original article

Ephedrine requirements during spinal anesthesia for cesarean delivery in Jordanian parturients: association with β2-adrenoceptor gene variants

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BACKGROUND: Maternal hypotension after spinal anesthesia for cesarean delivery is common. Many studies performed on the β2-adrenoceptor (β2AR) gene variants and their association with vasopressor requirements during and after neuroaxial block have contradictory conclusions.

OBJECTIVES: The aim of the study was to evaluate the influence of the β2AR in codons 16 and 27 on the incidence of maternal hypotension and ephedrine consumption after spinal anesthesia for cesarean delivery in an Arab ethnic group.

DESIGN: A prospective gene association study.

SETTING: Jordan University Hospital from 1 July 2013 to 31 January 2014.

PATIENTS AND METHODS: We enrolled parturients who underwent cesarean delivery under spinal anesthesia. Spinal anesthesia was performed with 10 mg plain bupivacaine along with 25 μg fentanyl. Hypotension was treated with ephedrine and the amount consumed in the first 30 minutes after spinal anesthesia was calculated. The β2AR genotype at codons 16 and 27 was determined. We studied the correlation between the β2AR genotype and the amount of ephedrine consumption after spinal anesthesia.

MAIN OUTCOME MEASURES: Amount of ephederine used.

RESULTS: Of 250 patients enrolled in the study, genotype and clinical data were available for 234 cases. Ephedrine was used in 94% of patients. There was a significant effect of β2AR genotype on ephedrine dose in the first 30 minutes after spinal anesthesia in codon 16 and 27. Arg16 homozygotes received less ephedrine (14.0 [11.2] mg) than Gly16 homozygotes (38.6 [25.7] mg) and Arg16Gly heterozygotes (33.42 [22.70] mg) (P<.0001). Gln27 homozygotes received less ephedrine (18.2 [12.8] mg) than Glu 27 homozygotes (47.5 [27.0] mg) and Gln27Glu heterozygotes (48.2 [23.7] mg). (P<.0001).

CONCLUSION: In an Arab ethnic group, the β2AR gene has a role in maternal hypotension after spinal anesthesia. The Gly16 and Glu27 alleles have a higher incidence of arterial hypotension and required a greater amount of vasopressor to treat hypotension compared with homozygous Arg16 and Gln27 carriers.

LIMITATIONS: Fasting time and hydration protocol, the use of a fixed dose of ephedrine, and relatively small sample size.

Local anesthetics placed in the subarachnoid space effectively block sensory, autonomic, and motor impulses by interacting with the anterior and posterior spinal nerve roots and the dorsal root ganglion as they pass through the cerebrospinal fluid (CSF). Maternal hypotension due to autonomic block and peripheral vasodilation is frequently noticed during spinal anesthesia for cesarean delivery.[1] Many strategies are used to counteract this hypotension and its effects on uteroplacental perfusion such as left uterine displace-

ment,[2] prophylactic fluid administration prior to spinal anesthesia or prophylactic or therapeutic vasopressors such as ephedrine or phenylephrine.[3] The severity of hypotension and the response to vasopressors varies from patient to patient. The β2-adrenoceptor (β2AR) has an important role in regulation of blood pressure and cardiac output.[4] Variation in the β2AR gene may have an effect on the severity of the decrease in blood pressure and response to vasopressors during spinal anesthesia. Mutations in the β2AR gene located on chromosome 5q31-32 have been shown to be associated with variable patient responses.[5] The two most common single-nucleotide polymorphisms (SNPs) in the β2AR gene occur at nucleotide position 46, which carries either adenine or guanine and results in an amino acid change at position 16 (arginine [Arg] or glycine [Gly]) and at nucleotide position 79, which carries either cytosine or guanine and results in an amino acid change at position 27 (glutamine [Gln] or glutamate [Glu]).[6,7]

Many studies have been performed on the β2AR gene variants and their association with vasopressor requirements during and after neuroaxial block.[8-12] Results of these studies are contradictory and further studies have been recommended in different races and in a larger sample. The current study was performed on an Arab ethnic group (Jordanian parturients). The aim of the study was to evaluate the influence of the β2AR in codons 16 and 27 on the incidence of maternal hypotension and ephedrine consumption after spinal anesthesia for cesarean delivery in Jordanian parturient in a prospective study.

PATIENTS AND METHODS

After approval from the scientific research committees at the Faculty of Medicine and the Deanship of Scientific Research at the University of Jordan, informed written consent was obtained from each patient involved in the study. Patients with a singleton pregnancy at 37 or more completed weeks of gestation were scheduled to undergo elective cesarean delivery under spinal anesthesia at Jordan University hospital. Exclusion criteria included hypertension, gestational hypertension, other cardiovascular disease, use of blood, blood product or colloid fluids during surgery, weight above 130 kg, use of steroids, magnesium sulfate, or adrenergic agonists or antagonists during pregnancy and American Society of Anesthesiologists physical status III or more.

Patients had nothing by mouth (food, drink) the night before surgery. On the morning of surgery, all patients received intravenous hydration with 500 mL lactated Ringer's solution one hour preoperatively via 18-gauge IV cannula in the dorsum of the hand. The patients were monitored by noninvasive arterial pressure (NIBP), continuous electrocardiography (ECG) and saturation of peripheral oxygen (SpO_2). Basal heart rate (HR) and blood pressure (BP) were recorded before starting anesthesia. All patients received 4 L/min of O_2 by simple face mask. With the patient in sitting position, spinal anesthesia was performed at the L3–L4 or L4–L5 interspace. Plain bupivacaine (0.5%), 10 mg, along with 25 μg fentanyl were injected intrathecally in a total volume of 2.5 mL via a 25-gauge pencil point needle slowly over 10 seconds. Women were immediately placed in a supine position. A lumber pelvic wedge was positioned under the right posterior superior iliac crest in all patients. Lactated Ringer's solution was administered at 25 mL/kg/h after the spinal anesthesia. An automated blood pressure cuff was programmed to cycle each minute. At each minute interval, hypotension was treated according to the planed strategy: if systolic blood pressure (SBP) decreased more than 20% from base line or SBP ≥95 <100 mm Hg, the patient was treated with 5 mg ephedrine. If we noticed SBP ≥90 <95 mm Hg, we gave 10 mg ephedrine. If SPB <90 mm Hg we treated the patient with 15 mg. The anesthetist recorded the blood pressure, heart rate every 3 minutes up to 30 minutes and the zero time was considered to be the first reading after spinal anesthesia. The amount of ephedrine given in the first 30 minutes after spinal anesthesia was recorded. About 4 mL of blood was withdrawn from the patient and sent in an EDTA tube to the genetics laboratory. The primary anesthesiologist had the right to stop the protocol if he felt there was any risk to the mother or fetus.

Sample collection

Blood samples were collected in EDTA tubes from maternal venous blood. DNA extraction was performed using the Puregene Blood Core Kit A (Qiagen, Maryland, USA) according to the manufacturers protocol. DNA quantity and quality were assayed by a spectrophotometer (Biorad, USA). DNA was stored at -20°C until use.

DNA amplification and RFLP (restriction fragment length polymorphism)

For codon 27, the total volume of the PCR reaction was 26 μL, which contained 300-500 ng of DNA, 0.38 mM of each deoxynucleoside triphosphates (dNTPs) (Promega, USA), 5μl buffer (100 mMTris-HCl, 15 mM $MgCl_2$, 500 mMKCl,pH 8.3), 20 pmol of each primer, and 0.13–0.63 U of TaqDNA polymerase (Promega, USA). The forward primer was 5'-GGCCCATGACCA-GATCAGCA-3'and the reverse primer was 5'-GAATGAGGCT-TCCAGGCGTC-3'. PCR amplification started with dena-

turation at 94°C for 4 minutes, followed by 30 cycles of denaturation (94°C, 1 minute), annealing (63°C, 1 minute), and extension (72°C, 1 minute). A final extension step was performed at 72°C for 10 minutes. The PCR product size was 353 bp (**Figure 1**). Restriction digestion was performed at 37°C for 2 hours using 0.4 U of Fun4H (New England Biolabs, USA). The digestion products were then loaded into 2% agarose gel. The following band sizes are expected for the relevant genotypes: 27, 55, 97, and 174 bp in Gln27 homozygotes; 27, 55, 97, 174, and 229 bp in Gln27Glu27 heterozygotes; and 27, 97, and 229 bp in Glu27 homozygotes.

For codon 16, the same PCR procedure was performed but using the following primers: forward 5'-CTTCTTGCTGGCACGCAAT-3, reverse 5'CCAGTGAAGTGATGAAGTAGTTGG-3'and and annealing temperature of 60°C. The PCR product size was 201 bp (**Figure 1**). For the RFLP, the digestion was carried out at 37°C for 1 hour using 2U of BsrDI (New England Biolabs, USA) and the products were loaded into 3% agarose gel. The expected bands sizes were: 14, 56, and 131 bp in Arg16 homozygotes; 14, 23, 56, 108, and 131 bp in Arg16Gly16 heterozygotes; and14, 23, 56, and 108 bp in Gly16 homozygotes.

DNA sequencing

For further genotype confirmation, selected representative DNA samples were sent for DNA sequencing (Macrogen, South Korea). The PCR products were purified using the QIAquick PCR Purification kit (Qiagen, Germany).

Statistical analysis

Collected data were coded and entered for subsequent analysis into SPSS, 20th version. Data were summarized as mean and standard deviation for age, weight, height, body mass index, gestational age, ephedrine dose, basal systolic blood pressure and basal heart rate. The difference in these parameters among the different genotypes was assessed by analysis of the variance (ANOVA) or Kruskal-Wallis (ephedrine dose) as appropriate. The difference in the number of women in whom ephedrine was not utilized among the different genotypes was assessed by chi square or Fisher exact test as appropriate. Normality of data was assessed by a Q-Q plot, P-P plot and Shapiro-Wilk test. Homogeneity of variance was evaluated by Levene's test.

RESULTS

Of 2477 deliveries from 1 July 2013 to 31 January 2014, 250 women were enrolled in the study (**Figure 2**). Genotype and clinical data were available for 234. Sixteen were excluded from the study because of missing or incomplete data (4 cases) or technical problems leading to errors in the spinal doses administered (4 cases). Two cases received blood transfusion and two cases received Voluven (6% hydroxyethyl starch in 0.9%

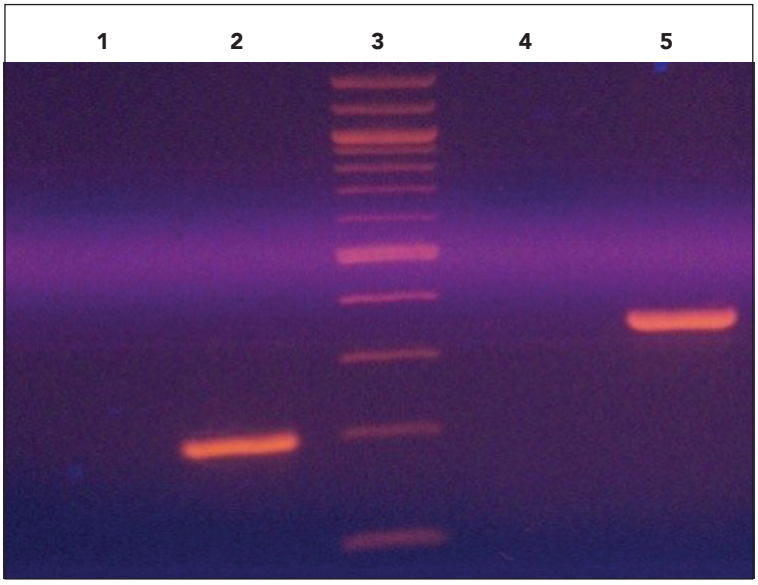

Figure 1. Representative PCR products for codons 16 and 27. Lanes 1 and 4 show non-template controls (NTC), while lanes 2 and 5 represent the PCR products for codons 16 (201 bp) and 27 (353 bp), respectively. Lane 3 contains a 100-bp ladder.

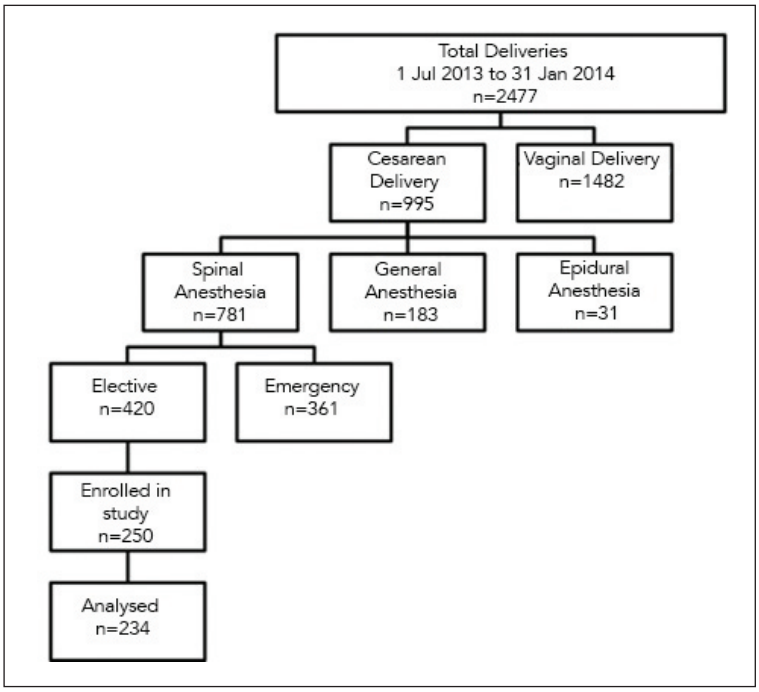

Figure 2. Flow diagram of participant disposition.

sodium chloride) during surgery and in four cases the primary anesthesiologist stopped the protocol.

For the 234 cases involved in the statistical analyses, the genotype distribution at codon 16 was 17% (n=40) Arg homozygous, 43% (n=101) Arg16Gly heterozygous, and 40% (n=93) Gly16Gly homozygous. At codon 27, the distribution was 53% (n=125) Gln homozygous, 41% (n=95) Gln27Glu heterozygous, and 6% (n=14) Glu homozygous. There was no statistically significant difference in maternal demographics (age, weight, height, body mass index (BMI), gestational age (GA), baseline systolic blood pressure (SBP), and baseline heart rate (HR) by to genotype at position 16 or 27 of the β2AR (**Tables 1 and 2**).

For codon 16 variants, there was a significant effect of β2AR genotype on ephedrine dose in the first 30 minutes after spinal anesthesia. Arg16 homozygotes received significantly less ephedrine (14 [11.22] mg) than Gly 16 homozygotes (38.55 [25.71] mg) and Arg16Gly heterozygotes (33.42 [22.70] mg) (*P*<.0001). For codon 27 variants, there was also a significant effect of β2AR genotype on ephedrine dose in the first 30 minutes after spinal anesthesia. Gln16 homozygotes received significantly less ephedrine (18.24 [12.75] mg) than Glu16 homozygotes (47.50 [27.01] mg) and Gln16Glu heterozygotes (48.16 [23.73] mg). (*P*<.0001). Analyses of diplotype pairs shows a significant difference in the ephedrine dosage. We had 6 diplotype products. The diplotype Arg16Gln27/ Arg16Gln27 required the least amount of ephedrine (14 [11.22] mg) and the highest dose of ephedrine needed was in diplotype Gly16Glu27/Gly16Glu27 (49.6±24.6 mg) (*P*<.0001) (**Table 3**).

Most women (219 of 234, 94%) received ephedrine treatment for hypotension. Only 15 women (6%) did not receive any ephedrine. For codon 16 variants, among Arg16 homozygotes, 7 of 40 (17.5%) did not require any ephedrine, whereas only 4 of 101 (4%) Arg16Gly heterozygotes and 4 of 93 (4.3%) Gly16 homozygotes did not receive any ephedrine (*P*=.016). For codon 27

Table 1. Demographic data in three groups of codon 16 genotypes.

	Codon 16 genotypes			*P* value
	Arg16Arg (N=40)	Arg16Gly (N=101)	Gly16Gly (N=93)	
Age (years)	32.1 (5.5)	32.2 (5.4)	32.6 (4.7)	.82
Weight (kg)	81.7 (11.6)	80.3 (11.1)	80.1 (9.9)	.71
Height (m)	1.63 (0.05)	1.64 (0.06)	1.63 (0.05)	.51
BMI (kg/m^2)	30.5 (3.8)	30 (4)	30.2 (3.7)	.78
GA (weeks)	38.3 (0.5)	38.1 (0.05)	38.2 (0.06)	.39
Basal SBP (mmHg)	127.2 (11.8)	126.5 (13)	126.2 (12.7)	.93
Basal HR (mmHg)	98.3 (12.9)	98.3 (12.1)	98.0 (12.5)	.98

Data expressed as the mean (standard deviation). BMI: body mass index, GA: gestational age, HR: heart rate, SBP: systolic blood pressure.

Table 2. Demographic data for three groups of codon 27 genotypes.

	Codon 27 genotypes			*P* value
	Gln27Gln (N=125)	Gln27Glu (N=95)	Glu27Glu (N=14)	
Age (years)	32.2 (5.3)	32.2 (5)	34.3 (4)	.33
Weight (kg)	80.3 (10.6)	81.2 (11.1)	76.2 (8.3)	.27
Height (m)	1.64 (0.05)	1.63 (0.05)	1.62 (0.05)	.41
BMI (kg/m^2)	30.0 (3.7)	30.5 (4)	29.2 (2.9)	.39
GA (weeks)	38.1 (0.6)	38.2 (0.6)	38.4 (0.5)	.4
Basal SBP (mmHg)	125.5 (12.1)	128.3 (13.4)	123 (10.6)	.15
Basal HR (mmHg)	98.2 (12.5)	98.1 (12.3)	98.7 (12.6)	.98

Data expressed as the mean (standard deviation). BMI: body mass index, GA: gestational age, HR: heart rate, SBP: systolic blood pressure.

Table 3. Ephedrine doses stratified by β2AR genotypes in codon 16 and 27 and by diplotype pairs.

Codon 16			
β2AR	**β2AR**	**Ephedrine (mg)**	***P* value**
Arg16 Arg	40	14 (11.2)	
Arg16 Gly	101	33.4 (22.7)	<.0001
Gly16 Gly	93	38.6 (25.7)	
Codon 27			
β2AR	**N (234)**	**Ephedrine (mg)**	***P* value**
Gln27 Gln	125	18.2 (12.8)	
Gln27 Glu	95	48.2 (23.7)	<.0001
Glu27 Glu	14	47.5 (27.0)	
Diplotype pairs			
β2AR	**N (234)**	**Ephedrine (mg)**	***P* value**
Arg16Gln27/Arg16Gln27	40	14 (11.2)	
Arg16Gln27/Gly16Gln27	51	20.8 (13.5)	
Arg16Gln27/Gly16Glu27	48	47 (22.4)	
Gly16Gln27/Gly16Gln27	34	19.4 (12.4)	<.0001
Gly16Gln27/Gly16Glu27	49	48.8 (25.8)	
Gly16Glu27/Gly16Glu27	12	49.6 (24.6)	

Data are presented as mean (standard deviation).

variants, 13 of 125 (10.4%) Gln homozygotes did not require vasopressor, compared to 1of 95 (1%) Gln27Glu heterozygotes and 1 of 14 (7.1%) Glu27 homozygotes (*P*=.01). For diplotype Arg16Gln27/Arg16Gln27, 7 of 40 (17.5%) did not require any ephedrine whereas, for diplotype Gly16Glu27/Gly16Glu27, all 12 patients recieved ephedrine (*P*=.024) (**Table 4**). The SBP decreased significantly in codon 16 for genotype Arg16 Gly and Gly 16 Gly in comparison to Arg 16 Arg genotype (**Figure 3**). SBP decreased significantly in codon27 for genotypes Gln 27 Glu and Glu 27 Glu compared with Gln 27 Gln genotype (**Figure 4**).

DISCUSSION

Hypotension during spinal anesthesia for cesarean section is secondary to sympathetic blockade and it can be harmful to the mother and fetus. Hypotension can cause a reduction in uterine and placental blood flow, fetal acidosis, and reduced maternal cardiac output that leads to symptoms such as nausea, vomiting, and altered consciousness. The incidence of hypotension during spinal anesthesia for elective cesarean delivery is very high, reaching up to 70% to 80% when pharmacological prophylaxis is not used.[13] Phenylephrine and ephedrine are used in treatment of maternal hypotension during cesarean section under spinal anesthesia.[14-16] In previous studies,[8,10] investigators used more than one vasopressor (ephedrine and phenylphrine), whereas in our study we used a single vasopressor (ephedrine) which provides more standardization.

In an Arab ethnic group, we found that individuals with the glycine allele at position 16 and/or the glutamate allele at position 27 in the β2AR gene required greater amounts of ephedrine compared with homozygous arginine at position 16 and homozygous glutamine at position 27. Few studies have evaluated β2AR and vasopressor requirements to treat hypotension during neuroaxial block. In one study in a North American cohort, results were contradictory to our results; they found that the homozygous Gly16 and Glu27 genotypes were less likely to require a vasopressor infusion to maintain blood pressure above hypotension thresholds, during the first 15 minutes after spinal anaesthesia for cesarean delivery.[8] In a Chinese cohort, Landau et al found that the maternal β2AR genotype did not affect ephedrine requirements during elective cesarean delivery.[10] Results obtained by Daher et al in Brazil,[11] supported their previous study[9] in which

Table 4. Analyses of patients who required no ephedrine during anesthesia. Stratified by β2AR genotypes in codon 16 and 27 and diplotype pairs.

Codon 16 β**2AR**	**N (234)**	**No Ephedrine**	***P* value**
Arg16 Arg	40	7(17.5%)	
Arg16 Gly	101	4(4%)	.016
Gly16 Gly	93	4(4.3%)	
Codon 27 β**2AR**	**N (234)**	**No Ephedrine**	***P* value**
Gln27 Gln	125	13(10.4%)	
Gln27 Glu	95	1(1%)	.01
Glu27 Glu	14	1(7.1%)	
Diplotype pairs β**2AR**	**N (234)**	**No Ephedrine**	***P* value**
Arg16Gln27/Arg16Gln27	40	7(17.5%)	
Arg16Gln27/Gly16Gln27	51	2(3.9%)	
Arg16Gln27/Gly16Glu27	48	1(2%)	.024
Gly16Gln27/Gly16Gln27	34	4(11.7%)	
Gly16Gln27/Gly16Glu27	49	1(2%)	
Gly16Glu27/Gly16Glu27	12	0	

Data are presented as frequency and percentage.

patients homozygous for the Arg16 genotype were protected against arterial hypotension after induction of spinal anaesthesia for cesarean delivery. In a more recent study that was performed in adult patients of Caucasian ethnicity undergoing major abdominal surgery, the results coincided with ours, as they found that after sympathetic block by thoracic epidural anesthesia, Gly16 and Glu27 allele carriers in the β2AR gene had greater vasopressor requirements to sustain arterial normotension compared to homozygous Arg16 and Gln27 carriers.[12] Such variation in results among different ethnic groups may confirm that data derived from genetic studies must always be considered with respect to ethnic background.

Even when we used a larger amount of ephedrine, the SBP was decreased highly in codon 16 in genotype Arg 16 Gly and genotype Gly 16 Gly in compare ro Arg 16 Arg genotype and also in codon 27 in genotype Gln 27 Glu and genotype Glu 27 Glu in compare ro Gln 27 Gln genotype. This result explains that the severity of decrease in SBP in the presence of glycine allele at position 16 and/or glutamate allele at position 27 in the β2AR was higher and quicker than the homozygous arginine at position 16 and homozygous glutamine at position 27.

The frequency of genotype might vary among different ethnic groups, resulting in a difference in haplotype patterns.[17] In our study, the haplotype Arg16Gln27/Arg16Gln27, which required the least amount of ephedrine (14.0 [11.2] mg) was seen in 17% of all cases. This diplotype occurred in 8% of the Caucasian group, 15% in the north American cohort, and in 34% in the Chinese cohort. In our study the haplotype Gly16Glu27/Gly16Glu27, which required the highest dose of ephedrine (49.6 [24.6] mg) was seen in 5% of all cases. This diplotype was seen in 29% of the Caucasian group, 7% of the north American cohort, and in none of the Chinese cohort.[8,10,12] This difference in haplotype distribution among different ethnic groups has been noticed in previous studies.[18,19] Even more, the diplotype Arg16Gln27/Arg16Gln27, which has a protective effect against hypotension, was highest in the Chinese cohort (34%) and the diplotype Gly16Glu27/Gly16Glu27, which has tendency to have hypotension after neuroaxial block, was least in this group. The maternal β2AR gene variants did not affect ephedrine requirement during cesarean delivery un-

der spinal anesthesia in the Chinese cohort.

Six percent of parturients (n=15) did not need ephedrine, which is similar to the Smiley et al study where 5% (9 from 170 patients) did not require treatment for hypotension. In those 15 patients who did not require ephedrine treatment in our study, more were homozygous Arg16 and Gln 27 carriers, and fewer were Gly16 and Glu allele carriers of the β2-adrenoceptor gene. In diplotype Arg16Gln27/Arg16Gln27, 7 of 40 (17.5%) patients did not require ephedrine, whereas in diplotype Gly16Glu27/Gly16Glu27 (n=12) none required ephedrine (*P*=.024). Analysis of the group that required no ephedrine after spinal anesthesia support the conclusion that the presence of genotype Arg 16 Arg or genotype Gln 27 Gln is protective against a decrease in SBP.

In this study, we observed that for all patients with genotype Arg16 Arg (n=40), their diplotype pairs were Arg16Gln27/Arg16Gln27 and the amount of ephedrine required was the least in all patients (14 [11.22] mg). Of 125 patients with genotype Gln27Gln, only 40 had diplotype Arg16Gln27/Arg16Gln27, and the other 85 had different diplotype pairs. Arg16Gln27/ Gly16Gln27 occurred in 51 patients and required 20.8 (13.5) mg ephedrine and Gly16Gln27/ Gly16Gln27 occurred in 34 patients and required 19.4 (12.4) mg ephedrine. All patients with genotype Gln27Gln required less ephedrine with the least for diplotype Arg16Gln27/ Arg16Gln27. Further work is required to explain whether both genotypes Arg 16 Arg and Gln 27 Gln or only the genotype Gln 27 Gln are primarily responsible for the decrease in the incidence of hypotension after spinal anesthesia.

In this study, all patients received intravenous hydration with 500 mL lactated Ringer's solution one hour preoperatively. The fasting time was variable; all patients started fasting at midnight of the day before surgery and the time of surgery was variable. Fasting time and hydration protocol are among the limitations of this study. Another limitation is the use of a fixed dose of ephedrine (5, 10 and 15 mg) with dose based on SBP. Titration of vasopressor dose will increase the accuracy of amount of ephedrine needed to restore blood pressure.

In conclusion, this study shows that the β2-adrenoceptor gene has a role in maternal hypotension after spinal anesthesia in an Arab ethnic group. Our findings demonstrate that the Gly16 and Glu27 alleles have a higher incidence of arterial hypotension and require a greater amount of vasopressor to treat hypotension compared with homozygous Arg16 and Gln27 carriers. Further studies in different ethnic groups with larger sample sizes and a more accurately titrated dose of vasopressor should be conducted to better clarify these effects.

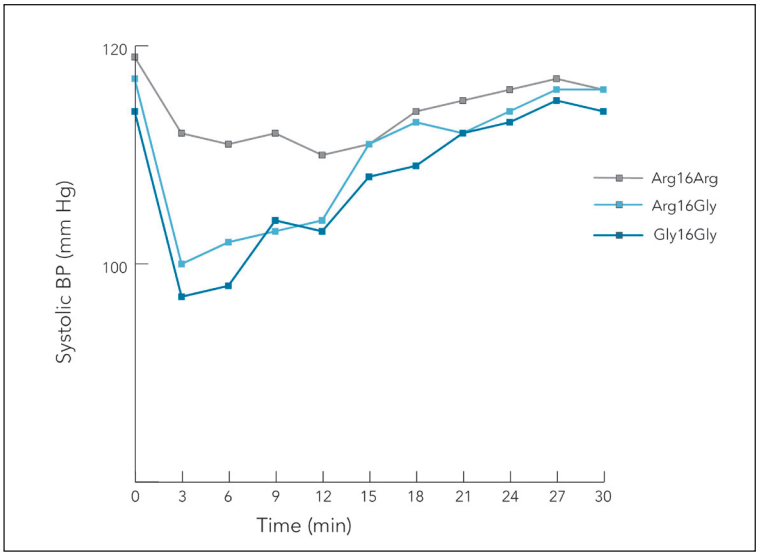

Figure 3. Systolic blood pressure variation over 30 minutes after spinal anesthesia for the codon 16 genotypes.

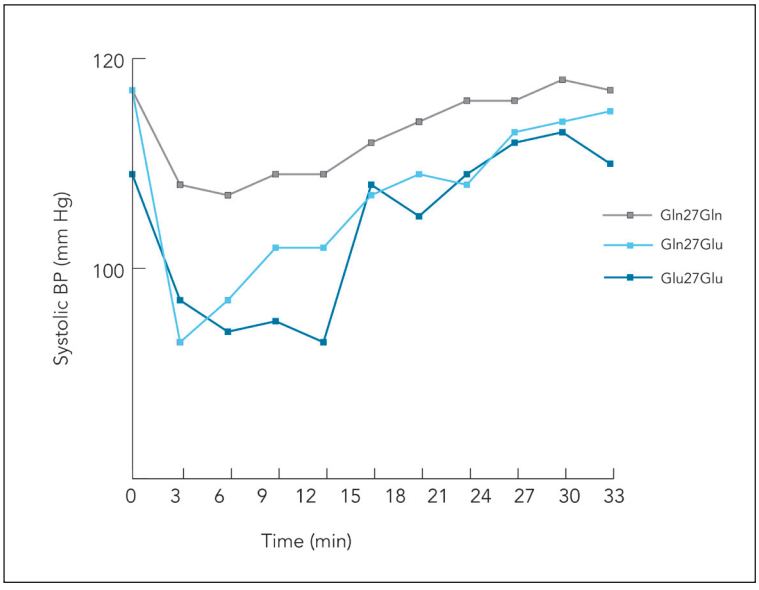

Figure 4. Systolic blood pressure variation over 30 minutes after spinal anesthesia for the codon 27 genotypes.

Declaration of conflict of interest

None declared.

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