Original Article
Predictive value for cumulative heart rate exposure in new-onset impaired fasting glucose and diabetes mellitus

Lixia Sun¹,²*, Chunhui Li³*, Jiqiang Liu⁴, Haiyan Li⁵, Hualing Zhao³, Lu Song⁶, Yiming Wang⁶, Shuohua Chen⁷, Jie Liu⁸, Ruiying Zhang³, Quanhui Zhao³, Hongliang Cong¹, Shouling Wu³

¹Department of Cardiology, Tianjin Chest Hospital Affiliated to Tianjin Medical University, Tianjin 300070, China; ²Department of Emergency, The Affiliated Hospital of North China University of Science and Technology, Tangshan 063000, China; ³Department of Cardiology, Kailuan Hospital Affiliated to North China University of Science and Technology, Tangshan 063000, China; ⁴Department of Intensive Care Medicine, ⁵Department of Endocrinology, Beidaihe Hospital, Qinhuangdao 066100, China; ⁶Department of Hepatobiliary Surgery, ⁷Health Care Center, Kailuan Hospital Affiliated to North China University of Science and Technology, Tangshan 063000, China; ⁸Department of Cardiology, The Affiliated Hospital of North China University of Science and Technology, Tangshan 063000, China. *Equal contributors.

Received October 23, 2016; Accepted November 23, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: To analyze the predictive value for cumulative heart rate exposure (cumHR) in new-onset impaired fasting glucose (IFG) and diabetes mellitus. The prospective cohort study included 101510 participants of Kailuan Company. During a follow-up of nearly 6 years, 33461 participants were recorded. Cumulative incidence of diabetes was calculated as new-onset diabetes, IFG and its development of each group using life table method. Statistical analysis was performed with Log-rank test to compare the different cumulative incidences of each group. Cox proportional hazard model and natural spline were used to further analyze the Hazard ratio (HR) and 95% confidence interval (95% CI) of cumHR. During the follow-up period of mean 2.22±0.38 years, new-onset diabetes were 1244 (3.7%) cases in total, new-onset IFG were 2060 (7.5%) cases in the ideal glucose group, 533 (17.5%) cases IFG developed into diabetes mellitus. Log-rank test indicated that the cumulative incidences in different cumHR groups of total people, ideal glucose people and IFG people had significant statistical differences (P<0.05). Cox proportional hazard model showed that when cumHR increased every standard deviation (SD), the HR (95% CI) of IFG, new-onset diabetes, IFG developed into diabetes were 1.21 (1.16~1.26), 1.22 (1.16~1.29), 1.13 (1.03~1.24) respectively. Natural spline analysis exhibited a similar ‘J’ curve relationship between cumHR and new-onset IFG, new-onset diabetes and IFG developed into diabetes. The increase of cumHR had a predictive value for new-onset IFG and new-onset diabetes.

Keywords: Cumulative heart rate exposure, diabetes mellitus, impaired fasting glucose, IFG developed into diabetes mellitus, prospective study

Introduction

A worldwide Epidemiological Survey in 2011 reported type 2 diabetes has reached 300 million cases and expected to increase to 500 million by 2030 [1]. A recent study from Chinese adult population observed that the prevalence of diabetes was 11.6% and of pre-diabetes was 50.1%, respectively [2]. Several factors, such as age [3], blood pressure [4], body mass index [5] and life style [6], gene [7], have been confirmed to be associated with development and progression of diabetes. Recently an hot concern is that heart rate, as a rough indicator of autonomic nervous system, associated with prevalence of diabetes [8-11].

However, the results about diabetes have not come to a concrete conclusion. ARIC study first reported the relationship between heart rate and diabetes in 2003 [8]. After that, researchers from Japan and Australia such as Nagaya et al. [9], Shigetoh et al. [10], Grantham et al. [11] discovered the predictive value for heart rate increase in diabetes. But Carnethon and co-workers [12] found that by adjusting body mass index (BMI), the baseline heart rate seemed to have no predictive value for long term diabetes.
The results of these studies above concerned about heart rate and diabetes appeared to be different. That’s may because of heart rate was just measured once, and could not represent a long time heart rate level.

Cumulative exposure is the sum up of exposure dose multiplied by exposure time, which can estimate the long term effect of some risk factors more accurately. It is known that studies on cumulative exposure are relatively rare throughout the world. A prospective study of diabetes in England [13] put out that cumulative high blood glucose could increase the risk of complications in diabetes firstly. Lately Navar-Boggan and coworkers [14] pointed out cumulative hyperlipidemia exposure could increase the risk of coronary heart disease. Zemaitis etc. discovered high cumulative blood pressure exposure was related to renal damage [15]. In theory, the cumulative heart rate (cumHR) represents long-term heart rate levels more accurate. But there were no studies of the relationship between cumulative heart rate exposure and new-onset impaired fasting glucose (IFG) and diabetes. Therefore we performed a study according to the Kailuan cohort (registered number: ChiCTR-TNC-11001489) and analyzed the predictive value for cumulative heart rate exposure in new-onset IFG and diabetes.

### Materials and methods

#### Study population

We collected the data from Kailuan community in Tangshan city in northern China, which represented the Chinese population from a socio-economic perspective.

Briefly, in 2006-2007, 101510 employees and retired workers in Kailuan Company completed questionnaires by interviews and received physical examinations in 11 hospitals responsible for health care of this community. These participants were then followed through 2008-2009, 2010-2011, 2012-2013 with repeated questionnaires and physical examinations. We included 47828 participants who had taken all the fourth examinations and had completed data. The starting point of follow-up was the third time of physical examination in 2010-2011 and ending point was the fourth. We considered new-onset diabetes and IFG as the endpoint events.

The protocol for this study was in accordance with the guidelines of Helsinki Declaration, and was approved by the Ethics Committee of Kailuan Medical Group, Kailuan Company. All the participants gave their written informed consent.
Inclusion and exclusion criteria

In the current study, participants were included if they: (i) received all the physical examination during the follow-up years; (ii) had no physical disability and could walk independently to receive the physical examination; (iii) could complete the questionnaire with cognitive competence; (iv) agreed to take part in the study and gave their written informed consent. The exclusion criteria were: (i) refused to participate in this research; (ii) lack of data for heart rate (N=6685), fasting blood glucose (FBG) and history of diabetes (N=826); (iii) have the history of atrial fibrillation, myocardial infarction or taking pills of β blockers or calcium antagonists (N=1230); (iv) developed into diabetes during the follow-up period from 2006-2011 or taken hypoglycemic drugs (N=5626). Finally, we included 33461 people in our cohort, among whom 27386 were the ideal glucose group (FBG <6.1 mmol/L) and 3042 were IFG group (6.1 mmol/L ≤FBG <7.0 mmol/L).

Epidemiological survey and anthropometric parameters

The epidemiological survey and anthropometric parameters in this study were in accordance with the previous published articles by our research group [16]. Smoking was defined as having at least one cigarettes a day in the recent year; drinking was 100 ml/day (alcohol contents >50%) of alcohol lasts for more than one year; physical training was aerobic exercise (eg. walking, jogging, balls, swimming) ≥3 times/week, ≥30 min/time.

Assessment of FBG and other biochemical indicators

Blood samples, after an overnight fast, were collected from cubital vein for 5 ml at 7-9 am in the physical examination day. After separating and extracting serum, a same group of laboratory technicians tested the biochemical indicators using automatic biochemistry analyzer (Hitachi 7600, Tokyo, Japan). The indicators included FBG, total cholesterol (TC), triglyceride (TG) and high sensitivity C reaction protein (hs-CRP). Glucose (GO) Assay kits was provided by Biosino in Beijing, China. FBG was measured with the hexokinase/glucose-6-phosphate dehydrogenase method. The coefficient of variation using blind quality control specimens was no more than (≤) 2.0% (5.55 mmol/L), and liner ceiling was 33.3 mmol/L.

Assessment of heart rate and calculation of cumHR

After a 5-min or longer rest, heart rate was recorded based on the results of a 12-lead electrocardiogram performed with participants in the supine position. The average inverse of the interval between R-waves for five consecutive QRS complexes was used to determine heart rate. cumHR was calculated in line with the method of cumulative exposure to blood pressure [15]. cumHR=[(HR1+HR2)/2 × time 1-2]+[(HR2+HR3)/2 × time 2-3], HR1, HR2, HR3 were the first, second and third time of physical examination heart rate. Time 1-2, time 2-3 were the time interval of two adjacent measure-
CumHR, IFG and diabetes

Incident IFG and diabetes

We considered the starting point of follow up as the third time of physical examination in 2010-2011 and the endpoint was the fourth. The endpoint events were new-onset diabetes and IFG. In line with the American Diabetes Association guidelines, participants were identified as having diabetes mellitus if they were currently treated with anti-diabetic drugs, or had a FBG concentration 7.0 mmol/L. IFG was defined as FBG concentration between 6.1 and 7.0 mmol/L without diabetes history and hypoglycaemic agents.

Statistical analysis

Participants were divided into four categories based on cumHR quartiles. The data of physical examination during the follow up years were collected from the 11 hospitals and then gathered a Oracle 10.2 g database. The data analyses were performed using SPSS 19.0, data in normal distribution were presented as mean ± standard deviation (±s), data in skewed distribution were logarithmic transformed and then presented as mean ± standard deviation (±s). Using Variance analysis we compared differences among more than two groups. LSD (equal variance) and Dunnett T3 (heterogeneity of variance) were implied to compare mean values between groups. Enumeration data were showed in percentage (%) and comparison among groups were conducted with χ² test. Cumulative incidence of diabetes was calculated using life table method as new-onset diabetes, new-onset impaired fasting glucose and its development of each group. Log-rank test was performed to compare the different cumulative incidences of each group.

Cox proportional hazard model and natural spline were used to further analyze the Hazard ratio (HR) and 95% confidence interval (95% CI) of cumHR. To account for the potential confounding effects due to 11 participating hospitals, we used Cox proportional hazards model with a sandwich covariance matrix as a random effect. We fitted three multivariate proportional hazards models, confirmation of the proportional hazards assumption being satisfied. Model 1 considered new-onset IFG/new-onset diabetes/IFG developed into diabetes as the dependent variable, cumHR increased every standard deviation as the independent variable;
model 2 further adjusted the age and gender on the basis of model 1; model 3 further adjusted SBP, baseline HR, BMI, FBG, TC, IgTG, IgCRP, smoking, drinking, physical training, anti-hypertensive treatment on the basis of model 2. Natural spline analysis exhibited a curve relationship between cumHR and new-onset IFG, new-onset diabetes and IFG developed into diabetes.

Two-sided $P$-values were reported for all analyses. A $P<0.05$ was considered to be statistically significant. All statistical analyses were performed by SPSS for windows, version 19.0 (SPSS Inc, Chicago, Illinois, USA).

Results

General information

The mean age of participants (N=33461) with 76.5% men (N=25607) and 23.5% women (N=7854) was 47.26±11.56 years at baseline. We separated the cumHR as quartiles (Q1: cumHR ≤265.50 bpm × year; Q2: 265.5 < cumHR ≤289.37 bpm × year; Q3: 289.37 < cumHR ≤318.25 bpm × year; Q4: cumHR ≥318.25 bpm × year) and found that with cumHR increasing, most indicators went up as well ($P<0.05$), such as age, systolic blood pressure (SBP), diastolic blood pressure (DBP), baseline heart rate (HR), FBG in the three times of physical examination (FBG_1, FBG_2, FBG_3), TC, low density lipoprotein cholesterol (LDL-C), IgTG, IgCRP level and smoking, drinking, physical training, hypotensor taking proportion (Table 1).

Cumulative incidence

In a follow-up period of mean 2.22±0.38 years, the new-onset diabetes were 1244 (3.7%) cases of total, new-onset IFG were 2060 (7.5%) cases in the ideal glucose group, 533 (17.5%) cases IFG developed into diabetes. Log-rank test indicated that the cumulative incidences in different cumHR groups of total people, ideal glucose people and IFG people had a significant statistical difference ($P<0.05$). The cumulative rates of new-onset diabetes in total people and new-onset IFG in ideal glucose people increased as the cumHR went up, while the rate IFG developed into diabetes did not increase (Table 2).

Cox proportional hazard model and natural spline analysis

We considered new-onset IFG, new-onset diabetes, IFG developed into diabetes as the depen-
dent variable and cumHR as the independent variable to conduct the cox proportional hazard model test. After adjusting the confounding factors such as age, gender, SBP, HR, BMI, TC, FBG, smoking, drinking, physical training and anti-hypertensive treatment, results showed that when cumHR increased every SD, the HR (95% CI) of IFG, new-onset diabetes, IFG developed into diabetes were 1.21 (1.16–1.26), 1.22 (1.16–1.29), 1.13 (1.03–1.24) respectively (Table 3). Natural spline analysis exhibited a similar ‘J’ curve relationship between cumHR and new-onset IFG, new-onset diabetes and IFG developed into diabetes (Figures 1-3).

Gender (men and women) and age (youth: ≤39 years old; middle age: 40-59 years old; old age: ≥60 years old) were stratified in the Cox propor-

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of endpoints according to the quartiles of cumHR in the Kailuan study, China

<table>
<thead>
<tr>
<th></th>
<th>New-onset IFG</th>
<th></th>
<th>New-onset diabetes</th>
<th></th>
<th>IFG developed into diabetes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Model 1</td>
<td>CumHR</td>
<td>1.18 (1.14–1.23)</td>
<td>&lt;0.001</td>
<td>1.22 (1.17–1.28)</td>
<td>&lt;0.001</td>
<td>1.11 (1.02–1.21)</td>
</tr>
<tr>
<td>Model 2</td>
<td>CumHR</td>
<td>1.16 (1.12–1.21)</td>
<td>&lt;0.001</td>
<td>1.20 (1.14–1.26)</td>
<td>&lt;0.001</td>
<td>1.09 (1.001–1.03)</td>
</tr>
<tr>
<td>Model 3</td>
<td>CumHR</td>
<td>1.21 (1.16–1.26)</td>
<td>&lt;0.001</td>
<td>1.22 (1.16–1.29)</td>
<td>&lt;0.001</td>
<td>1.13 (1.03–1.24)</td>
</tr>
<tr>
<td>Baseline HR</td>
<td>0.98 (0.98–0.99)</td>
<td>&lt;0.001</td>
<td>0.98 (0.98–0.99)</td>
<td>&lt;0.001</td>
<td>0.99 (0.98–1.00)</td>
<td>0.005</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.29 (1.19–1.41)</td>
<td>&lt;0.001</td>
<td>1.32 (1.17–1.49)</td>
<td>&lt;0.001</td>
<td>1.12 (0.91–1.37)</td>
<td>0.295</td>
</tr>
<tr>
<td>Men</td>
<td>1.19 (1.13–1.24)</td>
<td>&lt;0.001</td>
<td>1.20 (1.13–1.28)</td>
<td>&lt;0.001</td>
<td>1.13 (1.02–1.26)</td>
<td>0.026</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;39 years old</td>
<td>1.12 (0.96–1.32)</td>
<td>0.157</td>
<td>1.23 (0.99–1.50)</td>
<td>0.057</td>
<td>0.90 (0.86–1.45)</td>
<td>0.671</td>
</tr>
<tr>
<td>39–59 years old</td>
<td>1.21 (1.15–1.26)</td>
<td>&lt;0.001</td>
<td>1.22 (1.15–1.30)</td>
<td>&lt;0.001</td>
<td>1.16 (1.04–1.28)</td>
<td>0.006</td>
</tr>
<tr>
<td>≥60 years old</td>
<td>1.31 (1.18–1.46)</td>
<td>&lt;0.001</td>
<td>1.27 (1.09–1.48)</td>
<td>&lt;0.001</td>
<td>1.14 (0.88–1.48)</td>
<td>0.328</td>
</tr>
</tbody>
</table>

Note: cumHR: cumulative heart rate. Model 1 considered new-onset IFG/new-onset diabetes/IFG developed into diabetes as the dependent variable, cumHR increased every standard deviation as the independent variable; model 2: adjusting for age and gender; model 3: adjusting for model 2 and SBP, baseline HR, BMI, FBG, TC, IgTG, IgCRP, smoking, drinking, physical training, anti-hypertensive treatment.
Cross-sectional study in 2007 [17] demonstrated that heart rate had a significant linear correlation with IFG in prediabetic states. Another study about Cantonese by Yang et al. [19] reported that each 10 beats/min increase in heart rate was associated with 29% increased diabetes risk and 15% increased pre-diabetes risk. The other research including 637 Japanese by Shigetoh et al. [10] pointed out a heart rate more than (> ) 80 beats/min, comparable to the baseline heart rate less than (< ) 60 beats/min, could positively predict insulin resistance (IR) and diabetes 20 years later, with the OR (95% CI) being 2.20 (1.04–5.07) and 5.39 (1.34–21.8) respectively. As mentioned above, Wang et al. [18] also discovered faster baseline resting heart rate had relationship with higher risk of IFG, new-onset diabetes and IFG developed into diabetes after 4 years’ follow-up, and the HRs (95% CI) were 1.11 (1.09–1.13), 1.23 (1.19–1.27), 1.13 (1.08–1.17). However, heart rate has an inconformity in the predict value of diabetes. Carnethon et al. [12] failed to identify that baseline heart rate predicted the occurrence of long-term diabetes after adjusting for BMI. The possible reason is that his study come from the almost overweight characteristic population in Chicago, America, and higher BMI conceal the role of heart rate.

What’s more, our natural spline analysis exhibited a similar ‘J’ curve relationship between cumHR and endpoint events in three groups, which indicated a higher risk in IFG and new-onset diabetes (Figures 1-3). Interestingly, the baseline heart rate presented a slightly protective effect to the occurrence of new-onset IFG and diabetes after adding it in our model, which remained unexplainable and needed to further explore.

For the middle age and old people, the risen of cumHR could increase the risk of new-onset IFG and new-onset diabetes in male or female (Table 3). As to the IFG group, though there were no increasing trends in diabetes as cumHR increased in the whole people, male or female, the incidence of endpoints was statistically different in the cumHR quartiles (Table 2). Afterwards the cox proportional hazard model referred cumHR as the risk factor in IFG developed into diabetes, especially in middle aged and male people (Table 3). Hu et al. [3], Chan et al. [5] confirmed the association between age, BMI and diabetes, and the reason may be that youth group had not come to the endpoint.
events and the middle aged and male were more intend to become obesity. This study affirmed again that age, gender associated with the prevalence of diabetes.

Faster heart rate, which is the reflection of an unbalanced automatic nervous system, has some correlation with sympathetic nerve hyperactivity (SNH) [20]. Someone believed that SNH could cause an acute or chronic insulin resistance [21]. The probable mechanisms were as follows: (i) SNH caused contraction of skeletal muscle vascular, decreased the blood flow, and reduced the absorption of glucose in skeletal muscle [22]; (ii) SNH was related to risk factors of diabetes such as hypertension, metabolic syndrome and decreased insulin sensitivity [23-25]. Moreover, resting heart rate associated with age, gender, cardiorespiratory fitness and physical activity. A sedentary lifestyle and obesity, as other causes of faster heart rate, were also risk factors for diabetes prevalence and progression [5].

Cumulative exposure is influenced by exposure time and level, which can predict the chronic damage of the body. Our study was advantaged in the calculation of cumHR by 3 times’ (6 years’ follow-up) resting heart rate, which could more precisely estimated the predictive value to diabetes than single heart rate. In addition, our study unveiled the use of cumulative exposure index in clinical work besides science work and its immeasurable value to human health. The repeated measurements of clinical data, through collecting and sorting, will vastly encourage an era of the explosion in medical data.

Resting heart rate is related to new-onset diabetes as is known. But the single measurement of heart rate is influenced by diet, temperature, lifestyle and many other factors, which can not represent the long term heart rate level. After all our study was the first to reveal predictive value of cumHR to new-onset IFG and diabetes in the world. We discovered that increasing level of cumHR was predictive to new-onset IFG and diabetes and also the value was independent to resting heart rate. The current study showed that higher risk of new-onset IFG and diabetes were related to cumHR increase, which suggested that monitoring and maintaining heart rate at a normal and low level during long term is necessary for diabetes prevention.

This study is the first of its kind that assessed predictive value for cumulative heart rate exposure in new-onset impaired fasting glucose and diabetes mellitus in China. This study was advantaged in the calculation of cumHR by 3 times’ (6 years’ follow-up) resting heart rate, which could more precisely estimated the predictive value to diabetes than single heart rate. This study unveiled the use of cumulative exposure index in clinical work besides science work and its immeasurable value to human health.

However, several limitations should be considered in interpreting the current results. Firstly, our cumHR was a result of 6 years’ follow-up and we used it to predict the new-onset diabetes and IFG after 2 years later. The observation time was relatively short that the endpoint events may not yet occurred. Secondly, we included 783 calcium antagonists’ users, who may have taken non-dihydropyridine drugs as well. That may influence heart rate and thus caused result bias. Thirdly, we tried to adjust those confounders when evaluated the predictive value of cumHR, but some factors were still not included such as temperature and genetic factors.

Conclusions

Our findings provide further evidence that increase of cumHR had a predictive value for new-onset IFG and new-onset diabetes among Chinese adults.

Acknowledgements

This study was supported by the Group Company of Chinese Kailuan. The contributions of the general practitioners of the Kailuan Study are gratefully acknowledged. SLW is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure of conflict of interest

None.

Address correspondence to: Hongliang Cong, Department of Cardiology, Tianjin Chest Hospital Affiliated to Tianjin Medical University, No.261 Tai'erzhuang Road (South), Tianjin 300070, China. Tel: +86 13702102871; E-mail: cnhongliangcong@126.com; Shouling Wu, Department of Cardiology,
Kailuan Hospital Affiliated to North China University of Science and Technology, Tangshan 063000, China. Tel: +86 13932517670; E-mail: drwusl@163.com

References


