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CORRESPONDENCE

Ketonaemia during cardiopulmonary bypass surgery: a prospective observational study

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Editor—Ketone bodies are rarely monitored in the perioperative period, except in cases of suspected diabetic ketoacidosis (DKA). DKA is commonly defined as an excess of beta-hydroxybutyric acid (BHB >3.0 mM) in combination with metabolic acidosis (pH <7.30), demanding urgent intervention. Although surgical stress is known to promote ketogenesis, it is poorly understood to what extent this occurs during cardiac surgery with cardiopulmonary bypass.[1] Less known is the influence of type 2 diabetes mellitus (T2D) on this process.[2] In times of increasing use of sodium-glucose co-transporter 2 inhibitors (SGLT2i) for multiple conditions, concerns have been raised about DKA occurring more frequently within the perioperative period.[3] We investigated ketonaemia development during cardiac surgery in patients with and without T2D to provide a reference for physicians to facilitate perioperative ketone measurement interpretation. We hypothesised that ketone levels would increase significantly from baseline levels (0.1–0.4 mM) during surgery in both groups, with a more pronounced effect in patients with T2D.[4]

The Medical Ethics Committee (W21_473#21.525) approved this single centre observational cohort study, which was conducted at the Amsterdam UMC between March 2022 and March 2023 per our prospectively published protocol (NCT05225467), and adhering to international good clinical practice guidelines and Dutch law regarding medical research in humans. We included adult patients undergoing elective cardiac surgery with cardiopulmonary bypass without type 1 diabetes mellitus, a history of ketoacidosis, pregnancy, or SGLT2i use (the expected number of SGLT2i users was limited and could confound the study aim to provide a baseline reference). We included two patient cohorts of equal size according to T2D status (grouped as T2D− or T2D+). We sampled arterial blood at four time points: before induction of anaesthesia (T1), at the start of aortic cross-clamping (T2), at the end of aortic cross-clamping (T3), and after closure of the sternum (T4). We performed blood gas analysis using a Rapidpoint 500e (Siemens Healthcare Diagnostics Inc, Erlangen, Germany), and measured beta-hydroxybutyric acid (BHB) using a StatStrip® Connectivity Ketone meter (Nova Biomedical, Waltham, MA, USA). Outcomes were defined as the difference between baseline and peak ketone concentration and between-group differences. We performed an exploratory analysis of patients receiving intraoperative insulin for glucose control. Statistical analysis was performed using IBM SPSS® statistics v. 26 (Armonk, NY, USA). Changes in ketone concentrations from baseline and between-group comparisons were analysed using the unpaired and paired Student *t*-test, respectively. Full details and additional analyses are provided in the Supplementary materials. We included 54 patients, 27 in the

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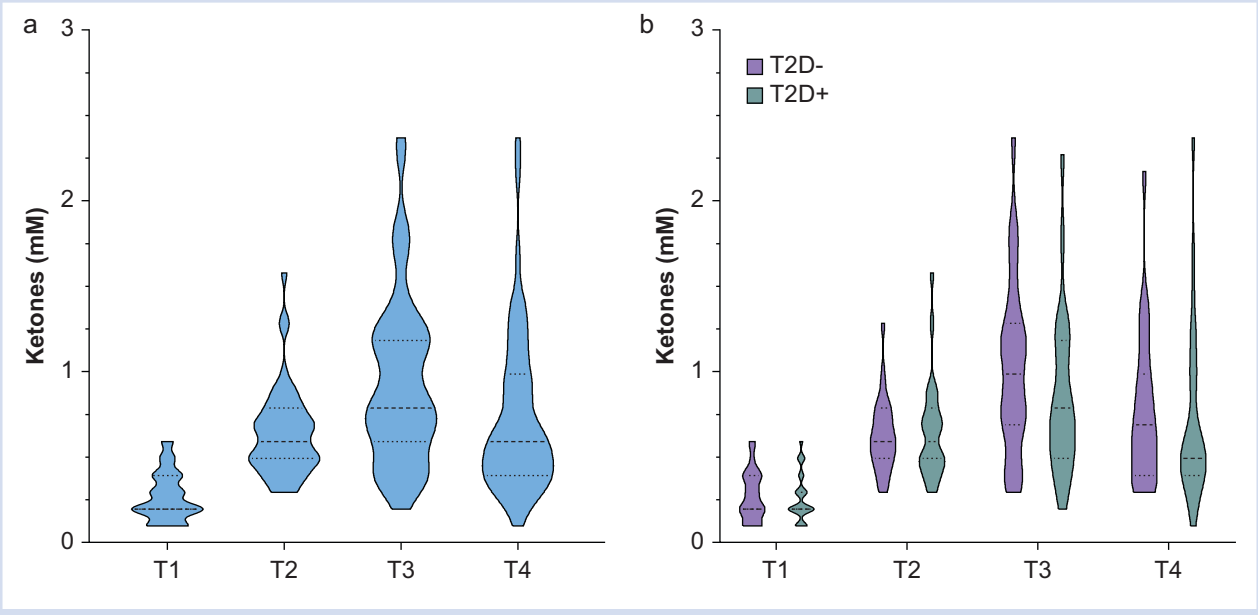

Fig 1. Distribution of intraoperative ketone measurements at four time points. (a) All patients. (b) Distributions separated for patients with and without type 2 diabetes mellitus. T1, before induction; T2, start of aortic cross-clamp; T3, end of aortic cross-clamp; T4, closure of sternum; T2D−, patients with no history of diabetes mellitus; T2D+, patients with type 2 diabetes mellitus.

T2D− group and 27 in the T2D+ group. Data collection was complete for all included patients and available for analysis without missing data.

During surgery, ketone levels increased significantly, from 0.27 (SD 0.14) mM at T1 to a maximum of 0.95 (0.5) mM (difference 0.68 mM, 95% confidence interval [CI] 0.56–0.80 mM, $P<0.001$). The distribution of ketone concentrations is shown in Figure 1, demonstrating an intraoperative peak at T3. Ketone concentrations did not differ significantly between the T2D− and T2D+ cohorts. We observed no incidences of metabolic acidosis (predefined as pH <7.3 with bicarbonate <15 mM) or ketoacidosis (acidosis with ketones >3.0 mM). The pH values at T3 were similar for both groups (7.35 [0.4] for T2D− and 7.35 [0.4] for T2D+), and glucose concentrations differed significantly (T2D+ 8.7 mM, 95% CI 8.2–9.2 mM, and TD− 6.6 mM, 95% CI 6.0–7.1 mM) (mean difference 2.1 mM, 95% CI 1.4–2.9 mM, $P<0.001$).

Fifteen patients received insulin intraoperatively, five in the T2D-group and 10 in the T2D+ group for either hyperglycaemia or hyperkalaemia (>5.0 mM). At T4, these patients had significantly lower ketone concentrations (0.55 [0.32] mM) compared with patients without insulin (0.82 [0.50] mM) (mean difference −0.27, 95% CI 0.04–0.51, $P=0.022$).

This study demonstrates that ketone concentrations increase significantly from normal physiological levels during cardiac surgery. Despite a >300% increase in ketone concentrations from baseline, the highest ketone level detected was 2.4 mM, remaining below the commonly accepted threshold (3.0 mM) for diagnosis of ketoacidosis. We observed no significant differences in ketosis between patients with or without T2D. Furthermore, our findings confirm the ketogenesis-suppressing effects of insulin, as ketone concentrations were lower in patients receiving insulin for glucose control.[5]

Although many clinicians associate ketonaemia with complications of metabolism such as (diabetic) ketoacidosis, there is considerable evidence that ketone bodies in the absence of metabolic acidosis have cardioprotective effects.[6–8] In addition, ketones are an effective alternative fuel source for cardiac and cerebral tissue, which can attenuate the effects of tissue ischaemia, ischaemia/reperfusion injury, and impaired glucose and fatty acid utilisation, which are especially relevant in the setting of cardiac surgery.[6–9] Perioperative ketogenesis has recently gained clinical relevance owing to heightened awareness of perioperative SGLT2i-induced ketoacidosis.[3] As such, the fact that ketogenesis increased during cardiac surgery is relevant to clinicians managing perioperative patients using an SGLT2i.

Overall, this study agrees with previous research showing ketonaemia in cardiac surgery patients, describing perioperative increases in ketone bodies, including insulin-induced suppression.[5,10,11] Of note, one study in coronary artery bypass graft patients observed peak ketone levels 6 h after the operation, which normalised over the consecutive 12 h.[10] Future research should consider a longer follow-up period. Although our study was adequately powered to detect changes in ketone levels, it is limited in the potential of detecting other potential factors influencing ketogenesis (such as insulin). The effect of SGLT2i could affect this process, and their effects should be explored further in surgical settings.

In conclusion, we observed a significant increase in ketonaemia in patients with and without diabetes mellitus undergoing cardiac surgery. We see this as especially relevant for the correct interpretation of the incidental ketoacidosis occurring in the context of perioperative SGLT2i use.

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Authors' contributions

Validation: LS, XL
Formal analysis and visualization: LS, AH
Investigation: LS, XL, AH
Writing the original manuscript: LS
Review and editing of the manuscript: XL, NW, BP, DvR, JH, AH
Supervision: NW, BP, DvR, JH, AH
Conceptualisation: DvR, JH
Methodology: DvR, JH, AH
Project administration: DvR, JH, AH
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Declaration of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2024.05.022.

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