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Minimal model-derived insulin sensitivity, insulin secretion and glucose tolerance: relationships with blood rheology

Jean-Frédéric Brun[a,*], Emmanuelle Varlet-Marie[b,c], Eric Raynaud de Mauverger[a] and Jacques Mercier[a]

[a]*INSERM U1046, Physiopathologie & Médecine Expérimentale du Cœur et des Muscles, Equipe d'Explorations Métaboliques (CERAMM), Université Montpellier 1, Université Montpellier 2, Département de Physiologie Clinique, Hôpital Lapeyronie CHU Montpellier, France*
[b]*Laboratoire de Biophysique & Bio-Analyses, Faculté de Pharmacie, Université Montpellier I, France*
[c]*Laboratoire Performance Santé Altitude, Sciences et Techniques des Activités Physiques et Sportives, Université de Perpignan Via Domitia, France*

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Abstract. Insulin resistance is associated with a mild hyperviscosity syndrome, which is more closely related to insulin resistance than to the clinical scoring of the metabolic syndrome. In studies using the intravenous glucose tolerance test with minimal model analysis we reported that low insulin sensitivity (SI) is associated with increased erythrocyte aggregability (EA). Actually, this issue is confusing because insulin resistance is often associated with compensatory hyperinsulinemia (insulin being a hormone with reported hemorheologic effects) and that a decline in insulin secretion has marked metabolic effects that modify blood rheology. From the intravenous glucose tolerance test (IVGTT) the minimal model allows the calculation of SI, insulin response, and an overall glucose tolerance parameter termed "disposition index" (DI) that measures whether insulin response is adequate or not for the level of insulin sensitivity. In this study we assessed SI, insulin response, and DI during an IVGTT in 335 subjects of both genders (age 8–77 yr; BMI 14–67 kg/m^2). SI was only correlated (negatively) with EA (Myrenne M $r = -0.285$; $p = 0.0001$; M1 $r = -0.240$ $p = 0.003$). Fasting insulin was also correlated (positively) with EA (Myrenne M $r = 0.233$, 0.00880; M1 $r = 0.320$ $p = 0.0003$; SEFAM TA $r = -0.342$ $p = 0.04$; SEFAM S_{60} $r = 0.419$ $p = 0.01$) and SEFAM RBC disaggregation thresholds ($\gamma S = r = 0.372$ $p = 0.025$; $\gamma D = r = 0.504$ $p = 0.002$). Fasting DI (SI x fasting insulin) is negatively correlated to M ($r = -0.274$; $p = 0.002$) and M1 ($r = -0.225$; $p = 0.01$) but also positively to whole blood viscosity ($r = 0.168$; $p = 0.01$) and hematocrit ($r = 0.142$; $p = 0.05$). Stimulatory DI (SI x insulin peak) fails to be correlated with any parameter of EA but is negatively correlated to whole blood viscosity ($r = -0.150$; $p = 0.02$) and plasma viscosity ($r = -0.163$; $p = 0.01$). This study confirms that red cell aggregability is associated with insulin resistance and hyperinsulinemia, but plasma viscosity seems to be more related to overall glucose tolerance than to either SI or insulinemia.

Keywords: Insulin sensitivity, minimal model, hemorheology, erythrocyte deformability, blood viscosity, erythrocyte aggregation

*Corresponding author: Dr. Jean-Frédéric Brun, MD, PhD, INSERM U1046, Physiopathologie & Médecine Expérimentale du Cœur et des Muscles, Equipe d'Explorations Métaboliques (CERAMM), Université Montpellier 1, Université Montpellier 2, Département de Physiologie Clinique, Hôpital Lapeyronie CHU Montpellier, France. Tel.: +33 467338284; Fax: +33 467338986; E-mail: j-brun@chu-montpellier.fr.

1. Introduction

Relationship between SI and rheology have been reported since 1994, by our team [9, 11] and others [19, 25]. Insulin resistance appears to be associated with a mild hyperviscosity syndrome, which is more closely related to insulin resistance than to the clinical scoring of the metabolic syndrome [1]. In studies using the intravenous glucose tolerance test with minimal model analysis we reported that low SI is associated with increased erythrocyte aggregability [8, 26] and increased plasma viscosity.

Actually, this issue is confusing because insulin resistance is often associated with compensatory hyperinsulinemia (insulin being a hormone with reported hemorheologic effects) and that a decline in insulin secretion has marked metabolic effects that modify blood rheology. From the IVGTT the minimal model allows the calculation of SI, insulin response, and an overall glucose tolerance parameter termed "disposition index" (DI) that measures whether insulin response is adequate or not for the level of insulin sensitivity [5, 23]. In this study we assessed SI, insulin response, and DI during an IVGTT in a large sample of subjects of both genders.

2. Materials and methods

2.1. Subjects

Study subjects are described on Table 1. They were selected in order to display a wide range of body mass indices (from 17 to 39 kg/m^2) which could be thus expected to show various levels of insulin, insulin sensitivity and blood viscosity, allowing to analyze the relationships among all these parameters. The studies were performed in accordance with the regulations of the local medical ethic committee of Montpellier, France, in accordance with the revised Helsinki Declaration.

2.2. Body composition

Body composition was assessed with a multifrequency bioelectrical impedancemeter Dietosystem Human IM Scan that uses low intensity (100–800 μA) at the following frequencies: 1, 5, 10, 50, and 100 kHz. Analysis was performed with a home-made software based on Kyle's "Geneva equation" for fat-free mass [21] and body water evaluation according to Jaffrin's developments of the Hanai's mixture conductivity theory [20].

Table 1
Characteristics of the 335 study subjects (122 men, 213 women) in whom insulin sensitivity was measured with the minimal model

Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m^2)	WHR	%fat	BP max	BP min
37.95	78.10	156.47	28.25	0.86	33.43	9.06	5.65
± 0.91	± 1.28	± 2.19	± 0.42	± 0.01	± 3.28	± 0.85	± 0.53

BMI: body mass index; WHR: waist-to-hip ratio; %fat: percentage of body fat; BP max: systolic blood pressure; BP min: diastolic blood pressure.

2.3. IVGTT with minimal model analysis

Although no alimentary restriction was imposed, subjects were asked to fast for 12 hrs before the beginning of the test at 9 : 00 A.M. A cannula was placed in the cephalic vein at the level of the cubital fossa for blood sampling at various times, while glucose injection was performed in the controlateral cephalic vein. Glucose (0.5 g/kg, solution at 30%) was slowly injected during 3 min. Insulin (0.02 units/kg body weight *i.e.* 1 or 2 units) was injected intravenously immediately after time 19. Blood samples were drawn twice before the glucose bolus and at 1, 3, 4, 8, 10, 15, 19, 20, 22, 30, 41, 70, 90 and 180 min following the onset of the glucose injection [6]. The minimal model analysis from the IVGTT was performed according to the method reported by Bergman [6] using the software TISPAG regularly used in our laboratory [10], which uses a nonlinear least square estimation. This program produced the values for S_I and S_G. In the minimal model, S_I represents the dose-response effect on glucose disposal of an increase in insulin above baseline, while S_G is an evaluation of the rate of glucose disposal that would be observed even without any change in insulin levels [7]. Calculations of these parameters were described previously [6, 10].

2.4. Laboratory measurements

Viscometric measurements were done at very high shear rate ($1000\,s^{-1}$) with a falling ball viscometer (MT 90 Medicatest, F-86280 Saint Benoit) [14, 17]. The coefficient of variation of this method ranges between 0.6 and 0.8%. We measured with this device apparent viscosity of whole blood at native hematocrit, plasma viscosity, and blood viscosity at corrected hematocrit (45%) according to the equation of Quemada [27]. RBC aggregation was measured with laser backscattering (erythroagregometer SEFAM – AFFIBIO) [13, 15]. Indices of red blood cells (RBC) aggregation: (c): primary time of aggregation TA; (d) secondary time of aggregation TF; (e) index of structure Is; partial disaggregation threshold γD and total disaggregation threshold γS; (f) indices S_{10} et S_{60} which quantify the mean importance of aggregation at 10 and 60 sec. The updated guidelines for hemorheological laboratory techniques [4] were taken into account.

3. Results

S_I was only correlated (negatively) with EA (Myrenne: M $r=-0.285$ $p=0.0001$; M1 $r=-0.240$ $p=0.003$). Accordingly, "insulin resistance" $1/S_I$, *i.e.* the reciprocal of S_I was negatively correlated with EA (Myrenne: M $r=-0.142$ $p=0.033$; M1 $r=-0.174$ $p=0.021$; SEFAM: TA $r=0.228$ $p=0.005$; S_{10} $r=-0.324$ $p=0.039$; S_{60} $r=0.425$ $p=0.0056$) and red cell rigidity "k" ($r=-0.142$ $p=0.033$), with whole blood viscosity ($r=-0.132$ $p=0.03$) and hematocrit ($r=-0.271$ $p=0.00001$) (Table 2). Fasting insulin was also correlated (positively) with EA (Myrenne: M $r=0.235$ $p=0.009$; M1 $r=0.320$ $p=0.0003$; SEFAM: TA $r=-0.342$; $p=0.04$; S60 $r=0.419$; $p=0.01$) and RBC disaggregation thresholds (γS $r=0.372$ $p=0.025$; γD $r=0.504$ $p=0.002$) (Table 2). Fasting DI (SI x fasting insulin) is negatively correlated to M ($r=-0.274$ $p=0.002$) and M1 ($r=-0.225$ $p=0.01$) but also positively to whole blood viscosity ($r=0.168$ $p=0.01$) and hematocrit ($r=0.142$ $p=0.05$) (Table 2). Stimulatory DI (SI $\times$ insulin peak) fails to be correlated with any parameter of EA but is negatively correlated to whole blood viscosity ($r=-0.150$ $p=0.02$) and plasma viscosity ($r=-0.163$ $p=0.01$) (Table 2).

Table 2
Correlations among hemorheological factors and measurement of glucose disposal

	Hct	Whole blood viscosity	Plasma viscosity	Tk	k	M	M1	TA	S_{10}	S_{60}	γS	γD
SI	$r=0.105$	$r=0.090$	$r=-0.044$	$r=0.037$	$r=0.042$	$r=-0.285$	$r=-0.240$	$r=-0.009$	$r=-0.06$	$r=0.031$	$r=-0.192$	$r=-0.226$
	NS	NS	NS	NS	NS	$p=0.0001$	$p=0.003$	NS	NS	NS	NS	NS
Ib	$r=0.032$	$r=0.046$	$r=-0.026$	$r=0.057$	$r=0.054$	$r=0.235$	$r=0.3198$	$r=-0.342$	$r=0.419$	$r=0.283$	$r=0.3722$	$r=0.50391$
	NS	NS	NS	NS	NS	$p=0.009$	$p=0.0003$	$p=0.038$	$p=0.01$	NS	$p=0.025$	$p=0.002$
SI × Ib	$r=0.142$	$r=0.168$	$r=-0.028$	$r=0.067$	$r=0.079$	$r=-0.274$	$r=-0.225$	$r=-0.034$	$r=-0.040$	$r=0.052$	$r=-0.128$	-0.133
	$p=0.05$	$p=0.01$	NS	NS	NS	$p=0.002$	$p=0.01$	NS	NS	NS	NS	NS
SI × AIRg	$r=0.047$	$r=-0.150$	$r=-0.163$	$r=-0.056$	$r=-0.077$	$r=-0.055$	$r=-0.067$	$r=0.053$	$r=-0.081$	$r=0.013$	$r=-0.111$	-0.0852
	NS	$p=0.019$	$p=0.011$	NS	NS	NS	NS	NS	NS	NS	NS	NS

Hct: hematocrit; Tk: red cell rigidity index according to Dintenfass; k: red cell rigidity index according to Quemada; M and M1: erythrocyte aggregability indexes given by the Myrenne erythroaggregometer; TA, S_{10}, S_{60}, γS, γD: parameters of red cell aggregation given by the SEFAM-Affibio erythroaggregometer, NS: non significant.

4. Discussion

This study confirms that insulin resistance is associated with raised red cell aggregation, as does hyperinsulinemia which is also associated with decreased RBC disaggregability as measured with the SEFAM disaggregation thresholds. The new finding is that whole blood viscosity and plasma viscosity are rather related to the disposition index AIRg × SI which measures overall glucose tolerance and depends on the dynamic response of insulin to glucose for a given level of insulin resistance.

Due to the magnitude of the sample we are able to analyze in terms of correlations the relationships that we previously described in difference among quartiles of distribution. This allows to analyze them multiparametrically and thus helps to clarify this complex picture.

The issue of insulin resistance and metabolic syndrome is conflicting since the current clinical definitions of the metabolic syndrome do no longer refer to insulin resistance, so that there are actually non-insulin resistant patients with the metabolic syndrome and insulin resistant patients without the metabolic syndrome [18]. However, insulin resistance is undoubtedly the pivotal pathogenetic factor in this story [22, 24, 31]. In this study we based the analysis on insulin resistance measured with the minimal model which is, beside the glucose clamp, an "alternative gold standard" [6].

Most abnormalities related to insulin resistance are able to modify blood rheology [12]: hypertriglyceridemia, low HDL cholesterol, hypertension, endothelial dysfunction, raised fibrinogen, low grade inflammation. The respective influence of all of them is hard to delineate.

It appears that increased red cell aggregation is a very early phenomenon that characterizes insulin resistance at a stage where it is still compensated by an increase in insulin. When this compensatory hyperinsulinism vanishes, the syndrome worsens and there is a rise in plasma viscosity. Therefore, high η_p reflects a further step in insulin resistance, as indicated by the decrease in disposition index which means that, although still high, insulin levels are now relatively insufficient. We have previously shown that this rise in plasma viscosity is corrected by insulin-sensitizing procedures such as exercise training [2, 16]. Presumably, this increase in plasma viscosity is explained by the combination of several metabolic disturbances, including high triglycerides and high fibrinogen.

By contrast, what explains an early increase in aggregability before the decompensation of insulin resistance has long be unexplained. It seems logic now to explain this abnormality by a direct effect of insulin resistance on endothelial function [24], resulting in increased levels of proaggregant proteins like fibrinogen. Interestingly, fibrinogen levels are directly correlated to the extent of insulin resistance [29, 30].

In conclusion, this study confirms that RBC aggregation in the insulin resistance (so-called 'metabolic syndrome') is associated with insulin resistance and hyperinsulinemia, but it also indicates that η_p seems to be more related to overall glucose tolerance than to either SI or insulinemia. Thus, RBC aggregation and η_p are likely to reflect two successive evolutionary stages in the evolution of insulin resistance.

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