Effects of fasting and/or postprandial glucose on heart rate recovery in patients with coronary heart disease

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Aim. – The impact of both fasting and postprandial glycaemia on heart rate recovery (HRR) has not been studied in patients with coronary heart disease (CHD). For this reason, we sought to determine the relationships between HRR and both fasting and postprandial glycaemia.

Methods. – A total of 4079 patients with baseline fasting plasma glucose (FPG) levels and 706 patients with 2-hour postprandial glucose (2hPG) levels were identified from the Coronary Artery Surgery Study registry, a database of 24,958 patients with suspected or proven CHD who had undergone cardiac catheterization between 1974 and 1979. Median long-term follow-up was 14.7 years (interquartile range: 9.8–16.2 years). The relationships between HRR and both FPG and 2hPG were studied.

Results. – In univariate analyses, increasing levels of both FPG and 2hPG were significantly associated with lower HRR. In multivariate models adjusted for age, exercise tolerance in METs, resting heart rate and maximum systolic blood pressure during exercise testing, FPG remained significantly associated with HRR while 2hPG did not.

Conclusion. – Both raised FPG and decreased HRR are independent predictors of total and cardiovascular (CV) mortality in subjects with CHD. Our data suggest that the mortality risk associated with elevated FPG may in part be due to deleterious effects on autonomic regulation of CV function, as reflected by lower HRR. Further studies are required to determine whether or not non-pharmacological and/or pharmacological treatments of increased fasting glucose have a beneficial influence on HRR.

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Keywords: Exercise testing; Heart rate recovery; Glycaemia; Prognosis; Coronary heart disease

Résumé

Effet de la glycémie à jeun et/ou postprandiale sur la fréquence cardiaque de récupération chez les patients coronariens.

But. – L’impact de la glycémie à jeun et postprandiale sur la fréquence cardiaque de récupération (FCR) n’a pas été étudié chez les patients coronariens. Nous avons souhaité déterminer la relation entre la FCR et la glycémie à jeun et postprandiale.

Méthodes. – Nous avons identifié 4079 patients avec une mesure de glycémie à jeun (GJ) et 706 patients avec une glycémie postprandiale mesurée deux heures après le repas (GP-2h), à partir du registre « Coronary Artery Surgery Study ». Cette base de données comprend 24 958 patients avec une maladie coronaire suspectée ou prouvée ayant subi une cathétérisation cardiaque entre 1974 et 1979. Le suivi médian à long terme était de 14,7 ans (écart interquartile : 9,8 à 16,2). La relation entre la fréquence cardiaque de récupération après une épreuve d’effort, la GJ et la GP-2h ont été étudiées.

Résultats. – Dans les analyses univariées, la GJ et la GP-2h sont associées à une FCR significativement plus faible. Dans l’analyse multivariée ajustée pour l’âge, la tolérance à l’effort en METS, la fréquence cardiaque de repos et la pression artérielle systolique maximale lors de l’épreuve d’effort, la GJ est demeurée associée de façon significative à la FCR tandis que la GP-2h ne l’était plus.

Conclusion. – Une augmentation de la GJ ainsi qu’une FCR diminuée sont des prédicteurs indépendants de mortalité totale et cardiovasculaire chez les patients coronariens. Nos données suggèrent que le risque de mortalité associé à une augmentation de la GJ pourrait être en partie dû à des effets délétères sur la régulation autonome de la fonction cardiovasculaire tels qu’observés par une FCR diminuée. De nouvelles études sont nécessaires.

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nécessaires pour déterminer si un traitement pharmacologique ou non pharmacologique d’une GJ augmentée pourrait avoir un impact bénéfique sur la FCR.

Mots clés : Épreuve d’effort ; Fréquence cardiaque de récupération ; Glycémie ; Pronostic ; Maladie coronarienne

1. Introduction

Of the various heart rate prognostic variables provided by exercise testing (ET), heart rate recovery (HRR) has been shown to be associated with total and cardiovascular (CV) mortality and/or morbidity [1–13]. The rise in heart rate during ET is considered to be a combination of increased sympathetic and decreased parasympathetic activation [14], whereas the fall in heart rate immediately after exercise is considered to be a function of reactivation of the parasympathetic nervous system [11,15]. Impaired autonomic regulation of CV function, including abnormal HRR, is a feature of diabetes mellitus that is associated with a poor prognosis [5]. Among the milder disorders of glucose metabolism, including impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), IGT, as measured following an oral glucose tolerance test (OGTT), has been shown to be an independent risk factor for non fatal and fatal CV events in patients without documented CHD [16–18]. In contrast, conflicting results between IFG and prognosis have been reported in the literature: some studies [16,19,20] have suggested no relationship between IFG and CV risk, whereas more recent studies do suggest a relationship [21,22]. The present authors recently reported, in a large CHD sample. It is unclear whether both fasting and postprandial glucose levels have similar and additive effects on cause and CV mortality, while postprandial (2-hour post-meal) glucose was not associated with excess morbidity or mortality after a median follow-up period of 15 years [18].

Fasting plasma glucose (FPG) is strongly and independently associated with abnormal HRR in healthy individuals and diabetic patients [5,23,24]. The relationship between postprandial glucose metabolism, FPG and HRR, however, has not been studied in a CHD population. It is unclear whether both fasting and postprandial glucose levels have similar and additive effects on HRR. Thus, the objectives of the present study were to determine, in a large and well-characterized CHD population, the:

- relationship between HRR and both fasting (normoglycaemia, IFG and diabetes) and postprandial (normoglycaemia, postprandial hyperglycaemia and diabetes) glucose and;
- relative contributions of fasting and postprandial glucose to the presence of abnormal HRR.

2. Materials and methods

2.1. Patient population and follow-up

The Coronary Artery Surgery Study (CASS) registry includes 24,958 patients with suspected or proven CHD enrolled at 15 centres throughout North America between 1974 and 1979. Patients had annual scheduled follow-ups until 1982, after which their vital status was obtained through a mail-in survey completed between 1989 and 1991. Vital status for non-responders was obtained from the National Death Index for patients in the United States, and from next of kin, medical records and death certificates in Canada. Follow-up was complete for 96% of patients in the registry by the closing date of December 31, 1992. Patients without death records available were considered still living. Cardiovascular mortality was defined according to the International Classification of Diseases, eighth revision, using codes 390–458.

2.2. Clinical variables

These were derived from the CASS registry and obtained at the time of enrolment in the study, and included age, gender, medical history of diabetes, hypertension, hypercholesterolaemia, smoking and beta-blocker use. Additional variables studied were systolic and diastolic blood pressure, serum cholesterol, triglycerides, FPG, 2-hour postprandial (post-meal; 2hPG) glucose, left ventricular ejection fraction and extent of coronary disease. Postprandial blood glucose measurements were performed 2 hours after patients had consumed a so-called ‘average’ breakfast [17]. All blood-marker measurements were performed at the time of blood collection from fresh samples. The number of diseased coronary arteries was based upon whether or not the left anterior descending artery, left circumflex artery or right coronary artery had ≥ 70% diameter stenosis, or whether the left main artery had a ≥ 50% diameter stenosis. Left main artery disease was considered two-vessel disease in the presence of a right-dominant coronary circulation, and three-vessel disease in the presence of a left-dominant coronary circulation. Coronary angiograms were interpreted using visual estimation in the CASS registry.

2.3. Normal glycaemia, impaired fasting glucose, postprandial hyperglycaemia and unknown diabetes

Patients with known or treated diabetes (dietary or pharmacological treatment) were excluded from our analyses. Normoglycaemia was defined as FPG less than 5.6 mmol/L (100 mg/dL), IFG as FPG 5.6–6.9 mmol/L (100–125 mg/dL) and undiagnosed diabetes mellitus as FPG greater or equal to 7.0 mmol/L (≥ 125 mg/dL) in the absence of pharmacological therapy [25]. In the second analysis using only 2hPG levels, normoglycaemia was defined as a 2hPG less than 7.8 mmol/L (≤ 140 mg/dL), postprandial hyperglycaemia (PHG) as a 2hPG 7.8–11.0 mmol/L (140–199 mg/dL) and undiagnosed diabetes as a 2hPG greater or equal to 11.1 mmol/L (≥ 200 mg/dL) [26].
2.4. Exercise testing and heart rate measurements

Exercise testing (ET) was performed on a motor-driven treadmill using a modified maximum Bruce protocol [27]. The stages at which exercise was started and stopped were recorded, as was the duration of the test. Grounds for test discontinuation were those used in standard clinical practice [27]. All measurements were obtained from baseline ET. The peak or maximum heart rate during ET and %HRRes were obtained with the patient standing on the treadmill at completion of the modified Bruce protocol. Heart rate recovery (HRR) was calculated as the maximum heart rate – post-exercise heart rate reserve (%HRRes) was computed as (MaxHR – resting heart rate) / (220 – age – resting heart rate) × 100. Maximum age-predicted heart rate was calculated as 220 – age. Exercise capacity (in metabolic equivalents or METS) was estimated on the basis of the speed, slope and duration of exercise on the treadmill [28].

2.5. Statistical analysis

Results are expressed as means ± SD (standard deviation) or median (min, max) for continuous variables and as frequency (%) for categorical variables. Univariate analyses [one-way Anova (analysis of variance) or Kruskal-Wallis test for continuous variables and Pearson’s chi-square test for categorical variables] were used to compare the different glucose level groups. Ancova (analysis of covariance) was also performed to identify the independent contributions of fasting and postprandial glucose to HRR, after adjusting for prespecified variables thought to be associated with HRR (age, exercise tolerance in METs, resting heart rate, maximum systolic pressure during ET). Maximum heart rate during ET and %HRRes were excluded from the analysis due to multicollinearity with HRR. A P value less than 0.05 was considered statistically significant. Statistical analyses were performed with SAS version 8.02 software.

3. Results

3.1. Baseline characteristics

A total of 2674, 1118 and 287 patients were identified as normal, IFG and undiagnosed diabetes, respectively, and included in our first analysis (Table 1). With increasing FPG levels, an increase was also noted in mean age, serum triglycerides, 2hPG, history of hypertension and extent of CHD. Similarly, body weight, body mass index (BMI) and smoking prevalence were higher in the IFG and undiagnosed diabetes groups compared with the normal group.

The 2-hour postprandial blood glucose measurements were available for 706 patients. For our second analysis using 2hPG levels only, 440, 193 and 73 patients were identified as normal,
PPH and undiagnosed diabetes, respectively (Table 2). The PPH patients had a risk factor profile that was intermediate between the normoglycaemic and diabetic patients. BMI, serum triglycerides, fasting and postprandial glycaemia were all significantly higher in diabetic patients compared with PPH patients.

### 3.2. Exercise testing parameters

#### 3.2.1. Fasting glycaemia classification

Patients with diabetes had lower exercise capacity and heart rate reserve compared with patients with IFG and normoglycaemic subjects. Those with IFG or diabetes had higher resting heart rates and lower maximum heart rates and HRR compared with normoglycaemic subjects (Table 3).

#### 3.2.2. Postprandial glycaemia classification

Exercise capacity, maximum heart rate and heart rate reserves were significantly lower in patients with PPH compared with normoglycaemic subjects (Table 4). Patients with both PPH and diabetes had significantly lower HRR compared with normoglycaemic subjects.

### 3.3. Glucose metabolism and impaired heart rate recovery

In univariate analyses, both fasting and postprandial glucose were significantly correlated with HRR ($r = -0.14$, $P = 0.001$ and $r = -0.14$, $P = 0.002$ for fasting and postprandial glucose, respectively). Altogether, 509 subjects were identified for whom ET and fasting and postprandial glucose data were all concomitantly available in the registry database. Of this sample, and after adjusting for prespecified confounders (age, resting heart rate, maximum systolic blood pressure during ET and exercise tolerance), FPG remained significantly associated with HRR (parameter estimate: $-3.9; 95\%$ CI: $-6.9$, $-0.8; P = 0.037$) while postprandial glycaemia did not.

### 4. Discussion

The principal findings of our present study are:

- increases in both fasting and postprandial glucose were significantly associated with decreased HRR, and;
- FPG remained an independent predictor of HRR in multivariate models, whereas postprandial glucose did not.

The present study is the first to evaluate the relationship between HRR and increases in both fasting and postprandial glucose in CHD patients, and our findings are in accordance with previous data showing reduced HRR in adults with IFG [5] or diabetes [23]. In contrast, no previous studies have examined the potential relationship between postprandial glycaemia and HRR. However, the present findings are also consistent with our previous data in CHD patients showing:
Exercise parameters in subjects with normoglycaemia, postprandial hyperglycaemia and diabetic mellitus.

<table>
<thead>
<tr>
<th>Exercise parameters</th>
<th>Normoglycaemia (FPG &lt; 100 mg/dL) (n = 2674)</th>
<th>Impaired fasting glucose (FPG 100–125 mg/dL) (n = 1118)</th>
<th>Undiagnosed diabetes (FPG ≥ 126 mg/dL) (n = 287)</th>
<th>P value (Anova)</th>
<th>Intergroup differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>METs</td>
<td>Means ± SD</td>
<td>Means ± SD</td>
<td>Means ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>66.6 ± 2.9</td>
<td>64.1 ± 3</td>
<td>59.7 ± 3</td>
<td>0.0041</td>
<td>b**, c*</td>
</tr>
<tr>
<td>Resting SBP (mmHg)</td>
<td>72.0 ± 13</td>
<td>75.1 ± 14</td>
<td>77 ± 15</td>
<td>&lt;0.0001</td>
<td>a, b, c*</td>
</tr>
<tr>
<td>Resting DBP (mmHg)</td>
<td>134.9 ± 20.8</td>
<td>137.6 ± 21.7</td>
<td>137.3 ± 23.0</td>
<td>0.002</td>
<td>a***</td>
</tr>
<tr>
<td>Maximum HR (bpm)</td>
<td>84.0 ± 11.7</td>
<td>85.1 ± 12.1</td>
<td>85.3 ± 13.2</td>
<td>0.025</td>
<td>a*</td>
</tr>
<tr>
<td>Maximum SBP (mmHg)</td>
<td>139.2 ± 26</td>
<td>137.6 ± 26</td>
<td>133 ± 26</td>
<td>0.0005</td>
<td>a*, b***, c*</td>
</tr>
<tr>
<td>Maximum DBP (mmHg)</td>
<td>173.9 ± 29.8</td>
<td>174.8 ± 31.4</td>
<td>169.8 ± 29.7</td>
<td>0.057</td>
<td>–</td>
</tr>
<tr>
<td>HRR reserve (%)</td>
<td>69.0 ± 24</td>
<td>67.2 ± 25</td>
<td>63 ± 26</td>
<td>0.0019</td>
<td>b**, c*</td>
</tr>
</tbody>
</table>

FPG: fasting plasma glucose; METs: metabolic equivalents; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; HRR: heart rate recovery; 2hPG: 2-hour postprandial glucose; a: normoglycaemia vs impaired fasting glycaemia; b: normoglycaemia vs diabetes; c: impaired fasting glycaemia vs diabetes; *P < 0.05; **P < 0.01; ***P < 0.001.

- The harmful influence of impaired HRR on both total and CV mortality [29]; and:
- The independent impact of increases in FPG on total and CV mortality, and the lack of any prognostic impact of postprandial glucose [18].

Impaired fasting glycaemia and IGT (as reflected by PPH) appear to result from different pathophysiological mechanisms. IGT can result from peripheral insulin resistance [30], whereas IFG may be a manifestation of defective insulin secretion [31,32]. Abnormal HRR after exercise is a marker of the reduced parasympathetic activity found in patients with CHD and/or diabetes [12,23]. During recovery from exercise, parasympathetic vagal reactivation is primarily responsible for the important reduction of heart rate [11,15,23].

However, the mechanisms by which plasma glucose may be associated with abnormal HRR remain unclear. Importantly, as mentioned above, IFG and IGT (as reflected by PPH) appear to result from different pathophysiological mechanisms, and impaired HRR is present in those with CHD and/or diabetes [12,23]. A recent report documented increased FPG in association with decreased vagal tone [24], while weight-loss and lowering plasma glucose levels improved HRR in obese patients [32]. Other authors have suggested that higher plasma insulin levels are also related to autonomic dysfunction [23,32], with a decrease in the high-frequency component of the RR interval during spectral analysis of heart rate variability reflecting a reduction in vagal autonomic activity. A reduction in fasting glucose was shown to be the strongest predictor of HRR improvement in obese men who undertook a weight-loss programme, while a reduction in triglyceride-to-HDL-cholesterol ratio, a marker of insulin resistance, was a less important predictor of HRR in the same study [33]. Finally, of 90 middle-aged patients with type 2 diabetes undergoing exercise stress testing, insulin resistance as measured by homeostasis model assessment (HOMA-IR) showed no relationship with HRR [34]. Our present results are consistent with these findings: insulin resistance as measured by postprandial glucose had a less pronounced effect on HRR compared with FPG. In contrast, Lind et al. [35], in a small cohort of 70-year-old men without obesity or insulin resistance, found HRR to correlate inversely with insulin sensitivity as measured by the hyperinsulinaemic–euglycaemic clamp technique.
The present study also showed that subjects with increased fasting glucose in the non diabetic and diabetic range had higher resting heart rates, lower maximum heart rates and lower heart rate reserves (diabetics only), suggesting not only reduced parasympathetic activity after maximum-intensity exercise, but additional abnormalities of autonomic function, including increased sympathetic nervous system activity at rest and/or limited activation of the sympathetic system during exercise [36,37]. These two abnormalities of autonomic function have been linked to a higher risk of all cause and cardiovascular mortality [36,37], including a greater risk of sudden death [36]. With respect to postprandial glucose, only those with PPH in the non diabetic range had a lower exercise tolerance and lower heart rate reserve compared with normoglycaemic subjects, whereas HRR was similarly reduced in both those with PPH and diabetes compared with normoglycaemic subjects. These findings perhaps suggest less perturbation of autonomic regulation of CV function in subjects with elevated postprandial glucose compared with those with raised FPG.

Limitations of the present study include the fact that a single blood specimen taken on study entry was used to define each patient’s glycaemic status. Second, postprandial blood glucose was measured using 2-hour post-meal blood glucose levels, which may have varied considerably due to what was consumed as well as geographical factors. However, several studies comparing blood glucose and insulin responses in OGTT’s after various standardized meals have shown strong correlations between post-challenge glucose values using either method [38–41]. Third, data for postprandial glucose was available for only a minority of subjects, and no specific explanation is proposed for this except to note that this test was considered unusual at the time the study was undertaken. As a consequence, our multivariate Ancova model included relatively few subjects with concomitant data available for FPG, postprandial glucose and exercise stress testing compared with the entire study population from the CASS registry. Finally, there have been considerable advances in the management of CHD patients since the present study was completed. Nevertheless, our data demonstrating the relationship between HRR and mortality are consistent with more recent data.

In conclusion, fasting, but not postprandial, glucose was an independent predictor of HRR in our large CHD sample population. These findings are consistent with our previous data showing the independent prognostic value of both HRR and FPG for the prediction of total and CV mortality [29]. Our data also suggest that abnormalities of fasting glucose may negatively influence long-term prognoses through their greater impact on autonomic CV regulation compared with abnormalities of postprandial glucose metabolism. However, further studies are required to determine whether or not treatment of raised FPG with lifestyle measures, including exercise, diet and weight loss, can restore autonomic function and lead to normalization of HRR.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


