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Target blood pressure management during cardiopulmonary bypass improves lactate level after cardiac surgery: A randomized controlled trial

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Abstract

Background: Hyperlactacidemia seriously affects the prognosis of cardiac surgery patients. This study was to explore the impact of target blood pressure management during cardiopulmonary bypass (CPB) on blood lactate level after cardiac surgery.

Methods: Enrolled in this study were patients ≥ 18 years who were scheduled for cardiac valve surgery between January, 2020 and June, 2020 at Shanghai Chest Hospital. The enrolled patients were randomized into a low mean arterial pressure (L-MAP) group (target MAP between 50-60mmHg) and a high mean arterial pressure (H-MAP) group (target MAP between 70-80 mmHg). Norepinephrine was titrated during CPB to maintain MAP at the target level. Blood lactate levels in the two groups were detected before operation (T0), at the end of CPB (T1), at the end of operation (T2), 1 h after operation (T3), 6 h after operation (T4) and 24 h after operation (T5) as the primary outcome. The secondary outcome was the dose of epinephrine and dopamine within 24 h after operation, at the time of extubation, during ICU stay, at the time of readmission within 30 days, and mortality in 1 year.

Results: There was no significant difference in blood lactate level between the two groups at T0, T4 and T5. The lactate level in H-MAP group was significantly lower than that in L-MAP group (1.68 ± 0.73 , 2.33 ± 0.93 and 2.90 ± 1.09 $\text{mM} \cdot \text{L}^{-1}$ vs. 2.29 ± 1.12 , 3.63 ± 1.86 and 4.60 ± 2.24 $\text{mM} \cdot \text{L}^{-1}$) at T1, T2 and T3. The dose of epinephrine within 24 h after operation, at the time of extubation and during ICU stay in L-MAP group was significantly higher than that in H-MAP group.

Conclusions: Target MAP management in patients with relatively high levels of MAP during CPB could decrease the blood lactate level, reduce epinephrine consumption, and shorten the time of extubation and length of ICU stay after surgery, thus improving the prognosis of cardiac surgery

patients.

Trial registration: This single-center single-blind RCT has completed the registration of the Chinese Clinical Trial Center at 8/1/2020 with the registration number ChiCTR2000028941.

Key words: Target blood pressure; cardiopulmonary bypass; mean arterial pressure; lactate; cardiac surgery

Background

Hyperlactacidemia usually occurs after cardiac surgery, which may seriously affect the prognosis of patients concerned [1]. Some retrospective studies have shown that the increased blood lactate level is an independent risk factor of postoperative mortality in cardiac surgery patients[2]. Blood lactate level can also predict the prognosis of cardiac surgery patients[3]. Therefore, alleviating the postoperative hyperlactacidemia acquires vital importance in improving the prognosis of cardiac patients[4].

The blood flow presents a beating characteristic in normal heart activities. However, non-physiological advection perfusion is adopted during cardiopulmonary bypass (CPB) in many heart centers. Unlike advection perfusion that provides kinetic energy to normalize blood flow, pulsatile perfusion reduces potential energy under the same mean arterial pressure (MAP), resulting in decreased blood flow in capillaries and microcirculation perfusion. Thus, we supposed that a relative high MAP during CPB may benefit microcirculation perfusion in reducing blood lactate level, which is a sensitive indicator of bad microcirculation perfusion. Based on the Guidelines for CPB in 2019 European Adult Cardiac Surgery[5], it is safe to maintain the MAP between 50 and 80 mmHg during CPB. However, a higher MAP within the recommended range during CPB acquires a lower postoperative blood lactate level in clinical practices. To verify the observed clinical phenomenon, we conducted a randomized controlled trial (RCT) to observe the impact of target blood pressure management by norepinephrine titration[6] during CPB on the lactate level after cardiac surgery, hoping that the obtained results could provide guidance for blood pressure management during CPB so as to improve the prognosis of cardiac surgery patients.

Methods

Clinical data

This single-center single-blind RCT study was approved by the Shanghai Chest Hospital of Shanghai Jiaotong University research ethics board (KS1960) at 31/10/2019, and has completed the registration of the Chinese Clinical Trial Center at 8/1/2020 with the registration number ChiCTR2000028941. This study was performed by adhering to the Consolidated Standards of Reporting Trials (CONSORT) statement. Enrolled in the study were 40 patients who were scheduled for cardiac valve surgery in the Cardiovascular Surgery Department of Shanghai Chest Hospital (Shanghai, China) from January, 2020 to June, 2020. All the enrolled patients signed informed consent without knowing their groups. The inclusion criteria were patients older than 18 years with a New York Heart Association Class

(NYHAC) level II-III, blood lactate level $< 1.6 \text{ mM} \cdot \text{L}^{-1}$, alanine aminotransferase (ALT) $< 50 \text{ U} \cdot \text{L}^{-1}$, creatinine (Cr) $< 111 \text{ } \mu\text{M} \cdot \text{L}^{-1}$, blood urea nitrogen (BUN) $< 9.5 \text{ mM} \cdot \text{L}^{-1}$, and brain natriuretic peptide (BNP) $< 100 \text{ pg} \cdot \text{ml}^{-1}$ who required observation in the intense care unit (ICU) after surgery.

The exclusion criteria were patients who underwent reoperation within 24 h after the initial operation due to surgical factors.

Interventions and measurements

The enrolled patients were randomized into a low mean arterial pressure (L-MAP) group (target MAP between 50-60 mmHg) and a high mean arterial pressure (H-MAP) group (target MAP between 70-80 mmHg) based on the random numbers generated by EXCEL software in a 1:1 ratio.

The randomization sequence was generated by a staff not otherwise involved in the current study.

MAP in L-MAP group was controlled between 50-60 mmHg based on the clinical situation with

phenylephrine or vasodilator. MAP in H-MAP group was targeted between 70-80mmHg by intermittent intravenous phenylephrine (maximum dose in 2 mg), followed by norepinephrine pumping [maximum dose in $0.4 \mu\text{g}\cdot(\text{kg}\cdot\text{min})^{-1}$]. MAP was controlled above 65mmHg by epinephrine and dopamine after CPB and in the ICU. The blood lactate level in the two groups was measured before operation (T0), at the end of CPB (T1), at the end of operation (T2), 1 h after operation (T3), 6 h after operation (T4) and 24 h after operation (T5).

Study endpoints

The primary outcome was the blood lactate level at T0, T1, T2, T3, T4 and T5. The secondary outcome was the dose of epinephrine and dopamine within 24 h after operation, at the time of extubation, during ICU stay, at the time of readmission within 30 days, and at the time of death in 1 year.

Anesthesia and CPB

Patients in the two groups were treated with the same anesthesia and CPB management. Radial arterial cannulation and arterial blood gas analysis were carried out before anesthesia induction. General anesthesia was induced with $0.8 \mu\text{g}\cdot\text{kg}^{-1}$ sufentanil, $0.12 \text{ mg}\cdot\text{kg}^{-1}$ midazolam, $2 \text{ mg}\cdot\text{kg}^{-1}$ propofol and $0.15 \text{ mg}\cdot\text{kg}^{-1}$ Cis-atracurium intravenously. Drugs were target controlled and infused with propofol in $8 \text{ mg}\cdot(\text{kg}\cdot\text{h})^{-1}$, remifentanil in $0.1 \mu\text{g}\cdot(\text{kg}\cdot\text{h})^{-1}$ and Cis-atracurium in $0.1 \text{ mg}\cdot(\text{kg}\cdot\text{h})^{-1}$ in the maintenance period. All patients underwent CPB based on the Guidelines for CPB in 2019 European Adult Cardiac Surgery[5]. After splitting the sternum, CPB was established through the ascending aorta, superior and inferior vena cava. Cardioplegia was perfused through

the aortic root or coronary opening. CPB was prefilled with 1000 ml hydroxyethyl starch and 500 ml lactated Ringer. CPB started after systemic heparinization and ACT > 480 s. The perfusion flow was maintained at $2.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ and the mixed venous blood oxygen saturation was maintained above 75% in the mild hypothermia condition. Intraoperative blood glucose was controlled to $8 \text{ mM} \cdot \text{L}^{-1}$ by insulin infusion. The ascending aorta was blocked and myocardial protective solution was infused through the aortic root or coronary opening when the nasopharyngeal temperature was $32\text{-}34^{\circ}\text{C}$. After operation, rewarming, ascending aorta recovery, cardiac rebeating and auxiliary circulation were carried out until hemodynamics became stable and the nasopharyngeal temperature reached 36.8°C . CPB was stopped and protamine was injected to neutralize heparin. The patient was sent to the ICU for observation after surgery.

Statistical analysis

Continuous variables including age, body mass index (BMI), left ventricular ejection fraction (LVEF), clinical data and blood lactate level were recorded as the mean $\pm$ standard deviation (SD) and analyzed by independent t-test. Classified variables including sex, ASA classification, hypertension, diabetes prevalence, NYHAC and surgical types were recorded as numbers or percentages and analyzed by Chi-square test.

Sample size calculation

Hyperlactacidemia was defined as the blood lactate level above $3 \text{ mM} \cdot \text{L}^{-1}$ and the normal level was below $1.6 \text{ mM} \cdot \text{L}^{-1}$ in the perioperative period based on references. The study expected that the lactate level could be restored to the normal range through target blood pressure

management. The sample size was calculated by t-test of the mean difference between two groups. The test level was $\alpha = 0.05$, the test efficiency was $(1-\beta) = 0.8$, and the calculated sample size was 2×13 subjects. Finally, 2×20 subjects were enrolled to make up for data attrition and other causes of missing.

Results

Baseline characteristics

The basic characteristics of the enrolled patients are summarized in Table 1. There were no significant differences in age, sex, BMI, ASA classification, hypertension, diabetes prevalence, LVEF and NYHAC classification between the two groups.

Table 1 Baseline characteristics of the patients

Characteristics	L-MAP Group (n=20)	H-MAP Group (n=20)	<i>P</i> Value
Age (yr.)	58.10 ±13.68	59.70±13.3	0.827
Sex (M/F)	12/8	8/12	1.000
BMI (kg•m ⁻²)	23.61±3.53	22.94±4.57	0.500
ASA (II/III)	5/15	3/17	0.695
Hypertension, n(%)	7(35)	8 (40)	1.000
Diabetes prevalence, n(%)	1(5)	1 (5)	1.000
LVEF (%)	59.35±6.20	61.95±5.61	0.451
NYHAC (II/III)	7/13	12/8	0.205

Abbreviations: MAP, mean arterial pressure; BMI, body mass index; ASA, American Society of

Anesthesiologists; LVEF, left ventricular ejection fraction; NYHAC, New York Heart Association.

Clinical data

As shown in Table 2, the surgical types for all enrolled patients included: aortic valve replacement (AVR, $n=6$), aortic valvuloplasty (AVP, $n=3$), mitral valve replacement (MVR, $n=4$), mitral valvuloplasty (MVP, $n=3$), tricuspid valvuloplasty (TVP, $n=2$), simultaneous aortic and mitral valvuloplasty (AVP+MVP, $n=2$), simultaneous aortic valve replacement + mitral valve replacement (or mitral valvuloplasty) + tricuspid valvuloplasty (AVR+MVR/MVP+TVP, $n=8$), and simultaneous mitral valve replacement (or mitral valvuloplasty) + tricuspid valvuloplasty (MVR/MVP+TVP, $n=12$). There were no statistical differences in surgical types between the two groups. As shown in Table 3, there was no statistically significant difference between two groups in the heart rate (HR) before induction, HR at 30 min after CPB, HR at the end of operation, MAP before induction, MAP at 30 min after CPB, MAP at the end of operation, MAP at 1 h, 6 h and 24 h after operation, the time below the target blood pressure during CPB, hematocrit (HCT) during CPB, HCT at the end of surgery, blood glucose during CPB, surgery time, aortic occlusion time, CPB time, post CPB time, Cr after operation, Cr at 6 and 24 h after operation, BUN after operation, BUN at 6 and 24 h after operation, the dose of dopamine within 24 h after operation, urine volume during CPB, urine volume within 24 h after operation, at the time of readmission within 30 days, and at the time of death in 1 year. However, the dose of epinephrine within 24 h after operation, the time of extubation and days of ICU stay after surgery in L-MAP group were significantly higher than those in H-MAP group.

Table 2 Surgical types

Surgical types, n (%)	Low MAP Group (n=20)	High MAP Group (n=20)	P Value
AVR	1 (5)	5 (25)	
AVP	2 (10)	1 (5)	
MVR	3 (15)	1 (5)	
MVP	2 (10)	1 (5)	
TVP	0 (0)	2 (10)	
AVP+MVP	2 (10)	0 (0)	
AVR+MVR +TVP	0 (0)	2 (10)	
AVR+MVP+TVP	4 (20)	2 (10)	
MVR +TVP	5 (25)	1 (5)	
MVP+TVP	1 (5)	5 (25)	0.214

Abbreviations: MAP: mean arterial pressure; AVR: aortic valve replacement; AVP: aortic valvuloplasty; MVR: mitral valve replacement; MVP: mitral valvuloplasty; TVP: tricuspid valvuloplasty.

Table 3 Perioperative clinical data

Clinical Data	L-MAP Group (n=20)	H-MAP Group (n=20)	P Value
HR before induction (bpm)	78.3±6.8	81.2±5.8	0.321
HR at 30 min after CPB (bpm)	88.1±10.9	87.3±12.1	0.827
HR at end of operation (bpm)	91.9±8.3	87.4±10.8	0.147
MAP before induction (mmHg)	80.8±15.1	83±18.1	0.698
MAP at 30 min after CPB (mmHg)	65.9±9.4	67.0±8.3	0.697
MAP at end of operation (mmHg)	68.6±7.9	69.8±7.6	0.638
MAP at 1 h after operation (mmHg)	70.2±12.5	77.0±10.7	0.072
MAP at 24 h after operation (mmHg)	72.7±18.3	70.6±8.8	0.646
Time below target blood pressure during CPB (min)	8.5±8.0	8.5±10.0	1
HCT during CPB (%)	27.6±4.6	27.8±3.9	0.892
HCT at end of surgery (%)	31.5±4.1	30.3±3.5	0.317
Blood glucose during CPB (mM•L ⁻¹)	8.51±1.5	8.44±1.7	0.874
Surgery time (min)	277.3±44.4	266.3±72.4	0.576
Aortic occlusion time (min)	103.2±24.0	106.8±30.5	0.505
CPB time (min)	144.3±33.3	146.8±37.6	0.808
Post CPB time (min)	89.4±34.1	74.7±21.5	0.112
Creatinine after operation (μM•L ⁻¹)	78.2±20.8	6.6±2.0	0.558
Creatininr at 6 h after operation (μM•L ⁻¹)	78.8±24.8	6.7±1.6	0.690
Creatintin at 24 h after operation (μM•L ⁻¹)	76.5±22.1	8.3±3.1	0.706
Urea nitrogen after operation (mM•L ⁻¹)	74.7±16.4	6.4±2.3	0.774
Urea nitrogen at 6 h after operation (mM•L ⁻¹)	76.0±19.0	6.7±1.9	0.928
Urea nitrogen at 24 h after operation (mM•L ⁻¹)	79.6±29.7	8.2±3.0	0.935
Epinephrine within 24 h after operation (mg)	1.1±1.4	0.27±0.71	0.024*
Dopamine within 24 h after operation (mg)	251.3±201.6	149.4±164.6.8	0.088
Urine volume during CPB (ml)	455±281.9	695±539.7	0.086
Urine volume within 24 h after operation (ml)	3129.3±786.5	3003.5±668.5	0.589
Extubation time (h)	23.75±19.4	14.4±4.7	0.042*
Days of ICU stay (h)	53.6±27.4	33.1±14.9	0.008**
Readmission within 30 days (n)	0	0	null
Mortality in 1 year (%)	0	0	null

Statistically significant ($P<0.05$ ** $P<0.01$). Abbreviations: CPB: cardiopulmonary bypass; MAP:

mean arterial pressure; HCT: hematocrit; ICU: intensive care unit.

Blood lactate value

As shown in Table 4, there was no significant difference in blood lactate level between the two groups at T0, T4 and T5. Lactate level in H-MAP group was significantly lower than that in L-AP group (1.68 ± 0.73 , 2.33 ± 0.93 and 2.90 ± 1.09 $\text{mM}\cdot\text{L}^{-1}$ vs. 2.29 ± 1.12 , 3.63 ± 1.86 and 4.60 ± 2.24 $\text{mM}\cdot\text{L}^{-1}$) at T1, T2 and T3. In addition, lactate level in H-MAP group was under 3 $\text{mM}\cdot\text{L}^{-1}$ at T2 and T3, when it was still higher than 3 $\text{mM}\cdot\text{L}^{-1}$ in L-MAP group.

Table 4 Blood lactate level ($\text{mM}\cdot\text{L}^{-1}$)

Time points	Low MAP Group	High MAP Group	<i>P</i> Value
	(n=20)	(n=20)	
T0	1.14 ± 0.33	1.12 ± 0.40	0.890
T1	2.29 ± 1.12	1.68 ± 0.73	0.050*
T2	3.63 ± 1.86	2.33 ± 0.93	0.008**
T3	4.60 ± 2.24	2.90 ± 1.09	0.004**
T4	6.23 ± 4.45	4.29 ± 3.13	0.120
T5	2.35 ± 1.38	2.08 ± 1.24	0.503

Statistically significant ($P<0.05$ ** $P<0.01$)). Abbreviations: MAP: mean arterial pressure.

Discussion

The cause for hyperlactacidemia falls into two types: one is insufficient perfusion or hypoxia of the tissue such as shock or ischemia [7], and the other is activation of the pyruvate replacement pathway due to underlying diseases such as liver diseases, malignant tumors or mitochondrial myopathy [8]. Insufficient perfusion or hypoxia occurs widely during CPB after cardiac surgery,

which forms the focus of this study. Most currently available guidelines for the treatment of severe septic shock patients recommend the use of norepinephrine to increase MAP above 65 mmHg when the volume therapy loses effectiveness, which is believed to be beneficial to improving circulatory perfusion and lactic acidosis [9]. So sufficient MAP is the main controllable factor to ensure microcirculation perfusion. It is common knowledge that the lactate level directly reflects the perfusion condition and is closely related to the prognosis of patients. Thus, we hypothesized that organ perfusion could be improved by appropriately adjusting MAP during CPB although the perfusion flow is constant. In this study, we observed the impact of target blood pressure management during CPB on lactate level after cardiac surgery and found that the blood lactate level in H-MAP group was significantly lower than that in L-MAP group at the end of surgery and 24 h after surgery, suggesting that maintaining a relative higher perfusion pressure (MAP 70-80mmHg) during CPB was more conducive in improving perfusion and oxygen supply to reduce lactate level after surgery, and this conclusion was further confirmed by the shortened time of extubation, reduced length of ICU stay, and use of less epinephrine to circulation support during 24 h after operation in H-MAP group. In addition, MAP before anesthesia induction showed no significant difference between the two groups. Although studies have shown that blood pressure before anesthesia induction does not reflect the actual blood pressure of patients [10], maintaining the MAP close to the level before anesthesia induction during CPB will benefit the patients. Knowing that hyperlactacidemia during CPB is closely related to the postoperative mortality in cardiac surgery, it is important to redress the risk factors of hyperlactacidemia [11], which is defined as perioperative blood lactate level above $3 \text{ mM} \cdot \text{L}^{-1}$ [12]. In both groups, blood lactate reached the level of hyperlactacidemia at the end of surgery and 6 h after surgery.

However, the lactate level in H-MAP group was still significantly lower than that in L-MAP group. We further compared HR, MAP, HCT, blood glucose, surgery time, aortic occlusion time, and CPB time and post CPB time, finding no statistical differences between the two groups. In H-MAP group, blood lactate was under $3 \text{ mM} \cdot \text{L}^{-1}$ at the end of operation, and 1 h after operation by targeting MAP to 70-80 mmHg during CPB, while patients in L-MAP group were still in a hyperlactacidemic state, suggesting that insufficient perfusion is one of the key factors leading to hyperlactacidemia after cardiac surgery.

Most current studies on how to maintain a safer MAP during CPB focus on the relationship between MAP and postoperative acute kidney injury (AKI) or cognitive dysfunction. Although there was no significant difference in postoperative cognitive dysfunction between H-MAP group (70-80 mmHg) and L-MAP group (40-50 mmHg)[13, 14], maintaining a relative high MAP level during CPB could effectively reduce the occurrence of AKI [15]. However, there were no statistical differences in Cr, BUN and urine volume between the two groups in this study, mainly because we targeted MAP between 50-60 mmHg in L-MAP group instead of 40-50 mmHg. This result is consistent with the conclusion that maintaining high MAP during CPB could improve perfusion and reduce postoperative the lactate level.

We found that certain individual differences mattered much in target blood pressure management. Preoperative basic blood pressure and the antihypertensive drugs used by the patients should all be taken into consideration when performing blood pressure management precisely. There are also some limitations in this study. For instance, this is a single-center with a limited number of cases, and therefore multi-center larger-sample studies are required in the

future. Based on the finding that relative high MAP improved tissue perfusion during CPB, our future study will monitor the peripheral circulation during CPB by ultrasound and calculate oxygen supply and consumption for more convincing evidence [16].

Conclusion

Target MAP management between 70-80 mmHg during CPB could better ameliorate the lactate level after cardiac surgery compared with MAP between 50-60 mmHg. A relative high blood pressure may be more conducive to improving tissue perfusion and oxygen supply, reducing the lactate level, and shortening the time of extubation and length of ICU stay, all of which are beneficial to the prognosis of cardiac surgery patients.

Declarations

Abbreviations

CPB: cardiopulmonary bypass; ICU: intense care unit; NYHAC: New York Heart Association Class;

BMI: body mass index; LVEF: left ventricular ejection fraction; ASA: American Society of

Anesthesiologists ; HR: heart rate; HCT: hematocrit; Cr: creatinine; BUN: blood urea nitrogen;

MAP: mean arterial pressure; AVR: aortic valve replacement; AVP: aortic valvuloplasty; MVR:

mitral valve replacement; MVP: mitral valvuloplasty; TVP: tricuspid valvuloplasty.

Ethics approval and consent to participate

Written informed consent was obtained from all participants. The study was approved by the Shanghai Chest Hospital of Shanghai Jiaotong University research ethics board (KS1960) at 31/10/2019. This trial was registered on Chinese Clinical Trial Center at 8/1/2020 with the registration number ChiCTR2000028941. <http://www.chictr.org.cn/index.aspx>

Consent for publication

All authors agree for publication.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

Authors' contributions

J.W., B.H., conceived and designed the clinical study; Q.M., L.S., and X.Ch., performed the clinical study; D.W., and Zh.G., analyzed the data and drew graphs and tables; M.X., drafted this manuscript; All authors approved the final manuscript.

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CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



