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A comparison of postoperative blood lactate concentrations and kinetics in cardiac surgical patients receiving and not receiving metformin

Fotini Ampatzidou
Cardiothoracic ICU Department, George Papanikolaou General Hospital, Thessaloniki, Greece
https://orcid.org/0000-0003-0775-035X
Corresponding author: fampatzidou@gmail.com

Konstantinos Diplaris
Cardiothoracic ICU Department, George Papanikolaou General Hospital, Thessaloniki, Greece
https://orcid.org/0000-0003-3420-141X

Odysseas Drosos
BChir University of Cambridge, United Kingdom
https://orcid.org/0000-0001-7695-727X

George Drossos
Cardiothoracic ICU Department, George Papanikolaou General Hospital, Thessaloniki, Greece
https://orcid.org/0000-0002-5511-1272

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ABSTRACT

Aim. Early discontinuation of metformin before cardiac surgery is advised by several national societies, although no hard evidence exist supporting this practice. This precaution is mostly extrapolated by data on different clinical settings. The aim of this study is to investigate the impact of preoperative metformin use on lactate concentrations and lactate clearance during the first postoperative day following cardiac surgery.

Material and Methods. Among 367 consecutive patients who underwent elective on-pump cardiac surgery from January 2019 to October 2019, 109 were diabetics, 74 of whom were treated with metformin. Data on lactate concentrations and clearance during the first postoperative day were prospectively collected on arrival in the ICU, as well as after H6, H12 and H24 in the ICU and subsequently compared. A subgroup analysis focusing only on the diabetic patients was also performed. Repeated measures multivariate analysis of variance (MANOVA) was used to investigate the data on the basis of the group, time and their interaction effects.

Results. Lactate concentrations were the same for both groups upon arrival in the ICU. Interestingly, metformin users presented lower lactate concentrations than non-users on the following measurements ($p = 0.003$ at 6 h and $p = 0.01$ at 24 h). No significant interaction was found between the two groups ($p = 0.76$). No difference was found between the two groups in terms of lactate clearance ($p = 0.53$). In the subgroup analysis no difference was observed between metformin users and non-users, either on lactate concentrations ($p = 0.61$), or on lactate clearance ($p = 0.86$).

Conclusions. In the intensive care unit setting following heart surgery, the use of metformin up until the night before surgery was not associated with increased postoperative lactate concentrations or impaired lactate clearance.

Introduction

Metformin is a biguanide with excellent properties in terms of glycemic control which makes it a first choice oral agent for the treatment of patients with diabetes mellitus [1]. However, conflicting data exist regarding its impact on lactate kinetics [2, 3]. Moreover, its use has been associated with the Metformin Associated Lactic Acidosis (MALA), a rare, but potentially fatal complication, with a nearly 50% mortality rate, occurring mostly in patients with preexisting renal, cardiac or hepatic dysfunction [4].

Additionally, MALA is more common in metformin users with concomitant acute pathologic conditions, such as sepsis, acute liver dysfunction, tissue hypoperfusion, or acute kidney dysfunction due to hypovolemia.

This potential threat has lead several national societies and institutions to recommend its discontinuation prior to surgery [5–7].

Lactate and lactate elimination rate have a prognostic value in cardiac surgical patients [8, 9]. In this setting, however, hyperlactatemia could be due to either excess lactate production due to tissue hypoperfusion, or a decreased rate of lactate metabolism and clearance. High lactate concentration is an indicator of hemodynamic dysfunction. If metformin leads to an increase in lactate levels, it may be misinterpreted as hemodynamic compromise which should be rapidly corrected, particularly in this group of patients. This may result in unnecessary fluid resuscitation, or in the administration of inotropes. To this point no guidelines on the perioperative use of metformin have been issued by the European, or the American Associations of Anesthesiology. In our department, treatment with metformin is discontinued only on the day of the surgery, and it is restarted 48 hours postoperatively.

Aim

The aim of this study is to investigate whether the continued use of metformin prior to elective cardiac surgery has any impact on lactate concentrations and clearance during the early postoperative period.

Material and Methods

Study Design

In our department, 367 consecutive patients underwent elective on-pump cardiac surgery from January 2019 to October 2019. This group included 109 patients with diabetes mellitus, 74 of whom were treated with metformin. The rest of the diabetic patients (35 patients) were treated either with different oral agents, or with insulin. In our institution, we do not discontinue metformin prior to surgery in diabetic patients who use it to control their blood glucose levels.

For the purpose of this study, we compared postoperative blood lactate concentrations in patients using metformin (n = 74) and those of non-users (n = 293). A subgroup analysis focusing on the diabetic patients (n = 109) was also conducted to control for diabetes status as a possible confounder. Demographic and perioperative characteristics were recorded for the entire cohort.

In all patients, arterial blood samples were taken postoperatively on 4 time points: arrival in the ICU, H6, H12 and H24 after ICU arrival. Lactate concentration in mmol/L was measured in these samples with a Radiometer ABL800 FLEX point-of-care whole blood analyzer. As epinephrine may elevate lactate concentration without tissue hypoperfusion, its dose of continuous administration in μγ/Kg/min was recorded at the same time points. In order to exclude potential liver failure, causing a low lactate metabolism, the maximum values of liver enzymes, aspartate (AST) and alanine (ALT) transaminases, were recorded for each patient. Lactate concentrations and lactate clearance were compared between groups over time.

Lactate clearance was calculated using the following formula:

$$\frac{Lac\ ar - Lac\ t}{Lac\ ar}$$

where Lac ar. stands for the lactate concentration measured on arrival in the ICU and Lac_t for the lactate concentration at a specific time point (t).

Lactate clearance as defined here is an indicator of lactate elimination rate, and does not represent a pharmacokinetic parameter.

A positive value indicates a decrease in lactate blood concentration over time and, hence, its

clearance from the body, whereas a negative value indicates the inability to clear lactate from the blood circulation.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. Continuous variables are reported as means and standard deviation, whereas categorical values as counts and percentages. Comparisons between groups were performed using Wilcoxon signed-rank test for continuous variables, while comparisons of categorical variables were performed by means of the Chi-square test, or Fisher's exact test for extreme proportions, as appropriate. Statistical tests were based on a two-sided significance level of 0.05. The repeated measures multivariate analysis of variance (MANOVA) was performed to investigate the group, time and their interaction effects.

The SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) was used to perform statistical analyses. Any potential outlier was included in the analysis and no imputation methods were considered.

Results

Baseline characteristics and perioperative parameters for the entire cohort are shown in **Table 1**. Preoperative parameters did not differ between the two groups. Metformin users had a significantly shorter CPB time by a mean of 13 minutes. Data regarding lactate measurements are shown in **Table 2**. Lactate concentrations were the same for both groups upon arrival in the ICU. Interestingly, metformin users presented lower concentrations of lactates than non-users in terms of the following measurements.

Figure 1 shows lactate concentrations for the two patient groups over time. In both groups, lactate values significantly decreased over time indicating a good clearance from the body. The interaction between groups was not significant. As shown in **Figure 2** lactate clearance increased over time, although no significant difference was found between the two groups on MANOVA. (**Table 3**).

A subgroup analysis including only patients with diabetes mellitus was also performed. Pre and perioperative characteristics of these patients

Table 1. Demographics and baseline characteristics of patients on the entire cohort analysis

	All patients (n = 367)	Metformin users (n = 74)	Non metformin users (n = 293)	p-value
Age (y)	66.5 ± 10.0	67.0 ± 8.4	66.4 ± 10.4	0.933
Female gender(%)	67 (18.3%)	10 (13.5%)	57 (19.5%)	0.237
EuroScore II	2.0 ± 2.4	1.6 ± 1.2	2.1 ± 2.6	0.292
Body Mass Index	28.7 ± 4.6	29.1 ± 4.8	28.6 ± 4.5	0.481
Smokers	130 (35.4%)	27 (36.5%)	103 35.2%)	0.830
GFR	79.7 ± 24.8	80.9 ± 24.9	79.4 ± 24.8	0.885
GFR < 60ml/min	73 (19.9%)	16 (21.6%)	57 (19.5%)	0.676
Peripheral Vascular Disease	65 (17.7%)	16 (21.6%)	49 (16.7%)	0.324
Chronic Obstructive Pulmonary Disease	33 (9.0%)	10 (13.5%)	23 (7.8%)	0.123
NYHA status:				
1	209 (56.9%)	46 (62.2%)	163 (55.6%)	0.397
2	140 (38.1%)	27 (36.5%)	113 (38.6%)	
3	15 (4.1%)	1 (1.4%)	14 (4.8%)	
4	3 (0.8%)	0 (0%)	3 (1%)	
LV Ejection Fraction	54.0 ± 11.1	52.7 ± 10.9	54.3 ± 11.2	0.262
Bypass Time	105.0 ± 38.8	94.1 ± 39.3	107.7 ± 38.3	0.033

Table 2. Repeated measures Multivariate ANalysis Of VAriance of lactate concentrations in the entire cohort (N = 367)

Lactate concentration (mmol/L)	Metformin users (n = 74)	Non metformin users (n = 293)	p-value	Group Effect	Time Effect	Time*Group Effect
On arrival	3.7 ± 0.2	4.1 ± 0.1	0.2069	0.0338	<0.0001	0.7595
6h	2.9 ± 0.3	3.3 ± 0.1	0.1846			
12h	1.6 ± 0.2	2.1 ± 0.1	0.0035			
24 h	1.3 ± 0.1	1.7 ± 0.1	0.0112			

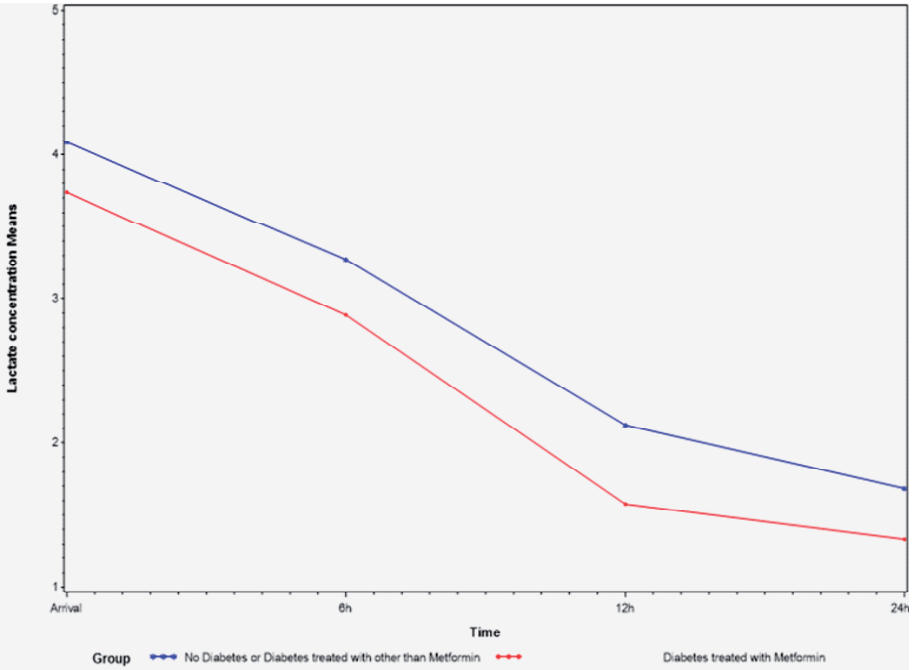

Figure 1. Lactate Concentration over time (all patients). In both groups (diabetics treated with metformin vs. the rest of the cohort), lactate levels significantly decreased over time

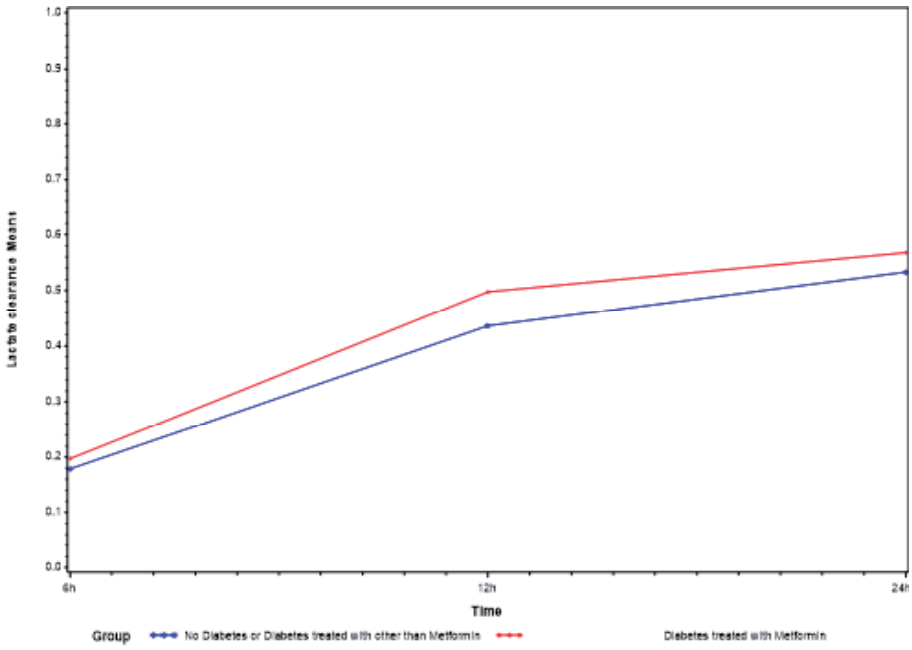

Figure 2. Lactate Clearance over time (all patients). Lactate clearance increased over time, although no significant difference was found between the two groups (diabetics treated with metformin vs. the rest of the cohort)

Table 3. Repeated measures Multivariate ANalysis Of VArianc of lactate clearance in the entire cohort (N = 367)

Lactate clearance	Metformin users (n = 74)	Non metformin users (n = 293)	p-value	Group Effect	Time Effect	Time*Group Effect
6h	0.2	0.2	0.7097	0.2536	<0.0001	0.5292
12h	0.5	0.4	0.1126			
24h	0.6	0.5	0.2552			

are presented in **Table 4**. Metformin users demonstrated a better patient profile with lower Euroscore II and a higher GFR than non-users. These findings were to be expected as insulin dependent diabetics are included in the non-metformin users group, and insulin dependent diabetes mel-

Table 4. Demographics and baseline characteristics of diabetic patients included in the subgroup analysis

	TOTAL (n = 109)	Metformin users (n = 74)	Non Metformin users (n = 35)	p-value
Age (y)	68.1 ± 8.4	67.0 ± 8.4	70.3 ± 8.1	0.059
Female gender	20 (18.3%)	10 (13.5%)	10 (28.6%)	0.058
EuroScore II	2.2 ± 2.5	1.6 ± 1.2	3.3 ± 3.9	0.026
Body Mass Index	28.9 ± 4.8	29.1 ± 4.8	28.4 ± 4.9	0.453
Smokers	35 (32.1%)	27 (36.5%)	8 (22.9%)	0.155
GFR	77.0 ± 25.7	80.9 ± 24.9	68.9 ± 25.8	0.041
GFR < 60ml/min	28 (25.7%)	16 (21.6%)	12 (34.3%)	0.158
Peripheral Vascular Disease	25 (22.9%)	16 (21.6%)	9 (25.7%)	0.635
Chronic Obstructive Pulmonary Disease	16 (14.7%)	10 (13.5%)	16 (17.1%)	0.294
NYHA status:				
1	65 (59.6%)	46 (62.2%)	19 (54.3%)	0.673
2	42 (38.5%)	27 (36.5%)	15 (42.9%)	
3	2 (1.8%)	1 (1.4%)	1 (2.9%)	
4	0 (0%)	0 (0%)	0 (0%)	
Preoperative LV Ejection Fraction	53.1 ± 11.2	52.7 ± 10.9	53.9 ± 11.9	0.619
Bypass time	100.4 ± 43.2	94.1 ± 39.3	113.7 ± 48.4	0.251

Table 5. Repeated measures Multivariate ANalysis Of VAriance of lactate concentrations in the subgroup of diabetic patients (N = 109)

Lactate concentration (mmol/L)	Metformin users (n = 74)	Non metformin users (n = 35)	p-value	Group Effect	Time Effect	Time*Group Effect
On arrival	3.7 ± 0.2	4.3 ± 0.3	0.2061	0.2045	<0.0001	0.6112
6h	2.9 ± 0.2	3.3 ± 0.3	0.3789			
12h	1.6 ± 0.1	1.8 ± 0.2	0.2517			
24h	1.3 ± 0.1	1.4 ± 0.1	0.3523			

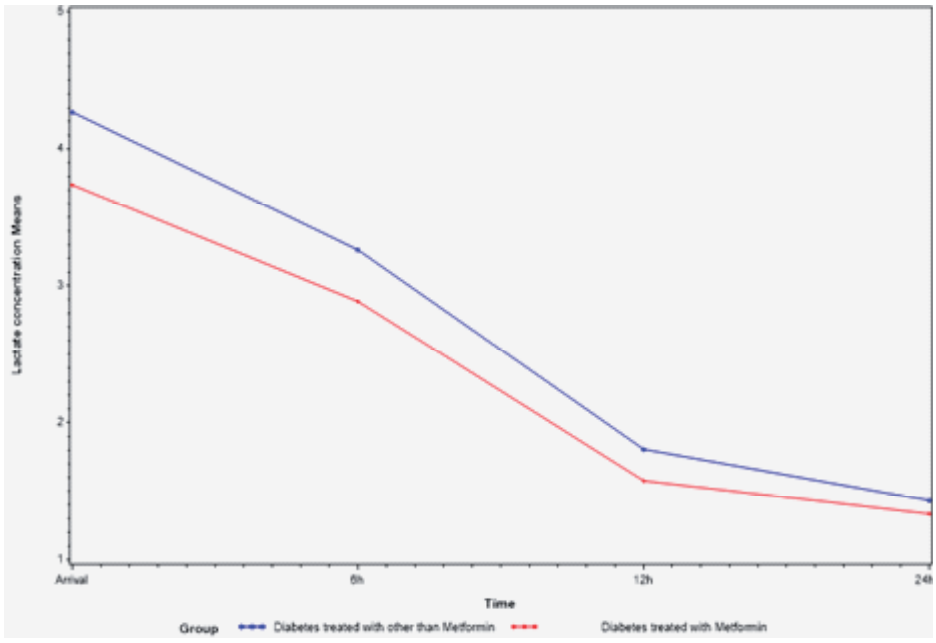

Figure 3. Lactate Concentration over time (diabetics). In both groups (diabetics treated with metformin vs. diabetics treated with other drugs, or insulin), lactate values significantly decreased over time

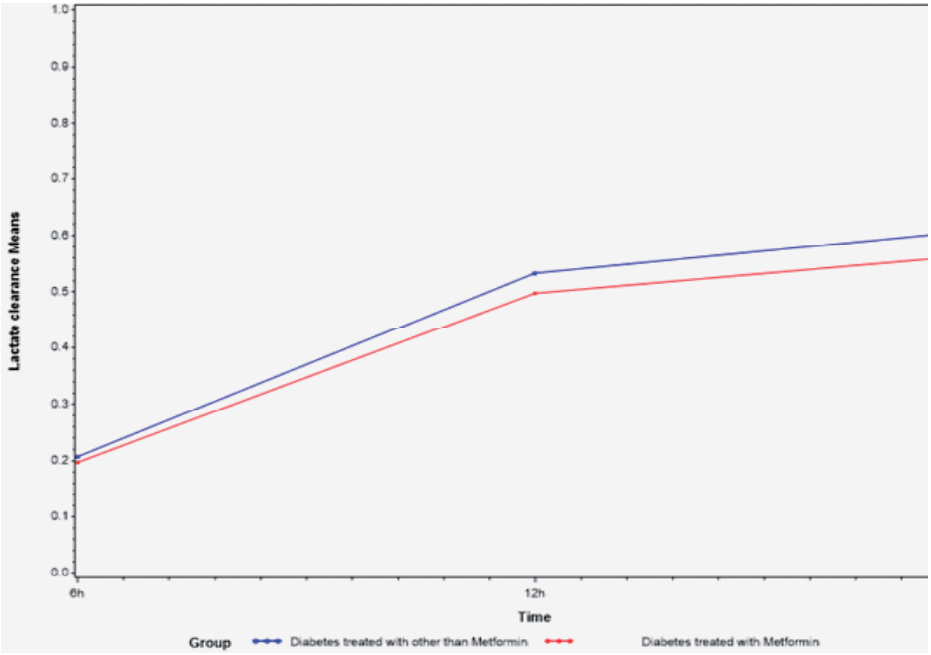

Figure 4. Comparison between 2 groups (diabetics treated with metformin vs. diabetics treated with other drugs, or insulin): lactate clearance increased over time

Table 6. Repeated measures Multivariate ANalysis Of VAriance of lactate clearance in the subgroup of diabetic patients (N = 109)

Lactate clearance	Metformin users (n = 74)	Non metformin users (n = 35)	p-value	Group Effect	Time Effect	Time*Group Effect
6h	0.2	0.2 ± 0.1	0.9093	0.5991	<0.0001	0.8621
12h	0.5	0.5 ± 0.1	0.5850			
24h	0.6	0.6	0.2954			

litus constitutes a known perioperative risk factor. Patients treated with metformin tended also to be mostly male and younger than the rest of the diabetic population; nevertheless, these tendencies did not reach statistical significance.

Table 5 shows data with regard to the lactate measurements for patients of the subgroup analysis. No differences were found between the two groups. Lactate concentrations decreased significantly over time in all patients indicating a good clearance as shown in **Figure 3**. Lactate clearance increased over time in both groups (**Figure 4**). No differences on lactate clearance were found between the two groups of the subgroup analysis (**Table 6**).

Discussion

Hyperlactatemia represents a marker of tissue hypoxia/hypoperfusion mainly through anaerobic glycolysis. Increased blood lactate levels are associated with significant morbidity and mortality in different groups of patients [10–12]. In cardiac surgery, lactate and lactate clearance have prognostic value [8, 9, 12]. Hyperlactatemia can be the result of either excess lactate production due to tissue hypoperfusion, or a decreased rate of lactate metabolism and clearance. However, different physiologic states, such as a stress response, the hyperdynamic stage of sepsis, or β-2 adrenergic receptors stimulation, commonly used in cardiac surgery, may increase lactate formation resulting in transient hyperlactatemia without tissue hypoxia [13, 14].

Metformin enhances tissue sensitivity to insulin, increases peripheral uptake of glucose, decreases glucose absorption in the digestive tract, suppresses neoglycogenesis and decreases fatty acid oxidation, thus making it a first choice oral agent in the treatment of diabetes mellitus in patients with normal kidney and liver func-

tions. However, its use has been associated with impaired lactate kinetics, hyperlactatemia and lactic acidosis [2–4]. MALA is an extremely rare event with an estimated incidence of 0.03 to 0.06 per 1000 patient-years [1, 15], and occurs when there is an imbalance between increased lactate production and impaired metabolism/reduced clearance. Metformin plasma levels >5 μg/mL are generally found when metformin is implicated as the cause of lactic acidosis [16] when the therapeutic range is at <2μg/mL [17].

Guidelines with regard to the perioperative care of the National Institute for Health and Care Excellence (NICE), the French Society of Anaesthesia and Intensive Care Medicine (SFAR) and the British National Formulary recommend the discontinuation of metformin before surgery [5–7]. To this day no guidelines have been provided on its perioperative use issued by any international association of anesthesia. In our institution, metformin is not discontinued until the day of the surgery.

In our study we compared lactate levels and lactate clearance between patients treated with or without metformin undergoing cardiac surgery with the use of cardiopulmonary bypass (CPB). In this patient population metformin use was not associated with increased postoperative lactate levels or impaired lactate clearance. Oddly, metformin users showed lower lactate levels and a better clearance than the rest of the cohort at 12h postoperatively, as well as lower lactate concentrations at 24h postoperatively. This could be partially explained by a shorter mean CPB time of 10 minutes in metformin users, although such a time period is clinically rather short to account for a difference in lactate concentrations.

We also performed a subgroup analysis focusing on patients with diabetes mellitus. No differences were found in postoperative lactate concentrations and clearance between patients treated with metformin and diabetics treated with different antiglycemic agents.

These results are in accord with two other recently published studies. Nazer et al. [18] in 2017 and Bano et al. [19] in 2019 studying diabetic patients undergoing CABG reported no impact of metformin use up-until the night before surgery in postoperative lactate concentrations. Our study included not only CABG patients, but also patients receiving all types of cardiac surgery with the use of cardiopulmonary bypass (CPB). In addition to their action, in our population we also explored lactate kinetics. Compared to absolute lactate values, lactate clearance seems to be a more meaningful prognostic parameter. Rapid clearance of lactate is a strong indicator of a better outcome in numerous different critical care settings [10, 11]. Patients using metformin in our study had a better lactate clearance at 12h postoperatively, although a group effect was not demonstrated overall between the two groups.

Similar results were reported in different ICU patient settings. Doenyas-Barak et al. [20], studying diabetic patients in septic shock with lactic acidosis, also found better outcome results in metformin users. Moreover, Park et al. [2], studying patients with severe sepsis or septic shock, found that metformin users had higher lactate levels in the early phase of resuscitation which normalized over the initial 24-h period. Lee et al. [3], however, found no association of metformin with hyperlactatemia.

Timing of hyperlactatemia onset also plays an important role in prognosis. Early-onset hyperlactatemia defined chronically from the beginning of CPB to arrival in the ICU has been associated with an increased lactate production from the myocardium as well as from the peripheral tissues. This type seems to be a more severe form as compared to the late onset hyperlactatemia, occurring 6 to 12 hours post admission in the ICU, with the associated postoperative mortality of 14.9% and 3.6% respectively [21–23]. In our study, lactate concentrations decreased over time during the first 24 postoperative hours, and lactate clearance increased steadily in the same period. This pattern was the same in all patient groups studied implying no effect of metformin on the type of hyperlactatemia.

In order to explain further our results, it is vital to investigate the possible causes and types of hyperlactatemia post cardiac surgery in more detail. In this setting, different mechanisms were proposed to contribute to the final measured lactate concentration: liver dysfunction due to transient hypoperfusion, hypothermia, bacterial translocation and endotoxin release resulting from decreased splanchnic flow [24]. Moreover, the use of inotropes such as adrenaline also promotes lactate formation. We used the GFR MDRD formula to assess the renal function

A few of our patients in the elective procedures group exhibited postoperative lactic acidosis. In all those cases, postoperative low cardiac syndrome, cardiac tamponade, or extreme hypovolemia seemed to be the main causative factors for lactic acidosis.

There are several limitations to our study. First of all, this is a single centre retrospective study. Moreover, the number of patients included was small, and it is possible that including a larger number of patients would have shown a statistically significant difference between the study groups. However, in our results we did not detect even a tendency towards higher lactate levels in metformin users. On the contrary, a small, but significant, difference was noted in favor of the metformin users group. Finally, and most importantly, this is an observational study lacking a control group of metformin users in whom the drug was discontinued prior to the surgery and its results should be interpreted as such. Further studies including an adequately powered randomized controlled study are needed to define the proper timing of metformin discontinuation before the surgery.

Conclusions

In conclusion, in a post cardiac surgery ICU setting, using metformin up until the night before surgery was not associated with increased lactate levels or impaired lactate clearance. Further studies are necessary before issuing guidelines with regard to the proper preoperative use of metformin.

Authors' roles and individual contributions

Fotini Ampatzidou – conceptualization, methodology, validation, investigation, resources, writing – original draft.
Konstantinos Diplaris – methodology, software, formal analysis, writing – original draft.
Odysseas Drosos – formal analysis, investigation, writing - original draft.
George Drossos – Validation Writing – review and editing, visualization, supervision.

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Conflict of interest statement
The authors declare no conflict of interest.

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References

1. Bailey CJ, Turner RC: Metformin. N Engl J Med 1996; 334: 574-579. DOI: https://doi.org/10.1056/NEJM199602293340906
2. Park, Joongmin; Hwang, Sung Yeon; Jo, Ik Joon; Jeon, Kyeongman; Suh, Gee Young; Lee, Tae Rim; Yoon, Hee; Cha, Won Chul; Sim, Min Seob; Carriere, Keumhee Chough; Yeon, Seungmin; Shin, Tae Gun Impact of Metformin Use on Lactate Kinetics in Patients with Severe Sepsis and Septic Shock SHOCK: May 2017 - Vol 47: 5 - p 582–587. DOI: https://doi.org/10.1097/SHK.0000000000000782
3. Lee EY, Hwang S, Lee YH, et al. Association between Metformin Use and Risk of Lactic Acidosis or Elevated Lactate Concentration in Type 2 Diabetes. Yonsei Med J. 2017;58(2):312– 318. DOI: https://doi.org/10.3349/ymj.2017.58.2.312
4. De Fronzo R et al. Metformin-associated lactic acidosis: Current perspectives on causes and risk Metabolism. 2016 Feb;65(2):20-9. DOI: https://doi.org/10.1016/j.metabol.2015.10.014
5. National Institute for Health and Clinical Excellence, Type 2 Diabetes Clinical Guideline 87. Available from: http://www.nice.org.uk/cg87
6. The Electronic Medicines Compendium Metformin summary of product characteristics Available from medicine/23244/SPC#CLINICAL_PRECAUTIONS
7. Cheisson G., Jacqueminet S., Cosson E., Ichai C., Leguer A-M, Nicolescu-CatargiB. Perioperative management of adult diabetic patients. Preoperative period Anaesthesia Critical Care & Pain Medicine2018;37:9-19. DOI: https://doi.org/10.1016/j.accpm.2018.02.020
8. Kapoor P, Mandal B, Chowdhury U, et al. Changes in myocardial lactate, pyruvate and lactate-pyruvate ratio during cardiopulmonary bypass for elective adult cardiac surgery: early indicator of morbidity. J Anaesthesiol Clin Pharmacol 2011; 27(2): 225–232. DOI: https://doi.org/10.4103/0970-9185.81819
9. Ranucci M, De Toffol B, Isgrò G, et al. Hyperlactatemia during cardiopulmonary bypass: determinants and impact on postoperative out-come. Critical Care 2006; 10: R167. DOI: https://doi.org/10.1186/cc5113
10. Zhang Z., Xu X. Lactate Clearance Is a Useful Biomarker for the Prediction of All-Cause Mortality in Critically Ill Patients: A Systematic Review and Meta-Analysis Crit Care Med2014; 42:2118–2125. DOI: https://doi.org/10.1097/CCM.0000000000000405
11. Bakker J, Nijsten MW, Jansen TC. Clinical use of lactate monitoring in critically ill patients. Ann Intensive Care. 2013;3(1):12. DOI: https://doi.org/10.1186/2110-5820-3-12
12. Lopez-Delgado JC, Esteve F, Javierre C, Torrado H, Rodriguez-Castro D, Carrio ML, et al. Evaluation of serial arterial lactate levels as a predictor of hospital and long-term mortality in patients after cardiac surgery. J Cardiothorac Vasc Anesth. 2015;29:1441–53. DOI: https://doi.org/10.1053/j.jvca.2015.04.024

13. Vincent, J., Quintairos e Silva, A., Couto, L. et al. The value of blood lactate kinetics in critically ill patients: a systematic review. Crit Care 20, 257 (2016). DOI: https://doi.org/10.1186/s13054-016-1403-5
14. Levy B, Desebbe O, Montemont C, Gibot S. Increased aerobic glycolysis through beta2 stimulation is a common mechanism involved in lactate formation during shock states. Shock 2008; 30: 417–21. DOI: https://doi.org/10.1097/SHK.0b013e318167378f
15. Eppenga W.L., Lalmohamed A., Geerts A.F., Derijks H.J., Wensing M., Egberts A., et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. Diabetes Care. 2014; 37: 2218-2224. DOI: https://doi.org/10.2337/dc13-3023
16. Glucophage (metformin hydrochloride) and Glucophage XR (extended-release) prescribing information. Bristol-Myers Squibb, Bristol, NJ2009
17. Graham G.G., Punt J., Arora M., Day R.O., Doogue M.P., Duong J.K., et al. Clinical pharmacokinetics of metformin. Clin Pharmacokinet. 2011;50:81–98. DOI: https://doi.org/10.2165/11534750-000000000-00000
18. Nazer RI, Alburikan KA. Metformin is not associated with lactic acidosis in patients with diabetes undergoing coronary artery bypass graft surgery: a case control study. BMC Pharmacol Toxicol. 2017;18(1):38. DOI: https://doi.org/10.1186/s40360-017-0145-6
19. Bano T, Mishra SK, Kuchay MS, et al. Continuation of Metformin Till Night Before Surgery and Lactate Levels in Patients Undergoing Coronary Artery Bypass Graft Surgery. Indian J Endocrinol Metab. 2019;23(4):416–421. DOI: https://doi.org/10.4103/ijem.IJEM_114_19
20. Doenyas-Barak K, Beberashvili I, Marcus R, Efrati S. Lactic acidosis and severe septic shock in metformin users: a cohort study. Crit Care. 2016; 20:10. DOI: https://doi.org/10.1186/s13054-015-1180-6
21. Minton J, Sidebotham DA. Hyperlactatemia and Cardiac Surgery. J Extra Corpor Technol. 2017;49(1):7-15
22. Maillet J. M., Le Besnerais P., Cantoni M., et al. Frequency, risk factors, and outcome of hyperlactatemia after cardiac surgery. Chest. 2003;123:1361–6. DOI: https://doi.org/10.1378/chest.123.5.1361
23. Hajjar LA, Almeida JP, Fukushima JT, et al. High lactate levels are predictors of major complications after cardiac surgery. J Thorac Cardiovasc Surg. 2013;146(2):455-460. DOI: https://doi.org/10.1016/j.jtcvs.2013.02.003
24. Mustafa I, Roth H, Hanafiah A, et al. Effect of cardiopulmonary bypass on lactate metabolism. Intensive Care Med. 2003;29(8):1279-1285. DOI: https://doi.org/10.1007/s00134-003-1860-6