

Effect of norepinephrine and phenylephrine on lactate levels during cardiopulmonary bypass in diabetic patients

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Abstract

Objective: To determine the effect of norepinephrine and phenylephrine on lactate levels in diabetic patients during on-pump coronary artery bypass grafting procedure.

Method: The quasi-experimental study was conducted at the Armed Forces Institute of Cardiology, National Institute of Heart Diseases, Rawalpindi, Pakistan, from June 2023 to January 2024, and comprised type-2 diabetic patients of either gender aged 18-65 years underwent on-pump coronary artery bypass grafting. The patients were non-randomly allocated into groups I and II. To maintain mean arterial pressure 65-90mmHg during the procedure, Group I was given phenylephrine 0.2-0.3mg diluted in 50ml normal saline, while Group II was given norepinephrine 0.05-0.1 mg diluted in 50ml normal saline. Serum lactate levels were measured before anaesthesia induction, before cardiopulmonary bypass, at cooling, at rewarming and before shifting to the intensive care unit. The effect of vasopressor type on serum lactate levels was evaluated. Data was analysed using SPSS 25.

Result: Of the 140 patients, 70(50%) were in Group I; 47(67.1%) male and 23(32.9%) female with mean age 55.50 ± 7.34 years. There were 70(50%) patients in Group II; 50(71.4%) male and 20(28.6%) female with mean age 55.36 ± 6.79 years ($p > 0.05$). Overall, 45(32.1%) patients had controlled diabetes, while 95(67.9%) had uncontrolled diabetes. Group II patients demonstrated higher mean lactate levels during cooling, rewarming and prior to intensive care unit transfer ($p < 0.05$).

Conclusion: Phenylephrine demonstrated better metabolic control, suggesting it may be a preferable vasopressor in diabetic patients during cardiac surgery.

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Introduction

Cardiopulmonary bypass machine (CPB) plays an essential role in cardiac surgery, especially in procedures such as coronary artery bypass grafting (CABG). As a temporary substitute, CPB temporarily takes over the heart and lungs' functions, maintaining adequate systemic perfusion, oxygenation and temperature control during surgery. While the use of CPB is vital for maintaining circulatory stability, it also presents several challenges, particularly relating to tissue perfusion and oxygenation.^{1,2} Despite significant advancements in CPB techniques, lactic acidosis develops in roughly one-third of patients during CPB, which correlates with tissue hypoperfusion, increased in-hospital mortality, Low-Cardiac-Output Syndrome (LCOS), prolonged intensive care unit (ICU) stay, organ dysfunction, and other postoperative complications, highlighting the necessity to minimise lactate accumulation and to preserve

adequate tissue perfusion.^{3,4} Serum lactate sampling offers a sensitive indicator of hypoperfusion during CPB, particularly when mixed venous oxygen saturation (SvO₂) and pulse oximetry readings become unreliable under hypothermic conditions.⁵ Moreover, intraoperative lactate concentrations exceeding 5mmol/L have been independently linked to higher in-hospital mortality and postoperative complication rates.

Preserving mean arterial pressure (MAP) within a narrow window during CPB is vital to maintaining the perfusion of critical organs. The European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Cardiothoracic Anaesthesiology and Intensive Care (EACTAIC), and the European Board of Cardiovascular Perfusion (EBCP) 2024 guidelines recommend a MAP target of 50-80mmHg throughout adult CPB.^{6,7} To achieve this, clinicians administer vasopressors routinely, most notably norepinephrine and phenylephrine, which raise systemic vascular resistance and thereby sustain arterial pressure.⁸ By augmenting vascular tone, these agents support MAP and help preserve cardiac output and end-organ blood flow.⁹

In Pakistan, type 2 diabetes mellitus (T2DM) is present in 64% of CABG patients, and impairs microcirculatory flow

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via hyperglycaemia-driven endothelial dysfunction and exaggerated alpha (α)-adrenergic vasoconstriction. Metabolic inflexibility and reduced mitochondrial oxidative capacity further compromise lactate uptake and oxidation, leading to diminished clearance.¹⁰⁻¹³ Although both norepinephrine and phenylephrine have been extensively evaluated for their haemodynamic actions, to our knowledge, no study to date has directly compared their effects on perioperative lactate kinetics in T2DM patients undergoing on-pump CABG. The current study was planned to fill the gap in literature by comparing serial serum lactate trajectories in diabetic CABG patients receiving norepinephrine versus phenylephrine during CPB, hypothesising that phenylephrine would attenuate lactate elevations more effectively.

Patients and Methods

The quasi-experimental study was conducted at the Armed Forces Institute of Cardiology (AFIC), National Institute of Heart Disease (NIHD), Rawalpindi, Pakistan, from June 2023 to January 2024. After approval from the institutional ethics review board, the sample size was calculated using OpenEpi calculator¹⁴ in the light of literature¹⁵ with 90% power, 95% confidence interval (CI) and 5% margin of error. The final sample was inflated by >80% to enhance statistical precision, improve external validity, and account for potential exclusions due to intraoperative protocol deviations. A non-probability, consecutive sampling technique was used to enrol eligible patients.

Those included were patients of either gender aged 18-65 years with T2DM, diagnosed on the basis of fasting plasma glucose (FPG) ≥ 126 mg/dL, 2-hour plasma glucose ≥ 200 mg/dL during oral glucose tolerance test (OGTT), or glycated haemoglobin (HbA1c) $\geq 6.5\%$. OGTT data was extracted from preoperative reports. Also, the patients were classified as American Society of Anaesthesiologists (ASA) grade II or III, and had stable haemodynamics (systolic blood pressure [SBP] >90 mmHg and heart rate [HR] 60-100bpm), and had aortic cross-clamp time ≤ 120 minutes. Written consent prior to inclusion was obtained from all the patients. Patients with severe liver or kidney disease, uncontrolled hypertension, valvular heart disease, septal defects, aortic aneurysm/dissection, or those requiring emergency surgeries were excluded. Pregnant or breastfeeding women, patients with a history of severe allergic reactions to norepinephrine or phenylephrine, and those using drugs that could interact with these vasopressors were also excluded.

Allocation to phenylephrine Group I and norepinephrine Group II was performed using a non-random, consecutive allocation strategy based on the attending cardiac

anaesthesiologist's intraoperative preference and standard departmental practice at the time of surgery. No computer-generated randomisation or allocation concealment was applied, giving the study an open-label design. Blinding of clinicians was not feasible due to the pharmacological differences and preparation protocols of the vasopressors. However, laboratory personnel measuring serum lactate levels were not involved in group allocation.

During CPB, vasopressors were administered as intermittent IV boluses to maintain MAP at 65-90mmHg, consistent with departmental practice at our institution and in line with a prior AFIC-based study comparing phenylephrine and noradrenaline during CPB, which used the same MAP target range.¹⁵ Phenylephrine was administered to Group I patients in bolus doses of 0.2-0.3mg diluted in 50mL normal saline, while norepinephrine was given to Group II in bolus doses of 0.05-0.1mg diluted in 50ml normal saline. Dosing was not weight-based, but titrated to achieve the predefined MAP target. The selected dose ranges reflected commonly used Equi pressor bolus doses in adult cardiac surgery practice, and were determined based on departmental standard operating procedures (SOPs).

Serum lactate levels were measured at multiple time points of the surgery. The primary outcome was serum lactate level measured immediately before shifting to ICU, while serum lactate levels before anaesthesia induction, before CPB initiation, at cooling, and at rewarming were taken as secondary outcomes, and measured using the Stat Profile Ultra C analyzer (Nova Biomedical, Waltham, MA). The same anaesthetic protocol was adhered to for all patients, including midazolam, morphine, propofol, cisatracurium and ventilation support.

Data was collected using standardised proforma. Data was analysed using SPSS 25. Continuous variables were presented as mean $\pm$ standard deviation (SD), while categorical variables were reported as frequencies and percentages. Baseline continuous variables were compared between the groups using independent samples t-test, whereas categorical variables were analysed using the chi-square test. A mixed repeated-measures analysis of variance (ANOVA) was employed to compare mean lactate levels across time points within and between the groups. A mixed repeated-measures ANOVA was performed to evaluate the effect of vasopressor type on serum lactate levels across five intraoperative time points. Mauchly's test and Greenhouse-Geisser correction were used where necessary. $P \leq 0.05$ was considered statistically significant.

Results

Of the 60 patients assessed, 140(87.5%) were included

(Figure 1). Of them, 70(50%) were in Group I; 47(67.1%) male and 23(32.9%) female with mean age 55.50 ± 7.336 years. There were 70(50%) patients in Group II; 50(71.4%) male and 20(28.6%) female with mean age 55.36 ± 6.785 years. Overall, 45(32.1%) patients had controlled diabetes,

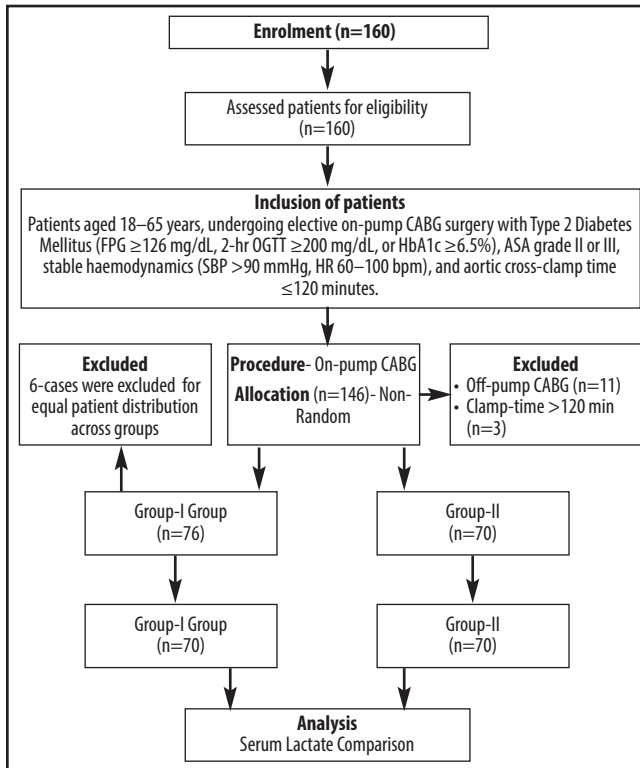


Figure-1: The patient recruitment process.

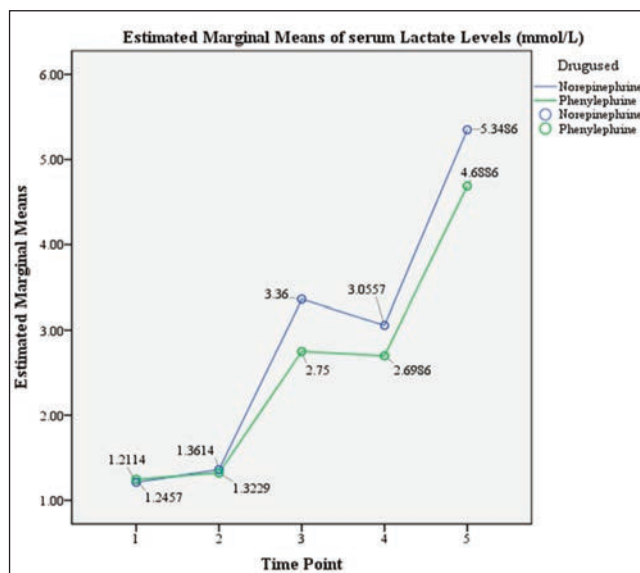


Figure-2: Trend of serum lactate levels over time in norepinephrine and phenylephrine groups (time points: 1=before anaesthesia induction, 2=before cardiopulmonary bypass [CPB], 3=at cooling, 4=at rewarming, 5=before shifting to the intensive care unit [ICU]).

while 95(67.9%) had uncontrolled diabetes. There were no significant differences between the groups (Table 1).

Estimated marginal means demonstrated comparable baseline lactate levels between the groups, but lactate concentrations were consistently higher in Group II during cooling, rewarming and post-CPB ($p < 0.05$). After CPB and before the patients' shifting to ICU, Group II demonstrated a higher mean lactate concentration effect compared to Group I (5.35 ± 0.22 mmol/L [95% CI: 4.917–5.780 mmol/L] vs 4.69 ± 0.22 mmol/L [95% CI: 4.257–5.120 mmol/L]) vs While evaluating the effect of vasopressor type on serum lactate levels across the five intraoperative time points, it was seen that the assumption of sphericity was violated ($p < 0.001$). Therefore, Greenhouse-Geisser correction was applied ($\epsilon = 0.597$). There was a significant main effect of

Table-1: Baseline characteristics of the study participants (n=140).

Parameters	Group-I Phenylephrine (n=70)	Group-II Norepinephrine (n=70)	p-value
Gender n(%)			
Male	47(67.1%)	50(71.4%)	0.714
Female	23(32.9%)	20(28.6%)	
Mean Age (years)	55.50 ± 7.336	55.36 ± 6.785	0.905
Haemoglobin (g/dL)	13.30 ± 1.741	13.28 ± 1.677	0.939
Ejection Fraction (%)	48.31 ± 8.317	48.80 ± 9.180	0.743
HbA1c (%)	8.42 ± 2.252	8.29 ± 2.163	0.728
HbA1c <7.0%	23(32.9%)	22(31.4%)	1.00
HbA1c ≥7.0%	47(67.1%)	48(68.6%)	
Blood Pressure (mmHg)	119.91 ± 17.24	123.73 ± 18.411	0.208
ASA Status n(%)			
ASA-II	6(8.6%)	4(5.7%)	0.743
ASA-III	64(91.4%)	66(94.3%)	

HbA1c: Glycated haemoglobin, ASA: American Society of Anaesthesiologists.

Table-2: Serum lactate levels (mmol/L) at different time points in the study groups.

Drug Used	Time Point	Mean±SE (mmol/L)	95% Confidence Interval
Norepinephrine	Before anaesthesia induction	1.21 ± 0.05	1.106-1.316
	Before CPB	1.36 ± 0.08	1.214-1.509
	At Cooling	3.360 ± 0.11	3.139-3.581
	At rewarming	3.06 ± 0.12	2.818-3.293
	Before shifting to ICU	5.35 ± 0.22	4.917-5.780
Phenylephrine	Before anaesthesia induction	1.25 ± 0.05	1.141-1.351
	Before CPB	1.32 ± 0.08	1.175-1.470
	At Cooling	2.75 ± 0.11	2.529-2.971
	At rewarming	2.69 ± 0.12	2.461-2.936
	Before shifting to ICU	4.69 ± 0.22	4.257-5.120

SE: Standard error, CPB: Cardiopulmonary bypass, ICU: Intensive care unit.

Table-3: Effect of time points and vasopressor type on serum lactate levels.

Effect	F-value	p-value	Partial η^2
Time Point (Greenhouse-Geisser corrected)	316.47	<0.001	0.696
Time Point × Drug Interaction	3.36	0.028	0.024
Drug (Between-subjects effect)	11.77	0.001	0.079

time on lactate levels ($p < 0.001$), representing changes in lactate concentration during CPB. A significant interaction was observed between time and the vasopressor group ($p = 0.028$), indicating that lactate trajectories differed between the groups. Additionally, a significant between-subjects effect was found ($p = 0.001$), with Group II having higher overall lactate levels compared to Group I (Table 3).

Discussion

The present study evaluated the effect of norepinephrine and phenylephrine on intraoperative serum lactate dynamics in T2DM patients undergoing on-pump CABG. Baseline demographic and clinical variables were comparable between the groups, thereby limiting potential confounding from preoperative factors. A significant effect of time on lactate levels ($p < 0.001$) was notable, reflecting the expected intraoperative rise during CPB. A significant between-subject effect of vasopressor type was also observed ($p = 0.001$), with higher overall lactate concentration in the norepinephrine group. Furthermore, a significant time-by-drug interaction ($p = 0.028$) suggested that the magnitude of lactate elevation varied across intraoperative phases, depending on vasopressor choice. Specifically, norepinephrine was associated with higher lactate levels during cooling, rewarming and prior to ICU transfer ($p < 0.05$) despite comparable MAP targets.

Although these differences were statistically significant, their clinical relevance warrants careful interpretation. A prior large-scale analysis has demonstrated that arterial lactate levels exceeding 5 mmol/L during CPB are associated with increased in-hospital mortality and postoperative complications, including renal dysfunction and prolonged ICU stay.⁴ In the present study, the mean lactate levels prior to ICU transfer slightly exceeded this threshold in the norepinephrine group (5.35 mmol/L), whereas those in the phenylephrine group remained below it (4.69 mmol/L). While the absolute difference of approximately 0.66 mmol/L may appear modest, crossing an established prognostic threshold may reflect a clinically meaningful increase in metabolic stress during CPB, particularly in diabetic patients with microvascular dysfunction. However, as postoperative outcomes were not directly assessed in the current cohort, these findings should be interpreted with caution.

Moreover, the distinct pharmacology of norepinephrine and phenylephrine likely explains the current findings. Phenylephrine, a selective α -agonist, increases vascular resistance without engaging beta (β)-adrenergic pathways. By contrast, norepinephrine's combined α/β activity sustains MAP while activating β_1 - and β_2 -receptors in peripheral tissues, thereby enhancing cyclic adenosine

monophosphate (cAMP)-mediated glycolysis and glycogenolysis. This non-hypoxic hyperlactataemia mechanism, demonstrated in astrocyte models where norepinephrine increased lactate output by 20-50% via β_1 -receptor and cAMP signalling,¹⁶⁻¹⁹ provides a compelling explanation for the elevated lactate trajectories observed in the current study's norepinephrine group. Furthermore, in diabetic patients who already exhibit endothelial dysfunction and impaired lactate clearance, such β -adrenergic-driven metabolic stimulation may be even more pronounced.

Evidence from animal models further reinforces a dual effect of norepinephrine on perfusion and regional hypoxia. In atherosclerotic rabbits, prolonged norepinephrine infusion reduced vasa vasorum flow and upregulated hypoxia-inducible factor- α (HIF- α) and vascular endothelial growth factor (VEGF), indicating localised hypoxia.²⁰ Similarly, in a rabbit model of endotoxic shock, norepinephrine maintained systemic pressure but decreased jejunal mucosal perfusion, underscoring its potential to compromise splanchnic flow independent of preserved macrocirculatory pressure.²¹ In contrast, phenylephrine's exclusive α -agonism appears to spare terminal microcirculatory beds²² in diabetics, thereby preserving capillary perfusion and minimising ischaemic insult.

The current findings align with Abdullah et al., who reported higher lactate levels with norepinephrine versus phenylephrine during CPB in non-diabetic CABG patients.¹⁵ However, their cohort excluded diabetic individuals, a key distinction given this population's additional metabolic and microvascular vulnerabilities. In contrast, Canty et al. observed that a low-dose norepinephrine infusion (3-5 $\mu\text{g min}^{-1}$) throughout on-pump bypass reduced haemodilution and intraoperative red blood cell (RBC) transfusion without raising serum creatinine, and implied preserved tissue perfusion with stable lactate levels,²³ highlighting that norepinephrine's metabolic effects may differ by dosing regimen and patient characteristics. Conversely, Ziyaeifard et al. found no differences in haemodynamics, arterial blood gases, or cerebral oxygenation among epinephrine, norepinephrine and phenylephrine during CPB,²⁴ highlighting that vasopressor effects on metabolism may vary by patient group and study design.

The current study has several limitations. First, it employed a single-centre, quasi-experimental design without randomisation, which may have introduced selection bias and limited generalisability of the findings. Second, the study's scope was confined to serial serum lactate measurements at predefined CPB stages, and it did not

assess direct mechanistic endpoints, such as micro-circulatory flow, tissue oxygenation or receptor-specific signalling. Third, the context for vasopressor comparison in diabetic CPB patients remains poorly represented in the literature, restricting the depth of comparative discussion. Finally, while the current findings generate hypotheses regarding β -adrenergic-driven lactate production and α -mediated perfusion effects, prospective, multicentre randomised controlled trials (RCTs) and targeted mechanistic studies are required to confirm causality and to inform optimal vasoconstrictor selection.

Conclusion

Norepinephrine significantly elevated serum lactate levels compared to phenylephrine in diabetic patients undergoing CABG with CPB. Despite similar lactate levels before anaesthesia induction and CPB initiation, norepinephrine's effect on lactate was notably higher during cooling, rewarming and at the end of CPB, suggesting that phenylephrine may be a preferable option for managing lactate levels during CPB in diabetic patients, potentially influencing clinical decisions regarding vasopressor use in this population.

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Conflict of Interest: None.

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Author Contribution:

HN: Study design, data acquisition, analysis, interpretation, drafting, critical review and final approval.

MIA: Concept, study design, critical review and final approval.

NA: Study design, data analysis, interpretation, drafting, critical review and final approval.

MRN: Concept, data acquisition, critical review and final approval.