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Optimal Management of Hypotension During Cesarean Delivery Under Spinal Anesthesia

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Keywords

• Obstetric anesthesia • Cesarean delivery • Spinal hypotension
• Left uterine displacement • Vasopressor choice • Fluid coloading

Key points

- The management of hypotension under spinal anesthesia for cesarean delivery has evolved remarkably, with previous obstetric dogmas being questioned and novel strategies showing success in robust clinical trials.
- Ongoing investigations are showing that aortocaval compression and its clinical ramifications are neither as ubiquitous nor as straightforward as previously thought.
- Phenylephrine administered via infusion is superior to the use of ephedrine in terms of maternal hemodynamic control and neonatal acid-base status.
- Crystalloid coloading, which can be given quickly and facilitates vasopressor administration, is an effective method for the prevention of hypotension under spinal anesthesia.

INTRODUCTION

Spinal anesthesia was first used for cesarean delivery in the United States in 1941 [1]. Since that time, hypotension during neuraxial anesthesia for cesarean delivery has plagued obstetric anesthesia. Without prophylactic treatment, hypotension occurs in up to 80% of patients undergoing spinal anesthesia for cesarean delivery [2]. Spinal hypotension results in decreased uteroplacental blood flow, fetal acidosis, and maternal symptoms such as nausea, vomiting,

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and decreased consciousness [3]. If severe enough, hypotension can lead to complete maternal cardiovascular collapse [4]. As such, finding the solution to spinal anesthesia–induced hypotension has been likened to discovering the Holy Grail of obstetric anesthesia [5,6].

Maternal death from spinal anesthesia is now rare; however, this was a common occurrence just 50 years ago. Holmes [7] titled his 1957 review, "Spinal Analgesia And Caesarean Delivery; Maternal Mortality." Studies around this time focused on the detrimental effects of aortocaval compression from the supine gravid uterus on maternal hemodynamics and fetal status [8,9]. As a result, management strategies largely targeted maternal positioning to relieve vasculature collapse [10]. Early prevention and treatment measures also included increasing maternal blood volume and decreasing venous capacitance, through techniques such as fluid preloading and compression stockings. As the understanding of hypotension during spinal anesthesia has evolved, so has the management, and what were once considered standard management techniques (ie, left uterine tilt, fluid preloading, lower extremity compression) might now be deemed outdated (Table 1).

This review provides an overview of the definition and pathophysiology of spinal anesthesia–induced hypotension, compares strategies for the prevention and treatment of maternal hypotension, and reviews recent literature supporting a conventional approach to management.

HYPOTENSION DURING SPINAL ANESTHESIA

In the absence of a neuraxial-induced sympathectomy, up to 10% of term women experience hypotension in the supine position [11]. This condition results from compression of the inferior vena cava (IVC) by the term gravid uterus when supine [12]. The disorder has been coined supine hypotensive syndrome of pregnancy. Compression of the IVC results in reduced preload and

Table 1
Chronology of selected events in the evolution of the management of spinal-induced hypotension

1935	Angiography first suggests vascular compression in supine parturients
1953	Supine hypotensive syndrome described
1968	Angiography further defines vascular compression in supine parturients
1972	Crawford wedge and concept of 15° lateral tilt developed
1974	Ephedrine shown to be superior to alpha-agonists in pregnant ewes
2002	Systematic review reports ephedrine, compared with phenylephrine, results in decreased fetal pH
2004	Crystalloid coload shown to be superior to crystalloid preload
2010	Phenylephrine preferred vasopressor and studies show benefit of infusion compared with bolus dosing
2015	In first controlled study, norepinephrine is used to adequately maintain maternal CO and SBP
2015	Traditional concept of aortocaval compression challenged by MRI study

Abbreviations: CO, cardiac output; SBP, systolic blood pressure.

increased maternal heart rate via the baroreceptor-mediated reflex. Symptoms commonly include maternal lightheadedness, dizziness, nausea, and general discomfort [13]. At the extreme, maternal and neonatal death have been attributed to supine hypotensive syndrome of pregnancy [14]. Parturients normally have a well-developed collateral venous system, which enables adequate venous return through the azygous, hemiazygos, and ascending lumbar veins in the event of IVC occlusion [15]. However, in patients with supine hypotensive syndrome, venous collateralization and compensatory mechanisms are apparently less effective.

Hypotension during spinal anesthesia may be exaggerated in patients with supine hypotensive syndrome. Such patients experience baseline symptoms from inadequate preload, which can worsen following neuraxial anesthesia. Spinally administered local anesthetics induce a vasomotor sympathectomy, resulting in decreased systemic vascular resistance (SVR) and redistributed blood volume to the splanchnic and lower extremity circulations [16,17]. The degree of hypotension seems proportional to block height and some investigators have used low-dose bupivacaine spinal anesthesia to reduce hemodynamic alterations [18,19]. For example, Van de Velde and colleagues [20] showed that the mean lowest systolic blood pressure (SBP) was higher in patients receiving 6.5 mg of hyperbaric intrathecal bupivacaine compared with 9.5 mg (102 ± 16 mm Hg vs 88 ± 16 mm Hg; $P < .05$). In addition to causing less vasodilation, a lower block level is less likely to affect cardioaccelerator fibers originating from thoracic spinal levels 1 to 4 [21]. Once cardioaccelerator fibers are blocked, vagal stimulation predominates, potentially resulting in bradycardia. Cardiac output (CO) is directly related to heart rate and so any reduction in heart rate results in a decrease in CO, presuming stroke volume remains constant.

Recent advances in minimally invasive cardiac monitoring have provided additional insight into the hemodynamic effects of spinal anesthesia. Multiple recent trials have made use of continuous CO monitoring and suprasternal ultrasonography to monitor CO under spinal anesthesia. Langesaeter and colleagues [22] were the first to use the LiDCOplus, a minimally invasive hemodynamic monitor, to measure CO, SVR, and SBP in pregnant women undergoing spinal anesthesia for cesarean delivery. The device uses an arterial line to detect arterial waveform changes based on injected lithium concentrations [22,23]. Women were randomized to low-dose or higher-dose (7 mg vs 10 mg, respectively) isobaric bupivacaine (with sufentanil 4 μg) spinal anesthesia and a prophylactic phenylephrine infusion (0.25 μg/kg/min) versus placebo. They showed significantly lower mean differences in SBP and CO changes from baseline after spinal anesthesia within the group receiving low-dose bupivacaine and prophylactic phenylephrine compared with higher-dose bupivacaine and placebo, which is expected given the increased vasodilatory effects from greater amounts of local anesthetic. What was perhaps a more significant finding from this study was the immediate increase in CO and decrease in SVR associated with spinal anesthesia; this effect was present in all patients,

regardless of randomization. No significant differences in stroke volume were found between groups, indicating that CO changes were primarily heart rate driven. In patients without minimally invasive monitoring, heart rate is regarded as the best surrogate marker of CO under spinal anesthesia [23]. Because placental circulation and fetal oxygenation depend more on the maintenance of maternal CO than SBP, an anesthetic plan should optimize all hemodynamic variables, not solely SBP [24,25].

Invasive, even minimally invasive, monitoring is rarely required in the obstetric population and is typically reserved for the highest-risk parturients. As a result, most studies on the cardiovascular response to spinal anesthesia focus on the prevention and treatment of hypotension. Hypotension has multiple definitions in the obstetric anesthesia literature. Definitions have included (1) SBP less than 90 mm Hg or less than 100 mm Hg, (2) SBP less than 80% of baseline, and (3) greater than a 25% decrease in SBP from baseline [26–30]. In practice, surveyed anesthesiologists use different SBP thresholds for vasopressor use, with most using a decrease in SBP greater than 20% [31]. This article does not specifically state the definition for hypotension used for each study discussed; however, it is important to note that such heterogeneity can confound study comparisons.

MATERNAL POSITIONING

In the supine position, the gravid uterus completely occludes the IVC. Bieniarz and colleagues [32] used angiography in the 1960s to determine the degree of vasculature collapse and found that both the IVC and the aorta are compressed when a parturient lies supine (see Table 1). Nonanesthetized parturients typically tolerate aortocaval compression well without significant cardiovascular effects as the result of collateral blood flow. However, during neuraxial anesthesia the induced sympathectomy may result in fetal compromise. Crawford and colleagues [33]were among the first anesthesiologists to draw attention to this matter (see Table 1). They examined 150 women undergoing elective cesarean delivery with general anesthesia, tilting 63 of those patients to the right with the use of a 15° rubber wedge. The remaining 87 women were supine. They found a statistically significant difference in mean umbilical artery pH of newborns from the tilted group, 7.31 versus 7.27 in the nontilted group ($P < .001$). Their study conditions are hardly generalizable to contemporary obstetric anesthesia practice. All women had general anesthesia, there was no mention of vasopressor use, and most patients were tilted to the right, per obstetrician preference. However, tilting mothers laterally 15° has essentially remained obstetric anesthesia dogma for decades.

So, should clinicians still be tilting? The 2016 "Practice Guidelines of Obstetric Anesthesia," established by the American Society of Anesthesiologists and the Society for Obstetric Anesthesia and Perinatology, recommends maintaining left lateral tilt until time of delivery [34]. A Cochrane Review performed just 3 years prior showed that, overall, positioning does not affect the incidence of maternal hypotension [35]. Work by Higuchi and colleagues [36] showed the potential reason for this lack of association (see Table 1). They performed abdominal MRI of 10 healthy pregnant and nonpregnant women in 4 different

positions: supine and left lateral tilt at 15°, 30°, and 45°. Imaging showed that the IVC was almost completely collapsed by the gravid uterus in supine parturients. Among the parturient group, IVC volume was only significantly different between the supine and 30° and 45° tilt positions, with no difference found between supine and 15° tilt. Imaging also showed no significant difference in aortic volumes in either group, regardless of amount of tilt. This finding suggests that, in nonanesthetized parturients, CO remains stable, whereas cardiac preload may only start to improve when a 30° to 45° angle is assumed.

Thoracic bioimpedance cardiography has been used to continuously monitor CO, stroke volume, and heart rate with position changes in term, nonanesthetized patients with singleton pregnancies [37]. Bamber and colleagues showed that the full left lateral position resulted in the greatest CO. However, the difference compared with other left tilt positions, including 5° and 12.5°, were nonsignificant. Even supine positioning did not result in a significant mean difference in CO [36]. Rees and colleagues [38] similarly studied the effects of extreme positioning on CO, but with patients under spinal anesthesia. However, they did not monitor CO directly but used signs and symptoms suggestive of low CO, such as maternal nausea, vomiting, and bradycardia. Comparing women in complete left lateral position versus 15° of left tilt following spinal anesthesia, they found no significant presumed changes in CO.

Lateral tilt and left uterine displacement are unlikely to independently solve hypotension during spinal anesthesia. Studies show that not only is it ineffective but it is usually applied inaccurately, as shown by Jones and colleagues [39]. They asked anesthetists to estimate the amount of lateral tilt they had applied during elective cesarean deliveries. Estimated tilt ranged from 7° to 35°, whereas measured tilt did not exceed 15°. If the goal is to prevent IVC obstruction and improve cardiac preload, anesthesia providers would have to tilt parturients to at least 30° (Fig. 1). Such a position would be uncomfortable for the patient and inconvenient for the obstetrician (Fig. 2); however, there are case reports of cesarean deliveries performed in the complete lateral position [37,40,41]. For patients with supine hypotensive syndrome of pregnancy, tilt

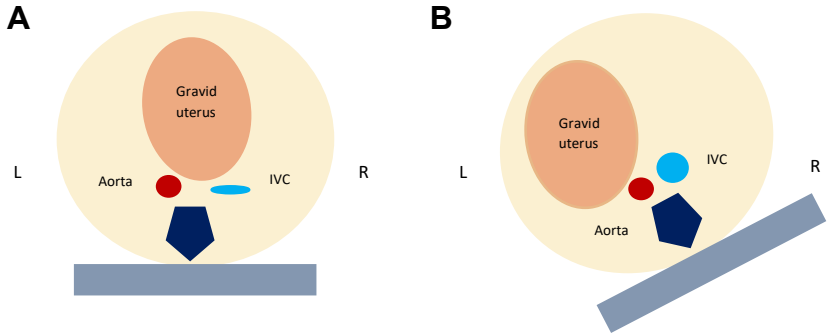

Fig. 1. (*A*) Near-complete IVC occlusion by the gravid uterus in the supine position. (*B*) Relief of IVC occlusion observed at 30° tilt, an angle impractical for cesarean delivery. L, left; R, right.

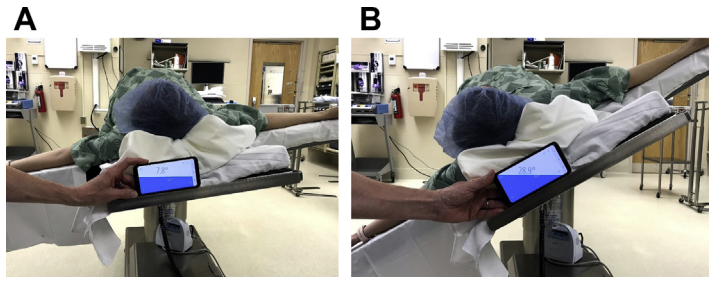

Fig. 2. Maternal positioning during cesarean delivery under spinal anesthesia. (*A*) When positioning the parturient for cesarean delivery following a neuraxial anesthetic, even experienced anesthesia providers typically apply far less than the traditionally recommended 15°. (*B*) The operating room table pictured is maximally tilted with a resulting inclinometer reading of slightly less than 30°. In order to effectively relieve compression of the vena cava, more than 30° of tilt is required, which is poorly tolerated by both patients and surgeons.

should be used. For otherwise asymptomatic parturients, a mild degree of tilt, at the discretion of the anesthesia provider and the obstetrician, may not help but it does not hurt.

EPHEDRINE VERSUS PHENYLEPHRINE

Until a decade or two ago, ephedrine was the preferred vasopressor for the prevention and treatment of spinal-induced hypotension [42]. Early work in pregnant ewes showed improved fetal acidosis when ephedrine was used for hypotension following spinal anesthesia [43]. Compared with pure alpha-agonists, ephedrine caused less vasoconstriction of the uteroplacental circulation, resulting in improved fetal oxygenation [44]. Ephedrine, through indirect beta-agonism, was thought to increase maternal CO and augment uteroplacental blood flow. The use of ephedrine for hypotension was considered gold standard, as shown by surveys of the time. In 1999, 95% of obstetric anesthesiologists in the United Kingdom preferred ephedrine as their sole vasopressor [45]. However, ephedrine's ubiquitous use started to come into question as systematic reviews and later randomized controlled trials unveiled effects on human fetal pH.

In 2002, Lee and colleagues [46] performed a quantitative, systematic review of 7 randomized controlled trials of ephedrine versus phenylephrine given for hypotension for spinal anesthesia during cesarean delivery. When given for the prevention and treatment of hypotension, they found no difference in the incidence of hypotension with the use of ephedrine or phenylephrine (relative risk [RR], 1.0; 95% confidence interval [CI], 0.96–1.06). Limiting analysis to trials specifically of the treatment of hypotension, again, there was no difference between groups. However, they did find statistical significance when comparing umbilical artery pH. Neonates born to mothers receiving phenylephrine had higher umbilical artery pH values (weighted mean difference, 0.03; 95% CI, 0.02–0.04), implying improved uteroplacental perfusion with phenylephrine.

Subsequent prospective studies investigated the effects of phenylephrine, ephedrine, or a combination of the two on maternal cardiovascular and fetal acid-base status. Based on an equipotency ratio of approximately 80:1, phenylephrine 100 μg and ephedrine 5 to 8 mg are typically used for both bolus and infusion dosing [2,47–49]. When administered as a prophylactic bolus dose, ephedrine and phenylephrine show similar efficacy in effectively treating maternal hypotension [47,48]. When used as an infusion, phenylephrine shows superiority over ephedrine. Not only is phenylephrine as an infusion associated with significantly less nausea and vomiting but it more effectively prevents hypotension [49]. More importantly, fewer fetuses are acidotic (pH<7.2) following exposure to phenylephrine versus ephedrine for the management of hypotension following spinal anesthesia.

What this suggests, and what has been supported by additional studies, is that fetal acidosis in the setting of ephedrine use is related to a direct ephedrine effect [50]. Ephedrine stimulates fetal beta-adrenergic receptors, increasing fetal oxygen demand and anaerobic metabolism [51,52]. More often than not, a mixed respiratory and metabolic acidosis results [50]. Although neonatal Apgar scores do not seem to differ between ephedrine and phenylephrine use, studies show increased neonatal complications, such as intraventricular hemorrhage, gastrointestinal dysfunction, and death, in those with metabolic acidosis at birth [53]. As a result, the fetal acidosis observed with ephedrine use has been convincing enough to shift practice to the use of phenylephrine for the prevention and treatment of hypotension following neuraxial anesthesia [47,49–52].

PHENYLEPHRINE INFUSION VERSUS BOLUS

Although phenylephrine is now considered the vasopressor of choice for spinal-induced hypotension during cesarean delivery, the ideal dose and mode of delivery have been debated. Double-blinded studies randomizing patients to either prophylactic phenylephrine infusions or rescue bolus doses have shown conflicting results. In a double-blind, randomized controlled trial of infusion versus the bolus technique, Doherty and colleagues [54] showed improved SBP control in parturients administered phenylephrine boluses. However, this effect was only present within the first 6 minutes after spinal injection and was not deemed clinically significant. The lack of significance may have been the result of the high phenylephrine infusion rate used in the study (120 μg/min). When phenylephrine is delivered at lower infusion rates, this technique may be superior to bolus administration. Siddik-Sayyid and colleagues [55] randomized patients to variable-rate phenylephrine infusions with as-needed boluses versus rescue phenylephrine bolus only. The primary outcome measure was the number of physician interventions to maintain SBP within 20% of baseline. The infusion was initiated at a rate of 0.75 μg/kg/min (equating to 50 μg/min in a 70-kg parturient) immediately after spinal injection and was titrated to maintain goal SBP parameters. The incidence of hypotension was significantly lower in the infusion group, as was the median number of required physician interventions, defined as needing

to make any change to the infusion versus giving additional boluses. It must be appreciated that phenylephrine bolus dosing in these studies was performed as treatment of hypotension rather than prophylaxis. In practice, clinicians frequently administer phenylephrine boluses in response to an increase in maternal heart rate, preceding the expected decrease in SBP. Had the infusions been started only after an observed hypotensive episode, the results may have differed significantly.

As a result of ease of delivery and potential hemodynamic benefit, prophylactic phenylephrine infusions have gained favor. The recommended infusion rate ranges from 25 to 50 μg/min, as shown by multiple randomized trials as well as a recently published international consensus statement on the management of hypotension with vasopressors during cesarean section under spinal anesthesia [56]. Compared with higher-dose infusions, with rates reaching 75 to 100 μg/min, low-dose rates equally maintain maternal SBP [57,58]. High-dose infusions may be detrimental to hemodynamic homeostasis. Phenylephrine at fixed rates of 100 μg/min often results in reactive hypertension with additional physician involvement required to reduce blood pressure [58,59]. Such reactive hypertension can precipitate a baroreceptor-mediated bradycardia, which in turn may result in reduced maternal CO.

Investigators have recently used noninvasive monitoring to study specifically the effects of phenylephrine on maternal CO and other hemodynamic parameters. Stewart and colleagues [57] used a handheld suprasternal ultrasonography device to obtain CO measurements in women receiving different rates of phenylephrine (25 μg/min, 50 μg/min, and 100 μg/min) after spinal anesthesia. CO decreased significantly with increasing phenylephrine rate, with a maximum 22% reduction in CO in the group receiving 100 μg/min. Stroke volume remained unchanged in each group. This finding indicates that heart rate changes provide the best indication of CO changes during cesarean delivery under spinal anesthesia [23]. It is important to highlight that most cesarean deliveries during neuraxial anesthesia are performed with the use of noninvasive blood pressure monitoring, and vasopressor choices are based on information obtained from such routine monitors.

SBP is the hemodynamic variable most commonly used as an indicator of adequate hemodynamic control. However, adequate SBP does not necessarily correlate with adequate maternal CO, placental blood flow, and fetal oxygenation. As shown by Stewart and colleagues [57], variable phenylephrine infusion rates provide satisfactory SBP control, but higher rates result in reduced CO. In healthy women with healthy fetuses, a small resultant decrease in CO is unlikely to cause clinically significant effects. However, fetuses with already compromised uteroplacental blood flow may not tolerate additional decreases in perfusion.

It can be concluded that although phenylephrine infusions are effective for maintaining maternal blood pressure and provide an efficient method of vasopressor administration for anesthesia providers, parturient-specific and fetal-specific conditions must be taken into account [60]. In addition, a so-called

Goldilocks approach should be taken when using infusions, using an algorithm as suggested in Fig. 3. A dose high enough to counteract sympathectomy-induced vasodilation, but low enough to avoid excessive vasoconstriction and reduced CO, should be chosen.

OTHER VASOPRESSORS

Ephedrine and phenylephrine are the dominant vasopressors in obstetric anesthesia. At a time when ephedrine was preferred, there was some investigation into infusions of angiotensin II, which seemed promising because it did not result in the tachycardia and fetal acidosis seen with ephedrine use [61]. Although angiotensin II did not gain favor, it showed the benefits of a potential vasopressor that does not affect maternal heart rate and fetal acid-base status. Recently, norepinephrine has shown similar promise [62,63]. Norepinephrine exerts a strong alpha-agonist effect, helping to counteract the decrease in SVR that accompanies spinal anesthesia. Unlike phenylephrine, it has weak beta-adrenergic activity, which promotes positive chronotropy and maintains maternal heart rate and CO. In the treatment of septic shock, norepinephrine is a first-line vasopressor because of evidence showing improved regional and global perfusion, lower lactate concentrations, and improved urine output compared with other vasopressors, including phenylephrine [64]. Although hypotension induced by septic shock and spinal anesthesia differ in pathophysiology, it is worth noting the potential for improved perfusion with norepinephrine use.

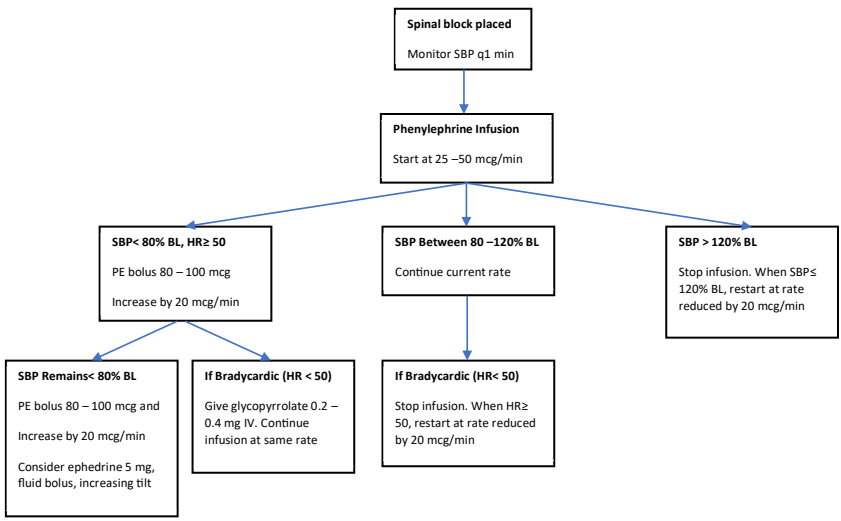

Fig. 3. Phenylephrine infusion titration. Interventions based on changes in SBP every 1 minute. Titration based on work from Refs. [55] and [104]. BL, baseline; HR, heart rate; IV, intravenous; PE, phenylephrine; q, every.

Ngan Kee and colleagues [63] first pioneered work with norepinephrine use in the obstetric population in 2015. Using a norepinephrine to phenylephrine potency ratio of 20:1, they randomized parturients to receive a norepinephrine infusion, rates ranging from 0 to 5 μg/min, or a phenylephrine infusion, rates ranging from 0 to 100 μg/min. At the time of spinal anesthesia for cesarean delivery, patients received a fluid coload and infusion initiation. The infusion was regulated by a computer-controlled, closed-loop feedback system. Although no difference in SBP control was found, patients receiving norepinephrine had significantly greater CO over time (median 102.7% [interquartile ratio (IQR]) 94.3%–116.7%] for norepinephrine vs 93.8% [85.0%–103.1%] for phenylephrine, $P = .004$, median difference 9.8%, 95% CI of difference between medians 2.8%–16.1%). In addition to providing insight into the hemodynamic benefits of norepinephrine, this study suggested that the norepinephrine to phenylephrine potency ratio is lower than 20:1, as previously thought. A potency ratio closer to 13:1 to 16:1 has been suggested by additional work with norepinephrine in the obstetric population [65,66]. In comparison, administering a 100-μg phenylephrine bolus would equate to administering a 6-μg to 8-μg norepinephrine bolus [66].

Subsequent work by Ngan Kee and colleagues [67] showed the efficacy of a manually controlled variable-rate norepinephrine infusion, comparing infusion with bolus norepinephrine use. Parturients receiving norepinephrine via infusion had fewer episodes of hypotension ($P<.001$) compared with those receiving norepinephrine via bolus technique. CO was the same between groups; however, CO values were not available for all study participants. Those receiving norepinephrine as an infusion received an overall higher median rate (dose divided by time to uterine incision) of vasopressor (2.22 μg/min vs 0.28 μg/min) compared with the bolus group. This finding shows that, at low concentrations, at rates much lower than typically used in the intensive care setting, norepinephrine has the potential to effectively decrease the incidence of maternal hypotension during spinal anesthesia.

Obstetric anesthesia providers have expressed some concern regarding norepinephrine use in the obstetric population [62]. This concern arises from systematic reviews and case reports documenting varying degrees of tissue injury following peripheral administration of norepinephrine [68]. However, patients included in these reviews are often septic, have coexisting vascular disease, and require high doses of vasopressor to maintain perfusion. As such, norepinephrine use in healthy parturients is hardly comparable with use in critically ill patients. In addition, norepinephrine used in obstetric studies is formulated in dilute concentrations (5 μg/mL) and is administered at rates much lower than those typically given in the intensive care setting [65,67]. As Carvalho and Dyer [62] suggest, norepinephrine is a promising vasopressor for the management of hypotension during spinal anesthesia. However, before clinicians undergo another paradigm shift in the choice of vasopressor use for

cesarean delivery, additional studies will need to confirm norepinephrine's maternal and fetal safety.

FLUID MANAGEMENT

There has been a paradigm shift from ephedrine to phenylephrine use and bolus phenylephrine to infusion phenylephrine use. Fluid type and timing of delivery has also been subject to shifting practice, based on studies of crystalloid versus colloid and fluid preload versus coload. A fluid preload has typically been defined as a bolus of intravenous fluid, ranging from 1 to 2 L, delivered 10 to 20 minutes before spinal anesthesia [69]. A coload is a fluid volume administered immediately after induction of neuraxial anesthesia, and typically completed within 5 minutes [70–72].

PRELOAD VERSUS COLOAD: CRYSTALLOID

Traditional prevention of hypotension during spinal anesthesia supported the use of crystalloid preloading, but studies have failed to show any benefit from this practice [29]. The reason behind this is likely 2-fold. First, crystalloid solutions redistribute from the intravascular to interstitial space within a short period of time. Following a 10-minute infusion of lactated Ringer, less than 50% of the solution is retained with the central compartment at 30 minutes postinfusion [73]. Using indocyanine green concentration to measure blood volume, Ueyama and colleagues [74] showed that only 28% of a lactated Ringer preload infused over 30 minutes remained intravascularly at the end of this half hour. If a preload crystalloid volume is given, by the time a patient experiences sympathectomy-mediated spinal hypotension, most of the crystalloid has already left the intravascular space. Crystalloid preload thus fails to provide additional intravascular volume at the time when it is required to prevent hypotension. Second, any volume load results in atrial stretch, stimulating release of atrial natriuretic peptide (ANP). When a preload is administered, the resulting ANP release induces peripheral vasodilatation and fluid excretion, leading to decreased available intravascular volume coinciding with hypotension from an evolving spinal block [75]. In contrast, coloading provides additional intravascular volume at the time of maximal vasodilatation. When administered concurrently with vasopressors, such as a phenylephrine infusion, a crystalloid coload results in a significantly lower incidence of hypotension (incidence 1.9% [95% CI, 0.3%–9.9%] in phenylephrine/coload group vs 28.3% [95% CI, 18.0%–41.6%] in phenylephrine/minimal fluid maintenance group, $P = .0001$) [59].

PRELOAD VERSUS COLOAD: COLLOID

Colloid coloading has failed to show the benefits found from crystalloid coloading [76]. Colloid preloading has been proposed to increase intravascular volume at a time coinciding with spinal sympathectomy and hypotension better than coloading. Hydroxyethyl starch 6% (HES) has been the most commonly studied colloid in obstetric literature [27,70–72,77–79]. HES and other colloids,

such as dextrans, gelatins, and albumin, are large molecules that increase intravascular oncotic pressure and effectively retain plasma volume longer than crystalloid solutions. At 30 minutes after preload with 1.0 L of HES, 100% of colloid has been found to remain within circulation [74]. In a study of 26 parturients undergoing spinal anesthesia for elective cesarean delivery, a 1.0-L HES preload resulted in a significantly lower incidence of hypotension compared with administration of 0.5 L-HES and 1.5-L lactated Ringer preload [74]. When giving HES as a coload, investigators have shown no benefit compared with preloading [70,71]. Other than a significant increase in cardiac output 5 minutes after spinal following an HES preload, Teoh and Sia [70] found no difference in CO at further time points and no difference in SBP at any time. Siddik-Sayyid and colleagues [71] confirmed these results, finding no difference in the incidence of hypotension, severe hypotension (defined as SBP<80 mm Hg), or total amount of vasopressor required following spinal anesthesia. The lack of observed hemodynamic benefit from preloaded HES may be explained again by the release of ANP. Any potential increase in plasma volume from colloid administration may be offset by resultant vasodilation and natriuresis.

VARIED FLUID PRELOADING VERSUS COLOADING COMBINATIONS

Additional studies have investigated the effects of various combinations of fluid type and timing. Tamilselvan and colleagues [78] conducted a double-blind, randomized controlled study of the hemodynamic impact of fluid type given before spinal anesthesia for elective cesarean delivery. A crystalloid solution (Hartmann solution) 1.5 L or 6% HES 0.5 or 1.0 L were delivered 30 minutes before combined spinal-epidural anesthesia. Cardiac parameters were measured with the use of suprasternal ultrasonography throughout this period. Although there was no significant difference in the incidence of hypotension between fluid groups, the study was underpowered for this specific outcome. However, CO remained significantly higher than baseline in the 20 minutes postspinal only in the group receiving HES 1.0 L [78]. For elective cesarean deliveries, clinicians potentially have time to preload patients a half hour before anesthesia. However, this approach is impractical for the large percentage of cesarean deliveries that are unplanned. Coloading can be given quickly and can help deliver concurrently administered vasopressors. McDonald and colleagues [72] randomized patients to a coload of HES 1.0 L or Hartmann solution in addition to a phenylephrine infusion set at 100 μg/min, initiated at the time of spinal injection. Postspinal, the incidence of hypotension was the same between groups and there were no between-group differences in CO. When given as a coload, colloid likely has no advantage over crystalloid.

When given as a preload, colloids may confer some benefit over crystalloid. However, HES 6% (hetastarch), the colloid most researched in the obstetric literature, is no longer routinely available and so future research endeavors will need to study the potential benefits of colloid alternatives. For example,

human albumin has not been extensively studied in the obstetric population but may be a viable colloid option for hypotension management and an area for future research. In the interim, hypotension during spinal anesthesia can be efficiently and effectively managed with a 1-L to 2-L crystalloid coload, initiated at the time of spinal block placement and administered over approximately 5 minutes. Not only does this increase intravascular volume at the time of maximal sympathectomy but it facilitates the delivery of concurrently given vasopressors.

SEROTONIN ANTAGONISTS

Although the major cause of hypotension following spinal anesthesia is secondary to sympathetic blockade, the Bezold-Jarisch reflex (BJR) may also contribute to cardiovascular instability. This reflex causes a triad of vasodilation, bradycardia, and hypotension [79]. Stimulation of receptors in the ventricular walls (mechanoreceptors and chemoreceptors) has been implicated in the BJR. In response to decreased venous return, intracardiac mechanoreceptors are stimulated, resulting in cardiac afferent fiber activation and bradycardia. Such bradycardia may be protective, enabling increased diastolic filling time during a period of reduced preload [80]. Chemoreceptors responding to 5-hydroxytryptamine3 (5-HT3 [serotonin]) also contribute to the BJR, as shown by inhibition of the reflex with the use of 5-HT3 antagonists in animal models [81,82]. Animal model results have subsequently been replicated in humans. Results from 2 recent meta-analyses suggest that the use of prophylactic 5-HT3 receptor antagonists reduces the incidence of hypotension during spinal anesthesia [83,84]. Both meta-analyses included randomized controlled trials from the obstetric and nonobstetric populations. Subgroup analyses on the obstetric populations showed significantly lower incidences of hypotension, bradycardia, and nausea/vomiting. For the prevention of hypotension and bradycardia, the number needed to treat was 5.3 and 7.6, respectively [83]. Ondansetron was the most frequently used 5-HT3 antagonist; however, granisetron was given in one obstetric randomized controlled trial.

Although it seems that 5-HT3 antagonists play a role in the prevention of spinal-induced hypotension, there is a large amount of heterogeneity and some degree of publication bias within these analyses [84]. The high heterogeneity was related to the differences in spinal medication, vasopressor use, and fluid management. Half of the obstetric trials included in the Heesen and colleagues[83] analysis used ephedrine as the pressor of choice, making such results less applicable to recommended practice with phenylephrine use. A recent study by Karacaer and colleagues [85] investigated the effect of ondansetron as part of an anesthetic that more fully embraces current accepted practice. Patients scheduled for elective cesarean delivery received a crystalloid coload and norepinephrine 5-μg boluses for refractory hypotension. A prophylactic 8-mg dose of ondansetron compared with saline placebo did not reduce

the incidence of hypotension. However, it did result in a significantly lower requirement for norepinephrine ($P = .009$).

Should all parturients undergoing spinal anesthesia for cesarean delivery receive 5-HT3 antagonists? There are not enough prospective data to conclude that higher doses (eg, 8 mg of ondansetron) of 5-HT3 antagonists prevent hypotension during spinal anesthesia for cesarean delivery. With regard to administering 4 mg of ondansetron, providing such low doses is unlikely to cause harm and may help prevent maternal nausea and vomiting during spinal anesthesia for cesarean delivery [83,84].

LOWER EXTREMITY MANIPULATION

The goal of lower extremity manipulation, via leg compression or elevation, is to increase venous return to the central circulation following spinal-induced sympathectomy [86]. Studies have investigated lower extremity elevation and various methods of mechanical compression, including elastic bandages, sequential compression devices, and thromboembolic deterrent stockings, to prevent hypotension following spinal anesthesia [87–91]. Of these studies, Rout and colleagues [91] enrolled one of the largest groups of parturients. They randomized 97 parturients undergoing elective cesarean delivery with spinal anesthesia to 1 of 3 interventions: leg elevation to 30°, leg elevation plus wrapping with elastic bandages, or no elevation with sham bandages (control). Compared with the control group, the leg-wrapped group showed a 5-fold decrease in the incidence of hypotension (odds ratio [OR], 5.3; 95% CI, 1.7–16.3). Leg elevation seemed to have no influence on hypotension.

Although other investigators have shown similar moderate success with lower extremity manipulation, the benefit remains controversial. A recent Cochrane Review analyzed 11 studies with a total of 705 women, comparing lower limb compression with control. Compression prevented hypotension after spinal anesthesia with an average RR of 0.61 (95% CI, 0.47–0.78; I2 = 65%); however, the review deemed the evidence as overall very low quality [92]. In addition, many of the included studies used fluid preloading and ephedrine as the primary vasopressor, making them less comparable with recommended practice. Kuhn and colleagues [93] addressed this issue by performing a randomized, double-blinded, placebo-controlled study in which women undergoing elective cesarean delivery received phenylephrine, leg wrapping, or no treatment under spinal anesthesia. Every patient received a 1-L coload and those randomized to phenylephrine received a 0.25-μg/kg bolus followed by 0.25-μg/kg/min infusion at the time of spinal block. Study design included the LiDCOplus monitor, enabling continuous hemodynamic monitoring of CO and SVR. The phenylephrine group experienced significantly less hypotension compared with the leg-wrapping and control groups. Although continuous CO was reduced in those receiving phenylephrine, SVR was significantly higher in this group. In addition, a rapid and profound reduction in SVR preceded a decrease in blood pressure in all 3 groups, confirming that a sudden and marked arterial vasodilatation is the main hemodynamic effect of spinal

anesthesia. The decrease in SVR was only attenuated by phenylephrine, which highlights that leg wrapping does not counteract arterial dilatation. Thus, the prophylactic alpha-1 agonist action of phenylephrine is the more physiologic approach to prevention of spinal-induced hypotension.

For elective, low-risk cesarean deliveries in which this is no time constraint, lower extremity compression devices can be considered. Although they are unlikely to significantly prevent hypotension during spinal anesthesia, leg wrapping may provide some additional preload. For urgent or emergent deliveries, leg compression is an unnecessary component of hypotension management, given the availability of vasopressors and fluid coloading, which are more likely to effectively and efficiently prevent and treat hemodynamic instability.

HYPOTENSION MANAGEMENT IN NONELECTIVE, HIGH-RISK PREGNANCIES

Most studies investigating hypotension following spinal anesthesia have been performed in low-risk parturients undergoing elective, primary cesarean deliveries. As such, obstetric anesthesia has developed gold standards of hypotension management based on healthy mothers and fetuses. It is important to question whether such standards of care are appropriate, for example, for parturients with cardiac disease or with growth-restricted fetuses. In a retrospective observational study of 385 parturients having spinal anesthesia for high-risk cesarean deliveries, there was no statistical difference in fetal pH between patients receiving ephedrine, phenylephrine, or no vasopressor for prophylaxis and treatment of hypotension [51]. High-risk deliveries were defined as cesarean deliveries for pregnancy-induced hypertension, prolonged rupture of membranes, cord prolapse, dystocia, and nonreassuring fetal heart tracings. This lack of difference in fetal pH may be caused by the lower median dose of ephedrine administered, 12 mg (IQR, 6–18 mg) before delivery, compared with doses given in studies of low-risk, elective cesarean deliveries [49,51,94]. Prospective, randomized controlled trials have shown similar findings. In a study of emergency cesarean deliveries under spinal anesthesia performed for acute fetal compromise, Jain and colleagues [95] showed no difference in fetal acidosis between women receiving ephedrine or phenylephrine (umbilical artery pH <7.2, 31.1% in ephedrine group and 20% in phenylephrine group; $P = .22$).

The lack of difference in fetal acidosis between parturients receiving ephedrine and phenylephrine may also be explained by the fact that many women undergoing nonelective cesarean deliveries are laboring. The earliest study describing this effect was performed by Clark and colleagues [96]. They found that healthy women in early labor undergoing cesarean delivery with spinal anesthesia had a significantly lower rate of hypotension compared with nonlaboring women ($P<.05$). It was proposed that uterine contractions delivering additional blood volume to the central compartment contributed to this effect.

Patients with hypertensive disorders of pregnancy have also been shown to require less vasopressor for the treatment of hypotension from spinal anesthesia [97]. Studies within this patient population are limited, but evidence from

prospective trials shows this association. Aya and colleagues [98] performed the first study of the incidence of spinal-induced hypotension in preeclamptic compared with healthy parturients. They showed a significantly lower risk of hypotension in patients with preeclampsia with severe features undergoing spinal anesthesia for scheduled cesarean delivery compared with normotensive parturients (OR, 0.17; 95% CI, 0.05–0.58; $P = .006$) and proposed that this is caused by the underlying pathophysiology of the disease. Preeclampsia results in altered vascular endothelium, decreased vascular tone regulation, and increased sympathetic activity [99,100]. As a result, preeclamptic patients may be less susceptible to the sudden decrease in sympathetic tone related to spinal anesthesia.

For preeclamptic patients, clinicians can expect to see less hypotension during spinal anesthesia and potentially a greater effect from vasopressor use. As Sharwood and colleagues[101] also proposed, preeclamptic patients are less dependent on sympathetic output and are potentially more sensitive to sympathomimetic medications. Should preeclamptic patients require vasopressor support, either phenylephrine or ephedrine can be considered, with care taken to carefully titrate so as not to cause iatrogenic hypertension. Fluid delivery in this patient population should also be conservative. Preeclamptic patients are less likely to require a 1-L to 2-L crystalloid coload and delivery of such fluid may potentially lead to volume overload.

SUMMARY AND FUTURE DIRECTIONS

Over the past several decades, the subspecialty of obstetric anesthesia has witnessed a progressive evolution in the management of hypotension with spinal anesthesia during cesarean delivery. The work of dedicated researchers has provided insight into the pathophysiology, the consequences, and the optimal prevention and treatment of maternal hypotension. Current recommended practices for the prevention of hypotension during spinal anesthesia are outlined in Fig. 4. Such practices include administration of 1 to 2 L of crystalloid

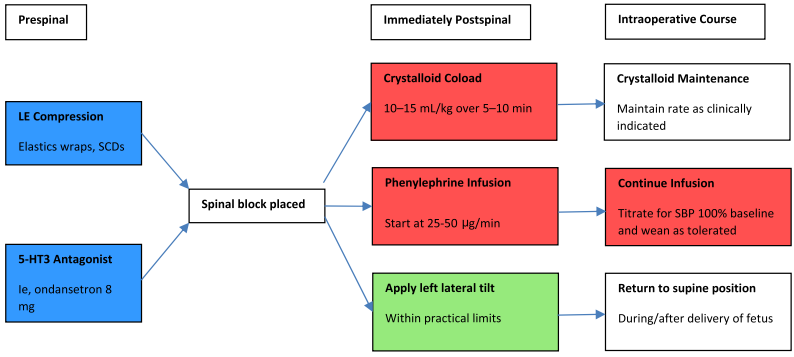

Fig. 4. Management techniques for prevention of hypotension under spinal anesthesia. Code color represents level of recommended implementation: red, high; green, moderate; blue, low. LE, lower extremity; SCD, sequential compression device.

as a coload (or 500 mL of 0.5-L to 1.0-L colloid preload, time permitting) and initiation of a phenylephrine infusion of 25 to 50 μg/min at the time of spinal block placement. Lateral tilt may or may not be used, depending on the presence of preexisting supine hypotension of pregnancy and the response to the measures discussed earlier, keeping in mind that there are few disadvantages to continuing the practice of routinely tilting parturients [102–104]. The treatment of hypotension should include vasopressor infusion titration to maintain SBP near baseline, while ensuring that reactive hypertension does not occur.

Although conventional management prevents and treats hypotension in most patients, clinicians should continue to strive for successful management in every patient. Future work will help to fine tune the current standard practice. Such fine-tuning is likely to include methods to maintain maternal CO rather than SBP, given evidence that placental blood flow depends more on CO than systolic pressure [23]. The advent of minimally invasive and noninvasive cardiac monitoring, such as LiDCOplus, thoracic bioimpedance, and suprasternal cardiac ultrasonography, and their validation in the obstetric population, have provided the opportunity to continuously monitor maternal CO. The growth of point-of-care ultrasonography will also make it possible to titrate fluids and vasopressors based on cardiac filling and function. Perhaps 5-HT3 antagonists will be shown to provide consistent additional benefit, particularly in patients who may be susceptible to the BJR following spinal anesthesia. Norepinephrine infusions might become routinely adopted as concerns regarding the safety of peripheral intravenous administration are fully addressed. Obstetric anesthesia is entering an era in which delivery of care will not only be further optimized but individualized for each mother and her baby.

References

[1] DeCarle DW. Spinal anesthesia in cesarean section. JAMA 1954;154(7):545–9.
[2] Saravanan S, Kocarev M, Wilson RC, et al. Equivalent dose of ephedrine and phenylephrine in the prevention of post-spinal hypotension in caesarean section. Br J Anaesth 2006;96:95–9.
[3] Marx GF, Cosmi EV, Wollman SB. Biochemical status and clinical condition of mother and infant at cesarean section. Anesth Analg 1969;48:986–93.
[4] Comito C, Bechi L, Serena C, et al. Cardiac arrest in the delivery room after spinal anesthesia for cesarean section: a case report and review of literature. J Matern Fetal Neonatal Med 2018;1–3; https://doi.org/10.1080/14767058.2018.1517321.
[5] Macarthur A. Solving the problem of spinal-induced hypotension in obstetric anesthesia. Can J Anaesth 2002;49:536–9.
[6] Campbell JP, Stocks GM. Management of hypotension with vasopressors at cesarean section under spinal anesthesia-have we found the holy grail of obstetric anesthesia? Anaesthesia 2018;73:3–6.
[7] Holmes F. Spinal analgesia and caesarean section; maternal mortality. J Obstet Gynaecol Br Emp 1957;64:229–32.
[8] Ang CK, Tan TH, Walters WA, et al. Postural influence on maternal capillary oxygen and carbon dioxide tension. BMJ 1969;3:201.
[9] Goodlin RC. Aortocaval compression during cesarean section. Obstet Gynecol 1971;37:702.

[10] Colon-Morales MA. A self-supporting device for continuous left uterine displacement during cesarean section. Anesth Analg 1970;49:223.
[11] Howard BK, Goodson JH, Mengert WE. Supine hypotensive syndrome in late pregnancy. Obstet Gynecol 1953;1:371–7.
[12] Humphries A, Ali Mirjalili SA, Tarr GP, et al. The effect of supine positioning on maternal hemodynamics during late pregnancy. J Matern Fetal Neonatal Med 2018;1–8; https://doi.org/10.1080/14767058.2018.1478958.
[13] Lanni SM, Tillinghast J, Silver HM. Hemodynamic changes and baroreflex gain in the supine hypotensive syndrome. Am J Obstet Gynecol 2002;187:1636–41.
[14] De-Giorgio F, Grassi VM, Vetrugno G, et al. Supine hypotensive syndrome as the probable cause of both maternal and fetal death. J Forensic Sci 2012;57:1646–9.
[15] Golub RM, Parsons RE, Sigel B, et al. A review of venous collaterals in inferior vena cava obstruction. Clin Anat 1992;5:441–51.
[16] Mueller RP, Lynn RB, Sancetta SM, et al. Studies of hemodynamic changes in humans following induction of low and high spinal anesthesia. II. The changes in splanchnic blood flow, oxygen extraction and consumption, and splanchnic vascular resistance in humans not undergoing surgery. Circulation 1952;6:894–901.
[17] Tihtonen K, Koobi T, Yli-Hankala A, et al. Maternal hemodynamics during cesarean delivery assessed by whole-body impedance cardiography. Acta Obstet Gynecol Scand 2005;84:355–61.
[18] Leo S, Sng BL, Lim Y, et al. A randomized comparison of low doses of hyperbaric bupivacaine in combined spinal-epidural anesthesia for cesarean delivery. Anesth Analg 2009;109:1600–5.
[19] Teoh WH, Thomas E, Tan HM. Ultra-low dose combined spinal-epidural anesthesia with intrathecal bupivacaine 3.75mg for cesarean delivery: a randomized controlled trial. Int J Obstet Anesth 2006;15:273–8.
[20] Van de Velde M, Van Schoutbroeck D, Jani J, et al. Combined spinal epidural anesthesia for cesarean section: dose dependent effects of hyperbaric bupivacaine on maternal hemodynamics. Anesth Analg 2006;103:187–90.
[21] Miller RD. Miller's anesthesia. 8th edition. Philadelphia: Churchill Livingstone/Elsevier; 2015.
[22] Langesaeter E, Rosseland LA, Stubhaug A. Continuous invasive blood pressure and cardiac output monitoring during cesarean delivery. Anesthesiology 2008;109:856–63.
[23] Dyer RA, Reed AR, van Dyk D, et al. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. Anesthesiology 2009;111:753–65.
[24] Skjoldebrand A, Eklund J, Johansson H, et al. Uteroplacental blood flow measured by placental scintigraphy during epidural anaesthesia for caesarean section. Acta Anaesthesiol Scand 1990;34:79–84.
[25] Sharkey AM, Siddigui N, Downey K, et al. Comparison of intermittent intravenous boluses of phenylephrine and norepinephrine to prevent and treat spinal-induced hypotension in cesarean deliveries: randomized controlled trial. Anesth Analg 2018. [Epub ahead of print].
[26] Calvache JA, Munoz MF, Baron FJ. Hemodynamic effects of a right lumbar-pelvic wedge during spinal anesthesia for cesarean section. Int J Obstet Anesth 2011;20:307–11.
[27] Tawfik MM, Hayes SM, Jacoub FY, et al. Comparison between colloid preload and crystalloid co-load in cesarean section under spinal anesthesia: a randomized controlled trial. Int J Obstet Anesth 2014;23:317–23.
[28] Kaufner L, Karekla A, Henkelmann A, et al. Crystalloid coloading vs. colloid coloading in elective Caesarean section: postspinal hypotension and vasopressor consumption, a prospective, observational clinical trial. J Anesth 2019;33:40–9.

[29] Dyer RA, Farina Z, Joubert IA, et al. Crystalloid preload versus rapid crystalloid administration after induction of spinal anaesthesia (coload) for elective caesarean section. Anaesth Intensive Care 2004;32:351–7.
[30] Ngan Kee WD. Prevention of maternal hypotension after regional anaesthesia for caesarean section. Curr Opin Anaesthesiol 2010;23:304–9.
[31] Allen TK, Muir HA, George RB, et al. A survey of the management of spinal-induced hypotension for scheduled cesarean delivery. Int J Obstet Anesth 2009;18:356–61.
[32] Bieniarz J, Crottogini JJ, Curuchet E, et al. Aortocaval compression by the uterus in late pregnancy: II. An arteriographic study. Am J Obstet Gynecol 1968;100:203–17.
[33] Crawford JS, Burton M, Davies P. Time and lateral tilt at Caesarean section. Br J Anaesth 1972;44:477–84.
[34] Practice guidelines for obstetric anesthesia: An updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology. Anesthesiology 2016;124:270–300.
[35] Cluver C, Novikova N, Hofmeyr GJ, et al. Maternal position during caesarean section for preventing maternal and neonatal complications. Cochrane Database Syst Rev 2013;28:1–44.
[36] Higuchi H, Takagi S, Zhang K, et al. Effect of lateral tilt angle on the volume of the abdominal aorta and inferior vena cava in pregnant and nonpregnant women determined by magnetic resonance imaging. Anesthesiology 2015;122:286–93.
[37] Bamber JH, Dresner M. Aortocaval compression in pregnancy: The effect of changing the degree and direction of lateral tilt on maternal cardiac output. Anesth Analg 2003;97:256–8.
[38] Rees SG, Thurlow JA, Gardner IC, et al. Maternal cardiovascular consequences of positioning after spinal anaesthesia for Caesarean section: Left 15-degree table tilt vs. left lateral. Anaesthesia 2002;57:15–20.
[39] Jones SJ, Kinsella SM, Donald FA. Comparison of measured and estimated angles of table tilt at Caesarean section. Br J Anaesth 2003;90:86–7.
[40] Waldron KW, Wood C. Cesarean section in the lateral position. Obstet Gynecol 1971;37:706–10.
[41] Coffman JC, Legg RL, Coffman CF, et al. Lateral position for cesarean delivery because of severe aortocaval compression in a patient with Marfan Syndrome: a case report. A A Case Rep 2017;8:93–5.
[42] Morgan P. The role of vasopressors in the management of hypotension induced by spinal and epidural anaesthesia. Can J Anaesth 1994;41:404–13.
[43] Shnider S, DeLorimier AA, Holl JW, et al. Vasopressors in obstetrics: I. Correction of fetal acidosis with ephedrine during spinal hypotension. Am J Obstet Gynecol 1968;102:911–9.
[44] Ralston DH, Shnider SM, DeLorimier AA. Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. Anesthesiology 1974;40:354–70.
[45] Burns SM, Cowan CM, Wilkes RG. Prevention and management of hypotension during spinal anaesthesia for elective Caesarean section: a survey of practice. Anaesthesia 2001;56:794–8.
[46] Lee A, Ngan Kee WD, Gin T. A quantitative, systemic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2002;94:920–6.
[47] Prakash S, Pramanik V, Chellani H, et al. Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anaesthesia for caesarean delivery: a randomized study. Int J Obstet Anesth 2010;19:24–30.
[48] Thomas DG, Robson SC, Redfern H, et al. Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section. Br J Anaesth 1996;76:61–5.

[49] Ngan Kee WD, Lee A, Khaw KS, et al. 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. Anesth Analg 2008;107:1295–302.
[50] Cooper DW, Carpenter M, Mowbray P, et al. Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology 2002;97:1582–90.
[51] Cooper DW, Sharma S, Orakkan P, et al. Retrospective study of association between choice of vasopressor given during spinal anaesthesia for high-risk caesarean delivery and fetal pH. Int J Obstet Anesth 2010;19:44–9.
[52] Ngan Kee WD, Khaw KS, Tan PE, et al. Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology 2009;111:506–12.
[53] Low JA, Panagiotopoulos C, Derrick EJ. Newborn complications after intrapartum asphyxia with metabolic acidosis in the term fetus. Am J Obstet Gynecol 1994;170:1081–7.
[54] Doherty A, Ohashi Y, Downey K, et al. Phenylephrine infusion versus bolus regimens during cesarean delivery under spinal anesthesia: a double-blind randomized clinical trial to assess hemodynamic changes. Anesth Analg 2012;115:1343–50.
[55] Siddik-Sayyid SM, Taha SK, Kanazi GE, et al. A randomized controlled trial of variable rate phenylephrine infusion with rescue phenylephrine boluses versus rescue boluses alone on physician interventions during spinal anesthesia for elective cesarean delivery. Anesth Analg 2014;118:611–8.
[56] Kinsella SM, Carvalho B, Dyer RA, et al. International consensus statement on the management of hypotension with vasopressors during cesarean section under spinal anesthesia. Anaesthesia 2018;73:71–92.
[57] Stewart A, Fernando R, McDonald S, et al. The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. Anesth Analg 2010;111:1230–7.
[58] Allen TK, George RB, White WD, et al. A double-blind, placebo-controlled trial of four fixed rate infusion regimens of phenylephrine for hemodynamic support during spinal anesthesia for cesarean delivery. Anesth Analg 2010;111:1221–9.
[59] Ngan Kee WD, Khaw KS, Ng FF. Prevention of hypotension during spinal anesthesia for cesarean delivery: an effective technique using combination phenylephrine infusion and crystalloid cohydration. Anesthesiology 2005;103:744–50.
[60] Ngan Kee WD. Phenylephrine infusions for maintaining blood pressure during spinal anesthesia for cesarean delivery: finding the shoe that fits. Anesth Analg 2014;118:496–8.
[61] Vincent RD, Werhan CF, Norman PF, et al. Prophylactic angiotensin II infusion during spinal anesthesia for elective cesarean delivery. Anesthesiology 1998;88:1475–9.
[62] Carvalho B, Dyer RA. Norepinephrine for spinal hypotension during cesarean delivery: another paradigm shift? Anesthesiology 2015;122:728–30.
[63] Ngan Kee WD, Lee SW, NG FF, et al. Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery. Anesthesiology 2015;122:736–45.
[64] Avni T, Lador A, Lev S, et al. Vasopressors for the treatment of septic shock: systematic review and meta-analysis. PLoS One 2015;10:e0129305.
[65] Ngan Kee WD. A random-allocation graded dose-response study of norepinephrine and phenylephrine for treating hypotension during spinal anesthesia for cesarean delivery. Anesthesiology 2017;127:934–41.
[66] Onwochei DN, Ngan Kee WD, Fung L, et al. Norepinephrine intermittent intravenous boluses to prevent hypotension during spinal anesthesia for cesarean delivery: a sequential allocation dose-finding study. Anesth Analg 2017;125:212–8.

[67] Ngan Kee WD, Lee SWY, Ng FF, et al. Prophylactic norepinephrine infusion for preventing hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2018;126:1989–94.
[68] Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. J Crit Care 2015;30:653.e9-17.
[69] Jackson R, Reid JA, Thorburn J. Volume preloading is not essential to prevent spinal-induced hypotension at Caesarean section. Br J Anaesth 1995;75:262–5.
[70] Teoh WH, Sia AT. Colloid preload versus coload for spinal anesthesia for cesarean delivery: the effects on maternal cardiac output. Anesth Analg 2009;108:1592–8.
[71] Siddik-Sayyid SM, Nasr VG, Taha SK, et al. A randomized trial comparing colloid preload to coload during spinal anesthesia for elective cesarean delivery. Anesth Analg 2009;109:1219–24.
[72] McDonald S, Fernando R, Ashpole K, et al. Maternal cardiac output changes after crystalloid or colloid coload following spinal anesthesia for elective cesarean delivery: a randomized controlled trial. Anesth Analg 2011;113:803–10.
[73] Svensen C, Rodhe PM, Olsson J, et al. Arteriovenous differences in plasma dilution and the distribution kinetics of lactated Ringer's solution. Anesth Analg 2009;108:128–33.
[74] Ueyama H, He YL, Tanigami H, et al. Effects of crystalloid and colloid preload on blood volume in the parturient undergoing spinal anesthesia for elective cesarean section. Anesthesiology 1999;91:1571–6.
[75] Pouta AM, Karinen J, Vuolteenaho OJ, et al. Effect of intravenous fluid preload on vasoactive peptide secretion during caesarean section under spinal anaesthesia. Anaesthesia 1996;51:128–32.
[76] Carvalho B, Mercier FJ, Riley ET, et al. Hetastarch co-loading is as effective as preloading for the prevention of hypotension following spinal anaesthesia for caesarean delivery. Int J Obstet Anesth 2009;18:150–5.
[77] Arora P, Singh RM, Kundra S, et al. Fluid administration before caesarean delivery: does type and timing matter? J Clin Diagn Res 2015;9:UC01–4.
[78] Tamilselvan P, Fernando R, Bray J, et al. The effects of crystalloid and colloid preload on cardiac output in the parturient undergoing planned cesarean delivery under spinal anesthesia: a randomized trial. Anesth Analg 2009;109:1916–21.
[79] Campagna JA, Carter C. Clinical relevance of the Bezold-Jarisch reflex. Anesthesiology 2003;98:48–58.
[80] Sander-Jensen K, Marving J, Secher NH, et al. Does the decrease in heart rate prevent a detrimental decrease of the end-systolic volume during central hypovolemia in man? Angiology 1990;41:687–95.
[81] Yamano M, Ito H, Kamato T, et al. Characteristics of inhibitory effects of serotonin (5-HT)3-receptor antagonists, YM060 and YM114 (KAE-393), on the von Bezold-Jarisch reflex induced by 2-Methyl-5HT, veratridine and electrical stimulation of vagus nerves in anesthetized rats. Jpn J Pharmacol 1995;69:351–6.
[82] Yamano M, Kamato T, Nishida A, et al. Serotonin (5-HT)3-receptor antagonism of 4,5,6,7-tetrahydrobenzimidazole derivatives against 5-HT-induced bradycardia in anesthetized rats. Jpn J Pharmacol 1994;65:241–8.
[83] Heesen M, Klimek M, Hoeks SE, et al. Prevention of spinal anesthesia-induced hypotension during cesarean delivery by 5-hydroxytryptamine-3 receptors antagonists: a systematic review and meta-analysis and meta-regression. Anesth Analg 2016;123:977–88.
[84] Gao L, Zheng G, Han J, et al. Effects of prophylactic ondansetron on spinal anesthesia-induced hypotension: a meta-analysis. Int J Obstet Anesth 2015;24:335–43.
[85] Karacaer F, Biricik E, Unal I, et al. Does prophylactic ondansetron reduce norepinephrine consumption in patients undergoing cesarean section with spinal anesthesia? J Anesth 2018;32:90–7.

[86] Sun LH, Ling QD, Sun WZ, et al. Lower limb wrapping prevents hypotension, but not hypothermia or shivering, after the introduction of epidural anesthesia for cesarean delivery. Anesth Analg 2004;99:241–4.
[87] Van Bogaert LJ. Prevention of post-spinal hypotension at elective cesarean section by wrapping of the lower limbs. Int J Gynaecol Obstet 1998;61:233–8.
[88] Bhagwanjee S, Rocke DA, Rout CC, et al. Prevention of hypotension following spinal anaesthesia for elective caesarean section by wrapping of the legs. Br J Anaesth 1990;65:819–22.
[89] Sood PK, Cooper PJ, Michel MZ, et al. Thromboembolic deterrent stockings fail to prevent hypotension associated with spinal anaesthesia for elective caesarean section. Int J Obstet Anesth 1996;5:172–5.
[90] Sutherland PD, Wee MY, Weston-Smith P, et al. The use of thromboembolic deterrent stockings and a sequential compression device to prevent spinal hypotension during caesarean section. Int J Obstet Anesth 2001;10:97–102.
[91] Rout CC, Rocke DA, Gouws E. Leg elevation and wrapping in the prevention of hypotension following spinal anaesthesia for elective cesarean section. Anaesthesia 1993;48:304–8.
[92] Chooi C, Cox JJ, Lumb RS, et al. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. Cochrane Database Syst Rev 2017;(8):CD002251.
[93] Kuhn JC, Hauge TH, Rosseland LA, et al. Hemodynamics of phenylephrine infusion versus lower extremity compression during spinal anesthesia for cesarean delivery: a randomized, double-blind, placebo-controlled study. Anesth Analg 2016;122:1120–9.
[94] Cooper DW, Gibb SC, Meek T, et al. Effect of intravenous vasopressor on spread of spinal anesthesia and fetal acid-base equilibrium. Br J Anaesth 2007;98:649–56.
[95] Jain K, Makkar JK, Subramani Vp S, et al. A randomized trial comparing prophylactic phenylephrine and ephedrine for maintaining blood pressure during spinal anesthesia for emergency cesarean delivery in cases of acute fetal compromise. J Clin Anesth 2016;34:208–15.
[96] Clark RB, Thompson DS, Thompson CH. Prevention of spinal hypotension associated with cesarean section. Anesthesiology 1976;45:670–3.
[97] Henke VG, Bateman BT, Leffert LR. Focused review: spinal anesthesia in severe preeclampsia. Anesth Analg 2013;117:686–93.
[98] Aya AG, Mangin R, Vialles N, et al. Patients with severe preeclampsia experience less hypotension during spinal anesthesia for elective cesarean delivery than healthy parturients: a prospective cohort comparison. Anesth Analg 2003;97:867–72.
[99] Schobel HP, Fischer T, Heuszer K, et al. Preeclampsia: a state of sympathetic hyperactivity. N Engl J Med 1996;335:1480–5.
[100] Ashworth JR, Warren AY, Baker PN, et al. Loss of endothelium-dependent relaxation in myometrial resistance arteries in preeclampsia. BJOG 1997;104:1152–8.
[101] Sharwood-Smith G, Drummond GB. Hypotension in obstetric spinal anaesthesia: a lesson from pre-eclampsia. Br J Anaesth 2009;102:291–4.
[102] Lee AJ, Landau R, Mattingly JL, et al. Left lateral table tilt for elective cesarean delivery under spinal anesthesia has no effect on neonatal acid-base status. Anesthesiology 2017;127:241–9.
[103] Lee AJ, Landau R. Aortocaval compression syndrome: time to revisit certain dogmas. Anesth Analg 2017;125:1975–85.
[104] Farber MK, Bateman BT. Phenylephrine infusion: driving a wedge in our practice of left uterine displacement. Anesthesiology 2017;127:212–4.