Comparison of Methods for Calculating the Rate of Appearance of Exogenous Glucose

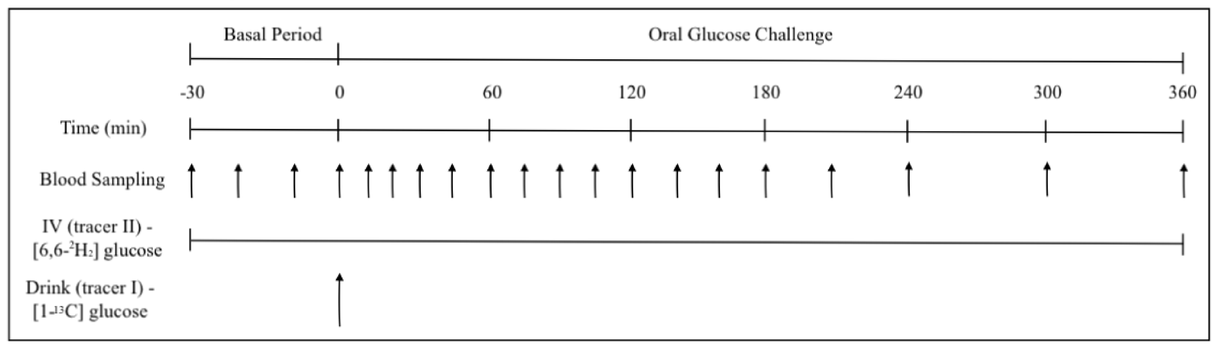
Kai Bartlette[1], Bryan C. Bergman, PhD[3], Kristen J. Nadeau, MD, MS[2], Melanie Cree-Green, MD, PhD[2,*], Cecilia Diniz Behn, PhD[1,2,*]

[1]Department of Applied Mathematics and Statistics, Colorado School of Mines, [2]Division of Endocrinology, Department of Pediatrics, University of Colorado Anschutz Medical Campus, [3]Division of Endocrinology and Metabolism, University of Colorado Anschutz Medical Campus, *co-senior author

Introduction

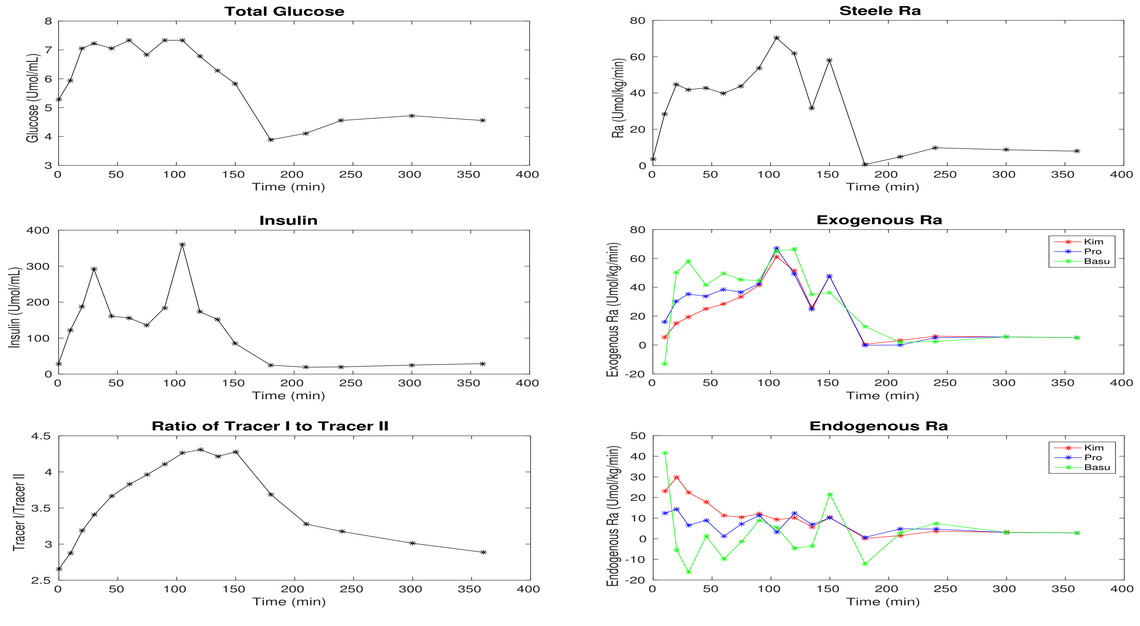
Understanding the contributions of hepatic glucose release to hyperglycemia following a meal is crucial for gaining insight into insulin resistance (IR) and assessing novel therapies for metabolic disorders. Using an oral glucose tolerance test (OGTT) protocol with two stable isotope tracers, both the rate of appearance of exogenous glucose (Ra_{exo}) coming from the drink and the suppression of endogenous glucose (Ra_{endo})in response to the drink may be computed. In previous work, investigators have proposed several different methods for computing the rate of appearance of exogenous glucose. The aim of this project was to compare the implementation and results of these methods applied to OGTT data from a cohort of obese adolescent girls. Obtaining a reliable estimate of the rate of appearance of exogenous glucose represents a key input to differential equation based models of whole body glucose-insulin dynamics used to quantify hepatic and muscle IR.

OGTT Study Design:



Results

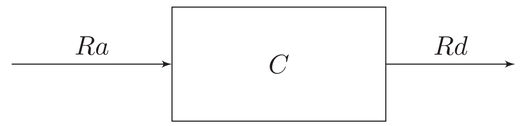
Results for Subject 10:



Methods

Nonsteady State Model for Total Rate of Appearance of Glucose (Steele, Ann N Y Acad Sci., 1959)

Uses mass balance equations for total glucose and tracer II to determine the rate of appearance of total glucose, Ra:



$$Ra = \frac{F - pV\,C\,\frac{dE}{dt}}{E} \qquad (1)$$

where F is the infusion rate of tracer II, pV is the volume of distribution, C is the concentration of glucose and E is the enrichment of tracer II.

Clamp Model for Ra_{exo} (Kim et al., Nutr Metab, 2014)

Assumes E_D and E_P are fixed for each time interval and computes Ra_{exo} as a proportion of total Ra:

$$Ra_{exo} = Ra\frac{E_P}{E_D} \qquad (2)$$

where E_D and E_P are enrichments of tracer I from the test drink and plasma, respectively.

One Pool Model for Ra_{exo} (J. Proietto, Horm Metab Res Suppl, 1990)

Uses known total Ra and Steele's non-steady state equation with tracer I to solve for F; the variable infusion rate of tracer I represents the rate of appearance of tracer I, Ra_{13C} due to gut absorption. Ra_{13C} is scaled by the enrichment of tracer I in the drink to obtain Ra_{exo}:

$$F_2 = Ra_{13C} = Ra \cdot E + pV \cdot C \cdot \frac{dE}{dt} \qquad (3)$$

$$Ra_{exo} = \frac{F_2}{Ei} \qquad (4)$$

where F_2 is the appearance rate of tracer I in plasma, E is the enrichment of tracer I and Ei is the enrichment of tracer I in the drink., respectively.

One Compartment Model for Ra_{exo} (Basu et al., Am J Physiol Endocrinol Metab, 2003)

Assumes one compartment model and uses mass balance equations for both tracers to determine Ra_{13C}; as in (4), Ra_{13C} is scaled by the enrichment of the drink to obtain Ra_{exo}:

$$Ra_{13C} = \frac{F_{2H}}{G_{2H}/G_{13C}} - \frac{pVG_{13C}}{G_{2H}/G_{13C}}\frac{d(G_{2H}/G_{13C})}{dt} \qquad (5)$$

where F_{2H} is the infusion of tracer II, pV is the volume of distribution, G_{13C} and G_{2H} are the concentrations of tracer I and tracer II in plasma, respectively.

Conclusions and Future Work

The greatest variability among estimates of Ra_{exo} occurred in the first ~90 minutes following ingestion of the test drink. This corresponds to the time period when the tracer I/tracer II ratio changes rapidly, and it likely reflects differences among the methods in the handling of dynamic enrichments. These methods also yield different rates and degrees of suppression of Ra_{endo} including non-physiologic negative Ra_{endo} values. A two-compartment model or a protocol using variable infusion of tracer II may address this issue and will be investigated in future work.

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