Haemodynamic stability during anaesthesia induction with propofol – impact of phenylephrine. A double-blind, randomised clinical trial.

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ABSTRACT

Background. We studied the effects of a parallel phenylephrine infusion during bispectral index guided anaesthesia induction with propofol on haemodynamic parameters. We hypothesised that mean arterial pressure and cardiac index would be better maintained in the group of patients receiving the phenylephrine infusion during induction.
Methods. We studied ASA I-III patients scheduled for oncological abdominal surgery. Forty patients randomly received either a 0.9% NaCl or a phenylephrine (0.5 μg/kg/min) infusion during the induction of anaesthesia with propofol to a bispectral index value of 60. Mean arterial pressure, stroke volume index and systemic vascular resistance index were recorded, starting at one minute before induction for 20 minutes, at one-minute intervals.
Results. After induction of anaesthesia before intubation mean arterial pressure and stroke volume index decreased significantly compared to baseline in both groups, while the systemic vascular resistance index increased slightly. At the end of measurements, mean arterial pressure (66 ± 11 vs. 94 ± 14 mmHg; 0.9% NaCl vs. phenylephrine group $p<0.01$) and stroke volume index (34.2 ± 9.1 vs. 44.0 ± 9.7 ml/m²; 0.9% NaCl vs. phenylephrine group $p<0.01$) were lower in both groups in comparison to baseline values, but were better maintained in the phenylephrine group, whereas systemic vascular resistance index was higher than at baseline (2308 ± 656 vs. 3198 ± 825 dynes s/cm⁵/m²; 0.9% NaCl vs. phenylephrine group $p<0.01$) with significant differences between groups.
Conclusion. Our study shows that a continuous phenylephrine infusion can attenuate the drop in mean arterial pressure and stroke volume index during anaesthesia induction with propofol.
Key words: anaesthetics, propofol, monitoring, depth of anaesthesia, consciousness monitors, bispectral index, sympathetic nervous system, phenylephrine, measurement techniques, cardiac output

INTRODUCTION

Maintaining haemodynamic stability during induction and maintenance of anaesthesia is an important task for the anaesthesiologist. A recent meta-analysis has shown that propofol-based anaesthesia has no detrimental effect on survival. (1) However, anaesthesia induction with propofol is usually associated with a decrease in mean arterial pressure (MAP) and cardiac index (CI) after administration of the drug. (2) Various approaches to addressing this problem have been described in the literature, ranging from the use of different intravenous anaesthetic agents, (3) the use of titration to individualize the dosage of the induction agent with the use of bispectral index (BIS, Covidien, USA) guidance, (4) use of different opioids in different dosages (5,6) and using drugs affecting the stress response before induction. (7)
Phenylephrine is a vasoconstrictor acting on both venous and arteriolar vascular beds thereby increasing both venous tone and systemic vascular resistance index (SVRI) and CI. (8) It is commonly used to treat hypotension during general and regional anaesthesia. (9,10) However, if we aim to maintain haemodynamic stability during induction of anaesthesia with drugs known to cause haemodynamic compromise, especially in high risk elderly patients, preventing hypotension might be the preferred approach rather than simply treating the unwanted event. In the literature we found no study evaluating the haemodynamic effects of a continuous infusion of phenylephrine during induction of general anaesthesia with propofol, although such an approach has been studied in parturients receiving spinal anaesthesia for caesarean section. (11,12)
Due to the vasoconstrictor effects of phenylephrine, we hypothesised that MAP and CI would be better maintained in the group of patients receiving a continuous phenylephrine infusion during anaesthesia induction with propofol. The aim of our study was to evaluate the effect of a continuous phenylephrine infusion on maintenance of haemodynamic parameters during BIS guided induction of anaesthesia with propofol in a double blind randomized controlled trial. MAP was taken as the primary outcome variable and CI, stroke volume index (SVI), SVRI and heart rate (HR) were taken as secondary outcome variables.

MATERIALS AND METHODS

Ethical approval for this study was provided by the National Medical Ethics Committee of Slovenia (Ref.: 229/09/13). The study was registered at ISRCTNregistry (www.isrctn.com): ISRCTN81365561. We included 50 ASA I-III patients scheduled for oncological abdominal surgery. Written informed consent was obtained from each patient.

Exclusion criteria were: chronic alcoholism, intravenous drug use, body mass index >30, anticipated difficult intubation (Mallampati 3 and 4), serum creatinine > 120 μmol/l, valvular heart disease, left ventricular ejection fraction < 30%, systolic pressure higher than 160 and/or diastolic 95 mmHg at the beginning of measurements.

All patients were fasted overnight, had the same bowel cleansing procedure, and took their regular medication on the morning of surgery, except angiotensin-converting-enzyme inhibitors. The patients were premedicated with midazolam (0.1± 0.02 mg/kg), orally, one hour before surgery. Upon arrival, a 16G i.v. line was inserted and an infusion of Lactated Ringers' solution, 10 ml/kg was administered. A radial arterial line for arterial pressure measurements and a LiDCOrapid monitor for measuring CI (LiDCO Cardiac Sensor Systems, Cambridge, UK) were attached. The BIS electrodes were placed on the patient's forehead and connected with the BIS – monitor.

Patients were randomly assigned to the treatment and control group with respect to the drug infused during and after the induction of anaesthesia. Sealed envelopes prepared by the primary investigator were used for randomisation. The phenylephrine group received an infusion of phenylephrine 0.5 μg/kg/min starting at the same time as the infusion of propofol and running till the end of measurements.In the 0.9% NaCl group, an infusion of 0.9% NaCl ran during the same period. The infusion pumps (Alaris, Cardinal Health, Ireland) were prepared independent of the investigators by a nurse in the recovery room.

The study protocol is shown in Figure 1. One minute after baseline haemodynamic measurements were taken, fentanyl (Fentanyl, Janssen-Cilag Pharma, Belgium) 3 μg/kg was administered. Two minutes after fentanyl administration, an infusion of propofol (Propoven Fresenius 1%, Fresenius Kabi, Bad Homburg, Germany) 0.5 mg/kg/min was started. Parallel with the propofol infusion, we started the infusion of phenylephrine or 0.9% NaCl. At the loss of the palpebral reflex, rocuronium 0.6 mg/kg was given i.v. When the BIS value reached 60, the infusion of propofol was stopped and the dose of propofol recorded. Laryngoscopy commenced when BIS was below 50. After tracheal intubation, the patient's lungs were ventilated (Dräger-Primus, Germany) with oxygen and air (1:1) and sevoflurane, up to 1.5 vol%, which was titrated to maintain the BIS values between 40 and 60. MAP, CI, HR and BIS measurements were recorded pre-fentanyl and at one minute intervals for 20 minutes. Data were stored in an IBM-compatible computer. SVRI was calculated as follows: SVRI=MAP/CI*80. SVI was calculated as follows: SVI=1000*CI/HR. End-tidal CO_2 ($etCO_2$) and end-tidal sevoflurane (etSevo) were measured every 3 minutes after intubation.

Hypotension (MAP≤55 mmHg) was treated with phenylephrine 50 μg i.v. boluses until resolved.

Hypertension (MAP≥100 mmHg) was treated by stopping the infusion of the study solution. If hypertension persisted, it was treated with fentanyl 1 μg/kg- maximum of three doses- and afterwards with a nitro-glycerine infusion (10-100 μg/min). Bradycardia (HR≤40 min-1) was treated with atropine 0.3 mg i.v., up to three doses, and afterwards with boluses of ephedrine 5 mg i.v. Tachycardia (HR≥90 min-1) was treated with fentanyl 1 μg/kg, up to three times.

Data were analysed with IBM SPSS Statistics 18 statistical software. Data were tested for normality using Kolmogorov-Smirnov test. Patients' characteristics and baseline values were compared using a t test for independent samples and $\chi 2$ where appropriate. ANOVA for repeated measurements with Greenhouse-Geiser correction was used to compare the changes in haemodynamic parameters over time and between the two treatment groups. In adition, t test for independent samples was performed to compare the haemodynamic effects between the two groups, and the t test for paired samples to compare haemodynamic data at baseline, before intubation, after intubation and at the end of measurements. To account for multiple comparisons $P < 0.01$ was considered statistically significant.

Sample size calculation to detect a difference in MAP of 20 mmHg (SD 17 mmHg) among treatment groups with a probability level of 0.01 and power of 0.80 yielded a sample size of 16 patients for each treatment group.

RESULTS

We randomized 50 patients. Ten patients were excluded from analysis due to technical problems with monitors and due to increased MAP at the beginning of measurements. Therefore, 40 patients were included in the analysis. The CONSORT Flow Diagram is shown in Figure 2.

No significant differences between the two groups with respect to patient characteristics, diagnoses (Table 1) and baseline haemodynamic measurements (Table 2) were noticed. The mean dose (SD) of propofol (89.8 ± 20.5 vs. 96.7 ± 35.9 mg; 0.9% NaCl vs. phenylephrine group; p=0.23; t test independent samples), the time until the loss of palpebral reflex (297 33 vs. 301 34 s; 0.9% NaCl vs. phenylephrine group; p=0.75; t test independent samples) and the time until tracheal intubation (420 ± 41 vs. 430 ± 52 s; 0.9% NaCl vs. phenylephrine group; p=0.49; t test independent samples) also showed no significant differences between the groups. Haemodynamic data measured during the study for both study groups are shown in Table 2. In Figure 3, the percent of changes from baseline value during 20 minutes of measurements are shown. There were no significant differences between the two groups with respect to MAP, CI, SVRI, HR and stroke volume index (SVI) comparing the baseline values at T1 (Table 2).

As shown with ANOVA for repeated measurements (Table 2, Figure 3) CI, MAP, SVI and HR decreased significantly over time and SVRI increased significantly. MAP, SVI and SVRI were significanty higher in the phenylephrine group compared to the 0.9% NaCl group. CI was higher (p=0.030) and HR was lower (p=0.044) in the phenylephrine group and these differences were approaching statistical significance.

A detailed analysis of changes over time reveals that after induction of anaesthesia immediately before intubation (T3-T6) MAP, CI, and SVI decreased significantly compared to baseline in both groups, while the SVRI slightly increased (Table 2, Figure 3). After induction of anaesthesia immediately before intubation (T3-T6) HR also decreased, but the changes were significant only in NaCl group (Table 2, Figure 3).

After intubation, a transient increase in MAP was seen in both groups (T8) but values were still below baseline. MAP was significantly lower in the 0.9% NaCl group compared to the phenylephrine group in the period between3 minutes after intubation until the end of measurements (T10-T20), but was significantly lower than

Table 1. Patient characteristics, primary and secondary diagnosis and medication used in patients receiving 0.9% NaCl or phenylephrine infusion during anaesthesia induction with propofol.

		0.9% NaCl (n=21)	Phenylephrine (N=19)	p
Age (yr)		62.2 ± 9.7	66.6 ± 8.5	0.14
Gender (m/f)a		14/7 (67%/33%)	14/5 (74%/26%)	0.74
Height (cm)		170.8 ± 7.2	171.6 ± 7.3	0.75
Weight (kg)		76.3 ± 10.7	80.2 ± 10.3	0.25
Primary diagnosisa	Colorectal carcinoma	9 (43%)	1 (5%)	0.06
	Gastric carcinoma	3 (14%)	4 (21%)	
	Liver metastasis	4 (19%)	7 (37%)	
	Pancreatic carcinoma and bile duct cancer	5 (24%)	7 (37%)	
Secondary diagnosisa	Hypertension	12 (57.1%)	10 (52.6%)	0.78
	Myocardial infarction (status post)	1 (4.8%)	2 (10.5%)	0.49
	Stroke/ TIA	1 (4.8%)	1 (5.3%)	0.94
	Diabetes mellitus	6 (28.6%)	3 (15.8%)	0.33
	Auto-immune disease	0 (0%)	0 (0%)	-
	Hypo-/Hyperthyroidism	0 (0%)	0 (0%)	-
	Depression	1 (4.8%)	1 (5.3%)	0.94
Drug therapy	Calcium antagonists	3 (14.3%)	3 (15.8%)	0.89
	Beta-blockers	3 (14.3%)	6 (31.6%)	0.19
	ACE-inhibitors	5 (23.8%)	5 (26.3%)	0.86
	Sartans	1 (4.8%)	1 (5.3%)	0.94
	Diuretics	0 (0%)	3 (15.8%)	0.06
	Glucocortiocoids	0 (0%)	0 (0%)	-
	Oral hypoglycaemics/Insulin	6 (28.6%)	3 (15.8%)	0.33
	Thyroid hormone replacement therapy	0 (0%)	0 (0%)	-

Values are mean ± SD (t test independent samples)
a = values are number of cases (percent) ($\chi 2$ test)
ACEI, angiotensin-converting-enzyme inhibitors; COPD, chronic obstructive pulmonary disease; TIA, transitory ischaemic attack.

Table 2. Heart rate (HR), Mean Arterial Pressure (MAP), Cardiac Index (CI), Systemic Vascular Resistance Index (SVRI) and Stroke Volume Index (SVI) values are represented at different time points.

Time (min)	MAP (mmHg)		CI (ml/min/m2)		SVI (ml/m2)		HR (s-1)		SVRI (dynes s/cm5/m2)	
	0.9% NaCl	Phenyle-phrine	0.9% NaCl	Phenyle-phrine	0.9% NaCl	Phenyle-phrine	0.9% NaCl	Phenyle-phrine	0.9% NaCl	Phenylephrine
T1	100 ± 14	104 ± 13	3.82 ± 1.20	3.46 ± 1.09	52.3 ± 12.3	52.4 ± 10.2	72 ± 11	66 ± 15	2107 ± 627	2409 ± 647
T3	97 ± 17	100 ± 14	3.70 ± 1.28	3.27 ± 1.09†	51.8 ± 12.4	51.4 ± 10.3	70 ± 14	64 ± 16†	2124 ± 616	2482 ± 702
T6	84 ± 12†	90 ± 19†	3.09 ± 0.91†	2.68 ± 0.88†	45.3 ± 11.4†	44.1 ± 10.1†	68 ± 7†	61 ± 12	2140 ± 592	2596 ± 668
T8	87 ± 23	97 ± 20	3.23± 1.30†	2.67 ± 0.64†	42.2 ± 13.5†	43.4 ± 9.6†	75 ± 11*	63 ± 12*	2124 ± 477*	2796 ± 686*†
T10	76 ± 17*†	94 ± 20*†	2.88 ± 1.22†	2.50 ± 0.75†	39.4 ± 13.3†	43.8 ± 9.9†	72 ± 12*	58 ± 13*†	2131 ± 650*	2902 ± 667*†
T15	64 ± 10*†	91 ± 13*†	2.27 ± 0.88†	2.27 ± 0.52†	35 ± 9.9*†	43.9 ± 8.9*†	64 ± 10*†	52 ± 9*†	2217 ± 685*	3064 ± 605*†
T20	66 ± 11*†	94 ± 14*†	2.24 ± 0.84†	2.27 ± 0.54†	34.2 ± 9.1*†	44.0 ± 9.7*†	64 ± 10*†	52 ± 10*†	2308 ± 656*†	3198 + 825*†
ANOVA	df=3.6 F=9 p=0.000		df=3.2 F=59 p=0.000		df=3.2 F=76 p=0.000		df=3.5 F=23 p=0.000		df=3.5 F=2.6 p=0.044	
Time	df=3.6 F=9 p=0.000		df=3.6 F=3 p=0.030		df=3.2 F=14 p=0.000		df=3.5 F=2.6 p=0.044		df=3.3 F=6.6 p=0,000	
Group										

Data are mean ± SD.

* p<0.01 between groups (t test for independent samples)
T1 = baseline (1st minute)
T3 = 3rd minute of measurements
† p<0.01 with respect to baseline (t test for paired samples)
T6 = 6th minute - before Intubation
T8 = 8th minute - after Intubation
T10 = 10th minute of measurements
P = phenylephrine group
T15 = 15th minute of measurements
S = 0.9% saline group
T20 = 20th minute of measurements
ANOVA = parameters for repeated measures ANOVA with a Greenhouse-Geisser correction for within (Time) and between (Group) group comparison

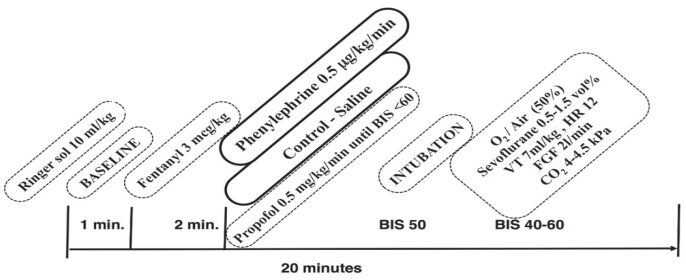

Figure 1. Study protocol

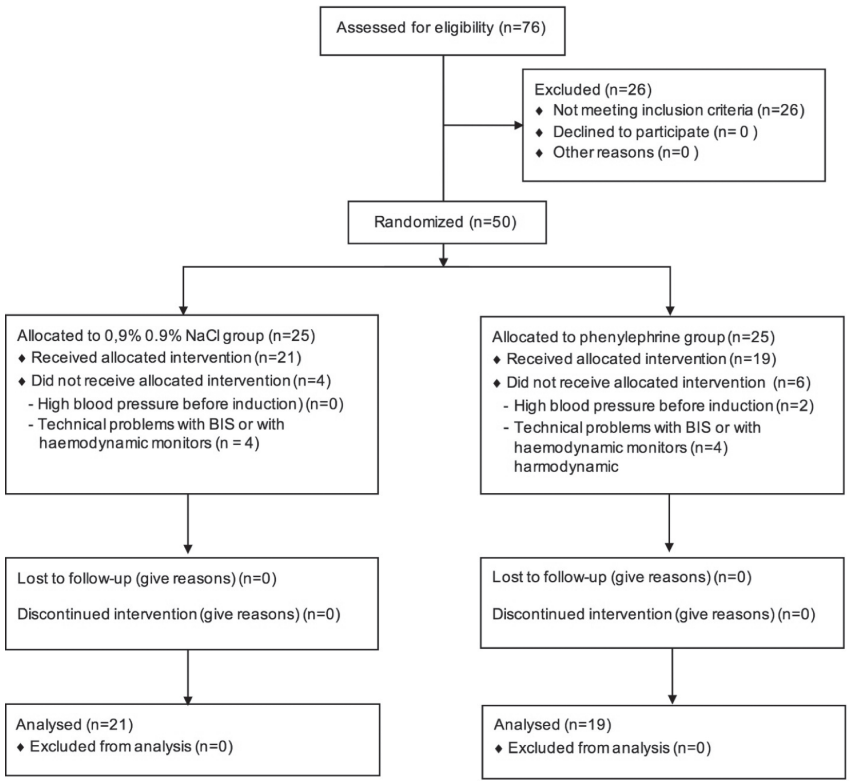

Figure 2. Flow diagram of the study

baseline in both groups (Table 2, Figure 3). CI was significantly decreased after ETI and remained significantly decreased compared to baseline values in both groups until the end of measurements (T8-T20) (Table 2, Figure 3). The time course of the percent change in CI (Figure 3) shows that the parameter was better maintained in the phenylephrine group.

SVI was significantly decreased after intubation compared to baseline values in both groups, but was significantly higher in the phenylephrine group compared to the 0.9% NaCl group at the end of measurements (T15-T20) (Table 2, Figure 3).

SVRI remained significantly increased after intubation in the phenylephrine group (T8-T20), but slightly increased in the NaCl group reaching a statistically significant difference at the end of measurements (T20) (Table 2, Figure 3). SVRI in the phenylephrine group was significantly increased compared to the 0.9% NaCl group after intubation until the end of measurements (T8-T20) (Ttable 2, Figure 3).

After intubation, HR transiently significantly increased (T8) in the 0.9% NaCl group more than in the phenylephrine group. After that, HR decreased significantly in both groups until the end of measurements (T15-T20) After intubation, until the end of measurements, HR was significantly decreased in the phenylephrine group compared to the 0.9% NaCl group (T8-T20) (Table 2, Figure 3).

After induction of anaesthesia, the BIS value decreased significantly in both groups with no differences between the groups (Figure 3). There were no significant difference between groups after intubation regarding etCO2 and inspiratory and expiratory etSevo.

Due to hypotension, five patients in the 0.9% NaCl group received one or more boluses of phenylephrine. No additional phenylephrine boluses were administered in the phenylephrine group. Due to hypertension in three patients in the P group, the infusion of phenylephrine was stopped. No additional fentanyl or nitroglycerine was given. Due to bradycardia, two patients in the P group received 0.3 mg of atropine. We did not observe any signs of ischaemia, ECG or ST-segment changes in any patient.

DISCUSSION

We studied the influence of a phenylephrine infusion on BIS guided induction in general anaesthesia patients scheduled for major abdominal surgery. Our study showed that MAP was better maintained after induction in patients receiving a phenylephrine infusion. The better maintenance of MAP was caused primarily by an increase in SVRI in the phenylephrine group; however, important differences between the groups in parameters defining CI (HR and SVI) were also measured.

We used the BIS guided approach to titrate propofol during induction to a BIS value of 60, when the propofol infusion was stopped. The so called "hysteresis" of propofol causes a further decrease of BIS after stopping the propofol infusion. (13) Since there is also a time delay of the BIS value on the display monitor (10-15 seconds or even more), (14) after stopping the propofol infusion the BIS value continued to decrease until ETI was performed at a BIS value of approximately 50. With this approach we could decrease the dose of propofol well below the recommended 1.5-2.5 mg/kg range (15) (in our study 89.8 ± 20.5 mg in the 0.9% NaCl group and 96.7 ± 35.9 mg in the phenylephrine group). We decided to use the above mentioned speed of propofol infusion on the basis of already described pharmacokinetics and pharmacodynamics reported in the literature (0.5 and 0.75 mg/kg/min). (16-18)

The differences between the groups in

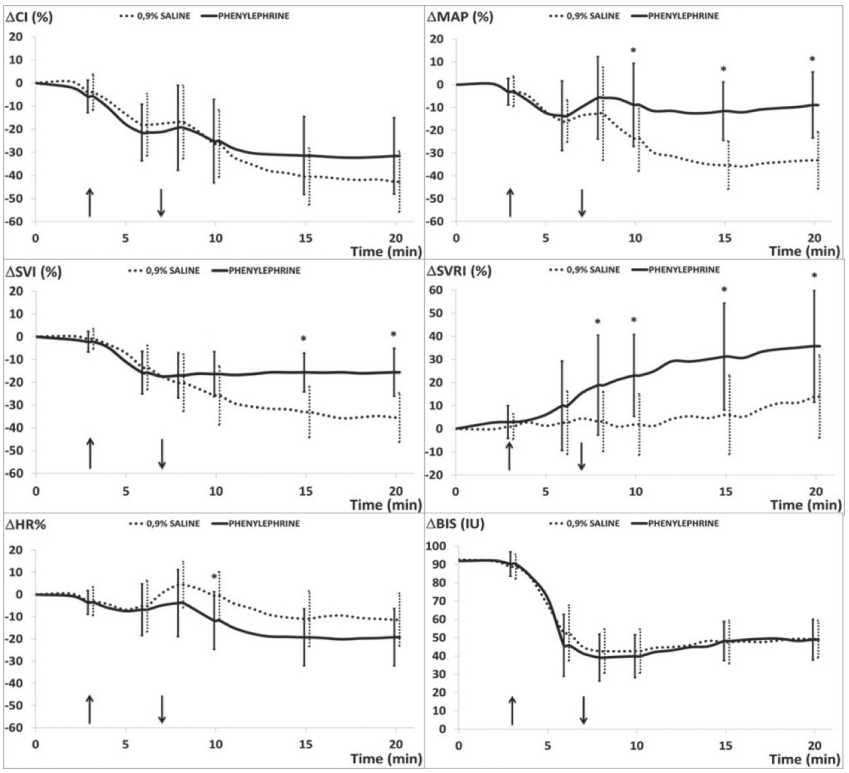

*Figure 3. Time course of the percent change in mean arterial pressure, cardiac index, stroke volume index, systemic vascular resistance, heart rate, absolute bispectral index value changes and repeated measures ANOVA data in patients receiving 0.9% NaCl or phenylephrine infusion during anaesthesia induction with propofol (MAP = mean arterial pressure, SVI = stroke volume index, CI = cardiac index, HR = heart rate, SVRI = systemic vascular resistance, BIS = bispectral index; ANOVA = repeated measures ANOVA with a Greenhouse-Geisser correction parameters for within (Time) and between (Group) group comparison; * p<0.01 between the groups (t test for independent samples); ↑ = start of the induction, ↓ = tracheal intubation).*
Black solid and dashed lines show the mean values of the parameters in the population, and the error bars show the SD.

nominal SVI and CI were measured with the LiDCORapid. Nominal values are derived and estimated from a population based nomogram. (19,20) However, in our study we were interested in trends of SVI and CI rather than the actual values. In addition, the LiDCORapid only requires a standard radial arterial line and uses pulse power analysis for the measurement of nominal SV. (21)

Phenylephrine is a potent vasoconstrictor acting predominantly on 1 receptors influencing both the venous and arterial vascular beds and exerts mild ionotropic effects only when administered at high concentrations. (8,22,23) The effect of phenylephrine at dosages used in our study is on both venous and arteriolar vasoconstriction with the latter demonstrated by an increase in SVRI, whilst at lower doses the effect may be predominantly on venous tone. The increase in SVRI was accompanied by a higher MAP in the P group of patients.

After propofol induction, nominal CI decreased to the same degree in both groups. This was caused by a significant decrease in SVI and HR. Several parameters influenced the decrease in CI in our study. Propofol venodilation decreases preload and SVI. (24) The mechanisms for venodilation during general anaesthesia and its physiological consequences have been reviewed recently. (25) Additional parameters causing a decrease in preload and SVI are the addition of sevoflurane and positive pressure ventilation of the lungs after intubation. The main cause for the tendency towards bradycardia in both groups was probably administration of the opioid (fentanyl) and after intubation the decrease in sympathetic tone. Nevertheless, all the changes mentioned above apply to the same extent to both groups of patients in our study.

However, important differences between the groups were measured in the extent of changes in parameters defining the nominal CI. After induction and intubation, SVI was significantly higher in the phenylephrine group while HR was significantly lower in the phenylephrine group, in comparison to the 0.9% NaCl group. Baroreceptor reflex activation is probably one important reason for this difference. Since MAP was higher in the phenylephrine group, this led to a decrease in HR thereby prolonging the filling period of the heart and increasing the SVI. Another reason for the higher SVI in the phenylephrine group of patients is probably the vasoconstrictor effect of phenylephrine on the venous vascular bed, which has been reported in the literature. (22) In Figure 2, percent changes of haemodynamic parameters are shown. We can see that in the last 10 minutes of measurements the percent change CI is better maintained in the phenylephrine group of patients. Thus, the difference in SVI between groups is actually higher than the difference in HR, which could probably be explained by the venoconstrictor effect of phenylephrine increasing the preload to the heart and increasing the SVI. A similar observation was reported recently by Poterman and co-workers (26) while studying the effects of phenylephrine and norepinephrine on peripheral tissue oxygenation.

In the literature we found no studies evaluating haemodynamic changes during BIS guided induction of general anaesthesia with propofol with a parallel infusion of phenylephrine. Imran and co-workers (27) evaluated the effects of induction of anaesthesia with propofol (using a 2.5 mg/kg dosage) combined with a bolus administration of either 0.9% NaCl or phenylephrine 50 μg and 100 μg. Only a 100 μg dose effectively attenuated the hypotension during induction. BIS and CI were not measured in their study.

Additional phenylephrine boluses were given to five patients in the 0.9% NaCl group. In the phenylephrine group two patients needed atropine for treatment of bradycardia and in three patients the infusion of the study solution was stopped due to hypertension. This confirms the clinical observation, that the dosage of phenylephrine infusion during induction should be individualized to the patient's needs. The infusion rate (0.5 μg/kg/min) was based on the study by Allen and co-workers. (11) The authors evaluated four different infusion rates of phenylephrine for prevention of hypotension after spinal

anaesthesia for caesarean delivery. The infusion rates of phenylephrine of 100 and 75 μg/min were associated with an increased incidence of hypertension in comparison with the infusion rates 25 and 50 μg/min. The infusion rate of phenylephrine in our study was between the two lower recommended dosages, but was obviously too high for three of our patients. However, prophylactic administration of phenylephrine markedly reduces the fall in MAP at induction. Recent large scale restrospective studies, such as the study by Walsh and co-workers (28), have shown that even very short periods of low MAP may be associated with poor outcome. So any degree of hypotension is best avoided and the phenylephrine infusion can be stopped any time in case of an exagerated effect.

Our study shows that we can attenuate the decrease in MAP during anaesthesia induction with propofol by administering a continuous phenylephrine infusion during the induction period. The primary clinical effect of the phenylephrine infusion at dosages used in our study is the increase in SVRI. Additional improvements in haemodynamics during induction of anesthesia with propofol might be achieved by starting a lower (0.25 g/kg/min), venoconstricting dose of phenylephrine much earlier in the induction sequence, e.g., following insertion of the arterial line and obtaining baseline haemodynamic parameters. In addition, reducing the bradycardic effects of fentanyl, by prophylactic use of anti-cholinergics, might better maintain heart rate and thus cardiac output. Such an approach needs to be assessed with further studies.

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