# Determinants and Prognostic Value of Cardiovascular Autonomic Function in Coronary Artery Disease Patients with and without Type 2 Diabetes

**Running title:** Autonomic function and coronary artery disease

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## ABSTRACT

**OBJECTIVE** Cardiovascular autonomic dysfunction is a common finding among patients with coronary artery disease (CAD) and type 2 diabetes (T2D). The reasons and prognostic value of autonomic dysfunction in CAD patients with T2D are not well known. **RESEARH DESIGN AND METHODS** We examined the association between heart rate recovery (HRR), 24-hour HR variability (SDNN) and heart rate turbulence (HRT), and echocardiographic parameters, metabolic, inflammatory, and coronary risk variables, exercise capacity, and presence of T2D among 1060 patients with CAD (age 67 ± 8 years, 69% males, 50% patients with T2D). Secondly, we investigated how autonomic function predicts a composite endpoint of cardiovascular death, acute coronary event, stroke, and hospitalization for heart failure during a 2-year follow-up. **RESULTS** In multiple linear regression model, exercise capacity was a strong predictor of HRR ($R = 0.34$, $p < 0.001$), SDNN ($R = 0.33$, $p < 0.001$), and HRT ($R = 0.13$, $p = 0.001$). In univariate analyses, a composite endpoint was predicted by reduced HRR (hazard ratio 1.7, 95% CI 1.1–2.6, $p = 0.020$), reduced SDNN (hazard ratio 2.0, 95% CI 1.2–3.1, $p = 0.005$), and blunted HRT (hazard ratio 2.1; 95% CI 1.3–3.4; $p = 0.003$) only in patients with T2D. After multivariate adjustment, none of the autonomic markers predicted the endpoint, but hs-CRP remained an independent predictor. **CONCLUSIONS** Cardiovascular autonomic function in CAD patients is associated with several variables, including exercise capacity. Autonomic dysfunction predicts short-term cardiovascular events among CAD patients with T2D, but it is not as strong independent predictor as hs-CRP.

Cardiovascular autonomic function, which can be assessed e.g. by measuring post-exercise heart rate (HR) recovery and by analyzing HR variability and HR turbulence from ambulatory electrocardiograph (ECG) recordings, has been shown to be altered among patients with ischemic heart disease (1-3). These three methods describe partly different aspects of autonomic regulation. The decline of HR within the first minute after cessation of exercise is caused mainly by parasympathetic reactivation, sympathetic withdrawal being more prominent two minutes after exercise (4). Therefore, HR recovery immediately after exercise can be considered to reflect short-term vagal reactivity. Standard deviation of all normal R-R intervals (SDNN) reflects global 24-hour HR variability, including all the cyclic components responsible for fluctuations in sinus rate, and can be considered a marker of long-term vagal tone (5, 6). Long-term HR variability is also partly influenced by physical activity at the time of recordings (7, 8). HR turbulence describes short-term fluctuations in sinus rhythm following spontaneous ventricular premature complexes (9, 10). Overall, the HR turbulence measurement provides an indirect assessment of baroreflex sensitivity (9).

Previous studies have suggested that autonomic dysfunction among cardiac patients may be explained by abnormalities in cardiac structure and/or function, e.g. angiographic severity (11, 12), extension of myocardial infarction (13), and the severity of left ventricular dysfunction (14), as well as by markers of inflammation (15, 16). However, in the population without cardiac disease, autonomic function has been observed to be associated with several cardiac risk factors such as obesity (17, 18), hypercholesterolemia (19), reduced physical activity (20-22) and low physical fitness (22-24). Type 2 diabetes, which is a common co-morbidity among coronary artery disease (CAD) patients, is also associated with abnormal cardiovascular regulation (25). The role of these features as determinants of the autonomic function of patients with CAD is not well known. Therefore, we hypothesized that autonomic dysfunction in CAD patients may be related not only to abnormal cardiac function and/or structure but also to other cardiovascular risk factors. Moreover,

we assumed that type 2 diabetes has some effect on autonomic dysfunction among CAD patients. In addition, we wanted to study whether autonomic markers can provide short-term prognostic information independent of other risk variables in the stable CAD population without a recent acute coronary event.

## RESEARCH DESIGN AND METHODS

***Subjects and study protocol:*** This study is part of the larger ARTEMIS (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection) study, which is being conducted in the Division of Cardiology of Oulu University Hospital (Oulu, Finland) and is registered at ClinicalTrials.gov, Record 1539/31/06, Identifier number NCT01426685. The goals of the ARTEMIS study are to compare cardiovascular autonomic markers, ECG markers, and biomarkers between CAD patients with and without type 2 diabetes, and to assess the prognostic value of these markers in predicting cardiovascular events among CAD patients with and without type 2 diabetes during 2- and 5-year follow-ups. The study population of this sub-study consisted of 530 stable CAD patients and 530 CAD patients with type 2 diabetes recruited from the consecutive series of patients who had undergone coronary angiography in the Division of Cardiology of Oulu University Hospital (Oulu, Finland) 3–6 months before inclusion in the assessment of their risk profile. More than 80% of the patients had undergone coronary intervention 3–6 months before entering the study, and almost half of the patients had experienced an acute coronary event more than 3 months before the enrollment into the risk profile study (see Table 1). The patients with and without type 2 diabetes were matched in terms of age, sex, left ventricular ejection fraction, history of myocardial infarction, and angiographic severity of CAD. Patients with age < 18 years or > 85 years, impaired glucose tolerance or impaired fasting glucose, NYHA class IV, a permanent pacemaker or implantable cardioverter defibrillator (ICD), planned ICD implantation, or end-stage renal failure needing dialysis were excluded from this study, as well as patients who had a life expectancy < 1

year or who were psychologically or physically (due to any other illness) unfit for participation in the study. The study was performed according to the Declaration of Helsinki, the local committee of research ethics of the Northern Ostrobothnia Hospital District approved the protocol, and all the subjects gave written informed consent.

Type 2 diabetes was verified according to the WHO criteria (26). Patients who had a fasting capillary plasma glucose level ≥ 7.0 mmol/l and/or a 2-hour post-load value ≥ 12.2 mmol/l in the oral glucose tolerance test or were on hypoglycemic medication based on prior diagnosis of diabetes were classified as having type 2 diabetes. Left ventricular systolic function was assessed by 2-D echocardiography (Simpson method) and diastolic function by tissue Doppler echocardiography. Blood samples and urine samples were obtained for the analysis of renal function, microalbuminuria, inflammation markers, blood lipids, plasma glucose, and glycated hemoglobin (HbA1c) levels. Blood pressure was measured in a supine position after a 10-min resting period. All laboratory measurements and exercise tests were done after a 12-hour overnight fast and the patients were instructed to avoid smoking before the tests.

***Exercise testing and heart rate recovery:*** The patients performed an incremental symptom-limited maximal exercise test on a bicycle ergometer for assessment of maximal exercise capacity. The test was started at 30 W, and the work rate was increased by 15 W in men and 10 W in women every minute until voluntary exhaustion. Maximal workload was calculated as the workload at the end of the test and maximal exercise capacity was calculated from the workloads during the last minute of the test. The patients moved to a supine position within 30 s after cessation of exercise and no cool-down period was allowed. HR recovery was calculated as the reduction in HR from the rate at maximal exercise to the rate one minute after cessation of exercise. A 15-lead ECG (GE Healthcare, CAM-14, Freiburg, Germany) was collected during the exercise and 10 min after the exercise.

***Ambulatory 24-hour ECG:*** A 24-hour ambulatory ECG was recorded with a digital Holter recorder (Medilog AR12, Huntleigh Healtcare, UK) with an accuracy of four msec and saved on a computer for further analysis with custom-made software (HEARTS software, Heart Signal Oy, Oulu, Finland). From the total of 1060 patients, 27 patients did not undergo the 24-hour ECG recording and 66 patients were excluded from the analysis due to a large amount of technical and biological disturbances, e.g. periods of atrial fibrillation. In total, 496 CAD patients and 471 CAD patients with type 2 diabetes were included in the analyses of 24-hour ECG recordings. A HR turbulence was measured from 423 CAD patients and 414 CAD patients with type 2 diabetes.

To exclude all undesirable beats, the R–R intervals were edited by visual inspection using the interpolation method. This method replaces edited, removed R-R intervals with a local average of the previous accepted normal R-R intervals (27). SDNN was used as a time-domain measure of HR variability. Post-ectopic HR turbulence was analyzed according to a previously published method (10). The HR turbulence slope was defined as the maximum slope of the regression line assessed over any sequence within five subsequent sinus R-R intervals during the first 15 sinus beats following an ectopic beat, as described earlier (28). During the measure of cardiovascular autonomic function by 24-hour ambulatory ECG recording, patients were advised to carry on their normal daily routine without any limitation.

***Follow-up and endpoints:*** The follow-up was 2 years after the patient's first measurement in the ARTEMIS study in Oulu University Hospital. The endpoint was defined as a combination of cardiovascular complications including cardiovascular death, acute coronary event, stroke, and hospitalization for heart failure. The follow-up data were collected from patient records of Oulu University Hospital and the mortality statistics of Statistics Finland and the Causes of Death Register. The patients who were alive were also contacted by telephone after 2 years. The follow-up was completed for 427 CAD patients and 525 patients with type 2 diabetes until January 2013, at the time the query was run.

***Statistical analyses:*** A Kolmogorov-Smirnov Z-test was performed for all variables to assess the assumption of Gaussian distribution. Since some of the data were skewed, a Spearman's nonparametric test was used to assess the correlations between HR recovery, SDNN, HR turbulence, and potential predictors, including demographic characteristics, laboratory measurements, echocardiographic parameters, markers of inflammation, and exercise capacity. Linear regression analyses with stepwise regression analyses were used to construct the predictive regression models for HR recovery, SDNN, and HR turbulence. The group variable (type 2 diabetes) and all the significant demographic, laboratory, and echocardiographic variables which correlated with autonomic markers in the Spearman's correlation analyses ($p < 0.05$) and medication were included as covariates in the linear regression analyses. SDNN and HR turbulence slope had non-Gaussian distribution and were transformed into natural logarithms before the parametric statistical tests.

Because the cutoff values of autonomic markers have not been previously defined for this type of population with stable CAD, the optimal cutoff value for each of the measures of autonomic function was defined from receiver operating characteristic (ROC) curves as the maximum sum of sensitivity and specificity below the median with sensitivity of at least 20% using a composite of cardiovascular complications as the endpoint. Univariate Cox regression analysis was used to obtain values for hazard ratio with 95% confidence intervals for categorized autonomic markers. Thereafter, multivariate Cox regression analysis was performed, including covariates which were associated with a composite cardiovascular endpoint: sex, age, presence of type 2 diabetes or HbA1c, high-sensitivity C-reactive protein (hs-CRP), triglycerides, microalbuminuria, left ventricular systolic and diastolic function, and exercise capacity. Cox regression analyses were also performed for the sub-group of CAD patients with ($n = 525$) and without type 2 diabetes ($n = 427$). The statistical analyses were performed using SPSS software, versions 19.0 and 21.0 (SPSS Inc., Chicago, USA). A p value $< 0.05$ was considered statistically significant.

## RESULTS

The demographic characteristics and medication of the study population are presented in Table 1.

***Determinants of heart rate recovery:*** All significant correlations between HR recovery and other potential variables are presented in Table 2. In CAD patients with and without type 2 diabetes, HR recovery had the strongest univariate correlation with exercise capacity ($r = 0.55$), age ($r = -0.41$), fasting plasma glucose ($r = -0.29$), and left ventricular diastolic function ($r = -0.29$, $p < 0.001$ for all). CAD patients with type 2 diabetes had reduced HR recovery compared with their counterparts without diabetes ($23 \pm 11$ vs. $29 \pm 11$ bpm, $p < 0.001$). Similarly, patients who used calcium antagonists had reduced HR recovery compared with those who did not take these drugs ($23 \pm 11$ vs. $27 \pm 12$ bpm, $p < 0.001$). When all factors that correlated with HR recovery were entered into a stepwise linear regression model ($R = 0.60$, $p < 0.001$), exercise capacity ($R = 0.34$, $p < 0.001$), age ($R = -0.24$, $p < 0.001$), type 2 diabetes ($R = 0.09$, $p = 0.002$), hs-CRP ($R = -0.10$, $p < 0.001$), left ventricular diastolic function ($R = -0.07$, $p = 0.007$), calcium antagonists ($R = -0.06$, $p = 0.013$), and triglycerides ($R = -0.06$, $p = 0.024$) emerged as the significant predictors of HR recovery for the CAD patients with and without type 2 diabetes.

***Determinants of heart rate variability:*** Significant correlations between SDNN and other potential variables are presented in Table 2. In CAD patients with and without type 2 diabetes, SDNN had the strongest univariate correlation with exercise capacity ($r = 0.40$), fasting plasma glucose ($r = -0.32$), and HbA1c level ($r = -0.26$, $p < 0.001$ for all). CAD patients with type 2 diabetes had reduced SDNN compared with their counterparts without diabetes ($124 \pm 41$ vs. $149 \pm 39$ ms, $p < 0.001$). When all factors that correlated with SDNN were entered into a stepwise linear regression model ($R = 0.48$, $p < 0.001$), exercise capacity ($R = 0.33$, $p < 0.001$), type 2 diabetes ($R = 0.16$, $p = 0.001$), triglycerides ($R = -0.11$, $p < 0.001$), left ventricular mass index ($R = 0.09$, $p =$

0.003), hs-CRP (R = -0.09, p = 0.004), BMI (R = 0.09, p = 0.008), depression score (R = -0.08, p = 0.013), and albuminuria (R = -0.07, p = 0.028) were the significant predictors of SDNN in CAD patients with and without type 2 diabetes.

***Determinants of heart rate turbulence slope:*** Significant correlations between HR turbulence slope and other potential variables are presented in Table 2. In the CAD patients with and without type 2 diabetes, there was a clear positive correlation between HR turbulence slope and exercise capacity (r = 0.23, p < 0.001) and negative correlations between HR turbulence slope and age (r = -0.18), fasting plasma glucose (r = -0.18), and HbA1c (r = -0.17, p < 0.001 for all). CAD patients with type 2 diabetes had reduced HR turbulence slope compared with their counterparts without diabetes (7.30 ± 7.85 vs. 8.94 ± 8.37 ms/RR, p < 0.001). Similarly, patients who used calcium antagonists had reduced HR turbulence slope compared with those who did not take these drugs (6.74 ± 6.90 vs. 8.62 ± 8.51 ms/RR, p = 0.001). When all factors that correlated with HR turbulence slope were entered into a stepwise linear regression model (R = 0.38, p < 0.001), exercise capacity (R = 0.13, p = 0.001), left ventricular systolic (R = 0.18, p < 0.001) and diastolic function (R = -0.11, p = 0.002), calcium antagonists (R = -0.07, p = 0.026), depression score (R = -0.09, p = 0.008), age (R = -0.12, p = 0.002), and HDL cholesterol level (R = 0.10, p = 0.005) were significant predictors of HR turbulence slope in CAD patients with and without type 2 diabetes.

***Prognostic value of cardiovascular autonomic function:*** During the follow-up period, 127 patients (13%) reached a composite endpoint, including 16 patients (2%) with cardiovascular death, 78 (8%) with acute coronary events, 29 (3%) with strokes, and 16 (2%) patients hospitalized for heart failure. In the ROC analysis, areas under the curve were 0.606 (p = 0.001), 0.552 (p = 0.072), and 0.564 (p = 0.020), respectively for HR turbulence, SDNN and HR recovery. In univariate analyses with optimal cutoff points, both blunted HR turbulence slope (< 3.4 ms/RR), SDNN (< 110 ms), and HR recovery (< 21 bpm) were powerful predictors of a composite endpoint (hazard ratio 2.1, 95% CI 1.4–3.2, p < 0.001; hazard ratio 1.9, 95% CI 1.3–2.7, p = 0.001; hazard ratio 1.6;

95% CI 1.1–2.2, p = 0.012, respectively) in the total population. The sensitivity, specificity, and positive and negative predictive accuracy for the optimal cutoff points were 42%, 76%, 21% and 90% for HR turbulence, 39%, 76%, 19% and 89% for SDNN and 44%, 67%, 17% and 89% for HR recovery. However, after multivariate adjustment, none of the autonomic markers remained predictive of a composite endpoint (Table 3).

Among CAD patients with type 2 diabetes, cardiovascular endpoints occurred in 80 (15%) patients, including 10 (2%) cardiovascular deaths, 43 (8%) acute coronary events, 23 (4%) strokes, and 14 (3%) hospitalizations for heart failure. A composite endpoint was predicted by blunted HR turbulence slope (n = 133), SDNN (n = 172), and HR recovery (n = 239) in univariate analyses (hazard ratio 2.1, 95% CI 1.3–3.4, p = 0.003; hazard ratio 2.0, 95% CI 1.2–3.1, p = 0.005; hazard ratio 1.7; 95% CI 1.1–2.6, p = 0.020, respectively). The sensitivity, specificity, and positive and negative predictive accuracy for the optimal cutoff points were 50%, 71%, 24% and 89% for HR turbulence, 51%, 66%, 21% and 89% for SDNN and 58%, 57%, 19% and 88% for HR recovery. After multivariate adjustment, hs-CRP remained as the only independent predictor of a composite endpoint (Table 3, Figure 1).

Among patients with CAD alone, cardiovascular complications occurred in 47 (11%) patients (p = 0.05 compared with CAD patients with type 2 diabetes), including 6 (1%) cardiovascular deaths, 35 (6%) acute coronary events, 6 strokes, and 2 (1%) hospitalizations for heart failure. None of the autonomic markers predicted cardiovascular endpoints in univariate or multivariate analyses in CAD patients without type 2 diabetes (Table 3, Figure 1).

## CONCLUSIONS

The present study shows that low exercise capacity, age, type 2 diabetes, and hs-CRP are the most important determinants of cardiovascular autonomic function in stable CAD patients with and without type 2 diabetes. HR turbulence was also influenced by left ventricular systolic function.

Autonomic function assessed by either HR recovery, HR variability, or HR turbulence predicted short-term cardiovascular endpoints in univariate analyses in CAD patients with type 2 diabetes, but not in their counterparts without type 2 diabetes. However, autonomic measures did not provide independent short-term prognostic information, even in the patients with type 2 diabetes, after adjusting for clinical, demographic, and echocardiographic risk variables, including a marker of low-grade inflammation, which remained as the independent prognostic marker.

Many studies have found an association between autonomic function and exercise capacity or physical fitness in the general population and in various patient groups, including cardiac patients (22, 23, 29-31). Both impaired HR recovery and HR variability are related to reduced exercise capacity. The results of our study are consistent with previous studies and indicate that abnormalities in HR recovery and HR variability strongly correlate with low exercise capacity in CAD patients. Moreover, we also found a similar association between HR turbulence and exercise capacity, which has not been reported earlier.

Autonomic dysfunction, assessed by blunted HR recovery, has been shown to be associated with an increased level of fasting plasma glucose in CAD patients without type 2 diabetes (32). In previous study, we found that blunted HR recovery was more common among CAD patients with type 2 diabetes than in those without (31), and similar to our results, Nonaka et al. (33) demonstrated that abnormal HR recovery is associated with type 2 diabetes in patients with suspected CAD. We also found in the present study, as expected, a significant association between autonomic function, fasting plasma glucose, and HbA1c levels among CAD patients with and without type 2 diabetes. Moreover, type 2 diabetes was one of the strongest predictors of HR recovery and SDNN, but it did not predict HR turbulence. Therefore, our present study confirmed the relationship between autonomic dysfunction and type 2 diabetes also among the patients with stable CAD.

Previous studies have suggested that autonomic dysfunction in CAD patients is associated with the angiographic severity and degree of coronary occlusion, but not with a history of previous myocardial infarction (11, 12). The results regarding the association between left ventricular function and autonomic markers have been variable. Szydlo et al. (34) found an association between lower HR variability and left ventricular systolic dysfunction, which also seems to be the key factor influencing HR turbulence parameters in CAD patients (35). However, some recent studies did not find significant correlations between decreased HR recovery and left ventricular systolic dysfunction (12, 33). In the present study, we observed a weak correlation between a history of myocardial infarction and all three measurements of autonomic function, while left ventricular systolic function correlated only with the HR turbulence.

In patients with CAD, depressive symptoms are associated with cardiac autonomic dysfunction (36). Also, inflammatory markers are inversely correlated with autonomic function among CAD patients (15, 16). In our study, both depression score and hs-CRP level were negatively associated with all three autonomic markers, but depression score did not independently predict autonomic function in the multiple linear regression analyses.

Most previous association studies have usually used only one measure of the autonomic nervous system — either HR recovery or HR variability — whereas the determinants of HR turbulence are less well studied. In the present study, cardiovascular autonomic function was measured by three different methods which describe partly different aspects of autonomic regulation. Post-exercise HR recovery can be considered to reflect short-term vagal reactivity, SDNN is a marker of long-term vagal tone and HR turbulence provides an indirect assessment of baroreflex sensitivity. Moreover, previous studies have mainly examined the association between autonomic function and only a few associated factors, whereas in the present study we have taken account many potential determinants of autonomic function at the same time. Furthermore, we concentrated here on studying the short-term prognostic value of autonomic markers in patients

with a stable CAD, whereas previous studies have mainly focused on long-term prognostic value of post-infarction patients. It can be speculated that the risk profiles and their predictive value may change over time, especially after an acute coronary event. Recent studies have shown that autonomic function measured late after an acute myocardial infarction predicts mortality better than measurements performed in the early post-infarction phase (28, 37, 38). Therefore, analysis of factors predicting cardiovascular complications after stabilization of an acute coronary event may in fact provide more relevant clinical information.

The univariate analysis showed that all three autonomic markers predicted short-term cardiovascular complications in CAD patients with type 2 diabetes, but not in their counterparts without type 2 diabetes. This emphasizes the role of autonomic markers as predictors of short-term cardiovascular events, especially in patients with type 2 diabetes and stable CAD. In agreement with many similar studies in other populations (5, 9), the positive predictive accuracy of HR turbulence and HR variability remained at a relative low level also in patients with type 2 diabetes. However, the negative predictive values were high, suggesting that well preserved autonomic function prevents the early occurrence of cardiovascular events in this group of patients. HR turbulence had the highest positive predictive value and the highest hazard ratio for cardiovascular events. The results are in agreement with a previous sub-study of a German post-infarction population which showed that HR turbulence was a strong predictor of mortality in patients with type 2 diabetes (39).

The prognostic value of autonomic function in CAD patients with type 2 diabetes did not remain statistically significant after multivariate adjustment, including hs-CRP, a marker of low-grade inflammation. Biasucci et al. (40) have investigated a prognostic role for hs-CRP in patients with acute coronary syndrome during a 1-year follow-up. Interestingly, their findings were opposite to the results of our study, which suggested that hs-CRP is strongly associated with death and AMI, especially in patients without type 2 diabetes, but not in patients with type 2 diabetes. However,

Biasucci et al. had enrolled a relatively small number of patients with unstable angina (n = 251), and hard events were observed in only 7 patients with type 2 diabetes, whereas we report the prognostic power of hs-CRP for cardiovascular events in a larger population with type 2 diabetes and stable CAD.

The prognostic part of the present study was limited by a relatively short follow-up and a mixture of various endpoints. The low number of endpoints in the CAD patients without type 2 diabetes limits the generalizability of the results in terms of the negative predictive value of the autonomic markers. Similarly, the negative predictive value of these markers in multivariate analysis in patients with type 2 diabetes may be partly due to the small sample size and the short follow-up. However, we wanted specifically to study the short-term prognostic values of risk markers which could provide insight into the therapeutic targets of the well-defined population of CAD patients who had recently undergone coronary angiography and most of who were treated with a recent coronary intervention. In this respect, the independent prognostic power of hs-CRP is of potential interest in patients with type 2 diabetes, suggesting that therapeutic interventions to reduce inflammation might be of pivotal importance in attempting to reduce early cardiovascular complications of patients with type 2 diabetes and CAD. A larger sample size of the on-going study will reveal the definite value of hs-CRP in this context.

It is notable that the present measurements of autonomic function were performed under continued prescribed medication, and majority of the patients (88%) were treated with beta blockers. However, the use of beta blockers did not independently predict autonomic function in the multiple linear regression analyses probably because of low number of patients in the non-user group. During the follow-up, cardiovascular endpoints occurred in 119 (14%) patients, who were treated with beta blockers and in 8 (8%) patients without beta blocker medication. Although the difference in incidence of cardiovascular endpoints was not statistically significant, it is possible that the users of beta blockers may be at increase risk of short-term cardiovascular events. A large

survey in patients with stable CAD without a recent myocardial infarction also showed that the composite endpoint, including cardiovascular death, nonfatal myocardial infarction, stroke, hospitalization for atherothrombotic events or a revascularization procedure, was higher among the users vs. non-users of beta blocking drugs in the current era (41).

In conclusion, cardiovascular autonomic function in CAD patients is associated with several variables, including exercise capacity, age, inflammation, and left ventricular systolic function. Although autonomic dysfunction predicts short-term cardiovascular events among CAD patients with type 2 diabetes, it did not provide independent prognostic information after multivariate adjustment with other risk variables. The definite role of hs-CRP in risk stratification of CAD patients with type 2 diabetes needs further investigation.

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J.J.K. analyzed and interpreted data, and wrote and reviewed the drafts of the article. A.M.K. contributed to the statistical analyses, and reviewed the final draft of the article. A.J.H.; O-P.P.; E.S.L.; M.A.P.; O.H.U. and P.S.M.H. contributed to the data collection and reviewed the final draft of the article. H.V.H. and M.P.T contributed to the design of the ARTEMIS study, guided the process of data analysis and interpretation, and read and reviewed the drafts of the article. M.P.T is the guarantor of this work and, as such, has full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## FIGURE LEGEND

**Figure 1.** Heart rate recovery (HRR) (A), heart rate variability (SDNN) (B), and heart rate turbulence slope (HRT) (C) as predictors of a composite endpoint of cardiovascular death, acute coronary event, stroke, or hospitalization for heart failure in Kaplan-Meier survival analysis. Red colour describes the coronary artery disease patients with type 2 diabetes (T2D+) and blue colour describes the coronary artery disease patients without type 2 diabetes (T2D-).

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Table 1. Demographic characteristics of coronary artery disease patients.

| | Study population n = 1060 |
|---|---|
| Patients with T2D, n | 530 (50) |
| Men, n | 731 (69) |
| Age, year | 67 ± 8 (39–85) |
| Height, m | 1.69 ± 0.9 (144–196) |
| Weight, kg | 81 ± 16 (46–147) |
| BMI, kg/m$^2$ | 28.3 ± 4.7 (18.0–48.0) |
| Waist-hip ratio | 0.96 ± 0.09 (0.68–1.75) |
| Systolic BP, mmHg | 147 ± 23 (87–239) |
| Diastolic BP, mmHg | 78 ± 11 (42–115) |
| Current smokers, n | 95 (9) |
| Depression score | 5.1 ± 4.8 (0–30) |
| **History of AMI** | |
| NSTEMI, n | 313 (30) |
| STEMI, n | 167 (16) |
| **Revascularization** | |
| PCI, n | 624 (59) |
| CABG, n | 250 (24) |
| **Cardiac function** | |
| LVEF, % | 65 ± 9 (20–87) |
| LVEDD, mm | 50 ± 6 (31–80) |
| LVMI, g/m$^2$ | 105 ± 26 (36–222) |
| E/E’ | 10.9 ± 4.0 (4.2–31.0) |
| SDNN, ms | 137 ± 42 (47–331) |
| HR turbulence slope, ms/RR | 8.12 ± 8.15 (0.20–64.4) |
| **Bicycle stress test** | |
| max exercise capacity, METs | 6.0 ± 1.8 (2.2–12.0) |
| max workload, W | 117 ± 42 (31–227) |
| max ST segment depression, mV | -0.13 ± 0.07 (-0.41–0) |
| max HR, bpm | 123 ± 22 (70–210) |
| HR recovery, bpm | 26 ± 12 (0–75) |

| | |
|---|---|
| **Laboratory analyses** | |
| HbA1c, % | 6.4 ± 1.1 (4.6–15.4) |
| HbA1c, mmol/mol | 46 ± 12 (27–145) |
| Fasting plasma glucose, mmol/l | 6.5 ± 1.9 (3.9–21.2) |
| Total cholesterol, mmol/l | 4.0 ± 0.8 (2.0–7.8) |
| HDL cholesterol, mmol/l | 1.3 ± 0.3 (0.6–2.9) |
| LDL cholesterol, mmol/l | 2.3 ± 0.7 (0.7–5.9) |
| Triglycerides, mmol/l | 1.4 ± 0.8 (0.3–10.4) |
| hs-CRP, mg/l | 2.2 ± 4.5 (0.1–74.4) |
| Creatinine clearance, ml/min | 93.2 ± 34.8 (28.6–268.3) |
| Microalbuminuria, mg/l | 18.0 ± 62.7 (1.6–1390.0) |
| Albumin-creatinine ratio, mg/mmol | 2.4 ± 8.9 (0.1–227.9) |
| **Medication** | |
| Beta blockers, n | 934 (88) |
| ACEI/ARB, n | 658 (62) |
| Lipids, n | 952 (90) |
| Anticoagulants, n | 1030 (97) |
| Calcium antagonists, n | 260 (25) |
| Nitrates, n | 426 (40) |
| Diuretics, n | 368 (35) |

Values are mean ± SD (min–max) or number of subjects (%). T2D, type 2 diabetes; BP, blood pressure; AMI, acute myocardial infarction; NSTEMI, no-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVMI, left ventricular mass index; E/E', ratio of early transmitral flow velocity to early diastolic mitral annulus velocity; SDNN, standard deviation of all R-R intervals; HR, heart rate; METs, metabolic equivalents; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; ACEI, angiotensin conversion enzymes inhibitor; ARB, angiotensin receptor blocker; ACEI/ARB, patients using at least one of them.

Table 2. Significant correlations between heart rate recovery, heart rate variability, and heart rate turbulence slope and demographic characteristics, features of type 2 diabetes, laboratory measurements, and echocardiographic parameters in coronary artery disease patients.

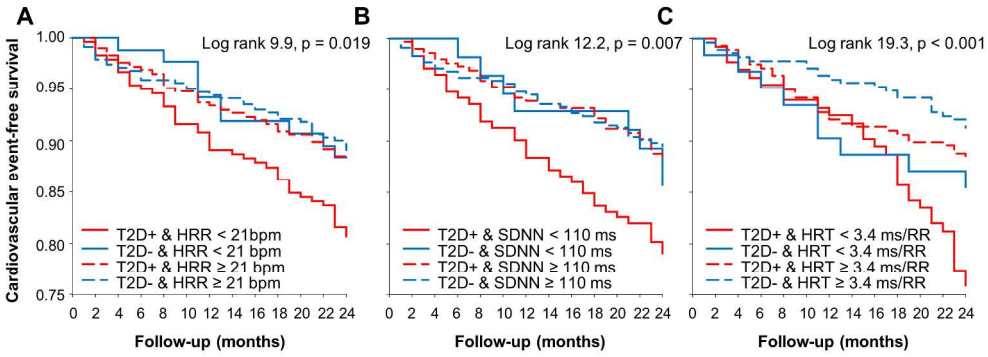
| | HR recovery | | SDNN | | HR turbulence | |
|---|---|---|---|---|---|---|
| | r value | p value | r value | p value | r value | p value |
| **Demographic characteristics** | | | | | | |
| Age | -0.41 | <0.001 | -0.07 | 0.024 | -0.18 | <0.001 |
| BMI | -0.22 | <0.001 | -0.19 | <0.001 | -0.11 | 0.002 |
| Systolic BP | -0.13 | <0.001 | 0.04 | ns | -0.01 | ns |
| Exercise capacity | 0.55 | <0.001 | 0.40 | <0.001 | 0.23 | <0.001 |
| Depression score | -0.15 | <0.001 | -0.17 | <0.001 | -0.15 | <0.001 |
| **Features of T2D** | | | | | | |
| Fasting plasma glucose | -0.29 | <0.001 | -0.32 | <0.001 | -0.18 | <0.001 |
| HbA1c | -0.24 | <0.001 | -0.26 | <0.001 | -0.17 | <0.001 |
| Albuminuria | -0.20 | <0.001 | -0.15 | <0.001 | -0.14 | <0.001 |
| Creatinine clearance | 0.21 | <0.001 | -0.06 | ns | 0.07 | 0.035 |
| Albumin-creatinine ratio | -0.24 | <0.001 | -0.19 | <0.001 | -0.11 | 0.002 |
| **Inflammation** | | | | | | |
| hs-CRP | -0.22 | <0.001 | -0.16 | <0.001 | -0.15 | <0.001 |
| **Lipid profile** | | | | | | |
| HDL cholesterol | 0.11 | 0.001 | 0.14 | <0.001 | 0.10 | 0.006 |
| Triglycerides | -0.15 | <0.001 | -0.17 | <0.001 | -0.09 | 0.013 |
| **Cardiac function** | | | | | | |
| History of AMI | -0.09 | 0.005 | -0.07 | 0.035 | -0.09 | 0.013 |
| LVEF | 0.03 | ns | 0.03 | ns | 0.12 | 0.001 |
| LVEDD | 0.05 | ns | 0.14 | <0.001 | 0.00 | ns |
| E/E’ | -0.29 | <0.001 | -0.18 | <0.001 | -0.19 | <0.001 |
| LVMI | -0.11 | <0.001 | 0.06 | 0.046 | -0.10 | 0.003 |

HR, heart rate; SDNN, standard deviation of all R-R intervals; BP, blood pressure; T2D, type 2 diabetes; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; E/E’, ratio of early transmitral flow velocity to early diastolic mitral annulus velocity; LVMI, left ventricular mass index.

Table 3. Heart rate recovery, heart rate variability, and heart rate turbulence slope as predictors of a composite endpoint of cardiovascular death, acute coronary event, stroke, and hospitalization for heart failure during a 2-year follow-up in coronary artery disease patients.

| | Univariate | | Multivariate* | | Significant covariates | | |
|---|---|---|---|---|---|---|---|
| | Hazard ratio (CI) | p value | Hazard ratio (CI) | p value | | Hazard ratio (CI) | p value |
| **All patients** | | | | | | | |
| HRR < 21 bpm | 1.57 (1.11–2.23) | 0.012 | 0.91 (0.59–1.41) | 0.679 | Exercise capacity | 0.82 (0.70–0.96) | 0.014 |
| | | | | | hs-CRP | 1.03 (1.00–1.06) | 0.015 |
| | | | | | Ejection fraction | 0.98 (0.96–1.00) | 0.034 |
| SDNN < 110 ms | 1.86 (1.27–2.71) | 0.001 | 1.34 (0.88–2.04) | 0.168 | Ejection fraction | 0.97 (0.96–0.99) | 0.006 |
| | | | | | hs-CRP | 1.03 (1.00–1.05) | 0.048 |
| HRT slope < 3.4 ms/RR | 2.14 (1.43–3.20) | <0.001 | 1.44 (0.92–2.25) | 0.113 | Ejection fraction | 0.97 (0.95–0.99) | 0.008 |
| | | | | | hs-CRP | 1.03 (1.00–1.06) | 0.034 |
| **CAD patients with T2D** | | | | | | | |
| HRR < 21 bpm | 1.69 (1.09–2.64) | 0.020 | 1.29 (0.75–2.23) | 0.360 | hs-CRP | 1.03 (1.01–1.06) | 0.006 |
| | | | | | HbA1c | 1.20 (1.03–1.40) | 0.021 |
| SDNN < 110 ms | 1.96 (1.23–3.14) | 0.005 | 1.57 (0.94–2.62) | 0.084 | hs-CRP | 1.03 (1.00–1.06) | 0.026 |
| HRT slope < 3.4 ms/RR | 2.08 (1.28–3.40) | 0.003 | 1.63 (0.94–2.82) | 0.084 | hs-CRP | 1.03 (1.01–1.06) | 0.022 |
| **CAD patients without T2D** | | | | | | | |
| HRR < 21 bpm | 1.05 (0.52–2.11) | 0.888 | 0.53 (0.23–1.20) | 0.126 | Exercise capacity | 0.69 (0.54–0.89) | 0.005 |
| SDNN < 110 ms | 1.35 (0.63–2.90) | 0.448 | 0.93 (0.42–2.07) | 0.865 | Ejection fraction | 0.96 (0.93–1.00) | 0.028 |
| | | | | | Exercise capacity | 0.77 (0.60–0.99) | 0.043 |
| HRT slope < 3.4 ms/RR | 1.78 (0.83–3.83) | 0.140 | 1.23 (0.54–2.80) | 0.616 | Ejection fraction | 0.96 (0.92–0.99) | 0.018 |
| | | | | | Exercise capacity | 0.74 (0.55–0.99) | 0.045 |

HRR, heart rate recovery; SDNN, standard deviation of all R-R intervals; HRT, heart rate turbulence; hs-CRP, high-sensitivity C-reactive protein.* Adjusted for sex, age, presence of type 2 diabetes (HbA1c in CAD patients with T2D), hs-CRP, triglycerides, albuminuria, left ventricular systolic and diastolic function, and exercise capacity.

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