Uncoupling Between Heart Rate Variability and Heart Rate During Exercise and Recovery as a Predictor of Cardiovascular Events

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Abstract

Heart rate (HR) variability (HRV) is a non-invasive cardiac autonomic marker, which, in normal conditions, is inversely associated with the underlying HR. This study investigates the hypothesis that uncoupling between HRV and HR during exercise and recovery may indicate increased cardiovascular risk. UK Biobank participants without underlying cardiovascular disease (n=48,671, 46.3% male 56.3±8.2 years old) underwent an ECG exercise stress test. Uncoupling between HR and HRV was measured as $\upsilon = 1 - r_{HR,HRV}$, where r indicates the Spearman's correlation coefficients between the HR profile and the instantaneous HRV power. Cox regressions were used to assess the association between the uncoupling index, υ, and major adverse cardiovascular events (MACE). Models were adjusted for age, sex, body mass index, blood pressure, resting HR, HR increase and decrease during exercise and recovery, respectively. During a median follow-up of 10 years, incidence of MACE was 2.9%. In the adjusted model, 1 standard deviation increase in log-transformed υ was associated with MACE, with hazard ratio (95% confidence interval) = 1.09 (1.03, 1.15), p=0.004. In conclusion, in middle-aged man and women without underlying cardiovascular disease, the uncoupling between HR and HRV during exercise and recovery was associated with MACE.

1. Introduction

Heart rate (HR) variability (HRV) is an established noninvasive marker of cardiac autonomic activity [1]. Low HRV is a marker of impaired autonomic function and it is linked with increased risk of sudden cardiac death in post-myocardial infarction patients and with poor prognosis [2] in the general population [3]. In physiological conditions, HRV is closely related to the underlying HR, with increasing HR being associated with reduced HRV.

HRV is usually measured at rest, but the assessment of the autonomic nervous system response to physical or mental stressors, which is characterized by a dynamic interplay of sympathetic and parasympathetic withdrawal and reactivation [4], could provide additional insights into cardiovascular health and complementary prognostic information. The HRV response to exercise and recovery from exercise has been proposed as a marker of autonomic reactivity [4]–[7], but its long-term association with the onset of CVD in healthy individuals is unknown.

This study investigates the hypothesis that uncoupling between HRV and HR during exercise and recovery may indicate increased cardiovascular risk.

2. Methods

Participants from the UK Biobank who underwent an ECG test during 2009-2010 and 2012-2013 were included in this study (as part of UK Biobank application number 8256). The UK Biobank study has approval from the North West Multi-Centre Research Ethics Committee, and all participants provided informed consent [8].

The ECG (GE CardioSoft, Lead I, sampling frequency 500 Hz) was measured during a standardized exercise stress test using a stationary bicycle, including 15 seconds resting phase (pre-exercise), 6-minute graded activity and 1-minute recovery. The description of the protocol is available on-line [9]. Exclusion criteria for this study included: previous self-reported or diagnosed cardiovascular events identified through Hospital Episode Statistics and including ischaemic, congenital, and valvular heart disease, cardiomyopathies, heart failure, atrial and ventricular arrhythmias, stroke, vascular disease, and myocarditis (as in previous studies [10], [11]); incomplete exercise stress test underlying an inability to exercise; insufficient signal quality. After exclusions, 48,671 participants (46.3% male, 56.3±8.2 years old) were
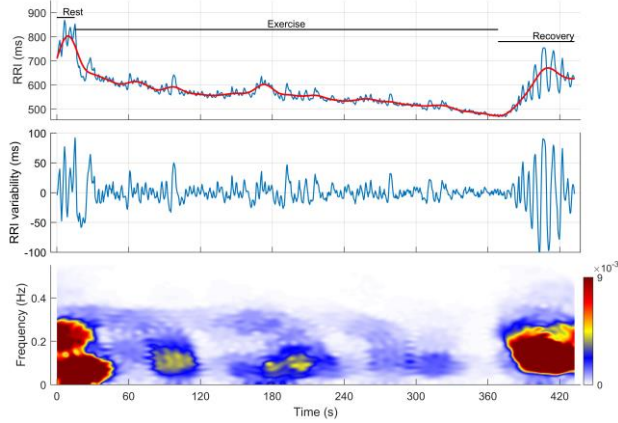
Figure 1. Top: Heart rate (blue) and heart rate profile (red) during exercise and recovery are reported in milliseconds. Middle: Heart rate variability measured as the difference between heart rate and heart rate profile. Bottom: Time-frequency representation of heart rate variability.

Figure 2: Time course of heart rate profile (x_{RR}, in red) and instantaneous power of heart rate variability (P_{RRV}, in black) are rescaled and represented together to highlight their similarity. The correlation coefficient between x_{RR} and P_{RRV} is reported in the figure.

considered in the study. During a median follow-up of 10 years, incidence of major adverse cardiovascular events (MACE) was 2.9%. MACE was defined as the first diagnosis of myocardial infarction, heart failure or life-threatening ventricular tachycardia in the hospital episode statistics.

The RR interval time series was derived from the raw ECG signal using software developed in our group [12]. The RR interval profile, x_{RR}, was estimated by resampling (sampling rate 4 Hz) and low-pass filtering (cut-off frequency 0.04 Hz) the beat-to-beat RR interval time series. The instantaneous power of RRV, P_{RRV}, was estimated using multitaper spectrograms [13], as in previous HRV studies [14], [15]. First, RRV signal was derived by subtracting x_{RR} from the instantaneous HR signal (resampled version of the RR interval time series); Then the multitaper spectrogram was measured, and finally the instantaneous power, P_{RRV}, was obtained by integrating the spectrogram over the spectral band 0.04 – 0.50 Hz. Uncoupling between RR and RRV was measured as $\upsilon = 1 - r_{RR,RRV}$, where r indicates the Spearman's correlation coefficients between and x_{RR} and P_{RRV}. The index υ was then log-transformed and used as a predictor of MACE. Cox regression models were used to assess the association between υ and MACE. Models were adjusted for age, sex, body mass index, blood pressure, resting heart rate, heart rate increase and decrease during exercise and recovery. All continuous variables were normalized to have zero mean and 1 standard deviation before entering the model.
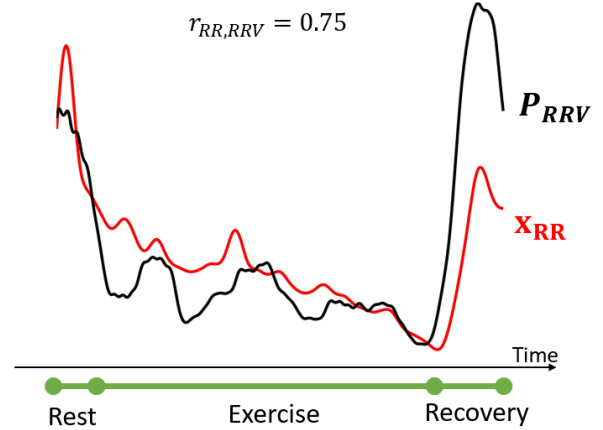
3.   Results

An example of instantaneous RR and RRV is shown in Figure 1, with the RR interval decreasing during the exercise phase and then increasing rapidly during the 1-minute recovery. The heart rate profile, x_{RR}, is obtained by low pass filtering the instantaneous RR signal, and it is shown in red. The panel in the middle show the RRV signal obtained subtracting x_{RR} from the instantaneous RR signal. RRV oscillates around zero, with large oscillations at rest, then decreased during exercise and increased again during recovery. The panel at the bottom shows the time-frequency representation of RRV, with the magnitude of the time-frequency spectra coded by colours. The instantaneous power of RRV, P_{RRV}, was estimated from this time-frequency representation and it is reported in Figure 2 alongside x_{RR}. In this figure, the amplitude of x_{RR} and P_{RRV} were normalized to cover a similar range and highlight their correlation, which was equal to r=0.75. The slight misalignment between the descent and increase in x_{RR} and P_{RRV} was due to the temporal filtering necessary to estimate the multitaper spectrogram. This was equal for all recordings and has therefore limited effect on the results. Figure 3 reports the distribution of the correlation coefficients, $r_{RR,RRV}$.

The uncoupling index, υ, was associated with increased risk of MACE, with hazard ration (95% confidence interval) of 1.33 (1.26 – 1.40), P=2.1x10^{-25}. After adjusting for risk factors, the association was partially attenuated, but remained statistically significant with hazard ratio equal to 1.08 (1.02-1.14), P=0.006 (see Table 1 for the full adjusted model).
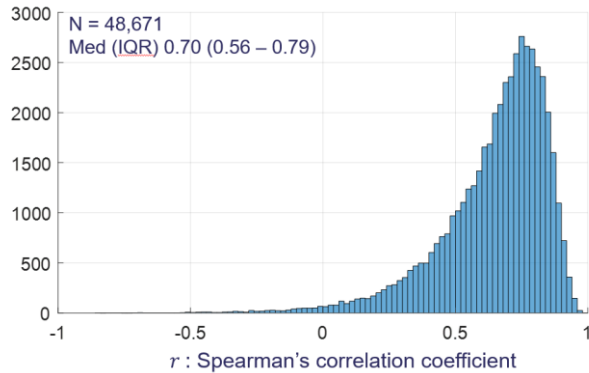
Figure 3. Distribution of the correlation coefficients between x_{RR} and P_{RRV} across the entire population.

Unadjusted model		
$u_{RR,RRV}$	1.33 (1.26 − 1.40)	2.1 E-25
Adjusted model		
$u_{RR,RRV}$	1.08 (1.02 − 1.14)	6.1 E-03
Age	1.65 (1.55 − 1.76)	2.8 E-52
Sex	2.88 (2.56 − 3.24)	2.0 E-69
BMI	1.22 (1.16 − 1.29)	5.2 E-13
SBP	1.21 (1.14 − 1.28)	4.2 E-11
ΔRR_{rec}	0.84 (0.78 − 0.90)	6.1 E-06
ΔRR_{ex}	1.06 (0.98 − 1.14)	1.2 E-01

Table 1. Results from Cox regression models assessing the association between predictors and major adverse cardiovascular events. Data are reported as hazard ratio (95% confidence intervals) and P-values.

4. Discussion

This study assessed the hypothesis that uncoupling between HR and HRV during exercise and recovery from exercise may be related to increased risk of long-term MACE. Analysis of a large cohort of middle-aged men and women without cardiovascular disease confirmed this hypothesis. The association between the uncoupling index and MACE remained significant after adjusting for several risk factors including age sex, body mass index, blood pressure, resting HR, HR increase and decrease during exercise and recovery. This suggests that the uncoupling index captures information which is complementary to these risk factors and has a prognostic value. Interestingly, the uncoupling index remained significantly associated with MACE even after adjusting for HR recovery, an established autonomic marker of vagal rebound and a predictor of cardiovascular disease [16], which may be

indicative of subclinical cardiac autonomic impairment. This study has several strengths. First, the sample size is very large, over 48 thousand participants. Second, the UK Biobank provides detailed physiological measurements from specialized tests and diagnoses and outcomes from hospital episode statistics [8], which allows to exclude participants with previous cardiovascular disease, adjust for several risk factors and follow-up participants for a decade. Finally, we used advanced time-frequency analysis [13], [14] to quantify the time course of HRV oscillation during exercise and recovery, a highly non-stationary condition during which classical spectral analysis cannot be conducted. Further studies should investigate the prognostic value of risk score that incorporates the uncoupling index and assess their utility for early preventative strategies against cardiovascular disease.

5. Conclusions

In a large cohort of middle-aged men and women without cardiovascular disease, the uncoupling between heart rate and heart rate variability during exercise and recovery was associated with increased long-term risk of major adverse cardiovascular disease, independent of standard risk factors and other markers of impaired autonomic function.

Acknowledgements

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