Terlipressin infusion versus norepinephrine infusion for management of postcoronary artery bypass grafting refractory hypotension: a comparative study

Ahmed M. El-Shaarawy[a], Tarek A. Marei[c], Hisham M. Elbatanony[b]

Departments of [a]Anesthesia, [b]Cardiothoracic Surgery, Faculty of Medicine, Beni Suef University, Beni Suef, [c]Department of Anesthesia, Faculty of Medicine, Cairo University, Cairo, Egypt

Correspondence to Ahmed M. El-Shaarawy, MD, 7 Ali Ebn Abi Taleb Street, Agouza, Cairo, 12411, Egypt. Tel: +20 114 101 5584/ +20 106 605 8397;
e-mail: drshaarawy@gmail.com

Received 9 May 2017
Accepted 17 December 2017

The Egyptian Journal of Cardiothoracic Anesthesia 2017, 11:31–37

Objective
The aim was to evaluate outcome of diabetic patients who developed refractory hypotension after coronary artery bypass grafting (CABG) surgery on using terlipressin (TP) versus norepinephrine (NE) infusions.
Patients and methods
A total of 44 patients were divided into two groups: group NE received NE infusion (0.1 μg/kg/min) and group TP received TP infusion (2 μg/kg/h). On cardiopulmonary bypass weaning (0 h), hemodynamic parameters, levels of blood glucose (BG) and blood lactate, serum creatine kinase-MB, and cardiac troponin T were determined. If systolic less than 90 mmHg and/or mean arterial pressure (MAP) less than 60 mmHg persisted after 5 min of adequate volume resuscitation, vasopressor infusions were started and hemodynamic parameters were recorded. If initial doses failed to achieve adequate hemodynamic stability at 10 min, the dose was increased. Postoperative levels of studied parameters were estimated.
Results
NE significantly whereas TP nonsignificantly increased heart rate. Both infusions induced persistently higher MAP at 10 min, 30 min, and 4 h compared with 0 h, with nonsignificantly higher MAP with TP versus NE. Both infusions increased BG levels compared with 0 h estimates, with significant difference with NE. At 24 h, serum creatine kinase-MB levels were significantly lower with TP than NE, whereas serum cardiac troponin T levels showed nonsignificant difference. Lactate clearance rate was significantly higher with TP.
Conclusion
Vasopressor infusion improved hemodynamics. TP did well than NE with significant increase of blood pressure measures but minimized cardiac ischemic risk and the increase of BG and blood lactate levels.

Keywords:
coronary artery bypass grafting surgery, diabetes mellitus, norepinephrine, refractory hypotension, terlipressin

Egypt J Cardiothorac Anesth 11:31–37

1687-9090

Introduction

Perioperative hemodynamic instability is a major concern especially during general anesthesia for individuals with autonomic dysfunction [1]. Cardiac autonomic neuropathy is a serious complication among both type 1 and type 2 diabetic patients [2], with a prevalence ranging between 20 and 65% depending on the duration of the diabetes mellitus [3], but poor glycemic control plays a pivotal role in its pathogenesis [2].

Hypotension after cardiac surgery is characterized by profound vasodilation and loss of systemic vascular resistance [4], normal-to-increased cardiac index and by being refractory to fluid resuscitation or high dose of vasopressor [5]. Postcardiac surgery refractory hypotension is associated with significant morbidity and mortality [4].

Multiple preoperative and operative factors predispose to or could predict the development of postcardiac surgery refractory hypotension [6]. Pre-existing endothelial cell activation may result in endothelial desensitization that leads to suppression of myocardial release of endothelial cell activation markers on reperfusion [7]. Cardiopulmonary bypass (CPB) increased the risk of developing postoperative (PO) hypotension after coronary artery bypass grafting (CABG), especially in patients with dialysis-dependent chronic renal failure [8]. The pathogenesis also involves the activation of contact, coagulation, and complement systems and the

activation of leukocytes, platelets, and endothelial cells, resulting in an imbalance in the regulation of the vascular tone [4].

Vasopressors include pure vasoconstrictors such as phenylephrine and vasopressin (VP) and inoconstrictors such as dopamine, norepinephrine (NE), and epinephrine. These medications increase mean arterial pressure (MAP) by augmenting vascular tone [9].

Terlipressin (TP) (triglycyl-lysine VP) is a long-acting synthetic analog of arginine VP [10]. It is a prodrug that is converted to the lysine VP in the circulation after the *N*-triglycyl residue is cleaved by endothelial peptidases, resulting in a 'slow release' of the vasoactive lysine VP [11]. The effect half-life of TP is 6 h [12], and its elimination half-life is 50 min [13] TP acts through V1 receptors in the vascular smooth muscle cells found mainly in the splanchnic circulation causing splanchnic vasoconstriction, which is responsible for increasing systemic vascular resistance and reducing heart rate (HR) [14].

The current study was designed to evaluate the outcome of diabetic patients who developed refractory hypotension after CABG surgery on using TP versus NE infusions.

Design

This was a prospective comparative clinical study.

Setting

The study was conducted in Beni Suef University Hospital, Beni Suef, Egypt.

Patients and methods

The current study was conducted since January 2014 till August 2016. The study protocol was approved by the Local Ethical Committee. Patients who signed written fully informed consent were enrolled in the study.

Diabetic patients with normal ventricular function and mean pulmonary artery pressure (12–15 mmHg) and undergoing elective CABG surgery were eligible for evaluation, and only patients who developed hypotension with MAP less than 60 mmHg and/or systolic arterial blood pressure (SBP) less than 90 mmHg for more than 5 min despite adequate volume resuscitation were enrolled in the study.

Exclusion criteria included presence of peripheral vascular disease; hepatic or kidney dysfunction; unstable preoperative conditions such as severe arrhythmia, heart failure, or cardiogenic shock; and if emergency CPB was indicated.

Patients were evaluated clinically to ensure inclusion and exclusion criteria. Collected data included age; sex; BMI; duration of diabetes; maintenance antidiabetic therapy; hemodynamic data including SBP, diastolic blood pressure (DBP), and MAP; HR; and ejection fraction. Results of preoperative investigations of fasting blood glucose (BG) and glycated hemoglobin levels were also obtained. Patients who were maintained on antiplatelet therapy, angiotensin-converting enzyme inhibitors, and calcium channel blockers, stopped therapy for at least 1 week before surgery.

Patients' randomization

Patients were randomly divided into two equal groups according to the vasopressor infusion used. Group title was written in folded up paper prepared by an assistant blinded to the study and enclosed in sealed envelopes. Envelops were chosen by the patient before surgical interference.

Study groups

The patients were divided into two groups:

(1) Group NE included patients who receive NE (Levophed; Hospira Inc., Brussels, Belgium) infusion that was prepared by an assistant blinded to the protocol as 0.1 mg/ml in physiological (0.9%) saline and given at rate of 0.1 μg/kg/min.
(2) Group TP included patients who receive TP acetate (Glypressin, 1 mg/5 ml; Ferring Pharmaceuticals, Saint Prex, Switzerland) infusion prepared by an assistant blinded to the study as 2 μg/ml in physiological (0.9%) saline and given at rate of 2 μg/kg/h. Both infusions were prepared in equal volumes of isotonic saline.

Anesthetic procedure

All patients were premedicated by intravenous midazolam 2–3 mg. Intraoperative monitoring included five-lead ECG with ST segment analysis, invasive arterial blood pressure measurement, pulse oxygen saturation, end-tidal carbon dioxide, and inspiratory and end-tidal anesthetic concentrations. Anesthesia was induced with 1.5–2 mg/kg propofol, 5–10 μg/kg fentanyl, and 0.1 mg/kg pancronium to facilitate tracheal intubation. After induction of anesthesia, right internal jugular vein was cannulated using a 7-F three-way central catheter; a urinary catheter was introduced for measurement of urine output (UOP), and a transesophageal

echocardiographic (TEE) probe was introduced and advanced to the midesophagus. A comprehensive TEE examination was performed according to the American Society of Echocardiography/Society of Cardiovascular Anesthesiologists (ASE/SCA) guidelines to assess ventricular function and to exclude any associated cardiac abnormality. Anesthesia was maintained using sevoflurane 1.5–2% in oxygen and increments of fentanyl of 2–3 μg/kg. Minute ventilation was adjusted to maintain PCO_2 between 30 and 35 mmHg.

Cardiopulmonary bypass and surgical procedure

Standard CPB was established with moderate hemodilution (hematocrit value of 20–25%), mild hypothermia (down to 34–35°C), and a constant pump flow of 2.5 l/min/m^2. Myocardial arrest was induced by warm blood antegrade cardioplegia, which is repeated every 20–30 min. Collected operative data included cross-clamp time, CPB time, total operative time, and number of grafts. PO UOP and blood loss from the chest drains were recorded hourly for the first 24 h.

Experimental protocol

(1) At time of CPB weaning and immediately before start of vasopressor infusion (0 h) HR, SBP, DBP, MAP, and central venous pressure were recorded, and blood samples were obtained for estimation of 0 h levels of BG and blood lactate (BL) and serum creatine kinase-MB (CK-MB) and cardiac troponin T (cTT).
(2) If SBP is less than 90 mmHg and/or MAP less than 60 mmHg, TEE was performed to assess left ventricular loading conditions and to exclude decrease in ventricular function as the cause of hypotension. If TEE detected decrease in cardiac preload and adequate ventricular function, optimization of preload was achieved by first reinfusing blood from the cardiotomy reservoir and then by titrating intravenous fluids.
(3) In case of persistent hypotension after 5 min of adequate volume resuscitation (central venous pressure: 8–12 mmHg), vasopressor infusion assigned for each group was started, and hemodynamic parameters were recorded 10 min, 30 min, and 4 h after the start of infusion by an anesthesiologist blinded to the study protocol.
(4) In case of failure of the initial doses of the study drugs to achieve adequate hemodynamic stability and MAP was sustained less than 60 mmHg or SBP less than 90 mmHg at 10 min after initiation of vasopressor infusion, the dose was progressively titrated to increase blood pressure to the desired values.

Outcome data

(1) Primary outcome was defined as the ability of the vasopressor infusion to correct hypotension to achieve SBP greater than 90 mmHg and/or MAP greater than 60 mmHg.
(2) Secondary outcome included evaluation of the effect of vasopressor infusions on the following items:
    (a) BG levels that were estimated at 4, 8, and 12 h after infusion started.
    (b) Serum CK-MB and cTT levels that were estimated at 12 and 24 h after infusion started.
    (c) Tissue perfusion as judged by amount of UOP that was determined at 4, 12, and 24 h after infusion start, and BL levels that were estimated at 4 and 12 h after infusion start. Moreover, lactate clearance rate (LCR) was calculated as initial BL levels estimated at 0 h minus 4 h and 12 h level and divided by 0 h BL level [15].
(3) Other evaluated parameters included duration of ICU stay and amount of chest tube drainage.

Statistical analysis

Sample size was calculated using the standard nomogram proposed by Kraemer and Thiemann [16], and a sample size of greater than or equal to 40 patients was determined to be sufficient to detect a difference at the 5% significance level and give the trial 80% power [17]. Sample size and power were re-calculated and ensured using Power and Sample Size Calculation Software program provided by Department of Biostatistics, Vanderbilt University. Obtained data were presented as mean±SD, ranges, numbers, and ratios. Results were analyzed using one-way analysis of variance with post-hoc Tukey HSD test and χ^2-test. Statistical analysis was conducted using the SPSS (version 15, 2006) for Windows statistical package (SPSS Inc., Chicago, Illinois, USA). *P* value less than 0.05 was considered statistically significant.

Results

Throughout the study period, 44 diabetic patients developed post-CABG refractory hypotension and fulfilled the inclusion criteria, and they were randomly divided into two equal groups. There was a nonsignificant ($P>0.05$) difference between both groups regarding preoperative and operative data as shown in Table 1.

NE infusion progressively increased HR with significant difference, with incremental increase from

0 h to 10 min to 30 min, whereas TP infusion nonsignificantly increased HR. Moreover, NE infusion induced significantly higher HR than TP infusion at 10 min, 30 min, and 4 h. Mean SBP measurements were increased significantly with both NE and TP at 30 min and 4 h after start of infusion, with significantly higher SBP with TP than NE infusion at 4 h only. Mean DBP measures were significantly higher in both groups at 10 min, 30 min, and 4 h compared with 0 h measures, with significant difference between 30 min and 4 h measures. In group TP, 30 min and 4 h DBP measures were significantly higher compared with 10 min DBP measures, with significantly higher 4 h versus 30 min measures. However, DBP measures were nonsignificantly higher with TP than NE infusions. Despite the nonsignificant difference in MAP measures between both groups, MAP measures showed progressive significant increase till 4 h after start of infusion with significantly higher MAP at 4 h versus 30 min measures with TP, but nonsignificantly with NE infusion (Table 2).

Both infusions induced increased BG levels since start and peaking at 4 h after start of infusion, then declined gradually to a significantly lower level at 12 h compared with 0 h levels. Estimated BG levels were significantly higher with NE than TP infusion throughout the 12 h after start of infusion. Estimated serum CK-MB and cTT levels were higher at 0 h in both groups and started to decrease gradually with nonsignificant difference versus 12 h levels, whereas the difference was significant versus 24 h measures. TP infusion induced significantly lower CK-MB levels at 24 h compared with both their respective 12 h levels and levels estimated in patients of NE

Table 1 Preoperative and operative data of patients who developed refractory hypotension and their categorization according to vasopressor used for management

Data	Group NE	Group TP	*P* value
Age (years)	58.3±6.6	54.5±8.3	0.106
Sex			
Males	14 (63.6)	12 (54.5)	0.543
Females	8 (36.4)	10 (45.5)	
BMI data			
Weight (kg)	82.5±9	84.2±5.2	0.427
Height (cm)	169.9±4	169.3±2.5	0.535
BMI (kg/m^2)	28.6±3.4	29.4±1.9	0.345
ASA grade			
I : II : III	3 : 8 : 11	2 : 7 : 13	0.805
DM data			
Duration of DM (years)	4.7±1.2	4.4±1.1	0.356
FBG (mg/ml)	169±5.9	171±6.5	0.512
HbA1c (%)	7.2±0.47	7.3±0.53	0.295
Insulin : oral hypoglycemic therapy	9 : 13	12 : 10	0.365
Euroscore	4.82±2.1	4.91±1.88	0.882
Hemodynamic data			
Heart rate (beats/min)	83±3.3	81.5±2.8	0.119
SBP (mmHg)	120.4±3.6	118.9±4.1	0.214
DBP (mmHg)	80.3±3.5	79.5±3.7	0.461
MAP (mmHg)	93.7±2.5	92.6±2.7	0.231
EF (%)			
Frequency			
<60	15 (68.2)	17 (77.3)	0.863
>60	7 (31.8)	5 (22.7)	
Mean	58.6±5.12	57.3±4.29	0.467
CI (l/min/m^2)	3.24±1.15	2.94±1.27	0.417
Operative findings			
Clamping time (min)	60.5±11.4	57±11.1	0.315
CPB time (min)	84±4.9	81±8	0.141
Operative time (min)	192±20	180±24.7	0.084
Number of grafts	3.8±0.8	4.1±0.8	0.266

Data are presented as mean±SD, numbers, and ratios and percentages are in parenthesis; ASA, American Society of Anaesthesiologists; BMI, Body mass index; CPB, cardiopulmonary bypass; DBP, diastolic blood pressure; DM, diabetes mellitus; EF, ejection fraction; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; MAP, mean arterial pressure; NE, norepinephrine; *P*, significance of difference between both groups; SBP, systolic blood pressure; TP, terlipressin.

Table 2 Hemodynamic data determined after start of infusions compared with that estimated at the start of infusion

Parameters	Time	Group NE	Group TP	*P* value
HR (beats/min)	0 h	85±2.8	83.5±3.6	0.081
	10 min	88±3.2*	85.7±5.7	0.046
	30 min	91±3.6*,†	85.9±7	0.003
	4 h	91.9±3.1*,†	87.6±6.8	0.017
SBP (mmHg)	0 h	80.2±5.5	79±4.7	0.892
	10 min	82.5±6.2	86.5±4.3	0.697
	30 min	106.3±12.9*,†	113.4±8.1*,†	0.077
	4 h	107.4±2.9*,†	115.1±3.8*,†	0.010
DBP (mmHg)	0 h	50.4±2.1	49.6±2.6	0.899
	10 min	67.8±5.1*	64.8±6.1*	0.484
	30 min	72±6.1*	71±5*,†	0.817
	4 h	76.1±6*,†	77±4.8*,†,‡	0.774
MAP (mmHg)	0 h	60.4±1.4	59.2±2.6	0.798
	10 min	74±4.3*	70.7±5.4*	0.377
	30 min	83.4±7*,†	85.1±4.7*,†	0.629
	4 h	86.2±8.1*,†	89.7±3.7*,†,‡	0.203

Data are presented as mean±SD; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; NE, norepinephrine; *P*, significance of difference between both groups; SBP, systolic blood pressure; TP, terlipressin; *Significant difference versus 0 h measures; †Significant difference versus 10 min measures; ‡Significant difference versus 30 min measures.

Table 3 Laboratory data of patients who developed refractory hypotension after start of infusion

Parameters	Groups		*P* value
	Group NE	Group TP	
Random blood glucose (mg/dl)			
0 h	193±23.2	189.7±18	0.592
4 h	217±28.7*	196.3±14.3	0.011
8 h	201±19.2†	187±20	0.041
12 h	192±16.2†,‡	182±16.7†	0.044
Cardiac enzymes			
CK-MB (U/l)			
0 h	36.1±25.4	32.4±17.4	0.355
12 h	27.2±13.6	24.3±12.1	0.638
24 h	21.7±17.3*	18.8±13.4*,†	0.009
cTT (ng/ml)			
0 h	0.73±0.39	0.66±0.35	0.733
12 h	0.59±0.27	0.56±0.23	0.338
24 h	0.53±0.23*	0.41±0.21*	0.527
Blood lactate (mmol/l)			
0 h PO	3.59±1.1	3.38±1.37	0.783
4 h PO			
Level	2.66±0.74*	2.42±0.98*	0.389
LCR (%)	24.4±11.9	40.1±11	0.001
12 h PO			
Level	2.07±0.47*	1.56±0.62*,†	0.066
LCR (%)	39.9±14.6†	51.5±12.5†	0.018
UOP (ml/kg/hr)			
0 h	0.42±0.22	0.44±0.25	0.744
4 h	0.99±0.2*	1.15±0.27*	0.029

Data are presented as mean±SD; CK-MB, creatine kinase-MB; cTT, cardiac troponin T; LCR, lactate clearance rate; NE, norepinephrine; PO, postoperative; *P*, significance of difference between both groups; TP, terlipressin; UOP, urine output; *Significant difference versus 0 h; †Significant difference versus 4 h; ‡Significant difference in relation to 8 h.

group. Correction of hypotension in both groups improved tissue perfusion, and this was reflected as improved tissue oxygenation as evidenced by progressive decrease of BL with significantly higher LCR and significant increase of UOP. TP infusion significantly improved tissue perfusion than NE infusion as manifested by significantly higher LCR at 4 and 12 h with significantly increased UOP (Table 3).

PO data showed nonsignificant difference ($P>0.05$) between patients of both groups (Table 4).

Discussion

Both NE and TP infusions significantly improved blood pressure measures in comparison with 0 h measures, but NE significantly increased, whereas TP nonsignificantly increased HR. These findings spotlight on a more beneficial effect of TP infusion manifested as persistently higher MAP with less burden on heart, thus, indicating its appropriateness as a first-line management of patients who developed post-CABG refractory hypotension.

These data support those previously reported with the use of VP infusion in similar cases, wherein Masetti *et al.* [18] detected that VP infusion significantly increased SBP in patients who developed hypotension refractory to maximal doses of NE after complex cardiac operations employing CPB. Moreover, Hasija *et al.* [19] documented the prophylactic effect of VP infusion for prevention of post-CPB hypotension, and Elgebaly and Sabry [20] reported that VP infusion is beneficial for adjusting PO hemodynamic profile, with reduction of the required doses of catecholamine, and improves left ventricular systolic function. Moreover, Yimin *et al.* [21] found VP was better than NE to keep hemodynamic stability of patients undergoing CABG surgery.

The obtained results also coincided with comparative studies using TP and NE infusion for correction of refractory hypotension secondary to varied disease states, where Ibrahim *et al.* [22] found perioperative TP during liver transplantation improved MAP with less need for catecholamines particularly after reperfusion. Moreover, Xiao *et al.* [23] and Choudhury *et al.* [24] showed that continuous infusion of TP can help NE achieve good resuscitation effect by improving tissue blood flow, stabilizing hemodynamics, and protecting organ function in patients with septic shock. Furthermore, Goyal *et al.* [25] found both TP and NE significantly

Table 4 Postoperative data of patients who developed refractory hypotension

Parameters	Groups		*P* value
	Group NE	Group TP	
Duration of mechanical ventilation (h)	4.9±1.4	4.5±1.1	0.275
Duration of ICU stay (h)	64±15.4	60.5±11.9	0.404
Amount of sternal wound drainage (ml)	1100±176.6	1060±127.3	0.394

Data are presented as mean±SD; NE, norepinephrine; *P*, significance of difference between both groups; TP, terlipressin.

increased MAP with significant decrease in serum creatinine in patients with hepatorenal syndrome.

Both NE and TP infusions induced increased BG that peaked at 4 h and declined gradually till 12 h, with significantly higher levels with NE than TP. These data indicated a more hyperglycemic effect of NE than VP. In trials to explore the underlying mechanism for the effect of both NE and VP infusions on glucose homeostasis, experimentally, Connolly *et al.* [26] and Liang and Cincotta [27] documented that NE enhances gluconeogenesis by stimulating peripheral precursor release and increasing intrahepatic gluconeogenic efficiency, and van den Thillart *et al.* [28] found NE infusion lowered plasma free fatty acid levels and raised plasma glucose level for several hours. On the contrary, Aoyagi *et al.* [29] found VP-resistance conditions resulting from V1a-receptor deficiency leads to impaired glucose homeostasis. Recently, Taveau *et al.* [30,31] experimentally documented that acute injection of VP induces a dose-dependent glycemic effect.

Correction of hypotension and achieving hemodynamic stability did not impose definite cardiac risk as increased DBP allows improved cardiac muscle blood supply with subsequent cardiac performance as evidenced by gradual decrease of serum cardiac ischemia markers. Similarly, Okamoto *et al.* [32] detected gradual decrease of CK-MB and cTT levels at 6 and 12 h PO than at 0 hr PO, with nonsignificant differences between patients who received VP or NE infusions for catecholamine-unresponsive shock after cardiac surgery.

Moreover, correction of hypotension improved tissue perfusion and oxygenation as reflected by progressive decrease of BL concentrations with concomitant increased LCR. Despite the reported nonsignificant difference between effect of NE and TP on BL levels, LCR was significantly higher with TP than with NE at 4 and 12 h PO. Such finding goes in hand with Wacharasint *et al.* [33] who predicted a beneficial response of high BL concentration in patients with septic shock to VP than NE and with Barzegar *et al.* [34] who documented that LCR after 24 h was significantly higher with VP than NE infusions.

The reported significantly higher LCR with TP could be attributed to improved patients' microcirculation with subsequent improved substrate utilization. In line with this suggestion, Barzegar *et al.* [34] attributed improved LCR to the effect of VP on tissue hypoperfusion or to its catecholamine-sparing effect, and Hessler *et al.* [35] documented that VP-receptor agonists do not negatively influence macrovascular and microvascular coupling as compared with NE, and a higher selectivity for the V1a-receptor seems to improve microvascular circulation.

Conclusion

Refractory hypotension after on-pump CABG has deleterious effects on body hemodynamics and tissue perfusion and oxygenation. Vasopressor infusion allowed improved hemodynamics. TP infusion is more appropriate for these patients, especially diabetics who were vulnerable to develop hyperglycemic complications that may be aggravated by the glucogenic effect of NE. Moreover, TP was found to be better for improving tissue perfusion; thus, it facilitated shift from anaerobic to aerobic cellular respiration and protected kidneys against injury.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Huang CJ, Kuok CH, Kuo TB, Hsu YW, Tsai PS. Pre-operative measurement of heart rate variability predicts hypotension during general anesthesia. Acta Anaesthesiol Scand 2006; 50:542–548.

2 Oakley I, Emond L. Diabetic cardiac autonomic neuropathy and anesthetic management: review of the literature. AANA J 2011; 79: 473–479.

3 Lozano T, Ena J. Cardiovascular autonomic neuropathy in patients with diabetes mellitus. Rev Clin Esp 2017; 217:46–54.

4 Omar S, Zedan A, Nugent K. Cardiac vasoplegia syndrome: pathophysiology, risk factors and treatment. Am J Med Sci 2015; 349: 80–88.

5 Carley M, Schaff J, Lai T, Poppers J. Methylene blue for vasoplegia when on cardiopulmonary bypass during double-lung transplantation. A Case Rep 2015; 5:127–130.

6 Levin MA, Lin HM, Castillo JG, Adams DH, Reich DL, Fischer GW. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. Circulation 2009; 120:1664–1671.

7 Kortekaas KA, Lindeman JH, Reinders ME, Palmen M, Klautz RJ, de Groot PG, *et al.* Pre-existing endothelial cell activation predicts vasoplegia after mitral valve surgery. Interact Cardiovasc Thorac Surg 2013; 17:523–530.

8 Hossne Junior NA, Miranda M, Monteiro MR, Branco JN, Vargas GF, Pestana JO, *et al.* Cardiopulmonary bypass increases the risk of vasoplegic syndrome after coronary artery bypass grafting in patients with dialysis-dependent chronic renal failure. Rev Bras Cir Cardiovasc 2015; 30:482–488.

9 Jentzer JC, Coons JC, Link CB, Schmidhofer M. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. J Cardiovasc Pharmacol Ther 2015; 20:249–260.

10 Moreau R, Asselah T, Condat B, de Kerguenec C, Pessione F, Bernard B, *et al.* Comparison of the effect of terlipressin and albumin on arterial blood volume in patients with cirrhosis and tense ascites treated by paracentesis: a randomised pilot study. Gut 2002; 50:90–94.

11 Rodriguez-Perez F, Groszmann RJ. Pharmacologic treatment of portal hypertension. Gastroenterol Clin North Am 1992; 21:15–40.

12 Blei AT, Groszmann RJ, Gusberg R, Conn HO. Comparison of vasopressin and triglycyl-lysine vasopressin on splanchnic and systemic hemodynamics in dogs. Dig Dis Sci 1980; 25:688–694.

13 Nilsson G, Lindblom P, Ohlin N, Berling R, Vernersson E. Pharmacokinetics of terlipressin after single I.V. doses to healthy volunteers. Drug Exp Clin Res 1990; 16:307–314.

14 Won YJ, Lim BG, Chung D, Park E, Kim H, Lee IO, *et al.* Use of terlipressin in an elderly patient with moderate aortic valve stenosis accompanied by episodic atrial fibrillation during liver transplantation: a case report. Transplant Proc 2016; 48:3203–3206.

15 Mizock BA, Falk JL. Lactic acidosis in critical illness. Crit Care Med 1992; 20:80–93.

16 Kraemer HC, Theimann S. How many subjects? Statistical power analysis in research. Newbury Park, CA: Sage 1987.

17 Murphy KR, Myors B. Statistical power analysis: a simple and general model for traditional and modern hypothesis tests. 2nd ed. Mahwah, NJ: Lawrence Erlbaum Associates Inc.; 2003.

18 Masetti P, Murphy SF, Kouchoukos NT. Vasopressin therapy for vasoplegic syndrome following cardiopulmonary bypass. J Card Surg 2002; 17:485–489.

19 Hasija S, Makhija N, Choudhury M, Hote M, Chauhan S, Kiran U. Prophylactic vasopressin in patients receiving the angiotensin-converting enzyme inhibitor ramipril undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2010; 24:230–238.

20 Elgebaly AS, Sabry M. Infusion of low-dose vasopressin improves left ventricular function during separation from cardiopulmonary bypass: a double-blind randomized study. Ann Card Anaesth 2012; 15:128–133.

21 Yimin H, Xiaoyu L, Yuping H, Weiyan L, Ning L. The effect of vasopressin on the hemodynamics in CABG patients. J Cardiothorac Surg 2013; 8:49.

22 Ibrahim N, Hasanin A, Allah SA, Sayed E, Afifi M, Yassen K, *et al.* The haemodynamic effects of the perioperative terlipressin infusion in living donor liver transplantation: a randomised controlled study. Indian J Anaesth 2015; 59:156–164.

23 Xiao X, Zhang J, Wang Y, Zhou J, Zhu Y, Jiang D, *et al.* Effects of terlipressin on patients with sepsis via improving tissue blood flow. J Surg Res 2016; 200:274–282.

24 Choudhury A, Kedarisetty CK, Vashishtha C, Saini D, Kumar S, Maiwall R, *et al.* A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock. Liver Int 2016; 37:552–561.

25 Goyal O, Sidhu SS, Sehgal N, Puri S. Noradrenaline is as effective as terlipressin in hepatorenal syndrome type 1: a prospective, randomized trial. J Assoc Physicians India. 2016; 64:30–35.

26 Connolly CC, Steiner KE, Stevenson RW, Neal DW, Williams PE, Alberti KG, *et al.* Regulation of glucose metabolism by norepinephrine in conscious dogs. Am J Physiol 1991; 261(Pt 1):E764–E772.

27 Liang Y, Cincotta AH. Increased responsiveness to the hyperglycemic, hyperglucagonemic and hyperinsulinemic effects of circulating norepinephrine in ob/ob mice. Int J Obes Relat Metab Disord 2001; 25: 698–704.

28 Van den Thillart G, Vianen G, Ponce MC, Lelieveld H, Nieveen M, van Raaij M, *et al.* Differential role of adrenoceptors in control of plasma glucose and fatty acids in carp, Cyprinus carpio (L.). Am J Physiol Regul Integr Comp Physiol 2001; 281:R615–R624.

29 Aoyagi T, Birumachi J, Hiroyama M, Fujiwara Y, Sanbe A, Yamauchi J, *et al.* Alteration of glucose homeostasis in V1a vasopressin receptor-deficient mice. Endocrinology 2007; 148:2075–2084.

30 Taveau C, Chollet C, Waeckel L, Desposito D, Bichet DG, Arthus MF, *et al.* Vasopressin and hydration play a major role in the development of glucose intolerance and hepatic steatosis in obese rats. Diabetologia 2015; 58: 1081–1090.

31 Taveau C, Chollet C, Bichet DG, Velho G, Guillon G, Corbani M, *et al.* Acute and chronic hyperglycemic effects of vasopressin in normal rats, involvement of v1a receptors. Am J Physiol Endocrinol Metab. 2016; 312:E127–E135.

32 Okamoto Y, Nohmi T, Higa Y, Seki K, Yamashita A. Vasopressin does not raise cardiac enzymes following cardiac surgery: a randomized double-blind clinical trial. J Cardiothorac Vasc Anesth 2015; 29:46–51.

33 Wacharasint P, Nakada TA, Boyd JH, Russell JA, Walley KR. Normal-range blood lactate concentration in septic shock is prognostic and predictive. Shock 2012; 38:4–10.

34 Barzegar E, Ahmadi A, Mousavi S, Nouri M, Mojtahedzadeh M. The therapeutic role of vasopressin on improving lactate clearance during and after vasogenic shock: microcirculation, is it the black box? Acta Med Iran 2016; 54:15–23.

35 Hessler M, Kampmeier TG, Rehberg S. Effect of non-adrenergic vasopressors on macro-and microvascular coupling in distributive shock. Best Pract Res Clin Anaesthesiol 2016; 30:465–477.