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Intensive insulin therapy reduces microdialysis glucose values without altering glucose uterion or improving the lactate/pyruvate ratio after traumatic brain injury. All statistical analysis was performed in R (v.3.4.3; <http://www.r-project.org/>) using the packages: nlme, rms, mgcv, mice, survival, eurl, and ggplot2. Aerobic hyperglycolysis, wherein anaerobic glycolysis is upregulated despite sufficient oxygen availability, has been demonstrated to be a common early phenomenon in both preclinical models and human TBI patients [27]. Czosnyka M, Czosnyka Z, Smielewski P. The weakness of the relationship between LPR and PbtO₂ concurs with the growing evidence that LPR>25 is not only a marker of hypoxia / ischaemia (which are nowadays uncommon, with modern neurocritical care), but LPR can become elevated even when PbtO₂ levels are regarded as "adequate"—suggesting mitochondrial dysfunction. Shaded region indicates 95%CI for the fit. Jalloh I, Helmy A, Shannon RJ, et al. Oddo M, Schmidt JM, Carrera E. Patients had continuous measurement of intracranial pressure (ICP), arterial blood pressure (ABP), brain tissue oxygenation (PbtO₂), and cerebral metabolism and were managed according to a standardized therapeutic protocol. pp25368635.30. At a mean level, the secondary increase in LPR was due primarily to increasing lactate, whereas the trend for decreasing pyruvate was driven by a decrease in its concentration. Home A, Smith AB, Smith AB, et al. Hypothalamic and pituitary gland function after severe traumatic brain injury: a systematic review of clinical, physiological, and neurological outcome and therefore that therapy directed at normalising metabolism has the potential to improve outcomes. The non-linear relationships identified between LPR and CPB, PbtO₂, PRx, and brain glucose directly suggest therapeutic goals that could be adopted to improve cerebral metabolism. Cerebral perfusion and stroke. 1998;15(12): pp.1059–66. 2012;32(7):1152–66. 3. Arach removal route via the so-called glymphatic system—paravascular channels in the brain, which facilitate clearance of waste products, including lactate, from the brain interstitial fluid into the CSF and thence into lymph vessels [24, pml:28207601.6. Furthermore, interrogating the derivatives of the fitted curves allows evidence of natural threshold in the inter-relationships that can potentially inform treatment plans. pml:27481936.25. Front Neurosci, 2015;9:112. pml:23017022.7. In brief, patients were sedated, paralysed, and mechanically ventilated to a target PaCO₂ of 4.5–5 kPa. Vasopressors are used to maintain a cerebral perfusion pressure (CPP) of 55–65mmHg. In response to elevated intracranial pressure there was a staged application of osmotherapy, external ventricular drainage, hypothermia, barbiturate coma, and ultimately decompressive craniectomy. Simpson GL. Modelling paleocological time series using generalized additive models. A combined microdialysis and FDG-PET study of glucose metabolism in head injury. To mitigate any bias of a small proportion of extreme outliers when calculating summary statistics the data were Winsorized at the 0.00125 quantile, i.e. data that were either above or below the 99.875th and 0.125th quantile, respectively, were changed to be equal to the respective quantile. Hutchinson PJ, O'Connell MT, Seal A et al. 1994;91: pp.10625-9. Furthermore, patient-level random effects and autoregressive error terms can also be included. Relationship between lactate-pyruvate ratio (LPR) and other physiological parameters. In each panel a GAMM fit of glucose (A), CPP (B), PRx (C), and PbtO₂ (D) against LPR is shown alongside the corresponding linear regression model. However, it is important to note that the latter approach does not account for the fact that the observed LPR values are themselves dependent on the underlying physiological state, accounting for strong autocorrelations inherent in physiological time series. 2007;99: pp.mpl:19009177. These latter processes are potentially modifiable influences on patients' outcome and are the focus of current and experimental interventions in neurointensive care. pml:29690859.23. These are key questions to address in taking forward the present findings to inform clinical treatment of patients. Outcome could not be determined in 37 (6.0%) of patients. pml:7938003.17. Traumatic brain injury: intensive care management. In the CNS there is evidence that glia and neurons are metabolically coupled in the so-called 'Astrocyte-Neuron Lactate Shuttle' (ANLS) [16–18]. Wood SN, 2017;11:422. Moro N, Ghavini S, Harris NG, Hovda DA, Sutton RL. Ordinal proportional hazards regression was performed with the lrm function from the rms package. 48.9% of microdialysis samples where pyruvate and lactate were assayed demonstrated LPR >25. 2011 May 18;31(20):7477–85. 2006;34(4): pp. Prx demonstrated a similar temporal trend in both outcome groups but was significantly higher (reflecting more impaired autoregulation) in those with unfavourable outcome. The canonical model of cellular respiration commences with glucose entering the cytosol, proceeding along the series of enzymes of the glycolytic pathway to pyruvate (with net gain of two ATP molecules), which in turn enters the mitochondrion to feed the TCA cycle and the electron transport chain, producing a further 34 molecules of ATP. Within that study, in those patients with LPR>25, mitochondrial dysfunction and neuroglycopenia were most frequent. Targeting CPP to minimise Prx (i.e. optimise autoregulation) may be beneficial in ameliorating metabolic dysfunction. Glymphatic clearance controls state-dependent changes in brain lactate concentration. Consensus statement from the 2014 International Microdialysis Forum. In addition to microdialysis, 461 (74.5%) patients had ABP, ICP, and PbtO₂ data recorded in ICIM+ . G0802251) and Raymond and Beverly Sackler Foundation Senior Research Fellowships in England and the Wellcome Research Fellowship in the United Kingdom. This work was supported by grants from the Wellcome Trust, the UK Medical Research Council, the UK Research Leadership Awards, the Wellcome Foundation Senior Surrogate Fellowship, the Wellcome Biomedical Research Centre, Cambridge, and the NIHR Global Health Research Group for Neurotrauma Competing Interests: The authors have nothing to disclose. The authors of this manuscript have the following competing interests: JAH is an employee of Techmanic (Newton Abbott, UK), the manufacturer of the cranial access device used in this study. 2017;23: pp.103–9. We examined the prognostic value of microdialysis parameters, and the inter-relationships with other neuroimaging modalities to identify interventions that improve metabolism. MC and PS have financial interest in a part of licensing fee for ICIM+ software (Cambridge Enterprise Ltd., UK). pml:28742817.16. Markus HS, Tao C, Hu X, Li H, You C, Machler P, Wyss MT, Elsayed M, et al. pml:18936695.31. 2017 Jun;37(6):2112–2124. Univariate comparison of individual mean LPR was not significantly different between unfavourable and favourable outcome groups when averaged over the first 24h from injury but was significantly different when averaged over the first 72h of injury (Figure 1 median [IQR]: 25.8 [11.0] vs. GAMMs are therefore well served to analyse time-series/longitudinal data of differing duration from multiple individuals. 2009;151: pp. Consistent with the GAMM models, LPR was significantly higher when with glucose

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