West-Ward Pharmaceutical Corp.

Advisory Committee Briefing Document

Phenylephrine Hydrochloride Injection, USP - NDA 203826

10 mg/mL, 1 mL Fill in 2 mL Single-Dose Vial

Indication "to increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension"

FDA Advisory Committee Meeting

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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In-text Tables

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACEI	angiotensin-converting enzyme inhibitor
AERS	Adverse Event Reporting System
AII	angiotensin II
ANOVA	analysis of variance
ARB	angiotensin receptor blocker
ARDS	adult respiratory distress syndrome
AV	atrioventricular
BP	blood pressure
BRS	baroreceptor sensitivity
CABG	coronary artery bypass graft
CAD	coronary artery disease
CEA	carotid endarterectomy
CHF	congestive heart failure
CI	cardiac index
CKD	chronic kidney disease
CO	cardiac output
CPB	cardiopulmonary bypass
CRDAC	Cardiovascular and Renal Drugs Advisory Committee
CVP	central venous pressure
DAP	diastolic arterial pressure
DBP	diastolic blood pressure
DO_2I	oxygen delivery index
E	early peak
E_{max}	maximum possible effect
EC_{20}	dose required to increase MAP by 20 mmHg
ECG	electrocardiogram
ED_{50}	median effective dose
EDV	end-diastolic volume
EF	ejection fraction
EOT	end-of-text
EP	epinephrine
Eph	ephedrine
FBF	forearm blood flow
FDCA	Food, Drug, and Cosmetic Act
FOI	Freedom of Information
FVR	forearm vascular resistance
HF	heart failure

Abbreviation	Definition
HOCM	hypertrophic obstructive cardiomyopathy
HR	heart rate
HVOS	hepatic vein oxygen saturation
IC	intracavernosal
ICU	intensive care unit
IDDM	insulin-dependent diabetes mellitus
IM	intramuscular
IMA	internal mammary artery
IQR	interquartile range
IV	Intravenous
kg	kilogram
LQTS	long QT syndrome
LV	left ventricular
LVEF	left ventricular ejection fraction
LVF	left ventricular function
LVSWI	left ventricular stroke work index
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MAOI	monoamine oxidase inhibitor
MVO_2	myocardial oxygen consumption
OLT	orthotopic transplantation
PAOP	pulmonary artery occlusion pressure
PCG	phonocardiograph
PCO_2	partial pressure of carbon dioxide
PCWP	pulmonary capillary wedge pressure
PD_{20}	phenylephrine dose required to increase mean blood pressure by 20 mmHg
PE	phenylephrine
PK	pharmacokinetics
PO	oral, orally
PPV	pulse pressure variation
PRS	post-reperfusion syndrome
PV	pharmacovigilance
PVC	premature ventricular contractions
PVR	pulmonary vascular resistance
QTc	corrected QT
QTd	QT dispersion
RV	right ventricular

Abbreviation	Definition
SaO_2	maternal oxygen saturation
SAP	systolic arterial pressure
SBP	systolic blood pressure
SC	subcutaneous
SOC	System Organ Class
SV	stroke volume
SVI	stroke volume index
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
SVT	supraventricular tachycardia
TDR	transmural dispersion of repolarization
TEAP	transesophageal atrial pacing
TEE	transesophageal echocardiography
TMF	transmitral flow
Tp-e	the interval between the peak and the end of the T wave
TVR	total vascular resistance
UA	umbilical arterial
$UAPO_2$	umbilical arterial oxygen pressure
USP	United States Pharmacopeia
UV	umbilical venous
$UVPO_2$	umbilical venous oxygen pressure
VB	venous bypass
VO_2	oxygen consumption
VO_2I	oxygen consumption index

1. INTRODUCTION

1.1 Background

West-Ward Pharmaceutical Corp. (West-Ward) has submitted a 505(b)(2) literature-based application focused on the parenteral use of Phenylephrine Hydrochloride Injection, USP, in perioperative settings and for the treatment of patients in shock. West-Ward believes that the extensive published literature support the nonclinical profile, clinical pharmacology, and clinical efficacy and safety of the proposed Phenylephrine Hydrochloride Injection, USP, drug product in the aforementioned settings.

Phenylephrine has been used as a vasopressor, mydriatic, and decongestant agent. West-Ward's proposed drug product is a parenteral solution dosage form. Parenteral phenylephrine has been used in different medical settings, notably in critical care, cardiology, and anesthesia for over 75 years. Currently, ephedrine and phenylephrine are the most common vasoactive agents in the obstetric setting for the management of maternal hypotension following spinal anesthesia. A recent survey[1] of members of the Society for Obstetric Anesthesia and Perinatology found that of respondents who used vasopressors prophylactically during scheduled cesarean delivery, 23% used phenylephrine, 32% used ephedrine, and 33% based their choice on heart rate. Further, for the treatment of spinal anesthesia-induced hypotension, 26% used phenylephrine, 32% used ephedrine, and 41% used either agent, depending upon heart rate. In another survey, 235 pharmacists indicated that in the surgical/trauma intensive care unit (ICU), phenylephrine was 1 of the 3 most commonly chosen first-line vasopressors (norepinephrine and dopamine were the others).[2] Phenylephrine also is frequently used for hemodynamic support in patients in septic shock in the United States. A large, retrospective, cohort analysis by Lindenauer et al[3] revealed that among 33,749 patients with septic shock treated at 404 hospitals in the United States, the following vasopressor usage was reported: dopamine, 64.5%; norepinephrine, 50.1%; phenylephrine, 22.9%; vasopressin, 10.3%; and epinephrine, 8.7%.

Phenylephrine's unique properties among other sympathomimetics are well understood, and its reasonable safety profile and effectiveness continue to secure this drug product's position in many of the treatment regimens used by critical care, cardiology, and anesthesiology physicians. West-Ward believes that the published data support the clinical pharmacology, safety, and efficacy of parenterally administered phenylephrine to increase blood pressure (BP) in acute hypotensive states, such as shock and perioperative hypotension.

This briefing document was prepared by West-Ward in response to the questions presented by the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) and in support of the proposed indication for Phenylephrine Hydrochloride Injection, USP, drug product.

2. QUESTION 1

We are interested in the type of evidence needed to establish clinical benefit for drugs to be used for the treatment of acute hypotension. The type of evidence could range from an increase in BP to more stringent requirements, ie, avoidance of irreversible morbidity or improvement in survival. Between these extremes, some might view improvements in organ function, organ and/or tissue perfusion, or tissue oxygenation as clinical benefits. We recognize that the type of evidence could depend on the specific clinical setting.

Please discuss your views on the type of evidence needed to demonstrate a clinical benefit in the setting of:

- **shock**
- **perioperative hypotension**
- **"acute hypotensive states"**

SPONSOR'S RESPONSE

2.1 Acute Perioperative Hypotension

Hypotension (typically defined as systolic blood pressure [SBP] < 90 mmHg or < 80 mmHg or ≥ 20% decrease from baseline) in the spinal anesthesia setting results from a sympathetic nervous system block that decreases both venous return to the heart and cardiac output (CO) and/or decreases systemic vascular resistance (SVR)[4] and is estimated to occur in about one-third of patients undergoing spinal anesthesia.[5] Acute perioperative hypotension also may occur after general anesthesia, particularly in the setting of cardiopulmonary bypass (CPB). Prolonged intraoperative hypotension is associated with increased mortality[6] as well as both cardiac and noncardiac adverse effects.[7, 8] In the perioperative setting, therefore, restoration of BP is the immediate goal of vasopressor therapy, and increased BP is the appropriate endpoint for a drug such as phenylephrine that exerts its vasoconstriction effects via specific binding to α_1-adrenergic receptors.

While maintenance of tissue perfusion and other downstream effects represent the overall clinical benefit achieved after restoring BP with phenylephrine, other patient variables may affect this outcome, as well as morbidity and mortality. In support of this reasoning, Bijker et al[9] found no association between intraoperative hypotension and the risk of dying within 1 year after surgery, using a Cox regression analysis after adjustment for

confounding factors. Specific endpoints reported in the literature submitted in the Sponsor's application are discussed below. The Sponsor included all endpoints reported in the studies for sake of completeness; the Sponsor believes, however, that increases in BP or decreases in frequency of hypotension are the most appropriate endpoints for evaluation of a drug, such as phenylephrine, that acts as a short-term vasoconstrictor.

2.2 Cesarean Delivery

In the setting of cesarean delivery, untreated hypotension may have mild to serious detrimental effects in the mother (mild: nausea, vomiting; severe: unconsciousness, pulmonary aspiration, apnea, cardiac arrest) and in the neonate (hypoxia, acidosis, low Apgar scores).[10] The immediate goal of vasopressor or other therapy is to restore maternal BP without compromising uterine blood flow. All 26 randomized controlled studies of phenylephrine in the setting of cesarean delivery submitted in the Sponsor's application examined BP as an endpoint; 24 of the 26 studies also examined neonatal outcome as a safety, rather than an efficacy endpoint. Most studies also examined heart rate as an additional endpoint, and some examined frequencies of maternal nausea and vomiting. In a few studies,[11, 12] additional hemodynamic parameters (eg, CO, end-diastolic volume [EDV], SVR, total vascular resistance [TVR]) were examined. All 26 studies showed that phenylephrine significantly increased maternal BP, and none showed detrimental effects on the neonate.

A more comprehensive examination of the endpoints and outcomes in the subset of 6 randomized, double-blind, well-controlled, and appropriately analyzed studies[13, 14, 15, 16, 17, 18] of phenylephrine use during cesarean delivery are summarized below and in End-of-Text Table 1. Of note is that 2 randomized, double-blind, controlled studies that were included in the application were not included in this summary: a study by Langesaeter et al[19] used an inappropriate pairwise comparison in the data analysis, and a study by Allen et al[20] had a nonhemodynamic primary endpoint that was not met. These 2 studies are further addressed in Question 3.

The primary efficacy endpoint in all 6 studies was the change in BP or frequency of hypotension. Effects on heart rate and neonatal outcomes were included as safety endpoints in all 6 studies. Frequencies of nausea and vomiting were examined in 3 of the 6 studies. Outcomes in these 6 studies are shown in End-of-Text Table 2 and summarized below.

2.2.1 Effects on BP

All 6 studies[13, 14, 15, 16, 17, 18] showed efficacy of phenylephrine for increasing BP in the setting of cesarean delivery under neuraxial anesthesia. In 4 of the 6 studies, phenylephrine was associated with a similar frequency of hypotensive episodes as was ephedrine.[13, 14, 15, 21] In 1 study,[16] phenylephrine and ephedrine increased SBP to a similar extent (borderline higher SBP for phenylephrine), and in the remaining study,[17] phenylephrine was superior to placebo for preventing hypotensive episodes and resulted in higher systolic arterial pressure (SAP) over the course of the study compared with placebo.

2.2.2 Effects on Heart Rate

In 5 of the 6 studies, phenylephrine treatment resulted in greater decreases in heart rate than did ephedrine or placebo.[13, 14, 15, 17, 21] In 1 study,[16] similar changes in heart rate were observed with phenylephrine and ephedrine.

Three of the 6 studies[14, 15, 16] reported a higher frequency of bradycardia in patients treated with phenylephrine compared with those treated with ephedrine, although the difference between the treatment groups did not reach significance in one[16] of the 3 studies. One study reported a higher frequency of tachycardia in patients treated with ephedrine.[15]

2.2.3 Effects on Nausea and Vomiting

Three studies examined frequencies of nausea and vomiting. In 2 studies, no differences in frequencies of these outcomes were observed for patients treated with either phenylephrine or ephedrine.[13, 16] In 1 study, patients treated with phenylephrine had lower frequencies of nausea and vomiting than did patients treated with ephedrine.[15]

2.2.4 Neonatal Outcome

In the 5 actively controlled studies[13, 14, 15, 16, 21] effects of phenylephrine on neonatal outcomes (Apgar scores, umbilical cord indices) were similar or better than those observed with ephedrine. In the placebo-controlled study,[17] neonatal health was similar in neonates born to mothers treated by continuous infusion of phenylephrine to that of neonates born to mothers treated with placebo and phenylephrine rescue (as needed).

2.2.5 Summary

Collectively, results from these randomized, double-blind, well-controlled and appropriately analyzed studies indicate that BP is the appropriate endpoint for studies examining the efficacy of phenylephrine for increasing BP in the setting of cesarean delivery under neuraxial anesthesia. Other downstream effects of increasing BP

(decreased nausea and vomiting and prevention of negative neonatal outcomes) have been observed in clinical studies, but these effects have the potential to be affected by other variables, such as comorbid conditions. While decreased heart rate, a direct side effect of phenylephrine treatment, may be of concern in certain patients, no untoward adverse effects were reported as a result of the intraoperative decreases in heart rate observed in these studies of women undergoing cesarean delivery under neuraxial anesthesia. The effect of phenylephrine on heart rate is discussed in the response to Question 4 (safety outcomes) (refer to Section 5).

2.3 Other Neuraxial Surgery

Both of the randomized studies of phenylephrine in the setting of nonobstetric surgeries under neuraxial anesthesia[22, 23] used BP or frequency of hypotension as the primary endpoint. Other endpoints were heart rate and CO. Endpoints are listed in End-of-Text Table 3. The crossover study by Brooker[20] compared phenylephrine and epinephrine and included 13 patients undergoing the following types of surgical procedures under spinal anesthesia: 5 orthopedic; 6 urologic; and 2 gynecologic. The study by Cheng et al[22] compared 3 doses of phenylephrine and placebo and involved 80 patients undergoing inguinal hernia repair under epidural anesthesia. Although the study by Cheng et al,[22] as noted in Question 3 (Section 4), did not meet the primary endpoint, which was an overall analysis of variance (ANOVA) comparison of differences in mean arterial pressure (MAP) among controls and 3 phenylephrine dose groups, the Sponsor believes that the results of the study are adequate to support the indication of phenylephrine for increasing BP in the perioperative setting. This issue is discussed further in the response to Question 3.

Outcomes for each of the endpoints are shown in End-of-Text Table 4 and summarized below.

2.3.1 Blood Pressure

In a study by Brooker et al,[24] MAP, systolic arterial pressure (SAP), and diastolic arterial pressure (DAP) were significantly increased by phenylephrine. Epinephrine caused a significant increase in MAP and SAP, but not DAP. The numbers of bolus rescue infusions or rate increases to restore BP were similar during treatment with each vasopressor. In the study by Cheng et al,[22] although the planned primary endpoint comparing mean MAP over time among the 4 groups did not show significance (also see Question 3), the planned analyses did show significant negative correlations between hypotension and phenylephrine dose and between the use of rescue ephedrine and phenylephrine dose: the proportions with hypotension for the control,

50, 100, or 200 µg phenylephrine groups were 45%, 55%, 35%, and 15% , respectively ($r = –0.254$; $P = 0.023$) and the proportions of patients who required rescue medication were 40%, 40%, 20%, and 10%, respectively ($r = –0.275$; $P = 0.013$). Post-hoc analyses (see End-of-Text Table 4) comparing MAP between treatment groups at individual time points also demonstrate that phenylephrine significantly increased BP in this setting.

2.3.2 Heart Rate

In the study by Brooker et al,[24] heart rate was significantly decreased by phenylephrine and significantly increased by epinephrine. There were no subsequent adverse effects related to the increased heart rate; 2 patients required additional treatment to correct severe bradycardia following phenylephrine infusion. In the study by Cheng et al,[22] there were no overall differences in time courses of heart rate across groups, but a significant effect of dose by time was observed ($P = 0.0148$).

2.3.3 Other Hemodynamic Endpoints

In the study by Brooker et al,[24] stroke volume (SV) was unchanged by phenylephrine and was significantly increased by epinephrine. Further, CO was significantly decreased by phenylephrine and was significantly increased by epinephrine. In the study by Cheng et al,[22] foot temperature was increased in all groups, with no significant difference overall or between pairs of groups, indicating no evidence of peripheral vasoconstriction in the patients undergoing inguinal hernia repair under epidural anesthesia.

2.3.4 Summary

Taken together, these 2 randomized, double-blind studies support the use of increased BP/frequency of hypotension as the primary variable for considering the efficacy of phenylephrine for increasing BP in the perioperative setting.

2.4 Cardiac and Vascular Surgery

Hypotension related to general anesthesia is dependent upon the agents used and usually results from decreased CO or SVR. In particular, the use of vasopressors is commonplace during cardiac bypass surgery, where anesthesia-induced arterial hypotension may be exacerbated by the underlying myocardial insufficiency.[25] In this setting, vasopressors not only provide control of arterial BP, but also ensure adequate graft perfusion.[26] Of 4 randomized, controlled studies (1 double-blind; 3 open-label) of phenylephrine in the setting of cardiac surgery submitted in the Sponsor's application,[27, 28, 29, 30] two used BP as the primary endpoint and 2 used BP as a secondary endpoint, with primary endpoints of graft flow or splanchnic effects after coronary artery bypass graft (CABG).[28,30] Additionally, these studies examined other hemodynamic

parameters such as CO, heart rate, SV, systemic vascular resistance index (SVRI), cardiac index (CI), left ventricular function (LVF) , pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), left ventricular stroke work index (LVSWI), and pulmonary artery occlusion pressure (PAOP). One randomized controlled study of phenylephrine in the setting of noncardiac vascular surgery (endarterectomy) used BP as a primary endpoint, as well as other hemodynamic parameters and measures of cardiac function as secondary endpoints.

2.4.1 Nonhemodynamic Endpoints

In the study by DiNardo et al,[28] saphenous vein graft flow was not significantly increased by phenylephrine, whereas norepinephrine and epinephrine both significantly increased flow. Internal mammary artery (IMA) graft flow was significantly decreased by phenylephrine, but was increased by the other vasopressors. Thus, treatment with phenylephrine did not meet the required outcome with respect to graft flow (primary efficacy endpoint). In the study by Nygren et al,[30] perfusion of the gastrointestinal mucosa was not impaired by either phenylephrine or norepinephrine. Thus, the primary efficacy endpoint was met.

2.4.2 Blood Pressure

In each of the 4 CABG studies, phenylephrine was shown to effectively and significantly increase BP in the setting of general anesthesia. In the studies by Goertz et al[27] and DiNardo et al,[28] phenylephrine was as effective as norepinephrine and epinephrine for increasing BP in patients under general anesthesia for CABG surgery. In the study by Baraka et al,[29] phenylephrine was effective for increasing BP in patients who experienced hypotension during cardiac surgery. In the study by Nygren et al,[30] phenylephrine was as effective as norepinephrine for increasing MAP following CABG. In the study by Smith et al,[31] in patients undergoing elective endarterectomy, BP was maintained within 5 mmHg of the prestudy value in all patients. Among patients in the high-dose anesthetic groups, 76% required phenylephrine at the time of skin incision, and all required phenylephrine to maintain BP during carotid occlusion. These results support the ability of phenylephrine to increase BP during hypotensive states due to general anesthesia.

2.4.3 Heart Rate

Goertz et al[27] reported that both phenylephrine and norepinephrine caused a significant decrease in heart rate in patients undergoing CABG, whereas only phenylephrine had this effect in the patients undergoing valve replacement. In the study by DiNardo et al,[28] heart rate was not significantly changed by any of the vasopressors. In the study by Baraka et al,[29] heart rate was significantly decreased with phenylephrine and

norepinephrine, but not with epinephrine. In the study by Nygren et al,[30] heart rate was not significantly changed with phenylephrine or norepinephrine. In the study by Smith et al[31] in patients undergoing elective endarterectomy, heart rate was similar across all 4 groups (control anesthetic and anesthetic plus phenylephrine).

2.4.4 Other Cardiac Function Parameters

Goertz et al[27] reported that LVF was impaired only in the CABG/phenylephrine group. No impairment was observed in patients undergoing valve replacement. In the study by DiNardo et al,[28] the CI was significantly decreased after infusion of phenylephrine, but was not changed after infusion of norepinephrine or epinephrine. CVP were not significantly changed by any of the vasopressors. PCWP was not significantly changed with phenylephrine or norepinephrine, but was significantly increased with epinephrine. LVSWI was significantly increased by all 3 vasopressors. In the study by Baraka,[29] CO was not changed with phenylephrine or norepinephrine, while epinephrine caused a significant increase. PCWP was increased significantly by all 3 vasopressors. SVR was significantly increased by phenylephrine or norepinephrine, but was not changed with epinephrine. In the study by Nygren,[30] CVP and PAOP showed small, but significant increases with both phenylephrine and norepinephrine. CI and SV were not significantly changed with either vasopressor. SVRI was significantly increased with both vasopressors. In the endarterectomy study by Smith et al,[31] patients who received a higher concentration of anesthetic plus phenylephrine had a higher wall stress (both anesthetic groups). All 4 groups had similar stump pressures (the marker surgeons used for adequacy of collateral carotid flow). No difference could be found in wall stress or incidence of myocardial ischemia between isoflurane and halothane. The patients who received phenylephrine had a 3-fold greater incidence of myocardial ischemia (see Question 4, Section 5) than did the patients who had lower level anesthesia to maintain similar systolic BPs and stump pressures.

However, in a review of the study by Smith et al,[31] Ertmer et al[25] suggested that the adverse effects in this study were due to the high doses of the anesthetics, and that the higher concentrations of anesthetic resulted in a level of anesthesia that was too deep. The authors of this review proposed that the higher rate of myocardial infarction was due to the high dose of anesthetic, rather than to phenylephrine, and that, while phenylephrine appeared to be safe for use during carotid surgery, it should not be used to counteract anesthesia that is too deep.

2.4.5 Summary

All 5 studies in cardiac or noncardiac vascular surgery showed that phenylephrine significantly increased BP in this setting. While other hemodynamic endpoints were also examined, the endpoint of BP represents the immediate and direct effect of phenylephrine. The studies adequately support the indication of increased BP in the perioperative setting. Although 1 study[28] failed to meet the primary endpoint (saphenous vein graft flow), the study nevertheless documented significantly increased BP, which is the action of the drug in question. While adequate graft flow is essential for patients undergoing CABG, other variables unrelated to the choice of vasopressor may impact graft flow. Safety concerns regarding heart rate, left ventricular (LV) function, and graft flow are addressed in Question 4 (Section 5).

2.5 Shock

In the setting of shock, hypotension occurs due to the vasodilation, increased capillary permeability, and decreased SVR resulting from the massive cytokine-mediated inflammatory response. Hypotension reduces tissue perfusion pressure causing tissue hypoxia and resultant ischemia. Restoration of BP is the first goal of vasopressor therapy and usually follows attempts at fluid resuscitation. Improvements in tissue perfusion, oxygenation, etc, are a direct result of increasing BP; however, other patient characteristics (such as the etiology of the underlying infection, patient age, timing of diagnosis, intravascular volume status, and comorbid conditions) may also have an impact on such subsequent effects following restoration of BP. Many variables will affect morbidity and mortality in patients experiencing acute hypotension, even if BP is adequately restored. Phenylephrine is a potent α-adrenergic-specific vasoconstrictor that increases SBP, diastolic blood pressure (DBP), and MAP, without affecting inotropy or chronotropy, although reflex bradycardia may occur (refer to Section 5.2). Phenylephrine is frequently used for hemodynamic support in patients in septic shock in the United States, as shown in a large, retrospective, cohort analysis by Lindenauer et al.[3]

Two randomized, double-blind, controlled studies of phenylephrine in the setting of septic shock[32, 33] were included in the Sponsor's application. Both studies demonstrated the efficacy of phenylephrine for increasing BP in patients in septic shock. Blood pressure changes were one of the primary endpoints in both studies. Additional endpoints examined in the 2 studies included heartrate, SVRI, oxygen delivery index (DO_2I), oxygen consumption index (VO_2I), PAOP, lactate, stroke volume index (SVI), hepatic vein oxygen saturation (HVOS), response and survival rates, and occurrence of arrhythmias.

2.5.1 Blood Pressure

In a study by Morelli et al,[32] phenylephrine and norepinephrine were compared as first-line therapy in 32 patients with septic shock. Both drugs significantly increased MAP from baseline to the target of 65 to 75 mmHg over a study period of 12 hours. In the study by Jain and Singh,[33] phenylephrine and norepinephrine were compared as second-line therapy in 54 patients with dopamine-resistant septic shock (ie, persistent hypotension after fluid resuscitation and dopamine infusion). Results demonstrated significant increases in SBP and MAP, and similar rates of hemodynamic response (SBP > 90 mmHg and MAP > 75 mmHg for 6 hours) and survival for both treatment groups. Data from these studies demonstrate that administration of phenylephrine is as efficacious as norepinephrine when used as initial or second-line hemodynamic support of patients in septic shock.

2.5.2 Heart Rate

In the study by Morelli et al,[32] heart rate was significantly decreased by both phenylephrine and norepinephrine. In the study by Jain and Singh,[33] heart rate was significantly decreased with norepinephrine, but was unchanged with phenylephrine.

2.5.3 Other Hemodynamic Endpoints

In the study by Morelli et al,[32] SVRI and LVSWI were significantly increased by both phenylephrine and norepinephrine. The PVR index increased significantly only in the phenylephrine group. Dobutamine requirements were similar between the 2 groups. Other systemic hemodynamic parameters, as well as indicators of regional hemodynamics, acid-base homeostasis, and oxygen transport were similar for both treatment groups.

In the study by Jain and Singh,[33] SVRI, DO_2I, VO_2I, and HVOS were significantly increased by both phenylephrine and norepinephrine. SVI was significantly increased with norepinephrine but was unchanged with phenylephrine. PAOP increased significantly only with norepinephrine. Posttreatment CI was not significantly changed in either group. Urinary output was significantly increased in both groups.

2.5.4 Response and Survival

In the study by Morelli et al,[32] the mortality rates were similar for phenylephrine and norepinephrine (63% and 56%, respectively). The length of ICU stay also was similar for the 2 groups. In the study by Jain and Singh,[33] response rates were 20 of 27 (74%) for phenylephrine and 19 of 27 (70%) for norepinephrine, and survival rates were 12 of 27 (44%) for phenylephrine and 11 of 27 (41%) for norepinephrine.

2.5.5 Other Endpoints

In the study by Morelli et al,[32] regional hemodynamics, acid-base homeostasis, and oxygen transport were similar with both vasopressors. New-onset tachyarrhythmia rates also were similar: 2 of 16 for phenylephrine and 1 of 16 for norepinephrine. Urine output and creatinine clearance were similar between the groups as were troponin I plasma concentrations. In the study by Jain and Singh,[33] posttreatment serum lactate was significantly decreased by both phenylephrine and norepinephrine, and fluid infusion was similar for both groups.

2.5.6 Summary

Phenylephrine was as efficacious as norepinephrine for increasing BP when used as initial hemodynamic support of patients with septic shock. Within each study, mortality rates were not significantly different for patients treated with either vasopressors.

2.6 Other Acute Hypotensive States

2.6.1 Other Types of Shock

Use of phenylephrine in other types of shock is less well studied. Vasopressors with pure α-adrenergic action, such as phenylephrine, are generally contraindicated in cardiogenic shock, but conclusions from several review articles suggest that careful and limited use of phenylephrine is possible in patients in cardiogenic shock. Clinical trials investigating phenylephrine for the treatment of hypotension in anaphylactic shock are lacking. Conclusions from 2 review articles suggest that phenylephrine should be available for limited use in the armamentarium for treatment of anaphylactic shock, as supplementary therapy for persistent hypotension, or in patients with coronary insufficiency. Clinical trials investigating phenylephrine for the treatment of hypotension in vasodilator shock following cardiac surgery also are lacking.

2.6.2 Other Hypotensive States

Randomized, blinded, controlled studies of intravenous phenylephrine are lacking in acute hypotensive states accompanying other conditions, such as myocardial infarction, flash pulmonary edema, congestive heart failure, orthostatic hypotension, cardiogenic shock, burn-related shock, trauma, stroke, neurogenic shock, gastrointestinal hemorrhage, anaphylaxis (blood transfusions and drug reactions), and dialysis (Refer to Section 5).

2.6.3 Use in Children

Randomized, well-controlled studies of phenylephrine have not been conducted in children. Three nonrandomized uncontrolled studies suggest that phenylephrine is efficacious for treatment of children experiencing acute hypotension due to tetralogy of

Fallot, neurocardiogenic syncope, or traumatic brain injury.[34-36] One case report demonstrated restoration of BP in a child undergoing kidney transplant.[37]

2.7 Summary

The indication sought for phenylephrine for intravenous infusion is "to increase BP in acute hypotensive states, such as shock and peri-operative hypotension." Phenylephrine's rapid onset and short duration of action (15 to 20 minutes) in causing vasoconstriction and increased BP indicate that BP is the appropriate endpoint. Additional downstream outcomes have been reported in the literature submitted, as described above, and serious untoward effects were not seen, although some precautions are warranted (see Question 4). The Sponsor makes no claim that phenylephrine will ensure decreased morbidity or mortality in patients experiencing acute hypotension, as the underlying cause of the hypotension varies, as do the comorbid conditions of such patients. In both the perioperative setting and in shock, the use of phenylephrine is intended as one drug in the armamentarium used to manage the patient, and is specifically used to treat the associated acute hypotension and not other aspects of the patient's underlying condition. As such, the Sponsor believes that an endpoint of increased BP is appropriate for the use of intravenous phenylephrine in the varied perioperative settings of acute hypotension described above, as well as for the acute hypotension associated with septic shock and in various settings of acute hypotensive episodes in children.

3. QUESTION 2

In considering the effects of drugs in acute hypotensive states, does it matter whether we consider systolic BP or mean arterial BP? If there are advantages and disadvantages of the two measures, which one is preferred?

SPONSOR'S RESPONSE

BP is generally measured to assess systemic perfusion. SBP and DBP actually reflect only one individual beat of the heart (contraction and relaxation cardiac pressures, respectively) and, therefore, have the potential to be misleading. For example, DBP can be affected by peripheral vasoconstriction and SBP by a hypo- or hyperdynamic left ventricle. In contrast to SBP and DBP, MAP provides an indication of the average perfusion pressure across the entire cardiac cycle. Because diastole represents two-thirds of the cardiac cycle and systole takes up one-third of the cycle, MAP can be estimated according to the following equation:

$$MAP = (2 \times DBP + SBP)/3$$

The true MAP can be calculated as follows:

$$MAP = (CO \times SVR) + CVP$$

MAP is considered to represent the perfusion pressure that exists at the organ/tissue level in the body and, as such, is the physiologic driving force behind blood flow to organs and tissues. Because tissue hypoperfusion is the pathophysiologic endpoint of low BP, MAP, rather than SBP or DBP, MAP would be a preferred parameter in settings where tissue perfusion could be compromised. Perfusion can be insufficient (as indicated by a low MAP) in the presence of normal SBP, if CO is too low.

Among the 15 randomized, blinded, controlled studies that provide the best evidence of the efficacy of phenylephrine for increasing BP in acute hypotensive states, 9 studies included MAP for assessing BP.[13, 15, 17, 28, 29, 30, 32, 33, 38] Five studies in cesarean delivery[13, 14, 15, 16, 21] and 1 study in noncardiac vascular surgery[31] examined SBP. Although MAP would have been the preferred parameter for ensuring adequate tissue perfusion, in the 5 studies in cesarean delivery, the investigators also reported neonatal outcomes. Because neonatal outcomes were favorable with phenylephrine, the data reflect the adequacy of tissue perfusion to the fetus.

Among 4 nonrandomized, uncontrolled clinical reports on the use of phenylephrine in children, the 3 involving the settings of Tetralogy of Fallot,[34] neurocardiogenic

syncope,[35] or traumatic brain injury[36] examined MAP. The fourth pediatric study, involving kidney transplant[37] examined SBP, as well as other endpoints that ensured adequate blood flow in the donor organ.

In summary, while MAP may be the preferred measure of BP at the tissue level, SBP can be considered sufficient for demonstrating efficacy of phenylephrine in the setting where tissue perfusion was monitored by a separate endpoint.

4. QUESTION 3

Few of the publications submitted were randomized, double-blind, placebo-controlled studies. Two of these (Allen, Cheng) did not meet the primary endpoint; Langesaeter did not control for multiplicity and involved an incorrect pairwise comparison. How much should the Agency rely on these studies?

Based on the above, do the data support a claim for:

- **shock**
- **perioperative hypotension**
- **"acute hypotensive states"**

SPONSOR'S RESPONSE

4.1 Perioperative Hypotension

As noted above in the response to Question 1, six randomized, double-blind, well-controlled, and appropriately analyzed studies support the efficacy of phenylephrine in the setting of cesarean delivery under neuraxial anesthesia (see Section 2.2). The studies by Allen et al[20] and Langesaeter et al[19] are not included in this group of 6 studies. As noted by the Agency, the study by Langesaeter[19] used inappropriate statistical methods. The study by Allen et al[20] used a nonhemodynamic endpoint (number of physician interventions) that was confounded by episodes of both hypotension and hypertension. The Sponsor has not included this study in the summary described in Section 2.1 under Question 1. As noted in the response to Question 1, the combined results from 6 randomized, blinded, well-controlled studies in cesarean delivery are sufficient to demonstrate the efficacy of phenylephrine for increasing BP in the setting of acute hypotension.

In the setting of other surgeries performed under neuraxial anesthesia, 2 studies[22, 24] are considered adequate, as noted in the response to Question 1 (see Section 2.3). In the study by Cheng et al,[22] results of the primary overall comparison (ANOVA) of mean MAP over time in the placebo and 3 phenylephrine dose groups was not significant, nor was the interaction of dose and time significant. The comparison of mean MAP over time did not allow detection of differences at individual time points. However, results of the planned primary analysis did show significant negative correlations between phenylephrine dose and frequency of hypotensive episodes ($P = 0.023$) and between

phenylephrine dose and frequency of rescue injections (P = 0.013), as detailed above (see Section 2.3).

In the setting of cardiac or vascular surgery under general anesthesia (see Section 2.4), 1 randomized, double-blind controlled study (Goertz et al[27]) and 4 randomized, open-label controlled studies (DiNardo et al,[28] Baraka et al,[29] Nygren et al,[30] and Smith et al[31]) demonstrated that phenylephrine effectively and significantly increase BP in the setting of general anesthesia.

The Sponsor believes that the totality of the findings from these 15 studies, 11 of which were randomized, double-blind, and controlled and 4 of which were randomized, controlled, and open-label, are sufficient to demonstrate the efficacy of phenylephrine in the perioperative setting.

4.2 Shock

Refer to the response to Question 1 (Section 2.5) for a summary of the data from 2 randomized, double-blind, controlled studies of phenylephrine for increasing BP in the setting of septic shock.

5. QUESTION 4

Safety data in the application were obtained from publications and postmarketing reports.

There is no overall exposure analysis.

a. **How confident should the Agency be that the safety profile has been well characterized in the submission?**

b. **Is there additional safety information that the Agency should request? If so, should this information be requested pre-approval or post approval?**

SPONSOR'S RESPONSE

5.1 Drug Exposure

Although a formal overall exposure analysis was not performed by the Sponsor for this 505(b)(2) application, the efficacy and safety data presented in the Sponsor's application show that phenylephrine has been used for decades in a wide range of patient populations, disease states, clinical settings, dosages, and methods of administration and that it is a reliable, well-tolerated drug.

5.1.1 Marketing and Recent Usage Data

Although it is not possible to determine the actual extent of current exposure to phenylephrine, marketing data is presented for perspective. For the past 2 years, the total units (10 mg/mL vial and 1 mL ampoules) of phenylephrine sold (by Baxter, American Regent Laboratories, Parenta Pharmaceuticals, and Teva) have averaged about 2,000,000 units per quarter.

As described in Section 1.1, recent survey data show that ephedrine and phenylephrine are the most common vasoactive agents in the obstetric setting for the management of maternal hypotension following spinal anesthesia.[1] Other surveys demonstrate that phenylephrine is 1 of the 3 most common first-line vasopressors used in the surgical/trauma ICU,[2] and it also is frequently used for hemodynamic support in patients in septic shock in the United States.[3]

5.1.2 Exposure in Published Literature

Parenteral phenylephrine has been used in different medical settings, notably in critical care, cardiology, and anesthesia, for over 75 years. The first publications on the clinical

use of phenylephrine date back to 1937 (see Section 5.3.1), and its use in clinical trials has continued over the ensuing decades. The safety profile of patients administered phenylephrine to treat or prevent hypotension was summarized in the Sponsor's application. Overall, it was shown that phenylephrine was a safe and well tolerated drug.

5.1.2.1 Clinical Studies in Obstetric Patients

For the setting of cesarean delivery, 29 efficacy studies presented in the Sponsor's application were reviewed for maternal adverse events and fetal outcomes (adverse events). The findings are summarized in End-of-Text Table 9. Across these 29 studies, 1270 mothers were exposed to phenylephrine to treat hypotension associated with cesarean delivery.

5.1.2.2 Clinical Studies in Nonobstetric Patients

Twenty-five studies were presented in the Sponsor's application, summarizing the safety profile of phenylephrine in the settings of nonobstetric surgeries under neuraxial anesthesia, cardiac and noncardiac general surgery under general anesthesia, and the treatment of hypotension due to septic shock (refer to End-of-Text Table 10). Across these 25 studies, 922 patients were exposed to phenylephrine.

5.1.2.3 Use in Baroreceptor Sensitivity (BRS) Studies

Twenty-one representative BRS studies (in which patients are administered phenylephrine to increase BP to a predetermined level so that the baroreceptor reflex elicited by the rapidly increased BP can be measured) are summarized in End-of-Text Table 11. Across these 25 studies, 3539 patients were exposed to phenylephrine. Populations represented in these studies included 2618 post-MI patients (including 1284 patients after acute MI in 1 study), 514 patients with chronic heart failure, 220 patients with type 2 diabetes, 54 with hypertension, 36 with portal hypertension, and 36 healthy volunteers.

5.1.3 Use in Pediatric Patients

In the Sponsor's application, 3 clinical studies and a case report were presented describing the use of intravenous phenylephrine in children (from 7 days to 17 years). Taken together, 68 children were exposed to phenylephrine to treat hypotension in the settings of tetralogy of Fallot (4 patients), neurocardiogenic syncope (16 patients), traumatic brain injury (47 patients), and kidney transplantation (1 patient). Refer to Section 5.6.1.2 for a further discussion of the use of phenylephrine in children.

5.1.4 Case Reports and Nonintravenous Use

In addition to clinical studies, the literature was searched for case reports of patients with adverse reactions to phenylephrine. In addition to its use as a vasopressor, phenylephrine has been used as a mydriatic and decongestant agent, and has been administered in oral, ophthalmic, and intranasal dosage forms. Given that much of the use of phenylephrine has been ocularly (topical or subconjunctival injection) or nasally administered, case reports of adverse events following the use of these formulations were reviewed so that phenylephrine's safety profile could be completely characterized.

5.1.5 Current Practice

Intravenous phenylephrine is widely used in the setting of anesthesia-induced hypotension and to correct acute hypotension in various settings, including shock. Conclusions from 2 review articles (Yazbek and Kleinman[39] and Ellis et al[40]) suggest that phenylephrine should be available for limited use in the armamentarium for treatment of anaphylactic shock, as supplementary therapy for persistent hypotension, or in patients with coronary insufficiency. Additionally, Costanzo et al,[41] on behalf of several task forces of the International Society of Heart and Lung Transplantation, recommended the following practice for heart transplant recipients: "Continuous infusion of α-adrenergic agonists including phenylephrine, norepinephrine, or epinephrine can be used to maintain adequate mean arterial pressure."

With regard to its use in children, Carcillo and Cunnion[42] suggest the use of phenylephrine as a possible second-line vasopressor, depending upon the contribution of hypovolemia, cardiac dysfunction, and vascular dysfunction associated with ongoing septic shock. Shanthi[43] lists phenylephrine as a vasopressor for use in the treatment of shock in children. (Refer to Section 5.6.1.2 for a further discussion of the use of phenylephrine in children.)

5.1.6 Concentration-Response and Dose-Response Analysis of Phenylephrine (Post-hoc Analysis)

A post-hoc concentration-response and dose-response analysis of the published literature data for intravenous phenylephrine was performed, using the primary effects of phenylephrine on BP and heart rate.

Because none of the 8123 clinical pharmacology citations retrieved from the literature searches were found to contain concentration-exposure data for phenylephrine, pharmacokinetic (PK) modeling and simulation were used to construct a concentration-exposure analysis. The PK data were taken from the published literature.

Pharmacodynamic data were taken from 18 articles that contained adequate dose-response information.

Data from healthy subjects were used to profile the drug exposure-response relationship by plotting exposure (dose infused or plasma concentration) against changes in 1 of the 4 pharmacological measurements: SBP, DBP, MAP, or heart rate. Additional demographic parameters (where available) that were investigated to determine any influence on the exposure-response relationship, including hypertension, age (young vs old), sex, race, (Caucasian vs Nigerian), coronary artery disease (CAD), coronary artery bypass surgery, diabetes, coadministration of atropine, and prior administration of noradrenaline (also refer to Section 5.6 for a discussion of the use of phenylephrine in special populations).

Using pooled data from healthy subjects, a linear increase in SBP, DBP, and MAP resulted from an increase in phenylephrine exposure. Phenylephrine caused an initial decrease in heart rate followed by a more pronounced response as drug exposure increased.

a. How confident should the Agency be that the safety profile has been well characterized in the submission?

5.2 General Effects on Cardiovascular Parameters

As a direct, selective α_2-adrenoreceptor agonist, phenylephrine increases SVR, thereby increasing BP. In normal subjects (aged 16 to 37 years), the resultant increase in afterload resulted in bradycardia, reductions of CI (9.6%; $P < 0.05$) and mean velocity of circumferential fiber shortening (Vcf) of 11.2% ($P < 0.001$) without changes in ejection fraction (EF).[44] Additionally, CO was found to be decreased in healthy pregnant women undergoing a caesarean delivery.[45] In some conditions such as pulmonary hypertension, right ventricular (RV) failure, or subaortic stenosis, CO may decrease. Decreased CO due to increased afterload (increased SVR) can worsen areas of myocardial ischemia.

It has been shown that α-adrenergic simulation causes an increase in PVR, in addition to bradycardia and potential reduction in CO, which may negatively impact pulmonary and systemic hemodynamics in some disease states.

Effects on the myocardium due to increased afterload include increased wall tension and increased myocardial oxygen demands.[46] Additionally, phenylephrine may cause transient impairment of global LV function.[47]

Bradycardia

The major effect of phenylephrine on the heart is a reflex, vagally mediated bradycardia.[44, 48]

Phenylephrine, resulting in a sudden rise in BP, can cause baroreceptor stimulation, increased vagal tone, and depression of AV nodal conduction, producing a transient heart block.[49] Vagally mediated AV block is typically benign from a mortality standpoint but may lead to dizziness and syncope.

In clinical trials, bradycardia is often reported as an adverse reaction, and in such reports it is among the most commonly occurring reactions. Mild bradycardia (above 50 bpm) is well tolerated in most patients; however, it may lead to decreased CO, which may not be tolerated in patients with fixed stenotic vascular lesions or sinus node (AV) block or in the elderly.

No serious consequences following the occurrence of decreased heart rate or bradycardia were reported in any of the randomized, controlled studies described in Section 2.

5.3 Adverse Reaction Data from Published Literature

5.3.1 First Trials of Phenylephrine

The earliest account of phenylephrine use in the treatment of hypotension was published in 1937 by Johnson,[50] who described the use of subcutaneous phenylephrine in patients with hypotension due to surgical procedures, after traumatic injury, or for prophylaxis during spinal anesthesia. Subsequent reports in 1952 and 1953 by Cohen and Butterworth[51] (1 patient), Fink et al[52] (5 patients) and Gootnick and Knox[53] (32 patients) examined the use of phenylephrine for shock associated with MI. Other early publications reported the use of phenylephrine for shock due to other etiologies: surgical shock, hemorrhagic shock, and emergency shock in 5 patients,[54] shock associated with neurogenic trauma in 62 patients,[55] and shock due to various causes in 4 patients.[56] Additionally, a 1962 paper by Torii and Kinoshita[57] suggested that immediate treatment with a sympathomimetic agent such as adrenaline, noradrenaline, or phenylephrine (2.5-5.0 mg, subcutaneous [SC] or intramuscular [IM]) was warranted in anaphylactic shock following serum or vaccine injections and desensitization therapies.

5.3.2 Clinical Trials to Treat or Prevent Hypotension

5.3.2.1 Safety Data in Efficacy Studies

Obstetric Studies

In obstetric studies, most common maternal adverse events reported in studies in which phenylephrine was used to treat or maintain BP in women undergoing cesarean delivery under spinal anesthesia were bradycardia, reactive hypertension, and nausea and vomiting.[58] (Refer to End-of-Text Table 9).

In multiple obstetric studies, fetal effects of phenylephrine were study endpoints, predominantly evaluating fetal acid-base status, as measured with umbilical venous or arterial pH and Apgar scores. These show the safety of phenylephrine in this population. (Refer to End-of-Text Table 9).

Nonobstetric Studies

Fifteen of the 25 nonobstetric (cardiac and noncardiac) studies from the published literature, presented in the Sponsor's application (refer to End-of-Text Table 10), did not mention whether adverse events occurred during the study. Of those that did, adverse events included severe hypertension, mental confusion, myocardial ischemia, first-degree atrioventricular (AV) block, and new-onset tachyarrhythmias.

Negative findings were mentioned in 5 of the 25 publications: Brooker et al[24] indicated that there were no perioperative cardiovascular adverse events and the frequency of arrhythmias was low and similar between the phenylephrine, epinephrine, spinal anesthesia, and baseline groups. No ST segment changes consistent with ischemia were observed. Mutch et al[59] concluded that phenylephrine is safe and does not place the heart at increased risk of ischemia during endarterectomy. According to Borum et al,[60] no patient experienced a new postoperative neurologic deficit; and there was no evidence of myocardial injury. One patient receiving phenylephrine plus transesophageal atrial pacing (TEAP) developed a first-degree AV block. Gregory et al[61] stated that there was no clinical evidence of impaired organ function with phenylephrine. Flancbaum et al[62] reported that no hemodynamic instability, dysrhythmia, myocardial ischemia, chest pain, or fatalities were observed in their study. Nishikawa[63] concluded that phenylephrine was safe and effective in reducing the incidence of hypotension associated with spinal anesthesia in normotensive and hypotensive elderly patients.

5.3.3 Safety Data in Baroreceptor Sensitivity Studies

The widespread use of phenylephrine to estimate sensitivity of the baroreflex for use as a prognostic indicator in CAD, including in large multicenter, prospective studies by Mortara et al[64] in 815 patients and LaRovere et al[65] in 1284 patients,[66] provides additional exposure and safety data (refer to End-of-Text Table 11). Phenylephrine is dosed to elicit a rapid increase in BP to a predetermined level in patients, and the resulting vagally mediated baroreceptor response is measured. In 3 of the 21 studies presented in the Sponsor's application, no adverse events were presented or discussed. Of those that reported adverse events, the events included transient headache, extrasystoles, pulsus alternans, atrial flutter, bradycardia, inadequate increase in arterial pressure, excessive number of ectopic beats, and MI or serious ventricular arrhythmia. Most indicated that no adverse effects were observed during or after phenylephrine injections (Mortara et al[67]); Airaksinen et al[68]; James et al[69]; Mimura et al[70]), the drug was well tolerated,[71] or that no significant (LaRovere et al[65]) or untoward (Tham et al[72]) adverse effects were observed during phenylephrine therapy. LaRovere et al[73] reported that no signs or symptoms of heart failure or complex arrhythmias were observed during phenylephrine administration.

5.4 Use of Nonintravenous Formulations in Published Literature

There have been rare reports of a rapid increase in BP with ophthalmic and nasal routes of administration of phenylephrine. In ophthalmology, phenylephrine is used for mydriasis, as a provocative test for angle-closure glaucoma, and as an adjunct in the treatment of anterior uveitis and secondary glaucoma. With this route, however, phenylephrine can be systemically absorbed. Rare adverse events from topical instillation of phenylephrine have been reported, including coronary occlusion, acute hypertension, ventricular arrhythmias, MI, and stroke; these events, although uncommon, can be lethal.[74]

5.5 Safety Data from Spontaneous Report Sources

Because of the very nature of spontaneous data, a quantitative assessment of adverse events from spontaneously reported databases is limited; therefore, a primarily qualitative analysis of the data was undertaken for the Sponsor's submission. Data was obtained from the Baxter Pharmacovigilance (PV) Database and the FDA's Spontaneous Reporting System (SRS) and the Adverse Event Reporting System (AERS) databases.

5.5.1 Sponsor's Database

A search of the Baxter Global database from 2005 to April 25, 2009 identified 146 adverse event reports that listed phenylephrine as a suspect product. The majority of these reports (73% [107 of 146] of reports) were from the published literature. The route of administration of phenylephrine was recorded in 125 of 146 (86%) reports. Of the 146 reports, intravenous use was reported in 82 (56%), intrathecal/epidural in 38 (36%), nonintravenous (transplacental, retrobulbar, intracorpus cavernosum or topical) in 5 (3%), and was not reported or unknown in 21 (14%). The primary indication was for the treatment of hypotension (90 of 146 [61.6%] reports).

A total of 203 adverse events were reported. Almost half of the events (92 [45.3%]) were from the Injury, Poisoning and Procedural Complications System Organ Class (SOC)—primarily drug exposure during pregnancy (85 [41.9%]); followed by the General Disorders and Administrative Site Conditions SOC (32 [15.8%])—primarily drug ineffective (19 [9.4%]); Cardiac Disorders SOC (31 [15.3%])—primarily bradycardia (20 [9.9%]); and Respiratory, Thoracic, and Mediastinal Disorders SOC (12 [5.9%])—primarily lung infiltration (9 [4.4%]).

As shown in Table 1, the most frequently reported adverse events were drug exposure during pregnancy, bradycardia, drug ineffective, and lung infiltration. The remaining adverse events occurred at a frequency of less than 2%.

Table 1.
Most Frequently Reported (≥ 2) Adverse Events
Phenylephrine Postmarketing Adverse Event Reports From Baxter Global PV Database 2005 Through November 12, 2009

MedDRA Preferred Term	No. (%) of Adverse Events (N = 203)
Drug exposure during pregnancy	85 (41.9)
Bradycardia	20 (9.9)
Drug ineffective	19 (9.4)
Lung infiltration	9 (4.4)
Blood lactic acid increased	3 (1.5)
Blood pressure decreased	3 (1.5)
Hypotension	3 (1.5)
Aphasia	2 (1.0)
Cardiac arrest	2 (1.0)
Chest pain	2 (1.0)
Hypertension	2 (1.0)
Medication error	2 (1.0)
Pulmonary edema	2 (1.0)
Ventricular extrasystoles	2 (1.0)

5.5.2 Data from FDA's Spontaneous Databases

Information that is available from the FDA's SRS and AERS databases are limited to the adverse event term, the reporter identified suspect drug, concomitant medications, and, where available, event seriousness and outcome, drug dose and route of administration, indication for use, and patient data (age and sex). Medical histories and narrative data are not provided; therefore, a determination of a causal association between the events and the suspect drug is not possible.

The data comprise 1521 adverse event reports with 6265 adverse events where phenylephrine was the suspect (in 537 reports) or concomitant (in 1053 reports) drug, reported through December 2010. In 97 reports with 259 adverse events, the intravenous route or 'injection' formulation of phenylephrine was used and phenylephrine was considered a primary or secondary suspect drug. Of the 259 adverse events, the most frequently reported events were bradycardia (18 events), drug exposure during pregnancy (15 events), medication error (14 events), hypertension (12 events), and lung infiltration (9 events) (see End-of-Text Table 12).

A fatal outcome was reported in 218; of these, phenylephrine was administered as a suspect drug in 33 and a concomitant medication in 185. Of the 537 reports (reporting a total of 1587 adverse events) with phenylephrine as suspect (all formulations), 162 were serious and 261 were nonserious. Seriousness was not provided in 114 reports. Of the serious cardiac adverse events, 97 were cardiac arrhythmias (both atrial and ventricular arrhythmias), including 26 reports of bradycardia, 18 reports of tachycardia, and 14 reports of cardiac arrest; 5 were heart failure events, and 4 were myocardial disorders, including 1 report of LV dysfunction; and 41 reports of changes in cardiac and electrocardiogram (ECG) tests.

5.6 Clinical Trial Exposure in Special Populations as Reported in Published Literature

5.6.1 Vasoconstrictive Effect in the Elderly, Pregnant Women, and Children

5.6.1.1 Elderly

In a clinical pharmacology study, Harada et al[75] reported that in healthy young men (age range, 21-43 years) and elderly men (age range, 55–83 years), after phenylephrine infusion, the mean dose required to preconstrict hand veins (ED_{80}) did not significantly differ between the young and elderly men (571 ± 230 ng/min vs 834 ± 409 ng/min, respectively).

From the post-hoc analysis of clinical pharmacology data (refer to Section 5.1.6), elderly subjects appeared to be more sensitive to the effects of phenylephrine compared with young subjects with regard to SBP. The changes in DBP are slightly more pronounced in young subjects compared with elderly subjects, and age does not appear to modify the MAP response to phenylephrine. Young subjects showed a greater decrease in heart rate compared to the elderly, and the rate of decrease appears to be similar in both groups.

Furthermore, data from clinical studies support the use of phenylephrine for the treatment of adults, including the elderly.

5.6.1.2 Use in Pediatric Patients (Safety Data from Published Literature and Spontaneous Databases)

5.6.1.2.1 Intravenous Route

Clinical Studies

Few studies have been conducted with the intravenous use of phenylephrine for BP management in pediatric patients. In 3 nonrandomized uncontrolled studies, suggesting that phenylephrine is efficacious for the treatment of children experiencing acute hypotension due to tetralogy of Fallot,[34] neurocardiogenic syncope,[35] or traumatic brain injury,[36] specific adverse events or a poor outcome related to phenylephrine were not mentioned. The drug appeared to be tolerated when given intravenously to prevent neurocardiogenic syncope during head-up tilt,[35] to increase BP following traumatic brain injury,[36] or to treat hypoxemic spells in tetralogy of Fallot.[34]

Case Reports from Published Literature

Kim et al[37] described the use of high-dose phenylephrine to maintain BP in a 2-year-old boy with chronic hypotension due to chronic renal failure, undergoing renal transplantation. Since BP remained low during induction of anesthesia and intubation, phenylephrine infusion was added, replacing dopamine. The patient's SBP increased satisfactorily once the infusion rate of phenylephrine reached 15 µg/kg/min, and this dose was maintained through the first hour in the postanesthesia care unit. According to the authors, phenylephrine proved more successful than dopamine at maintaining SBP at the desired level intraoperatively and postoperatively in this child.

There were 2 case reports describing adverse events with intravenous administration of phenylephrine in children. Carter[76] reported bilateral fixed and dilated pupils following administration of phenylephrine during surgery for correction of an atrial septal defect and fashioning of a pulmonary arterial gusset in a 6-year-old girl. Her BP, heart rate, and arterial blood gases were satisfactory throughout the procedure. Vutskits et al[77] described bradycardia during surgery, after the administration of phenylephrine for hypotension, in a girl approximately 40 months of age with aromatic L-amino acid decarboxylase (AADC) deficiency. A continuous infusion of dopamine was started, which established a stable BP. Extubation and the postoperative period were uneventful.

5.6.1.2.2 Other Routes of Administration

Most reports in pediatric patients involved ocular or nasal routes of administration of phenylephrine, primarily to produce mydriasis or to prevent bleeding in ocular or nasal surgical procedures. Early studies used phenylephrine alone in ocular formulations in

infants, although more recent evaluations use phenylephrine combined with other ocular drugs, such as tropicamide. There have been case reports in the literature reporting cardiovascular adverse events in children and gastrointestinal adverse events in premature infants after phenylephrine administration.

Clinical Studies

A case series and 5 clinical studies that included safety information following ocular administration of phenylephrine were presented in the Sponsor's submission. Fraunfelder et al[78] conducted an observational case series of literature reports provided to the FDA of adverse systemic reactions to topical ocular phenylephrine 10% applied in pledget form. Two patients reported adverse reactions following a single exposure: 1 child, aged 4.5 years, developed hypertension and pulmonary edema and another child, aged 1 year, developed hypertension.

Borromeo et al[79] conducted a double blind, controlled study comparing the effects of low dose (2.5%) phenylephrine versus high dose (10%) phenylephrine eyedrops in 7 healthy low birth-weight neonates. The infants who received 10% phenylephrine had an increase in SBP (from 12-16 mmHg) and DBP (10-14 mmHg), while infants receiving 2.5% phenylephrine had stable BP. Neither concentration had an effect on heart rate or respiratory rate. In an open trial of 10% phenylephrine ophthalmic instillation in 8 low birth-weight infants, BP increase was variable (SBP ranged from 6-22 mmHg and DBP ranged from 4-18 mmHg) but was detected within 5 minutes, and lasted about 70 minutes. All infants with ophthalmic phenylephrine instillation developed blanching of their eyelid skin that appeared 10 to 15 minutes after application and persisted at least 60 minutes.

Lees and Cabal[80] instilled 1 drop of 0.5% tropicamide and 2.5% phenylephrine as an ocular solution in each eye, in the first 26 hours of life in 7 preterm infants. A significant increase in SBP, DBP, and mean ABP was detected using continuous recordings of neonatal heart rate and ABP. The increase in ABP was detected at 2 minutes, peaked at 8 minutes, and remained at significantly higher levels for 30 minutes after instillation. Heart rate was not significantly affected. In 3 infants, there was eyelid and periorbital blanching, lasting from 3 minutes to 5 hours.

Elibol et al[81] examined the efficacy and systemic effects of ocular instillation of standard versus micro-sized drops of phenylephrine (18 infants) in infants requiring diagnostic pupil dilatation. Mean BP increased significantly from baseline when standard drops

were administered ($P < 0.01$); however, no significant change was seen with administration of microdrops.

Two recent studies with a lower dose (2.5%) of phenylephrine in combination with tropicamide have not demonstrated a systemic effect related to increased BP, hyperexcitability, or other behavioral or neurologic changes.[82, 83]

Case Reports

Adverse events were reported in 6 case reports in children (ranging in age from 3 weeks to 8 years) with the ocular use of phenylephrine used alone or in combination with other ocular drugs.[84-89] Reported adverse events among the 6 case reports included severe hypertension, arrhythmia, cyanosis, and pulmonary edema.

Additionally, 3 case reports of gastrointestinal adverse events occurring with ocular administration of phenylephrine combined with cyclopentolate or tropicamide in 4 premature infants were reported in the literature: Lim et al[90] described 2 premature infants (delivered prematurely at 25 and 26 weeks' gestation) with transient paralytic ileus; Sarici et al[91] reported inhibition of duodenal motor activity and delayed gastric emptying in a 2-month-old premature infant; and Shinomiya et al[92] reported renal failure in a 29-day old infant (weighing 674 g). In all 4 cases, the events were transitory, and the infants recovered without any untoward side effects.

Spontaneous Reports from the FDA and Sponsor's Databases

There were 29 spontaneous reports in the FDA database with phenylephrine as a suspect drug in patients 18 years of age or less. Of the 29 reports, 22 provided the phenylephrine route of administration. None listed an intravenous or injectable route; reported routes were nasal (2 reports), ophthalmic (8 reports), oral (6 reports), inhalational (1 report), subconjunctival (1 report) or transplacental (2 reports). Of the 29 cases, adverse event terms reported in more than 1 case were pulmonary edema (5 reports), apnea (2 reports), and bradycardia (2 reports).

From the Baxter PV database, of the 146 reports with intravenous phenylephrine use, there were 2 reports in children: 1 in a child less than 1 year old and, and 1 in a child between 10 and 19 years old.

5.6.1.2.3 Summary

Reported pediatric adverse events are similar to those reported in adults, and primarily include cardiovascular events, consistent with the effects of phenylephrine as a pure

vasoconstrictor. The phenylephrine safety profile in children, as used under monitored conditions, appears similar to that in adult patients.

5.6.1.3 Pregnancy

In a clinical pharmacology study, Landau et al[93] observed that the mean dose of phenylephrine required to achieve 50% constriction was almost 7 times greater in pregnancy versus postpartum.

5.6.2 Phenylephrine's Vasoconstrictor Effect in Subpopulations of Patients in Various Disease States

5.6.3 Use in Patients with Cardiovascular or Respiratory Disease

Section 2.4 discusses clinical trials of phenylephrine for hypotension in cardiac and vascular surgery that included examination of additional hemodynamic parameters (Section 2.4.4). Investigations have evaluated the effects of phenylephrine on the myocardium, coronary perfusion, myocardial oxygen demand, ventricular performance, and CO. These studies have been conducted in normal subjects as well as in patients with CAD and myocardial infarction, arrhythmias, heart failure, ventricular dysfunction, pulmonary hypertension with RV failure, and cardiomyopathies. These effects are briefly described in the paragraphs that follow.

Coronary Artery Disease

In CAD, vasoconstriction in fixed stenotic segments of coronary arteries during exercise suggests that myocardial ischemia could be worsened by coronary vasoconstriction mediated by an α-agonist and resultant decreased oxygen supply.[94] Multiple studies and case reports indicate the potential for angina, and potential MI, in patients with preexisting coronary lesions.[95-97] Alpha-adrenergic vasoconstriction of coronary arteries, with and without decreased ventricular compliance and LV failure, may affect subendocardial perfusion diminution of epicardial blood flow, together with increased ventricular wall tension, may cause ischemia in the subepicardial regions, resulting in increased myocardial ischemia in CAD.

Arrhythmias

Phenylephrine has been shown to be effective for the termination of supraventricular tachycardia (SVT).[98] With the use of phenylephrine, premature ventricular contractions (PVCs) and isolated cardiac arrhythmias, including ventricular arrhythmias, have also been reported. In a study by Weiss et al,[48] of the 10 patients who were experiencing PVCs at the time of drug testing, 5 patients exhibited a significant ($P < 0.005$) decrease in

the percentage of ventricular heart beats that were PVCs during phenylephrine administration compared with placebo; the average PVC incidence fell from 10.8/min to 1.5/min and the mean heart rate decreased from 63.2 bpm to 48.5 bpm. In 1 patient, phenylephrine induced an increase in %PVCs (from 0 to 3.4%; $P < 0.025$), and PVC incidence increased from 0 to 1.5/min. The ECG effect of phenylephrine (0.05 mg by rapid intravenous injection) was studied in 80 patients (19 normal subjects; 22 with autonomic lability; 23 with compensated and 16 with decompensated heart disease).[99] It was observed that 3 normal subjects had a "bigeminy-like" response; 8 individuals experienced extrasystoles (ventricular or AV); 1 young healthy subject (found on follow up to have rheumatic heart disease) experienced Wenckebach periods; 1 patient (with myocardial damage) experienced a 2:1 block after temporary AV dissociation; and in 1 patient, complete bundle branch block disappeared under the influence of phenylephrine. Rare case reports of arrhythmia in patients administered phenylephrine have been published.[98, 100] Phenylephrine does not seem to affect the clinical effectiveness or safety of implantable defibrillators.[101]

Ventricular Dysfunction

Patients with preexisting ventricular dysfunction demonstrate significantly decreased CO in response to increased afterload,[102, 103] and MVO_2 is greater.[104] In patients with LV dysfunction, significant ($P < 0.001$) increases in shortening load and MVO_2 were observed in response to phenylephrine.[104] Moreover, changes in MVO_2 were strongly correlated with changes in coronary blood flow (CBF) ($r = 0.98$; $P > 0.01$). Further, the increase in MVO_2 was inversely related to LV mass in patients who received phenylephrine ($r = –0.41$; $P < 0.01$). However, MVO_2 and CBP increased less rapidly with increases in shortening load in patients with a recent history of CHF. Smith et al[105] noted that patients with moderate-to-severe LV dysfunction required significantly higher ($P < 0.05$) cumulative doses of phenylephrine after CPB compared with normal patients or those with mild LV impairment.[100]

When phenylephrine was given to patients with LV dysfunction in another study,[106] patients who developed rales were found to have increased pulmonary blood flow, whereas normal patients did not exhibit an increased pulmonary blood flow.

Heart Failure

In a study of the vasoconstrictive effect of phenylephrine in patients with congestive heart failure (CHF), phenylephrine was shown to reduce forearm blood flow (FBF) and increase forearm vascular resistance (FVR) similarly in control subjects and in patients

with CHF, without affecting BP or heart rate.[107] Landzberg et al[108] found a dose-related increase in myocardial contractility in both normal subjects and in patients with CHF after intracoronary infusion of phenylephrine. The α-adrenergic effect of phenylephrine was determined to be significantly reduced ($P < 0.03$) in patients with CHF compared with normal subjects; and in CHF patients, its effect was significantly smaller ($P = 0.045$) in patients with EF of 20% or less. Other studies have also found this decreased responsiveness to phenylephrine in patients with severe CHF.[109, 110]

Pulmonary Hypertension and RV Impairment

In patients with pulmonary hypertension and RV impairment, phenylephrine may cause an increase in mean right ventricular end-diastolic pressure and wedge pressure,[111] a decrease in mean CO,[112] and an increase in right atrial pressure and peripheral vascular resistance index,[113, 114] which can be deleterious in patients with preexisting RV failure.[98]

In a review article by Lake,[115] the use of α-adrenergic agonists, such as phenylephrine, to increase BP in patients with pericardial disease should be avoided, although the use of vasopressors to increase coronary perfusion may at times be used to improve ventricular performance. Lake further states that bradycardia, which might further decrease CO, should also be avoided in patients with pericardial disease.

Cardiomyopathy

Kawano et al[116] demonstrated that in patients with hypertrophic cardiomyopathy phenylephrine-mediated vasoconstriction is substantially reduced in the peripheral circulation, and this impairment was not related to baseline plasma levels of norepinephrine and epinephrine. In a study by Hardarson,[117] the mean LV ejection time index was shortened from 435 to 410 msec after the intravenous administration of 0.5 mg of phenylephrine in 7 patients with hypertrophic obstructive cardiomyopathy (HOCM), whereas in 4 control patients, this interval was prolonged from 378 to 395 msec ($P < 0.001$). In a case report, phenylephrine was reported to be beneficial after an uneventful, scheduled cesarean delivery in a patient with hypertrophic obstructive cardiomyopathy (HOCM).[118]

5.6.3.1 Diabetes

In the post-hoc analysis of clinical pharmacology data, diabetic patients were shown to be hypersensitive to α-adrenoreceptor agonists like phenylephrine (refer to Section 5.1.6).

Three studies were identified that support the vasoconstrictive effect of phenylephrine in patients with insulin-dependent diabetes mellitus (IDDM), both symptomatic and asymptomatic. Two studies using the dorsal hand vein technique (Bodmer et al[119] and Eichler et al[120]) found that phenylephrine increased vasoconstriction in all study groups. In Bodmer's study in 3 groups (patients with microalbuminuric IDDM, normoalbuminuric IDDM patients, and nondiabetic subjects), phenylephrine administration resulted in a dose-dependent vasoconstrictor response with no significant differences at any dose level, and similar log ED_{50} values, in all groups. Johnstone et al[121] found phenylephrine increased FVR and decreased FBF.

5.6.3.2 Raynaud's Disease

Two controlled studies showed that patients with idiopathic Raynaud's disease have increased sensitivity to phenylephrine.[122, 123]

5.6.3.3 Autonomic Dysfunction (Including Diabetic Neuropathy)

Dysfunction of the nervous system comprises a variety of disorders, including orthostatic intolerance (OI), neurally mediated syncope, pure autonomic failure, multiple system atrophy (Shy-Drager syndrome), dopamine-beta-hydroxylase deficiency, and baroreflex failure.[124] Patients with autonomic dysfunction,[122, 124-128] including patients with spinal cord injury,[129, 130] may demonstrate an exaggerated BP response to phenylephrine and, due to loss of baroreflex sensitivity, will exhibit a lesser degree of reflex bradycardia. Tank et al[131] showed that sensitivity to phenylephrine, as tested by bolus injections, was approximately 10 times higher in patients with autonomic failure than in healthy controls. This increased sensitivity to phenylephrine, which may be marked, is also noted in nonintravenous dosing formulations (see Section 5.4). Therefore, regardless of its route of administration, a smaller starting dose and slower dose escalation of phenylephrine with close monitoring is recommended in these patients. When assessing adrenergic function or baroreceptor sensitivity, pressor response tests have previously been shown to be reproducible and safe, but careful selection of subjects (such as exclusion of patients with ischemic heart disease or autonomic neuropathy) and close monitoring are necessary.[126]

5.6.3.3.1 Diabetes-Related Autonomic Dysfunction

Disorders of autonomic function in diabetes mellitus have long been recognized. Hypersensitivity to phenylephrine in diabetic patients was described in 1975 by Low[132] as "denervation hypersensitivity." Kikuchi et al[133] determined that mean BP was significantly increased ($P < 0.05$) after phenylephrine administration (33 ± 4 mmHg) in diabetic patients, compared with healthy controls (10 ± 2 mmHg), confirming the

hypersensitivity to α-adrenoreceptor agonists in diabetic patients with autonomic neuropathy. In a review of perioperative considerations in patients with diabetes, Kadoi[134] stated that diabetic patients may develop hemodynamic instability in response to vasopressor or vasodilator administration during anesthesia and that vasopressor support is needed more often in diabetic patients with autonomic neuropathy than in those without autonomic neuropathy. Bolus infusion of ephedrine, phenylephrine, or atropine sulfate may be used for transient improvement of hemodynamics.

5.6.3.3.2 Use of Nonintravenous Formulation in Patients With Autonomic Dysfunction

Increased pressor response to phenylephrine in topical ocular formulation has also been observed in patients with idiopathic OI[135] and progressive autonomic failure,[136] and in patients with IDDM[137] and diabetic retinopathy.[138] Kim et al[137] found that after administration of phenylephrine eyedrops, SBP and DBP increased significantly ($P < 0.01$) in IDDM patients. In some instances, alarming rises in BP were observed. The authors noted that the longer the duration of the diabetes and the older the patient taking the sympatholytic drugs, the more predictable the hypertensive response to phenylephrine. However, it was also reported that a young healthy man who received 3 drops of phenylephrine intraoperatively, developed hypertension and cardiac arrhythmia. The authors concluded that the administration of phenylephrine eyedrops preoperatively may be hazardous to patients with long-standing IDDM or in hypertensive patients receiving reserpine or guanethidine.

Robertson[135] in an open-label study administered topically stepwise doses of phenylephrine until an increase in pressure of 25 mmHg was achieved. The maximum pressure increment was achieved in the idiopathic orthostatic hypotensive patients with less than 20% of the dose required in the normal subjects. No pressor effect to the drug was observed in normal subjects. The increase in arterial BP appeared within 10 minutes and remained for at least 60 minutes after phenylephrine instillation. Subjective adverse effects were mild, but 2 patients described piloerection and 1 patient reported increased awareness of heart beat. No abnormalities of rhythm were noted. Robertson concluded that the usual phenylephrine concentration of 10% used in practice would have delivered a 4-fold greater amount of drug, possibly leading to dangerously high BP responses.

Clark and Ewing[136] in a controlled study of patients with progressive autonomic failure (PAF) found that pupil dilation in response to topical phenylephrine was significantly higher ($P < 0.001$) in patient with PAF. Additionally, in a randomized, controlled, double-blind study in diabetic patients with retinopathy, Weiss et al[138] observed that 2.5% phenylephrine administered topically had no effect on DBP; however, 41% of patients

administered phenylephrine had an increase of greater than 5 mmHg in their SBP compared with 8% of patients in the group administered saline. The authors conclude that caution should be used when administering phenylephrine to diabetic patients with retinopathy.

5.6.3.4 Hepatic Impairment

The effect of phenylephrine on peripheral vessels in patients with hepatic impairment was evaluated in 3 studies, all of which demonstrated a decreased responsiveness to phenylephrine, using the dorsal hand vein method. Bierbrier et al[139] showed that patients with biopsy-proven cirrhosis, compared with normotensive controls, had a decreased sensitivity to phenylephrine-mediated vasoconstriction. Albillos et al[140] showed that in patients with documented cirrhosis and in control subjects, phenylephrine caused dose-dependent decreases in FBF, without changes in MAP. However, at the lowest dose of phenylephrine (0.3 µg/min), a significant reduction in FBF was observed in control subjects, but not in cirrhotic patients. In another study by Albillos et al,[141] the sensitivity of the forearm blood vessels to phenylephrine was significantly decreased in orthotopic transplantation (OLT) patients with and without hypertension, with no impairment in maximal response.

Since the clinical implications of phenylephrine's gastrointestinal and hepatic effects are not fully known, caution with the use of phenylephrine is warranted. However, phenylephrine has been used successfully in OLT and in patients with cirrhosis. Acosta et al[142] investigated whether ventricular dysfunction or acute vasodilation caused postreperfusion syndrome (PRS), ie, significant hypertension at the time of graft reperfusion, during OLT. Thirty-two cirrhotic patients were divided into 2 groups: 1) patients with PRS who were treated with successive bolus doses of 0.1 mg phenylephrine (10 patients) and 2) patients without PRS (22 patients). Systolic ventricular function was normal during reperfusion. Since ventricular function was ruled out as a possible cause of PRS, the authors surmise that the habitual cause of hypotension was vasodilation. This may explain why phenylephrine was effective in treating PRS.

Hyperresponsiveness to phenylephrine was demonstrated in 1 study in cirrhotic patients with ascites compared with normal subjects. Pinzani et al[143] evaluated the pressor response in hypotensive cirrhotic patients with ascites (7 women and 8 men) and in 14 normotensive healthy subjects (5 women and 10 men). Following an intravenous bolus dose of phenylephrine (100 µg), healthy subjects showed a slight increase in mean BP (MBP) and decrease in heart rate, and the patients with cirrhosis showed a markedly greater increase in MBP. Changes in MBP and heart rate were significantly different in

the 2 groups studied ($P < 0.0001$ and $P < 0.003$, respectively), suggesting α_1-adrenoreceptor hyperresponsiveness in hypotensive cirrhotic patients in the presence of markedly increased norepinephrine levels.

Other studies, however, have shown a decreased responsiveness to phenylephrine in patients with cirrhosis. MacGilchrist et al[144] found that, compared with controls, the cirrhotic patients exhibited similar reductions in heart rate, with no significant lowering of BP. The BP response to phenylephrine was attenuated in the cirrhotic patients, as indicated by the significant increase ($P < 0.05$) in the phenylephrine dose required to increase mean BP by 20 mmHg (PD_{20}). Study results suggest that the pressor reactivity of sympathetic and nonsympathetic agonists is impaired in patients with severe cirrhosis and BRS may be enhanced.

Arranz et al[145] studied autonomic function and BRS in cirrhotic patients with portal hypertension. Although MAP increased in a dose-dependent manner in both groups following phenylephrine injections, the mean increase was lower in patients with portal hypertension compared with control patients, indicating a decreased response to phenylephrine in patients with portal hypertension. In patients with portal hypertension, BRS values were significantly lower ($P < 0.001$) than in the control subjects.

Wu et al,[146] in a retrospective study, compared the use of vasopressor agents without volume expansion to venovenous bypass (VB) for hemodynamic control over an 8-year period. Of the 50 patients who received a vasopressor during cross clamping in OLT, 14 received phenylephrine; 10, dopamine; 29, epinephrine; and 8, norepinephrine. Some patients received more than one vasopressor. The median phenylephrine dose administered was 200 µg (range, 100-1400 µg). Compared with patients in the VB group, patients in the vasopressor group had a significantly shorter clamping duration ($P = 0.034$) and shorter warm ischemia time ($P < 0.001$), which may help liver-allograft recovery. During the entire procedure, urine output was similar between the VB and vasopressor groups ($P = 0.930$), suggesting that the use of low-dose vasopressor for a brief clamping period does not adversely affect perioperative renal function. In 1 patient in the vasopressor group, postoperative temporary dialysis for renal dysfunction was required. Intraoperative death or cardiac arrest did not occur. One patient in the vasopressor group died in the intensive care unit (ICU) of pneumonia and adult respiratory distress syndrome (ARDS) secondary to aspiration, and 2 (2.1%) patients in the vasopressor group developed hepatic artery thrombosis requiring re-transplantation, which was similar to that reported in the literature (2.5%). Taken together, the results indicate that modest doses of a vasopressor without volume expansion or venovenous

bypass (VB) can maintain hemodynamic stability during the anhepatic phase of cavaplasty OLT without adversely affecting the liver allograft, kidneys, or heart.

Furthermore, phenylephrine has successfully been used in OLT to reduce the use of blood products, as shown in a recent pilot study by Massicotte et al,[147] investigating an alternate method for assessing intravascular volume and management of fluids and vasopressors during OLT in 30 patients. Boluses and infusion of phenylephrine (mean dose was 1890 ± 1443 µg), were given after phlebotomy (late dissection phase). The study results indicated that phlebotomy decreased PVP (along with CO, PAP, PCWP, CVP, and transesophageal echocardiographic (TEE) measurements of transmitral flow [TMF] early peak [E] velocity) and phenylephrine increased CVP, SVR, and arterial blood pressure but had no significant effect on PVP (or CO, PAP, PCWP). It is postulated that the decreased PVP, which was unaffected by phenylephrine infusion, may contribute to the decrease in operative blood loss during OLT.

In a case report, Willingham et al[148] described the successful use of phenylephrine, with epinephrine, norepinephrine, and vasopressin, in a 74-year-old man who developed hypertension during OLT for cryptogenic cirrhosis.

5.6.3.5 Hypertension

From the post-hoc analysis (refer to Section 5.1.6), in hypertensive patients, changes in SBP were linear with increasing exposure. However, young hypertensive patients had an increased sensitivity to phenylephrine compared with hypertensive elderly patients, in whom a minimal effect on the exposure-response relationship was demonstrated. Hypertension did not affect changes in DBP or heart rate in either the young or old.

Patients with essential hypertension exhibit an increase in vascular resistance. Eichler et al[149] studied venous responsiveness to phenylephrine in men with stable, mild-to-moderate essential hypertension and in healthy, normotensive men. This dose-response study showed that the maximum possible effect (E_{max}) and $logED_{50}$ were similar in both groups. The findings also showed a considerable intersubject variability in the phenylephrine responses in both study groups. From these findings, the authors concluded that the pressor response to α-adrenergic stimulation in hypertensive patients is due to structural and geometric changes in the arterial wall, rather than to an increased responsiveness of postsynaptic α-adrenergic receptors.

Closas et al[150] found that hypertensive patients and normotensive subjects had a similar pressor response to phenylephrine.

5.6.3.6 Renal Impairment

Lee et al[151] concluded that the few studies published to date have not shown evidence of adverse effects on renal function with phenylephrine. Besides increasing SVR, phenylephrine also constricts the renal vasculature and decreases the regulation of renal blood flow; but in the presence of a low SVR, phenylephrine increases renal perfusion pressure. Support of MAP greater than 70 mmHg with phenylephrine during CPB has been shown to increase creatinine clearance compared with patients in whom MAP was not corrected.[152] However, Bennett et al[153] evaluated creatinine clearance in a randomized controlled study of patients during elective CPB surgery given phenylephrine versus AII to maintain SVR, some of whom were on angiotensin-converting enzyme inhibitors (ACEIs) for heart failure at least 6 months prior to surgery. Patients were randomized to receive either 2.5 mg of AII or 10 mg of phenylephrine. Neither drug caused significant changes in creatinine clearance up to 48 hours postoperatively. However, it was noted that patients with preoperative heart failure required higher doses of the study drugs, and 1 patient, after failing to respond to 20 mg of phenylephrine, was switched to AII and showed a normal response.

Urine output was studied in surgical patients and in patients with shock requiring vasopressor support by Toyoda et al[154] in a retrospective study in 114 patients undergoing thoracic (30 patients), upper abdominal (37 patients), or colorectal surgery (47 patients). Urine output was significantly higher in the group who received a large dose of the local anesthetic and continuous prophylactic infusion of a vasopressor (initially phenylephrine 1.0 mg/h followed by ephedrine 10 mg/h), compared with the group who received a small dose of the local anesthetic and no prophylactic vasopressor. Additionally, urine output was higher in elderly patients.

Gregory et al,[61] also in a retrospective analysis, evaluated urine output during the use of phenylephrine, along with inotropic agents, in the hemodynamic support of 13 surgical ICU patients in septic shock (10 men and 3 women). Patients were resuscitated with blood or crystalloids, and those with persistent vasodilation and hypotension received phenylephrine, titrated to maintain MAP > 70 mmHg. For inotropic support, dobutamine or dopamine, were administered to 11 patients. During phenylephrine treatment, mean urine output increased significantly ($P < 0.05$) from 54 ± 45 mL/h to 90 ± 51 mL/h, and 11 of 12 evaluable patients maintained a urine flow > 0.5 mL/kg•h. Of the 11 patients, 6 did not receive concomitant dopamine and 2 were receiving phenylephrine alone. The 2 patients receiving phenylephrine alone and 2 patients receiving phenylephrine and low-dose dopamine experienced tachyarrhythmias.

In a clinical pharmacology study, Abiose et al[155] observed that the dose of phenylephrine required to produce 50% constriction was lower in patients with renal impairment compared with control subjects. Gadegbeku et al[156] showed that the pressor reactivity of phenylephrine is enhanced and BRS is impaired in patients with chronic kidney disease (CKD) compared with matched control subjects and intermediate in patients with hypertension.

However, in patients on dialysis, Lübbecke and Wizemann[157] determined that, prior to dialysis, phenylephrine-induced, dose-dependent increases in SBP were similar in chronically hemodialyzed patients with and without hemodialysis-induced severe symptomatic hypotension. Brodde and Daul[158] in a study in patients on maintenance hemodialysis and not on antihypertensive therapy (2 groups, high BP and low BP) and healthy volunteers, noted that the dose required to increase MAP by 20 mmHg (EC_{20}) was similar between the high BP dialysis group and the control subjects (229 ± 39 µg vs 216 ± 33 µg, respectively); however, the EC_{20} was significantly higher in the low BP group (419 ± 57 µg; $P < 0.05$). Of note, dialysis treatment duration had been longer in this low BP group (58 ± 16 months [range, 20-155 months) than in the high BP group (29 ± 9 months [range, 4-104 months]).

5.7 QT Prolongation Without Increased QT Dispersion

Based on the mechanism of action of phenylephrine and the resulting reflex bradycardia, phenylephrine may influence the QT interval. Literature was reviewed to assess available data for QT prolongation with phenylephrine and to evaluate its clinical significance for proarrhythmic events. Seven studies were identified that support the cardiovascular safety of phenylephrine (refer to Table 2).

The long QT syndrome (LQTS) is a disorder where cardiac ion channels produce prolonged ventricular repolarization. The diagnosis of LQTS is usually based on electrocardiogram (ECG) patterns, clinical symptoms, and genetic findings, although 40% of all LQTS patients have borderline or normal QT intervals. The LQTS can be congenital (genetic mutations coding the cardiac ion channels) or acquired. Clinically, LQTS is characterized by syncope, cardiac arrest, and occasionally by a history of seizures. Patients with LQTS are at risk of torsades de pointes and ventricular fibrillation. Women with LQTS are at significant risk for cardiac events during pregnancy and the postpartum period, with 10% having their first cardiac event postpartum. The prevalence of LQTS is about 1 per 1100 to 3000.[159]

The QT interval, measured in lead II on the ECG, inversely varies with heart rate: as the heart rate slows, the QT interval is lengthened. To correct for variations in heart rate,

Bazett's equation is frequently used to calculate the corrected QT (QTc), which equals the QT interval divided by the square root of the RR interval, where QT is the time from the start of the Q wave to the end of the T wave (in seconds) and RR is the cycle time in seconds. The QT interval may be prolonged or precipitated by drugs, electrolyte imbalances, toxins, and certain medical conditions.[159]

Phenylephrine, as an α-adrenergic agonist that produces a vagally mediated bradycardia in response to vasoconstriction-induced increases in afterload, increases the heart rate and thus the QTc in healthy subjects and patients with LQTS, but generally does not affect the QT dispersion (QTd), ie, the difference between the longest and shortest QT interval on a 12-lead ECG. A QTc interval > 440 ms is generally considered prolonged.[159]

Table 2.
Effect of Phenylephrine on QT Interval

Reference	Type of Study	Summary of Findings
Mitrani et al[160]	Randomized, prospective study in patients with normal sinus rhythm (investigated whether phenylephrine increased the energy required to induce ventricular fibrillation)	The endpoint of the phenylephrine infusion was a sustained and steady increase in SBP by at least 20 mmHg and up to 80 mm Hg.
Sun et al[161]	LQTS patients (effect of α- [phenylephrine] and β-adrenergic (epinephrine) stimulation on QT interval dispersion)	Epinephrine, but not phenylephrine, increased QTd in congenital (LQTS).
Yee et al[111]	Randomized, single-blind, placebo-controlled crossover design, with or without atropine (effects of cardiac afterload induced by phenylephrine on QTd)	Phenylephrine caused a gradual increase in BP, paralleled by a significant decrease in heart rate. Both QTmax and the linearly corrected QTcmax significantly increased, but the Bazett-corrected QTcmax was not significantly altered by changes in BP caused by phenylephrine. Phenylephrine caused a significant increase in QTd and QTcd, both with and without atropine. Changes in QTd and QTcd were significantly correlated with changes in SBP and DBP.
Khositseth et al[162]	Genotyped LQTS1, LQTS2 patients (effect of phenylephrine on QTd and transmural dispersion of repolarization, or TDR)	After phenylephrine administration there was no significant change in absolute QT interval in any group.
Kaufman et al[163]	LQTS1 and LQTS2 subjects (investigated whether LQTS can be unmasked in genetically abnormal subjects with normal or borderline QT intervals by autonomic manipulation)	At maximal bradycardia after phenylephrine administration, the QT interval and QTc were similar in all groups (LQTS1 & 2, and controls).
Magnano et al[164]	Healthy subjects (evaluated the effects of autonomic modulation on the U wave)	A decrease in heart rate was accompanied by an increase in QT interval.
Guillon et al[165]	Women scheduled for cesarean delivery under spinal anesthesia	Phenylephrine did not modify the Tp-e or QTc intervals.

5.8 Drug-Drug Interactions

Phenylephrine is an adrenergic drug whose mode of action is to directly combine with receptor sites. When phenylephrine is used in combination with other substances, interaction is most likely if competition for one of the receptor sites exists.[114]

In patients with CAD and impaired LV function undergoing coronary artery revascularization, Schwinn et al[166] determined correlations between the PD_{20} and various patient characteristics. In these patients, the PD_{20} was not correlated with calcium channel blockers, β-adrenergic blockers, diuretics, nitrates, or digoxin

Drug-drug interaction studies with phenylephrine are summarized in this section and in End-of-Text Table 12.

5.8.1 Cardiovascular Drugs

5.8.1.1 Adrenergic Receptor Agonists and Antagonists (Direct and Indirect)

α-Adrenergic Blocking Agents

Coadministration of α-blocking agents decreases responsiveness to vasopressors and may decrease responsiveness to phenylephrine.[167, 168] The α_1-blockers are used in the treatment of high BP, benign prostatic hyperplasia, and Raynaud's disease. Patients taking other drugs that have α-blocking properties, eg, amiodarone or phenothiazine derivative such as chlorpromazine, may also show decreased responsiveness to phenylephrine.

α-Adrenergic Agonists

Coadministration of α_1-specific agonists could potentiate the responsiveness to phenylephrine. Coadministration of agents with α_2-agonist activity, such as clonidine, augments the pressor response to phenylephrine, although phenylephrine has been used to treat hypotension and bradycardia produced by clonidine preanesthesia.

β-Adrenergic Blocking Drugs (β-Blockers)

In patients taking large doses of sympathomimetic amines, such as phenylephrine and phenylpropanolamine, β-blockers may occasionally be responsible for severe hypertension. Cases of increased BP response to phenylephrine in patients concurrently taking β-blockers have been reported.[169, 170] Some, but not all, controlled clinical trials indicate there may be an increase in pressor response; therefore, the use of phenylephrine in these patients should be monitored closely.

Calcium Channel Blockers

Patients on calcium channel blockers may exhibit a decreased responsiveness to phenylephrine according to some studies[171-173]; however, it is effective in patients chronically on calcium channel blockers to maintain BP during anesthesia.[174]

Angiotensin-Converting Enzyme Inhibitors (ACEIs)

ACEIs and angiotensin receptor blockers (ARBs) are widely used for the treatment of hypertension, and in patients with cardiovascular disease, diabetes, and renal disease. Inhibition of ACE prevents the production of AII, a potent vasoconstrictor, as well as potentiates bradykinin, a vasodilator.[153]

In a dorsal hand vein study[175] in normal subjects, ACEIs exhibited a decreased responsiveness to the vasoconstrictor effects of phenylephrine, as indicated by an increased ED_{50}, although the lipophilic ACEI (quinapril) was more potent than the hydrophilic ACEI (enalapril) at attenuating α-adrenoreceptor sensitivity. However, in a placebo-controlled trial, after 6 weeks' treatment with enalapril, the PD_{20} was significantly decreased with enalapril compared with placebo.[171] Finally, in a third study,[176] patients taking nifedipine and doxazosin displayed a significant decrease in pressor response to phenylephrine, as seen by the increase in PD_{20} from baseline; whereas the pressor responsiveness to phenylephrine was unchanged following enalapril.

Although the findings are not consistent, given the wide-spread use of ACEIs on a long-term basis and because the prolonged use of ACEIs after cardiac events results in an increased baseline sensitivity of BRS, adjusting phenylephrine dose requirements upward to achieve adequate BP response in acute hypotension may be warranted in patients using ACEIs.[177, 178] From studies in surgical patients on ACEIs with anesthesia-related hypotension, it is clear that phenylephrine is an effective treatment.

Other Cardiovascular Drugs

Sympatholytic drugs, such as the guanidine derivatives debrisoquine (an antihypertensive drug) and guanadrel (an adrenergic neuronal blocking agent), act by preventing the release of norepinephrine from adrenergic nerve endings in response to sympathetic nerve stimulation.[179] In normotensive subjects receiving guanadrel, an enhanced venous responsiveness to phenylephrine was observed,[180] while in hypertensive patients, debrisoquine augmented the pressor response to phenylephrine.[181]

\Ferrari et al[182] observed that the BRS response to phenylephrine was significantly potentiated with digoxin.

5.8.2 Central Nervous System Drugs

Monoamine Oxidase Inhibitors (MAOIs)

The pressor effect of sympathomimetic pressor amines is markedly potentiated in patients receiving monoamine oxidase inhibitors (MAOIs).[183, 184] Therefore, caution should be used when initiating pressor therapy in these patients, and the initial dose should be small. Ideally, these medications would be discontinued prior to surgery; however, in controlled medical settings, phenylephrine may be successfully used for the treatment of anesthesia-induced hypotension in patients on MAOIs.[185]

As with MAOIs, phenylephrine should be used with caution with MAOI-like drugs, such as procarbazine (an alkylating chemotherapy drug), linezolid (an anti-infective for resistant gram-positive bacteria, and rasagiline, an anti-Parkinson medication.

Tricyclic Antidepressants

The pressor response of adrenergic agents may also be potentiated by tricyclic antidepressants,[186, 187] which inhibit norepinephrine reuptake in adrenergic neurons, resulting in increased stimulation of adrenergic receptors. This potentially exaggerates the pressor response to sympathomimetic agents. If concomitant use is necessary, initial dose and rate of administration of the sympathomimetic should be reduced, and cardiovascular status, including BP, should be monitored closely.[188] Although clinical data are lacking, it may be prudent to follow the same precaution with mixed-acting sympathomimetic agents.

Ergot Alkaloids

Additive or synergistic increases in BP or ischemic response may occur when ergot alkaloids are combined with peripheral or central vasoconstrictors.[189] Ergot alkaloids produce arterial vasoconstriction by stimulating α-adrenergic and serotonin receptors and inhibiting endothelial-derived relaxation factor release.[179]

Halothane Anesthesia

Vasopressors may cause serious cardiac arrhythmias during halothane anesthesia and, therefore, should be used with caution[190] in this setting. However, the decreased

vasoconstrictor response to phenylephrine, as demonstrated in the studies presented in this section, does not appear to be clinically significant.[174, 190-192]

5.8.3 Anticholinergics

Administration of atropine-with phenylephrine may result in lowered SBP and DBP responses, as noted in a study by Levine and Leenen.[193] Phenylephrine administration resulted in a slight elevation of arterial pressure in small portion of atropinized subjects premedicated with meperidine.[194]

5.8.4 Endocrine, Metabolism, and Antidiabetic Agents

Oxytocin

Due to its effects on α-receptors, phenylephrine, coadministered with oxytocin, may result in excessive BP elevation; however, newer studies have found phenylephrine may be used successfully to treat the decrease in BP seen with oxytocin use.[195, 196, 197]

Steroids

Steroids enhance sensitivity to the pressor effect of phenylephrine as evidenced in studies by Hoen et al[198] and Annane et al[199] using hydrocortisone.

Insulin

It appears that phenylephrine decreases the clearance rate of insulin in healthy men (O'Callaghan et al[200]), and that insulin attenuates the pressor responsiveness to phenylephrine in diabetic patients without autonomic neuropathy (Yamamoto et al[201]); however, the clinical significance of these findings in the setting of the use of phenylephrine in acute hypotensive states is not known.

5.8.5 Other Interactions: Use of Phenylephrine in the Presence of Fatty Acids

Haastrup et al[103] evaluated the systemic effects of fatty acids on vascular α_1–adrenergic receptor-mediated reactivity and examined the possible role of elevated triglycerides in pressor activity in normotensive subjects. The pressor response to phenylephrine was enhanced following Intralipid with or without heparin. Across all study conditions, changes in levels of triglycerides and fatty acids correlated with changes in MAP responses to phenylephrine.

5.9 Conclusion: Risk/Benefit Statement

The benefit of phenylephrine has been well documented over decades of its use. Phenylephrine's unique properties among other sympathomimetics, its well understood and reasonable safety profile, and its effectiveness continue to secure this drug product's position in many of the treatment regimens used by critical care, cardiology, and anesthesiology physicians. Published data to support the clinical pharmacology, safety, and efficacy of parenterally administered phenylephrine are summarized in the Sponsor's application.

b. Is there additional safety information that the Agency should request? If so, should this information be requested pre-approval or post-approval?

SPONSOR'S RESPONSE

The Sponsor believes the literature safety data, with appropriate precautions, as indicated above, are sufficient for the target indication of increasing blood pressure in acute hypotensive states.

6. END-OF-TEXT TABLES

End-of-Text Table 1. Endpoints in Randomized, Double-Blind, Controlled Studies of Phenylephrine for Treatment of Hypotension During Cesarean Delivery Under Neuraxial Anesthesia

References	Population	N	PE	Control	Methods	Endpoint(s)
Moran et al[13]	Elective cesarean delivery	60	80 μg IV bolus initial; 40 to 80 μg repeats (n = 31)	Eph, 5 to 10 mg (n = 29)	IV boluses administered when SBP decreased 5 mmHg from baseline	• Frequency of hypotension • Nausea and vomiting • HR • Neonatal effects
Thomas et al[14]	Elective cesarean delivery	38	100 μg (n = 19)	Eph, 5 mg (n = 19)	IV boluses administered when SBP decreased ≥ 10% from baseline.	• Frequency of hypotension • HR • Neonatal effects
Ngan Kee et al[18]	Non-elective cesarean delivery	204	100 μg (n = 102)	Eph, 10 mg (n = 102)	IV boluses administered when SBP decreased to < 100 mmHg.	• Frequency of hypotension • HR • Neonatal effects
Gunda et al[15]	Elective cesarean delivery	100	100 μg (n = 50)	Eph, 5 mg (n = 50)	IV boluses of vasopressor administered when SBP decreased to ≤ 90 mmHg and/or by ≥ 30% from baseline	• Frequency of hypotension • Nausea and vomiting • HR • Neonatal effects
Prakash et al[16]	Elective cesarean delivery	60	100 μg (n = 30)	Eph, 6 mg (n = 30)	IV boluses administered when SBP decreased to ≤ 80% of baseline	• Frequency of hypotension • Nausea and vomiting • HR • Neonatal effects
Ngan Kee et al[202]	Elective cesarean delivery	50	100 μg/ min (n = 26)	Placebo (saline) (n = 24)	IV CI PE or saline started immediately after injection of anesthetic; infusion stopped if SAP > baseline; restarted or continued when SAP ≤ baseline. Rescue injections if SAP < 80% of baseline: 100 μg PE for controls; saline for PE group	• Frequency of hypotension • SAP changes • HR • Neonatal effects

Abbreviations: CI, continuous infusion; Eph, ephedrine; HR, heart rate; IV, intravenous; PE, phenylephrine; SAP, systolic arterial pressure; SBP, systolic blood pressure.

End-of-Text Table 2. Efficacy and Safety Outcomes in Randomized, Double-Blind, Controlled Studies of Phenylephrine for Treatment of Hypotension During Cesarean Delivery Under Neuraxial Anesthesia

References	Blood Pressure Results	Other Results	Neonatal Effects	Conclusions
Moran et al[13]	• Hypotension occurred in 1 pt in the Eph group and in no pt in the PE group	• HR significantly decreased with PE: mean change of -26 bpm for PE vs +13 bpm for Eph (P = 0.001) • Frequency of nausea and vomiting: PE, 25%; Eph, 28%	• All fetal acid–base values (UA pH; UA PCO_2; UA and UV base deficits) were within normal limits for both groups • UA pH: was significantly higher in the PE group (P = 0.001) and UA PCO_2 and UA and UV base deficits were significantly lower in the PE group (P = 0.024; p = 0.002; P = 0.0002, respectively)	• PE is as effective as Eph for increasing BP in this setting • PE resulted in decreased HR relative to Eph; there were no differences in rates of nausea and vomiting • PE does not impair neonatal health in this setting
Thomas et al[14]	• Median frequency of hypotension • PE: 0 (range, 0-6); Eph: 0 (range, 0-4) • PE increased to within 10% of baseline	• Mean decrease in maternal HR • PE: -28.5%; Eph: -14.4% • Intermittent bradycardia requiring treatment: PE: 11 of 19 women; Eph: 2 of 19 pts (P = 0.005)	• Fetal acid-base characteristics were similar or better for PE vs Eph – UA pH significantly higher with PE – Baseline UA pulsatility index and fetal HR similar for PE and Eph – Small, but statistically significant reduction in fetal HR with PE – No relationship between UA pH and maximum percentage change in SAP or CO with either vasopressor • All infants had Apgar scores of ≥ 7 at each time point	• PE is as effective as Eph for increasing BP in this setting • PE resulted in decreased HR relative to Eph • PE does not impair neonatal health in this setting
Ngan Kee et al[18]	• Proportion experiencing hypotension • PE, 73%; Eph, 73% • Median (IQR) number of episodes per pt: PE, 1.0 (0-3.3); Eph, 2.0 (0.3-3.0)	• Minimum HR was lower with PE than with Eph • No difference in maximum HR • No pt required atropine	• Fetal acid-base characteristics were similar or better with PE vs Eph: – UA and UV pH values, UA and UV O_2 content, and UA and UV pH and base excess: similar for PE and Eph – UA and UV lactate concentration and $UAPO_2$ and $UVPO_2$: lower for PE than Eph • Neonatal Apgar scores: similar for PE and Eph	• PE is as effective as Eph for increasing BP in this setting • PE resulted in decreased HR relative to Eph • PE does not impair neonatal health in this setting

End-of-Text Table 2. Efficacy and Safety Outcomes in Randomized, Double-Blind, Controlled Studies of Phenylephrine for Treatment of Hypotension During Cesarean Delivery Under Neuraxial Anesthesia (continued)

References	Blood Pressure Results	Other Results	Neonatal Effects	Conclusions
Gunda et al[15]	• Hypotension – PE: 94% of patients received 1 dose and 6% received 2 doses – Eph: 92% of patients received 1 dose and 8% received 2 doses	• Mean HR: significantly decreased with PE and increased with Eph • Bradycardia: PE: 12%; Eph: 2% • Nausea: EPH, 18% ; PE, 8% • Vomiting: EPH, 14% ; PE, 0 • Tachycardia: EPH, 16%; PE, 0	• Neonatal Apgar scores at both 1 min and 5 minutes were similar for PE and EPH	• PE is as effective as EPH for increasing BP in this setting • PE associated with decreased HR and bradycardia; EPH associated with tachycardia, nausea, and vomiting • PE does not impair neonatal health in this setting
Prakash et al[16]	• Median maximal SBP – PE: 127 mmHg (range, 100-150 mmHg); EPH: 122 mmHg (range, 110-140 mmHg) (P = 0.059)	• Median maximal SBP • PE: 127 mmHg (range, 100-150 mmHg); EPH: 122 mmHg (range, 110-140 mmHg) (P = 0.059) • Bradycardia (HR < 60 bpm) • PE: 17%; EPH: 0; suggestive of a baroreceptor reflex mechanism (P > 0.05) • Nausea: EPH, 13%; PE 0 (P >0.05) • Vomiting: EPH, 3.3%; PE, 0 (P >0.05)	• Neonatal UA and UV pH significantly greater for PE group vs EPH • Apgar scores and neurobehavioral scores were similar in the 2 groups	• PE is as effective as EPH for increasing BP in this setting • PE and EPH had similar effects on HR • PE does not impair neonatal health in this setting
Ngan Kee et al[202]	• Frequencies of hypotension – PE 23%; control: 88% (P < 0.0001) • SAP over the course of the study – Higher for PE vs placebo (P < 0.0001)	• HR over the course of the study • Lower for PE vs placebo (P < 0.0001)	• No significant differences in UA or UV blood gasses (pH, PCO_2, PO_2, base excess) for PE and placebo • NS differences in Apgar scores in the two groups	• PE was superior to placebo for preventing hypotension in this setting • PE resulted in decreased HR relative to EPH • PE does not impair neonatal health in this setting

Abbreviations: CI, continuous infusion; EDV, end-diastolic volume; EPH, ephedrine; HR, heart rate; IQR, interquartile range; IV, intravenous; NS, not significant; PE, phenylephrine; pt, patient; SBP, systolic blood pressure; SV, stroke volume; UA, umbilical artery; $UAPO_2$, umbilical arterial oxygen pressure; UV, umbilical vein; $UVPO_2$, umbilical venous oxygen pressure.

End-of-Text Table 3. Endpoints in Randomized, Double-Blind, Controlled Studies of Phenylephrine for Treatment of Hypotension During Non-obstetric Procedures Under Neuraxial Anesthesia

References	Population	N	PE	Control	Methods	Endpoint(s)
Brooker et al[24]	Elective surgery (orthopedic, urologic, gynecologic	N = 13 (10 M, 3 F); median age 62.5 yrs	40 µg IV bolus, then 0.5 µg/kg per min IV CI (n = 13)	EP, 4 µg bolus, then 0.05 µg/kg per min CI (n = 13)	Crossover treatment: vasopressor administered at hypotension (15% decrease in SAP) in randomized order; 10-min washout before switch to opposite treatment.	• Increase in BP (SBP, DBP, MAP) • HR • CO
Cheng et al[22]	Inguinal hernia repair	N = 80 (63 M, 17 F); mean age 65 yrs	50, 100, or 200 µg IV bolus (n = 20 each)	Saline (n = 20)	Prophylaxis study. Hypotension defined as MAP < 80% of baseline.	<u>Primary planned</u> • Overall differences in BP, including dose and time effects • Correlation between dose and frequency of hypertension and frequency of rescue medication • Overall differences in HR, including dose and time effects • Foot skin temperature <u>Post-hoc</u> • Proportion with hypotension • HR at individual time points

Abbreviations: EP, epinephrine; F, female; HR, heart rate; IV, intravenous; M, male; PE, phenylephrine.

End-of-Text Table 4. Efficacy and Safety Outcomes in Randomized, Double-Blind, Controlled Studies of Phenylephrine for Treatment of Hypotension During Non-Obstetric Surgery Under Neuraxial Anesthesia

References	Blood Pressure Results	Other Results	Conclusions
Brooker et al[24]	• SBP: significantly increased by PE and EP • DBP and MAP: PE effective; EP not effective	• HR significantly decreased by PE and increased by EP • CO significantly decreased by PE and increased by EP • SV not changed by PE; significantly increased by EP	• PE was more effective than EP for increasing BP during neuraxial anesthesia for urologic, gynecologic, or orthopedic surgeries
Cheng et al[22]	Planned Primary • BP changes across groups not significant • Dose x time not significant for MAP • Proportion with hypotension: PE, 0, 50, 100, or 200 µg: 45%, 55%, 35%, and 15%, respectively (significant negative correlation (r = -0.254; P = 0.023) • Significant negative correlation between dose and frequency of rescue medication (r = -0.275; P = 0.013) Post-hoc • MAP significantly different for 200 µg vs 50 µg at 15 min (P = 0.0005) • MAP significantly different for 200 µg vs placebo at 20 min (P = 0.0006) • Frequency of hypotension: – 200 µg group significantly lower than placebo or 50 µg group (P = 0.0094)	Planned • HR changes across groups not significant • Dose x time significant for HR (P = 0.0148) • Foot temperature similar increase in all groups Post-hoc • 200 µg significantly higher % baseline HR than control at multiple time points	• PE dose was inversely associated with the frequency of hypotension in this setting • PE 200 µg had the lowest frequency of hypotension in this population and setting

Abbreviations: CO, cardiac output; DBP, diastolic blood pressure; EDV, end-diastolic volume; EP, epinephrine; HR, heart rate; IV, intravenous; MAP, mean arterial pressure; PE, phenylephrine; pt, patient; SBP, systolic blood pressure; SV, stroke volume.

End-of-Text Table 5. Endpoints in Randomized, Controlled Studies of Phenylephrine for Treatment of Hypotension During Cardiac and Noncardiac Vascular Surgery Under General Anesthesia

Author	Population	N	PE	Control	Methods	Endpoint(s)
Goertz et al[27]	CABG; valve replacement	N = 24 (17 M, 7 F); median age 61 yrs for CABG group; 62 yrs for valve replacement group	1 µg/kg IV bolus (n = 24)	NE 0.05 µg/kg (n = 24)	Double-blind crossover; 14 pts with hypotension during CABG; 10 pts with hypotension during elective aortic valve replacement; hypotension defined as a > 10% decrease in BP relative to the lowest BP in the 24 hours prior to surgery; PE (1 µg/kg) or NE (0.05 µg/kg) infused after induction of anesthesia; second drug was infused after return of hemodynamic parameters to baseline.	• BP • Other hemodynamics
DiNardo et al[28]	CABG	N = 28 (26 M, 2 F); median age 61.7 yrs	IV CI; titrated to effect (n = 16)	NE (n = 21) EP (n = 19) (both titrated to effect)	Open-label crossover; pts randomized to receive 2 of the 3 treatments; vasopressor administered after termination of CPB by IV CI; doses titrated to raise MAP by 20 mmHg, with stabilization for 5 minutes. Second infusion given after hemodynamic parameters returned to baseline.	Primary • Graft flow Secondary • BP • Other hemodynamics • Other hemodynamics
Baraka et al[29]	CABG	N = 30 (sex NR); age 40-75 yrs; all pts had LVEF > 0.4	100 µg IV bolus (n = 10)	NE 10 µg (n = 10); EP 10 µg (n = 10)	Open-label; vasopressors administered after induction of anesthesia. Hemodynamic parameters measured before and after administration of the pressor; all measurements made within 10-20 minutes after induction of anesthesia.	• BP • Other hemodynamics
Nygren et al[30]	CABG	N = 10 (9 M, 1 F); mean age 66 yrs	IV CI, titrated to MAP of 90 mmHg (n = 10)	NE, IV CI; titrated to MAP of 90 mmHg (n = 10)	Open-label; crossover; each vasopressor titrated to reach a target MAP of 90 mmHg. The second drug was infused after a 60-min washout and a predrug control period.	Primary • Splanchnic flow Secondary • Hemodynamics: BP

End-of-Text Table 5. Endpoints in Randomized, Controlled Studies of Phenylephrine for Treatment of Hypotension During Cardiac and Noncardiac Vascular Surgery Under General Anesthesia (continued)

Author	Population	N	PE	Control	Methods	Endpoint(s)
Smith et al[31]	Endarterectomy	N = 60 (38 M, 22 F; mean age, 68 yrs)	Experimental: Anesthetic + PE (n = 29) • high-dose isoflurane/ nitrous oxide + phenylephrine (n = 14) • high-concentration halothane plus PE (n = 15)	Control: Anesthetic alone; (n = 31) • low-dose isoflurane/ nitrous oxide (n = 16) • low-concentration halothane (n = 15)	Open-label; IV bolus dose titrated to effect; actual dose not reported PE infused as needed in the high anesthetic groups	• BP • Wall stress • Collateral carotid flow • Myocardial ischemia

Abbreviations: BP, blood pressure; CABG, coronary artery bypass graft; CI, continuous infusion; CPB, cardiopulmonary bypass; EP, epinephrine; F, female; IV, intravenous; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; M, male; NE, norepinephrine; PE, phenylephrine; Pop, population; pt(s), patient(s).

End-of-Text Table 6. Efficacy and Safety Outcomes in Randomized, Controlled Studies of Phenylephrine for Treatment of Hypotension During Cardiac and Noncardiac Vascular Surgery Under General Anesthesia

Author	Blood Pressure Results	Other Primary Efficacy Results	Other Results	Conclusions
Goertz et al[27]	• CABG group – PE MAP increased from 71-94 mmHg at the 60-second time point • Valve replacement group – PE MAP increased from 69-99 mmHg at the 60-second time point	—	• CABG group – PE and NE: HR decreased significantly • Valve replacement group – PE: HR decreased significantly • Indices of LV global function • Impairment in CABG/PE group only • Median fractional area change: significantly reduced (P = 0.0007) • Rate-corrected mean velocity of fiber shortening ($mVcf_c$) significantly reduced (P = 0.0001) • End-systolic wall stress significantly increased (P = 0.0001)	• PE is as effective as NE and EP for increasing BP in this setting • PE may impair LV function in patients with CAD
DiNardo et al[28]	Mean Doses • PE: 0.87 ± 0.37 µg kg/min • NE: 0.049 ± 0.036 µg/kg/min • EP: 0.032 ± 0.015 µg/kg/min Increase in mean MAP • PE from 75 ± 9 mmHg to 94 ± 11 mmHg (P = 0.0001) • NE from 75 ± 9 mmHg to 97 ± 10 mmHg (P = 0.0001) • EP from 74 ± 8 mmHg to 92 ± 12 mmHg (P = 0.0001)	• Saphenous vein graft flow: PE, NS increase; NE and EP, significantly increased flow • IMA graft flow: PE, significant decrease; NE and EP, significant increase	• Cardiac index: PE: decreased CI from 3 ± 0.8 to 2.6 ± 0.5 L/min per m^2); NE and EP, no change • HR: no change with PE or NE, or EP • CVP: no change with PE or NE, or EP • PCWP: no change with PE or NE; increase with EP • LVSWI: significantly increased with PE, NE, and EP	• PE is as effective as NE and EP for increasing BP in this setting
Baraka et al[29]	• MAP: PE, 35% increase (P < 0.0001); NE, 43% increase (P < 0.0001); EP, 33% increase (P < 0.001)	—	• CO: PE and NE, NS change; EP, 25% increase (P < 0.01) • PCWP: PE, 30% increase (P = 0.03); NE, 49% increase (P = 0.001); EP, 28% increase (P < 0.05) • SVR: PE, 58% increase (P = 0.002); NE, 37% increase (P = 0.001); EP: NS change • HR: PE, 8.6% decrease (P = 0.01) NE, 7.8% decrease (P = 0.03); EP, NS change	• PE is effective for increasing BP in this setting

End-of-Text Table 6. Efficacy and Safety Outcomes in Randomized, Controlled Studies of Phenylephrine for Treatment of Hypotension During Cardiac and Noncardiac Vascular Surgery Under General Anesthesia

Author	Blood Pressure Results	Other Primary Efficacy Results	Other Results	Conclusions
Nygren et al[30]	• MAP: PE, 35% increase ($P < 0.001$); NE, 33% increase ($P < 0.001$) Mean dose • PE = 0.50 ± 0.22 µg/kg/min • NE = 0.052 ± 0.009 µg/kg/mi	Splanchnic flow: perfusion of the gastrointestinal mucosa. Not impaired by PE or NE	• CVP and PAOP: small increase with both PE and NE ($P < 0.01$) • Cardiac index, HR, and SV: not significantly changed for PE or NE • SVRI: significantly increased with PE and NE	PE was as effective as NE effective for increasing MAP in this setting
Smith et al[31]	BP • Proportion requiring PE at the time of skin incision: 76% for high-dose anesthetic group • Proportion requiring PE during carotid occlusion: 100%	—	• Wall stress • Higher for high anesthetic plus PE • Adequacy of collateral carotid flow • Similar in all groups • Proportion with myocardial ischemia • PE had a 3-fold greater rate than no PE	PE was as effective for increasing MAP in patients experiencing hypotension in this setting

Abbreviations: BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, continuous infusion; CO, cardiac output; CPB, cardiopulmonary bypass; CVP, central venous pressure; EP, epinephrine; F, female; HR, heart rate; IA, intra-arterial; IMA, internal mammary artery; IV, intravenous; LVEF, left ventricular ejection fraction; M, male; MAP, mean arterial pressure; NE, norepinephrine; NR, not reported; NS, not significant; PE, phenylephrine; pt(s), patient(s); PCWP, pulmonary capillary wedge pressure; Pop, population; SV, stroke volume; SVR, systemic vascular resistance.
Notes: The study by Goertz et al[27] was double-blind; all others were open-label.

End-of-Text Table 7. Endpoints in Randomized, Double-Blind, Controlled Studies of Phenylephrine for Treatment of Hypotension in Septic Shock

Author	Population	N	PE	Control	Methods	Endpoint(s)
Morelli et al[32]	N = 32 (21 M, 11 F) median age, 70 yrs	IV cont inf; titrated (n = 16)	Titrated	NE, titrated to effect (n = 16)	PE and NE were titrated to achieve a MAP of 65 to 75 mmHg over a study period of 12 hrs	• MAP • SVRI • Mortality • Dose • HR • Arrhythmias
Jain and Singh[33]	N = 54 (28 M, 26 F); median age, 44 yrs. Patients had persistent hypotension after fluid resuscitation and dopamine infusion	IV cont inf; titrated (n = 27) in the presence of dopamine 25 µg/kg/min	Titrated	NE, titrated to effect (n = 27) in the presence of dopamine 25 µg/kg/min	Doses of the 2 vasopressors titrated to achieve all of the following: SBP > 90 mmHg, MAP > 75 mmHg, SVRI > 1100 dynes•s/cm^{5}m^2, CI > 28 L/min per m^2, DO_2I > 550 mL/min/m^2, and VO_2I > 150 mL/min/m^2. Response defined as maintenance of these targets for 6 hours.	• SBP, MAP • HR • SVI • CI • PAOP • Fluid infusion • Urinary output • Response and survival rates • Maximal dose

Abbreviations: CI, cardiac index; cont inf, continuous infusion; DO_2I, oxygen delivery index; F, female; HR, heart rate; IV, intravenous; M, male; MAP, mean arterial pressure; NE, norepinephrine; PE, phenylephrine; SBP, systolic blood pressure; SVRI, systemic vascular resistance index; VO_2I, oxygen consumption index.

End-of-Text Table 8. Efficacy and Safety Results in Randomized, Double-Blind, Controlled Studies of Phenylephrine for Treatment of Hypotension in Septic Shock

Author	Blood Pressure Results	Other Results	Conclusions
Morelli et al[32]	• MAP and SVRI increased by both PE and NE • Mean dose at 12 hrs for PE approx 3 µg/kg/min • Mortality rates: PE, 63%; NE, 56%	• HR: Decreased by both PE and NE • New-onset tachyarrhythmia rates: PE: 2/16; NE: 1/16 • CI: no changes • SVI: no changes	PE is as efficacious as NE for increasing MAP when used as initial hemodynamic support of patients with septic shock.
Jain and Singh[33]	• SBP, MAP significantly increased by both drugs • SVRI significantly increased by both drugs • Survival rates: PE: = 12/27 (44%) NE: survival rate = 11/27 (41%) • Maximal dose – PE: 3.28 ± 1.02 µg/kg/min (range, 0.5-8.5 µg/kg/min) – NE: 2.96 ± 0.28 µg/kg/min	• HR: PE significantly decreased; NE unchanged • SVI: PE significantly increased; NE unchanged • CI: unchanged in both groups • Fluid infusion: no differences between groups • Urine output: unchanged in either group	PE was as effective as NE for treatment of dopamine-resistant hypotension in patients in septic shock.

Abbreviations: CI, cardiac index; DO_2I, oxygen delivery index; F, female; HR, heart rate; IV, intravenous; M, male; MAP, mean arterial pressure; NE, norepinephrine; PE, phenylephrine; SBP, systolic blood pressure; SVRI, systemic vascular resistance index; VO2I, oxygen consumption index.

End-of-Text Table 9. Adverse Events and Fetal Outcomes in Clinical Studies (N = 29) in Obstetrics Phenylephrine Clinical Studies From Published Literature

Reference	N[a]	Phenylephrine Dose	Fetal Outcomes (Adverse Events)	Maternal Adverse Events
Adigun et al[203]	31	100 µg	Mean APGAR scores were similar between the groups.	Hypotension (N = 8); hypertension (N = 0); nausea (N = 3); vomiting (N = 0)
Alahuhta et al[204]	8	100 µg/mL bolus; 16.7 µg/min CI	Fetal heart rate was not affected by the administration of phenylephrine in any instance. The mean values reflecting the functional properties of the fetal heart did not change significantly at any time in the phenylephrine group, nor did the mean systolic peak velocities of the fetal pulmonary trunk or ascending aorta. All newborns had Apgar scores of 8 or more at 1 and 5 min. The mean pH values in the umbilical arterial and venous blood were 7.28 (range 7.14-7.32) and 7.37 (range 7.30-7.42) in the phenylephrine group. One baby had an umbilical arterial pH value under 7.15.	• Moderate hypotension (systolic < 90 mmHg) in 1 patient • Significant reduction in mean maternal heart rate
Allen et al[20]	81	25, 50, 75, or 100 µg/min	Umbilical cord blood gases same across groups. Apgar scores: There were no significant differences in 1- and 5-minute Apgar scores among the groups, with an average across groups of 8 at 1 minute and 9 at 5 minutes. Conclusion: Prophylactic fixed-rate PE infusions did not significantly reduce the number of physician interventions needed to maintain maternal predelivery SBP within 20% of baseline compared with placebo.	• PE 75 and 100 µg/min groups had higher incidence of predelivery hypertension compared with placebo (P < 0.001) • Bradycardia (PE 100 µg; N = 2) (Both patients had been treated with glycopyrrolate for bradycardia that was then followed by reactive hypertension, headache, neck pain) • Ventricular bigeminy (hemodynamically stable) (PE 50 µg; n = 1) • Intraoperative nausea/vomiting same across groups
Ayorinde et al[205]	54	2 mg and 4 mg	There was no significant difference in umbilical cord venous blood pH or APGAR scores. Conclusion: PE 4 mg IM or EPH 45 mg IM immediately after SPA induction reduce the severity of hypotension and reduce the need for rescue therapy.	• No patient developed hypertension/increase MAP of more than 25% • No patient developed bradycardia (HR < 60 bpm) • AEs with PE administration were not mentioned

End-of-Text Table 9. Adverse Events and Fetal Outcomes in Clinical Studies (N = 29) in Obstetrics Phenylephrine Clinical Studies From Published Literature (continued)

Reference	N[a]	Phenylephrine Dose	Fetal Outcomes (Adverse Events)	Maternal Adverse Events
Bjornestad et al[206]	20	50 µg (x 3)	Umbilical pH values and Apgar scores were similar in both groups. Conclusion: PE was a safe and effective method of ensuring stable blood pressure.	Incidence or severity of hypotension (defined as 30% decrease from initial SAP) no difference between groups. Severe hypotension: (N = 1) No arrhythmia or hypertension were observed in either group.
Cooper et al[207]	97	33 µg/min	Fetal acidosis less frequent PE (P = 0.004) and combination group (P = 0.005) than EPH. PE alone: lower incidence of fetal acidosis and maternal nausea and vomiting than EPH alone. PE and EPH combined: increased nausea and vomiting while not improving fetal blood gases than PE alone.	Nausea (17%); vomiting (0%); hypotension (48%). Mean HR was higher in the EPH than in the PE or combination group.
Cooper et al[208]	27	33 µg/min	Fetal acidosis (N = 2) UA pH: higher in PE vs EPH (P < 0.0001). 5-minute Apgar scores: higher in PE Conclusion: Longer spinal delivery intervals increase the risk of fetal acidosis developing with EPH (high incidence of fetal acidosis noted), but not PE.	Rostral spread of bupivacaine: less in PE vs EPH.
Das Neves et al[209]	114	Group 1: 0.15 µg/kg/min (prophylaxis); Group 2: 50 µg (prophylaxis); Group 3: 50 µg (treatment)	Apgar scores @ 1 min = 8 or lower in Group 3 (40%) than Groups 1 and 2 (P = 0.01). Conclusion: Prophylactic continuous infusion of PE initiated immediately after spinal block for cesarean section is more effective in reducing the incidence of hypotension and maternal and fetal side effects.	Incidence of hypotension was higher in Group 3 (85%), than Groups 1 (17.5%) and Group 2 (32.5%) (P < 0.001). Nausea: Group 1 (10%); Group 2 (15%); Group 3 (40%) Reactive hypertension: Group 1 (N = 1; resolved after discontinuation of PE. Bradycardia: Group 2 (N =1).
Defossez et al[210]	10	100 µg/mL bolus; 20 µg/min CI	Apgar scores (no difference). Umbilical blood gases (no difference).	MAP was higher and HR lower in Group 4 (continuous infusion PE). Maternal SaO_2 (no difference) Maternal blood loss (no difference) Side effects included nausea, vomiting, dizziness (both groups).
George et al[211]	45	Dose finding study: 100 µg starting dose	None reported.	No subjects experienced hypertension.

End-of-Text Table 9. Adverse Events and Fetal Outcomes in Clinical Studies (N = 29) in Obstetrics Phenylephrine Clinical Studies From Published Literature (continued)

Reference	N[a]	Phenylephrine Dose	Fetal Outcomes (Adverse Events)	Maternal Adverse Events
Gomaa et al[212]	30	4 mg	There was no undesirable effect on umbilical cord vein pH or Apgar scores at 1 and 5 min in groups. Conclusion: IM 50 mg EPH or IM 4 mg PE 10 minutes prior to spinal anesthesia is safe and effective in reducing the incidence and severity of hypotension during elective cesarean delivery.	Hypotension: EPH (N = 5 [16.5%]); PE (N = 6 [20%]); Control (N = 22 [73.0%]. MAP decrease: Control (34.3%); PE (19.5%); EPH (17.7%) HR increase: EPH (25%); Control (21%), PE (11%).
Gunda et al[15]	50	100 µg	Apgar scores of all neonates were satisfactory at birth.	Nausea (N = 4); vomiting (N = 0); bradycardia (N = 6); tachycardia (N = 0).
Langesaeter et al[19]	40	0.25 µg/kg/min	Conclusion: Low-dose bupivacaine (with sufentanil) combined with a low-dose infusion of PE and moderate cohydration gave the best hemodynamic stability during spinal anesthesia for cesarean delivery.	No reactive hypertension. HR lower in PE than placebo (P = 0.004). CO lower in PE than placebo (P = 0.009). SBP similar in PE and placebo (P = 0.331). Pruritus: 59 (73.8%), little or moderate pruritus and 9 (11.3%), severe pruritus (groups not specified).
Mohta et al[213]	30	50 µg/min	No Apgar score < 7 in either group. Umbilical cord blood gases similar both groups. Conclusion: PE and mephentermine are equally efficacious in preventing postspinal hypotension and are associated with similar neonatal outcome.	Hypotension (N = 2); bradycardia (N = 7 [23%]); reactive hypertension (N = 6 [20%]); vomiting (N = 1); nausea (N = 0).
Moran et al[214]	15	20 to 40 µg	UA blood gas did not differ between groups. Apgar >7 @ 1 min) and >9 @ 5 min. Conclusion: Infants of mothers who received PE had slightly more rapid habituation to light and a slightly greater sucking reflex.	None with PE.
Moran et al[13]	31	80 µg initial; 40-80 µg repeated as needed	Normal fetal acid–base values. Mean UA pH: 7.32.	Nausea and vomiting: 25%. HR change: –26 bpm; no patient had a HR decrease below 60 bpm.

End-of-Text Table 9. Adverse Events and Fetal Outcomes in Clinical Studies (N = 29) in Obstetrics Phenylephrine Clinical Studies From Published Literature (continued)

Reference	N[a]	Phenylephrine Dose	Fetal Outcomes (Adverse Events)	Maternal Adverse Events
Ngan Kee et al[21]	26	100 µg/min	Neonatal outcome was similar between the two PE groups. UA pH <7.2=2 (1 each group). Apgar score of 6 @ 1 min = 2 pts; (one of these neonates had a dysplastic kidney). Conclusion: Prophylactic PE infusion is a simple, safe, and effective method of maintaining arterial blood pressure during spinal anesthesia for cesarean delivery.	Bradycardia (N = 2); hypotension (N = 27); nausea/vomiting (N = 6), transient and related to decreased SBP.
Ngan Kee et al[17]	74	100 µg/min	No UA pH < 7.2 (UA pH was greatest in Group 100 at 7.32). Apgar = 6 (1 min): Group 100 = 1 patient. Conclusion: The results showed that umbilical artery pH was greatest and the incidence of nausea and vomiting was smallest when PE was titrated with the aim of maintaining maternal BP at 100% of baseline.	SBP and HR changes over time were significantly different among groups (P < 0.001). Bradycardia (N = 16); reactive hypertension (N = 7); hypotension (N = 49). Nausea/vomiting (N = 15): Grp 100 (N = 1); Grp 90 (N = 4); Grp 80 (N = 10).
Ngan Kee et al[18]	102	100 µg	No UA pH < 7.2. No Apgar score < 7. Conclusion: As the proportion of PE decreased and the proportion of EPH increased, hemodynamic control was reduced and fetal acid-base status was less favorable.	Hypotension (N = 1); hypertension (N = 12); bradycardia (N = 3); nausea or vomiting (N = 0).
Ngan Kee et al[202]	97	100 µg/min	pH (UA and UV) and Apgar scores were similar between PE and EPH. Lactate concentrations (UA and UV) were lower in PE than EPH. UA and UV PO_2 were lower in PE than EPH, although oxygen content was similar.	Nausea/vomiting (3.9%)

End-of-Text Table 9. Adverse Events and Fetal Outcomes in Clinical Studies (N = 29) in Obstetrics Phenylephrine Clinical Studies From Published Literature (continued)

Reference	N[a]	Phenylephrine Dose	Fetal Outcomes (Adverse Events)	Maternal Adverse Events
Ngan Kee et al[215]	106	100 µg/min	Neonatal outcomes were similar between groups. No umbilical arterial pH <7.2. Apgar score < 7 at 1 minute (all groups) (N = 2). Conclusion: Combination of a high-dose PE infusion and rapid crystalloid cohydration is effective at preventing hypotension during spinal anesthesia for cesarean delivery.	Maternal side effects were similar between the groups. Maternal bradycardia (N = 22); reactive hypertension (N = 50); hypotension (N = 16); nausea (N = 4); vomiting (N = 2).
Prakash et al[16]	30	100 µg	Neonates in PE group (vs EPH): higher UA pH (P = 0.01); higher venous pH (P = 0.002); higher base excess (P < 0.001). No Apgar scores < 7 either group Neurobehavioral scores similar PE vs EPH	HR < 60 bpm (N = 5); nausea (N = 0); vomiting (N = 0).
Ramanathan et al[12]	37	100 µg	Apgar scores and acid–base profiles were not different among groups.	None reported.
Sakuma et al[216]	16	33 µg/min	Umbilical artery pH was significantly higher with PE than with EPH.	PE prevented rostral spread of spinal bupivacaine. Hemodynamic changes were significantly different between the groups. AEs with PE administration were not mentioned.
Saravanan et al[217]	20	Dose-finding study; first patient treated by CI at 16.5 µg/h	Umbilical arterial blood gas analysis showed that pH was significantly (P = 0.01) higher at 7.30 for PE compared with 7.25 (0.09) for EPH. PE produced a better acid-base status than EPH.	No patient required glycopyrronium for the treatment of bradycardia, nor was tachycardia noted. Intervention by the non-blinded anesthetist was not required.
Tanaka et al[218]	50	Dose finding: 40 µg starting dose	UA pH < 7.2 (N = 2) (both cases Apgar scores were >7 at 1 and 5 minutes).	Hypotension (N = 10): 40-100 µg dose (1 pt each group); 110 µg dose (N = 2). Hypertension (N=14): 60-80 µg dose (1 pt each group); 110 µg (N = 6); 120 µg (N = 4). Nausea (N = 11): 40, 60, 70, and 90 µg dose (1 pt each group); 50 µg (N = 2); 110 µg (N = 5). In 7 cases, nausea accompanied hypotension. No bradycardia, vomiting, headache, chest pain, or shortness of breath.

End-of-Text Table 9. Adverse Events and Fetal Outcomes in Clinical Studies (N = 29) in Obstetrics Phenylephrine Clinical Studies From Published Literature (continued)

Reference	N[a]	Phenylephrine Dose	Fetal Outcomes (Adverse Events)	Maternal Adverse Events
Thomas et al[14]	19	100 µg	No neonatal UA pH < 7.2. No Apgar score < 7.	BP and CO changes did not differ between groups. 11 of 19 patients required atropine. Bradycardia > 50%.
Ueyama et al[11]	10	250 µg	Conclusion: The increase of TVR plays an important role for the prevention of spinal hypotension in patients with prophylactic PE administration.	In the PE group, decrease in CO was also accompanied with significant increase in TVR (P < 0.01), both returned to baseline prior to delivery. Hypotension: PE (0%).

Abbreviations: BP, blood pressure; CI, continuous infusion; CO, cardiac output; EPH, ephedrine; IM, intramuscular; IV, intravenous; PE, phenylephrine; SVRI, systemic vascular resistance index; TVR, total vascular resistance; UA, umbilical artery.
[a] Number of patients treated with phenylephrine.

End-of-Text Table 10 Adverse Events and Subject Outcomes in Nonobstetric Clinical Studies (N = 25) Phenylephrine Clinical Studies From Published Literature

Reference	Phenylephrine Route of Administration	Subject Outcomes	Adverse Events
Brooker et al[24]	40 µg IV bolus; 0.5 µg/kg/min IV CI	PE decreases HR and CO while restoring SBP, mean, and DBP.	The frequency of arrhythmias was low and similar between the PE, Epi, spinal anesthesia, and baseline groups. No ST segment changes consistent with ischemia. No perioperative cardiovascular adverse events.
Cheng et al[22]	0, 50 100, or 200 µg IV bolus	The incidence of hypotension was 45%, 55%, 35%, and 15% in Groups 1-4.	One patient experienced an episode of severe hypertension (BP 212/146 mmHg) and mental confusion, due to absorption of the PE-lidocaine mixture through a lacerated epidural vessel.
Nishikawa et al[219]	1.5 or 3 mg IM	Prophylactic IM injection of PE was safe and effective in reducing the incidence of hypotension associated with spinal anesthesia in normotensive and hypotensive elderly patients.	Hypotension (normotensive group, N = 3; hypertensive group, N = 6; hypertension (normotensive group, N = 1; hypertensive group, N = 2). HR $\leq$ 50 = 0 % decreases in HR same in groups.
Acosta et al[142]	0.1 mg IV bolus	PE was sufficient for treating PRS.	No AEs with PE were mentioned in the publication.
DiNardo et al[28]	0.87 µg/kg/min (mean)	PE infusion induced a NS flow increase through SV grafts and a significant decrease in flow through left IMA grafts With PE infusion vs control: MAP increased by 19 mmHg; CI decreased; LV stroke work index increased; no change in HR, PCWP, or CVP.	No AEs with PE were mentioned in the publication.
Baraka et al[29]	100 µg	MAP, SVR, and PCWP were significantly increased, HR was significantly decreased and CO showed no change.	No AEs with PE were mentioned in the publication.
Goertz et al[27]	1 µg/kg	HR transiently decreased in both agents. PE IV bolus in CAD patients—transient impairment of LV global function. Bolus PE is well tolerated in patients with valvular aortic stenosis.	No AEs with PE were mentioned in the publication.

End-of-Text Table 10 Adverse Events and Subject Outcomes in Nonobstetric Clinical Studies (N = 25) Phenylephrine Clinical Studies From Published Literature (continued)

Reference	Phenylephrine Route of Administration	Subject Outcomes	Adverse Events
Nygren et al[30]	0.50 ± 0.22 µg/kg/min	Neither intestinal mucosal perfusion nor gastric arterial PCO_2 gradient was changed by either vasopressor. PE induced a more pronounced global α-mediated splanchnic vasoconstriction compared with norepinephrine. PE and NE both increased MAP (by 35%), SVRI (by 46%), central venous pressure, and PAOP; and decreased HR.	No AEs with PE were mentioned in the publication.
Marino et al[220]	0.3 mg	Perfusion pressure and the oxygenator blood volume (reflecting venoconstriction) were significantly increased.	No AEs with PE were mentioned in the publication.
Schwinn et al[166]	20 to 400 µg	Fentanyl anesthesia is associated with decreased α_1-adrenergic responsiveness in patients with impaired ventricular function compared to patients with normal ventricular function. Less PE is required during CPB and aortic cross-clamp than during the awake state to produce the same pressor effect.	No AEs with PE were mentioned in the publication.
Schwinn et al[221]	50, 100, 150, or 200 µg	Bolus IV PE in patients with myocardial disease increases MAP and SVR, and simultaneously decreases CO. Hemodynamic changes for each of the 4 doses of PE were maximal at 42 sec after the drug was given.	No AEs with PE were mentioned in the publication.
Smith et al[105]	50 to 100 µg	Following CABG, patients with moderate-severe LV dysfunction may require higher doses of a-adrenoceptor	No AEs with PE were mentioned in the publication.

End-of-Text Table 10 Adverse Events and Subject Outcomes in Nonobstetric Clinical Studies (N = 25) Phenylephrine Clinical Studies From Published Literature (continued)

Reference	Phenylephrine Route of Administration	Subject Outcomes	Adverse Events
Butterworth et al[222]	150, 300, and 450 ng/kg/min		
Lobato et al[223]	1 µg/kg per min	PE significantly increased mean IMA blood flow, although it decreased in 4 subjects.	No AEs with PE were mentioned in the publication.
Skubas et al[224]	Titrated; actual dose NR	Increased MAP, SVR; didn't change SV.	No AEs with PE were mentioned in the publication.
Smith et al[31]	Titrated; actual dose NR	There were no differences detected between the anesthetics for systemic blood pressure, cerebral perfusion, and myocardial ischemia. Patients who received PE had an almost 3-fold greater incidence of myocardial ischemia, regardless of anesthetic agent.	Myocardial ischemia
Mutch et al[59]	Titrated; actual dose NR	No patient had evidence of myocardial ischemia as assessed by Holter monitoring during ICA cross-clamping when MAP was supported with PE infusion	No AEs with PE were mentioned in the publication. It was concluded that PE is a safe and does not place the heart at increased risk of ischemia during carotid endarterectomy.
Borum et al[60]	0.2 µg/kg/min	PE requirements were greater in patients receiving PE alone vs PE + TEAP.	No patient experienced a new postoperative neurologic deficit. There was no evidence of myocardial injury. One patient receiving PE + TEAP developed a first-degree AV block.
Jain and Singh[33]	Maximal infusion rate of PE required to achieve the target was 3.28 ± 1.02 µg/kg/min compared with 2 96 ± 0.28 µg/kg/min of norepinephrine, respectively	PE infusion is comparable to norepinephrine in reversing hemodynamic and metabolic abnormalities of sepsis patients Decreased HR ($P < 0.001$) and increase in SVI ($P < 0.001$) in the PE group compared with nonsignificant change in the norepinephrine group.	No AEs with PE were mentioned in the publication.
Morelli et al[32]	Titrated; mean 3 µg/kg/min	The MAP was significantly higher with NE compared with PE. No difference between groups in any other hemodynamic variable. Urine output and creatinine clearance were similar between groups.	2 of 16 patients experience new-onset tachyarrhythmias.

End-of-Text Table 10 Adverse Events and Subject Outcomes in Nonobstetric Clinical Studies (N = 25) Phenylephrine Clinical Studies From Published Literature (continued)

Reference	Phenylephrine Route of Administration	Subject Outcomes	Adverse Events
Gregory et al[61]	0.5-9 µg/kg/min to maintain MAP > 70 mmHg.	MAP (37%), SVRI (18%), left ventricular stroke work index, and SVI were significantly increased (P < 0.05) after PE administration and at the time of highest oxygen consumption. No change in HR and PAOP were observed. Blood lactate decreased and urine output increased (P < 0.05); serum creatinine concentrations remained unchanged.	No clinical evidence of impaired organ function during PE therapy. Conclusion: the use of PE as a component of hemodynamic support contributed to improvements in perfusion and stabilization of hemodynamic variables.
Patel et al[225]	IV CI; 25-200 µg/min, titrated to effect	Patients receiving norepinephrine and dopamine in septic shock required the addition of PE and vasopressin.	No AEs with PE were mentioned in the publication.
Yamazaki et al[226]	IV CI; Titrated; approx 70 µg/min required	PE increased SAP, CVP, MAP in both septic and cardiac groups.	No AEs with PE were mentioned in the publication.
Flancbaum et al[62]	0.5, 1.0, 2.0, 3.0, 4.0, and 8.0 µg/kg/min every 30 minutes	With increasing PE dose, MAP and SVRI increased linearly. The MAP increased an average of 44.8% over baseline, and SVRI increased an average of 54.6% for all patients. Conclusion: Predictable dose-dependent increase in MAP and SVRI with PE infusion. The CO was maintained by a compensatory increase in stroke volume (SV) in the presence of a decrease in HR.	No hemodynamic instability, dysrhythmia, myocardial ischemia, or chest pain. No fatalities during PE infusion.

End-of-Text Table 10 Adverse Events and Subject Outcomes in Nonobstetric Clinical Studies (N = 25) Phenylephrine Clinical Studies From Published Literature (continued)

Reference	Phenylephrine Route of Administration	Subject Outcomes	Adverse Events
Morelli et al[227]	IV titrated (mean 4.39 µg/kg/min) to maintain MAP 65-75 mmHg for 8 hrs.	Significant decrease in HR after replacing NE with PE. Hemodynamic parameters, global oxygen transport, and acid-base balance remained unchanged after replacing NE with PE. After switching back to norepinephrine, all variables returned to values obtained before PE infusion except creatinine clearance and gastric mucosal perfusion.	No AEs with PE were mentioned in the publication.

Abbreviations: CI, continuous infusion; CO, cardiac output; EPH, ephedrine; IM, intramuscular; IV, intravenous; NE, norepinephrine; MAP, mean arterial pressure; PE, phenylephrine; UA, umbilical artery.
[a] Number of patients treated with phenylephrine.

End-of-Text Table 11. Adverse Events or Other Safety Statements Related to Phenylephrine in Publications (N = 21) in Which Phenylephrine is Used in the Evaluation of BRS

Citation	Study Population	Dose	Outcome Measure	Adverse Events (AEs) and General Safety Comments Regarding PE
Farrell et al[228]	122 (117 male, 5 female; mean age 56 yrs) patients admitted to hospital with acute MI	Bolus over 15 seconds 0.2 mg followed by progressively larger doses until a rise in SBP of 15-40 mmHg was obtained. Test was repeated until at least 3 recordings were made with optimum bolus dose.	RR internal, BP	Transient headache, extrasystoles, pulsus alternans, atrial flutter Stated "There were no major complications after BRS testing. No patient developed signs or symptoms of MI or serious ventricular arrhythmias"
La Rovere et al[229]	78 men after a first MI	2 µg/kg to raise SAP more than 15 but less than 40 mmHg; additional injections were made increasing the dosage by increments of 25 µg/kg to a maximum of 3.5 µg/kg. Bolus injection at effective dose was repeated at least 2 times	HR (ECG), BP (brachial or radial arterial pressure)	Transient headache Stated "no signs or symptoms of acute myocardial ischemia"
Davies et al[230]	31 patients (20 patients who had heart failure due to CAD and 11 with dilated cardiomyopathy); 18 (13 male; 5 female) controls	2 µg/kg bolus, increasing by 50 µg/bolus until a rise in SBP of at least 15 mmHg. Bolus injection was repeated at least 3 times at the adequate dose	Slope of the linear relationship between the RR interval (via ECG with limb lead) and SBP (via Finapres)	Bradycardia
Raczak et al[231]	104 patients in sinus rhythm with a previous MI were enrolled consecutively into 2 groups according to their LVEF ≤ 40% (n = 52) or > 40% (n = 52)	2 µg/kg to raise SAP by 15-40 mmHg; if BP did not increase as expected, additional PE increments of 25 µg were added; bolus injection repeated 3 times at 10-min intervals at the dosage required to increase the SAP as desired	PE technique and Valsalva maneuver	3 patients had inadequate increase in arterial pressure or an excessive number of ectopic beats

End-of-Text Table 11. Adverse Events or Other Safety Statements Related to Phenylephrine in Publications (N = 21) in Which Phenylephrine is Used in the Evaluation of BRS (continued)

Citation	Study Population	Dose	Outcome Measure	Adverse Events (AEs) and General Safety Comments Regarding PE
Bonaduce et al[177]	25 patients (21 male, 4 female) referred to coronary care unit for a first transmural MI diagnosed by classic criteria; site of necrosis was anterior in 12 patients and inferior in 13 patients	2 µg/kg initially to raise SAP by > 15 and < 40 mmHg. If BP did not increase as desired, addition injections by 25 µg up to a max of 3.5 µg/kg; bolus injection repeated at least 3 times at the dose found to induce the required BP increase	SBP and RR intervals	Transient headache
Airaksinen et al[232]	47 patients (27 men) undergoing single-vessel coronary angioplasty for stenoses in the proximal or midportion of the vessel causing >50% reduction in the arterial diameter, with normal antegrade flow; 11 control patients (6 men) treated for chronic total occlusion of a coronary artery	150-200 µg	Slope of the linear relationship between the RR interval and SBP	Bradycardia
Okada et al[233]	210 patients with type 2 diabetes mellitus admitted to hospital for blood glucose control: 99 preserved BRS, mean age 55.6 years, 63 M, 36 F; 85 depressed BRS, mean age 60.6 years, 31 M, 54 F	2-3 µg/kg injected over 15 seconds to increase SBP by 15-40 mmHg	Initial onset of MACE	Adverse effects with phenylephrine were not mentioned in the article

End-of-Text Table 11. Adverse Events or Other Safety Statements Related to Phenylephrine in Publications (N = 21) in Which Phenylephrine is Used in the Evaluation of BRS (continued)

Citation	Study Population	Dose	Outcome Measure	Adverse Events (AEs) and General Safety Comments Regarding PE
Olshan et al[234]	10 male patients with adult-onset diabetes with no family history of HTN, in whom diabetes antedated the appearance of HTN; 7 pts were receiving insulin, 2 were taking oral hypoglycemics, and 1 controlled the diabetes through diet alone. Also 3 other groups: 13 healthy normotensive men who were not taking medication and had normal fasting blood sugar; 10 men with essential hypertension not taking antihypertensives for at least 3 wks; 13 uremic men undergoing long-term maintenance hemodialysis who had concomitant hypertension and varied causes of chronic renal failure, but no history of essential hypertension or diabetes	200-400 µg to increase MAP by 20-30 mmHg	BP, urine, multiple hemodynamic tests, including inhalation of amyl nitrite and intravenous administration of phenylephrine, before and after parasympathetic blockade with atropine, and the cold pressor test	Adverse effects with phenylephrine were not mentioned in the article
Farrell et al[235]	68 patients (7 to 10 days post-MI)	Initial test dose of 0.2 mg followed by progressively larger doses until an increase between 15 and 40 mmHg in SBP occurred; repeated until at least 3 recordings were made with the optimum dose.	Arterial pressure recorded via right femoral line with simultaneous recording of a single-lead ECG; BRS expressed as slope of the regression line relating RR interval changes to SAP	Adverse effects with phenylephrine were not mentioned in the article
Arranz et al[145]	BRS, portal hypertensive (n = 12) vs normals (n = 6), bolus dose PE	0.5 mL injection of increasing doses at 10-min intervals of 25, 50, 75, 100, and 150 µg	BRS and Valsalva ratio	None reported (clarify)

End-of-Text Table 11. Adverse Events or Other Safety Statements Related to Phenylephrine in Publications (N = 21) in Which Phenylephrine is Used in the Evaluation of BRS (continued)

Citation	Study Population	Dose	Outcome Measure	Adverse Events (AEs) and General Safety Comments Regarding PE
Mortara et al[67]	303 patients with dilated cardiomyopathy and moderate to severe HF	3 to 4 µg/kg to raise SAP by 15 to 30 mmHg by at least 3 bolus injections; if BP did not increase as desired, additional injections of 50 µg	HR and SAP (either directly from the radial/brachial artery or via Finapres); BRS determined via RR interval vs SAP	Stated: "No adverse effects were observed during or after PE injections"
Airaksinen et al[68]	32 patients with CAD	Not mentioned	Mean BRS slope	Stated: "PE was well tolerated and did not cause any significant side effects"
James et al[69]	54 subjects aged mean 70 years, range 60-81, divided into groups with combined systolic-diastolic HTN (CH group, n = 16), isolated systolic HTN (ISH group, n = 16), or normotension (NT group, n = 22)	50 mg then progressively increased in 50-mg steps as needed to a max of 200 mg to achieve peak BP rise of 20-40 mmHg, and the effective dose was repeated to obtain a minimum of 3 adequate responses	Pulse interval and BP responses to Valsalva maneuver	Stated: "PE was not associated with any side effects"
Mimura et al[70]	30 patients who had their first acute MI 2 weeks prior (15 underwent exercise training; and 15 did not)	80 to 120 µg; for arterial BRS, at least 3 bolus doses separated by 10-min intervals were injected	Arterial BP, HR, and MSNA; BRS calculated from RR interval and SAP; BR modulation of MSNA was also calculated	Stated: "No serious AE was observed during PE infusion"
Yuasa et al[236]	40 uncomplicated patients with acute MI	Not specified other than IV bolus to raise the SAP by 20 mmHg, repeated at least 3 times a dosage that induced the required BP increase and at not less than 10-min intervals	BP, HR	Stated: "Patient developed signs or symptoms of MI or serious ventricular arrhythmia"
Pleiner et al[71]	26 healthy male subjects, 20 to 33 years	PE 1%	BP, HR	Stated: "Drugs under study were well tolerated"

End-of-Text Table 11. Adverse Events or Other Safety Statements Related to Phenylephrine in Publications (N = 21) in Which Phenylephrine is Used in the Evaluation of BRS (continued)

Citation	Study Population	Dose	Outcome Measure	Adverse Events (AEs) and General Safety Comments Regarding PE
Raczak et al[237]	52 patients with remote MI and history of spontaneous VT: 20 patients with good hemodynamic tolerance and 27 patients with poor hemodynamic tolerance of VT; the remaining 5 in whom VT was not induced were excluded from further studies	2 µg/kg to raise SAP by 15-30 mmHg; if BP did not increase as expected, additional injections were made increasing PE by increments of 25-50 g; bolus injection repeated at 10-minute intervals at least 3 times at the dosage inducing required SAP increase	BP	Stated: "No adverse effects were observed after IV injection of PE"
Mortara et al[64]	815 patients. 359 (319 male, 40 female, mean age 56 years) who underwent angiography; 456 (401 male, 55 female, mean age 58 years) with no angiography	2 µg/kg; if systolic arterial pressure did not increase by 15-40 mmHg, additional PE injections were made by increments of 25-50 µg. Bolus injection was repeated at least 3 times at the dosage found to induce the required BP increase at not less than 10-minute intervals	HR, BP	Stated: "No adverse effects were observed during or after PE injections"
La Rovere et al[66]	Prospective study of 1284 patients with a recent MI; 1119 male/165 female; mean age 57 years; number < 65 years 968	2-4 µg/kg at least 3 bolus injections with intervals of 10 min to raise systolic arterial pressure by 15-40 mmHg	LVEF, HR, arrhythmia analysis, BRS from rate-pressure response to PE	Stated: "No significant adverse effects were observed during or after PE"
La Rovere et al[73]	180 patients; mean age 53 years; LVEF 23% with mild to severe CHF in sinus rhythm and stable clinical condition in a HF unit; 100 post-MI patients (mean age 57 years, LVEF 47%)	Not reported	BP	Stated: "No signs or symptoms of heart failure nor complex arrhythmias were seen during PE injection"

End-of-Text Table 11. Adverse Events or Other Safety Statements Related to Phenylephrine in Publications (N = 21) in Which Phenylephrine is Used in the Evaluation of BRS (continued)

Citation	Study Population	Dose	Outcome Measure	Adverse Events (AEs) and General Safety Comments Regarding PE
Tham et al[72]	10 healthy male volunteers, mean age 22	40-60 µ/min; rate of infusion increased gradually 40, 60, 100, 150, 200, 300, 400, 600, 1000, and 1500 µg/min until SBP increase by 30 mmHg from baseline or DBP exceeded 110 mmHg or the subject could not tolerate PE's effects	Not mentioned	Stated: "No untoward effects"

Abbreviations: AE, adverse event; BP, blood pressure; BRS, baroreceptor sensitivity; CAD, coronary artery disease; CH, combined systolic-diastolic HTN group; ECG, electrocardiogram; HF, heart failure; HR, heart rate; HTN, hypertension; ISH, isolated HTN group; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MSNA, muscle sympathetic nerve activity via microneurography; NT, normotension group; SAP, systemic arterial pressure; SBP, systolic blood pressure; VT, ventricular tachycardia; yrs, years

End-of-Text Table 12.
Summary of FOI Adverse Event Reports (in ≥ 2 Patients)
Data Through December 2010
Where Phenylephrine is a Suspect Drug and Route of Administration is IV, Injectable, or Neuraxial

MedDRA System Organ Class Preferred Term	**No. (%) of Adverse Event (N = 259)**
Cardiac Disorders	
Bradycardia	18 (6.9)
Cardiac arrest	5 (1.9)
Arteriospasm coronary	4 (1.5)
Cardio-respiratory arrest	3 (1.1)
Tachycardia	3 (1.1)
Ventricular tachycardia	3 (1.1)
Atrioventricular block complete	2 (0.8)
Mitral valve incompetence	2 (0.8)
Myocardial infarction	2 (0.8)
Stress cardiomyopathy	2 (0.8)
General Disorders and Administration Site Conditions	
Chest pain	3 (1.1)
Chest discomfort	2 (0.8)
Device failure	3 (1.1)
Drug ineffective	3 (1.1)
Injury, Poisoning and Procedural Complications	
Drug exposure during pregnancy	15 (5.7)
Medication error	14 (5.4)
Drug administration error	4 (1.5)
Overdose	3 (1.1)
Procedural complication	2 (0.8)
Investigations	
Blood pressure decreased	5 (1.9)
Electrocardiogram T wave inversion	4 (1.5)
Blood lactic acid increased	3 (1.1)
Blood pressure systolic increased	3 (1.1)
Blood creatinine increased	2 (0.8)
Blood pressure diastolic decreased	2 (0.8)
Blood pressure increased	2 (0.8)
Ejection fraction decreased	2 (0.8)
Electrocardiogram ST segment depression	2 (0.8)
Electrocardiogram ST segment elevation	2 (0.8)

End-of-Text Table 12.
Summary of FOI Adverse Event Reports (in ≥ 2 Patients)
Data Through December 2010
Where Phenylephrine is a Suspect Drug and Route of Administration is IV, Injectable, or Neuraxial (continued)

MedDRA System Organ Class Preferred Term	**No. (%) of Adverse Event (N = 259)**
Metabolism and Nutrition Disorders	
Propofol infusion syndrome	4 (1.5)
Metabolic acidosis	2 (0.8)
Nervous System Disorders	
Aphasia	4 (1.5)
Encephalopathy	3 (1.1)
Headache	3 (1.1)
Syncope	3 (1.1)
Unresponsive to stimuli	3 (1.1)
Psychiatric Disorders	
Delirium	3 (1.1)
Renal and Urinary Disorders	
Renal failure	2 (0.8)
Respiratory, Thoracic and Mediastinal Disorders	
Lung infiltration	9 (3.4)
Pulmonary edema	5 (1.9)
Acute pulmonary edema	2 (0.8)
Surgical and Medical Procedures	
Nerve block	2 (0.8)
Vascular Disorders	
Hypertension	12 (5.0)
Hypotension	7 (2.7)
Air embolism	2 (0.8)

End-of-Text Table 13. Drug Interaction Studies With Phenylephrine

Drug	Type of Study	Summary of Findings	Reference
Cardiovascular Drugs			
α-Adrenergic Blocking Agents			
Prazosin PO	Single-blind, randomized, crossover design in normotensive white men	Reduced venous responsiveness to phenylephrine	Sekkarie[180]
Trimazosin PO, IV	Healthy normotensive men	PE dose-response curve shifted to the right after IV and PO trimazosin	Vincent[168]
Terazosin	Healthy nonsmokers	5- to 7- fold shift to the right of PE dose-response curve; until day 25, when it shifted back to baseline	Vincent[238]
Prazosin	Healthy men	PE dose-response curve shifted to right; tolerance to prazosin noted after 4 days of dosing	Von Bahr[239]
Trimazosin	Normotensive men	PD_{20} was increased after trimazosin administration	Vincent[167]
Prazosin	Healthy normotensive men	4-fold increase in ED_{20} with prazosin	Shepherd[169]
Urapidil	Healthy women	4-fold increase in PD_{20}	Tomlinson[240]
Doxazosin	Placebo-controlled trial in patients with mild to moderate hypertension	PD_{20} significantly increased with doxazosin	Reid[171]
α-Adrenergic Agonists			
Clonidine	Randomized, controlled in awake and anesthetized normotensive patients	Preadministration of clonidine augmented the pressor responses to PE in awake and anesthetized patients	Inomata[241]
Clonidine	Randomized, double-blind, placebo-controlled study in patients with essential hypertension undergoing elective surgery	Clonidine increased sensitivity to PE	Parlow[242]
Clonidine	Patients scheduled for elective surgery	Clonidine augmented the pressor and HR responses to PE	Watanabe[243]
Angiotensin-converting enzyme inhibitors (ACEIs)			
Enalapril	Healthy men – vasoconstriction in hand vein	PE dose-response curve shifted to the right; ED50 was not significantly increased	Kimura[175]
Quinapril		PE dose-response curve shifted to the right; ED50 significantly increased	
Enalapril	Placebo-controlled trial in patients with mild-to-moderate hypertension	PD20 significantly decreased with enalapril	Reid[171]

End-of-Text Table 13. Drug Interaction Studies With Phenylephrine (continued)

Drug	Type of Study	Summary of Findings	Reference
Enalapril	Patients with essential hypertension	Pressor responsiveness to PE unchanged after enalapril	Donnelly[176]
Enalapril	Randomized, double-blind, single-dose, crossover study in normotensive, mildly sodium-depleted men	BRS higher after enalapril administration	Ibsen[244]
Captopril	Patients; after uncomplicated MI	BRS significantly higher after captopril	Bonaduce[177]
Captopril	Normal subjects	BRS was not increased after captopril	Kondowe[245]
Captopril	Severely hypertensive subjects	BRS was not increased after captopril	Warren[246]
Captopril, ramipril, cilazapril, or perindopril with anesthesia	Anesthesia-induced hypotension in patients with valvular heart disease	No difference in pressor response to PE in patients receiving ACEIs	Kwak[247]
ACEIs (not specified) with anesthesia	Patients on ACEIs undergoing elective cardiac surgery with CPB	Patients with preoperative HF required more vasopressor support with PE	Bennett et[153]
Angiotensin II Receptor Antagonists			
Losartan	Open, randomized-4-way crossover study in normotensive men	No change in venoconstrictor response to PE	Harada[248]
Candesartan	Patients with heart failure	BRS was significantly increased after candesartan	Vaile[178]
Beta-Adrenergic Blocking Drugs (Beta Blockers)			
Bisoprolol	Men	PE dose-response curve shifted to the right; ED_{50} increased by 155% with bisoprolol 5 mg and 289% with bisoprolol 10 mg	Abdelmawla[249]
Propranolol + atropine; and prazosin + propranolol + atropine	Healthy normotensive men	Lower ED20 with propranolol + atropine and slightly lower with prazosin + propranolol + atropine	Shepherd[169]
Propranolol, metoprolol	Randomized, double-blind study in patients with β-blockers	No increase in pressor effects with either propranolol or metoprolol	Myers[250]
Metoprolol	Patients with hypertension	PE dose-response curve was shifted to the left	Casiglia[170]

End-of-Text Table 13. Drug Interaction Studies With Phenylephrine (continued)

Drug	Type of Study	Summary of Findings	Reference
Calcium Channel Blockers			
Nifedipine, diltiazem	Healthy men	Both drugs significantly reduced venoconstrictor effects of PE	Schulte[251]
Verapamil	Healthy men	PE dose-response curve was shifted to the right	Abernethy and Winterbottom[252]
Nifedipine, verapamil, diltiazem	Healthy normotensive white men	Nifedipine and verapamil blocked the PE effect; diltiazem failed to block the PE effect	Andrawis[172]
Verapamil, nisoldipine	Randomized, placebo-controlled, crossover trial in normotensive men	Verapamil and nisoldipine significantly shifted the PE dose-response curve to right	Elliott[173]
Nifedipine	Placebo-controlled trial in patients with mild-to-moderate essential hypertension	PD_{20} was significantly increased	Reid[171]
Nifedipine (chronic therapy)	Patients undergoing elective CABG	Chronic nifedipine therapy plus halothane anesthesia did not modify the hemodynamic response to PE	Grum and Azmy[174]
Other Cardiovascular Drugs			
Guanadrel IV	Randomized, single-blind crossover study in normotensive white men	Enhanced venous responsiveness to phenylephrine	Sekkarie[180]
Debrisoquine	Double-blind study in hypertensive patients	Debrisoquine augmented the pressor effects of PE	Allum[181]
Digoxin	Open-label study in normotensive subjects and in patients with mild uncomplicated hypertension	BRS was significantly higher	Ferrari[182]
Central Nervous System Drugs			
Halothane (with oral PE)	—	Transient rise in BP but no arrhythmias	Condon[191]
Halothane	Normothermic patients with no cardiovascular or respiratory disease	HR unchanged or reduced in all but 1 patient; isolated extrasystoles in 2 patients	McIntyre[192]
Halothane	Patients undergoing elective CABG	Halothane did not alter the hemodynamic response to PE	Grum and Azmy[174]

End-of-Text Table 13. Drug Interaction Studies With Phenylephrine (continued)

Drug	Type of Study	Summary of Findings	Reference
Isoflurane	Before and during isoflurane anesthesia in men	FVR was attenuated in a dose-related manner during isoflurane anesthesia	Robinson and Ebert[253]
Isoflurane, desflurane	During isoflurane and desflurane anesthesia	FVR was attenuated by desflurane and isoflurane	Arain[254]
Anticholinergics			
Atropine	Atropinized patients, patients with mitral valve disease, a patient with essential arterial hypertension, and a patient with hypertrophic cardiomyopathy	Bolus injections of PE were safe and practical	Okoshi[194]
Atropine	Healthy men	PE SBP and DBP dose-response curves were shifted to the left	Levine and Leenen[193]
Monoamine Oxidase Inhibitors (MAOIs)			
Tranylcypromine, phenelzine		Marked potentiation of PE effects, which was greater with PO than IV PE	Elis[184]
MAOIs (not specified) with anesthesia	Patients on chronically maintained on MAOI therapy	Report of successful treatment with PE	El-Ganzouri[185]
Tricyclic Antidepressants (TCAs)			
Imipramine and MAOIs (phenelzine and tranylcypromine)		2- to 3-fold potentiation of PE effect with imipramine; 2.5-fold with tranylcypromine, and 2-fold with phenelzine pretreatment	Boakes et al[186]
TCAs	Healthy subjects	Decreased PE sensitivity with amitriptyline, ciclazindol, zimelidine (and lithium)	Ghose[126]
Ergot Alkaloids			
Ergonovine	Patients with angina at rest	Pressure was markedly elevated with PE, but no ECG changes suggesting myocardial ischemia	Chierchia[189]
Endocrine and Metabolism Agents			
Oxytocin	Randomized double-blind study of women undergoing elective Cesarean delivery	Used successfully to treat BP in women undergoing elective cesarean delivery	Sartain[195]

End-of-Text Table 13. Drug Interaction Studies With Phenylephrine (continued)

Drug	Type of Study	Summary of Findings	Reference
Steroids			
Hydrocortisone	Patients with moderate to severe injury due to trauma	ED_{50} decreased without a change in E_{max} after hydrocortisone; PE dose-response curve shifted to the left	Hoen[198]
Hydrocortisone	Open-label study in septic shock patients and healthy volunteers	E_{max} greater, but ED_{50} unchanged; Increased sensitivity to PE	Annane[199]
Antidiabetic Agents			
Insulin	Normotensive, nondiabetic men	PE increased plasma insulin concentrations	O'Callaghan[200]
Insulin	Diabetic patients with autonomic neuropathy	PE dose-response curve shifted to the right after insulin; PD_{20} was increased by 63%; the BRS was not affected	Yamamoto[201]
Other Interactions			
Fatty acids	Normotensive subjects	Pressor response to PE was enhanced	Haastrup[103]

7. REFERENCES

1. 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.
2. LeBlanc JM, Dasta JF, Hollenberg SM. North American survey of vasopressor and inotrope use in severe sepsis and septic shock. *Crit Care Shock* 2008;11:137-48.
3. Lindenauer PK, Rothberg MB, Nathanson BH, et al. Activated protein C and hospital mortality in septic shock: A propensity- matched analysis. *Crit Care Med* 2010;38:1101-7.
4. Drasner K, Larson MD. Spinal and epidural anesthesia. In: Stoelting R, Miller R, editors. Basics of anesthesia. 5th ed. Philidelphia: Churchhill Livingstone Elsevier; 2007. p. p. 268.
5. Carpenter RL, Caplan RA, Brown DL, et al. Incidence and risk factors for side effects of spinal anesthesia. *Anesthesiology* 1992;76:906-16.
6. Monk TG, Saini V, Weldon BC, et al. Anesthetic management and one-year mortality after noncardiac surgery. *Anesth Analg* 2005;100:4-10.
7. Lienhart A, Auroy Y, Pequignot F, et al. Survey of anesthesia-related mortality in france. *Anesthesiology* 2006;105:1087-97.
8. Chang HS, Hongo K, Nakagawa H. Adverse effects of limited hypotensive anesthesia on the outcome of patients with subarachnoid hemorrhage. *J Neurosurg* 2000;92:971-5.
9. Biljker JB, van Klei WA, Vergouwe Y, et al. Intraoperative hypotension and 1-year mortality after noncardiac surgery. *Anesthesiology* 2009;111.
10. Rosen M, Hughes S. Obstetrics. In: Stoelting R, Miller R, editors. Basics of anesthesia. 5th ed. Philadelphia: Churchill Livingstone Elsevier; 1987. p. p. 483.
11. Ueyama H, Hiuge Y, Takashina M, et al. Maternal cardiovascular effects of prophylactic ephedrine and phenylephrine for elective cesarean section undergoing spinal anesthesia. *Anesthesiology* 2002;96:A1051.
12. Ramanathan S, Grant GJ. Vasopressor therapy for hypotension due to epidural anesthesia for cesarean section. *Acta Anaesthesiol Scand* 1988;32:559-65.
13. Moran DH, Perillo M, LaPorta RF, et al. Phenylephrine in the prevention of hypotension following spinal anesthesia for cesarean delivery. *J Clin Anesth* 1991;3:301-5.
14. Thomas DG, Robson SC, Redfern N, 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.

15. Gunda CP, Malinowski J, Tegginmath A, et al. Vasopressor choice for hypotension in elective cesarean section: Ephedrine or phenylephrine? *Arch Med Sci* 2010;6:257-63.

16. 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 randomised study. *Int J Obstet Anesth* 2010;19:24-30.

17. Ngan Kee WD, Khaw KS, Ng FF. Comparison of phenylephrine infusion regimens for maintaining maternal blood pressure during spinal anaesthesia for caesarean section. *Br J Anaesth* 2004;92:469-74.

18. Ngan Kee WD, Khaw KS, Lau TK, et al. Randomised double-blinded comparison of phenylephrine vs ephedrine for maintaining blood pressure during spinal anaesthesia for non-elective caesarean section. *Anaesthesia* 2008;63:1319-26.

19. Langesaeter E, Rosseland LA, Stubhaug A. 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. *Anesthesiology* 2008;109:856-63.

20. 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.

21. 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.

22. Cheng JK, Pan MH, Wu KH, et al. Epidural phenylephrine attenuates hypotension induced by alkalinized lidocaine epidural anesthesia. *Anesth Analg* 1999;88:1322-6.

23. Brooker RF, Butterworth JF, Berman JM, et al. Comparison of epinephrine and phenylephrine for treatment of hypotension after subarachnoid block. *Anesthesiology* 1995;83:A782.

24. Brooker RF, Butterworth JF, Kitzman DW, et al. Treatment of hypotension after hyperbaric tetracaine spinal anesthesia. *Anesthesiology* 1997;86:797-805.

25. Ertmer C, Morelli A, Westphal M. The role of phenylephrine in perioperative medicine. In: Vincent J, editor. Yearbook of intensive care and emergency medicine Heidelberg: Springer-Verlag; 2009. p. 483-97.

26. Riley JB, Zaidan JZ. The immediate hemodynamic and metabolic effects of bolus injections of pharmacologic agents during cardiopulmonary bypass. *J Extra Corpor Technol* 1983;15:71-7.

27. Goertz AW, Lindner KH, Seefelder C, et al. Effect of phenylephrine bolus administration on global left ventricular function in patients with coronary artery disease and patients with valvular aortic stenosis. *Anesthesiology* 1993;78:834-41.

28. DiNardo JA, Bert A, Schwartz MJ, et al. Effects of vasoactive drugs on flows through left internal mammary artery and saphenous vein grafts in man. *J Thorac Cardiovasc Surg* 1991;102:730-5.

29. Baraka A, Haroun S, Baroody MA, et al. The hemodynamic effects of intravenous norepinephrine versus epinephrine and phenylephrine in patients with ischemic heart disease. *Middle East J Anesthesiol* 1991;11:53-62.

30. Nygren A, Thoren A, Ricksten SE. Vasopressors and intestinal mucosal perfusion after cardiac surgery: Norepinephrine vs phenylephrine. *Crit Care Med* 2006;34:722-9.

31. Smith JS, Roizen MF, Cahalan MK, et al. Does anesthetic technique make a difference? Augmentation of systolic blood pressure during carotid endarterectomy: Effects of phenylephrine versus light anesthesia and of isoflurane versus halothane on the incidence of myocardial ischemia. *Anesthesiology* 1988;69:846-53.

32. Morelli A, Ertmer C, Rehberg S, et al. Phenylephrine versus norepinephrine for initial hemodynamic support of patients with septic shock: A randomized, controlled trial. *Crit Care* 2008;12:R143.

33. Jain G, Singh DK. Comparison of phenylephrine and norepinephrine in the management of dopamine-resistant septic shock. *Indian J Crit Care Med* 2010;14:29-34.

34. Shaddy RE, Viney J, Judd VE, et al. Continuous intravenous phenylephrine infusion for treatment of hypoxemic spells in tetralogy of Fallot. *J Pediatr* 1989;114:468-70.

35. Strieper MJ, Campbell RM. Efficacy of alpha-adrenergic agonist therapy for prevention of pediatric neurocardiogenic syncope. *J Am Coll Cardiol* 1993;22:594-7.

36. Di Gennaro JL, MacK CD, Malakouti A, et al. Use and effect of vasopressors after pediatric traumatic brain injury. *Dev Neurosci* 2010;32:420-30.

37. Kim TW, Bailard N, Coveler LA. The anesthetic management of a child with chronic hypotension for renal transplantation. *J Clin Anesth* 2006;18:297-9.

38. Goertz A, Schmidt M, Lindner KH, et al. Cardiac effects of phenylephrine bolus administration during postural hypotension. *Eur J Anaesthesiol* 1993;10:381.

39. Yazbek NF, Kleiman NS. Therapeutic strategies for cardiogenic shock. *Curr Treat Options Cardiovasc Med* 2004;6:29-41.

40. Ellis TC, Lev E, Yazbek NF, et al. Therapeutic strategies for cardiogenic shock, 2006. *Curr Treat Options Cardiovasc Med* 2006;8:79-94.

41. Costanzo MR, Dipchand A, Starling R, et al. The international society of heart and lung transplantation guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010;29:914-56.

42. Carcillo JA, Cunnion RE. Septic shock. *Crit Care Clin* 1997;13:553-74.

43. Shanthi S. Management of shock. *Indian J Pract Pediatr* 2005;7:5-14.

44. Hirota Y, Suwa M, Hori K, et al. Dynamic echoventriculography. Noninvasive assessment of effects of nitroglycerin, phenylephrine, isoproterenol, and propranolol on the human cardiovascular system. *Jpn Heart J* 1978;19:719-31.

45. Ashpole K, Fernando R, Tamilselvan P, et al. Maternal cardiac output changes with phenylephrine and ephedrine infusions after spinal anaesthesia for elective caesarean section. *Int J Obstet Anesth* 2005;14:S5.

46. Leone BJ, Spahn DR. Prophylaxis and treatment of ischemia. *Int Anesthesiol Clin* 1992;30:155-76.

47. Goertz A, Lindner KH, Seefelder C, et al. Effects of phenylephrine bolus administration on global left ventricular function in patients with coronary artery disease. *Anesthesiology* 1992;77:A62.

48. Weiss T, Lattin GM, Engelman K. Vagally mediated suppression of premature ventricular contractions in man. *Am Heart J* 1975;89:700-7.

49. Ahlquist RP. Present state of alpha- and beta-adrenergic drugs part 1: The adrenergic receptor. *Am Heart J* 1976;92:661-4.

50. Johnson CA. Neosynephrine hydrochloride in the treatment of hypotension and shock from trauma or hemorrhage. *Surgery* 1937;65:458-63.

51. Cohen LR, Butterworth JS. Use of a pressor agent in shock accompanying myocardial infarction. *N Y State J Med* 1952;52:2038-9.

52. Fink TR, D'Angio CJ, Biloon S. Clinical study of shock following myocardial infarction. *JAMA* 1953;151:1163-5.

53. Gootnick A, Knox FH. Management of shock in acute myocardial infarction. *Circulation* 1953;7:511-22.

54. Ciesielski L, Stefanowska JI. Use of noradrenaline and phenylephrine ('neosynephrine') in treatment of shock. *Pol Tyg Lek* 1958;13:431-5.

55. Vigouroux RP, Fabre J, Cannoni M, et al. The use of massive doses of neosynephrine in neurosurgical practice. *Ann Anesthiol Fr* 1967;8:695-701.

56. Greder G. Treatment of shock by the new hypertensive drugs (noradrenaline and neosynephrine). A study of 20 cases. *Praxis* 1956;45:1061-8.

57. Torii T, Kinoshita S. Emergency therapy of anaphylactoid shock. *Naika* 1962;10:1018-21.

58. Halpern SH, Chochinov M. The use of vassopressors for the prevention and treatment of hypotension secondary to regional anesthesia for cesarean section. In: Halpern SH, Douglas J, editors. Evidence-based obstetric anesthesia: Blackwell Publishing; 2005. p. 101-7.

59. Mutch WA, White IW, Donen N, et al. Haemodynamic instability and myocardial ischaemia during carotid endarterectomy: A comparison of propofol and isoflurane. *Can J Anaesth* 1995;42:577-87.

60. Borum SE, Bittenbinder TM, Buckley CJ. Transesophageal atrial pacing reduces phenylephrine needed for blood pressure support during carotid endarterectomy. *J Cardiothorac Vasc Anesth* 2000;14:277-80.

61. Gregory JS, Bonfiglio MF, Dasta JF, et al. Experience with phenylephrine as a component of the pharmacologic support of septic shock. *Crit Care Med* 1991;19:1395-400.

62. Flancbaum L, Dick M, Dasta J, et al. A dose-response study of phenylephrine in critically ill, septic surgical patients. *Eur J Clin Pharmacol* 1997;51:461-5.

63. Nishikawa K, Yamakage M, Omote K, et al. Prophylactic intramuscular administration of small-dose phenylephrine blunts spinal anesthesia-induced hypotensive response in normotensive and hypertensive elderly patients. *Anesthesiology Abstracts of Scientific Papers Annual Meeting* 2002;96:A43.

64. Mortara A, Specchia G, La RMT, et al. Patency of infarct-related artery: Effect of restoration of anterograde flow on vagal reflexes. *Circulation* 1996;93:1114-22.

65. La Rovere MT, Maestri R, Mortara A, et al. Non-invasive assessment of baroreflex control in patients after myocardial infarction: Comparison with the phenylephrine method. *Eur Heart J* 1997;18:94.

66. La Rovere MT, Bigger JT, Jr., Marcus FI, et al. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet* 1998;351:478-84.

67. Mortara A, La Rovere MT, Pinna GD, et al. Arterial baroreflex modulation of heart rate in chronic heart failure. *Circulation* 1997;96:3450-8.

68. Airaksinen KE, Tahvanainen KU, Kuusela TA, et al. Cross spectral analysis in assessment of baroreflex gain in patients with coronary artery disease. *Ann Noninvasive Electrocardiol* 1997;2:229-35.

69. James MA, Robinson TG, Panerai RB, et al. Arterial baroreceptor-cardiac reflex sensitivity in the elderly. *Hypertension* 1996;28:953-60.

70. Mimura J, Yuasa F, Yuyama R, et al. The effect of residential exercise training on baroreflex control of heart rate and sympathetic nerve activity in patients with acute myocardial infarction. *Chest* 2005;127:1108-15.

71. Pleiner J, Heere-Ress E, Langenberger H, et al. Adrenoceptor hyporeactivity is responsible for Escherichia coli endotoxin-induced acute vascular dysfunction in humans. *Arterioscler Thromb Vasc Biol* 2002;22:95-100.

72. Tham TCK, Guy S, Riddell JG, et al. Circadian variation of alpha 1-adrenoceptor-mediated pressor response to phenylephrine in man. *J Pharm Pharmacol* 1996;48:526-8.

73. La Rovere MT, Mortara A, Parziale P, et al. Quantification of baroreflex sensitivity in chronic heart failure: Safety and reliability of the phenylephrine method with both invasive and non-invasive blood pressure determinations. *Eur Heart J* 1997;18:115.

74. Meyer SM, Fraunfelder FT. Phenylephrine hydrochloride. *Ophthalmology* 1980;87:1177-80.

75. Harada K, Ohashi K, Kumagai Y, et al. Influence of age on venodilator effect of isoproterenol and amrinone. *Eur J Clin Pharmacol* 1996;50:37-40.

76. Carter CA, Weston GA. Fixed dilated pupils following cardiac surgery. *Anaesthesia* 1987;42:1231-2.

77. Vutskits L, Menache C, Manzano S, et al. Anesthesia management in a young child with aromatic L-amino acid decarboxylase deficiency. *Paediatr Anaesth* 2006;16:82-4.

78. Fraunfelder FW, Fraunfelder FT, Jensvold B. Adverse systemic effects from pledgets of topical ocular phenylephrine 10%. *Am J Ophthalmol* 2002;134:624-5.

79. Borromeo-McGrail V, Bordiuk JM, Keitel H. Systemic hypertension following ocular administration of 10% phenylephrine in the neonate. *Pediatrics* 1973;51:1032-6.

80. Lees BJ, Cabal LA. Increased blood pressure following pupillary dilation with 2.5% phenylephrine hydrochloride in preterm infants. *Pediatrics* 1981;68:231-4.

81. Elibol O, Alcelik T, Yueksel N, et al. The influence of drop size of cyclopentolate, phenylephrine and tropicamide on pupil dilatation and systemic side effects in infants. *Acta Ophthalmol Scand* 1997;75:178-80.

82. Willems L, Allegaert K, Casteels I. Prospective assessment of systemic side effects of topical ophthalmic drug administration for screening for retinopathy of prematurity. *Paediatr Perinat Drug Ther* 2006;7:121-2.

83. Bolt B, Benz B, Koerner F, et al. A mydriatic eye-drop combination without systemic effects for premature infants: A prospective double-blind study. *J Pediatr Ophthalmol Strabismus* 1992;29:157-62.

84. Calenda E, Richez F, Muraine M. Acute hypertension due to phenylephrine eyedrops in a newborn. *Can J Ophthalmol* 2007;42:486.

85. Vaughan RW. Ventricular arrhythmias after topical vasoconstrictors. *Anesth Analg* 1973;52:161-5.

86. Van Der Spek AF. Cyanosis and cardiovascular depression in a neonate: Complications of halothane anesthesia or phenylephrine eyedrops? *Can J Ophthalmol* 1987;22:37-9.

87. Baldwin FJ, Morley AP. Intraoperative pulmonary oedema in a child following systemic absorption of phenylephrine eyedrops. *Br J Anaesth* 2002;88:440-2.

88. Varshney PG, Saxena KN, Sethi A, et al. Pulmonary oedema following topical phenylephrine administration in a child anaesthetised for cataract extraction. *Paediatr Anaesth* 2009;19:181-2.

89. Greher M, Hartmann T, Winkler M, et al. Hypertension and pulmonary edema associated with subconjunctival phenylephrine in a 2-month-old child during cataract extraction. *Anesthesiology* 1998;88:1394-6.

90. Lim DL, Batilando M, Rajadurai VS. Transient paralytic ileus following the use of cyclopentolate-phenylephrine eye drops during screening for retinopathy of prematurity. *J Paediatr Child Health* 2003;39:318-20.

91. Sarici SU, Yurdakoek M, Unal S. Acute gastric dilatation complicating the use of mydriatics in a preterm newborn. *Pediatr Radiol* 2001;31:581-3.

92. Shinomiya K, Kajima M, Tajika H, et al. Renal failure caused by eyedrops containing phenylephrine in a case of retinopathy of prematurity. *J Med Invest* 2003;50:203-6.

93. Landau R, Dishy V, Wood AJJ, et al. Disproportionate decrease in alpha- compared with beta-adrenergic sensitivity in the dorsal hand vein in pregnancy favors vasodilation. *Circulation* 2002;106:1116-20.

94. Gage JE, Hess OM, Murakami T, et al. Vasocontriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: Reversibility by nitroglycerin. *Circulation* 1986;73:865-76.

95. Heper G. Effects of afterload increase on systolic and diastolic functions of the myocardium after myocardial infarction. *Angiology* 2004;55:159-67.

96. Weber S, Chapsal J, Degeorges M. Coronary artery disease and alpha-adrenergic responsiveness. *J Cardiovasc Pharmacol* 1982;4:1077-8.

97. Del Greco M, Nollo G, Disertori M. Autonomic neural control during acute myocardial ischemia after phenylephrine infusion and subsequent nitroglycerin-induced hypotension and bradycardia. *G Ital Cardiol* 1999;29:76-80.

98. Tisdale JE, Patel RV, Webb CR, et al. Proarrhythmic effects of intravenous vasopressors. *Ann Pharmacother* 1995;29:269-81.

99. Gmachl E, Hochhauser H. Vascular investigations with phenylephrine. Part I. Electrocardiographic changes and general effect. . *Z Kreislaufforsch* 1954;43:145-58.

100. Youmans WB, Goodman MJ, Gould J. Neosynephrine in treatment of paroxysmal supraventricular tachycardia. *Am Heart J* 1949;37:359-73.

101. Barold HS, Shander G, Tomassoni G, et al. Effect of increased parasympathetic and sympathetic tone on internal atrial defibrillation thresholds in humans. *Pacing Clin Electrophysiol* 1999;22:238-42.

102. Baraka A. Alpha-adrenergic response in patients with ventricular dysfunction. *J Cardiothorac Vasc Anesth* 1991;5:533-5.

103. Haastrup AT, Stepniakowski KT, Goodfriend TL, et al. Intralipid enhances alpha1-adrenergic receptor mediated pressor sensitivity. *Hypertension* 1998;32:693-8.

104. Laskey WK, Reichek N, Sutton MSJ, et al. Myocardial oxygen consumption in left ventricular hypertrophy and its relation to left ventricular mechanics. *Am J Cardiol* 1983;52:852-8.

105. Smith CE, Higgins TL, Kraenzler EJ, et al. Alpha-adrenergic agonist drugs, left ventricular function, and emergence from cardiopulmonary bypass. *J Cardiothorac Anesth* 1990;4:681-6.

106. Slutsky R, Watkins J, Costello D. Radionuclide evaluation of the systolic blood pressure end systolic volume relationship response to pharmacologic agents in patients with coronary artery disease. *Am Heart J* 1983;105:53-9.

107. Indolfi C, Maione A, Volpe M, et al. Forearm vascular responsiveness to alpha 1- and alpha 2- adrenoceptor stimulation in patients with congestive heart failure. *Circulation* 1994;90:17-22.

108. Landzberg JS, Parker JD, Gauthier DF, et al. Effects of myocardial alpha 1-adrenergic receptor stimulation and blockade on contractility in humans. *Circulation* 1991;84:1608-14.

109. Yamaguchi I, Kurihara T, Maeda H, et al. The relationship between baroreflex sensitivity and paroxysmal atrial fibrillation. *J Am Coll Cardiol* 1993;21:479A.

110. Ellenbogen KA, Mohanty PK, Szentpetery S, et al. Arterial baroreflex abnormalities in heart failure. Reversal after orthotopic cardiac transplantation. *Circulation* 1989;79:51-8.

111. Yee KM, Lim PO, Ogston SA, et al. Effect of phenylephrine with and without atropine on QT dispersion in healthy normotensive men. *Am J Cardiol* 2000;85:69-74.

112. Rich S, Gubin S, Hart K. The effects of phenylephrine on right ventricular performance in patients with pulmonary hypertension. *Chest* 1990;98:1102-6.

113. Kwak YL, Lee CS, Park YH, et al. The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension. *Anaesthesia* 2002;57:9-14.

114. McCutcheon RS. Drug interaction. *Pharmindex* 1982;24:12-5.

115. Lake CL. Anesthesia and pericardial disease. *Anesth Analg* 1983;62:431-43.

116. Kawano S, Iida K, Nishi I, et al. Impaired peripheral vasoconstriction in response to alpha-adrenergic stimulation in patients with idiopathic hypertrophic cardiomyopathy. *Jpn Circ J* 1998;62:903-8.

117. Hardarson T, Curiel R. Study of clinical pharmacology of hypertrophic obstructive cardiomyopathy by noninvasive diagnostic investigations. *Br Heart J* 1973;35:865.

118. Ishiyama T, Oguchi T, Iijima T, et al. Combined spinal and epidural anesthesia for cesarean section in a patient with hypertrophic obstructive cardiomyopathy. *Anesth Analg* 2003;96:629-30.

119. Bodmer CW, Schaper NC, Janssen M, et al. Selective enhancement of alpha 2-adrenoceptor-mediated vasoconstriction in insulin-dependent diabetic patients with microalbuminuria. *Clin Sci* 1995;88:421-6.

120. Eichler HG, Blaschke TF, Kraemer FB, et al. Responsiveness of superficial hand veins to alpha-adrenoceptor agonists in insulin-dependent diabetic patients. *Clin Sci* 1992;82:163-8.

121. Johnstone MT, Creager SJ, Scales KM, et al. Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. *Circulation* 1993;88:2510-6.

122. Freedman RR, Sabharal SC, Desai N, et al. Increased alpha-adrenergic responsiveness in idiopathic Raynaud's disease. *Arthritis Rheum* 1989;32:61-5.

123. Freedman RR, Moten M, Migaly P, et al. Cold-induced potentiation of alpha 2-adrenergic vasoconstriction in primary Raynaud's disease. *Arthritis Rheum* 1993;36:685-90.

124. Vanderbuilt autonomic dysfunction center: Autonomic disorders. 2011 [updated May 25, 2010; cited 2011 October 18, 2011]; Available from: http://www.mc.vanderbilt.edu/root/vumc.php?site=adc&doc=4787.

125. Parris WCV, Goldberg MR, Hollister AS, et al. Anesthetic management in autonomic dysfunction. *Anesthesiol Rev* 1984;11:17-23.

126. Ghose K. Assessment of peripheral adrenergic activity and its interactions with drugs in man. *Eur J Clin Pharmacol* 1980;17:233-8.

127. Jacob G, Shannon JR, Costa F, et al. Abnormal norepinephrine clearance and adrenergic receptor sensitivity in idiopathic orthostatic intolerance. *Circulation* 1999;99:1706-12.

128. Jordan J, Shannon JR, Diedrich A, et al. Increased sympathetic activation in idiopathic orthostatic intolerance: Role of systemic adrenoreceptor sensitivity. *Hypertension* 2002;39:173-8.

129. Krum H, Louis WJ, Brown DJ, et al. Pressor dose responses and baroreflex sensitivity in quadriplegic spinal cord injury patients. *J Hypertens* 1992;10:245-50.

130. Koh J, Brown TE, Beightol LA, et al. Human autonomic rhythms: Vagal cardiac mechanisms in tetraplegic subjects. *J Physiol* 1994;474:483-95.

131. Tank J, Heusser K, Diedrich A, et al. A novel pharmacological approach to determining parasympathetic heart rate reserve in human subjects. *Clin Pharmacol Ther* 2010;88:630-3.

132. Low PA, Walsh JC, Huang CY, et al. The sympathetic nervous system in diabetic neuropathy. A clinical and pathological study. *Brain* 1975;98:341-56.

133. Kikuchi M, Gotoh E, Takasaki I, et al. Marked blood pressure reduction with alpha-adrenoreceptor blocker in diabetic patients with autonomic neuropathy. *Ther Res* 1995;16:228-32.

134. Kadoi Y. Perioperative considerations in diabetic patients. *Curr Diabetes Rev,* 2010;6:236-46.

135. Robertson D. Contraindication to the use of ocular phenylephrine in idiopathic orthostatic hypotension. *Am J Ophthalmol* 1979;87:819-22.

136. Clark CV, Ewing DJ. Ocular autonomic function in progressive autonomic failure. *Doc Ophthalmol* 1988;70:309-21.

137. Kim JM, Stevenson CE, Mathewson HS. Hypertensive reactions to phenylephrine eyedrops in patients with sympathetic denervation. *Am J Ophthalmol* 1978;85:862-8.

138. Weiss RS, Ernest JT, Goldstick TK, et al. Systemic blood pressure changes following topical phenylephrine in diabetics. *Invest Ophthalmol Vis Sci* 1986;27:6.

139. Bierbrier GS, Adams PC, Feldman RD. Vascular alpha-adrenergic responsiveness is reduced in cirrhosis. *Clin Pharmacol Ther* 1994;56:668-71.

140. Albillos A, Rossi I, Cacho G, et al. Enhanced endothelium-dependent vasodilation in patients with cirrhosis. *Am J Physiol* 1995;268:G459-64.

141. Albillos A, Cacho G, Barrios C, et al. Selective impairment of endothelium-mediated vasodilation in liver transplant recipients with cyclosporin A-induced hypertension. *Hepatology* 1998;27:332-8.

142. Acosta F, Sansano T, Contreras RF, et al. Phenylephrine treatment of the postreperfusion syndrome in liver transplantation. *Transplant Proc* 1999;31:2373-4.

143. Pinzani M, Marra F, Fusco BM, et al. Evidence for alpha 1-adrenoreceptor hyperresponsiveness in hypotensive cirrhotic patients with ascites. *Am J Gastroenterol* 1991;86:711-4.

144. MacGilchrist AJ, Sumner D, Reid JL. Impaired pressor reactivity in cirrhosis: Evidence for a peripheral vascular defect. *Hepatology* 1991;13:689-94.

145. Arranz CT, Chirico M, Costa MA, et al. Evaluation of autonomic function and baroreflex sensitivity in cirrhotic patients with portal hypertension. *Med Sci Res* 1997;25:193-5.

146. Wu Y, Oyos TL, Chenhsu RY, et al. Vasopressor agents without volume expansion as a safe alternative to venovenous bypass during cavaplasty liver transplantation. *Transplantation* 2003;76:1724-8.

147. Massicotte L, Perrault MA, Denault AY, et al. Effects of phlebotomy and phenylephrine infusion on portal venous pressure and systemic hemodynamics during liver transplantation. *Transplantation* 2010;89:920-7.

148. Willingham DL, Pelris P, Canabal JM, et al. Unexplained and prolonged perioperative hypotension after orthotopic liver transplantation: Undiagnosed systemic mastocytosis. *Liver Transpl* 2009;15:701-8.

149. Eichler HG, Ford GA, Blaschke TF, et al. Responsiveness of superficial hand veins to phenylephrine in essential hypertension. Alpha adrenergic blockade during prazosin therapy. *J Clin Invest* 1989;83:108-12.

150. Closas J, Genest J, Larochelle P, et al. Effects of phenylephrine on atrial natriuretic factor and renin-aldosterone system in normal subjects and patients with essential hypertension. *Arch Mal Coeur Vaiss* 1988;81:75-8.

151. Lee RWC, Di Giantomasso D, May C, et al. Vasoactive drugs and the kidney. *Best Pract Res Clin Anesthesiol* 2004;18:53-74.

152. Urzua J, Troncoso S, Bugedo G, et al. Renal function and cardiopulmonary bypass: Effect of perfusion pressure. *J Cardiothorac Vasc Anesth* 1992;6:299-303.

153. Bennett SR, McKeown J, Drew P, et al. Angiotensin in cardiac surgery: Efficacy in patients on angiotensin converting enzyme inhibitors. *Eur J Heart Fail* 2001;3:587-92.

154. Toyoda Y, Asano S, Katsumata K, et al. Combined general/epidural anesthesia and vasoconstrictors: Do vasoconstrictors decrease urine output? *Anesthesiology* 2003;99:A1066.

155. Abiose AK, Aronow WS, Moreno H, Jr, et al. Increased vascular alpha1-adrenergic sensitivity in patients with renal failure: Receiving recombinant erythropoeitin. *Am J Ther* 2007;14:427-34.

156. Gadegbeku CA, Shrayyef MZ, LaPorte FB, et al. Lipids enhance alpha1-adrenoceptor pressor sensitivity in patients with chronic kidney disease. *Am J Kidney Dis* 2004;44:446-54.

157. Lubbecke F, Wizemann V. Plasma catecholamines and alpha 1-adrenoceptor function in hemodialysis-associated hypotension. *Ren Fail* 1990;12:257-61.

158. Brodde OE, Daul A. Alpha- and beta-adrenoceptor changes in patients on maintenance hemodialysis. *Contrib Nephrol* 1984;41:99-107.

159. Drake E, Preston R, Douglas J. Brief review: Anesthetic implications of long QT syndrome in pregnancy. *Can J Anesth* 2007;54:561-72.

160. Mitrani RD, Miles WM, Klein LS, et al. Phenylephrine increases T wave shock energy required to induce ventricular fibrillation. *J Cardiovasc Electrophysiol* 1998;9:34-40.

161. Sun ZH, Swan H, Viitasalo M, et al. Effects of epinephrine and phenylephrine on QT interval dispersion in congenital long QT syndrome. *J Am Coll Cardiol* 1998;31:1400-5.

162. Khositseth A, Nemec J, Hejlik J, et al. Effect of phenylephrine provocation on dispersion of repolarization in congenital long QT syndrome. *Ann Noninvasive Electrocardiol* 2003;8:208-14.

163. Kaufman ES, Gorodeski EZ, Dettmer MM, et al. Use of autonomic maneuvers to probe phenotype/genotype discordance in congenital long QT syndrome. *Am J Cardiol* 2005;96:1425-30.

164. Magnano AR, Suleman S, Garan H, et al. Autonomic modulation of the U wave during phenylephrine and esmolol infusions. *J Electrocardiol* 2005;38:152-6.

165. Guillon A, Leyre S, Remerand F, et al. Modification of Tp-e and QTc intervals during caesarean section under spinal anaesthesia: Original article. *Anaesthesia* 2010;65:337-42.

166. Schwinn DA, McIntyre RW, Hawkins ED, et al. Alpha 1-adrenergic responsiveness during coronary artery bypass surgery: Effect of preoperative ejection fraction. *Anesthesiology* 1988;69:206-17.

167. Vincent J, Elliott HL, Meredith PA. The effect of cimetidine on the pharmacokinetics, pharmacodynamics and alpha 1-adrenoceptor responsiveness of trimazosin in man. *Eur J Clin Pharmacol* 1985;29:301-6.

168. Vincent J, Elliott HL, Meredith PA, et al. Trimazosin: Relationships between hypotensive effect, vascular responsiveness, and drug and metabolite concentrations. *J Cardiovasc Pharmacol* 1985;7:913-8.

169. Shepherd AMM, Kwan CM, Brodie CL, et al. Determination of alpha-adrenergic blocking potency. *Clin Pharmacol Ther* 1991;49:69-77.

170. Casiglia E, Gava R, Semplicini A. The mechanism of the antihypertensive effects of ketanserin: A comparison with metoprolol. *Br J Clin Pharmacol* 1986;22:751-2.

171. Reid JL, Donnelly R, Elliott HL, et al. Factors determining the response to angiotensin-converting enzyme inhibitors in hypertension. *Clin Physiol Biochem* 1990;8:1-5.

172. Andrawis NS, Craft N, Abernethy DR. Calcium antagonists block angiotensin II-mediated vasoconstriction in humans: Comparison with their effect on phenylephrine-induced vasoconstriction. *J Pharmacol Exp Ther* 1992;261:879-84.

173. Elliott HL, Pasanisi F, Summer DJ, et al. The effect of calcium channel blockers on alpha 1- and alpha 2- adrenoceptor-mediated vascular responsiveness in man. *J Hypertens* 1985;3:S235-7.

174. Grum DF, Azmy SS. Effect of chronic nifedipine therapy on the haemodynamic response to phenylephrine before and during halothane anaesthesia. *Eur J Anaesthesiol* 1992;9:35-41.

175. Kimura M, Umemura K, Kosuge K, et al. Attenuation by ACE inhibitor drugs of alpha-adrenoceptor sensitivity in human vessels: Possible differences related to drug lipophilicity. *Br J Clin Pharmacol* 1998;46:599-603.

176. Donnelly R, Elliott HL, Howie CA, et al. Vascular pressor responses in treated and untreated essential hypertension. *J Cardiovasc Pharmacol* 1990;16:191-6.

177. Bonaduce D, Petretta M, Morgano G, et al. Effects of converting enzyme inhibition on baroreflex sensitivity in patients with myocardial infarction. *J Am Coll Cardiol* 1992;20:587-93.

178. Vaile JC, Chowdhary S, Osman F, et al. Effects of angiotensin II (AT 1) receptor blockade on cardiac vagal control in heart failure. *Clin Sci* 2001;101:559-66.

179. Lemke TL, Williams DA, editors. Foye's principles of medicinal chemistry. 6th ed. Baltimore, MD and Philidelphia, PA: Lippincott Williams and Wilkins; 2008.

180. Sekkarie MA, Egan BM, Neubig RR, et al. Sensitization of human alpha 1- and alpha 2-adrenergic venous responses by guanadrel sulfate. *Clin Pharmacol Ther* 1990;48:537-43.

181. Allum W, Aminu J, Bloomfield TH, et al. Interaction between debrisoquine and phenylephrine in man. *Br J Clin Pharmacol* 1974;1:51-7.

182. Ferrari A, Bonazzi O, Gregorini L, et al. Modification of the baroreceptor control of atrio-ventricular conduction induced by digitalis in man. *Cardiovasc Res* 1983;17:633-41.

183. Stahl SM, Felker A. Monoamine oxidase inhibitors: A modern guide to an unrequited class of antidepressants. *CNS Spectrums* 2008;13:855-70.

184. Elis J, Laurence DR, Mattie H, et al. Modification by monoamine oxidase inhibitors of the effect of some sympathomimetics on blood pressure. *Br Med J* 1967;2:75-8.

185. El-Ganzouri AR, Ivankovich AD, Braverman B, et al. Monoamine oxidase inhibitors: Should they be discontinued preoperatively? *Anesth Analg* 1985;64:592-6.

186. Boakes AJ, Laurence DR, Teoh PC, et al. Interactions between sympathomimetic amines and antidepressant agents in man. *Br Med J* 1973;1:311-5.

187. Barar FS, Boakes AJ, Benedikter LB, et al. Interactions between catecholamines and tricyclic and monoamine oxidase inhibitor antidepressive agents in man. *Br J Pharmacol* 1971;43:472P-3P.

188. Risch SC, Groom GP, Janowsky DS. Interfaces of psychopharmacology and cardiology - part I. *J Clin Psychiatry* 1981;42:23-34.

189. Chierchia S, Davies G, Mongiardi F. Coronary vasospasm induced by combined alpha-adrenergic stimulation and ergonovine. *Clin Sci* 1982;62:54P-5P.

190. Maze M, Mason JDM. Aetiology and treatment of halothane-induced arrhythmias. *Clin Anaesthesiol* 1983;1:301-21.

191. Condon HA. Phenylephrine: A vasoconstrictor for use during halothane anaesthesia. *J Laryngol Otol* 1965;79:175-7.

192. McIntyre JW. Effects of phenylephrine during halothane anaesthesia in man. *Can Anaesth Soc J* 1965;12:634-40.

193. Levine MAH, Leenen FHH. Role of vagal activity in the cardiovascular responses to phenylephrine in man. *Br J Clin Pharmacol* 1992;33:333-6.

194. Okoshi K, Bregagnollo EA, Matsubara BB, et al. Characteristics of arterial hypertension in response to bolus injection of phenylephrine in atropinized patients. *Braz J Med Biol Res* 1993;26:605-8.

195. Sartain JB, Barry JJ, Howat PW, et al. Intravenous oxytocin bolus of 2 units is superior to 5 units during elective caersarean section. *Br J Anaesth* 2008;6:822-6.

196. Dyer RA, James MF. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. *Anesthesiology* 2009;111:753-65.

197. Dyer RA, Van Dyk D, Dresner A. The use of uterotonic drugs during caesarean section. *Int J Obstet Anesth* 2010;19:313-9.

198. Hoen S, Mazoit JX, Asehnoune K, et al. Hydrocortisone increases the sensitivity to α_1-adrenoceptor stimulation in humans following hemorrhagic shock. *Crit Care Med* 2005;33:2737-43.

199. Annane D, Bellissant E. Impact of corticosteroids on the vasomotor response to catecholamines in septic shock. *Reanimation* 2002;11:111-6.

200. O'Callaghan CJ, Komersova K, Louis WJ. Acute effects of blood pressure elevation on insulin clearance in normotensive healthy subjects. *Hypertension* 1998;31:104-9.

201. Yamamoto M, Takata S, Yagi S, et al. Effects of insulin on pressor responsiveness and baroreflex function in diabetes mellitus. *Jpn Circ J* 1986;50:943-8.

202. Ngan Kee WD, Khaw KS, Ng FF, et al. Prophylactic phenylephrine infusion for preventing hypotension during spinal anesthesia for cesarean delivery. *Anesth Analg* 2004;98:815-21.

203. Adigun TA, Amanor-Boadu SD, Soyannwo OA. Comparison of intravenous ephedrine with phenylephrine for the maintenance of arterial blood pressure during elective caesarean section under spinal anaesthesia. *Afr J Med Med Sci* 2010;39:13-20.

204. Alahuhta S, Rasanen J, Jouppila P, et al. Ephedrine and phenylephrine for avoiding maternal hypotension due to spinal anaesthesia for caesarean section. Effects on uteroplacental and fetal haemodynamics. *Int J Obstet Anesth* 1992;1:129-34.

205. Ayorinde BT, Buczkowski P, Brown J, et al. Evaluation of pre-emptive intramuscular phenylephrine and ephedrine for reduction of spinal anaesthesia-induced hypotension during caesarean section. *Br J Anaesth* 2001;86:372-6.

206. Bjornestad E, Iversen OE, Raeder J. Wrapping of the legs versus phenylephrine for reducing hypotension in parturients having epidural anaesthesia for caesarean section: A prospective, randomized and double-blind study. *Eur J Anaesthesiol* 2009;26:842-6.

207. 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.

208. Cooper DW, Gibb SC, Meek T, et al. Effect of intravenous vasopressor on spread of spinal anaesthesia and fetal acid-base equilibrium. *Br J Anaesth* 2007;98:649-56.

209. das Neves JFNP, Monteiro GA, de Almeida JR, et al. Phenylephrine for blood pressure control in elective cesarean section: Therapeutic versus prophylactic doses. *Rev Bras Anestesiol* 2010;60:391-8.

210. Defossez T, Lauwers M, Camu F. A comparison of ephedrine and phenylephrine boluses versus continuous infusion of ephedrine and phenylephrine during spinal anaesthesia for caesarean delivery. *Acta Anaesthesiol Belg* 2007;58:66.

211. George RB, McKeen D, Columb MO, et al. Up-down determination of the 90% effective dose of phenylephrine for the treatment of spinal anesthesia-induced hypotension in parturients undergoing cesarean delivery. *Anesth Analg* 2010;110:154-8.

212. Gomaa GA, Elewa SA. Prophylactic use of vasopressors for reduction of spinal anaesthesia-induced hypotension during caesarean section. *Egyptian J Anaesth* 2003;19:45-50.

213. Mohta M, Janani SS, Sethi AK, et al. Comparison of phenylephrine hydrochloride and mephentermine sulphate for prevention of post spinal hypotension. *Anaesthesia* 2010;65:1200-5.

214. Moran DH, Perillo M, Bader AM, et al. Phenylephrine in treating maternal hypotension secondary to spinal anesthesia. *Anesthesiology* 1989;71:A857.

215. 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.

216. Sakuma T, Sato M, Sato K, et al. Effects of intravenous vasopressor on spread of spinal anesthesia with 0.5% hyperbaric bupivacaine for caesarean delivery. *Jpn J Anesthesiol* 2010;59:691-5.

217. 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.

218. Tanaka M, Balki M, Parkes RK, et al. ED95 of phenylephrine to prevent spinal-induced hypotension and/or nausea at elective cesarean delivery. *Int J Obstet Anesth* 2009;18:125-30.

219. Nishikawa K, Yamakage M, Omote K, et al. Prophylactic IM small-dose phenylephrine blunts spinal anesthesia-induced hypotensive response during surgical repair of hip fracture in the elderly. *Anesth Analg* 2002;95:751-6.

220. Marino RJ, Romagnoli A, Keats AS. Selective venoconstriction by dopamine in comparison with isoproterenol and phenylephrine. *Anesthesiology* 1975;43:570-2.

221. Schwinn DA, Reves JG. Time course and hemodynamic effects of alpha-1-adrenergic bolus administration in anesthetized patients with myocardial disease. *Anesth Analg* 1989;68:571-8.

222. Butterworth JF, Strickland RA, Mark LJ, et al. Calcium does not augment phenylephrine's hypertensive effects. *Crit Care Med* 1990;18:603-6.

223. Lobato EB, Janelle GM, Urdaneta F, et al. Comparison of milrinone versus nitroglycerin, alone and in combination, on grafted internal mammary artery flow after cardiopulmonary bypass: Effects of alpha-adrenergic stimulation. *J Cardiothorac Vasc Anesth* 2001;15:723-7.

224. Skubas N, Barner HB, Apostolidou I, et al. Phenylephrine to increase blood flow in the radial artery used as a coronary bypass conduit. *J Thorac Cardiovasc Surg* 2005;130:687-92.

225. Patel GP, Grahe JS, Sperry M, et al. Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. *Shock* 2010;33:375-80.

226. Yamazaki T, Shimada Y, Taenaka N, et al. Circulatory responses to afterloading with phenylephrine in hyperdynamic sepsis. *Crit Care Med* 1982;10:432-5.

227. Morelli A, Lange M, Ertmer C, et al. Short-term effects of phenylephrine on systemic and regional hemodynamics in patients with septic shock: A crossover pilot study. *Shock* 2008;29:446-51.

228. Farrell TG, Odemuyiwa O, Bashir Y, et al. Prognostic value of baroreflex sensitivity testing after acute myocardial infarction. *Br Heart J* 1992;67:129-37.

229. La Rovere MT, Specchia G, Mortara A, et al. Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. *Circulation* 1988;78:816-24.

230. Davies LC, Francis D, Jurak P, et al. Reproducibility of methods for assessing baroreflex sensitivity in normal controls and in patients with chronic heart failure. *Clin Sci* 1999;97:515-22.

231. Raczak G, La Rovere MT, Pinna GD, et al. Assessment of baroreflex sensitivity in patients with preserved and impaired left ventricular function by means of the Valsalva manoeuvre and the phenylephrine test. *Clin Sci* 2001;100:33-41.

232. Airaksinen KE, Tahvanainen KU, Eckberg DL, et al. Arterial baroreflex impairment in patients during acute coronary occlusion. *J Am Coll Cardiol* 1998;32:1641-7.

233. Okada N, Takahashi N, Yufu K, et al. Baroreflex sensitivity predicts cardiovascular events in patients with type 2 diabetes mellitus without structural heart disease. *Circ J* 2010;74:1379-83.

234. Olshan AR, O'Connor DT, Cohen IM, et al. Baroreflex dysfunction in patients with adult-onset diabetes and hypertension. *Am J Med* 1983;74:233-42.

235. Farrell TG, Paul V, Cripps TR, et al. Baroreflex sensitivity and electrophysiological correlates in patients after acute myocardial infarction. *Circulation* 1991;83:945-52.

236. Yuasa F, Sumimoto T, Yokoe H, et al. Relationship between arterial baroreflex sensitivity and exercise capacity in patients with acute myocardial infarction. *Clin Physiol Funct Imaging* 2010;30:69-74.

237. Raczak G, Pinna GD, Maestri R, et al. Assessment of baroreflex sensitivity using phenylephrine test for prediction of haemodynamic tolerance of inducible ventricular tachycardia after myocardial infarction. *Kardiol Pol* 2001;54:177-82.

238. Vincent J, Dachman W, Blaschke TF, et al. Pharmacological tolerance to alpha 1 -adrenergic receptor antagonism mediated by terazosin in humans. *J Clin Invest* 1992;90:1763-8.

239. von Bahr C, Lindstroem B, Seideman P. Alpha-receptor function changes after the first dose of prazosin. *Clin Pharmacol Ther* 1982;32:41-7.

240. Tomlinson B, Renondin JC, Graham BR, et al. The effect of urapidil on responses to phenylephrine, angiotensin and isoprenaline in man. *Eur J Clin Pharmacol* 1991;41:1-3.

241. Inomata S, Nishikawa T, Kihara S, et al. Enhancement of pressor response to intravenous phenylephrine following oral clonidine medication in awake and anaesthetized patients. *Can J Anaesth* 1995;42:119-25.

242. Parlow JL, Sagnard P, Begou G, et al. The effects of clonidine on sensitivity to phenylephrine and nitroprusside in patients with essential hypertension recovering from surgery. *Anesth Analg* 1999;88:1239-43.

243. Watanabe Y, Iida H, Tanabe K, et al. Clonidine premedication modifies responses to adrenoceptor agonists and baroreflex sensitivity. *Can J Anaesth* 1998;45:1084-90.

244. Ibsen H, Egan B, Julius S. Baroreflex sensitivity during converting enzyme inhibition with enalapril (MK-421) in normal man. *J Hypertens* 1983;1:222-4.

245. Kondowe GB, Deering AH, Riddell JG, et al. The effect of acute and chronic captopril therapy on baroreflex function in man. *Br J Clin Pharmacol* 1988;25:315-21.

246. Warren SE, O'Connor DT, Cohen IM. Autonomic and baro reflex function after captopril in hypertension. *Am Heart J* 1983;105:1002-8.

247. Kwak HJ, Kwak YL, Oh YJ, et al. Effect of angiotensin-converting enzyme inhibitors on phenylephrine responsiveness in patients with valvular heart disease. *J Int Med Res* 2005;33:150-9.

248. Harada K, Kawaguchi A, Ohmori M, et al. Influence of losartan on alpha-adrenoceptor-mediated vasoconstrictor response in humans. *J Cardiovasc Pharmacol* 2000;36:45-9.

249. Abdelmawla AH, Langley RW, Szabadi E, et al. Bisoprolol attenuates noradrenaline- and phenylephrine-evoked venoconstriction in man in vivo. *Br J Clin Pharmacol* 1997;44:61-8.

250. Myers MG. Beta adrenoceptor antagonism and pressor response to phenylephrine. *Clin Pharmacol Ther* 1984;36:57-63.

251. Schulte KL, Laber E, Meyer SWA, et al. Alpha-adrenoceptor subtype in human hand veins and interaction between alpha-adrenceptor-mediated vasoconstriction and calcium entry blockers. *Int Angiol* 1985;4:79-81.

252. Abernethy DR, Winterbottom LM. Forearm vascular alpha 1-adrenergic blockade by verapamil. *Clin Pharmacol Ther* 1990;47:755-9.

253. Robinson BJ, Ebert TJ. Reduced vascular responsiveness to phenylephrine during isoflurane anesthesia in humans. *Anesthesiology* 1997;87:A303.

254. Arain SR, Williams DJ, Robinson BJ, et al. Vascular responsiveness to brachial artery infusions of phenylephrine during isoflurane and desflurane anesthesia. *Anesth Analg* 2002;94:1137-40.