# Estimating endogenous glucose production during exercise using heart rate: implications for diabetes management

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**Abstract**: Non-invasive, continuous Endogenous glucose production (EGP) estimation during exercise would help manage and automate insulin and glucose dosing during exercise, providing novel information to more effectively close the loop in managing glucose levels. This study used a combination of new study and literature data to determine relationships between blood lactate concentrations, heart rate (HR), and EGP. From these relationships, EGP can be estimated based on HR, which is continuously and non-invasively available at low cost in exercise. Participants for the exercise protocol were 10 sub-elite athletes who participated in at least 6 hours per week of endurance sports. Lactate as a function of HR during high intensity (HI) exercise has variability $R^2 = 0.49$. The variability in the model curve using independent literature values is $R^2 = 0.65$. Using these results to create a model of EGP as a function of HR gives an $R^2 = 0.80$. This method provides a continuous and non-invasive means of estimating EGP during exercise, including at HI, which is more rarely studied, and can be used to improve diabetes management in exercise.

*Keywords*: hepatic glucose production, diabetes, exercise, heart rate

## 1. INTRODUCTION

Glycemic management in diabetes requires balancing insulin dosing and glucose requirements in the body. Blood sugar levels can be affected by exogenous and endogenous sources of glucose. Nutrition is the main exogenous source and the liver produces endogenous glucose through glycogenolysis and gluconeogenesis. The kidney can also contribute a small amount of glucose (Ekberg et al., 1999), although not while exercising (Wahren et al., 1971).

Endogenous glucose production (EGP) helps maintain blood glucose levels during fasting and exercise. People with diabetes often struggle to maintain normoglycaemia during exercise because of difficulty estimating glucose demands. During exercise, EGP can increase up to 8 times the basal rate, depending on duration and intensity (Schiavon et al., 2013), and this increase needs to be considered for insulin dosing and diabetes management.

EGP is usually estimated using isotope tracers, arteriovenous difference, and nuclear magnetic resonance (NMR) spectroscopy, all of which require specialized equipment and are both time and clinically intensive. The ability to non-invasively and continuously estimate EGP during exercise would help manage insulin and glucose dosing during exercise, as well as help better automate insulin dosing devices, such as insulin pumps, in closing the loop in diabetes. This study estimates EGP during exercise based on readily available heart rate (HR) by first relating blood lactate concentration and HR, where lactate and EGP are related in literature studies. A range of study and literature data are used.

## 2. METHODS

### *2.1 Subject demographics*

Participants for the exercise protocol were 10 sub-elite athletes with a resting HR < 60 bpm who undertook at least 6 hours per week of endurance sports, predominantly running and cycling (Thomas et al., 2016). Table 1 shows the participant demographics. All participants provided informed consent and the research procedures and use of data were approved by the University of Canterbury Human Ethics Committee.

**Table 1. Participant demographics shown as median [inter-quartile range]** (Thomas et al., 2017)

| | |
|---|---|
| Number | 10 |
| Age (years) | 28 [23 37] |
| Sex (M/F) | 7/3 |
| BMI (kg/m$^2$) | 22 [21 24] |
| Resting HR (bpm) | 55 [53 56] |
| $VO_2$max (mL/kg/min) | 46 [39 59] |
| Trained cyclist (Y/N) | 7/3 |

### *2.2 High Intensity (HI) Exercise Protocol*

The exercise protocol began at 8am after an overnight fast. Participants were requested not to exercise the day before the test. For the first 60 minutes, subjects used a cycling stationary trainer (Cyclus 2, RBM elektronik-automation GmbH, Lepzig, Germany) in the submaximal endurance HR zone <70%VO2max with a resistance set to 2 W/kg for female and untrained cyclists or 2.5 W/kg for trained males. At 60 minutes, the work required increased by 20 W every 5 minutes

until exhaustion, which usually occurred around 90 minutes. At 30 minutes a glucose drink of 0.5g/kg body weight was consumed, and at exhaustion another glucose drink of 1g/kg body weight was consumed.

Blood lactate was measured using a handheld lactate measurement device (Lactate Pro, Arkray Inc, Kyoto, Japan). Lactate measurements were taken at the start and end of the submaximal period (t=0min and t=60min) and then every ~5 minutes until exhaustion, and two further measurements were taken after exhaustion. HR was measured using a standard chest strap device.

*2.3 Literature Data*

A literature search was conducted in PubMed using search terms including "*EGP*", "*glycogenolysis*", "*gluconeogenesis*", "*glucose production*", "*exercise*", "*liver*", and "*hepatic*". Abstracts were manually reviewed and studies using splanchnic arteriovenous difference or isotope tracers to measure hepatic or endogenous glucose production were included. Studies must also have provided HR data and lactate concentrations. All studies used cycling in their exercise protocol, and, with the exception of one study, used male subjects. Some subjects were tested multiple times in a study, such as when undertaking a training program, where they were "untrained" at the start, and "trained" after completing the program. Data from seven studies are shown in Table 2.

*2.4 Data Analysis and Modeling*

Data from the high intensity (HI) exercise trial was used to create a model of lactate concentration as a function of HR and compared to literature values. There was no EGP data available for the HI exercise trial. HR and blood lactate concentration were used to generate a model to estimate EGP rates in exercising individuals, and the HI estimates were compared to literature values. Data was consolidated and analysed using Matlab R2018b (The Mathworks, Natick, MA, USA).

The model curve was generated from the HI athlete data using Total Least Squares (TLS), to account for error and variability in both the HR and lactate measured variables (Golub and Van Loan, 1980; Markovsky and Van Huffel, 2007). The coefficient of determination, $R^2$, was calculated to assess resulting models as the variance in model-predicted lactate concentration determined from HR, assuming HR is error free. The lactate concentration, *LC*, model created from the HI study data took the following form:

$$LC = \frac{\alpha * HR}{(220 - HR)^{\beta}} \quad (1)$$

where *HR* is heart rate, and a maximum HR limit of 220 bpm was assumed, where lactate concentration can theoretically approach infinity at this value, which is not attainable in typical HI exercise. The shape of the curve, and the transition from low intensity exercise to HI exercise, is defined by the values of $\alpha$ and $\beta$. The resulting final lactate model was validated by independent comparison to the literature data using $R^2$ value.

**Table 2. Literature data of HR, EGP, and blood lactate concentration from cycling exercise studies.**

| Reference | N (#) | Sex | Heart rate (bpm) | EGP (mg/kg/min) | Blood Lactate (mmol/L) |
|---|---|---|---|---|---|
| (Ahlborg et al., 1974) | 6 | M | 53 | 1.94 | 1.06 |
| | | | 104 | 4.41 | 1.31 |
| | | | 108 | 4.39 | 1.32 |
| | | | 121 | 4.55 | 1.38 |
| | | | 129 | 3.46 | 1.80 |
| (Emhoff et al., 2013) | 6 | M | 62 | 2.60 | 0.6 |
| | | | 165 | 7.5 | 3.7 |
| (Emhoff et al., 2013) | 6 | M | 61 | 1.97 | 1.3 |
| | | | 172 | 7.5 | 4.3 |
| | | | 159 | 7.2 | 2.5 |
| | | | 156 | 8.5 | 4.3 |
| (Friedlander et al., 1997) | 19 | M | 68 | 2.69 | 0.78 |
| | | | 128 | 4.73 | 1.69 |
| | | | 158 | 5.84 | 3.25 |
| (Friedlander et al., 1997) | 19 | M | 68 | 2.74 | 0.85 |
| | | | 139 | 4.63 | 1.77 |
| | | | 156 | 5.81 | 2.66 |
| (Friedlander et al., 1998) | 17 | F | 66 | 2.81 | 0.91 |
| | | | 123 | 4.52 | 1.24 |
| | | | 156 | 5.53 | 2.86 |
| (Friedlander et al., 1998) | 17 | F | 66 | 2.96 | 0.85 |
| | | | 130 | 4.7 | 1.14 |
| | | | 153 | 6.0 | 2.12 |
| (Trimmer et al., 2001) | 8 | M | 49 | 1.95 | 1.5 |
| | | | 129 | 4.2 | 1.5 |
| | | | 160 | 6.2 | 3.3 |
| | | | 127 | 4.2 | 1.7 |
| | | | 160 | 5.8 | 3.4 |
| (Wahren et al., 1971) | 10 | M | 60 | 1.91 | 0.63 |
| | | | 94 | 2.34 | 1.01 |
| | | | 109 | 3.88 | 0.88 |
| (Wahren et al., 1971) | 9 | M | 60 | 1.91 | 0.63 |
| | | | 135 | 2.91 | 2.71 |
| | | | 146 | 5.27 | 2.02 |
| (Wahren et al., 1971) | 6 | M | 60 | 1.91 | 0.63 |
| | | | 140 | 4.63 | 2.75 |
| | | | 158 | 8.89 | 3.51 |
| (Webster et al., 2016) | 7 | M | 160 | 7.8 | 3.2 |
| | | | 164 | 6 | 2.8 |

The final EGP model took the form:

$$EGP = \gamma * HR + \delta * LC \quad (2)$$

Where *LC* is lactate concentration calculated from Equation (1) using *HR*. The values of $\gamma$ and $\delta$ were determined from literature values using a multi variable linear fitting tool. Finally, the models of lactate and EGP are combined to create a model of EGP as a function of HR.

*2.5 Analyses and Validation*

In use, Equations (1)-(2) deliver EGP using measured *HR* alone. Equation (1) was created using only the HI exercise study data. The values of $\gamma$ and $\delta$ in Equation (2) were determined using literature values and Equation (1) was used to determine *LC*. A high $R^2$ value indicates a model accurately capturing the dynamics of EGP as a function of *HR* from this data.

## 3. RESULTS

*3.1 Lactate and HR in high intensity exercise*

During intense exercise, lactate concentration increases non-linearly with increasing *HR*, as shown in Figure 1. The curve is defined:

$$Lactate_{exercise} = \frac{13.25 * HR}{(220 - HR)^{1.6}} \quad (3)$$

where the linear coefficient and exponent, $\alpha$ and $\beta$, were identified using TLS from the measured HI data.

The lactate curve has $R^2 = 0.49$. Basal lactate and resting HR data from the HI study are also shown in Figure 1, and included in the curve fit, suggesting the relationship may be valid from resting HR through an initial linear range and into nonlinear behaviour at HI exercise.

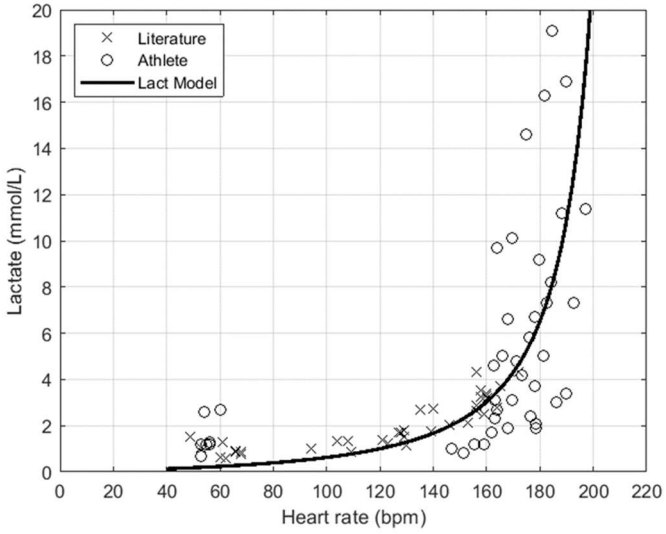


Figure 1. Blood lactate concentration shown as a function of HR for sub-elite athletes during intense exercise (circles). Literature values (x) for exercising participants is also shown. Model curve is solid line.

*3.2 Validation of lactate model compared to literature values*

For independent validation lactate and HR data from literature data in Table 2, predominantly found during lower intensity exercise was compared to the model curve, and is also shown in Figure 1. It can be seen the literature values are well-described by the model curve, with $R^2 = 0.65$ not including the athlete data, which is in fact a higher value than for the athlete data alone. During lower intensity exercise, the relationship between lactate and HR is linear, which is one cause of the higher correlation, where this study is unique in including high intensity data, which reshapes these relationships.

*3.3 EGP model*

Literature values were used to estimate EGP based on HR. At lower exercise intensities, and *HR* < ~160 bpm, the relationship is approximately linear. At higher intensity, the relationship is not linear as a function of HR. The addition of lactate measurement allows a relationship to be elucidated using Equations (2) and (3).

The relationship of HR and lactate concentration to EGP for trained individuals is defined:

$$EGP_{exercise} = 0.027 * HR + 0.73 * LC \quad (4)$$

Substituting Equation (3) into Equation (4) gives EGP as a function of HR for exercise, defined:

$$EGP_{exercise} = 0.027 * HR + \frac{9.67 * HR}{(220 - HR)^{1.6}} \quad (5)$$

Figure 2 shows this resulting function of EGP as a function of HR during exercise at all intensities. The independent literature data and estimated athlete data are also shown on the figure for comparison and validation. Variability of the independent literature validation data from the model of Equation (5) has a high value of $R^2 = 0.80$.

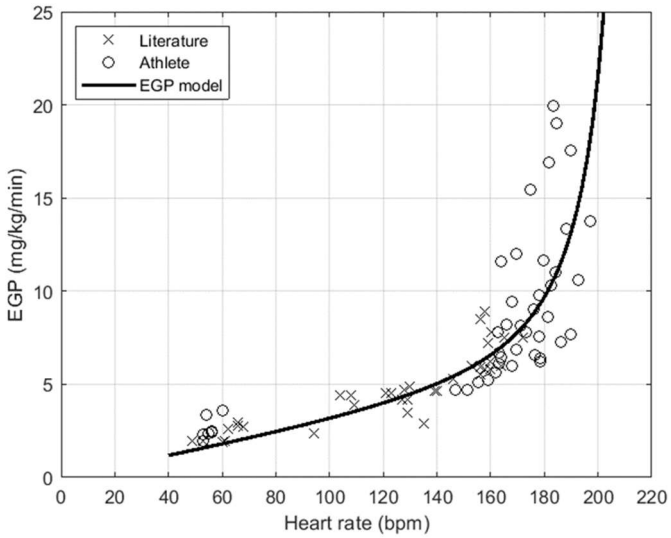


Figure 2. Estimated EGP as a function of HR. Model curve is solid line. Literature data (x) and high intensity estimates (circles) are shown.

## 4. DISCUSSION

This study used a combination of new study data and literature data to derive and identify relationships between blood lactate concentrations, HR, and EGP to create a non-invasive, easily measured, and continuous estimation of EGP. This method provides a novel means of estimating EGP using only HR during exercise, which can be used for diabetes management, where exercise is a significant confounding factor in glycaemic control (Breton, 2008). Better management of glucose levels in exercise can help reduce the incidence of unintended hypo- and hyper- glycemia.

### *4.1 Lactate and HR*

During exercise, blood lactate concentration increases because it is a product of muscle glycolysis (Brooks, 2009). The lactate threshold (LT) is the point at which lactate concentration increases exponentially and may be a better indicator of exercise intensity than HR (Goodwin et al., 2007). However, there are conflicting studies on the reproducibility of lactate concentration at a certain HR, introducing potential variability into any resulting model derived in the fashion presented here. In a study of elite cyclists, the HR associated with LT was stable (Lucia et al., 2000). In another study, the HR at a blood lactate marker of 4.0 mmol/L had variability (Grant et al., 2002). In this study, the variability between individuals is more important than the variability in an individual. Equation (3) defines the relationship between HR and lactate concentration and the $R^2$ value describes the variability from the model.

Both the high intensity athlete data and literature data can be described by the non-linear mathematical relationship of Equation (3), suggesting the relationship is robust and can be used from basal energy levels to above the lactate threshold during a single exercise session. In particular, Equation (3) captures the independent literature validation data very well.

The relationship between HR and lactate concentration is linear before LT, suggesting EGP could also be accurately predicted with a simpler linear relationship at exercise intensities below the LT. Equally, the ability to capture the data well with high $R^2$ values at all lactate and intensity levels, from basal to high intensity above LT, indicates the model presented is more complete across the full potential range of use. This portion of the model is thus robust and independently validated across the full physiological range for exercise.

### *4.2 EGP and HR*

Although it has been shown EGP can be suppressed from ingested glucose (Kowalski et al., 2017) and carbohydrate (Jeukendrup et al., 1999) in subjects at rest, the effect in the exercising individual has not been established. EGP has been shown to decrease after endurance exercise (Morrison et al., 2017). In addition, the stress hormone epinephrine released during exercise can suppress the inhibitory effects of insulin on EGP rate (Vicini et al., 2002), although the stimulatory effect of glucagon is greater than the inhibitory effect of insulin on EGP (Schiavon et al., 2013). Notably all these relationships have variability across individuals.

The exercise protocol for the high intensity athlete data included a glucose bolus at 30 minutes, and at exhaustion. Although this glucose administration would not be expected to affect the lactate levels, EGP may decrease when a glucose bolus is administered if insulin levels are increased. During intense exercise, the glucose in the blood stream may be utilized before a splanchnic hormone response is initiated.

### *4.3 Application to people with diabetes*

Estimating insulin and glucose requirements during exercise can be difficult for people with diabetes and can lead to severe dysglycaemic events. It has been shown exercise can help type 2 diabetes, and exercise should be encouraged (Lumb, 2014). Type 2 diabetes is partially characterized by dysfunction in insulin secretion and insulin action (Weyer et al., 1999) and this dysfunction can cause blood glucose levels during exercise to rise too high or drop too low if the glucose-insulin balance is not managed. In Type 1 diabetes, no or little insulin is secreted, and exogenous sources are required.

Insulin and glucagon are the main hormones regulating EGP during exercise (Wahren and Ekberg, 2007) and the dysregulation of insulin during diabetes can cause changes in EGP and blood glucose levels. Hepatic glycogenolysis is the main source of EGP during strenuous exercise (Wahren et al., 1971) and gluconeogenesis may contribute 30-40% of total glucose output in healthy people (Ahlborg et al., 1974). People with diabetes have abnormal glucose metabolism in the liver (Radziuk and Pye, 2001) with higher gluconeogenesis rates (Magnusson et al., 1992) and higher overall EGP production compared to healthy controls (Consoli, 1992).

Because of inter-individual variability and differences in liver glucose metabolism in people with diabetes, the EGP curve will differ. Adapting the EGP model for type 1 and type 2 diabetes using the same methodology could be used to improve management of glucose levels during exercise. Equally, the model presented could be validated in these groups to assess its generality, which is currently only demonstrated for healthy individuals, both trained and untrained.

### *4.4 Limitations*

The literature data consisted primarily of non-obese, male participants and used different methodologies to measure and assess EGP. People with obesity show higher gluconeogenesis, but total EGP is the same as non-obese persons (Muller et al., 1997). There were no subjects with diabetes. Thus, as noted, further validation may be required to demonstrate if the model is general enough or needs recalibration in metabolic dysfunction. However, the same methodology could be used to deliver a dysfunction specific model. Sex differences may also exist and further study is required.

All literature data started in the fasted state and was for a single bout of exercise. Repetitive types of exercise, such as intervals, or exercise completed when not in the fasted state may show different results. The high intensity athlete data in the literature consists of a very small sample size and although EGP was estimated during intense exercise, it was not directly measured. Thus, this aspect may lack full validation. However,

the ability of the model to deliver good fit to independent data at lower intensity exercise not included in model development adds some validation of this issue. Equally, the model assumes zero EGP at zero lactate, which provides a fixed point through this range and is itself realistic.

*4.5 Future work*

The effect of oral glucose boluses, or consumption of carbohydrate during exercise needs to be further explored to assess its impact on these relationships in terms of its potential inhibition of EGP independent of dynamics assessed by HR and lactate levels.

Differences in energy metabolism between trained and untrained individuals has been previously identified (Bergman et al., 2000; Gonzalez et al., 2016). Many individuals with Type 2 diabetes are sedentary and this may need to be considered when estimating EGP in these individuals.

There are many different devices for measuring HR. Use of a wrist-worn HR monitoring device that connects to a smart phone app would allow for real-time estimates of EGP. This is useful, both for the athlete requiring this knowledge for optimum recovery, and for the individual with diabetes who is regulating insulin and glucose.

## 5. CONCLUSION

The EGP of an exercising individual can be estimated using non-invasively measured HR instead of time, clinical, and resource intensive isotope tracer or NMR spectroscopy. The method and equations presented allow the EGP estimate to be used to manage diabetes or overall nutrition needs in healthy athletes in competition. Knowledge of EGP during exercise allows for insulin and glucose to be balanced. If an insulin pump is being used, the EGP estimate can be used in the algorithm for insulin dosing.

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