SUPPLEMENTARY DATA

Model II is described by the following set of differential equations.

$$f_{switch}(t) = \begin{cases} G(t) > g_b, 1 \\ G(t) \leq g_b, 0 \end{cases} \quad (1)$$

$$l_{sb}(t) = \frac{t \cdot (l_{max} - l_b)}{t_{max}} + l_b \quad (2)$$

$$\frac{V_P \cdot dL}{dt} = -V_P \cdot K_{01} \cdot (L(t) - l_{sb}(t)) + 2 \cdot V_L \cdot K_{12} \cdot G6P(t) \cdot f_{switch}; L(0) = l_b \quad (3)$$

$$\frac{V_L \cdot dG6P}{dt} = -V_L \cdot K_{12} \cdot G6P(t) + V_P \cdot K_{GK} \cdot (G(t) - g_b) \cdot f_{switch}; G6P(0) = 0 \quad (4)$$

Eq 1 represents a switching function. *G(t)* is plasma glucose concentration at a given time *t and* g_b is basal glucose as determined by the observations prior to the glucose bolus. f_{switch} *(t)* has value of 1 while plasma glucose (*G(t)*) is above basal glucose (g_b) and 0 when *G(t)* is bellow g_b. Eq 2 describes the "sliding baseline" for lactate in plasma. l_{max} is the plasma lactate value at the end of the experiment. t_{max} represents the time when the experiment ended. l_b is the average of the plasma lactate concentration prior to the glucose bolus. According to Eq 2 the value of l_{sb} will linearly increase or decrease throughout the observation period. We assume that due to the significant perturbation of the system, the steady state for several of glucose homeostatic hormones will be altered resulting in temporary change of the lactate baseline. Additionally, we assume that the transition to the new baseline state would be gradual. Finally, we assume that once plasma glucose returns to basal state that the glucokinase activity will cease and therefore the appearance of glucose-6-phosphate in liver and hepatic lactate production and subsequent lactate appearance in plasma will also end (Eq. 1). Lactate kinetics in plasma are linked to G-6-P kinetics in the liver via Eq 3. The clearance of plasma lactate, *L(t)*, is described by K_{01}, a fractional transfer rate with units min^{-1}. The appearance of lactate in plasma is described by parameter K_{12}, fractional transfer rate. In Eq 3 parameter K_{12} was multiplied by a factor of 2 because every mol of liver glucose 6-P, *G6P(t)*, converts to two mols of lactate. Parameters V_P and V_L represent the volumes of plasma and liver distribution spaces. We assumed the distribution plasma spaces for glucose and lactate are the same. Eq 4 describes the connection between liver glucose 6-P kinetics and plasma glucose. The elimination of G-6-P from liver is described by K_{12}, fractional transfer rate with units min^{-1}. Parameter K_{GK} describes the rate at which plasma glucose is converted to glucose 6-P with units min^{-1}. The model was formulated to capture the changes in all substrates and compartments above basal signified by the subtraction of the "sliding basal" lactate concentration from plasma lactate in Eq 3 and the subtraction of basal glucose from plasma glucose in Eq 4.

To examine the adequacy of our model we used the average (n=142) time course data for glucose and lactate (Fig S1). Initially, we used visual inspection to examine how well the model recreated the time course of the data and also we assessed the R^2 as quantification for the goodness of fit. Based on these criteria we rejected the one compartment model because the two compartment model had sufficiently better R^2. The second level of analysis included assessment of fractional standard deviation (FSD, Table S1) for the parameters of the model. Models with parameters that had FSD>100% were considered not to yield estimates of the parameters and were rejected such as the three compartment model for which we were unable to obtain estimates of the parameters.

SUPPLEMENTARY DATA

Supplementary Table 1. Average parameter estimates (n=142 subjects). Fractional standard deviation abbreviated as FSD.

Parameter	No. of Subjects	Median	Minimum	Maximum	FSD
K_{01}	142	0.0342	0.0097	0.2519	34%
K_{12}	142	0.0623	0.0112	0.2176	45%
K_{GK}	142	0.0019	0.0001	0.0064	35%

Supplementary Figure 1. Graphical depiction of the requirements for the model of lactate kinetics; (A) Time course of average glucose data for 142 subjects; (B) Time course of average lactate data (n=142).