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Heart Rate Recovery Index Evaluation in Prediabetic Patients

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SOUHRN

Kontext: Z hlediska veřejného zdraví představuje prediabetes jeden z hlavních rizikových faktorů pro rozvoj diabetu 2. typu. Index obnovy srdeční frekvence (heart rate recovery index, HRRI) je nezávislým ukazatelem autonomních funkcí a prediktorem rozvoje kardiovaskulárních onemocnění (KVO). Cílem našeho výzkumu bylo stanovit hodnotu HRRI u jedinců s prediabetem.
Metody: Do studie bylo zařazeno 400 pacientů navštěvujících kliniku kardiologie: 164 (41 %) žen a 316 (59 %) mužů. Podle Bruceho protokolu museli všichni účastníci absolvovat zátěžové EKG vyšetření na běžeckém pásu. Průběh obnovy srdeční frekvence se zaznamenává 1, 2, 3 a 5 minut po zátěžovém testu, přičemž se odečítá maximální srdeční frekvence jedince na konci testu od hodnoty naměřené během 1, 2, 3 a 5 minut zotavování.
Výsledky: Obě skupiny měly podobné hodnoty délky zátěže, metabolického ekvivalentu (metabolic equivalent of task, MET), maximální srdeční frekvenci i vstupní a maximální hodnoty systolického a diastolického krevního tlaku i změny těchto dvou parametrů ($p > 0,05$). Hodnoty HRRI po 1, 2, 3 a 5 minutách byly vyšší u pacientů, kteří prodělali onemocnění covid-19 ($p < 0,001$).
Závěry: Prediabetes má statisticky významný vliv na hodnotu HRRI. Prediabetes může působit na nervový i kardiovaskulární systém.

ABSTRACT

Background: Prediabetes is a major public health risk factor for type 2 diabetes. The heart rate recovery index (HRRI) shows autonomic function and predicts cardiovascular disease (CVD) independently. The objective of the research was to assess the HRRI in individuals with prediabetes.
Methods: The study comprised 400 cardiology clinic patients, 164 (41% female) and 316 (59% male). The Bruce protocol required treadmill stress ECGs for all patients. After the stress test, HRRIs were collected at 1, 2, 3, and 5 minutes. HRRI is calculated by subtracting the subject's maximal exercise HR at the end of the session from HR after 1, 2, 3, and 5 minutes of recovery.
Results: Both groups had a similar exercise time, METs, max. HR, baseline, max., and change in SBP and DBP ($p > 0.05$). HRRIs were higher in COVID-19 patients than controls at 1, 2, 3, and 5 minutes ($p < 0.001$).
Conclusions: Prediabetes has a significant influence on the HRRI. Prediabetes has the potential to impact neural-cardiovascular systems.

Keywords:
Cardiovascular diseases
Heart rate recovery index
Prediabetes

Introduction

By 2030, 470 million individuals would have impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), often known as prediabetes. Type 2 diabetes affects 200 million individuals globally. Decreased β-cell activity and increased insulin resistance characterise type 2 DM. Each year, 5–10% of prediabetics develop diabetes and the same percentage reverse their glucose levels. IFG and IGT rise before type 2 DM, according to recent research. IFG is 3–5% in 20–44-year-olds and 20–30% in 65–74-year-olds. IFG affects men more; however, this changes with age.[1,2]

Heart rate recovery index (HRRI) measures heart rate decreases following exercise stress testing. Blood pressure (BP), HR, and elecetrocardiography (ECG) normalise during HR recovery. Left ventricular dysfunction and decreased exercise capacity slow HR recovery. It takes 9 minutes. HR drops dramatically in the first 30 seconds after

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activity and then slows. This decline can be prevented by early atropine, suggesting vagal activation. The primary objective of this study was to assess the HRRI in individuals with prediabetes.[3,4]

Patients and methods

Between June 1 and November 1, 2016, 200 people with prediabetes and an equal number of healthy volunteers of the same gender signed up for the study at the clinic. Every participant had normal blood pressure and no heart disease. Current guidelines were used to diagnose prediabetes.[5] In prediabetics, fasting blood sugar was 5.6–6.9 mM and HbA_{1c} was 5.7–6.4%.[6] A local ethics committee approved this. All study participants provided informed consent.

Age, sex, and cardiac risk factors were collected from all participants. Excluded patients had cardiovascular disease (CVD) (arterial hypertension [HT], heart failure [HF], thyroid dysfunction, atrial fibrillation [AF], myocardial infarction [MI], or severe heart valve disease), chronic renal disease or impaired estimated glomerular filtration rate, malignant neoplastic diseases, chronic obstructive lung disease (COPD), or liver diseases.

An M-mode echocardiogram was performed using Vivid E9 equipment (Bioject Medical Technologies Inc., Portland, OR, USA) in the left lateral decubitus position. Images were collected using the American Society of Echocardiography (ASE) criteria.[7] Data on patients' demographics were recorded following a physical examination. Participants were assessed for smoking status using pack years. Everyone's blood glucose, lipid profile, and creatinine were recorded.

Cardiac stress testing

All participants underwent Bruce Protocol treadmill stress ECGs. For 48 hours before the test, medicines that might impact the results were stopped. The chest was shaved and alcohol-cleaned for artefact-free recording. The stress test used a Schiller CS-200 (Schiller AG, Baar, Switzerland). We measured BP and ECG every 3 minutes throughout the stress test and at the 1st, 2nd, 3rd, and 5th minutes of recovery after baseline. The American Heart Association (AHA) recommends 85% maximal HR to cease treadmill stress testing.[8]

After the stress test, HR, rest (systolic BP [SBP], diastolic BP [DBP]), exercise duration, capacity, maximal (HR, SBP, DBP), and HRRIs were measured after 1, 2, 3, and 5 minutes of recovery. When calculating HRRI, one subtracted their maximum exercise HR at the end of the exercise from their HR at 1, 2, 3, and 5 minutes of recovery.

Statistical analysis

Statistics were performed using Statistical Package for the Social Sciences (SPSS) 24.0 (Armonk, NY, USA). Data normality was confirmed using the Kolmogorov–Smirnov test. Mann–Whitney U and student's t-tests compared study groups' means and medians. Percentages were used for chi-square tests. The significance level was $p < 0.05$.

Table 1 – Characteristics of the study population

	Controls (n = 240)	Prediabetes (n = 240)	*p*-value
Age (years)	59.2±0.3	60.1±0.2	0.712
Gender, male, n (%)	150	166	0.152
BMI (kg/m^2)	26.1±0.2	28.2±0.3	**<0.001**
Clinic systolic BP (mmHg)	121.4±6.3	122.1±5.8	0.709
Resting diastolic BP (mmHg)	75.3±5.5	76.1±1.3	0.852
Fasting plasma glucose (mg/dL)	25.8±4.4	111.5±4.7	**<0.001**
HbA_{1c} (%)	4.7±0.2	6.2±0.2	**<0.001**
Cre (mg/dL)	0.82±0.2	0.87±0.1	0.156
TG (mg/dL)	177.1±3.8	198.5±3.2	**0.004**
HDL-C (mg/dL)	39.6±0.8	34.1±1.2	**0.012**
LDL-C (mg/dL)	101.8±3.4	128.3±5.7	**0.022**
TC (mg/dL)	144.6±7.0	193.6±6.8	**0.005**
WBC ($10^3 \times \mu L$)	7.3±2.1	8.6±2.8	0.512
Hgb (g/dL)	14.2±1.3	14.3±1.2	0.834
Ejection fraction (%)	54.1±0.6	53.7±0.7	0.774
Resting HR (beats/min)	86.4±1.2	88.2±1.0	0.362

Bold values indicate statistical significance.
BMI – body mass index; BP – blood pressure; Cre – creatinine; HbA_{1c} – glycolized hemoglobin; HDL – high-density lipoprotein; Hgb – hemoglobin; HR – heart rate; LDL – low-density lipoprotein; TC – total cholesterol; TG – triglyceride; WBC – white blood cell.

Table 2 – Exercise testing results among groups

	Controls (n = 240)	Prediabetes (n = 240)	*p*-value
Duration of exercise (min)	12.1±1.3	12.6±1.1	0.752
METs	12.4±1.2	12.1±1.5	0.758
Max. HR (beats/min)	176.5±6.3	170.2±5.4	0.556
Baseline SBP (mmHg)	110.4±6.7	113.6±7.8	0.314
Baseline DBP (mmHg)	70.2±2.4	72.2±2.6	0.516
Max. SBP (mmHg)	163.4±8.0	166.2±8.2	0.438
Max. DBP (mmHg)	81.1±6.9	84.9±6.5	0.678
SBP changes (mmHg)	40.0 (15–88)	41.4 (5–113)	0.456
DBP changes (mmHg)	7 (–9–45)	10 (–19–68)	0.474
HRRI1	35.1±5.3	23.8±7.3	**<0.001**
HRRI2	53.1±6.1	40.2±6.8	**<0.001**
HRRI3	61.2±6.5	50.1±7.5	**<0.001**
HRRI5	65.4±6.1	57.6±8.0	**<0.001**

*Student's t-test, Mann–Whitney U test. *p*-value <0.05.
HRRI – heart rate recovery index; max. DBP – maximum diastolic blood pressure; max. HR – maximum heart rate; max. SBP – maximum systolic blood pressure; MET – metabolic equivalent.

Results

Table 1 shows study group baselines. The prediabetic and control groups had mean ages of 60.1±0.2 and 59.2±0.3 years, respectively. Both groups had similar age, sex distribution, blood pressure, and HR (p >0.05). From controls to prediabetics, fasting glucose and HbA_{1c} levels increased (p <0.001). Significantly higher body mass index (BMI) in the prediabetic group compared to the control group (p <0.001). Prediabetics had slightly increased TC, TG, HDL, and LDL, respectively (p = 0.005, 0.004, 0.012, and 0.022). Creatinine, white blood cell (WBC), and hemoglobin (Hgb) showed a similar trend (p <0.05). LVEF were similar between groups (p >0.05).

Between groups, exercise duration, metabolic equivalent of tasks (METS), maximum HR, baseline, maximal, and change in SBP and DBP were comparable (p >0.05). HRRIs increased in prediabetes (p <0.001) at 1, 2, 3, and 5 minutes (**Table 2**).

Discussion

We found higher HRRIs at 1, 2, 3, and 5 minutes in prediabetes patients than controls. A meta-analysis of 20 studies found that nondiabetic glucose levels (100 mg/dL fasting plasma glucose and 140 mg/dL 2nd-hour glucose) were linked to 1.33 and 1.58 times more cardiovascular events than 75 mg/dL levels.

Although contradictory, some studies have connected IGT to autonomic dysfunction. Patient demographics, glucose dysmetabolism, and autonomic function testing cause study variability. Fourteen trials linked pre-diabetes to autonomic dysfunction.[9] Four of these 14 trials and two others included both IFG and IGT, eight only IGT, four solely IFG, and the KORA S4 trial had a second IFG category.[10] Despite variability, early glucose dysregulation decreases autonomic function, especially cardiovagal HRV indices. Early DAN typically alters cardiovagal responses.[11] Isak et al.[12] found no difference between IGT and NGT people. In studies comparing IFG with IGT, IGT was associated with more autonomic dysfunction.[13] Combined IFG and IGT cause more severe autonomic neuropathy.[10]

In a population-based sample of healthy people, fasting plasma glucose was strongly associated with abnormal HRRI, even after correcting for confounding factors. Those with resting heart rates ≥80 bpm had the highest connection between fasting plasma glucose and HRRI. Abnormal HRRI predicted death and impaired fasting glucose in normal plasma glucose patients. Fasting plasma glucose and low fitness were no longer linked after adjusting for confounding variables.[14]

We believe this is the first study to examine prediabetes and irregular HRRI. Previous investigations used power spectral analysis of heart rate variability to assess autonomic dysfunction and diabetes. Parasympathetic and sympathetic cardiac impacts may be distinguished by heart rate variability and frequency. Diabetes and decreased fasting hyperglycemia reduced heart rate variability in the Framingham Heart Study.[14]

Our study yields several crucial findings. Prediabetes was strongly associated with abnormal HRRI, a reliable autonomic dysfunction indicator, and all-cause mortality prediction.[14] It's uncertain how prediabetes causes irregular HRRI. Vagal reactivation drives post-exercise heart rate reduction. Poor HRRI indicates parasympathetic issues. In the Framingham Heart Study, fasting plasma glucose lowered vagal tone. Even minor glucose metabolism problems may disturb sympathetic and parasympathetic balance, according to our results. High glucose levels may alter autonomic function. Plasma insulin may cause autonomic neuropathy. Plasma insulin promoted vagal, sympathetic, and baroreflex activity, whereas weight loss decreased insulin levels and improved autonomic function.[14]

Recent studies demonstrate that obesity increases prediabetes and BMI. Food, exercise, and behavioural interventions may significantly reduce prediabetics' body weight and diabetes risk.[15] Prediabetics showed higher BMIs in our study. Lipid investigations showed higher LDL, TG, and TC and reduced HDL in prediabetics.[16] Our study found similar results.

Endothelial dysfunction, MI history, poor lipid profile, and poorly controlled diabetes lower HRRI.[14] Our findings showed that LDL-C and HDL-C varied across groups despite identical coronary risk factors. There was no association between these characteristics and the HRRI score.

Sympathetic hyperactivity increases circulatory preload and hemodynamic stress, leaving patients prone to CVD.[17] To avoid ischemic arrhythmia, parasympathetic activity lowers HR and BP.[18] Healthy and unhealthy cardiovascular function is controlled by the autonomic nervous system. Nishime et al.[19] found that individuals who failed to drop their HR by more than 12 beats in the first minute after exercise (HRRI at 1 minute in 20% of healthy middle-aged people is 12 beats per minute) had a fourfold higher mortality risk over five years. Unusual HRRI predicted 2.58 times more mortality in 5200 healthy persons.

Study limitations

This research has several limitations. First, prediabetes and HRRI may be less correlated due to the small patient pool. Second, individuals without coronary angiography cannot rule out subclinical coronary artery disease. Our patients exhibited no echocardiographic signs of ischemic heart disease and were asymptomatic. Third, we cannot confirm the proportion of prediabetics who developed diabetes. Lastly, the stress test did not evaluate HRV or baroreceptor sensitivity, which are indications of autonomic response. For broad clinical usage of HRRI, larger studies are needed.

Conclusions

After 1–5 minutes of recovery, prediabetics showed lower HRRI. The neuro-cardiovascular system may be harmed by prediabetes. Understanding how prediabetes impacts HRRI requires further research.

Conflict of interest
No conflict of interest.

Funding
There were no external funding sources for this study.

Ethical statement
In this study, artificial intelligence (AI)-supported ChatGPT technology was employed. Additionally, the authors claim that the work is devoid of plagiarism, including text and images created by AI.

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