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Brief Reviews

Cardiorespiratory fitness predicts insulin action and secretion in healthy individuals

Filip J. Larsen[a,b], Martin Anderson[c], Björn Ekblom[a,b], Thomas Nyström[d,*]

[a] Department of Physiology and Pharmacology, Karolinska Institutet, SE-171 77 Stockholm, Sweden
[b] The Swedish School of Sport and Health Sciences, Åstrand Laboratory of Work Physiology, SE-114 86 Stockholm, Sweden
[c] Department of Clinical Science and Education, Karolinska Institutet, Division of Clinical Physiology, Södersjukhuset AB, SE-118 83 Stockholm, Sweden
[d] Department of Clinical Science and Education, Karolinska Institutet, Division of Internal Medicine, Södersjukhuset AB, SE-118 83 Stockholm, Sweden

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ABSTRACT

Long-term cardiorespiratory fitness (CRF) and the development of type 2 diabetes mellitus are inversely correlated. Here, we examined the relationships between peak oxygen uptake (VO_2peak), on the one hand, and glucose infusion rate at rest (GIR_{rest}) and during exercise ($GIR_{exercise}$), as well as insulin secretion (both the early and late phases of response [area under the curve $\{AUC\}_{insulin}$]), on the other. Eight male and 4 female healthy, lean, nonsmoking volunteers were recruited. The VO_2peak was measured during graded exercise on a cycle ergometer until exhaustion was reached. The GIR_{rest} and $GIR_{exercise}$ were determined using a euglycemic-hyperinsulinemic clamp, and insulin secretion at rest was evaluated with an intravenous glucose tolerance test. The VO_2peak correlated positively to GIR_{rest} ($r = 0.81$, $P = .001$) and $GIR_{exercise}$ ($r = 0.87$, $P < .001$) and negatively to $AUC_{insulin}$ ($r = -0.64$, $P = .03$). The respiratory exchange ratio (RER) during insulin infusion was positively correlated to GIR_{rest} ($r = 0.83$, $P < .001$) and $GIR_{exercise}$ ($r = 0.86$, $P < .01$) and negatively correlated to both the early insulin response ($r = -0.86$, $P < .0001$) and $AUC_{insulin}$ ($r = -0.87$, $P = .001$). The VO_2peak accounted for 45% of the variability in RER ($R^2 = 0.45$, $P = .035$). In this healthy population, CRF and RER were highly correlated to insulin sensitivity and secretion, as well as to the ability to alter the substrate being oxidized during exercise. These findings highlight the importance of good CRF to maintaining normal insulin action.

1. Introduction

Most healthy subjects occasionally experience periods of insulin resistance, which are adjusted for adequately by enhanced insulin secretion by the pancreatic β-cells [1]. In contrast to the maintenance of normal glucose tolerance, individuals who develop type 2 diabetes mellitus (T2DM) are unable to compensate for defects in insulin action and/or

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* *Corresponding author*. Tel.: +4686163211; fax: +4686163146.
E-mail address: thomas.nystrom@sodersjukhuset.se (T. Nyström).

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secretion [2]. Such findings indicate that interventions designed to prevent diabetes in those at risk should begin at an early stage and target both insulin resistance and secretory dysfunction.

Physical activity is a strong predictor of a lower risk for T2DM and may thus provide an approach to slowing down or even reversing the ongoing increase in the incidence of this disease [3-5]. Peak oxygen uptake (VO_2peak) is considered to be the hallmark indicator of cardiorespiratory fitness (CRF), and poor CRF is associated with greater risk for T2DM [6]. The VO_2peak of individuals with insulin resistance and T2DM is generally reduced, concomitant with an attenuated capacity to transport and oxidize glucose and a decrement in cellular glycogen synthase activity [7]. At the same time, the extent to which CRF is correlated to insulin sensitivity and secretion in healthy, lean individuals is not yet fully understood. We aimed to evaluate VO_2peak and β-cell function in healthy subjects with different levels of CRF in connection with a euglycemic-hyperinsulinemic clamp at rest ($Clamp_{rest}$) and during exercise involving a submaximal workload ($Clamp_{exercise}$).

2. Methods

Eight men and 4 women (age, 29 ± 9.3 years) participated in this study. Subjects were healthy (without family history of T2DM), lean (body mass index [BMI], 23.4 ± 2.3 kg/m^2), nonsmokers, and with normal blood pressure (systolic, 116 ± 21 mm Hg; diastolic, 81 ± 9 mm Hg). Subjects had levels of physical activity ranging from sedentary to competition in endurance sports at a national level (VO_2peak, 36-71 mL kg^{-1} min^{-1}). All provided written informed consent before initiation of the experiments, and the study protocol was preapproved by the local ethics committee in Stockholm.

Initially, the CRF of these subjects was evaluated with a graded exercise test on a cycle ergometer (Monark 839E, Varberg, Sweden). The subjects were instructed to avoid all physical exercise or exertion for at least 36 hours before this test. They were also told to consume standardized meals during the 4-day period preceding the test, eating their last meal no later than 10:00 PM on the evening before. The initial workload corresponded to approximately 30% of VO_2peak and was elevated by 15 to 30 W every 30 seconds until exhaustion was reached. Heart rate was followed with a Polar heart rate monitor (Polar Electro, Kempele, Finland).

2.1. *Euglycemic-hyperinsulinemic clamp at rest and during exercise*

To allow repeated collection of arterialized venous blood for determination of glucose, a superficial dorsal vein on one hand was cannulated in the retrograde direction with a small 3-way needle and kept open by repeated flushing with physiological saline solution while this hand was kept warm with a heating pad (Hemocue, Ängelholm, Sweden). Throughout the clamp, insulin (Human Actrapid; Novo Nordisk, Malmö, Sweden) together with 20% dextrose (Fresenius Kabi, Uppsala, Sweden) was infused at a constant rate (20 mU m^{-2} min^{-1}) into the left antecubital vein of the opposite arm. Baseline blood samples were taken and initiated by infusion of a bolus dose of insulin during a period of 4 minutes, followed by a stepwise increase in the rate of glucose infusion (GIR) for 10 minutes. Thereafter, based on the monitoring of blood glucose levels once every 5 minutes, the GIR was adjusted to maintain a constant

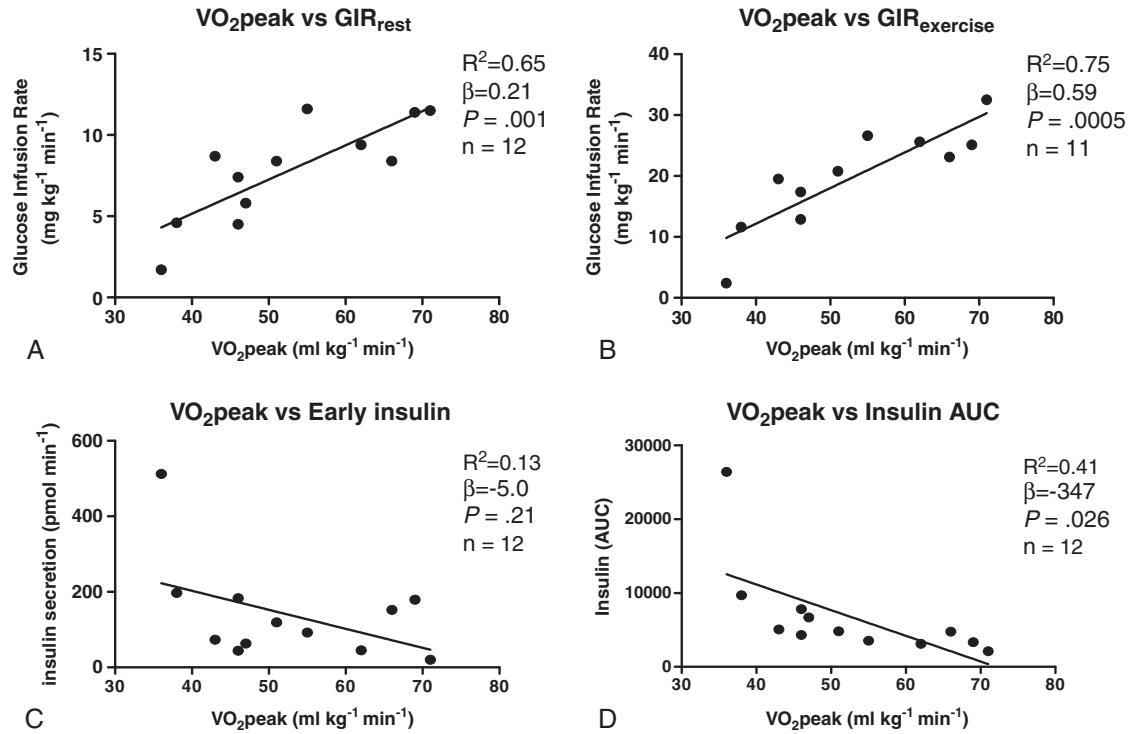

Fig. 1 – A to D, Correlation (Pearson [R^2] and the slope [ß]) between VO_2peak and GIR among healthy subjects with a wide range of cardiorespiratory fitness. A, GIR_{rest}. B, $GIR_{exercise}$. C, The early insulin response. D, The $AUC_{insulin}$.

concentration of 5 mmol/L [8]. After 120 minutes of clamp while resting in bed ($Clamp_{rest}$), the subjects began exercising on a cycle ergometer for 60 minutes with continued clamping ($Clamp_{exercise}$) at a workload of 45% of VO_2peak.

2.2. The intravenous glucose tolerance test

On the second experimental occasion following 12 hours of fasting, an intravenous glucose tolerance test (300 mg/kg in a 30% solution) was infused into the antecubital vein during 60 seconds; and blood samples were taken from the contralateral antecubital vein at 0, 2, 4, 6, 8, 10, 20, 30, 40, 50, 60, and 75 minutes to characterize the early period of insulin response (0-10 minutes) and the areas under the concentration curves for insulin ($AUC_{Insulin}$), C-peptide ($AUC_{C\text{-}peptide}$), and glucose ($AUC_{Glucose}$) [9].

2.3. Oxygen consumption and the respiratory exchange ratio during insulin stimulation

Oxygen uptake (VO_2), expired carbon dioxide, and pulmonary ventilation were analyzed with a computerized metabolic system involving a flowmeter connected to a mouthpiece (Jaeger Oxycon Pro, Hoechberg, Germany). The respiratory exchange ratio (RER) was calculated as expired carbon dioxide/VO_2 during the submaximal exercise (at 5, 25, and 55 minutes) during the clamp. Because it is well established that, during low-intensity exercise, in the absence of insulin infusion CRF is inversely correlated to RER [10], a high RER during such infusion indicates a shift in substrate utilization toward primarily carbohydrate oxidation. The net oxidation, reflected in the amount of glucose infused minus the amount oxidized, was calculated as described previously [11].

2.4. Statistical analyses

The values presented are means ± SEM. Correlation coefficients (r) and the slope (β) were calculated according to Pearson. Areas under the curve were calculated by the trapezoidal integration procedure. A 2-sided P value of $< .05$ was considered to be statistically significant. All of these analyses were performed using the statistical software package GraphPad Prism for PC (La Jolla, CA, USA).

3. Results

There was an almost perfectly linear relationship between GIR_{rest} (7.8 ± 0.9 mg kg^{-1} min^{-1}) and $GIR_{exercise}$ (19.8 ± 2.5 mg kg^{-1} min^{-1}) ($r = 0.94$, $P < .0001$). One subject exhibited a very low GIR_{rest} (1.9 mg kg^{-1} min^{-1}); and although not diabetic according to the definition formulated by the World Health Organization, repeated determination of his fasting plasma levels of glucose resulted in values of 5.8 and 5.9 mmol/L, and the corresponding value in connection with the 120-minute oral glucose tolerance test was 4.9 mmol/L. Because of nausea, one subject could not complete the exercise session, whereas for another, VO_2 data in connection with clamp during

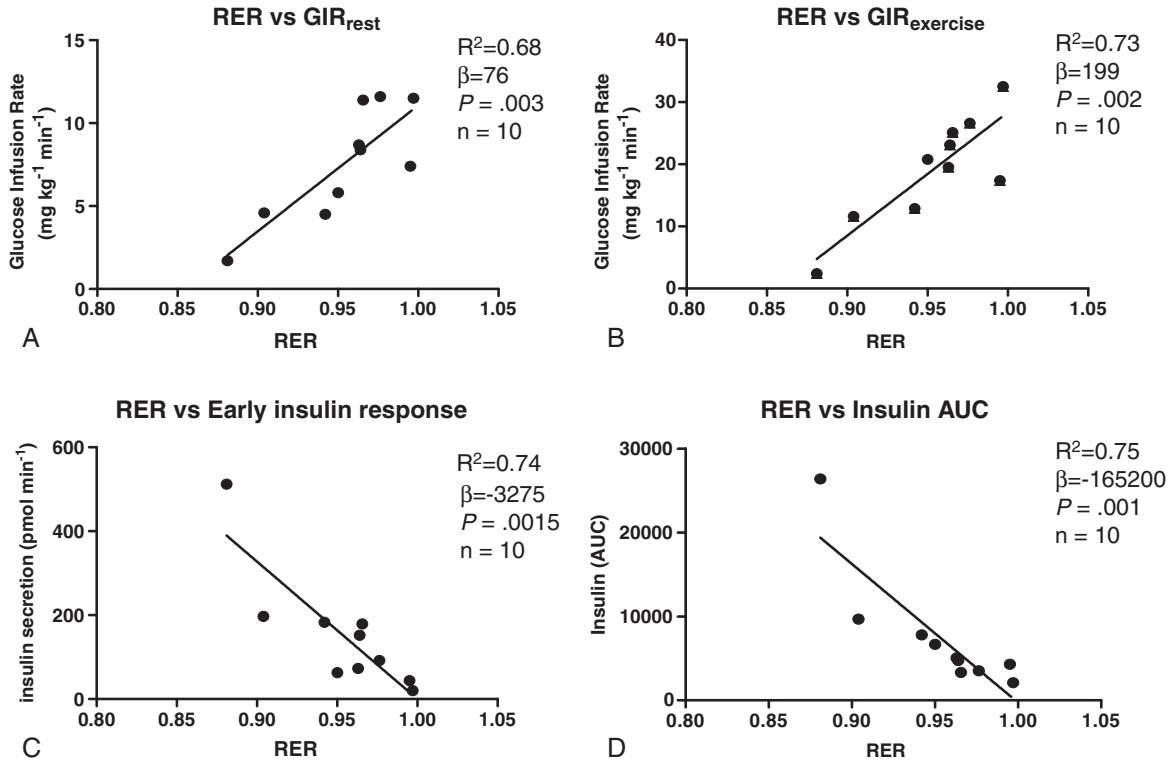

Fig. 2 – A to D, Correlation (Pearson [R^2] and the slope [ß]) between the RER and GIR among healthy subjects with a wide range of cardiorespiratory fitness. A, GIR_{rest}. B, $GIR_{exercise}$. C, The early insulin response. D, The $AUC_{insulin}$.

exercise were missing, so that Figs. 1B and 2A-D depict the values for the other 11 and 10 participants, respectively.

3.1. *BMI and insulin sensitivity/ß-cell function*

No significant correlations between BMI, on the one hand, and GIR_{rest} ($r = 0.45$, $P = .116$), $GIR_{exercise}$ ($r = 0.50$, $P = .144$), early insulin secretion ($r = 0.1$, $P = .82$), $AUC_{insulin}$ ($r = 0.22$, $P = .49$), $AUC_{C\text{-}peptide}$ ($r = 0.24$, $P = .45$), or RER ($r = 0.2$, $P = .59$), on the other hand, were observed. Although the relationship between BMI and VO_2peak was of borderline significance ($r = –0.57$, $P = .051$), there was no significant correlation between BMI and RER ($r = 0.2$, $P = .6$).

3.2. *VO_2peak and insulin sensitivity/ß-cell function*

The correlations between VO_2peak and GIR_{rest} (Fig. 1A) and $GIR_{exercise}$ (Fig. 1B) were highly significant. At the same time, there was a significant negative correlation between VO_2peak and $AUC_{insulin}$ (Fig. 1D) and $AUC_{C\text{-}peptide}$ ($r = –0.77$, $P = .004$), with no such association between VO_2peak and early insulin secretion (Fig. 1C). The VO_2peak was also significantly correlated with contraction-mediated GIR ($GIR_{contraction} = GIR_{exercise} – GIR_{rest}$), which reflects glucose uptake by the contracting muscles ($R^2 = 0.51$, $P = .009$). Finally, there was a trend toward a negative correlation between net glucose oxidation and VO_2peak ($r = –0.6$, $P = .07$).

3.3. *RER and insulin sensitivity/ß-cell function*

The correlations of RER to GIR_{rest} (Fig. 2A) and to $GIR_{exercise}$ (Fig. 2B) were also highly significant. The RER was significantly correlated to β-cell function in connection with the early insulin response (Fig. 2C), as well as to $AUC_{insulin}$ (Fig. 2D) and $AUC_{C\text{-}peptide}$ ($r = 0.93$, $P < .0001$). In addition, there was a positive correlation between RER and VO_2peak ($r = 0.68$, $P < .05$).

It could be argued that the correlations (Figs. 1 and 2) are due to the single outlier. When the values for this particular individual were omitted, the correlations obtained were still as high (ie, for Fig. 1C, $r = 0.54$, $P = .06$; Fig. 1D, $r = 0.78$, $P = .04$; Fig. 2C, $r = 0.74$, $P = .02$; and Fig. 2D, $r = 0.92$, $P = .0005$).

4. Discussion

The major findings documented here are the strong positive correlations of both VO_2peak and RER during insulin infusion to insulin sensitivity, along with a pronounced negative correlation to compensatory insulin secretion. The wide range of insulin sensitivity (GIR_{rest}) and the close association between VO_2peak and GIR, on the one hand, and insulin secretion, on the other, suggest that CRF exerts an important impact on both insulin-induced glucose uptake and insulin secretion. This association extends far beyond the range of VO_2peak values normally demonstrated by healthy, but untrained individuals [12]. This finding suggests that a very high level of aerobic fitness, such as that exhibited by our elite endurance athletes, is associated with enhanced insulin sensitivity, together with an attenuated requirement for insulin secretion in response to intravenous infusion of a given amount of glucose.

When exercise at approximately 45% of VO_2peak was performed in combination with infusion of insulin, the glucose uptake rose 2.5-fold; and the association between VO_2peak and $GIR_{exercise}$ was further enhanced, explaining as much as 75% of glucose uptake. It could be argued that this pronounced correlation was an artifact caused by the higher absolute workload and associated higher rates of glucose oxidation by the more well-trained subjects. However, the net glucose uptake (amount infused – amount oxidized) was negative in all of the participants, indicating that under these conditions endogenous carbohydrate stores are oxidized concomitantly with the infused sugar.

It is generally accepted that during exercise of the same intensity, endurance-trained athletes exhibit a RER that is lower than that of sedentary subjects, indicating a more pronounced contribution of fat oxidation to energy production in the former [12]. A RER value of close to 0.7 reflects predominantly oxidation of fat, whereas a value close to 1.0 indicates carbohydrate oxidation [10]. Interestingly, in the current study, the increase in VO_2peak could explain 45% of the variation of RER during insulin infusion. It can be estimated from our present findings that a VO_2peak of approximately 45 mL kg^{-1} min^{-1} is required to approach an RER value of 1.0. Body mass index could explain 20% of the variance in insulin sensitivity, whereas CRF could explain as much as 65% and 75% of this variance at rest and during exercise, respectively. The explanation for this poor association between BMI and CRF might simply be that we recruited only lean subjects, in contrast to other recent studies [13].

The special strengths of the present study are worth emphasizing: the healthy participants exhibited a wide range of CRF levels, and the pronounced associations between CRF and insulin action and secretion were all established using criterion standard procedures. However, certain weaknesses have to be mentioned as well. The small number of subjects raises concerns about the general applicability of our observations. Moreover, because this was a cross-sectional study, we cannot draw any conclusions concerning causal relationships.

5. Summary

Our present findings indicate that in healthy, lean individuals, VO_2peak predicts both serum levels of insulin and uptake of glucose due to muscle contraction. The positive correlation observed between VO_2peak/RER and GIR (compensated for by enhanced secretion of insulin) in those subjects with the lowest insulin sensitivity clearly demonstrates the importance of aerobic fitness in healthy subjects. There appears to be no upper limit to this correlation: even individuals with VO_2peak values far above average demonstrate elevated insulin sensitivity and, consequently, less need for insulin secretion in response to infusion of a given amount of glucose. The VO_2peak values of approximately 45 mL kg^{-1} min^{-1} appear to be sufficient to achieve maximal RER. Together, these findings highlight the benefits of maintaining good CRF on insulin regulation.

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Conflict of Interest

None of the authors has any conflict of interest.

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