HUMANS ARE NOT YEAST AND RARELY BECOME ANAEROBIC

Yeasts are eukaryotic microorganisms classified in the kingdom of fungi. Yeast utilize oxygen for aerobic cellular respiration however they anaerobically ferment carbohydrates to carbon dioxide and alcohols[1]. It is widely believed that humans behave like yeast; under favorable conditions they utilize oxygen to produce energy (ATP), however when oxygen delivery is inadequate they produce ATP and lactate anaerobically. Consequently, lactic acidosis is widely believed to be due to tissue hypo-perfusion with anaerobic metabolism[2]. Furthermore, lactate is believed to be produced anaerobically during vigorous exercise. From an evolutionary point of view the anaerobic production of energy would appear to be maladaptive; the anaerobic metabolism of glucose produces 5% of the ATP compared to aerobic metabolism insufficient to sustain the life of the organism.

A guiding principle of the resuscitation of critically ill patients is to increase oxygen delivery (DO_2) in order to increase oxygen consumption (VO_2). Furthermore, an increased blood lactate level is widely believed to be a marker of anaerobic metabolism and an indication to increase DO_2. Indeed the most recent iteration of the Surviving Sepsis Campaign guidelines recommend "*targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion*"[3]. This concept is however severely flawed as DO_2 has to fall to very low levels before oxygen consumption VO_2 falls and most patients with "shock" have normal levels of oxygen consumption. Ronco and colleagues determined the critical oxygen delivery threshold for anaerobic metabolism in critically ill humans while life support was being discontinued[4]. In this study the critical oxygen delivery threshold was 3.8 ± 1.5 ml/kg/min (266 ml/min in a 70 kg patient). Similarly, in a remarkable and rather unconventional study, van Woerkens *et al*. studied the relationship between VO_2 and DO_2 in a Jehovah Witness patient who was bleeding to death[5]. In this patient VO_2 became supply dependent below a DO_2 of 4.9 ml/kg/min (343 ml/min in a 70 kg man). Shibutani *et al*. studied the relationship between VO_2 and DO_2 in 58 patients undergoing cardiopulmonary bypass[6]. The critical value of DO_2 was identified to be 330 ml/min. These values translate into a cardiac output of approximately 2 l/min; it is likely that only pre-terminal moribund patients with "shock" would have such a low cardiac output. Furthermore, contrary to common belief, humans may tolerate severe hypoxaemia without developing anaerobic metabolism and increased lactate levels. Climbers without supplemental oxygen near the summit of Mount Everest have been reported to have a mean arterial partial pressure of oxygen (PaO_2) of 24.6 mmHg without evidence of neurocognitive abnormalities suggestive of cerebral hypoxia and with a normal lactate concentration (mean of 2.2 mmol/l)[7]. Moderate to high intensity exercise results in increased lactate levels. During intense exercise there is increased production of lactate in the cytosol of skeletal muscle with transport into the mitochondrion with oxidative catabolism via the tricarboxylic acid cycle and the production of energy[8]. This lactate shuttle serves as an energy source for exercising muscle. However, intracellular pO_2 remains normal even at maximum exercise[8].

While an elevated lactate concentration is widely believed to be a marker of inadequate tissue perfusion, inadequate cellular oxygen utilization and anaerobic metabolism, an overwhelming body of evidence suggests that in most clinical situations lactate is produced aerobically as part of the stress response[8]. If inadequate perfusion was the cause of increased blood lactate levels then increasing systemic or regional oxygen transport would correct the blood lactate levels. However, such an approach has not been associated with an increase in oxygen consumption or a decline in the lactate level[9,10] and this approach is associated with an increased risk of death[11]. In summary, while yeasts produce alcohols anaerobically, humans differ from yeasts in many respects and clinical data suggests that humans rarely if ever become anaerobic.

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