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# Lipids and ketones dominate metabolism at the expense of glucose control in pulmonary arterial hypertension: a hyperglycaemic clamp and metabolomics study

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Highly technical metabolic approaches show that fasting nutrient metabolism in pulmonary arterial hypertension favours lipid and ketone metabolism and that, in response to hyperglycaemia, pancreatic  $\beta$ -cell function is similar to control participants <http://bit.ly/2uihG2Q>

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**ABSTRACT** Individuals with idiopathic pulmonary arterial hypertension (PAH) display reduced oral glucose tolerance. This may involve defects in pancreatic function or insulin sensitivity but this hypothesis has not been tested; moreover, fasting nutrient metabolism remains poorly described in PAH. Thus, we aimed to characterise fasting nutrient metabolism and investigated the metabolic response to hyperglycaemia in PAH.

12 participants (six PAH, six controls) were administered a hyperglycaemic clamp, while 52 (21 PAH, 31 controls) underwent plasma metabolomic analysis. Glucose, insulin, C-peptide, free fatty acids and acylcarnitines were assessed from the clamp. Plasma metabolomics was conducted on fasting plasma samples.

The clamp verified a reduced insulin response to hyperglycaemia in PAH ( $-53\%$  *versus* control), but with similar pancreatic insulin secretion. Skeletal muscle insulin sensitivity was unexpectedly greater in PAH. Hepatic insulin extraction was elevated in PAH ( $+11\%$  *versus* control). Plasma metabolomics identified 862 metabolites: 213 elevated, 145 reduced in PAH ( $p < 0.05$ ). In both clamp and metabolomic cohorts, lipid oxidation and ketones were elevated in PAH. Insulin sensitivity, fatty acids, acylcarnitines and ketones correlated with PAH severity, while hepatic extraction and fatty acid:ketone ratio correlated with longer six-min walk distance.

Poor glucose control in PAH could not be explained by pancreatic  $\beta$ -cell function or skeletal muscle insulin sensitivity. Instead, elevated hepatic insulin extraction emerged as an underlying factor. In agreement, nutrient metabolism in PAH favours lipid and ketone metabolism at the expense of glucose control. Future research should investigate the therapeutic potential of reinforcing lipid and ketone metabolism on clinical outcomes in PAH.