho, MD PhD, FANZCA, FRCPC*



ED90
Truncated Dixon and Mood Method: 5.49 mcg (95% CI 5.15-5.83)
Isotonic Regression Method: 5.80 mcg (95% CI 5.01-6.59)

Anesth Analg 2017;125:212-218

Comparison of Intermittent Intravenous Boluses of Phenylephrine and Norepinephrine to Prevent and Treat Spinal-Induced Hypotension in Cesarean Deliveries: Randomized Controlled Trial

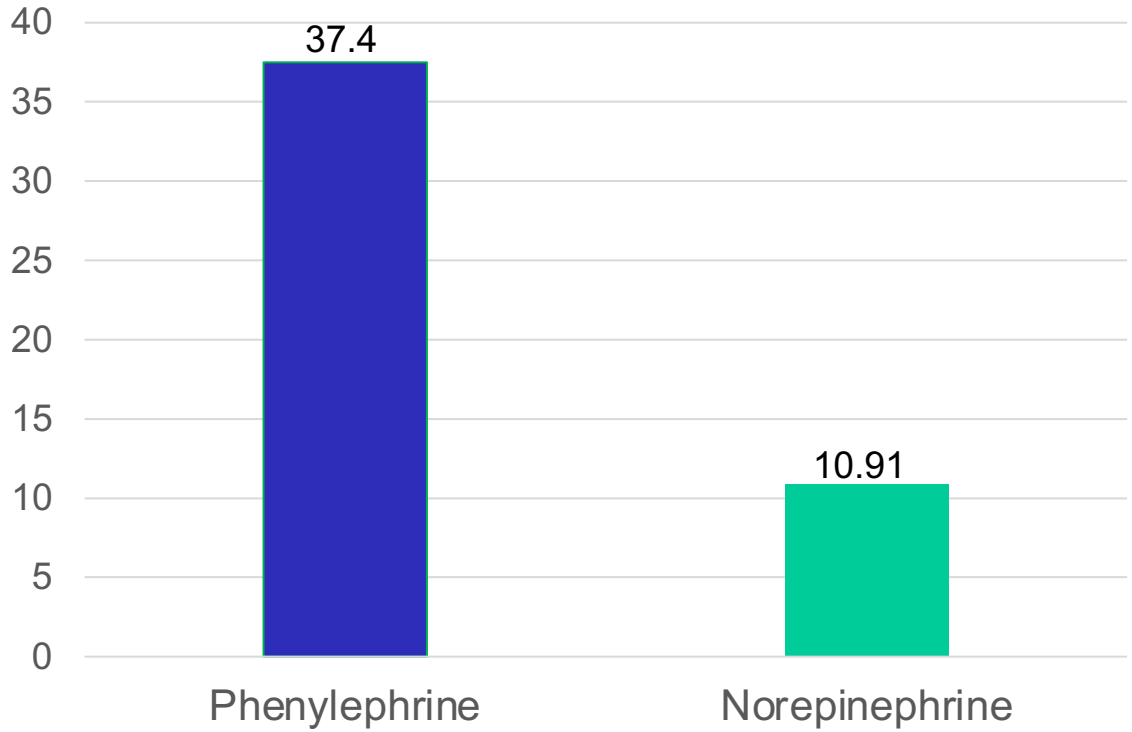
Aidan M. Sharkey, MD,* Naveed Siddiqui, MD, MSc,* Kristi Downey, MSc,* Xiang Y. Ye, MSc,†
Jennifer Guevara, MD,* and Jose C. A. Carvalho, MD, PhD*

112 women, elective cesarean deliveries
Standardized spinal anesthesia
Randomized to
phenylephrine 100 mcg bolus
norepinephrine 6 mcg

SBP and HR assessed every minute
Bolus of vasopressor given every time SBP < 100% baseline
If HR < 60 and vasopressor needed, ephedrine 5 mg was given
If SBP <80% for 2 assessments, ephedrine 10 mg was given

Anesth Analg 2019;129:1312-1318

Primary Outcome - Incidence of Bradycardia



Absolute reduction in the incidence of bradycardia : - 26.6%, 95% CI (- 41.7%, -11.5%)
Relative reduction in the incidence of bradycardia : 70.9%

Sharkey et al. Anesth Analg 2019; 129:1312-1318

Secondary outcomes

	Phenylephrine N = 56	Norepinephrine N = 56	p-value
Hypotension, %	39.3	38.2	0.9
Hypertension, %	10.7	9.1	0.77
Tachycardia, %	12.5	10.91	0.79
Nausea, %	32.1	27.3	0.57
Vomiting, %	7.1	1.8	0.17

Sharkey et al. Anesth Analg 2019; 129:1312-1318

Fetal Outcomes

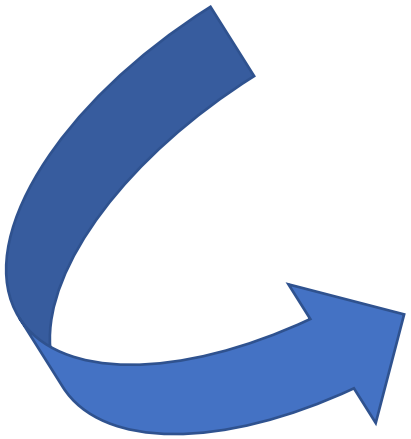
	Phenylephrine N = 56	Norepinephrine N = 56	p-value
Apgar score < 7 at 1 min and 5 min	0	0	
Umbilical arterial blood gases			
pH	7.25 (0.05)	7.24 (0.08)	0.82
pCO_2 (mmHg)	58.7(8.5)	56.2(10.5)	0.21
pO_2, (mmHg)	17.54(7.78)	17.87(8.10)	0.84
HCO_3^- (mmol/l)	25.27(1.95)	24.77(2.37)	0.25
Base Excess (mmol/l)	-2.8(-4.0, -1.7)	-2.5 (-4.1, -1.5)	0.83
Umbilical venous blood gases			
pH	7.31(0.05)	7.30(0.07)	0.27
pCO_2 (mmHg)	47.37(7.44)	48.06(8.30)	0.65
pO_2 (mmHg)	25.06(8.49)	24.18(7.25)	0.57
HCO_3^- (mmol/l)	23.70(1.51)	23.44(1.61)	0.39
Base Excess (mmol/l)	-2.7(-3.9, -1.9)	-2.95 (-4.2, -1.8)	0.44

Anaesthesia 2020, 75, 800–808 doi:10.1111/anae.14976

Review Article

A systematic review of phenylephrine vs. noradrenaline for the management of hypotension associated with neuraxial anaesthesia in women undergoing caesarean section

M. Heesen,[1] **N. Hilber,**[2] **K. Rijs,**[3] **R. Rossaint,**[4] **T. Girard,**[5] **F.J. Mercier**[6] and **M. Klimek**[7]



Anaesthesia 2021, 76, 743–747 doi:10.1111/anae.15363

Editorial

Noradrenaline – at best it is not worse. A comparison with phenylephrine in women undergoing spinal anaesthesia for caesarean section

M. Heesen,[1] **T. Girard**[2] and **M. Klimek**[3]

EJA

Eur J Anaesthesiol 2021; **38:**1077–1084

ORIGINAL ARTICLE

A randomised double-blind comparison of phenylephrine and norepinephrine for the management of postspinal hypotension in pre-eclamptic patients undergoing caesarean section

Medha Mohta, Lakshmi R, Geetanjali T. Chilkoti, Rachna Agarwal and Rajeev Kumar Malhotra

CONCLUSIONS In women with pre-eclampsia undergoing caesarean section, bolus doses of phenylephrine (50 μg) and norepinephrine (4 μg) used to treat hypotension after spinal anaesthesia are equally effective with similar neonatal and maternal outcomes.

MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

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Published: 2019.02.09

A Comparative Study of Bolus Norepinephrine, Phenylephrine, and Ephedrine for the Treatment of Maternal Hypotension in Parturients with Preeclampsia During Cesarean Delivery Under Spinal Anesthesia

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

E 1 Xian Wang*
BC 1 Mao Mao*
F 2 Shijiang Liu
AG 1 Shiqin Xu
D 3,4 Jianjun Yang

1 Department of Anesthesiology, Obstetrics and Gynecology Hospital Affiliated to Nanjing Medical University, Nanjing, Jiangsu, P.R. China
2 Department of Anesthesiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, P.R. China
3 Department of Anesthesiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, P.R. China
4 Department of Anesthesiology, Jinling Hospital Affiliated to Nanjing Medical University, Nanjing, Jiangsu, P.R. China

Conclusions

A bolus dose of norepinephrine (4 μg) showed similar efficacy for the maintenance of systolic blood pressure (SBP) when compared with bolus doses of phenylephrine (50 μg) and ephedrine (4 mg) in parturient women with preeclampsia with hypotension during spinal anesthesia and cesarean section. However, there was improved maternal safety for norepinephrine (4 μg) when compared with phenylephrine (50 μg) and improved maternal and neonatal safety when compared with ephedrine (4 mg). Therefore, bolus norepinephrine may act as a promising alternative to phenylephrine or ephedrine to

BJA

British Journal of Anaesthesia, 124 (3): e95–e107 (2020)

doi: 10.1016/j.bja.2019.09.045
Advance Access Publication Date: 4 December 2019
Review Article

REVIEW ARTICLE

Vasopressor drugs for the prevention and treatment of hypotension during neuraxial anaesthesia for Caesarean delivery: a Bayesian network meta-analysis of fetal and maternal outcomes

Preet M. Singh[1,*], Narinder P. Singh[2], Matthew Reschke[3], Warwick D. Ngan Kee[4], Arvind Palanisamy[1] and David T. Monks[1]

52 RCTs; 4126 patients

UA pH	metaraminol > mephentermine > norepinephrine > phenylephrine > ephedrine
UA BE	norepinephrine > mephentermine > metaraminol > phenylephrine > ephedrine
UA pCO2	norepinephrine > metaraminol > mephentermine > phenylephrine > ephedrine
Nausea/Vomiting	metaraminol > norepinephrine > mephentermine > phenylephrine > ephedrine
Bradycardia	ephedrine > norepinephrine > mephentermine > metaraminol > phenylephrine

Take Home Messages

- ✓Spinal anesthesia primarily affects afterload; preload changes are less
- ✓Crystalloid should be used in smaller amounts and as a co-load
- ✓Aortocaval compression alleviation is controversial, but may be important for some patients
- ✓Prevention of hypotension is superior to treatment; keep SBP tight
- ✓ Ephedrine the least preferred vasopressor (good choice in bradycardia)
- ✓Norepinephrine may be superior to other alpha agonists
- ✓Continuous infusion or boluses are similarly effective (more studies needed)