Mitochondrial redox state in the critically ill

K. A. Yassen1,3, H. F. Galley2, A. Lee1 and N. R. Webster2*

1Department of Anaesthesia, Royal Infirmary, Edinburgh, UK. 2Academic Unit of Anaesthesia and Intensive Care, University of Aberdeen, UK

Present address: 3Department of Anaesthesia, Liver Institute, Menoufiya University, Egypt

*Corresponding author: Academic Unit of Anaesthesia and Intensive Care, Institute of Medical Sciences, Forsterhill, Aberdeen AB25 2ZD, UK

Abnormal oxygen use and organ failure in the critically ill may result from ‘poisoning’ of mitochondrial function. Measurement of arterial ketone body ratio (AKBR) has been proposed to reflect mitochondrial redox state and may provide a useful marker to monitor mitochondrial function in the critically ill. We measured AKBR (acetoacetate to β-hydroxybutyrate) and plasma lactate concentrations in 20 critically ill patients, on 3 consecutive days after admission to the intensive care unit. Nine (45%) patients died (five with sepsis) within the 30-day follow-up period. AKBR increased significantly over the 3 days of the study in patients who died (P = 0.034) and decreased in those who survived (P < 0.0001). In addition, there was a significant difference between survivors and non-survivors (P = 0.015). We conclude that serial AKBR measurement may be useful in the management of septic patients.

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High mortality and morbidity in critically ill patients is frequently associated with multi-organ failure. Such patients have altered metabolism and high circulating lactate concentrations. Adaptive fat metabolism with preference for fat rather than carbohydrate as a source of calories also occurs. The pathophysiological changes which occur as a result may ‘poison’ the normal intracellular metabolic processes, resulting in abnormal oxygen use, cell death and organ dysfunction. For cells to maintain their functional and structural integrity, two types of reaction must take place: those that are energy-generating (ATP producing) and those that are energy-consuming (ATP utilizing). When mitochondrial function is impaired, energy production is suppressed and there is a decrease in the amount of energy in reserve. During mitochondrial ATP production, electrons are transported along the respiratory chain which uses NADH formed from the tricarboxylic acid (TCA) cycle. The redox state of the NAD+/NADH couple in the first step of the mitochondrial respiratory chain plays a key role in energy metabolism. After administration of a large dose of glucose to suppress gluconeogenesis, the arterial blood ketone body ratio (AKBR) (i.e. the ratio of acetoacetate:β-hydroxybutyrate), correlates closely with the mitochondrial redox state1 (Fig. 1).

Measurement of AKBR in patients undergoing liver transplantation has been used as a potential indicator of graft malfunction2 but redox changes in critically ill patients have not been studied widely. We measured AKBR in critically ill patients to evaluate the extent and time course of these early metabolic changes.

Methods and results

We studied 20 critically ill patients with acute physiological and chronic healthcare evaluation (APACHE II) scores of greater than 15, admitted to the intensive care unit at Edinburgh Royal Infirmary, after obtaining approval from the Ethics Committee and written informed consent. Median age of the patients was 59 (21–79) yr and median APACHE II score was 22.5 (15–38). Standard therapy was continued as usual. Blood samples were obtained from an indwelling arterial line into heparinized tubes, 30 min after i.v. administration of a bolus dose of glucose 15 g to suppress ketogenesis (day 1). Samples were placed immediately on ice and centrifuged at 1500 g for 10 min at 4°C. Plasma was stored at −70°C for later analysis. Sampling was repeated 24 h (day 2) and 48 h (day 3) later. Ten patients had septic shock according to standard criteria adopted by the American Association of Physicians/Society of Critical Care Medicine consensus conference.3 The remaining 10 patients had either chronic respiratory failure, ventricular failure, aortic aneurysm rupture or severe trauma. All
patients survived the 3 days of the study, but eight patients (40%) subsequently died, of whom five had septic shock.

AKBR was measured using the Ketorex C Kit (Genzyme Diagnostics, Kent, UK) which provides a quantitative measurement of the ketone bodies, acetoacetate and β-hydroxybutyrate, in arterial plasma using a modified endpoint enzymatic method based on that described by Williamson, Mellanby and Krebs. Plasma lactate concentrations were measured using an enzymatic technique with an oxygen electrode (Analox analyser).

Data were not normally distributed and were therefore log transformed for statistical analysis. Data are expressed as median (range) and were analysed by two-way analysis of variance using Microsoft SPSS. P<0.05 was taken as statistically significant.

AKBR decreased significantly over the 3 days of the study in patients who died (P=0.034) and increased in those who survived (P<0.0001) (Fig. 2). In addition, there was a significant difference between survivors and non-survivors overall (P=0.015).

Plasma lactate concentration did not change with time in critically ill patients but concentrations were higher in non-survivors than in survivors on day 2 (2.7 (1.4–9.2) and 1.8 (0.7–2.5) µmol litre⁻¹, respectively; P=0.015) and on day 3 (3.0 (1.9–9.0) and 1.4 (0.9–1.8) µmol litre⁻¹, respectively; P=0.0002). There was no difference between non-survivors and survivors on day 1 (2.1 (1.0–4.6) and 1.8 (0.8–3.6) µmol litre⁻¹, respectively). Lactate did not change with time in the subgroup of patients with septic shock who died.

Comment

We have shown that AKBR was lower in critically ill patients who died than in those who survived. Subgroup analysis suggests that this was most likely a result of sepsis as the group of patients who died with septic shock showed a significant decrease in AKBR over the 3 days of the study. AKBR reflects hepatic mitochondrial redox state and correlates closely with hepatic energy production. In animal models of sepsis, circulating ketone bodies decreased coupled with increased lactate concentrations. We also found that in common with many other previous studies, lactate concentrations increased in those critically ill patients who died.

Mitochondria are usually in a reduced state when oxygen delivery is normal, but if the redox state is further reduced such as in the critically ill, entry of acetyl coenzyme A into the tricarboxylic acid cycle (TCA) is inhibited. As a result, electron transport systems become saturated and eventually net release of hydroxybutyrate occurs as a method of redirecting reducing equivalents to other active tissues. This leads to an altered NAD⁺/NADH ratio and hence decreased AKBR, as there is decreased NADH available for the conversion of acetoacetate to β-hydroxybutyrate. In a rat model of sepsis using live Escherichia coli infusion which resulted in 100% mortality, AKBR was consistently less than 0.4. In another study in critically ill heart failure patients, an AKBR >0.7 was associated with 100% survival, whereas only 15% of those patients with an AKBR <0.7 survived. We also found that AKBR decreased progressively in critically ill patients who subsequently died, independent of the presence of sepsis, and AKBR was less than 0.4 in all non-surviving patients by day 3.

In summary, we have shown that AKBR decreased progressively in those critically ill patients with septic shock who died. As changes in AKBR reflect altered redox status, we suggest that AKBR may be a useful marker of hepatic oxygenation, although inhibition of mitochondrial processes may also produce such changes. Comparison with other markers of tissue oxygenation and the effects of modifying AKBR on outcome are now indicated.

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References


